

The National Academy Of Clinical Biochemistry

Presents

LABORATORY MEDICINE PRACTICE GUIDELINES

**EVIDENCE BASED PRACTICE FOR
POINT OF CARE TESTING**

EVIDENCE BASED PRACTICE FOR POINT OF CARE TESTING

EDITOR

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TABLE OF CONTENTS

Preface	8
Introduction	13
Chapter 1: Management	25
Quality Assurance and Medical Error	25
Does Management Improve the Quality of POCT?	29
Chapter 2: Bilirubin	39
Chapter 3: Utilization of Cardiac Biomarkers for Acute Coronary Care . . .	65
Chapter 4: Coagulation	85
Activated Partial Thromboplastin Time (aPTT)	87
Prothrombin Time (PT)/International Normalized Ratio (INR)	92
Activated Clotting Time (ACT)	95
Chapter 5: Critical Care	115
Arterial Blood Gases	119
Intensive Care Unit	119
Emergency Department	124
Cardiac Surgery: Adult and Neonatal	126
Glucose	128
Lactate	130
Magnesium	132
Cooximetry	135
Oxygen Saturation	135
Carboxyhemoglobin	137

Methemoglobin	138
Electrolytes	139
Emergency Department	139
Intensive Care Unit	140
Ionized Calcium	141
Emergency Department	141
Operating Room	142
Intensive Care Unit	142
Chapter 6: Diagnosis and Management of Diabetes Mellitus	167
Blood Glucose	169
Type 1 Diabetes Mellitus	170
Type 2 Diabetes Mellitus	173
HgbA1c Testing	180
Fructosamine	187
Blood Ketones	189
Urine Albumin	195
Chapter 7: Drugs and Ethanol	238
Use of POCT for Drugs of Abuse in the Clinical Setting	252
POC Drug Testing in Maternal-Fetal Medicine	254
POC Drug Testing in Pain Management	254
POC Drug Testing in Detoxification Clinics	255
Urine versus Alternative Matrices	257
Urine	258

Oral Fluid (Saliva)	259
Breath	262
Sweat	263
Other Matrices	264
Non-Clinical Applications of POCT for Drugs of Abuse and Ethanol . .	264
Other Issues	272
Chapter 8: Infectious Disease	284
Bioterrorism	285
<i>Clostridium difficile</i>	289
Infectious Mononucleosis	290
<i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i>	294
Group A Streptococcal Antigen Tests	296
Group B Streptococci	297
H. pylori	301
Influenza Virus	302
Respiratory Syncytial Virus	303
HIV Testing	305
<i>Trichomonas vaginalis</i> Vaginitis	319
Candida Vulvovaginitis	321
Bacterial Vaginosis	322
Chapter 9: Occult Blood	353
Chapter 10: Intraoperative Parathyroid Hormone Testing	387
Primary Hyperparathyroidism	388

Other Parathyroid Diseases	404
Localization	411
Secondary Questions	414
Chapter 11: pH	441
Chapter 12: Renal	463
Chapter 13: Reproduction	494
Urine/Serum hCG Testing	495
Urine LH Ovulation Tests	502
Non-Urine Ovulation Tests	508
pH/Nitrazine Tests for Premature Rupture of Membranes	510
Fern Tests for Premature Rupture of Membranes	514
Fetal Fibronectin Testing (fFN) for Premature Delivery	516
Appendix A Systematic Review Data Abstraction Forms	542
Appendix B Corporate Sponsors and Acknowledgements	546

Preface

This is the eleventh in the series of Laboratory Medicine Practice Guidelines (LMPG) sponsored by the National Academy of Clinical Biochemistry (NACB). The field of point of care testing (POCT), diagnostic testing conducted close to the site of patient care, was divided into disease and test specific focus areas. Groups of expert physicians, laboratorians and diagnostic manufacturers in each focus area were assembled to conduct systematic reviews of the scientific literature and prepare guidelines based on the strength of scientific evidence linking the use of point of care testing to patient outcome. To our knowledge, this is the most comprehensive review of the point of care literature to date.

It is hoped that these guidelines will be useful for those implementing new testing as well as those reviewing the basis of current practice. These guidelines should help sort fact from conjecture when applying testing to different patient populations and establish proven applications from off-label and alternative uses of point of care testing. These guidelines will also be useful in defining mechanisms for optimizing patient outcome and identify areas lacking in the current literature that are needed for future research.

The guidelines were presented in open forum at the AACC Annual Meeting (Los Angeles, CA, U.S.A.) in July 2004. Portions of these guidelines were also presented at several meetings between 2003 - 2005: CLMA Breakout Session (Salt Lake City, UT, U.S.A.) in June 2003, 37th Brazilian Congress of Pathology and Clinical Laboratory Medicine (Rio de Janeiro, Brazil) in September 2003, Maine Society for Clinical Laboratory Science Northeast Regional Joint Fall Conference (Portland, ME, U.S.A.) in October 2003, Association of Clinical Biochemists

(Dublin Ireland) in November 2003, LabMed2003 Alliance of Northeast AACC Local Sections (Providence, RI, U.S.A.) in November 2003, CLMA Breakout Session and ASCP simulcast audioconference (Atlanta, GA, U.S.A.) in March 2004, the Northern California American Association for Clinical Chemistry (AACC) local section (San Jose, CA, U.S.A.) in April 2004, Teleconference Network of Texas (San Antonio, TX, U.S.A.) in May 2004, the Beckman Conference (Boston, MA, U.S.A.) in May 2004, the AACC Critical and Point of Care Testing Division/IFCC meeting (Wurzburg, Germany) in June 2004, AACC Workshop (Los Angeles CA, U.S.A.) in July 2004, 23rd Annual Southwest Association of Clinical Microbiologists (San Antonio, TX) in September 2004, Mid-Atlantic Point of Care Coordinators Fall Symposium (Baltimore, MD, U.S.A.) in October 2004, East Coast Central Florida POCT Conference (Cocoa Beach, FL, U.S.A.) in October 2004, Northwest Medical Laboratory Symposium (Portland, OR, U.S.A.) in October 2004, Quality 2005 (Antwerp, Belgium) in March 2005, EuroMedLab (Glasgow, Scotland) in May 2005, AACC Upstate New York Local Section Spring Meeting (Rochester, NY, U.S.A.) in May 2005, American Society for Microbiology symposium (Atlanta, GA, U.S.A.) in June 2005, AACC workshop (Orlando, FL, U.S.A.) in July 2005, College of American Pathologists workshop (Chicago, IL U.S.A.), Dade Microbiology Symposia (Harrisburg, PA) in September 2005, 8th Annual Fall Clinical Pathology Symposium (Louisville, KY, U.S.A.) in November 2005. Participants at each meeting had the ability to discuss the merits of the guidelines and submit comments to the NACB website for formal response by the NACB during the open comment period from January 2004 through October 2005. A summary of these comments and revisions are presented at the end of each section of the guidelines when applicable.

Nonstandard abbreviations

LMPG, Laboratory Medicine Practice Guidelines; NACB, National Academy of Clinical Biochemistry; POCT, point of care testing; AACC, American Association for Clinical Chemistry; CLMA, Clinical Laboratory Management Association; ASCP, American Society of Clinical Pathologists; EBM, evidence based medicine; ED, Emergency Department; QA, quality assurance; QM, quality management; QC, quality control; EQA, external quality assessment; IQC, internal quality control; ISO, International Organization for Standardization; MDA, Medical Devices Agency; QI, quality improvement; HPLC, high pressure liquid chromatography; ACS, acute coronary syndrome; UA, unstable angina; MI, myocardial infarction; AMI, acute myocardial infarction; ECG, Electrocardiogram; POC, point of care; TAT, turnaround time; LOS, length of stay; PT, prothrombin time; aPTT, activated partial thromboplastin time; TEG, thromboelastography; INR, international normalized ratio; PST, patient self-testing; PSM, patient self-management; ACT, activated clotting time; PTCA, percutaneous transluminal coronary angioplasty; CCU, critical care unit; NICU, neonatal intensive care unit; SICU, surgical intensive care unit; PICU, pediatric intensive care unit; CICU, cardiac intensive care unit; OR, operating room; TTAT, therapeutic turnaround time; ABG, arterial blood gases; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation; CABG, coronary arterial bypass grafting; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study; SMBG, self-monitoring blood glucose; RCT, randomized controlled trials; DM, diabetes mellitus; ACE, acetone; AcAc, acetonacetate; BOHB, beta-hydroxybutyrate; DKA, diabetic ketoacidosis; UKB, urine ketone body; ESRD, end-stage renal disease; CVD, cardiovascular disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; CR, creatinine; UAE, urinary

albumin excretion; ADA, American Diabetes Association; AHRQ, Agency for Healthcare Research and Quality; BUN, blood urea nitrogen; NIDA, National Institute on Drug Abuse; SAMSHA, Substance Abuse and Mental Health Services Administration; MDMA, 3-4 methylenedioxymethamphetamine; GC-MS, gas chromatography mass spectrometry; CLT, central laboratory testing; THC, delta-9-tetrahydrocannabinol; THCCOOH, delta-9-tetrahydrocannabinol carboxylic acid; AFDC, aid to families with dependent children; AIDS, acquired immune deficiency syndrome; DHHS, Department of Health and Human Services; FDA, Food and Drug Administration; PCP, phencyclidine; COC, cocaine; OPI, opiates; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; HA, heterophilic antibodies; IM, infectious mononucleosis; PID, pelvic inflammatory disease; STD, sexually transmitted disease; GAS, group A streptococcus; GBS, group B streptococcus; CDC, Centers for Disease Control; NSAID, nonsteroidal anti-inflammatory drug; CLIA, Clinical Laboratory Improvement Amendments; RSV, respiratory syncytial virus; SUDS, single use diagnostic system; ART, anti-retroviral therapy; EIA, enzyme immunoassay; HAART, highly active anti-retroviral therapy; IFA, immunofluorescence assay; FOBT, fecal occult blood testing; CRC, colorectal cancer; AGA, American Gastroenterological Association; DDW, Digestive Diseases of the Week; DRE, digital rectal exam; HO, Hemocult; HOS, Hemocult Sensa; Hsel, HemeSelect; PPV, positive predictive value; HQ, HemoQuant; GI, gastrointestinal; PTH, parathyroid hormone; MIP, minimally invasive parathyroidectomy; VAP, video-assisted parathyroidectomy; MIRP, minimally invasive radioguided parathyroidectomy; GER, gastroesophageal reflux; DUA, dipstick urinalysis; CVDL, cardiovascular diagnostics laboratory or cardiac catheterization laboratory; P/Cr, protein/creatinine ratio; hCG, human chorionic gonadotropin hormone; LH, luteinizing hormone; BBT, basal body temperature monitoring; PROM, premature rupture of the

membranes; PPRM, preterm premature rupture of the membranes; fFN, fetal fibronectin; NPV, negative predictive value.

Introduction

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In this Laboratory Practice Medicine Guideline (LMPG), the National Academy of Clinical Biochemistry (NACB) is examining the application of evidence-based medicine to the form of diagnostic testing known as Point of Care Testing (POCT.) For the purpose of this document POCT is defined as "clinical laboratory testing conducted close to the site of patient care, typically by clinical personnel whose primary training is not in the clinical laboratory sciences or by patients (self-testing). POCT refers to any testing performed outside of the traditional, core or central laboratory." Based on this definition there are many synonyms for this form of testing -

- Point of care testing
- Ancillary testing
- Satellite testing
- Bedside testing
- Near patient testing
- Home testing
- Self-management
- Patient self-management

- Remote testing
- Physician's Office Laboratories

Evidence based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (1). (Table 1) It is the integration of best research evidence with clinical expertise and patient values. Best research evidence is comprised of both clinically relevant research as well as basic science. Additionally it is patient centered research that evaluates the accuracy and precision of diagnostic tests, the power of prognostic markers and the efficacy/safety of therapeutic, rehabilitative and preventive regimens. Clinical expertise encompasses the ability to use clinical skills and past experience to identify a patient's unique health state, to make diagnosis, and to evaluate the risks and benefits of interventions, taking into account the patient's personal values and expectations. The patient's unique preferences, concerns and expectations need to be integrated into the clinical decision process.

There is a need for establishing an evidence-based practice for POCT. POCT is an increasingly popular means of delivering laboratory testing. When used appropriately, POCT can improve patient outcome by providing a faster result and a shorter timeframe to therapeutic intervention. However, when over-utilized or incorrectly performed, POCT presents a patient risk. POCT may seem deceptively simple, but the test is not freely interchangeable with traditional core lab instrumentation in all patient care situations. POCT may seem inexpensive, but over-utilization and inappropriate test utilization leads to significant increases in cost of care. The value of POCT really needs to be demonstrated through well-designed randomized control trials.

This LMPG will systematically review the existing scientific evidence relating POCT to patient outcome, grade the literature, and draft guidelines regarding the optimal utilization of POCT devices in patient care. The objective of this EBM of the practice of POCT is to systematically review and synthesize the available evidence on the effectiveness of POCT with specific focus on outcomes in the areas of:

- 1) Patient/Health
- 2) Operational/ Management
- 3) Economic benefit

In the planning for this Laboratory Medicine Practice Guideline (LMPG), the practice of POCT was organized according to disease groups with an introductory section for quality assurance concepts that cross all disciplines. Focus groups were formed with clinician, laboratorian and industry representation. For a specific clinical use, pertinent clinical questions were formulated and a systematic review of the clinical literature was conducted, in order to develop practice guidelines. In this document the evidence for the application of POCT in following clinical areas will be examined:

- Bilirubin
- Cardiac Markers
- Coagulation
- Critical Care
- Diabetes
- Drug Testing
- Infectious Disease

- Occult Blood
- Parathyroid Testing
- pH
- Renal
- Reproduction

When one examines the scientific literature for evidence for the efficacy of POCT it is quickly ascertained that there are few randomized case-controlled studies. The majority of publications described method comparisons. POCT is compared to a core laboratory method and it is assumed that the similar results generate similar clinical outcomes. However this is not necessarily true for all patients and devices. When generalizing the scientific literature various characteristics have to be examined. Does the study population compare to the real world? Is there a recruitment and randomization bias associated with the sampling methodology? Will there be compliance issues with the personnel performing POCT, will staff perform POCT correctly and with the same emphasis as in the study? What is the true benefit of the convenience of POCT – is there any harm with delay due to laboratory confirmation? Clinical and analytical specificity and sensitivity are other factors that need to be evaluated.

An evidence-based review of POCT must include an 1) assessment of patient outcome associated with obtaining a “quality” test result, 2) an understanding of how the testing system is integrated into the overall healthcare management, and 3) an understanding of the process or processes that lead to the desired outcome. The laboratory is quantitative and quality focused and therefore uniquely positioned to consult on critical pathways of care.

The basic procedures used by the various workgroups for the systematic review of the POCT literature are outlined in the following tables. The strength/level of evidence was based on effect on the outcome surrogate and the type of trial/study. Determination of the cohesiveness/consistency of the various studies, i.e., does the body of evidence make sense and the study conclusions lead to the same result, was one of the factors for the final guidelines given for or against POCT in a particular environment. To achieve these objectives, focus groups developed pertinent clinical questions for how the test was being utilized in various clinical settings. It was understood that some settings might raise different questions for the same test when compared to other settings, e.g., In-patient vs. emergency room vs. coronary care, etc. Thus, the same POCT may be employed differently in clinical decision-making and patient management in different settings. The format for the questions was:

- What is the effect on *Outcome* when comparing *POCT to Core Lab Testing* (Identify comparison) for *screening patient for Disease X* (cite clinical application) in the *Emergency Room* (list patient population)?
- Does POCT for *Disease X* (clinical application/assay/disease) improve *Outcome* (list outcome of interest) in *Patients* (describe population or setting) compared to core lab testing (identify comparison being measured)?

The key components of the question are:

How - Clinical application (screening, diagnosis, management)

What - Comparison being measured (core vs POCT)

Where - Patient population or clinical setting (ED, home, clinic)

Why - Outcome (clinical, operational, economical)

Once the questions were developed key search terms were ascertained for the literature search. Searches were conducted on Medline or PubMed and were supplemented with the use of the National Guideline Clearinghouse, the Cochrane Group or EBM reviews. Additionally, authors' personal manuscript collections were utilized. Acceptable citations were limited to peer-reviewed articles with abstracts, those published in English and those involving human subjects.

Abstracts identified by the literature searches were reviewed by two individuals to determine initial eligibility or ineligibility for full text review, utilizing Form 1 (Appendix A) If there was not consensus, then a third individual reviewed the abstract(s). In order to be included in the full systematic review of the clinical question, manuscripts selected for full text review were examined for at least one relevant outcomes measurement. The systematic review consisted of creating evidence tables Form 2 (Appendix A) that incorporated the following characteristics:

- Study design – Prospective or retrospective, randomized, and controlled, patient inclusion/exclusion criteria, blinding, number of subjects, etc.
- Appropriateness of controls
- Potential for bias (consecutive or nonconsecutive enrollment)
- Depth of method description- full length report or technical brief
- Clinical application- screening, diagnosis, management
- Specific key outcomes and how they were measured
- Conclusions are logically supported

For the assessment of study quality, the general approach to grading evidence developed by the US Preventive Services Task Force (2) was applied. (Table 2) Once that was done then an

assessment of study quality was performed looking at the individual and aggregate data at three different levels (Forms 3 & 4); (Appendix A). At the first level the individual study design was evaluated, as well as internal and external validity. Internal validity is the degree to which the study provides valid evidence for the populations and setting in which it was conducted. External validity is the extent to which the evidence is relevant and can be generalized to populations and conditions of other patient populations and POCT settings.

The synthesis of the volume of literature constitutes the second level, Form 5 (Appendix A). Aggregate internal and external validity was evaluated as well as looking at the coherence/consistency of the body of data. How well does the evidence fit together in an understandable model of how POCT leads to improved clinical outcome. Ultimately, the weight of the evidence regarding the linkage of POCT to outcomes is determined by assessing the degree to which the various bodies of evidence (linkages) “fit” together. To what degree is the testing in the same population and condition in the various linkages? Is the evidence that connects POCT to outcome direct or indirect? Evidence is direct when a single linkage exists, but is indirect when multiple linkages are required to reach the same conclusion.

Final guidelines were made based on AHRQ classification (Table 3) (3). The guidelines are evidence based and require scientific evidence that the recipients of POCT experience better health outcomes than those who did not and that the benefits are large enough to outweigh the risks. Consensus documents are not research evidence and represent guidelines for clinical practice and inclusion of consensus documents was based on the linkages to outcomes, the reputation of the peer organization, and the consensus process utilized to develop the document.

Health outcomes, e.g., benefit/harm, are the most significant outcomes in weighing the evidence and drafting guidelines.

POCT is an expanding delivery option due to increased pressure for faster results. However, POCT should not be utilized as a core lab replacement in all patient populations without consideration of the test limitations and evaluation of the effect of a faster result on patient care. There is a need for quality POCT outcomes studies to be conducted. Laboratories should require evidence of outcomes for new tests and question clinical utility of ongoing tests.

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Table 1

Terminology associated with EBM
Consensus Recommendations – Advice on an aspect of patient care based on peer opinion
Clinical Protocols – Guidance covering an aspect of clinical care; standardizes practice, minimizes variation
Outcome Study – Scientific research defining the end result or effect of a change in patient management.
Systematic Review – Synthesis and grading of the quality of research literature, conducted in a predefined manner
Practice Guidelines – Systematically developed statement based on scientific evidence that guides patient management decisions for specific clinical conditions and decreases variation in clinical practice.
Critical Pathway – Evidence-based multidisciplinary plans of care, defining the optimal timing and sequences of clinical processes. Improves care by standardizing clinical practice and communication

Table 2

Levels of Evidence	
I	Evidence includes consistent results from well-designed, well-conducted studies in representative populations
II	Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
III	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Table 3

Strength of Recommendations	
A –	The NACB strongly recommend adoption; there is good evidence that it improves important health outcomes and concludes that benefits substantially outweigh harms
B –	The NACB recommends adoption; there is at least fair evidence that it improves important health outcomes and concludes that benefits outweigh harms.
C –	The NACB recommends against adoption; there is evidence that it is ineffective or that harms outweigh benefits.
I –	The NACB concludes that the evidence is insufficient to make recommendations; evidence that it is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

Chapter 1: Management

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Quality Assurance and Medical Error

This chapter is an evidence-based review and assessment of quality assurance practices associated with Point of Care testing. The literature regarding quality assurance (QA) and quality management (QM) of POCT is by and large not evidence based (1–6). This is due, in large part, to the difficulty of assessing the causal impact of POCT on medical errors. Even in the traditional clinical laboratory setting, the scientific basis of QA and QM is the last area to have the concepts of evidence based medicine (EBM) applied.

Does the application of Quality Assurance to Point of Care Testing reduce medical errors?

(Literature Search 1)

Guideline 1. *We recommend that a formal process of quality assurance of POCT be developed in support of risk management and a reduction in medical errors.*

Strength/consensus of recommendation: B

Level of evidence: III (Expert opinion)

Quality control (QC) and quality assurance are integral components forming the basis of the quality management hierarchy of the clinical laboratory (7). Since the performance goals of POCT are no different to those of the traditional clinical laboratory namely to:

- provide accurate and timely analyses
- provide reports that are useful to the clinician managing the patient
- make epidemiological information available to public health authorities
- make the best possible use of people, equipment and reagents in the interests of efficiency
- manage utilisation

The justification and benefits of QA when applied to POCT would seem to be self-evident.

QA goes beyond QC and focuses on the impact of laboratory testing on patient care. A QA program for laboratory services should establish:

- performance expectations that cover pre-analytical, analytical and post-analytical components of the service;
- performance expectations following consultation with user-physicians and other health care workers;
- periodic audit to determine that the service is meeting its established performance expectations;
- a program of performance comparisons to that of the central or core laboratory;
- periodic review of the service patterns of practice against established, validated, external benchmarks;
- review of the QA program findings by a management team.

Although much has been written in recent years regarding the use of POCT, including the health cost benefits, there remains a paucity of evidence on which to base conclusions or make recommendations. Existing documents (1-7) appear to be consensus statements by expert groups based on collective insight and experience but with no clear indication of the underlying evidence although likely that it falls mainly into category III (as defined in the introduction).

The recent evolution of POCT has focused on small user-friendly devices with limited but robust analytical capabilities. Users tend to identify with a particular device for a particular purpose and, thus, see that device in isolation. In reality, each device is serving a function that traditionally belonged in the central or core laboratory with its established quality management processes and procedures supported by technical and professional expertise. Frequently persons who lack the training and insight in laboratory-based testing carry out POCT in a clinical setting. Since POCT results are treated comparable to testing main laboratory for patient care, it follows that the quality requirements are the same regardless of the testing site, process, or procedure. At the same time the unique characteristics (location, operators, distribution, etc.) add special requirements to QA/QM. As most instruments themselves are robust in their analytical performance the QA program should specifically address pre- and post-analytical concerns.

Requirements for QA, internal QC and external quality assessment (EQA) of POCT have been stated in many publications (3 – 7). The recommendations are consensus-based and include:

- Quality assurance is an essential component of POCT and includes all the measures taken to ensure that investigations are reliable:

- Correct identification of the patient
- Appropriate test selection
- Obtaining a satisfactory specimen
- Analysing it and recording the results promptly and correctly
- Interpreting the result accurately
- Taking appropriate action
- Documenting all procedures for reference
- IQC requirements:
 - Procedure established for IQC at appropriate frequency
 - QC material procurement
 - Correction of non-conformities
- Users of POCT have a duty to participate in an EQA scheme and perform adequately as part of clinical governance. Questions to consider are:
 - what is the role of the central laboratory in providing or recommending EQA schemes for POCT
 - who is responsible for co-ordination of EQA within POCT; are necessary procedures in place
 - who will review performance
 - is support available for inadequate performance
 - can the central laboratory assist by providing parallel testing.

The draft international standard, ISO/DIS 22870 Point-of-Care (POCT) — Requirements for quality and competence (8), has been distributed for review and comment. This document was

prepared by Working Group #1 of ISO Technical Committee TC212. The Introduction states risk to the patient and to the facility can be managed by a well-designed, fully implemented, quality management system that provides for:

- Evaluation of new or alternative POCT instruments and systems
- Evaluation and approval of end-user proposals and protocols
- Purchase and installation of equipment
- Maintenance of consumable supplies and reagents
- Training, certification and re-certification of POCT system operators, and
- Quality control and quality assurance

The technical requirements part of the draft international standard details those relating to personnel, accommodation and environmental conditions, equipment, pre-examination procedures, examination procedures, assuring the quality of the examination procedures, post-examination procedures, and the reporting of results.

Does Management Improve the Quality of POCT?

The term management as used here identifies two major parts. The first encompasses personnel responsible for oversight of the institutional POCT program. Personnel can variously be an individual (director, co-ordinator) or a team (interdisciplinary committee, management committee). The second deals with the activities related to the regulation of all the processes needed to generate reliable POC test results. Processes should be defined to cover all aspects of the POCT project. Falling partly within this second section and partly as an independent adjunct to POCT processes, there is the field of Data Management. Here, data from the testing process,

including QC and patient results, as well as related information such as error types and frequencies and operator certification and competency, are collected and manipulated to provide information useful in monitoring and improving the total process.

Guideline 2: *We strongly recommend the use of an interdisciplinary committee to manage POCT* (Literature Search 2)

Strength/Consensus of recommendation: A

Level of evidence: II and III (Time controlled studies, descriptive studies and expert opinion – consensus documents)

In smaller sites an individual coordinator or director may be responsible for POCT but a committee structure is preferable especially for larger sites or institutions. The management structure must have official standing with the explicit support of the institutional Administration. Committees should be interdisciplinary in composition since this ensures input from stakeholders leading to a broader perspective on the POCT project and enhancing chances of success. Published studies have described improvements in many aspects of the POCT programs following the implementation of a management committee (3,9,10). Generally, there was no pre-existing structure. In addition, and lending weight to our recommendations, documents published by various accreditation and regulatory agencies propose, with varying degrees of insistence, that a management (interdisciplinary) committee be operational at any site performing POC testing (11-13). These documents take various forms including Guidelines, Position Statements, and Consensus Statements.

The interdisciplinary team structure, by providing a forum for discussion of different ideas and approaches, permits more universally acceptable solutions to project activities. There is no consensus as to the actual composition of the committee and indications are that this may vary on a project-by-project basis. As well, the frequency with which meetings are held should be flexible enough to minimise impact on time demands of committee members while maintaining maximum benefit. Thus, the Committee approach should provide adequate oversight with sufficient flexibility.

With respect to its mandate, the Committee is responsible for the development, implementation and monitoring of processes and related protocols that shall cover all aspects of the institution's POCT program. Note that this may include testing performed away from the principal site but which fall under the institutional jurisdiction. The UK MDA (12) states that Clinical Governance is the responsibility of the Institution and this responsibility also devolves onto the POCT committee. Clinical governance is defined as a framework through which organisations are accountable for continually improving the quality of their services and safeguarding high standards of care by creating in environment in which excellence in clinical care will flourish.

Processes should be defined to cover all aspects of the POCT project. This includes consideration of requests for POCT (needs evaluation), evaluation and selection of a device or test appropriate for the identified use, and all aspects of the testing process. This latter will include all phases of the analytical process (pre-analytical, analytical and post-analytical) as well as quality assurance (QA) aspects of the project including ongoing quality management (QM) and quality improvement (QI) initiatives. With respect to needs evaluation, the literature

suggests that while identifying a clinical need before proceeding with a POCT project is desirable, events sometimes overtake process (14). Regardless, post-facto monitoring of cost-effectiveness is important and can redress this problem.

Guideline 3: *We strongly recommend training programs to improve the quality of POCT.*

Strength/consensus of recommendation: A

Level of evidence: II (Cohort/case controlled study and time controlled study)

Studies have shown directly (7,15) and indirectly (2) that training and ongoing certification of operators should be one of the major priorities for effective POCT. As well, organisations such as the ISO (8) and the UK MDA (12) recognise and stress the importance of training for effective POCT. This relates to the fact that POCT usually involves many tests and devices as well as multiple operators, most of whom are not laboratory-trained personnel. This implies a lack of understanding of the principles of laboratory assays and good laboratory practices for ensuring the reliability of test results. As well there will be a lack of knowledge of the particular test method or system.

Training needs to cover all phases of the testing process including appropriate responses to unusual test results. Important pre-analytical steps include proper identification of the patient and sample acquisition while post-analytical issues include charting of results, verification of unanticipated results and notification of responsible persons. In this context, it is interesting that data from studies on laboratory-related errors indicate that the majority of incidents relate to the pre-analytical phase (16,17). There is reason to believe that similar issues exist with POCT (10,18). Finally, training, including the description of analytical procedural steps as well as

proper material handling, is best addressed by clearly written testing protocols that follow manufacturer's instructions.

Guideline 4: *We recommend Data Management as a mechanism to improve the quality of POCT.*

Strength/consensus of recommendation: B

Level of evidence: II and III (Time controlled study and expert opinion)

In any enterprise, data management is fundamental to quality and performance improvement and documentation of quality relies on data (2). Depending on the questions asked, analysing data can show quality trends thereby permitting decisions on actions to remedy or to improve the quality of the process (19). POCT, whether manual or instrumented, generates significant amounts of data. This includes identifiers associated with the patient testing process, results of all quality control and patient tests, as well as other data including reagent and material handling information such as lot numbers and expiry dates, unusual test results and specific responses to results. There is, for example, a wealth of evidence, particularly Class III, showing that evaluating POCT QC data permits responses for improvement in test quality. This may be by identifying inappropriately performing lots of reagents, by identifying trends resulting from improper material storage and handling, or by identifying operators who are employing improper testing technique. Thus overall data management can monitor compliance with the requirements for quality in POCT. Dyer (19), for example, showed that compliance problems with dating reagents, uncapped bottles and operational errors in POCT could be followed by nursing unit and corrective action taken. It is clear that data management, per se, does not improve the POCT

process. It is the monitoring of the data for events and trends, along with the existence and implementation of response protocols, which ensures success (15).

Manual POCT has the significant disadvantage that all information, including test results, material handling data and result reporting and comments have to be also manually entered into the database. This is not only time consuming but also prone to errors of omission and commission and so extra care must be taken in verifying the entry of these data. Instrumented POCT devices have a variable amount of data storage and transfer capability. This certainly improves the situation. However the lack of uniformity among these devices has led to the description of a Connectivity Standard for POCT devices (20). It is anticipated that this standard will eventually be adopted across the IVD industry.

Guideline 5: *We strongly recommend the use of Continuous Quality Improvement with Quality Indicator.*

Strength/consensus of recommendation: A

Level of evidence: II (Time controlled studies)

The POCT Management Committee is empowered to put QA programs in place and is responsible for monitoring and follow-up. Two traditional components of quality assurance, internal quality control and external quality assessment, monitor primarily the analytical process. However, as implied in the sections above, problems at any phase of the total process can influence the reliability of the test result. Thus the identification of specific, measurable indicators related to the quality of a POCT project or test permits monitoring and evaluation of the data. In turn this allows for the implementation of corrective measures or of measures to

enhance the process. This is supported by longitudinal studies (9,10,19,21), publications from Standards organisations (ISO, MDA, NCCLS)(1,5,8) as well as by expert opinion (11,22).

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Public Comments:

No public comments were received on the guidelines.

Chapter 2: Transcutaneous Bilirubin Testing

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The management of jaundice in neonates continues to be a challenging clinical problem. More recently, it has taken on increased importance due to factors such as early hospital discharge, increased prevalence of breastfeeding, and lack of adherence to prompt post-discharge follow-up testing of newborns (1,2). Jaundice in near-term and term newborns is clinically evident in over 60% of newborns during the first week after birth; it is usually benign but may lead to kernicterus if unmonitored or untreated (3). Because of the limitations on visual assessment of jaundice, especially in infants of darker skin color, clinicians have been advised to confirm suspected hyperbilirubinemia. Neonatal hyperbilirubinemia, defined as serum bilirubin concentrations $>221 \mu\text{mol/L}$ ($>12.9 \text{ mg/dL}$, conversion from $\text{mg/dL} \times 17.1 = \mu\text{mol/L}$), has been estimated to occur in up to 10% of newborns (3,4,5,6). A number of proposals have been made that would reduce the risk of kernicterus amongst these infants, including screening of newborns by measurement of total serum bilirubin, transcutaneous bilirubin concentrations (3,7,8), end-

expiratory carbon monoxide, or a combination of both (9). This guideline will focus on the use of transcutaneous bilirubin measurements for the evaluation of hyperbilirubinemia in healthy, term infants.

The ability to measure bilirubin simply, rapidly, and accurately, and in a variety of different settings is important for assessing hyperbilirubinemia and evaluating the risk of kernicterus. Laboratory-based measurement of bilirubin in serum or plasma using diazo-based chemical methods is the technique most often used to determine the concentration of bilirubin in newborns. However, bilirubin measured with chemical-based methods is often inaccurate due to interference from hemoglobin as a result of hemolysis. Visual inspection of the skin, sclera, and mucous membranes is a rapid and inexpensive technique for estimating bilirubin concentrations. In addition, documentation of the cephalo-caudal progression of jaundice can provide an indication of the increase in hyperbilirubinemia. Unfortunately, these methods are frequently inaccurate, especially when applied to newborns of mixed ethnicity or of diverse racial backgrounds (7). Another rapid noninvasive technique to assess bilirubin concentration is by transcutaneous spectrophotometric measurement. Transcutaneous bilirubin concentrations have been found to correlate extremely well with laboratory-based measurements. The purpose of this guideline is to evaluate the available literature and identify those studies that clearly demonstrate the utility of transcutaneous point-of-care bilirubin testing when compared to traditional clinical laboratory based measurement.

Does transcutaneous bilirubin measurement improve clinical outcome, shorten length of stay, or decrease readmission rate for newborns with hyperbilirubinemia, compared with measurement of

bilirubin in serum? (Literature Search 3)

Guideline 6: *Assessment of hyperbilirubinemia with use of transcutaneous bilirubin measurements may have utility in decreasing readmission rate of newborns with hyperbilirubinemia and monitoring bilirubin concentrations in newborns. To date, only one study has been published that addresses this issue. Further evidence is needed to evaluate whether transcutaneous bilirubin measurements improve clinical outcome, shorten length of stay, or decrease the readmission rate for newborns with hyperbilirubinemia.*

Strength/consensus of recommendation: I

Level of evidence: III (clinical experience, descriptive studies and opinion)

Literature Search 3 summarizes the results of our literature search of Medline OVID for peer-reviewed manuscripts that address the effect of transcutaneous bilirubin measurements on clinical outcome, length of stay, or readmission rates for newborns that have been previously discharged. The literature addressing transcutaneous bilirubin testing and these concerns is limited. The majority of studies that have been published compare transcutaneous bilirubin measurements with chemical measurements performed in the clinical laboratory. Generally, good agreement has been reported between transcutaneous bilirubin measurements and measurements performed using blood. This finding has led many investigators to speculate that transcutaneous bilirubin measurements will influence length of stay, clinical outcome, and readmission rates (10). Unfortunately, well designed prospective studies that address these issues are lacking. One study found the mean time savings associated with performing a transcutaneous bilirubin measurement compared with measurement of serum bilirubin in a central laboratory was two

hours and twenty-two minutes (11). It is not clear whether this time savings had any impact on length of stay or clinical outcome.

A recently published study by Petersen et al. (12) compared readmission rates for hyperbilirubinemia, length of stay, days of treatment with phototherapy, and the number of bilirubin measurements performed within the clinical laboratory prior to and following the implementation of transcutaneous bilirubin measurements. They retrospectively studied 6603 newborns for eight months prior to implementation of transcutaneous bilirubin measurements and for eight months following transcutaneous bilirubin measurements. Implementation of transcutaneous bilirubin measurements was not associated with any change in the mean length of stay for normal newborns, newborns with hyperbilirubinemia requiring phototherapy prior to discharge, or the number of days of treatment with phototherapy. However, these investigators did find a significant reduction in the number of hospital readmissions per 1000 newborns for clinically significant hyperbilirubinemia; from a mean (SD) of 4.5 (2.4) to 1.8 (1.7), and a statistically significant increase in the monthly incidence of phototherapy treatment prior to discharge from 5.9% (1.3) to 7.7% (1.3), following implementation of transcutaneous bilirubin measurements. They speculate that the convenience and rapid turnaround time of transcutaneous bilirubin testing may have encouraged more effective screening and identification of newborns with clinically significant hyperbilirubinemia.

Is there an optimum frequency, timing or site of transcutaneous bilirubin measurements that result in best agreement with bilirubin measurements performed using serum? (Literature Search 4)

Guideline 7: *Transcutaneous bilirubin measurements performed on the forehead or sternum are preferable to other sites, and provide similar correlation with bilirubin measurements performed in serum when infants have not been exposed to sunlight or phototherapy. Bilirubin concentrations should be assessed by measurement of total bilirubin in serum and/or transcutaneous bilirubin measurements within the first 24 hours after birth in all infants who are jaundiced. The need for and timing of repeat transcutaneous or serum bilirubin measurements should be assessed with the use of nomograms based upon the postnatal age and bilirubin concentration.*

Strength/consensus of recommendation: B

Level of evidence: II and III (well designed correlation trials, clinical experience, and consensus opinion)

The forehead and sternum have been the sites most frequently used for transcutaneous bilirubin measurements, and have been shown to correlate reasonably well with bilirubin measured in serum (10,13,14,15,16). The vast majority of studies that compared sites of transcutaneous bilirubin measurements have been performed with the Air-Shields meter, with fewer reports involving the BiliChek meter. Five studies with the Air-Shields meter found the sternum to provide the best agreement with serum bilirubin (17,18,19,20,21), six studies found no difference between readings taken from the forehead or sternum (13,22,23,24,25,26), and two studies reported that forehead readings became less reliable in infants greater than three days of age (27,28). The decrease in correlation between forehead readings and bilirubin measured in serum was presumably due to exposure of the head to sunlight. Two studies performed with the BiliChek meter found the forehead to be the preferred site for transcutaneous measurements

(29,30). Two studies found that transcutaneous bilirubin measurements taken at the forehead are lower in newborns who are crying, especially at higher concentrations of serum bilirubin (22,31).

One study of 336 Japanese newborns, not receiving phototherapy, evaluated eight different sites where transcutaneous measurements were made and compared these with serum bilirubin concentrations (13). Readings taken from the forehead, chest and sternum provided the best agreement ($r = 0.910 - 0.922$) with serum bilirubin measurements. Measurements taken from the abdomen and upper and lower back showed less agreement ($r = 0.89 - 0.888$), and measurements taken from the sole and heel demonstrated the poorest agreement with serum bilirubin ($r = 0.763 - 0.771$). A more recent study by Randeberg et al. (32) found that transcutaneous readings taken from the forehead correlated best with bilirubin measured in serum when compared to transcutaneous measurements taken from the heel, back or thigh. Other studies have found that the mean of individual readings taken from the forehead, chest and sternum correlated best with serum bilirubin concentrations (24,33). Maisels et al. (34) found better correlation between transcutaneous measurements and serum bilirubin concentrations when transcutaneous measurements were performed on the sternum ($r = 0.953$) as compared to the forehead ($r = 0.914$). They suggest that measurements from the sternum are less likely to be influenced by the effects of ambient light, particularly sunlight, and may be more desirable when measurements are taken after infants have been discharged.

The suggestion that capillary blood bilirubin concentrations are less than bilirubin found in arterial blood due to penetration of light through the vascular bed of infantile skin (35) has led some to speculate that the agreement between transcutaneous bilirubin concentrations and serum

bilirubin concentrations may be affected by the site of blood collection. Amato et al. (36) compared transcutaneous bilirubin measurements with serum bilirubin concentrations measured in capillary blood and arterial blood. They found that the site where the blood sample was collected did not influence the agreement between transcutaneous bilirubin values and serum bilirubin concentrations.

Recommendations have been made by the American Academy of Pediatrics Clinical Practice Guidelines for the frequency of performing serum or transcutaneous bilirubin measurements (7). These recommendations suggest that transcutaneous bilirubin and/or total serum bilirubin measurements be performed on every infant who is jaundiced within the first 24 hours after birth. Furthermore, the need for and timing of repeat transcutaneous or serum bilirubin measurements is dependent upon the postnatal age and bilirubin concentration. An hour-specific nomogram has been developed for determining the need for repeat measurements (3,4). However, it has been noted that an age-specific nomogram for newborns that addresses clinical risk factors for hyperbilirubinemia still needs to be developed (7). Guidelines have also been established recommending that, prior to discharge, all newborns be assessed for the risk of developing severe hyperbilirubinemia. PredischARGE assessment should be performed by measurement of bilirubin concentrations using total serum bilirubin or transcutaneous bilirubin, and/or assessment of clinical risk factors.

Is the measurement of bilirubin by use of a transcutaneous method contraindicated for use in newborns that are undergoing phototherapy, premature infants, or newborns that are ill?

(Literature Search 5)

Guideline 8: *Transcutaneous bilirubin measurements should not be performed on infants undergoing phototherapy. We also note that light exposure of infants who are discharged may also adversely impact the utility of transcutaneous measurements. The effect of gestational age on transcutaneous bilirubin measurements is less clear. Some reports suggest limiting the use of transcutaneous bilirubin measurements to newborns less than 30, 32 or 34 weeks gestation, while others suggest no effect of gestational age. There are too few studies available that address the effect of underlying illness in newborns and its effect on use of transcutaneous bilirubin measurements.*

Strength/consensus of phototherapy Recommendation: C

Level of evidence: II and III (well designed clinical trials, descriptive studies, and consensus opinion)

Strength/consensus of premature/gestational age recommendation: C

Level of evidence: II (well designed clinical trials, descriptive studies)

Strength/consensus of underlying illness recommendation: I

Literature Search 5 summarizes the results of our literature search of Medline OVID for peer-reviewed manuscripts that address the use of transcutaneous bilirubin measurements in newborns that are undergoing phototherapy, premature infants, or newborns that are ill. Although transcutaneous bilirubin measurements have been shown to correlate well with bilirubin concentrations measured in serum, there have been reports suggesting that transcutaneous measurements can be affected by a variety of factors including use of phototherapy, birth weight, gestational age, and postnatal age (17,22,27,37,38,39,40,41).

Phototherapy has been reported by numerous investigators to adversely effect the correlation between transcutaneous bilirubin measurements and bilirubin measured in serum, and none recommend use of transcutaneous bilirubinometry in infants undergoing phototherapy (17,21,30,38,40,42,43,44,45). Phototherapy results in a blanching of the skin. Values obtained with transcutaneous bilirubin measurements have been shown to decrease rapidly following the implementation of phototherapy. The average decrease in transcutaneous bilirubin measurements observed in one study of nine neonates was approximately 30% following 150 minutes of phototherapy, with much smaller decreases of approximately 4% seen in the subsequent 150 minutes (46). Another study reported a decrease in transcutaneous bilirubin measurements of 25% following two hours of phototherapy, and a 50% decrease after 12 hours. The decrease in transcutaneous bilirubin measurements is much greater than that seen in serum bilirubin concentrations (43). Exposure of infants to sunlight also has been found to adversely impact the correlation between transcutaneous and serum bilirubin measurements (22,27). This finding may limit the utility of transcutaneous bilirubin measurements on infants who are discharged and exposed to sunlight.

There is a lack of agreement on the effect of gestational age on the correlation between transcutaneous bilirubin measurements and bilirubin measured in serum. Two studies performed with the BiliChek meter suggested that this device only be used for infants greater than 30 weeks (38) or 32 weeks (30) gestational age. However, another study which compared the BiliChek meter versus serum bilirubin measured using HPLC found that gestational age did not affect the correlation between these two methods (29). One study, performed with the Air-Shields meter,

found that infants less than 34 weeks gestational age had poorer agreement between transcutaneous bilirubin measurements and bilirubin measured in serum (47).

One study used the BiliChek to evaluate the effect of newborn illness on transcutaneous measurements (30). These authors found that the presence of hypoxia, hypoglycemia, infection, respiratory distress syndrome, or severity of illness did not adversely impact transcutaneous bilirubin measurements. Another study, also performed using the BiliChek meter, found that infants with bleeding or abdominal problems had similar agreement between transcutaneous bilirubin and serum bilirubin measurements when compared with healthy newborns (38).

Are transcutaneous bilirubin measurements associated with decreased blood sampling compared to serum bilirubin measurements? Do transcutaneous bilirubin measurements decrease the incidence of complications associated with blood collection such as infection or osteomyelitis? (Literature Search 6)

Guideline 9: *There is insufficient evidence available to judge the impact of transcutaneous bilirubin measurements on number of blood samples collected from newborns. Whether there is any effect on complications of blood collection such as infection or osteomyelitis has not been adequately studied.*

Strength/consensus of recommendation: I

Measurement of serum bilirubin concentrations is one of the most frequent causes for collection of blood from newborn infants (48). Blood sampling involves pain for newborn infants, and infant stress may have long-term adverse consequences (49,50). In addition, there are other

potential complications associated with blood collection from neonates including the risk of infection and osteomyelitis (51).

One aspect of transcutaneous bilirubin measurements that has been reported which should theoretically help improve clinical outcomes, is the reduction in neonatal blood loss due to decreased blood sampling (10,14,23,30,52,53). These studies suggest that a 20 percent to 34 percent reduction in samples collected for bilirubin analysis could be achieved following implementation of transcutaneous bilirubin measurements. However not all investigators report any decrease in serum bilirubin measurements following the implementation of transcutaneous measurements. Bouchier et al. (18) found no difference in the number of serum bilirubin measurements performed following the introduction of transcutaneous bilirubin meter, and one study actually found an increase in the total number of bilirubin tests performed. Petersen et al. (12) found the mean number of laboratory measurements of serum bilirubin did not change following the introduction of transcutaneous bilirubin testing. However, the total number of bilirubin measurements (serum bilirubin plus transcutaneous bilirubin) increased from a mean (SD) per newborn of 0.37 (0.08) to 0.61 (0.13).

The implementation of transcutaneous bilirubin measurements and its impact on lessening the risk of infection or osteomyelitis has not been addressed. However, one would not expect any decrease in these complications if the implementation of transcutaneous bilirubin determinations does not decrease the number of samples collected for biochemical analyses.

How does the accuracy of transcutaneous bilirubin measurements compare with total bilirubin

measured in serum? (Literature Search 7)

Guideline 10: *We cannot recommend use of the ColorMate III bilirubinometer due to the very limited number of published articles describing the performance of this instrument. Evaluation of jaundice with the Air-Shields or BiliChek seems to provide similar accuracy when compared with serum bilirubin measurements. The BiliChek and Air-Shield have the advantage, compared with the ColorMate III, of not requiring a baseline measurement. Finally, we do not recommend assessment of bilirubin with use of the Ingram icterometer because of its reliance on observer visualization of depth of yellow color of the skin.*

Strength/consensus of recommendation: B

Level of evidence: II (well designed correlation trials, clinical experience, descriptive studies and opinion)

Literature Search 7 summarizes the results of our literature search of Medline OVID for peer-reviewed manuscripts that address the accuracy of transcutaneous bilirubin measurements when compared to bilirubin measured in serum. The literature addressing transcutaneous bilirubin testing and how it compares with serum bilirubin measurements is complicated by the fact that there are different instruments available for measuring transcutaneous bilirubin. Another important factor, often overlooked, is that the majority of studies that evaluate transcutaneous bilirubin measurements compare these measurements with bilirubin measured in serum by laboratory instruments that utilize diazo-based chemical methods. There is a recognized need to improve the precision and accuracy of bilirubin measurements performed in the clinical laboratory, especially in samples collected from neonates (54,55). Collection of blood from newborns is often hemolyzed and in vitro hemolysis is recognized as a source of error in

bilirubin measurements due to release of hemoglobin and other intracellular compounds that can interfere with chemical-based measurement of bilirubin. In vitro hemolysis also represents the most common cause for rejection of specimens within the clinical laboratory (56,57). There are several studies that have evaluated the accuracy and precision of transcutaneous bilirubin measurements compared to bilirubin measurements performed by HPLC (3,29,58). These studies suggest that transcutaneous bilirubin measurements may be used not only as a screening device, but also as a reliable substitute for standard serum bilirubin measurements. Evaluations of the accuracy of transcutaneous bilirubin measurements should be conducted utilizing the most accurate methods available for determination of serum bilirubin.

A factor needing to be considered when comparing transcutaneous bilirubin measurements and bilirubin measured in serum is that bilirubin measured by a transcutaneous method and bilirubin measured in serum may represent different physiological parameters. Rubatelli et al. (29) suggested that bilirubin measured in serum and transcutaneous bilirubin measurements do not measure the same parameter because laboratory-based methods measure bilirubin that is circulating in the blood, while transcutaneous methods measure the amount of bilirubin that has moved from the serum into the tissues. Whether or not transcutaneous bilirubin methods offer additional information not provided by serum bilirubin measurements remains to be determined (59).

The ColorMate III (Chromatics Color Sciences International Inc., New York, NY) transcutaneous bilirubinometer utilizes a Xenon flash tube and light sensors to measure wavelengths from 400 to 700 nm with filters to assess the reflectance of light at specific

wavelengths. One drawback to use of this device is that a baseline reading, obtained shortly after birth, is required for infants. One article described the use of this device on 2441 infants (10). Transcutaneous bilirubin results showed good correlation with bilirubin measured in serum ($r = 0.956$) and accuracy was not affected by race or weight. Repeated measurements of the same individual over a 30 minute time interval showed a coefficient of variation of 3.1% at a bilirubin concentration of 144 $\mu\text{mol/L}$ (8.4 mg/dL).

The Minolta/Air-Shields Jaundice Meter (Air-Shields, Hatboro, PA) uses two wavelengths (460 nm and 550 nm) and a dual optical path system to measure bilirubin transcutaneously. The original Jaundice Meter and the JM-102 model generated readings as a unitless numerical index that had to be correlated to the total serum bilirubin measured in each population subset, since race and gestational age significantly altered the results. Several studies reported better agreement between bilirubin measured with the Air-Shields transcutaneous bilirubin meter and serum bilirubin concentrations when baseline readings were performed (37,47,60,61). There is a lack of agreement concerning the correlation between transcutaneous bilirubin measurements and total bilirubin concentrations measured in serum. Some studies have reported that agreement between transcutaneous bilirubin measurements and bilirubin measured in serum are worse when serum bilirubin concentrations were greater than 205 $\mu\text{mol/L}$ (12 mg/dL) (11,62), while others report poorer agreement when serum bilirubin concentrations were less than 205 $\mu\text{mol/L}$ (12 mg/dL) (25). Finally, others suggest that agreement between transcutaneous and serum bilirubin are independent of bilirubin concentrations (24).

A number of studies have been performed comparing transcutaneous bilirubin measurements by the Air-Shields meter to serum bilirubin measured in the clinical laboratory. Correlation coefficients range from $r = 0.52$ to 0.96 , with vast majority of studies reporting correlation coefficients between $r = 0.70$ and 0.80 (1,13,16,18,33,34,42,60,63,64,65,66). Differences in study design, the particular model of Air-Shields meter that was used, study population tested, site where transcutaneous measurements were performed and method used to measure serum bilirubin concentrations probably account for the variability in the reported results. Studies performed with the most recent version of the Air-Shields meter, JM-103, show much better correlation with serum bilirubin when compared with the earlier JM-101 and JM-102 models (34). Many studies report that the Air-Shields meter performs better in infants with lighter skin compared with darker skinned newborns (37,15,60,47,62,67), although one study reported skin color to have no effect (23). A single study reported that the correlation between transcutaneous bilirubin measured with the Air-Shields device and serum bilirubin concentrations were adversely affected by the presence of hemolytic disease (68).

A recent transcutaneous meter that has been developed, BiliCheck (Respironics Inc., Murrysville, PA), utilizes reflectance data obtained from multiple wavelength readings from 400 nm to 760 nm. The use of multiple wavelength readings enable the instrument to correct for differences in skin pigmentation thereby eliminating the need for performing a baseline reading. When evaluated against measurement of serum bilirubin using HPLC as a reference method, the BiliChek device has been shown to be more accurate as compared to bilirubin measured using laboratory-based diazo techniques (3,29). Two studies performed a direct comparison between the BiliCheck and Air-Shields meters. One study of 64 newborns found no difference in

accuracy between the BiliChek and Air-Shields meters (69). The 95th percentile confidence interval for both meters was +/- 65 $\mu\text{mol/L}$ (3.8 mg/dL) compared with bilirubin measured in serum. Another study of 101 infants found the 95th percentile confidence interval of the Air-Shields meter to be +/- 68 $\mu\text{mol/L}$ (4.0 mg/dL) versus +/- 34 $\mu\text{mol/L}$ (2.0 mg/dL) for the BiliChek when compared with bilirubin measured in serum (70). Two studies found that, although the BiliChek meter showed good correlation with serum bilirubin measurements, the meter underestimated serum bilirubin concentrations by approximately 34 $\mu\text{mol/L}$ (2.0 mg/dL), with the effect being more prevalent at increased concentrations of bilirubin (1,71).

In addition to assessment of bilirubin with use of transcutaneous meters, the Ingram Icterometer (Thomas A. Ingram and Co., Birmingham, England; distributed in the United States by Cascade Health Care Products, Salem, OR) is also considered by some to be a type of transcutaneous bilirubin monitor. The Ingram icterometer consists of transparent Plexiglas® (Altuglas International, Philadelphia, PA) containing stripes of differing yellow hue. The accuracy of this semiquantitative method depends on the ability of the user to visualize the degree of yellow color of the skin. A limited number of published articles describe the use of the icterometer.

Comparison of bilirubin estimated with the icterometer with bilirubin concentrations measured in serum show correlation coefficients ranging from $r = 0.63$ to greater than $r = 0.90$ (16,72,73,74).

Is measurement of bilirubin with a transcutaneous device more cost effective when compared to bilirubin measurements performed in the clinical laboratory? (Literature Search 8)

Guideline 11: *There is insufficient evidence to evaluate the cost effectiveness of transcutaneous bilirubin measurements.*

Strength/consensus of recommendation: I**Level of Evidence: III** (descriptive studies, opinion)

Literature Search 8 summarizes the results of our literature search of Medline OVID for peer-reviewed manuscripts that address the cost effectiveness of transcutaneous bilirubin measurements. No studies have been performed to evaluate the actual costs associated with implementation of transcutaneous bilirubin measurements. Some studies suggest that the increased cost of transcutaneous bilirubin measurements is offset by a decrease in the need for serum bilirubin measurements (5,11,38). Petersen et al. (12) attempted to evaluate the costs associated with transcutaneous bilirubin measurements by estimating the impact of transcutaneous bilirubin measurements on hospital charges. They found that there were decreased charges as a result of fewer readmissions of newborns due to hyperbilirubinemia. However, the decrease in readmissions were offset by increased charges associated with transcutaneous bilirubin measurements, and an increased number of newborns treated with phototherapy prior to discharge following the introduction of transcutaneous measurements. The net result was a small but statistically insignificant increase in charges following the introduction of transcutaneous bilirubin measurements. Since these authors report charges associated with implementation of transcutaneous bilirubin measurements, it is still not clear what the implementation of transcutaneous measurements does to actual costs.

We note that measurement of total bilirubin in serum remains the standard of care for the assessment of newborn jaundice. Replacement of serum bilirubin measurements by a transcutaneous method will require substantial investigation to understand its limitations and

benefits. Clinical Practice Guidelines recently published by the American Academy of Pediatrics recommend that transcutaneous bilirubin measurement and/or a total serum bilirubin measurement be performed on every infant who is jaundiced, with repeat measurements performed based upon the degree of the initial hyperbilirubinemia, the age of the infant, and the evolution of the hyperbilirubinemia (7).

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Public Comments:

No public comments were received on the guidelines.

Chapter 3: Utilization of Cardiac Biomarkers for Acute Coronary Syndromes

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The disposition of patients with chest pain from the emergency department (ED) is one of the most difficult challenges that face caregivers. Admission of patients with a low probability of ACS often leads to excessive hospital costs (1). A strategy that is too liberal with regard to ED discharges may lead to higher numbers of patients released with acute myocardial infarction (AMI). Inappropriate discharge of ED patients who have AMI has been estimated to occur in 2–5% of patients and is the single most common cause of malpractice lawsuits against ED physicians (2,3).

The scope of the recommendations presented here involves utilization of cardiac biomarkers of cardiac injury in the ED. The clinical questions addressed include administrative issues and cost-effectiveness as well as clinical and technical performance of cardiac biomarkers. Search

strategies were utilized for to examine PubMed and EMBASE databases, see Literature Search 9. Only articles in the English language were included.

Who are the stakeholders that should be involved in developing an accelerated protocol for use of biomarkers for evaluation of patients with possible ACS?

Guideline 12: *Members of emergency departments, primary care physicians, divisions of cardiology, hospital administrations, and clinical laboratories should work collectively to develop an accelerated protocol for the use of biochemical markers in the evaluation of patients with possible ACS.*

Strength/consensus of recommendation: A

Level of evidence: III

No clinical trials have been performed to examine the outcome of collaborative development of accelerated protocols versus development of such protocols by one specific group. Although the recommendation that laboratorians should work with ED physicians, primary care physicians, cardiologists, and hospital administration may appear obvious (4), in actual practice decisions on testing protocols are often made without input from the laboratory. Laboratory directors must be aggressive in requesting that qualified personnel be part of organizational and operating committees when such discussions are being conducted, or should initiate the discussions themselves.

Many hospitals today have a dedicated area within the ED for the rapid rule-out of AMI. These areas are frequently designated as "chest pain centers", "heart emergency rooms", or some other term to indicate that the efficient evaluation and management of chest pain patients is a major

objective of that center (5-8). Essential for early AMI rule-out is frequent electrocardiographic testing and blood collections for the measurement of cardiac biomarkers. Patients with negative results for these tests most likely do not have an AMI. They may, however, have UA or other forms of acute cardiovascular disease. For these patients, it is appropriate to perform additional studies such as a stress test, echocardiogram, or radionuclide myocardial perfusion imaging for risk stratification. Establishment of a clinical practice guideline for the evaluation of patients with chest pain will reduce the variability of practices among physicians and institutions, and at the same time improve the accuracy of disposition decisions (9). However, consensus on the merits of this approach was overwhelmingly favorable.

Where should accelerated protocols for diagnosis or the rule-out of AMI be implemented?

Guideline 13: *For simplicity, this protocol should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with ACS while hospitalized.*

Strength/consensus of recommendation: B

Level of evidence: III

No clinical trials have been performed to examine the outcome of accelerated protocols in the ED versus other patient care locations. Consensus from the committee and feedback from conferences is that for "routine AMI diagnosis" of patients who are already hospitalized for other reasons, the same criteria should apply as are used in the ED. Some physicians or administrators may believe that rapid AMI rule-out of hospitalized patients is less important than rapid evaluation and disposition of ED patients. Nevertheless, the committee felt that the same protocol used in the ED is appropriate for routine AMI diagnosis because new therapies for ACS

are available, and, when appropriate, should be delivered rapidly(2). The use of a rapid AMI rule-out protocol will simplify the steps needed from the laboratory's perspective and provide clinicians optimum diagnostic measures for all patients. Consensus on the merits of this approach was favorable overall.

How should the effectiveness of accelerated protocols for diagnosis or the rule-out of AMI be assessed and measured?

Guideline 14: *Members of emergency departments, divisions of cardiology, primary care physicians, hospital administrations, and clinical laboratories should work collectively to use quality assurance measures, evidence-based guidelines, and monitoring to reduce medical error and improve the treatment of patients with possible ACS.*

Strength/consensus of recommendation: A

Level of evidence: III

Registry data CRUSADE have suggested that quality assurance activities improve patient outcomes. Consensus on the merits of this approach was overwhelmingly favorable.

What should be the reference point for reporting the temporal sequence of blood specimens for suspected ACS patients?

Guideline 15: *For routine clinical practice, blood collections should be referenced relative to the time of presentation to the ED and (when available) the reported time of chest pain onset.*

Strength/consensus of recommendation: A

Level of evidence: III

Although the time of chest pain onset for AMI patients is sometimes known, this information is less available or reliable for those with unstable angina or other cardiac diseases. It is common for these patients to report multiple episodes of chest pain over the hours or days before ED presentation. The pathophysiology of ACS is dynamic and includes intermittent closure and spontaneous reperfusion of coronary arteries with ruptured atherosclerotic plaques. In the elderly, or in patients with diabetes mellitus, there may be altered thresholds or a blunted response to pain. Indeed, there are many patients with ACS who experience silent ischemia and infarction (i.e., no pain during occlusive episodes) (10). The time of presentation is most reliable as a reference point; however additional information may be added when the actual time of chest pain (equivalent) is available. Thus many reviewers felt it important to also note the time of onset of chest pain, especially when there is a history of a single chest pain event (and not several events over many days), and when the time of onset as reported by the patient or family is deemed to be reliable. It may also provide an explanation as to why some clinical studies fail to document a consistent rise in the concentration of the marker, e.g., at 6 h, whereas other studies indicate that the markers were increased at this time point in all patients (e.g., when the majority of enrolled patients in the study present beyond 6 h of chest pain).

In addition to members of emergency departments, primary care physicians, divisions of cardiology, hospital administrations, and clinical laboratories, are there others who need to be involved in accelerated pathways for ACS patients?

Guideline 16: *The multidisciplinary team must include personnel knowledgeable about local reimbursement. Vendors should work with customers to help optimize cost-effective provision of biomarker testing.*

Strength/consensus of recommendation: A

Level of evidence: II

Biomarker testing cannot be justified if the laboratory or hospital cannot receive reasonable reimbursement for the service. Thus an important issue that must be resolved at each institution is reimbursement for testing. For example, the Center for Medicare and Medicaid Services announced that "it is not necessary to use troponin in addition to creatine kinase (CPT codes 82550-82554) (which includes the MB isoenzyme) in the management of patients with myocardial infarctions", suggesting that reimbursement will not be given when both tests are ordered (11). Private insurance companies may also limit reimbursements for cardiac biomarkers. Guidelines recommend use of cardiac troponin as the new standard for myocardial injury, but there is still a role for both CK-MB and cardiac troponin assays (See NACB Guidelines on "Cardiac Biomarkers of ACS").

How rapidly are results of cardiac biomarker testing needed by clinicians? What standard for measurement for TAT should be utilized?

Guideline 17: *The laboratory should perform cardiac marker testing with a turnaround time (TAT) of 1 hour, optimally 30 minutes, or less. The TAT is defined as the time from blood collection to the reporting of results.*

Strength/consensus of recommendation: A

Level of Evidence: II

AMI patients with ST-segment elevation on the ECG can be effectively treated with thrombolytic therapy, particularly if therapy is initiated within 12 h after the onset of chest pain.

Delays in implementation will reduce the success of this treatment. As such, the National Heart Attack Alert Program has made a recommendation to physicians to treat all AMI patients within 60 min of their arrival in the ED (12). However, results for serum cardiac markers are not needed in making this therapeutic decision.

Rapid testing and reporting of cardiac marker concentrations may produce other benefits for cardiac patients. Identification of high-risk patients by rapid troponin testing has been suggested to improve outcome in those patients eligible for advanced therapies (2,13). Patients with non-ST elevation AMI have been shown to benefit from early percutaneous intervention (14) or glycoprotein IIb/IIIa inhibitors (15). Rapid cardiac marker testing may lead to earlier detection and use of these therapies. Most (75%) of the 1352 ED physicians surveyed in a recent Q-probes Study by the College of American Pathologists believed that the results of tests measuring myocardial injury should be reported back to them in 45 minutes or less, using as the reference point the ordering time of the tests (4). Consensus of the committee and feedback on draft documents is that providing rapid testing will lead to more time-efficient disposition decisions. The factors that affect TATs include the delay in the delivery of the sample to the laboratory, the preanalytical steps necessary to prepare the sample, the analysis time, and deliver of results to the ordering physician. The committee acknowledges that the time taken for the delivery of samples to the laboratory is not always under the control of the laboratory. Nevertheless, laboratory personnel should work closely with hospital administrators, specimen couriers and nursing staff to minimize delays. TATs can be improved with the implementation of pneumatic tubes that deliver samples directly and rapidly to the central laboratory. The use of satellite

laboratories is another mechanism to reduce delivery time reporting TATs, improve clinician satisfaction and decrease length of patient stay in the ED (27).

It is complicated for laboratories to consistently (>90%) deliver cardiac biomarker results in <30 min, using laboratory-based serum or plasma assays. Results of cardiac marker testing are not used to guide thrombolytic therapy and there is no clear evidence that availability of rapid biomarker results leads to better patient outcomes. Moreover, rule-out of AMI from the ED requires results of serial sampling, which does not support need for a very rapid TAT on any single sample. The committee recognizes the controversy surrounding time from as well as the need for a standard definition of TAT (Figure 1). None the less, caregiver consensus clearly indicates that rapid availability of results is desirable and that time to patient disposition is expedited by rapid availability of cardiac biomarkers.

Is there a recommended strategy for laboratories that are unable to deliver cardiac biomarker results in a time frame of 1 hour from time of collection to result reporting?

Guideline 18: *Institutions that cannot consistently deliver cardiac marker TATs of approximately 1 hour should implement POC testing devices.*

Strength/consensus of recommendation: B

Level of evidence: II

Some laboratories do not have automated immunoassay analyzers, rapid tube delivery systems, or staffing to deliver results within 1 hour on a continuous or consistent basis. It has been suggested laboratory based TATs for myocardial injury do not meet the expectations of either laboratory personnel or emergency physicians (4).

Qualitative as well as quantitative POC testing devices are now available for myoglobin, CK-MB, cTnT, and cTnI (16-24), many in multimarker formats. These assays make use of anticoagulated whole blood, and have analyzer times of <20 minutes. Eliminating the need to deliver samples to the central laboratory and centrifugation enables TATs of <30 min. Results obtained with POC cardiac marker testing, compared with central laboratories, have universally suggested significant decreases in TAT (4,25-29).

The committee recognizes the lack of evidence supporting cardiac POC testing in the pre-hospital setting, although this use has shown some promise (30). Likewise, remote location testing, such as on cruise ships, may offer unique advantages but needs further investigation (31). Although outcome studies have shown that rapid availability of testing and reporting of results for cardiac markers, as well as b-type natriuretic peptide, reduces hospital length of stay and laboratory costs for cardiac patients (32-35), there are no outcome studies to validate the specific need for a 1 hour TAT.

However, there is some limited evidence that earlier treatment of high-risk ACS with GP IIb/IIIa inhibitors improves outcome (13,15), as well as early intervention with PCI (14,36). With the development of new therapeutic strategies for unstable angina and non-Q-wave AMI (37), the committee anticipates that early detection of any myocardial injury will also be beneficial in the management of these patients. For those patients who are ruled out for ACS, it is expected that fast TATs for laboratory data will lead to expedited patient discharge and a reduction in overall hospital costs. The NACB Committee encourages prospective outcome studies to examine the putative advantage of reporting TATs within 1 hour.

In addition, it is not clear what impact POC cardiac marker testing might have on patient satisfaction, a notoriously multifactorial issue.³⁸ However, consensus indicates that a shorter ED length of stay clearly improves patient satisfaction. Whether such satisfaction is a function of POC testing remains to be investigated.

What should be the performance specifications and characteristics of POC technology for measurement of cardiac biomarkers?

Guideline 19: *Performance specifications and characteristics for central laboratory and POC platforms should not differ.*

Strength/consensus of recommendation: A

Level of evidence: III

Consensus of the committee and that from various conferences indicates that the cardiac biomarker criteria for AMI will not differ based what type of assays are utilized or performance location. Thus it is obvious that specifications and performance characteristics for assays must be consistent, regardless of performance platform. Current specifications and performance characteristics for cardiac biomarker assays can be found in the NACB Laboratory Medicine Practice Guideline for Biomarkers of Acute Coronary Syndromes and Heart Failure; Analytical Considerations Section.

What stakeholder(s) should be involved in device and platform selection, training, operator competency assessment, maintenance of POC equipment, and compliance with regulatory requirements?

Guideline 20: *Laboratory personnel must be involved in selection of devices, the training of individuals to perform the analysis, the maintenance of POC equipment, the verification of the proficiency of operators on a regular basis, and the compliance of documentation with requirements by regulatory agencies.*

Strength/consensus of recommendation: A

Level of Evidence: III

POC devices are designed for testing to be performed at or near the bedside by primary caregivers. However, the responsibility for such testing must reside with the laboratory; involvement must include selection of POC devices, education, training, maintenance, and quality assurance (39). The success of POC testing programs will depend on cooperation and the acknowledgment of the laboratory's responsibility by hospital administrations, nursing staff, and the appropriate units within the hospital.

When the laboratory staff recognizes a situation of noncompliance, they must have the authority to remove POC testing devices and suspend testing from the area of the hospital where the testing was conducted until the deficiencies have been satisfactorily corrected.

Are qualitative (positive/negative) devices appropriate for assessment of cardiac biomarker results?

Guideline 21: *While it is recognized that qualitative systems do provide useful information, it is recommended that POC systems provide quantitative results.*

Strength/consensus of recommendation: C

Level of Evidence: II

The committee recognizes the lack of evidence suggesting improved outcomes utilizing quantitative systems versus qualitative. However, quantitative results offer particular strengths in risk stratification and low end sensitivity (40,41).

What is the process that should be used as new biomarkers are developed and introduced into clinical use?

Guideline 22: *Early in the process, manufacturers are encouraged to seek assistance and provide support to professional organizations such as the AACC or IFCC to develop committees for the standardization of new analytes. These organizations will determine the need for analyte standardization based on the potential clinical importance of the marker and gather the necessary scientific expertise for the formation of a standardization committee.*

Strength/consensus of recommendation: A

Level of Evidence: III

New markers will continue to be developed and examined for patients with acute coronary syndromes. When a marker such as cardiac troponin demonstrates major advantages over existing markers, there is an urgency of manufacturers to develop and market commercial assays. In the specific cases of CK-MB mass and cTnI assays, there were no cooperative attempts to develop reference materials or to standardize results.

The NACB Committee acknowledges that the exclusive release of new markers may be in the manufacturer's best interests in terms of profitability, and therefore, they may be reluctant to share ideas and needs with their colleagues. Nevertheless, the implementation of new tests is more easily integrated into the laboratory when these markers are available on a wide spectrum of analyzers, and it is in the best interests of the medical community and the in vitro diagnostic industry that assays correlate to one.

Assays for cardiac markers for early diagnosis, rule-out, triaging of patients from the ED, or for determination of successful reperfusion require markers that have a short assay TAT.

Irrespective of how the testing is performed (i.e., laboratory-based or POC testing), assays must meet minimum precision requirements. Imprecise assays at or near cutoff concentrations will adversely affect the clinical performance of the test. The committee understands the importance of establishing objective analytical goals for assays for new cardiac markers. This will assist manufacturers in the construction of new assays.

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Public Comments:

Drafts of these recommendations were presented at the 2004 A.O. Beckman Conference, held in Boston, MA and at the 2004 AACC Annual Meeting and Exposition in Chicago, IL. Feedback was captured by audiotape and issues discussed in detail by conference call. The document was reviewed by the IFCC Committee on Evidence Based Laboratory Medicine.

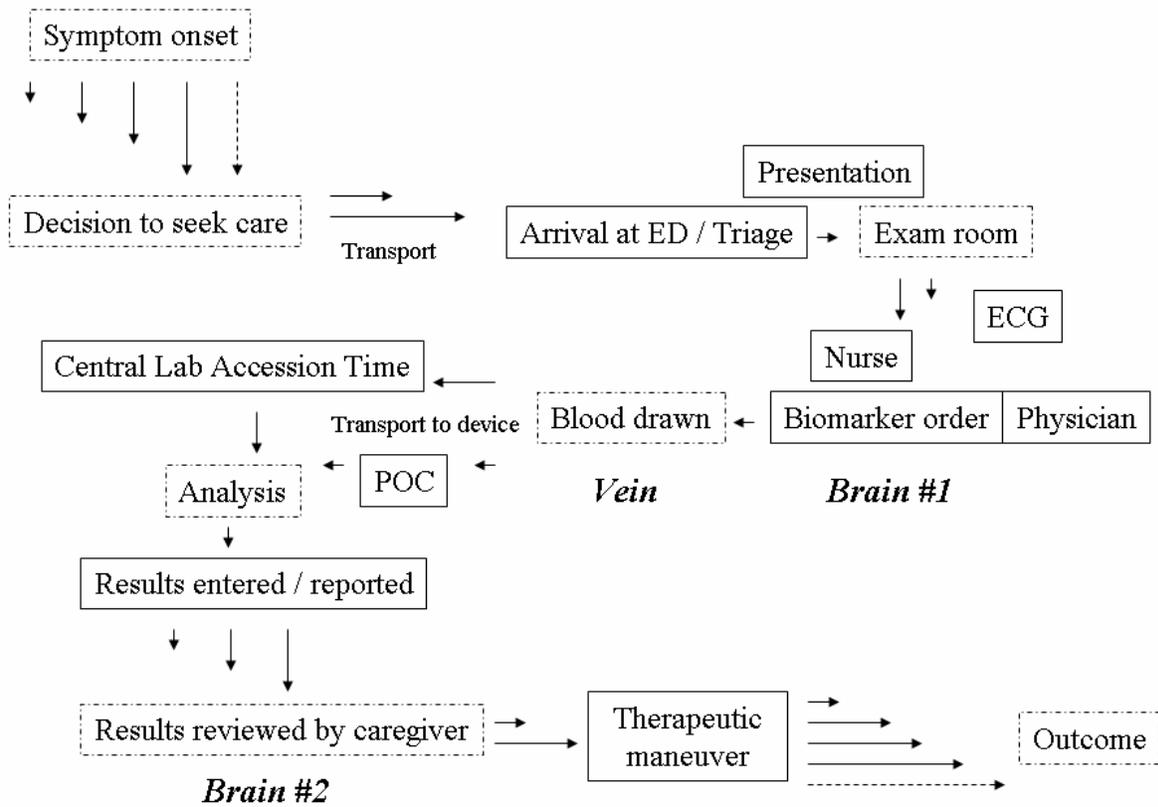


Figure 1.

Time point options available to define turnaround time (TAT). Solid boxes indicate times generally recorded or known (hard times), while dashed boxes indicate times generally not, or variably, recorded (soft times). Arrow length grossly represents time duration; dashed arrows indicate times with large variability.

Chapter 4: Coagulation

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Point of care coagulation testing has been termed the most rapidly growing point of care application in the hospital setting (1). This rapid growth implies a widespread acceptance of the use of point of care coagulation assays, yet it is unclear if documentation exists showing a clinical advantage to these methodologies. The purpose of this guideline is to evaluate the available literature and identify those studies, if any, which objectively demonstrate the utility of point of care coagulation testing when compared to more traditional laboratory analyses.

The term “coagulation testing” is used to describe an ever growing selection of diagnostic tests. These range from the traditional global coagulation assays, *i.e.*, the prothrombin time (PT) and activated partial thromboplastin time (aPTT), to assays specific to individual coagulation factors and their inhibition, *e.g.* factor VIII, fibrinogen, and anti-Factor Xa assays, to technologies designed to evaluate the process of clot formation and the influence of platelets and fibrinolysis on hemostasis, *i.e.*, Sonoclot and thromboelastography (TEG).

This Laboratory Medicine Practice Guideline (LMPG) is targeted to address two basic questions:

1. Is there evidence of improved clinical outcome from the use of point of care coagulation testing?

2. What is the evidence that the current “standards of care” in point of care coagulation are appropriate?

Considering the wide range of clinical applications for these assays, a decision was made to evaluate only the global coagulation assays: the activated clotting time (ACT), the aPTT and the PT, including the calculation of the international normalized ratio (INR). It will be left to later updates to address the important issues of individualized heparin and protamine dosing for cardiac surgery, thrombin time based tests, heparin level measurement, heparin neutralization verification and TEG analyses, among others. Also left to later updates are the clinical utility of these assays for monitoring novel anticoagulants such as direct thrombin inhibitors and direct factor Xa inhibitors as well as the use of available electronic tools for management of anticoagulation therapy.

A critical assumption made in this document is that all point of care coagulation monitoring instruments are equally accurate and precise. There are insufficient data to allow recommendations based on specific instrumentation for these tests, and it must be the responsibility of the individual facility to evaluate available systems prior to implementation in a clinical setting. Although many of the studies described in this document were performed using point of care instruments that are no longer available in the marketplace, the value of the studies remains and should not be discounted.

Literature searches were conducted through online databases (PubMed, Medline, BioMedNet) and private libraries maintained by members of the LMPG team. Articles identified from author collections were only included if they are indexed on one of the three public search engines. All

searches were performed using extremely broad search criteria. These searches were defined by the test name and any of the terms “bedside”, “point of care”, “near patient” or “whole blood”. The vast majority of the publications identified consisted of correlation analyses, either point of care to laboratory or between different point of care systems. Such studies were excluded from further consideration as they do not directly address the clinical utility of these systems. An overview of publications dealing with correlation analyses can be found in Zimmerman, 2000 (2).

Activated Partial Thromboplastin Time (aPTT)

Is there evidence of improved clinical outcome using point of care aPTT testing? (Literature Search 10)

Guideline 23: *We recommend that the use of point of care aPTT be considered a safe and effective alternative to laboratory aPTT testing for anticoagulation and hemostasis monitoring.*

Strength/consensus of recommendation: B

Level of evidence: I and II (at least one randomized controlled trial, small randomized controlled trials, non-randomized controlled trials, and multiple time series without intervention).

Guideline 24: *We strongly recommend that therapeutic ranges, workflow patterns and cost analyses be evaluated, and where necessary altered, during the implementation of point of care aPTT testing to ensure optimization of patient treatment protocols.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials and non-randomized controlled trials).

The literature regarding point of care aPTT, excluding straightforward analyses of correlation to the clinical laboratory aPTT, fall into three categories: Evaluations specifically designed to measure turn around time (TAT) (3-5); evaluations of diagnostic accuracy using laboratory measurement of anti-Factor Xa activity as the gold standard (6-11); and outcome studies (12-16). Prospective studies of TAT have evaluated multiple patient populations, laboratory systems and point-of-care monitors, and all have shown that TAT, defined as time from sample draw to time of result availability, is significantly reduced with point of care testing ($p < 0.001$ – $p < 0.05$) (3-5). These authors suggest that this significant reduction in TAT could lead to improved patient care, but do not directly address patient outcome questions.

The evaluations of diagnostic accuracy examined employ appraisals of clinical decision point agreement to determine if point of care aPTT monitors are as accurate as laboratory aPTT analyses for monitoring anticoagulation. All but one of these analyses use the chromogenic determination of anti-Factor Xa activity in the patient's blood as the standard for therapeutic decisions. The single investigation without anti-Factor-Xa values explored the efficacy of an aPTT assay as a pre-operative screening tool to predict which patients would exhibit severe bleeding following cardiac surgery. In this trial, Nuttal and colleagues (7) concluded that the Biotrack 512 point of care monitor had similar predictive value for bleeding tendency compared with standard laboratory tests (MLA Electra). Four articles reviewed evaluated point of care aPTT assays for monitoring heparin anticoagulation during continuous intra-venous heparin infusion. Therapeutic ranges in these studies were defined as 0.2 – 0.4 (6); 0.3 – 0.7 (9,11); or 0.36 – 0.82 (10) units/ml heparin as measured by chromogenic laboratory assays. In all reports,

the point of care system (Biotrack 512 (6), CoaguChek Plus (10), Hemochron 8000 (9), Hemochron Jr Signature (11), TAS (10)) showed reasonable agreement with anti-Xa levels, at least equivalent to the levels of agreement seen for the laboratory aPTT. Several authors noted that the oft-quoted target range of 1.5 – 2.5 times normal was inappropriate for both the point of care and laboratory systems (9,10). Solomon and colleagues drew similar conclusions when the CoaguChek Plus and TAS systems were evaluated for determination of the appropriate time to remove the femoral access sheath following interventional cardiology procedures (8).

Three trials were identified evaluating the use of point of care coagulation assays to guide transfusions following cardiac surgery (12-14). All three studies identified a sub-population of patients determined to have bleeding complications following heparin reversal with protamine. Two of the studies defined bleeding by visual inspection of the operative field at the end of procedure and implemented the point of care based transfusion algorithms using PT, aPTT and platelet count (12) or function as measured by the bleeding time (13) in the operating room. Both groups found significant reductions in post-operative bleeding and blood product usage in the algorithm group compared to patients transfused by routine procedures (central laboratory test results (12) or clinician discretion (13)). The third trial conducted by Capraro and colleagues (14), did not introduce point of care testing for transfusion until after the patients left the operating suite. Bleeding in this trial was defined as chest tube drainage exceeding 1.5 mL/kg/15 minutes following initial draining of the mediastinal tubes. In contrast to the other studies, these investigators found no difference in bleeding or blood product usage between the two groups across the hospital stay. In fact, the algorithm controlled group received more platelets during the first hour than the control group. The authors suggest that this difference may be due to the

use of the bleeding time to define the need for platelet transfusion. An explanation of the contradictory results between the Capraro study (14) and those by Despotis (12) and Nuttall (13) may lie in the time of algorithm initiation. Nuttall and coworkers noted that in both this and the Despotis studies, the lower number of coagulation product transfusions in the operating room in the algorithm group may have led to the significant reduction in bleeding observed in the intensive care unit. One explanation could be that the earlier directed transfusion therapy may have more efficiently corrected the hemostatic problems. If this is true, the lack of improved outcome in the Capraro evaluation may be due to the time of algorithm initiation. In any case, all these trials employed multiple point of care assays, so that the precise impact of the aPTT alone cannot be isolated from the other assays involved.

Point of care aPTT assays have also been an integral component of two large-scale, multicenter, randomized, controlled pharmaceutical trials. In a subset analysis of patients enrolled in GUSTO-I, Zabel and colleagues evaluated bleeding, transfusion requirements, recurrent ischemia and mortality at 30 days and one year for those patients monitored using point of care aPTT (CoaguChek Plus) compared to those monitored with local laboratory aPTTs (15). The point of care group had a higher percentage of patients in therapeutic range at 12 and 24 hours, less severe or moderate bleeding and fewer transfusions than the laboratory group ($p < 0.01$), although these patients exhibited somewhat higher rates of recurrent ischemia ($p = 0.01$). Mortality at 30 days and one year were equivalent in the two groups ($p = 0.27$ & $p = 0.38$, respectively).

As part of the PARAGON A clinical trial, investigators were required to employ point of care aPTT (Hemochron Jr) assays in order to maintain clinician blinding to therapeutic regimen (18). A strong statistical trend ($p=0.08$) was observed between time to therapeutic aPTT and the 30-day death or myocardial infarction combined endpoint. The authors suggest that a change in clinical protocol to include more frequent testing (PARAGON A required testing at 6 – 12 hour intervals) might improve patient outcomes by increasing the likelihood of attaining therapeutic levels more quickly. Becker and colleagues (16) arrived at a similar conclusion following a randomized controlled trial evaluating weight-adjusted versus empirical heparin dosing as well as point of care (CoaguChek Plus) versus laboratory aPTT management of 113 patients with active venous or arterial thromboembolic disease requiring intravenous heparin therapy. While the time between sample draw and dose adjustment was significantly shorter for the point of care group ($p=0.0001$), no change in test frequency was made and no differences were observed in time to target range or time within range between the point of care and laboratory groups.

The need to change procedures in order to optimize the advantages of point of care testing was directly demonstrated by Nichols and coworkers (17) in their prospective, non-randomized analysis of the effect of point of care testing on patient wait times before and after elective invasive cardiology and radiology procedures. The authors conclude that point of care testing must be integrated into clinical management pathways if the benefits of the reduced turn around times are to have positive clinical impact.

Prothrombin (PT)/ International Normalized Ratio (INR)

Is there evidence of improved clinical outcome using point of care PT testing? (Literature Search 11)

In the hospital?

Guideline 25: *We recommend that the use of point of care PT be considered a safe and effective alternative to laboratory PT testing for hemostasis monitoring.*

Strength/consensus of recommendation: B

Level of evidence: I and II (at least one randomized controlled trial, small randomized controlled trials, non-randomized controlled trials, and multiple time series without intervention).

Guideline 26: *We strongly recommend that critical ranges, workflow patterns and cost analyses be evaluated, and where necessary altered, during the implementation of point of care PT testing to ensure optimization of patient treatment protocols.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials, non-randomized controlled trials).

As seen for the aPTT, the vast majority of literature identified in this search consisted of clinical correlation analyses between point of care PT/INR monitors and hospital based laboratory systems. Fewer articles specifically addressed TAT for the PT test, but again, unsurprisingly, all these studies showed statistically significant improvement in TAT with point of care (4,5,19).

The studies by Despotis (12), Nuttall (13), Capraro (14) and Nichols (17) included PT testing in

their evaluations. These trials showed improved patient outcomes (12,13) or no effect on outcome (14) following cardiac surgery and reduced wait times surrounding interventional cardiology and radiology procedures (17). As with the aPTT discussion, the impact of the PT test itself cannot be isolated from other point of care tests employed or the procedural changes implemented for these study populations.

Two pharmaceutical treatment evaluations utilizing point of care (CoaguChek (20), ProTime (21)) PT monitoring were identified. While there were no INR specific endpoints described in these controlled trials, investigators participating in both studies noted that the warfarin anticoagulation arm of the study showed good therapeutic management.

Is there evidence of improved clinical outcome using point of care PT testing? In the anticoagulation clinic?

Guideline 27: *We recommend that the use of point of care PT be considered a safe and effective alternative to laboratory PT testing for oral anticoagulation monitoring and management.*

Strength/consensus of recommendation: B

Level of evidence: II and III (controlled trials without randomization, Cohort or case-control analytic studies, and opinions of respected authorities).

The use of point of care PT/INR devices has been shown to be safe and effective in several studies in oral anticoagulation clinic populations (22-25). In addition to evaluating the correlation of the point of care system (CoaguChek (22,24), ProTime (23)), patient and clinician satisfaction was assessed by questionnaire. Satisfaction was the only endpoint evaluated in the study by Choudry and colleagues (26). In these studies both the patients and the clinicians

preferred using fingerstick samples on the point of care system to venous sampling for laboratory testing. This is a rapidly growing management strategy for patients on long-term vitamin K antagonist anticoagulation in which a highly experienced, dedicated staff can help to provide optimal management to this patient population (25).

Is there evidence of improved clinical outcome using point of care PT testing? For Patient Self-testing / Self-Management?

Guideline 28: *We recommend the use of point of care PT as a safe and effective method for oral anticoagulation monitoring for appropriately trained and capable individuals.*

Strength/consensus of recommendation: B

Level of evidence: I, II, and III (at least one randomized controlled trial, small randomized controlled trials, non-randomized controlled trials, and opinions of respected authorities).

Another growing management strategy for oral anticoagulation monitoring is patient self-testing (PST) and its extension, patient self-management (PSM). In either scenario, the patient, or their caregiver, monitors the patient's INR at home with a point of care monitor. PST patients then report the result to the clinic or doctor responsible for their care who determines any required warfarin dose adjustments. PSM patients generally use an algorithm provided by a medical professional to adjust their own dose based on the INR reading. There have been a large number of studies evaluating the efficacy of PST and/or PSM compared to routine medical care (testing and dose adjustment by primary care physician) and to oral anticoagulation clinic care. Endpoints include time in therapeutic range as well as, in some trials, incidence of hemorrhage or thromboembolism. Several recent reviews of these studies have been published (27-30). In

each study, PST or PSM has been shown to be superior to routine medical care and at least equivalent to oral anticoagulation clinic management. One confounding factor in these studies is the frequency of PT/INR testing. The inverse correlation of time between tests and time in therapeutic range has been clearly demonstrated (31) and PST/PSM patients routinely monitor their PT/INR at higher frequencies than patients monitored by laboratory based strategies.

Activated Clotting Time (ACT)

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? (Literature Search 12)

In cardiovascular surgery?

Guideline 29: *We strongly recommend ACT monitoring of heparin anticoagulation and neutralization in the cardiac surgery arena.*

Strength/consensus of recommendation: A

Level of evidence: I and II (at least one randomized controlled trial, small randomized controlled trials, non-randomized controlled trials).

Guideline 30: *There is insufficient evidence to recommend specific target times for use in ACT managed heparin dosing during cardiovascular surgery.*

Strength/consensus of recommendation: I (conflicting evidence across clinical trials).

By far the largest number of outcome related publications for point of care coagulation testing is represented by studies performed in cardiac surgery or percutaneous coronary intervention

applications with the Activated Clotting Time (ACT). First described by Hattersley in 1966 (32), the use of the ACT to predict heparin requirements and the cardiopulmonary bypass surgery target recommendation was described by Bull and colleagues in 1975 (33,34). In general, these publications fall into one of two categories, those evaluating the use of the ACT to optimize heparin and protamine dosing and those studies that specifically examine patient outcome.

In the cardiovascular surgery studies, accurate dosing was defined as predicting the dose required to obtain an ACT above a predefined clotting time (range 400 – 600 seconds) (35-39).

Employing the Hemochron ACT test, these investigators clearly showed the differing heparin requirements between patients as well as between populations (36-38), most notably pediatric versus adult patients (35). Two studies evaluated the correlation of the ACT to heparin level determined either through laboratory assays (37) or using the Hepcon (now Medtronic HMS) system (40) to measure heparin level. Both studies support the use of the ACT showing good correlation to heparin level for ACTs below 600 seconds (37) and a strong correlation between post-operative bleeding and elevated ACTs following heparin reversal (40).

Cardiac surgery outcomes are defined as post-operative blood loss as measured by chest tube drainage over 12 or 24 hours, blood product usage and total heparin and/or protamine given. In all studies reviewed, if statistical analyses were employed, there was a statistically significant decrease in each of these parameters when ACT managed heparin dosing was compared to empirical dosing. The earliest studies (41-43) indicated reductions of near 50% in blood loss in the initial post-operative 12 hour period for patients monitored by ACT to optimize

anticoagulation versus those patients dosed empirically with 2 – 4 mg/kg heparin and additional heparin administered on a time post bolus basis.

Later studies, employing combinations of the Hemochron, HemoTec (now Medtronic ACTII) or HMS systems confirmed these findings (44-46) adding additional observations on reduced blood product usage (47,48). Interestingly, one study (49) noted no reduction in post-operative blood loss but significant reductions in intra-operative blood loss as well as heparin and protamine doses given for ACT monitored patients compared to the empirically dosed group ($p < 0.001$). Changes in dosing with ACT varied by trial with reports of increased (46) and decreased (41,44,49) heparin in the ACT group. All studies agreed that ACT monitoring reduced the total protamine dose (38,44-46,49) given. In one case, this reduction correlated closely with reduced 24 hour blood loss ($p = 0.02$) (45). The target times employed for the ACT monitored groups varied widely with each author recommending differing minimal ACTs for safe extracorporeal circulation. These recommendations range from 350 seconds (45) to targeting values in excess of 500 seconds (47) to achieve optimal patient outcomes.

Questions surrounding optimal target times are further confounded by evaluations comparing heparin coated or heparin bonded tubing versus standard tubing use in the extracorporeal circuit. These studies suggest comparable or improved outcomes using target times as low as 180 seconds with fully heparin bonded circuits when compared to either routine or heparin coated circuits with ACT targets of >450 seconds (50-52).

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal

target times to be used with ACT monitoring? In interventional cardiology?

Guideline 31: *We strongly recommend ACT monitoring of heparin anticoagulation and neutralization in interventional cardiology procedures.*

Strength/consensus of recommendation: A

Level of evidence: II (small randomized controlled trials, non-randomized controlled trials, and case controlled analytic studies from more than one center or research group).

Guideline 32: *We recommend the use of target times specific to ACT system used that differ if specific platelet inhibitors are used concurrently with heparin.*

Without intravenous platelet inhibitors, the evidence suggests that target of >250 seconds using the Medtronics ACTII or >300 seconds using the HEMOCHRON FTCA510 tube assay are appropriate.

Strength/consensus of recommendation: B

Level of evidence: II (small randomized controlled trials, non-randomized controlled trials, case controlled analytic studies from more than one center or research group).

Guideline 33: *With the intravenous platelet inhibitors abciximab or eptifibatide, a target of 200-300 seconds is recommended, with tirofiban a somewhat tighter range of 250 – 300 seconds is recommended.*

Strength/consensus of recommendation: B

Level of evidence: I (at least one randomized controlled trial).

Published references in the cardiac catheterization laboratory consist primarily of studies of patients undergoing percutaneous transluminal coronary angioplasty (PTCA) rather than other interventional procedures. Only one publication was identified which specifically examined patient outcomes comparing anticoagulation management with ACT to empirical, unmonitored heparin dosing (53). In this retrospective study, records were examined for 1200 sequential PTCA procedures. The group managed by ACT showed increased risk of abrupt or late vessel closure based on pre-procedure demographic analyses, yet showed a statistically significant reduced incidence of closure than the historic controls ($p < 0.05$). In studies of this population comparing the clinical utility of ACT monitoring versus fibrinopeptide A formation, ACTs exceeding 200 seconds were shown to be indicative of significant reduction of thrombin formation (54). The ACT was also shown to be superior to the laboratory aPTT for monitoring anticoagulation in this population as judged by heparin dose response (55) and cost (56) with similar clinical outcomes for the ACT and aPTT groups.

Other studies reviewed looked to establish optimal target times for patients undergoing PTCA to minimize both bleeding and ischemic complications. Ogilby and colleagues (57) reported no bleeding or ischemic complications in 108 patients treated with target Hemochron ACTs of >300 seconds, while Kaluski and coworkers (58) advocate lower levels of heparinization targeting ACTs (unspecified system) of 160 – 240 seconds. In this group of 341 patients, there were 6 occlusive events and one myocardial infarction within 14 days of procedure, but no bleeding complications.

Retrospective analyses of more than 1200 patients each were employed to identify patients who experienced abrupt vessel closure and case match them with at least twice their number of patients without ischemic complications (59,60). Ferguson and coworkers (59) were able to identify a target value of 250 seconds on the HemoTec system as significantly reducing ischemic complications ($p<0.001$). These investigators further determined, that a change in ACT on this system of less than 150 seconds in response to a 10,000 unit heparin bolus was also indication of increased thrombotic events. While Narins and colleagues (60) were unable to identify an ideal target time for the Hemochron system, their data also showed a significant increase in ischemic events in patients with lower ACTs ($p=0.004$). This study showed no relationship of elevated ACTs with increased bleeding complications. In contrast, Hillegass and colleagues (61) found a significant correlation ($p<0.001$) between elevated ACT times and bleeding in his prospective evaluation of 429 patients. Reviews of the existing literature by Ferguson (62) and Klein and Agarwal (63) in 1995 and 1996, respectively, both recommended that target times be ACT system specific and that optimal targets for PTCA are $>250 - 275$ seconds for HemoTec and $>300 - 350$ seconds for Hemochron ACTs. These values are lower than those arrived at by Chew and coworkers (64) in 2001 after their metaanalysis of data from 6 interventional trials, 5 including platelet inhibitors and one comparing heparin and bivalirudin anticoagulation. In these studies, 95% of the ACT results were obtained with Hemochron or Hemochron Jr ACTs, the remainder with the HemoTec. Chew's group concluded that the lowest composite ischemic event rate in patients receiving only heparin was seen in the ACT range of 350-375 seconds, with significant bleeding observed if the ACT exceeded 400 seconds.

Target time recommendations for patients receiving heparin with concurrent intravenous antiplatelet therapy are best obtained from the clinical trials of these antiplatelet agents (65-67). Both the EPILOG (65) and ESPRIT (66) studies showed an optimal outcome (minimizing both ischemic and bleeding events) when ACTs were maintained between 200 and 300 seconds in the presence of abciximab or eptifibatide, respectively. The EPILOG study employed Hemochron ACTs, while the type of ACT system in use was not reported for the ESPRIT. In the TACTICS trial (67), there was a clear relationship between ACT values below 250 seconds and ischemic complications ($p=0.043$) and a trend toward increased bleeding for clotting times in excess of 300 seconds ($p=0.08$).

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In extracorporeal membrane oxygenation?

Guideline 34: *We strongly recommend ACT monitoring to control heparin anticoagulation during extracorporeal membrane oxygenation (ECMO).*

Strength/consensus of recommendation: A

Level of evidence: III (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees).

Guideline 35: *We recommend that ACT target times for ECMO be determined based on the ACT system in use.*

Strength/consensus of recommendation: B

Level of evidence: III (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees).

Since 1990 the results of three large surveys of ECMO practices have been published (68-70). ACT monitoring was employed by all survey respondents in each year although the mix of systems changed from 1990 to 1996 (the 2002 survey did not list specific ACT instrumentation). Target ranges reported in 1990 for “typical” patients ranged from 180 – 240 to 220 – 260 with lower ranges for “bleeding” patients (68). The average target range reported in 2002 was 180 – 220 (70). Colby and colleagues (71) emphasized the need to set target ranges based on the ACT system in use. Without changing target ranges, changing the ACT system from the Hemochron 400 to the Hemochron Jr ACT-LR led to reduced circuit life and increased circuit clotting ($p=0.035$). Changing the target range from 200 – 220 to 220-240 for the Hemochron Jr system led to improved circuit longevity and reduced circuit clots ($p=0.049$). There were no differences in bleeding complications across the three treatment groups.

Is there evidence of improved clinical outcome using ACT testing? Is there evidence for optimal target times to be used with ACT monitoring? In other applications (e.g. vascular surgery, intravenous heparin therapy, dialysis, neuroradiology, etc.)?

Guideline 36: *There is insufficient evidence to recommend for or against ACT monitoring in applications other than cardiovascular surgery, interventional cardiology or extracorporeal oxygenation.*

Strength/consensus of recommendation: I

While several publications refer to the use of the ACT for a wide variety of other clinical applications, few focus on the ACT itself or its effect on patient outcome. Mabry and colleagues (72,73) have described the clinical utility of the ACT (manual or Hemochron) in monitoring patients in peripheral vascular surgery recommending targets of 180 – 200 seconds. Ouseph and

coworkers (74) showed the efficacy of defined Hemochron ACT based algorithms for increasing dialyzer reuse in patients requiring chronic hemodialysis. Simko and coworkers (75) found the ACT to be as useful as the aPTT for monitoring intravenous heparin therapy, while Smythe and colleagues (76) found the aPTT to be a more accurate monitor. Many studies state that ACTs are used for example, in neuroradiology, femoral sheath removal following cardiac catheterization procedures and electrophysiology, but these studies simply reference a target time without indication as to the clinical benefit of these procedures.

Overall, point of care coagulation testing is appropriate in a wide range of clinical applications. Implementation of point of care aPTT and PT testing in the in-patient setting may require evaluation and adjustment of institution established therapeutic targets, clinical decision points and general work flow in the area(s) affected by this testing. Whether or not implementation of point of care aPTT and PT testing in this environment can truly improve patient outcome is not yet clear and requires additional investigation, though there is a clear impact on turn around time and the availability of laboratory results.

Point of care PT/INR testing is required in the patient self-testing and patient self-management paradigms for oral anticoagulation therapy management. While it is still unclear whether the outcome improvements observed compared to routine care are due to the use of point of care or to the increased frequency of testing, the benefits of these management modalities are clear. There is a clear association of the frequency of INR testing and maintenance of therapeutic range.

The use of ACT testing in cardiac surgery and cardiac catheterization laboratories shows the strongest impact on improving patient outcome. Despite this clear evidence, the target times employed in these clinical arenas stem from historical clinician comfort rather than clear evidence, yet another area requiring future trials. Furthermore, the ACT is used in a large number of other clinical applications with some indication, but insufficient conclusive evidence, to determine optimal patient treatment. It is critical that trials be designed and conducted to determine the optimal use of this assay, and optimal target times for use of the ACT in all clinical arenas.

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Public Comments:

No public comments were received on the guidelines.

Chapter 5: Critical Care

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One of the strengths of this LMPG process is having balanced representation between scientists from academia and from industry. The Critical Care focus group contains three academic and three industry scientists. While all perceived conflicts of interest and bias from both industry and academia were discussed and brought to light in group teleconferences, the potential still exists for unperceived conflict of interest and bias. Please read this section with that in mind.

The term "conflict of interest" in science refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research. Conflicts of interest can affect other scholarly duties as well, but are particularly important to consider in biomedical and behavioral research because of the impact such conflicts can have on human health (1).

The definition used for “critical care setting” in this section is any clinical setting in which patients are managed who have major organ dysfunction, severe trauma, major surgical wounds,

general anesthesia, severe sepsis, or other high acuity disorders that require life-sustaining care. These settings include intensive care units (e.g., ICU, CCU, NICU, SICU, PICU, CICU), surgical suites (OR), emergency departments (ED), ambulance/helicopter transport systems, burn units, and chest pain/trauma/stroke units.

One of the most important characteristics of critical care settings is the potential for rapid (i.e., seconds to minutes) and clinically significant changes in a patient's status that may require prompt intervention. Blood pressure, heart rate and rhythm, temperature, respiration rate, and some biochemical markers can be thought of as "vital signs" that reflect these rapid changes and give evidence that a patient's physiology is unstable. In many of these situations, clinicians must be prepared to diagnose and treat these critical patients quickly to avoid subsequent damage to vital organs and systems. These environments present a potential opportunity for rapid, reliable, precise, and accurate diagnostic testing of critical biomarkers as a necessary part of the care of these patients, resulting in improvement in patient outcomes through real-time treatment of the physiological deterioration.

The required rapid diagnostic test result may be obtained from one of two general settings: the central laboratory setting or point of care testing (POCT) setting (e.g., a "STAT" lab, a satellite lab, a near-patient instrument, a bedside testing instrument). If the accuracy, imprecision, quality control, reliability, and cost-effectiveness are generally equivalent for the test settings, the "speed to treatment" or therapeutic turnaround time (TTAT; "vein to brain time") and how the TTAT relates to the time-before-irreversible cellular damage of vital organs become the driving forces

for the clinical decision of what rapid test setting should be used to optimally treat a given patient.

As presented in the following sections, there are an abundance of peer-reviewed papers that show that rapid TTAT is crucial in critical care settings. As mentioned above, two rapid test settings (i.e., central laboratory testing and POCT) can potentially meet the TTAT needs for a given hospital setting. However, most studies have shown that POCT, when compared directly to central laboratory testing, will result in a significant decrease in TTAT (2,3,4). Therefore, if decreased TTAT for a given critical care test leads to an outcome benefit in a given setting and if the clinical testing processes are optimized in that setting, the evidence points toward the use of POCT for that test/setting leading to a similar improved outcome. Often, POCT is placed into clinical settings without modifications in the processes that had been in place before the change. However, process changes are often required in clinical settings after POCT introduction and before improved outcomes due to reduced TTAT can be observed. Well-designed clinical studies (5,6) that fail to optimize processes (e.g., in-patient admission, responding to a 90 min central lab result vs. a 5 min POCT result) and/or variables (e.g., testing for non-critical analytes, measuring metric endpoints [e.g., LOS] instead of clinical endpoints [e.g., morbidity, mortality]; see sections below) with introduction of POCT may lead to equivocal results. Future clinical studies comparing POCT to central laboratory testing must take process management into account.

Although it has been recognized by many experienced clinicians and laboratorians that POCT has improved patient outcomes over the past 15 years, most of the evidence for improvement in patient outcomes, with the use of POCT in critical care settings, has been anecdotal or intuitive

as opposed to being elucidated through well-designed clinical studies. Therefore, more well-designed comparative patient outcome studies and evidence (i.e., each POCT setting vs. central lab testing) are necessary to more clearly define POCT's definitive role in improving health outcomes in critical care settings.

The following recommendations address the above issues with some of the most commonly measured analytes in the critical care setting: arterial blood gases (PO₂, PCO₂, pH), glucose, lactate, magnesium, cooximetry (O₂ saturation, carboxyhemoglobin, methemoglobin), sodium, potassium, chloride, and ionized calcium.

Literature searches were conducted through online databases (e.g., PubMed, Medline) and private libraries maintained by members of the focus group. Peer-reviewed articles from private libraries were utilized in the systemic review only if the citations and abstracts could be found in the online databases. The search strategy started with the general terms (e.g., point-of-care testing, bedside testing, etc.) and concluded in specific settings, disease states, and outcomes (e.g., emergency room, blunt trauma, mortality). Method comparison studies that compared a POCT system to central laboratory system for analytical correlation were excluded from the review.

The two clinical questions that we sought to address for each analyte and for a given clinical setting, disease state, and outcome measure were:

1. Is there evidence in the peer-reviewed literature that more rapid TTAT of a (lab test) result leads to (outcome) improvement, in the (setting) for patients with (disease)?

2. Does POCT of (lab test) for patients with (disease) in the (setting) improve (outcome), when compared to core laboratory testing?

Arterial Blood Gases

Arterial blood gases typically have uses in a variety of settings (including intensive care units, emergency department, cardiac surgery, and extracorporeal membrane oxygenation [ECMO]), each with its own requirements for speed in obtaining results.

Intensive Care Unit

Guideline 37: *There is fair evidence that more rapid TTAT of ABG results, in several types of ICU patients, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in at least some types of ICU patients.* (Literature Search 13)

Strength/consensus of recommendation: B

Level of evidence: I

A major concern for ICUs is the maintenance of tissue oxygenation, ventilation, and normal acid-base status. Because life-threatening changes in these parameters can occur suddenly, rapid results are often needed for effective monitoring and treatment in the ICU (7). The following paragraphs summarize studies that showed either a positive impact or little impact of rapid TTAT in the ICU setting.

In a report on two critically ill patients who required frequent arterial blood gas monitoring for

assessing pulmonary function and adjusting ventilator settings, some clinical and cost advantages were seen over several days in these ICU patients (8).

During high frequency oscillatory ventilation (HFOV) in preterm infants with severe lung disease, very rapid results were necessary to detect and evaluate the rapid changes in PO₂ and PCO₂ that occur with changes in oscillatory amplitude (9).

In patients with sepsis, early goal-directed therapy had a significant reduction in mortality (31%) compared to standard treatment protocol (47%). Among the parameters that were significantly different were central venous oxygen saturation (70% vs 65%) and pH (7.40 vs 7.36) (10).

In 12 cases of neonatal seizures, clinically-significant acidosis was found in 30% of neonates and the majority of seizures were not associated with intrapartum hypoxia or ischemia (11). In another study, an umbilical artery pH less than 7.0 was the most important blood gas parameter in predicting early onset of neonatal seizure (12). However, therapeutic TAT between a central blood gas lab, a satellite blood gas lab, and point of care testing devices was compared in a study (13). The article contained the following observations regarding TTAT and outcomes: 1. more frequent rapid blood gas testing did not often cause a change in treatment; 2. most blood gas results were used to confirm that treatment was going well (i.e., patient well-ventilated); and 3. glucose and electrolyte testing produced a change in treatment far more often than did blood gas testing.

Guideline 38: *There is fair evidence that POCT of ABG results in the ICU leads to improved clinical outcomes, when POCT is found to lead to reduce TTAT compared to the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in ICU patients. More prospective randomized controlled studies need to be performed.* (Literature Search 14)

Strength/consensus of recommendation: B

Level of evidence: II

Blood gas testing has been mentioned as the most-often needed POC test in the ICU (14,15). The observed advantages of POCT were decreased therapeutic TAT (TTAT), fewer errors, and reduced blood loss. There was much less evidence for earlier diagnosis, decreased LOS in ICUs, decreased costs or decreased mortality. In a neonatal/pediatric ICU, only a marginal improvement in TAT was achieved, and costs were comparable only if labor was not included in POC test costs (16).

Certain modes of POC testing may or may not be optimal for ICU use. An early report from 1990 described the essential nature of blood gas tests in ICU care at a single medical center, with both potential benefits and shortcomings of POC blood gas instruments (and pulse oximeters) mentioned (7). Benefits included: real-time treatment with reduced TTAT, reduction in unneeded therapies, more rapid administration of needed therapies, decrease in hospital/ICU stay, decrease in medical costs, reduction in laboratory errors (i.e., labeling, transport), and acceptance by clinicians and patients. Shortcomings included: less reliability (in general) compared to laboratory testing, pulse oximetry could not monitor PO₂, PCO₂, or pH so it could not be used

alone, no direct evidence for improved clinical outcomes, quality control issues with non-laboratory users, and more clinical studies were needed.

In some hospitals, the central laboratory can perform blood gas measurements as quickly as POCT methods. This was documented in a study at a large academic medical center (17). The quality in both settings was found to be satisfactory. Using a pneumatic tube system, the central laboratory's TTAT was equivalent to that of a satellite laboratory in a neonatal ICU. The total cost per reportable result was substantially higher for the satellite. Therefore, the cost-benefit analysis revealed that the central laboratory was an appropriate path for the ABG testing.

Staff satisfaction, comparing a central blood gas lab, a satellite blood gas lab, and other point of care testing devices, was evaluated (13). Therapeutic TAT was about the same for satellite and POC testing, with both much faster than central lab. The satellite lab scored the highest overall for staff satisfaction, with other types of POC blood gas testing being second.

In newborns on ventilators, use of an in-line device (SensCath) required less blood (1.2 vs 6.7 mL) and led to faster ventilator changes (2 vs 26 min), although no data suggested this improved outcomes (18).

In a study of blood gases measured by three techniques: intra-arterial probes, transcutaneous devices, and standard in vitro blood gas analyzers, although correlations were reasonable, the report noted that many intra-arterial probes failed during use and were much more expensive (19). An early report stands the test of time in its assessment and predictions of the limitations of

noninvasive devices, implantable blood gas sensors, and in-line sensors (20). While numerous technical problems have been found, most are related to formation of clots around the invasive sensor.

An interdepartmental team approach is often necessary to achieve the full potential benefits of POC testing. In one report, POCT was regarded as a supplement, not a replacement for, conventional laboratory services. Clinicians expressed a preference for rapid transport systems rather than bedside testing as the solution (15).

Guideline 39: *There is some evidence that POCT of ABG results in the ICU may lead to reduced costs when compared to the central laboratory testing but the balance of benefit to no benefit is too close to justify in a given hospital. We have no recommendation for POCT of ABG results being considered as a way to reduce costs in the ICU. More prospective randomized controlled studies need to be performed.* (Literature Search 15)

Strength/consensus of recommendation: I

Level of evidence: II

Using decision analysis methods, three models of postoperative POC blood gas testing for CABG patients were developed and evaluated for economic value. These were: 1. a STAT lab in a large tertiary care medical center with 15 min TAT; 2. STAT testing in a central laboratory of a large community hospital with a 30 min TAT; and 3. STAT testing in a central laboratory of a medium-large community hospital with a 45 min TAT (21). The cost savings related to faster TAT were primarily due to fewer adverse events and/or earlier detection of these adverse events. Some adverse clinical events benefited greatly by faster TAT (ventricular arrhythmias and

cardiac arrests), while others were relatively independent of TAT (postoperative bleeding and iatrogenic anemia). This study used clinical experts to define probabilities of adverse events leading to a mathematical analysis instead of a prospective clinical study.

Although blood gas testing was a small part of the testing evaluated, one report describes the process, the economics, the attitudes, and the clinical and economic benefits of implementing POC testing in a large medical center that previously had a variety of STAT-type laboratories (22). Although considerable cost savings (\$392,000 per year) were reported, the majority of these were in labor savings (\$495,000 per year), which more than made up for the otherwise increased cost (\$145,000 per year) of POC. POC is especially cost effective when it allows closure of a pre-POC laboratory that is extremely inefficient, as one described here which averaged less than one test/day per FTE (5.0 FTEs worked in this laboratory).

Emergency Department

Guideline 40: *There is fair evidence that more rapid TTAT of ABG results, in some ED patients, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in at least some types of ED patients.*

(Literature Search 16)

Strength/consensus of recommendation: B

Level of evidence: II

In a study of 116 non-intubated adult blunt trauma patients, about 20% had conditions possibly related to occult shock. Blood gas results helped recognize patients who were hyperventilating

($\text{PCO}_2 < 30$ mmHg) and who had unrecognized metabolic acidosis, patients with worse than expected metabolic acidosis, and patients with low PO_2 who responded to positive pressure ventilation (27). Because blood gas results could help to triage such patients from those who are more stable, they concluded that ABG analysis should be performed on all blunt trauma patients who meet even minimal severity criteria.

Guideline 41: *There is fair evidence that POCT of ABG results leads to improved clinical outcomes, in some types of ED patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in ED patients. More prospective randomized controlled studies need to be performed.* (Literature Search 17)

Strength/consensus of recommendation: B

Level of evidence: II

A review of 99 articles published between 1985 and 2001 on overall POC testing in the ED reported that: 1. POC technology appears to be reliable in an ED setting; 2. cost and connectivity are difficult but important issues for greater acceptance of POCT in the ED; 3. ultimately, improved patient care must be evaluated to offset the costs of POC testing (23). The impact of POC testing on outcomes in the ED, ICU, OR, and primary care, can be measured in a variety of ways. These include: mortality, morbidity, earlier or more effective intervention, lower cost while maintaining quality, safety, patient or physician satisfaction, and return to normal life-style (24).

For patients admitted to the ED, POC blood gas testing allowed a decision to be made an average

of 21 minutes earlier compared to central laboratory testing (25). This was apparently better than other POC tests, for which a rapid result by point of care testing led to a change in management in only 6.9% of patients. Another report similarly noted that, while electrolytes and BUN did not influence initial management of major trauma, Hb, glucose, blood gases and lactate occasionally helped reduce morbidity or save resources (26). Another report noted that rapid delivery of blood gas results was required for respiratory distress, severe trauma and head injury (24).

Portable POC devices are often used for patients transported to the ED by helicopter and ambulances. In one report, POC testing was expected to allow the crew to assess the patient, identify problems, and administer treatment earlier (28).

Cardiac Surgery: Adult and Neonatal

Guideline 42: *There is fair evidence that more rapid TTAT of ABG results in cardiac surgery patients leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ABG results be considered as a way to improve outcomes in cardiac surgery patients. (Literature Search 18)*

Strength/consensus of recommendation: B

Level of evidence: II

During cardiac surgery, blood gas and hemoglobin measurements are often used to calculate O₂ consumption and CO₂ production, with blood lactate measured to evaluate the presence of ischemia (29). Even when O₂ consumption is low during normothermic CPB, the normal blood lactates suggests there is no tissue ischemia present. In another study, the arterial PO₂ decreased

markedly during deep hypothermic circulatory arrest (DHCA) and the measurement of arterial PO₂ during DHCA may provide a surrogate method for determining maximum safe time under DHCA for adults (30).

In pediatric cardiac surgery, indwelling monitors are often not practical. Therefore, rapid blood gas and other test results often provide the only means to monitor the patient. Rapid blood gas results were noted to allow better control of cerebral blood flow and oxygen delivery in infants during cardiac surgery (32). Another report makes a strong case for rapid blood gas results during operations in neonates with congenital heart defects, during which ventilator adjustments are critical for optimal patient care (33). A recent study of 155 patients presented data that suggest that an abnormal lactate pattern may be useful in determining the timing of cardiopulmonary support initiation in hemodynamically stable patients with high or rising lactate values, before cardiac arrest or end-organ damage (34).

Guideline 43: *There is fair evidence that POCT of ABG results leads to improved clinical outcomes, in cardiac surgery patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of ABG results be considered as a way to improve outcomes in cardiac surgery patients. More prospective randomized controlled studies need to be performed.* (Literature Search 19)

Strength/consensus of recommendation: B

Level of evidence: II

A recent prospective study (with a historical control group) that included 2366 post-congenital heart surgery patients (710 pts in the POCT group; 1656 pts in the central laboratory control

group) evaluated oxygen debt (ischemia) in these critically ill patients as monitored by whole blood lactate (18). The study results showed a 50% reduction ($p=0.02$) in mortality overall, between the POCT cohort compared to the central laboratory cohort. Improvement was greatest in the neonates and highest risk patients (35).

In another clinical evaluation, POC testing during open-heart surgery of ABGs reduced the TAT from 25 min (central lab) to 3 min, and enhanced the care of patients (31).

Glucose

Glucose measurements typically have uses in a variety of critical settings, each with its own requirements for speed in obtaining results.

Guideline 44: *There is good evidence that more rapid TTAT of glucose results in, critical care patient settings, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of glucose results be considered as a way to improve outcomes in cardiac surgery patients.*

(Literature Search 20)

Strength/consensus of recommendation: A

Level of evidence: I

Four observations have been documented in the literature as important rationales for time-critical testing of glucose: 1) glucose levels may not be known at times when rapid therapeutic options (i.e., glucose or insulin infusions) can influence clinical outcomes (36-40); 2) glucose levels may change rapidly and dramatically in critically ill patients (37, 41); 3) there are time-dependent risks associated with hypoglycemia, ranging from symptoms of neuroglycopenia (e.g., headache,

confusion, blurred vision, dizziness, and epigastric discomfort) to seizures, loss of consciousness, irreversible damage, and even death (42-48, 65); and 4) there are also time-dependent risks associated with hyperglycemia including irreversible/ischemic brain damage, nosocomial infections, polyneuropathy, and mortality (37,46-48,49-64). Taken together, the composite clinical outcome information reveals a persuasive argument for the need for accurate and precise time-critical glucose results in many critical care settings.

In a landmark article (61), Van den Berghe et al demonstrated that intensive insulin therapy maintaining blood glucose at or below 110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical intensive care unit, regardless of whether they had a history of diabetes mellitus.

Guideline 45: *There is good evidence that POCT of glucose results leads to improved clinical outcomes, in critical care patient settings, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we strongly recommend that POCT of glucose results be considered as a way to improve outcomes in critical care patients. (Literature Search 21)*

Strength/consensus of recommendation: A

Level of evidence: I

In a landmark article (66), Furnary et al demonstrated that continuous insulin infusion eliminates the incremental increase in in-hospital mortality after coronary artery bypass grafting (CABG) associated with diabetes mellitus. They concluded that continuous insulin infusion should become the standard of care for glycometabolic control in patients with diabetes undergoing a

CABG procedure. Assuming the imprecision and accuracy of the POCT glucose assay is adequate, Furnary stated that POCT is a necessity for administering the Portland Protocol because there are points in the protocol where the insulin administration is adjusted every 30 minutes.

Lactate

Lactate measurements typically have uses in a variety of critical settings, each with its own requirements for speed in obtaining results.

Guideline 46: *There is good evidence that more rapid TTAT of lactate results in, critical care patient settings, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of lactate results be considered as a way to improve outcomes in cardiac surgery patients.*

(Literature Search 22)

Strength/consensus of recommendation: A

Level of evidence: I

To interpret lactate requires two key pieces of information: 1) an understanding of the clinical circumstance leading to the increase in lactate (e.g., late septic shock, exercise, liver compromise), and 2) the length of time that lactate has been elevated (which requires serial lactate analyses to give an estimate of cumulative oxygen debt). Depending on the clinical setting, recognizing an increase in lactate as soon as possible, coupled with immediate resuscitation, is usually associated with improved outcomes (67-100).

Any location handling critically ill patients (e.g., ED, OR, ICU) whose lactate levels may be elevated can better serve their patients by having rapid TTAT of lactate results including:

- a) in the ED, patients presenting with acute abdomen (67-70), acute myocardial infarction (71,72), asthma (73), cardiac arrest (74), cyanide poisoning (75-77), intracranial pressure (78), pulmonary embolism (79), occult illness (80-83), shock (84), need for transfusion (85), and trauma (86-88) may benefit;
- b) in the OR, patients with congenital heart surgery (89), intracranial pressure (78), liver transplant (90), shock (84), thoracoabdominal aortic aneurysm (91), and transfusion (85,88) may benefit; and
- c) in the ICU, patients include those with acute myocardial infarction (72), anemia of prematurity (85), circulatory shock (84,93), cyanide poisoning (75-77), ECMO (94,95), heart surgery (96-98), intracranial pressure (78), liver transplant (90), high-risk surgery (abdominal, vascular) (99), pulmonary embolism (79), transfusion (85,88), and burns (92) may benefit.

Rivers et al (100) showed that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock (as defined by lactate and other blood gas parameters), prior to admission to the intensive care unit, reduced the incidence of multiorgan dysfunction, mortality, and the use of health care resources. They concluded that the improved outcomes arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and demand.

Guideline 47: There is good evidence that POCT of lactate results leads to improved clinical outcomes, in critical care patient settings, when POCT is found to lead to reduced TTAT

compared to the central laboratory. Overall, we recommend that POCT of lactate results be considered as a way to improve outcomes in critical care patients. More prospective randomized controlled studies need to be performed. (Literature Search 23)

Strength/consensus of recommendation: B

Level of evidence: II

In a recent prospective study with a historical control group, a goal-directed therapy algorithm (based on serial lactate values obtained from a POCT device) was utilized in an attempt to test the hypothesis that rapid diagnostic testing combined with goal-directed therapy could reduce the mortality of patients after congenital heart therapy (35). The results showed that a 50% reduction ($p=0.02$) in mortality overall, between the POCT cohort compared to the central laboratory cohort. The most significant reductions in mortality were seen in neonates (73%; $p=0.02$) and patients undergoing higher risk operations (67%; $p=0.006$).

Magnesium

Magnesium measurements typically have uses in a variety of critical settings, each with its own requirements for speed in obtaining results.

Guideline 48: *There is fair evidence that more rapid TTAT of magnesium results in, critical care patient settings, leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of magnesium results be considered as a way to improve outcomes in critical care patient settings. (Literature Search 24)*

Strength/consensus of recommendation: B**Level of evidence: II**

Magnesium has clinical value in cardiovascular and oxidative stress/inflammatory settings (101-106). It is a cofactor in > 325 enzymatic reactions, including virtually all of the reactions involved in energy exchange. Its involvement with nucleoside triphosphate pumps makes it very important to electrolyte balance. This, in turn, makes it important to conduction and contraction and, therefore, to cardiac rhythm, cardiac output, and blood pressure. It is also a cofactor for enzymes involved in eliminating oxygen free radicals and controlling nuclear factor kappa B activation (cytokine and adhesion molecule production). In general, magnesium is a regulating factor in hemodynamics, vascular tone, reperfusion injury, platelet aggregation, and the inflammatory response (101-106).

Any location handling critically ill patients (e.g., ED, OR, ICU) with cardiovascular symptoms, or where reperfusion injury or an inflammatory response exists, may benefit from rapid TTAT of magnesium results to guide magnesium therapy. This includes patients experiencing electrolyte imbalances, being treated with inotropes (digoxin) and antiarrhythmic drugs, experiencing hypoxia, or receiving i.v. magnesium therapy:

- a) in the ED, patients presenting with ischemic heart disease (including AMI) (107-120), arrhythmia (110-113,117,121-124), asthma (125), cardiac arrest (126), cerebral vascular tension/vasospasm (111,127), coagulation problems (128), coronary vasospasm (111,129), digitalis toxicity (111-113,117,121,130), electrolyte imbalances from diuretics (112,113), adverse drug reactions (nitrates and ACE inhibitors) (131),

- head ache (132), head trauma (133-140), heart failure (112,121-124), hypotension (141), infarct (142), preeclampsia/eclampsia (111,157), seizures (141), sepsis (143-145), and stroke (111) may benefit;
- b) in the OR, patients presenting with arrhythmia (110,111,121,122,142), experiencing clotting problems (128), coronary vasospasm (111,129), cerebral vasospasm (111), head trauma/surgery (134,135,137-140), heart surgery (126,146-149), liver transplant (150), and stroke (111) may benefit; and
- c) in the ICU, patients presenting with ischemic heart disease (including AMI) (109-120), arrhythmia (110-113,117,121-124,142,151), cardiac arrest (126), cardiogenic shock (152), cerebral vascular tension/vasospasm (111,127), clotting (128), coronary vasospasm (111,129), cramps (159,160), digitalis toxicity (111-113,117,121,130), diuretic therapy (112,113), drug therapy (nitrates and ACE inhibitors) (131), head trauma/surgery (133-140), heart failure (112,121-124), heart surgery (146-149,151,153), hypotension (141), infarct (142), liver transplant (150), neonates from mothers receiving Mg therapy (155,158), pain (156), seizures (141,151), sepsis (143-145), shock (154), and stroke (111) may benefit.

Guideline 49: *There is insufficient evidence that POCT of magnesium results leads to improved clinical outcomes, in critical care patient settings. Overall, we recommend that prospective randomized controlled studies be performed.* (Literature Search 25)

Strength/consensus of recommendation: I

Level of evidence: III

Taken together, the composite TTAT information above (101-160) demonstrates that accurate and precise time-critical Mg results, supplied by POCT, may lead to better outcomes in critical care settings. However, no POCT outcome studies of magnesium in critical care patient populations were found.

Cooximetry

“Cooximetry” means measurement of hemoglobin pigments by dedicated multi-wavelength spectrophotometry. The instrument for that may be stand-alone or part of a blood gas analyzer. It usually measures and reports total hemoglobin, oxygen saturation ($= \text{HbO}_2 / (\text{HbO}_2 + \text{deoxyHb})$) or oxyhemoglobin fraction ($= \text{HbO}_2 / \text{tHb}$), carboxyhemoglobin (HbCO), and methemoglobin (MetHb).

Cooximetry typically have uses in a variety of clinical settings, each with its own requirements for speed in obtaining results.

Oxygen Saturation

Guideline 50: *There is fair evidence that more rapid TTAT of oxygen saturation results in, critical care patient settings, leads to improved clinical outcomes. Overall, we recommend that rapid TTAT of oxygen saturation results be considered as a way to improve outcomes in critical care patient settings. (Literature Search 26)*

Strength/consensus of recommendation: B

Level of evidence: II

Oxygen saturation by cooximetry can be used to check the pO_2 of blood gas analyzers, because oxygen saturation and pO_2 are tightly linked (through the oxygen hemoglobin equilibrium curve). A discrepancy between predicted and measured pO_2 may indicate an error.

Oxygen saturation by cooximetry can also be used to check the pulse oximeter, which is widely used for monitoring a patient's arterial oxygen saturation. Pulse oximetry is a non-invasive POCT technology that continuously measures the oxygen saturation of pulsating blood (by two wavelengths absorptiometry). A cooximeter, on the other hand, requires an arterial sample.

Pulse oximetry has been shown to reveal hypoxemic episodes accurately (161). In a number of clinical settings (e.g., asthma, obstetrics, neonatal ICU), pulse oximetry has been shown to improve outcomes (162,163,164).

Guideline 51: *POCT of oxygen saturation by cooximetry is not required in critical care settings.*

Overall, we recommend pulse oximetry as the preferred method. (Literature Search 27)

Strength/consensus of recommendation: C

Level of evidence: II

The applications of oxygen saturation by cooximetry do not require POCT. Pulse oximetry is preferred for POCT of oxygen saturation, rather than oxygen saturation by cooximetry.

Carboxyhemoglobin

Guideline 52: *There is good evidence that POCT of carboxyhemoglobin (HbCO) results leads to improved clinical outcomes, in critical care patient settings, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of carboxyhemoglobin (HbCO) results be considered as a way to improve outcomes in critical care patients. More prospective randomized controlled studies need to be performed. (Literature Search 28)*

Strength/consensus of recommendation: B

Level of evidence: II

The diagnosis of carbon monoxide (CO) poisoning requires that the physician suspects the condition and orders a determination of HbCO. Two studies demonstrate the benefit of screening of patients presenting with flu-like symptoms (165) or headache (166) for CO poisoning.

The studies were performed at two different emergency departments and involved all patients presenting with these symptoms in inner-city populations during the heating months. The emergency physicians suspected or diagnosed none of 20 patients with HbCO >10 % based on clinical examination alone, in spite of a prevalence of 20 % of this condition. The advantage of screening for CO poisoning is to avoid a return to a hazardous environment with potentially fatal consequences that may include the cohabitants.

A correct and timely diagnosis of occult CO poisoning in this setting requires easy access to POCT. A third study (167) used HbCO by cooximetry to screen all patients admitted from the

emergency department with diagnoses other than CO poisoning. In this population, only 0.4 % had HbCO > 10 %, one of whom was presenting with seizures.

Methemoglobin

Guideline 53: There is fair evidence that POCT of methemoglobin results leads to improved clinical outcomes, in critical care patient settings. Overall, we recommend that POCT of methemoglobin results be considered as a way to improve outcomes in critical care patients and that more prospective randomized controlled studies need to be performed. (Literature Search 29)

Strength/consensus of recommendation: B

Level of evidence: II

A literature review (168) describes 54 cases of benzocaine induced methemoglobinemia during intubation and endoscopy/bronchoscopy. Administration of the local anesthetic benzocaine may produce life-threatening methemoglobinemia. Early detection of the condition is necessary for timely intervention, and it can best be achieved with POCT.

Two studies describe increased MetHb in patients with sepsis and septic shock. One (169) compared MetHb between groups of patients in an ICU, and one (170) used MetHb as marker of endogenous nitric oxide production in children with septic shock in a pediatric ICU, and compared the results to a matched healthy control group. In both studies, MetHb was significantly higher in patients with sepsis. However, MetHb did not correlate with clinical markers or severity of illness. Sepsis is potentially lethal and must be diagnosed early.

Electrolytes (Na⁺, K⁺, Cl⁻)

Electrolyte measurements typically have uses in a variety of clinical settings, each with its own requirements for speed in obtaining results.

Emergency Department

Guideline 54: *There is fair evidence that POCT of potassium results leads to improved clinical outcomes, in ED patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of potassium results be considered as a way to improve outcomes in ED patients. More prospective randomized controlled studies need to be performed.* (Literature Search 30)

Strength/consensus of recommendation: B

Level of evidence: II

Several studies have shown that therapeutic TAT is clearly decreased when POCT is used for measurement of electrolytes in the ED, leading to faster decisions on patient management (171-175).

In one study using randomized controls, change in treatment where timing was critical took place in 7% of patients when POCT was used (171). However, there is no clear evidence that outcomes such as patient length of stay in the ED or in-hospital or total mortality are improved when POCT is used for initial ED screening (171,172). In one study (173), patient LOS in the ED was decreased to 3:28 from 4:22, but only for discharged patients, because patients destined to be hospitalized required further diagnostic testing not offered at the point of care.

Therapeutic TAT is shortened when POCT for electrolytes is used for screening of trauma patients in the ED (176). However, it is not clear that changes in patient management or outcomes result. One exception is measurement of K^+ , where there is some indirect evidence that availability of K^+ results in a time urgent manner (preoperatively) would improve patient outcomes (176). Rapid availability of Na^+ and Cl^- results appear not to be influential in changing treatment of trauma patients (176,177). An important benefit of using POCT to screen trauma patients is the ability to conduct analysis using small sample volumes, resulting in reduction in blood loss and reduced risk from transfusion when POCT is used (176).

No change in patient treatment in the ED resulted from measurement of electrolytes (Na^+ , K^+) using POCT during air transport to the ED (180).

Intensive Care Unit

Guideline 55: *There is little known evidence that POCT of electrolyte results leads to improved clinical outcomes, in the ICU setting. Overall, we have no recommendation for POCT of electrolyte results being considered as a way to improve outcomes in the ICU. Prospective randomized controlled studies need to be performed.* (Literature Search 31)

Strength/consensus of recommendation: I

Level of evidence: III

Therapeutic TAT (relative to the central laboratory) is improved when POCT (either near-patient testing or satellite lab) is used for the measurement of electrolytes in the adult ICU (177). ICU

staff also favored a dedicated satellite lab. There are few correlations between reduced TAT for electrolyte results in the ICU and improved patient outcomes. One important advantage of using POCT in the ICU is the ability to conduct analyses using small sample volumes, resulting in reduction in blood loss and reduced risk from transfusion when POCT is used (179).

Ionized Calcium

Ionized calcium measurements typically have uses in a variety of clinical settings, each with its own requirements for speed in obtaining results. Ionized calcium is a component of the critical care profile in the ED, OR, and ICU (181).

Emergency Department

Guideline 56: *There is fair evidence that POCT of ionized calcium results leads to improved clinical outcomes, in circulatory arrest patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of ionized calcium results be considered as a way to improve outcomes in circulatory arrest patients. More prospective randomized controlled studies need to be performed. (Literature Search 32)*

Strength/consensus of recommendation: B

Level of evidence: II

The availability of this test in the ED leads to faster TAT (within 5 mins) and reduced blood utilization. The significance of rapid ionized calcium measurement was stressed for cardiac arrest patients, since only 1-3% of these patients leave the hospital alive or impaired (182). The

patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy.

Operating Room

Guideline 57: *There is some evidence that POCT of ionized calcium results leads to improved clinical outcomes, in circulatory arrest patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of ionized calcium results be considered as a way to improve outcomes in circulatory arrest patients. More prospective randomized controlled studies need to be performed.* (Literature Search 33)

Strength/consensus of recommendation: B

Level of evidence: III

The significance of rapid ionized calcium measurement was stressed for patients undergoing cardiopulmonary bypass and liver transplant surgeries (181). The patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy.

Intensive Care Unit

Guideline 58: *There is fair evidence that more rapid TTAT of ionized calcium results in the ICU leads to improved clinical outcomes. Overall, we recommend that more rapid TTAT of ionized calcium results be considered as a way to improve outcomes in ICU patients.* (Literature Search 34)

Strength/consensus of recommendation: B

Level of evidence: II

The availability of this test in the ICU leads to faster TAT and reduced blood utilization. The significance of rapid ionized calcium measurement was stressed for shock burns and electrolyte imbalance patients; and those patients receiving blood transfusion. The patients require prompt evaluation of ionized calcium and other electrolytes for proper interpretation and prompt initiation of therapy (181).

An article by Singhi (183) that showed the significance and frequency of abnormalities of calcium in the PICU and the fact that mortality rate was higher in hypocalcemic patients. These hypocalcemic patients had longer hospital stays. In addition, Zivin (184) showed that hypocalcemia was associated with higher mortality and correlates with severity of illness.

Guideline 59: *There is fair evidence that POCT of ionized calcium results leads to improved clinical outcomes, in ICU patients, when POCT is found to lead to reduced TTAT compared to the central laboratory. Overall, we recommend that POCT of ionized calcium results be considered as a way to improve outcomes in ICU patients. More prospective randomized controlled studies need to be performed. (Literature Search 35)*

Strength/consensus of recommendation: B

Level of evidence: III

In a comprehensive review of criteria for POCT instrument evaluation, test menus, analysis times, and performance criteria, Kost (185) indicated that, in the critical care setting, ionized calcium measurement is obligatory because of the well-documented impact of ionized calcium

on vital functions such as conduction and contraction of muscle cells. Specific examples cited included impact of ionized calcium for critically ill individuals with sepsis, hypocalcemia crisis, hypotension, heart failure, hyperkalemic dysrhythmia, and electromechanical dissociation (186, 187). This review included references to the excellent correlation between the degree of hypocalcemia with mortality rate and the use of 0.70 mmol/l as a low limit threshold for ionized calcium (188). It eludes to the fact that POCT ionized calcium is critical for the continued proper management of critically ill patients and patients undergoing transplantation, cardiac, or other surgical procedure.

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Public Comments:

No public comments were received on the guidelines.

Chapter 6: Diagnosis and Management of Diabetes Mellitus

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Diabetes mellitus is one of the most common diseases in the world and constitutes one of the largest chronic disease burdens throughout the world. It is a disease that is defined by the biochemical abnormalities associated with changes in glucose metabolism, but is also characterized by a more complex pathophysiology. The morbidity and mortality associated with diabetes mellitus result from the complications of the disease which include both micro and macrovascular complications most commonly resulting in blindness, renal failure and cardiovascular disease. In 1992 the cost of diabetes in the United States was estimated to be \$98 billion, whilst in the United Kingdom it consumes approximately 10% of the healthcare budget.

In vitro biochemical testing plays a central role in the diagnosis and management of diabetes mellitus and the reader is referred to the National Academy of Clinical Biochemistry Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus (1).

The diagnosis of diabetes mellitus is based on an accurate assessment of the fasting blood glucose concentration, followed by a glucose tolerance test in the case of an equivocal result (1). Point of care testing (POCT) has no role to play in the diagnosis of diabetes although it may be used as a screening test preceding the use of a laboratory test. The role of a range of biochemical tests in the management of diabetes was systematically reviewed by Sacks et al and reported in the NACB guidelines referred to earlier (1). The management of diabetes today is largely guided by the work from the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes (2) and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes (3) which investigated the use of intensive treatment to maintain normoglycemia on the rate of progression of the complications of the disease.

Intuitively, the delivery of the biochemical testing through the modality of POCT has the potential to improve the quality of patient care and generate beneficial health outcomes. Indeed within the DCCT and UKPDS studies the majority of the blood glucose testing was undertaken by self-monitoring of blood glucose (SMBG), one style of POCT, albeit in the UKPDS the treatment decisions were made on the basis of the HbA1c result. There have been reports of a number of tests being performed by POCT and the literature will be reviewed in order to determine whether robust guidelines can be developed to support POCT in the management of

diabetes. The review will focus on SMBG, POCT of hemoglobinA1c in assessing glycemic control, fructosamine in assessing glycemic control, blood ketones for the assessment of diabetic crises, and urine albumin excretion (often referred to as “microalbuminuria” for the detection of renal dysfunction).

It should be stressed at the outset that ‘absence of evidence of effect does not constitute evidence of absence of effect’ (4). The following sections describe the recommendations made in relation to the main tests performed at the point of care in relation to the diagnosis and management of diabetes mellitus.

Blood Glucose

The following questions were searched in PubMed (682 different hits) and the Cochrane library (66 different hits) in December 2003. (Literature Searches 36 – 41) A total of 695 abstracts were found of which 53 were duplicates. The abstracts were read by two reviewers to determine whether the articles should be retrieved or not. Disagreement was solved by consensus or by the assessment of a third person. A total of 88 articles were retrieved. All the articles retrieved were compared to those found by Coster et al. (5), a systematic review dealing exclusively with self monitoring of blood glucose (SMBG). Papers on SMBG (guidelines 60 - 63 and 66 - 67) not included in this review were dealt with using the same methodology and added to those already assessed in (5). For hospital and point of care (POC) glucose testing (guidelines 64 and 65) all articles were selected. The role for urine glucose self testing is dealt with within the framework of guidelines 60 – 63 and 66 - 67.

The 88 retrieved articles were read by two people who selected and classified the relevant articles according to the forms in (5). Of the additional articles to those in (5), three were found that dealt with type 1 diabetes mellitus, 8 were found (7 after 2000) dealing with type 2 diabetes mellitus and we found no additional articles dealing with gestational diabetes. Concerning the secondary care setting (hospital and POC in the clinical departments), we found three articles. We did not find any previous reviews addressing hospital and POC in the secondary care setting.

Our recommendations are compared with those given by Coster et al (5), the World Health Organisation (6), the American Diabetes Association (ADA) (7), the National Academy of Clinical Biochemistry (NACB) (1) and the National Institute for Clinical Excellence (NICE) (8).

Type 1 Diabetes Mellitus

Does blood glucose self-testing (i.e. primary care setting) lead to an improved patient (clinical) outcome in diabetes mellitus? (Literature Searches 36 and 37)

Guideline 60: *There is insufficient evidence to recommend for or against routinely using SMBG. There is fair evidence that SMBG can improve health outcome. The balance between benefits and costs must be evaluated in each single environment. The consensus agreement to use SMBG in DM type 1 among experts is very strong (e.g. the American Diabetes Association (6)), and it is difficult to advise against SMBG. However greater objective evidence is still required to decide whether SMBG is really needed and which patients will benefit from it. If SMBG is going to be used, high quality instruments should be chosen and patients must be educated in the practical use as well as being instructed in how to use the results to monitor their insulin therapy. The*

evidence to support our view is from systematic reviews, randomised controlled trials (RCT) as well as controlled trials without randomization and cohort / case control studies. The evidence is, however, conflicting and our recommendation is therefore of type I, i.e. there is insufficient evidence to recommend for or against routinely using SMBG.

Strength/consensus of recommendation: I

Level of Evidence: I and II

We found 9 RCTs (9-17) of which one was not in (5). The review of Coster et al (5) found eight RCTs. Two of these showed improved diabetes control whereas six did not. In addition we found one RCT study (13) that dealt with 11 children aged 10-17 years who were followed for 3 months. The intervention group consisted of children performing continuous subcutaneous glucose monitoring in addition to SMBG whereas the control group was children performing ordinary SMBG. There was a slight effect in detecting asymptomatic nocturnal hypoglycemia as well as lowering the HbA1c of 0.6% without increasing the risk of severe hypoglycemia in the intervention group. The number of persons studied, however, was very small.

Sixteen studies (18-33) were excluded by (5) because they were not RCTs, Two more (34,35) were identified by our search. The study of Allen was a cross sectional cohort study in 415 persons up to 28 years that were followed for 4 – 6.5 years. The authors' main conclusions were that intensive insulin management and blood glucose monitoring independently predicted frequent but not severe hypoglycemia (34). In the study of Kaufman (35), 47 children were followed for 3 months using a continuous glucose monitoring system. A significant decrease of 0.2% HbA1c was found compared to conventional monitoring.

When comparing our results with the recommendations given by others (1,6-8), we find that WHO (6) gives the following recommendation concerning SMBG: “The insulin-treated patient is commonly requested to build up a “glycaemic profile” by self-measurement of blood glucose at specific times of the day (and night). A “7-point profile” is useful, with samples taken before and 90 min after breakfast, before and 90 min after lunch, before and 90 min after an evening meal, and just before going to bed. Occasionally patients may arrange to wake at 0300 h to collect and measure a nocturnal sample. The complete profile rarely needs to be collected within a single 24-hour period, and it may be compiled from samples collected at different times over several days. Measurement of glucose in urine: Insulin-treated patients who do not have access to facilities for self-measurement of blood glucose should test urine samples passed after rising, before main meals, and before going to bed.” However, this recommendation is not based on any stated evidence or references. The ADA (7) recommends that (a) SMBG is an integral component of diabetes therapy, (b) that SMBG should be included in the management plan and (c) to instruct the patient in SMBG and routinely evaluate the patient’s technique to use data to adjust therapy. The first recommendation is claimed to be based on “supportive evidence from well conducted cohort studies” whereas the two others are consensus statements. However their evidence seems to be based on consensus statements from 1987 and 1994 (36,37). Sacks et al (1) state that SMBG is recommended for all insulin-treated patients with diabetes. For type 1 patients, SMBG is recommended three or more times a day. This is a “B” recommendation using the same system as ADA (which is equivalent to level of evidence II), i.e. it is based on “supportive evidence from well conducted cohort studies”. In the references cited, however, the evidence for this is not obvious. Intuitively it is felt that close monitoring of blood glucose is needed in adjusting insulin dosage, and SMBG is the most practical way to carry this out.

However Coster (5) pointed out the lack of evidence to support this view, and we have not found data to strengthen the case for SMBG. Coster suggested further studies to examine whether certain groups of patients particularly benefit from SMBG. It is true that the DCTT study (2) showed intensive treatment of diabetics, including SMBG, is beneficial. However SMBG was also used to some extent in the control group, and it is difficult to objectively separate from this study the contribution of SMBG compared to other factors, such as education and more patient contact.

Type 2 Diabetes Mellitus

Guideline 61: Type 2, Insulin treated: *The evidence to support our view is from systematic reviews, RCT as well as controlled trials without randomization and cohort / case control studies). The evidence is, however, conflicting and our recommendation is therefore of type I i.e. there is insufficient evidence to recommend for or against routinely using SMBG. (Literature Searches 36 and 37)*

Strength/consensus of recommendation: I

Level of evidence: I and II

Guideline 62: Type 2, not insulin treated: *We conclude that the evidence is insufficient to recommend for or against routinely using SMBG. The evidence to support our view is both from systematic review, RCT, as well as controlled trials without randomization and cohort / case control studies. The evidence is conflicting with a lot of poor studies although there is some evidence that SMBG is not effective in improving glycemic control or avoiding hypoglycaemic*

attacks. Recommendation is therefore of type I i.e. we conclude that the evidence is insufficient to recommend for or against routinely using SMBG. If SMBG is going to be used, high quality instruments should be chosen and patients must be educated in the practical use as well as being instructed in how to use the results to monitor their insulin therapy. (Literature Searches 36 and 37)

Strength/consensus of recommendation: I

Level of evidence: I and II

Nine RCTs concerning SMBG type 2 DM were found, eight (38-45) of which were included in (5). The ninth by Schwedes et al (46) followed 250 patients with an intervention of six months. Blood glucose was measured six times (before and one hour after main meals) on two days per week. Patients were seen every six weeks by nurses who gave advice and assessed correct use of SMBG. A total of 10% of the patients were excluded because of non-compliance. In the per-protocol analysis, the use of a self-monitoring blood glucose device significantly reduced HbA1c levels by 1.0 +/- 1.08% compared with 0.54 +/- 1.41% for the control group ($p = 0.0086$). Body weight, total cholesterol, and microalbumin improved when using a glucometer, but there was no statistically significant difference between the two groups concerning these parameters. The study design has, however, been criticized (47). None of the RCTs included in the Coster review could show a similar effect. In a meta-analysis of four studies (39,40,43,45) performed by Coster et al (5), a non-significant decrease of 0.25% HbA1c was found. In a similar meta-analysis of three studies (34,40,42) comparing blood monitoring with urine monitoring, no difference in HbA1c was found. However most of these studies were performed before 1995, they did not address instrument quality. There was limited information on whether patients were educated in the use of the instruments and if they had information about what to do with the results. One

large RCT concerning the use of SMBG in type 2 diabetes is in progress in UK and will be finished in mid 2006 (Andrew Farmer).

Ten non-RCTs studies were found (48-57) by (5). In addition to these we found another six (58-63). Out of the ten cross-sectional studies, six showed no effect, three showed effects only on insulin treated patients and one showed an effect on all type 2 patients. Of the two case control studies one showed a possible effect whereas the other showed none. Of the four prospective cohort studies, two showed an effect whereas the other two did not. Our conclusions are similar to that given in other reviews (5,64,65). In a systematic review by Norris et al (66), it is concluded that “Positive effects of self-management training on knowledge, frequency and accuracy of self-monitoring of blood glucose, self-reported dietary habits, and glycemic control were demonstrated in studies with short follow-up (<6 months). Educational interventions that involved patient collaboration may be more effective than didactic interventions in improving glycemic control, weight, and lipid profiles. No studies demonstrated the effectiveness of self-management training on cardiovascular disease-related events or mortality; no economic analyses included indirect costs.” It is underlined that the importance of SMBG on other factors than HbA1c and long term complications may be underestimated. In another criteria based review article by Holmes and Griffiths (67) it is concluded that “The efficacy of blood and urine glucose monitoring testing, for people with type 2 diabetes, in improving glycemic control as measured by HbA1c levels is still questionable. A rigorous randomized controlled trial is needed to establish these answers although there is no evidence of harm. Clinical protocols that make recommendations for glucose monitoring strategies for people with type 2 diabetes should acknowledge that the evidence is weak. There is no basis to recommend one method above

another.”

The recommendations given in a guideline developed by The Royal College of General Practitioners, Diabetes UK, the College of Physicians and The Royal College of Nursing, for the National Institute of Clinical Excellence, (8) are all grade C, equivalent to level of evidence III (evidence from expert committee reports or opinions and or clinical experience of respected authorities). The recommendations given are that (a) self monitoring should not be considered as a stand alone intervention, (b) self monitoring should be taught if the need/purpose is clear and agreed with the patient and (c) self monitoring can be used in conjunction with appropriate therapy as part of integrated self care. WHO (2) gives the following recommendation, however, without any stated evidence: “Non–insulin–dependent patients do not need to monitor their urine so frequently (as type 1 diabetic patients).” No recommendations concerning SMBG are given. Sacks et al (1) state that “SMBG may help achieve better control, particularly when therapy is initiated or changed. However, there are no data to support this concept. The role of SMBG in patients with stable type 2 diabetes controlled by diet alone is not known.” See above for the ADA (6) recommendations.

Does blood glucose self testing (i.e. primary care setting) lead to an economic benefit in diabetes mellitus? (Literature Searches 36 and 37)

Guideline 63: *There is insufficient evidence of economical aspects to recommend for or against routinely using SMBG.*

Strength/consensus of recommendation: I (there is little evidence)

One study dealing with cost effectiveness of SMBG in type I DM found that urine monitoring

was cost-effective whereas blood monitoring was not (15). However these findings are difficult to transfer to other settings.

For type 2 diabetes patients no articles dealing with the possible economic benefit of SMBG were found.

Does blood glucose point of care testing in the hospital (i.e. secondary care setting) lead to an improved patient (clinical) outcome in diabetes mellitus, when compared with central laboratory testing? (Literature Searches 38 and 39)

Guideline 64: *There is insufficient evidence to recommend for or against routinely using POC glucose testing in the hospital.*

Strength/consensus of recommendation: I (there is little evidence)

No articles could be found dealing with clinical outcome or change in HbA1c, and recommendations will therefore depend on practical issues locally. Since most patients have a rather short stay in the hospital, it is obvious that studies addressing the question will be difficult to perform.

Does blood glucose point of care testing in the hospital (i.e. secondary care setting) lead to an economic benefit, when compared with central laboratory testing? (Literature Search 38 and 39)

Guideline 65: *We recommend against routinely using POC glucose testing in the hospital setting on economic grounds.*

Strength/consensus of recommendation: C

Level of evidence: II

Three articles were retrieved (68-70). Lee-Lewandrowski (68) found that bedside glucose testing is not inherently more expensive than centralized laboratory measurements, but implementation on inefficient care units with low utilization can add substantially to the cost. Much of the excess cost of the bedside method can be attributed to the high costs of quality control and quality assurance, training, and documentation. Nosanchuk et al (69) compared the operating cost of POC testing for glucose and an electrolyte/glucose/blood urea nitrogen chemistry panel with the cost of central laboratory stat testing in a 204-bed community hospital. In the scenarios studied, POC testing costs exceed central laboratory stat costs from 1.1 to 4.6 times. The more the POC testing is used, the greater the excess costs compared to the central laboratory. Cost analysis demonstrates that the investment in acquiring automated transport and data management systems for the authors' hospital was far less expensive than POC testing for both an individual stat test and on an annual cost basis. Parvin (70) et al addressed if a POC instrument shortened the length of stay of patients at the hospital. The POC testing held device performed Na, K, Cl, glucose and blood urea nitrogen testing. Stratifying patients by presenting condition (chest pain, trauma, etc.), discharge/admit status, or presence/absence of other central laboratory tests did not reveal a decrease in patient length of stay (LOS) for any patient subgroup during the experimental period and the median LOS was 209 min.

The evidence behind the recommendation is rather weak and may be challenged in the local environment. Practicality issues may for example be a reason for introducing POC glucose testing in the hospital, but one should try to document the effect of this intervention.

Does blood glucose point of care testing (primary and secondary care) lead to an improved

patient (clinical) outcome (mother and/or baby) in the case of the pregnant woman with gestational diabetes, when compared to central laboratory testing? (Literature Searches 40 and 41)

Guideline 66: *There is insufficient evidence to recommend for or against routinely using SMBG. The evidence to support our view is both from a systematic review RCT (5) as well as controlled trials without randomization and cohort / case control studies. The evidence is, however, conflicting and our recommendation is therefore of type I, i.e. there is insufficient evidence to recommend for or against routinely using SMBG. If SMBG is going to be used, high quality instruments should be chosen and patients must be educated in the practical use as well as being instructed in how to use the results to monitor their insulin therapy. It seems, however, rational to apply the same policy as for DM type I.*

Strength/consensus of recommendation: I

Level of evidence: II

We found no additional RCTs compared to the five RCTs (71-75) found by Coster et al. (5). Four of these are performed before 1984 and one in 1995 (71). The study from 1995 compared the effect of SMBG before or after meals and found that HbA1c was lower in the after meal monitoring group. The conclusion that this is due to SMBG, however, has been criticised (76).

We did not find any additional non RCTs compared to the six case series studies (77-82) found by Coster (5). These six are all from before 1992. From the present literature it can be summarised (5) that (a) patients with gestational diabetes manage as well with SMBG as patients admitted to intensive control at the hospital and (b) hospital utilisation can be decreased in

patients performing SMBG. Coster et al (5) is, however, reluctant to give any recommendation concerning the use of SMBG, but it is reasonable to think that the recommendations should be similar to those given for type I diabetes. The guidelines reviewed in this document (1,6-8) do not give any specific recommendations concerning gestational diabetes and SMBG.

Does blood glucose point of care testing (primary and secondary care) lead to an economic benefit in the case of the pregnant woman with gestational diabetes, when compared with central laboratory testing? (Literature Searches 40 and 41)

Guideline 67: *There is insufficient evidence of economical aspects to recommend for or against routinely using SMBG in gestational diabetes mellitus. No studies have evaluated the possible economic benefit of SMBG in gestational diabetes.*

Strength/consensus of recommendation: I

HbA1c Testing

The relationship between HbA1c and the mean blood glucose concentration over a period of weeks is now well established (83). Furthermore the role of HbA1c measurement in the management of diabetes is now also well established, largely as a result of the DCCT and UKPDS studies (2,3). Thus it is used as a measure of glycemic control (84), as well as an indicator of the risk of developing the complications associated with poor glycemic control (85,86). The HbA1c level is now also used in many healthcare systems to indicate the overall effectiveness of the diabetes management programs (87, 88). The measurement of HbA1c is now enshrined in several guidelines for the management of diabetes (89-92).

There are a large number of papers on POCT for HbA1c although the majority of them deal with the technical performance of the tests. Most papers describe the performance of the Bayer Diagnostics DCA 2000 system which employs a monoclonal antibody raised against a specific glycosylated amino acid sequence of HbA1c, in a light scattering immunoassay, encapsulated in a plastic cassette. Pope et al evaluated the system and found a coefficient of variation of 1.6% and 2.4% at HbA1c levels of 5.2% and 13.0% respectively. When used by four separate operators the coefficient of variation was less than 3.4%. The mean difference between the DCA and the laboratory HPLC method varied between -0.29% and -0.93% (absolute value) depending on the clinic source of the samples used in the comparison (93). Investigation of the clinical utility of the system in a small number of patients revealed that in half of those studied (9 out of 18) the use of POCT led to a change in treatment. John et al (94) found a within assay coefficient of variation of 1.9 to 3.1% and a between batch value of 2.2%, again with a good correlation of results with an HPLC method. Carter et al (95) studied the performance of the system in the primary care environment and found the performance to be 'valid and reliable'. Guerci et al (96) undertook a multicenter trial and found the system to be 'reliable and easy to use'. More recently other assay for HbA1c at the point-of-care have been developed although at present there are very few publications describing their performance. ECRI (formerly the Emergency Care Research Institute) recently reported on the performance of five HbA1c POCT systems. The evaluation focused on "the analyzers' accuracy, precision, and ease of use and provides purchasing guidance for different types of healthcare facilities" (97).

A search was conducted on Medline from 1990 to May 2004 and the results are summarized in Literature Search 42. A total of 14 papers were chosen for full review after reading the abstracts

from the 123 papers identified, of which 10 were cited in the recommendations. One additional paper was found by hand searching the references from the main papers cited.

Does the provision of the HbA1c result at the point of care lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 42)

Guideline 68: *We conclude that there is good evidence to support the use of POCT for HbA1c in both the primary and secondary care setting. The benefit comes from the diabetes specialist having the result at the time of the patient consultation. This recommendation assumes that the POCT is implemented under proper conditions e.g. trained and certificated operators, quality control and quality assurance and with an analytical system comparable with that used in the central laboratory. The evidence base would benefit from studies conducted over a longer period of time.*

Strength/consensus of recommendation: A

Level of evidence: I and II (two randomized controlled trials and two controlled trials).

There are four independent trials reported, together with a multifaceted health technology assessment, on POCT for HbA1c. Cagliero et al (98) reported on a randomized controlled trial (RCT) involving 201 type 1 and type 2 diabetic patients attending a secondary care diabetes center, in which patients were randomized to a consultation in which the clinician received immediate feedback on the HbA1c result as against the routine service when the result came back from the laboratory at a later date. A total of 37 patients were lost to follow up. The HbA1c results fell in the POCT group at 6 and 12 month follow up (-0.57 ± 1.44 and $-0.40 \pm 1.65\%$ respectively; $p < 0.01$) but did not fall in the control group (-0.011 ± 0.70 and $-0.019 \pm 1.16\%$ respectively; not significant). Thaler et al (99) in a controlled trial studied 1138 diabetic

individuals attending an urban diabetes center found that more appropriate management was achieved in those patients managed with HbA1c results generated by POCT ($p < 0.0001$), with fewer changes in treatment when the HbA1c was $< 7.0\%$, and more when $> 7.0\%$. Over the 2 to 7 month follow up period, the HbA1c levels rose more in the conventional group compared with the POCT group. Miller et al performed a similar study in an urban primary care setting (100) with 597 patients with diabetes. They found that treatment intensification was greater in those receiving POCT, and with increased HbA1c levels. Furthermore the HbA1c levels fell over the course of the study in the POCT group (8.4% to 8.1% , $p = 0.04$, compared with 8.1% to 8.0% , $p = 0.31$). Grieve et al (101) investigated the feasibility of introducing POCT for HbA1c together with other biochemical tests, studying 599 individual patient clinic visits. They found that there were more management changes made in the group of patients who had POCT HbA1c performed compared with the conventional approach, where the results were available at some later date (23 vs 18%) with the larger proportion made in those patients with increased HbA1c levels. They also studied patient and clinician satisfaction using questionnaires and found increased satisfaction levels in those clinic visits using POCT. In a retrospective study of two cohorts of patients attending clinics one using POCT for HbA1c and the other receiving results back at a later date, the mean HbA1c was significantly higher in the cohort receiving the results at a later date (8.66 ± 0.056 vs 7.79 ± 0.058 ; $p < 0.001$). Ferenczi et al (102) in a retrospective review of medical records of new referrals found that those patients receiving care using immediate HbA1c results showed a greater decrease in HbA1c compared to those where the result was communicated back two days later ($1.03 \pm 0.33\%$ vs $0.33 \pm 0.83\%$). Holman et al (103) used an alternative approach sending out bottles for patients to return containing a blood specimen. A total of 74% of the bottles sent out over one year were usable upon return and this

was associated with a reduction of the mean HbA1c result of 0.8% compared with the previous year ($p < 0.001$). It is also possible to bring the patient up to the clinic for phlebotomy the week before, although this may be less convenient for the patient.

There have been many studies on the role of education in diabetes management, the majority of which have dealt with education regarding blood glucose measurement, as well as studies covering aspects of lifestyle. Karter et al reported on the use of an intensive diabetes management program and the relation between blood glucose testing and HbA1c (62). Raji et al (104) reported a randomized trial comparing passive and intensive education and found that intensive education led to a substantial improvement in HbA1c. Levetan et al (105) studied the impact of computer-generated personalized goals in 150 patients using a randomized study design and found that these led to a reduction in the HbA1c. These illustrative studies show the importance of a holistic approach to disease management and the use of HbA1c as an indicator of treatment effectiveness and program compliance, for the clinician and the patient. Intuitively one expects HbA1c to play a role in this process.

Does the provision of the HbA1c result at the point of care lead to an economic benefit, when compared with central laboratory testing? (Literature Search 42)

Guideline 69: *We conclude that there is some evidence to show that POCT testing for HbA1c will lead to an economic benefit. However the data are limited and more detailed studies are required which should focus on the wider benefit of POCT i.e. beyond the immediate costs of providing the test and the change in clinic attendance. The evidence would benefit from studies*

conducted (and impacts judged) over a longer period of time.

Strength/consensus of recommendation: B

Level of evidence: II (randomised controlled trial and control trial, but small numbers)

Economic assessments of the use of diagnostic tests are rare and invariably the economic data are poor. In the field of laboratory medicine the main emphasis has been on the cost per test and there has been little attention given to the wider benefits of testing. The situation is no different in the case of POCT for HbA1c. Cagliero et al (98) in their study looked at the use of a wide range of health care resources including outpatient visits and contact time with staff and found that POCT did not lead to any significant change in the use of resources. Grieve et al (101) found the costs of POCT for HbA1c were higher than the laboratory provided service; when a laboratory analyzer was taken down to the clinic and run by a technologist the costs were marginally higher than the conventional laboratory service. However from an analysis of the retrospective cohort study they found that there was a reduction in clinic visits using the POCT modality (from 2.28 visits per year per patient to a figure of 1.81) which helped to ameliorate the increased cost of testing. The prospective trial of POCT was only undertaken for a three month period and a longer study is needed to provide more robust economic data.

Economic modelling from the DCCT and UKPDS studies do show an economic benefit from intensive glycaemic control with a long term benefit albeit at increased short term cost (106,107). An economic analysis of diabetes care in the Kaiser Permanente healthcare system has shown that improved glycaemic control does lead to an improved economic outcome when judged in terms of the long term benefit (108). This is primarily due to the reduction in hospital costs associated with emergency admissions, increased periods of hospital stay and more clinic visits.

It is only by modelling the use of POCT into this environment that the true economic assessment of POCT can be made.

Does patient self testing for HbA1c lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 42)

Guideline 70: *We cannot make a recommendation here because no studies have been reported.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies addressing the question)

What is the optimal frequency of HbA1c testing? Does more frequent testing lead to better outcomes? (Literature Search 42)

Guideline 71: *There are no studies that have investigated the optimal frequency of POCT for HbA1c and therefore we can only recommend that the guidelines generated from studies using a laboratory service for the measurement of HbA1c are adopted in the POCT setting. There are no studies that have formally investigated the frequency of measurement of HbA1c – in any setting. We therefore recommend that HbA1c testing is performed between 2 and 4 times per year in line with the patient's individual requirements. It is recommended that more frequent testing is required in those patients with extremely elevated HbA1c levels and less frequently in those with levels approaching the reference range.*

Strength/consensus of recommendation: I

Level of evidence: III (opinion of respected authorities based on clinical experience)

A systematic review on the frequency of blood glucose monitoring found that there were no studies which investigated the frequency of HbA1c measurement and its impact on health

outcomes but indicated that testing every 3 months in a type 1 diabetic individual would be reasonable (5).

Fructosamine

A search of Highwire and Pubmed was conducted; the details of the search and findings are summarized in Literature Search 43.

Does the provision of the fructosamine result at the point of care lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 43)

Guideline 72: *Inadequate data are available to determine whether provision of fructosamine at the point-of-care will improve glycemic control.*

Strength/consensus of recommendation: I

Does the provision of the fructosamine result at the point of care lead to an economic benefit, when compared with central laboratory testing? (Literature Search 43)

Guideline 73: *No studies have evaluated the possible economic benefit of fructosamine POCT.*

Strength/consensus of recommendation: I

Does patient self testing for fructosamine lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 43)

Guideline 74: *Published evidence does not support the hypothesis that patient self-testing for fructosamine (compared to central laboratory testing) leads to improved patient outcome.*

There are few published studies and the data are contradictory.

Strength/consensus of recommendation: C

Level of evidence: III

There are four published studies that have evaluated POCT fructosamine measurement in the management of patients with diabetes. The number of patients in most studies was relatively small (≤ 60 in all but one study). One study (109) had no control group and the clinical value of fructosamine cannot be evaluated. A second study (with 25 patients) showed that weekly fructosamine measurement improved glycemic control (110). In contrast, two larger studies (comparing 60 and 140 patients) observed that addition of fructosamine to standard glucose self-monitoring did not improve glycemic control (111,112). In fact, the last study (112) noted a statistically significant benefit in the control group (glucose alone) compared to the study group (glucose plus weekly fructosamine), revealing that adding measurement of fructosamine actually worsened glycemic control.

What is the optimal frequency of fructosamine testing? Does more frequent testing lead to better outcomes? (Literature Search 43)

Guideline 75: *No studies have addressed the optimal frequency of fructosamine POCT.*

Strength/consensus of recommendation: I

Patients performed weekly home fructosamine monitoring in most published studies. It should also be noted that the LXN Corporation InCharge device - used in most of the self-monitoring

studies - has been removed from the market and is not commercially available at the time of writing.

Blood ketones

Does the provision of the blood ketone result at the point-of-care lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 44)

Guideline 76: *In the light of the absence of studies addressing this question we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Level of evidence: II and III

A systematic review of the literature was conducted regarding the evidence for, or against, the clinical appropriateness (e.g., impact on patient outcomes and cost) of POCT for serum ketone measurements. Review of this question extended beyond the question of POCT to encompass the larger question of the utility of ketone measurement in diabetes. As the need to measure glucose, regardless of methodology (lab or near patient testing), in diagnosis and management of diabetes is self evident; at the outset, it was not clear that this concept extended to ketone measurement. As a result, the literature review was designed to address the broader topic of ketone measurement utility in diabetic disease management as well as the appropriateness of POCT for serum ketones.

A Medline search strategy was conducted using either Medical Subject Heading (MESH) or Freetext (FTXT) terms. The strategy is summarized in Literature Search 44 together with the 'hits' obtained.

Due to the vagaries (113) associated with ketonuria testing, the study was limited to serum ketone analysis. Citations that primarily focused on ketonuria monitoring; alcoholic ketoacidosis or reports of new/enhanced measurement methods were not included as part of the final review. Titles and or abstracts were all reviewed with the following questions in mind: Is there an indication that this citation discusses the use of serum ketones in some aspect of patient management OR does the citation reflect, in whatever fashion, a clinical use for serum ketone measurement. Ketones measured in the serum are either acetone (ACE), acetoacetate (AcAc) or beta-hydroxybutyrate (BOHB); however, most of the literature discusses BOHB. No distinction was made between specific ketone measured, method used or vendor represented. 200 citations were culled from this review. Of these 200, 19 citations were identified as most relevant with one of the citations being a brief report in parallel with a more replete later published study; therefore, there was a total of 18 reviewed citations.

In addition, a MEDLINE search for review articles from the past 10 years that discussed diabetic ketoacidosis (DKA) as well as consensus articles on the management of diabetes was performed to assess the current standard of care prescribed to diabetes; 13 citations were collected. In the 18 identified references, eleven studies (114-124) were specific for the use of serum POCT monitoring of beta-hydroxybutyrate (BOHB) levels and seven studies (125-131) discussed the clinical utility of serum ketone measurement based on a reference method.

Of the first group of citations, eight (114-116,118,120,122-124) were primarily studies that evaluated analytic characteristic of POC BOHB meter. All studies showed good accuracy (compared with reference lab result), precision and linearity of results. Three citations (119,121,124) compared near patient testing of serum BOHB levels with urine ketone body (UKB) measurement. All three concluded that serum BOHB was a better marker of ketosis than UKB. The studies reported in (119) and (121) were designed to evaluate BOHB compared to UKB in monitoring of recovery from DKA. Another study (117) compared the efficacy of insulin treatment regimens with cessation of ketosis as measured by near patient testing of BOHB. This was classified as an RCT.

Five citations (115,117,119- 121) looked at some aspect of diabetes with the use of ketones as a marker of disease diagnosis, management, prognosis or treatment. All of the studies were small cohort to anecdotal case reports (comparative studies). Three citations (120,122,130) compared serum BOHB (POCT and/or reference method.) with other biochemical parameters of DKA to determine the necessity, or lack thereof, for serum BOHB testing. A fourth study (123) compared biochemical parameters to serum BOHB with a different intended purpose (to determine if BOHB testing could replace serial measurements of standard biochemical testing). The former three similarly concluded that serum BOHB testing did not add any significant clinical information to the acute management of DKA except to sort out hyperglycemic excursions from DKA and to monitor a potential biochemical endpoint (cessation of ketosis). The latter fourth had a similar conclusion inferred from their discussion and conclusion.

Of the second group of citations (general clinical utility of serum ketone testing), (126) appeared to be a case control study (but classified by the National Library of Medicine as descriptive). Studies reported in (126) and (127) were classified as an RCT. The remainder were either descriptive or comparative. All supported the evidence that ketones were present in individuals with uncontrolled or poorly controlled diabetes. Only one citation (127) attempted to provide an outcomes-based analysis. In this study, patients admitted with clinical DKA who had both ACE and glucose measurements performed had a serum BOHB measurement performed. All (n=44) were positive for BOHB. It was noted that patients positive for ACE had significantly ($p = 0.005$) longer intensive care stays and significantly higher ($p = 0.05$) glucose levels. The study raises, but does not answer, the question that serum BOHB is a better discriminator of disease severity.

Thirteen citations were identified as review articles; consensus statements or practice guidelines for diabetes mellitus and/or diabetic ketoacidosis (132-142). All but two of the citations (132,136) recommended the use of either serum or urine ketones in some part of diabetes management. Six recommend ketone monitoring as an outpatient to detect early DKA in stress or hyperglycemic situations (1,133-136,141,142). Of those, two focused only on outpatient management (113,133). In addition, two citations specifically state that serum BOHB should be used preferably to urine (133,134) with two additional citations favoring serum but stating the need for further studies (1,113). Of the nine citations that discussed inpatient management, two (135,140) raised questions regarding the need for ketone measurement in acute diabetic management beyond diagnosis and a third (138) clearly stated that there was no need for ketone

body measurement in post diagnosis diabetic disease management since other biochemical parameters were clearly superior in monitoring acidosis. An excellent and detailed discussion on the specifics of ketogenesis in diabetes is given in (113).

No grade I studies were identified for ketone analysis in general or, in specific, for near patient analysis. None of the identified citations provided a strong evidence-based argument for the measurement of ketones in patients with diabetic ketoacidosis. There was no identified study that examined patient outcomes associated with performance or non-performance of serum ketone measurement for either methodology of testing (reference or near patient). The majority of references were classified, or classifiable as comparative studies with only two classified as an RCT. Multiple studies gave evidence that supported the argument that serum BOHB levels did not provide any additional information to DKA management than already given by routine biochemical parameters performed as part of the laboratory work up of DKA. There was agreement among all of the first group of citations that in physiologic terms, serum BOHB was a better analyte to measure than UKB and that POCT of BOHB provided results as good as laboratory reference methods. All of the first and second group of citations qualitatively agreed that elevated serum BOHB levels were characteristic for poorly controlled diabetes or DKA. There was consensus among the citations that serum BOHB was a good discriminator between hyperglycemic excursions and DKA. The recommendation (1,114,123,126,128,129) was also given in several citations for serum BOHB monitoring in stress situations such as infection or clinically “unwell” to determine if DKA was imminent.

The standard of care for ketone measurement in diabetic disease management varies by

recommended ketone for measurement and varies dependent on disease condition. There is general agreement that for crisis situations, serum ketone measurement is recommended for confirmation of DKA. Beyond diagnosis, there is varying opinion regarding the utility of ketone measurement in guiding treatment endpoints that range from no mention to unequivocal statements that there is no utility to ketone testing.

Among all identified articles, there was no disagreement on the existence of ketosis in stressed or poorly controlled diabetics. There should be no argument of this point as it supported by the physiology and biochemistry of diabetes. However, there are no studies that clearly support an absolute need for serum ketone measurement in diabetic disease management. There are relative needs such as DKA confirmation and distinction between hyperglycemic excursions and DKA. At home serum ketone monitoring is recommended for “stressed” individuals with diabetes to predict incipient DKA prior to advent of clinical symptoms; however, it does not appear to be practical as part of the daily routine monitoring. POCT inpatient serum ketone monitoring is also recommended to determine the biochemical endpoint of DKA management in light of treatment regimes that are based on degree of ketosis. On the other hand, there are several studies that question the need for serum ketone testing beyond diagnosis as their results are redundant in light of routine biochemical testing (TCO₂ and pH). Serum ketone POCT testing is associated with no harm (except redundant testing) and has qualitative supportive benefits but no data exists in support of an absolute testing indication. The majority of references are based on descriptive clinical experiences and expert opinion. While, a priori reasoning suggests that POCT serum ketone must play a relevant role in diabetic disease management, there are no good studies that demonstrate an absolute need for serum ketone testing in either reference or POCT

modalities.

Does the provision of the blood ketone result at the point-of-care lead to an economic benefit, when compared with central laboratory testing? (Literature Search 44)

Guideline 77: *In the light of the absence of studies addressing this question we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Grade of evidence: II and III

Does patient self testing for blood ketone lead to an improved patient (clinical) outcome, when compared with central laboratory testing?

Guideline 78: *In the light of the absence of studies addressing this question we make no recommendation for or against routinely providing POCT for blood ketones.*

Strength/consensus of recommendation: I

Grade of evidence: II and III

Urine Albumin

Does the provision of the urine albumin result at the point of care (i.e. secondary care setting) in the management of diabetes (e.g early detection of diabetic nephropathy) lead to an improved patient (clinical) outcome, compared with central laboratory testing? (Literature Search 45)

Guideline 79: *There are no studies that have formally addressed the issue of screening for early*

signs of renal disease in patients with diabetes mellitus through the use of urine testing for protein or albumin at the point of care. However there is clear evidence to demonstrate an increase in urinary excretion of albumin associated with early diabetic nephropathy.

Furthermore there are several guidelines that advocate the regular checking of the urine albumin excretion in patients with diabetes mellitus.

Strength/consensus of recommendation: I

Level of evidence: III

The renal complications of diabetes mellitus are classified as follows: macrovascular disease involving the coronary arteries, carotid arteries and peripheral vasculature (e.g, the aortic, iliac, femoral, popliteal and renal arteries); microvascular disease including retinopathy and diabetic nephropathy; and neuropathy including mononeuropathies, polyneuropathies and autonomic neuropathies. The renal complications of diabetes mellitus can be classified as follows: 1) diabetic vascular disease (renal artery atherosclerosis and arteriolosclerosis of afferent arterioles); 2) diabetic nephropathy; 3) increased susceptibility to infection; 4) atonic bladder (autonomic neuropathy); and 5) renal failure from radiocontrast dye where dehydration and dye toxicity can produce acute tubular necrosis. This discussion will focus on diabetic nephropathy.

Diabetic nephropathy involves glomerular damage that contributes to the development of hypertension and renal failure. Diabetic nephropathy affects 30% or more of cases of type 1 diabetes mellitus and 20% of cases of type 2 diabetes mellitus. Diabetes is the most common cause of end stage renal disease (ESRD) in the U.S. (143) Approximately 30% to 35% of dialysis patients have diabetes and 40% of all subjects beginning dialysis are diabetic (143). Despite a

more severe degree of hyperglycemia and a longer duration of diabetes in type 1 diabetes mellitus patients than in type 2 diabetes mellitus patients, more patients with type 2 diabetes mellitus have ESRD and are on dialysis than patients with type 1 diabetes mellitus (144). This is because about 90% of cases of diabetes result from type 2 diabetes mellitus versus only 10% of cases which result from type 1 diabetes mellitus. Renal failure is the second leading cause of death in type 1 diabetes mellitus (145). Cardiovascular disease (CVD) is the leading cause of death in type 2 diabetes mellitus: ~65% of type 2 diabetes mellitus patients will die of heart disease or stroke (146). However with improvements in the prevention and treatment of CVD more type 2 diabetes mellitus patients will live longer (147) and their risk for developing diabetic nephropathy will rise.

The etiologies of diabetic nephropathy include chronic hyperglycemia, hypertension, hyperlipidemia, intrarenal angiotensin II production and familial predisposition (148). The major factors contributing to the development and progression of diabetic nephropathy are chronic hyperglycemia and hypertension. Chronic hyperglycemia produces glomerular basement membrane (GBM) damage and induces mesangial proliferation of both mesangial cells and the mesangial matrix. Either systemic or intraglomerular hypertension (from hyperfiltration and flow shifts from destroyed glomeruli to healthy glomeruli) damages glomeruli and can produce ischemia. Hyperlipidemia is a modest risk factor for nephropathy (149). It is controversial to what degree a family history of diabetic nephropathy predisposes to diabetic nephropathy in the propositus (150). To date, no nephropathy-susceptibility genes have been identified.

Chronic hyperglycemia leads to non-enzymatic glycosylation (“glycation” is the preferred term for non-enzymatic addition of glucose) of many of the body’s proteins (151). Glycosylation of the GBM appears to decrease its negative charge. This impairs the selectivity of the GBM to retain proteins and the GBM becomes ‘leaky’ permitting proteinuria to develop (152). Increased blood volume from hyperglycemia induces glomerular hyperfiltration and produces intraglomerular hypertension. In aggregate, these factors produce glomerular damage. Glomerular damage is manifested in a 3 to 5 fold increased width of the GBM and mesangial proliferation. Thickening of the GBM and mesangial proliferation obliterate capillary loops leading to obstruction of individual nephrons. This ultimate loss of surface area for filtration of wastes produces chronic renal failure.

Glomerular damage and destruction leading to a loss of surface area for filtration leads to waste retention described as renal insufficiency or renal failure if the glomerular filtration rate (GFR) is sufficiently reduced. The National Kidney Foundation (www.kidney.org) defines reductions in GFR as follows:

<u>Degree of GFR decrease</u>	<u>mL/min/1.73 M²</u>
Mild	60 - 89
Moderate	30 – 59
Kidney failure	<15 (or dialysis)

Systemic volume overload (from fluid retention) and possible hyperreninism from diabetic renovascular disease produce hypertension. Hypertension further damages glomeruli through pressure injury and ischemia. A positive feedback loop with worsening hypertension and progressive renal failure ensues.

The earliest biochemical evidence of glomerular injury is minimal albumin excretion (minimal albuminuria, a.k.a.: microalbuminuria). Increased amounts of albumin are excreted because albumin is the most abundant plasma protein. The traditional urine dipstick is negative for protein at such low levels of protein excretion. Microalbuminuria indicates ‘incipient’ nephropathy (143). There are a number of guidelines that recommend screening for microalbuminuria for the early detection of renal disease in individuals with diabetes (153) and in individuals with hypertension (154).

There are 5 proposed stages in the development of diabetic nephropathy in type 1 diabetes mellitus (Table 1):

- I early hypertrophy-hyperfunction
- II glomerular lesions without clinical disease
- III incipient diabetic nephropathy
- IV clinical (overt) diabetic nephropathy
- V end-stage renal disease (ESRD)

Stage I (early hypertrophy-hyperfunction) is present after the diagnosis of type 1 diabetes mellitus and is a consequence of expanded blood volume from hyperglycemia. Hyperfunction relates to hyperfiltration (i.e., an elevated GFR). The kidneys are physically enlarged. Proteinuria is transient. GFR is elevated by 20-30%. With insulin treatment of type 1 diabetes mellitus and control of hyperglycemia, GFR normalizes. All type 1 diabetes mellitus patients progress to stage II nephropathy.

In stage II nephropathy (silent nephropathy), histologic glomerular lesions develop without other evidence of clinical disease. Systemic blood pressure is normal and proteinuria is absent.

Thickening of the GBM and mesangial cellular and matrix expansion occur. Such histological changes are visible after 3 to 5 years of type 1 diabetes mellitus. Progression to stage III nephropathy occurs in ~40% of type 1 diabetes mellitus patients.

Stage III nephropathy (incipient diabetic nephropathy) is recognized by increased albumin excretion [minimal albumin excretion (a.k.a. microalbuminuria)] despite a negative routine dipstick for protein. The low-end analytical sensitivity of the routine urine dipstick for albumin detection, at best, is a urine albumin concentration of 15 mg/dL (usually the urine dipstick lower limit of detection for protein varies between 15 and 30 mg/dL). At a detection limit of 15 mg/dL and a urine output of 2000 mL/day, the dipstick would detect 300 mg/day of albumin excretion or approximately 500 mg of protein excreted. Macroproteinuria is defined as >300 mg of albumin excreted per 24 hours. Microalbuminuria is routinely determined by immunoassay, e.g., radioimmunoassay, ELISA, radioimmunodiffusion or immunoturbidimetry.

Stage III is reached after 7-15 years of type 1 diabetes mellitus and can last for 5-15 years.

Progressive histologic changes occur in stage III nephropathy. There can be mild to moderate hypertension. Without intervention, progression to stage IV nephropathy occurs in ~80% to 100% of type 1 diabetes mellitus patients.

Albumin excretion can be studied and reported as a 24 hour collection (mg / 24 hours; this is considered the 'gold' standard), a timed urine collection (ug / minute) or a spot collection (e.g.,

AM urine) with the albumin to creatinine (Cr) ratio expressed (ug albumin / mg of Cr; or mg albumin / g of Cr). Urine albumin measurements are sometimes referred to as: urinary albumin excretion (UAE). The 24 hour collection is the most difficult sample to correctly obtain. For this reason, the albumin to creatinine ratio is advantageous. Within day variation of protein and albumin excretion is minimized when the ratio is employed (155). The albumin:creatinine ratio also displays good correlation with 24-hour collections (156-158)

All forms of albumin excretion can be measured in central laboratories. At the point-of-care, Bayer Diagnostics offers the DCA2000+ which can measure, in addition to hemoglobin A1c, urinary albumin and creatinine to determine microalbumin excretion using a specially designed cartridge for urine testing. Several studies have demonstrated significant analytical robustness for this system (159-162).

Dipsticks for minimal albumin excretion measurement are also available such as the Micral II (Roche Diagnostics Corp. Indianapolis, IN) (163) and ImmunoDip (Diagnostic Chemicals Limited, Prince Edward Island, Canada). Both of these sticks use antibodies to detect albumin. The Bayer Clinitek bench-top analyzer reads Clinitek Microalbumin strips (Bayer Diagnostics, Medfield, MA) that semiquantitatively determine albumin and creatinine using chemical methods (albumin: sulphonephthalein dye binding at pH 1.5; creatinine: peroxidase-like activity of copper creatinine complexes) (164-166). There are no current references for the Miles Laboratory Micro-Bumintest which was available during the late 1980s (167).

Microalbumin dipsticks measure albumin concentration and show fair to good correlations with standard immunoanalytic methods of albuminuria assessment (143). If such microalbumin dipsticks are positive, they are informative and require central laboratory confirmation. The Micral II dipsticks may be sensitive but display modest degrees of specificity that require central laboratory confirmation (168-170). On the other hand, some studies have found good specificity (92-98%) but lower sensitivity (58-78%) with the Micral II strips (171,172). In the single peer-reviewed publication concerning ImmunoDip, the ImmunoDip device exhibited good sensitivity but a specificity of only 80% (173). The Clinitek Microalbumin strips displayed good sensitivity (~95%) and a similar specificity (~80%) (174). Dipsticks that measure albumin and creatinine may reduce false positives and false negatives (174,175). Guidelines from the National Kidney Foundation state that whereas dipstick detection of proteinuria is adequate, the albumin to creatinine ratio is more reliable (176). Improving availability of any testing modality for proteinuria is desirable (177,178).

Repeated POCT measurements for the detection of minimal albumin excretion may not improve the sensitivity or specificity of microalbuminuria detection (179). Certainly the predictive value of POCT for microalbuminuria is affected by disease prevalence (180). A valid concern is that urine volume variation and sample dilution will produce a false negative result. In development is the 'MicroalbuminuriaNow' test for point-of-care testing. This product is conceived as a single-use, disposable device that can be used by patients at home or in clinics

<http://www.metrika.com/3medical/products.html>.

The theoretical advantage of point of care testing (POCT) is that results are immediately available. Unfortunately there are no data to suggest that the availability of microalbumin results at the time of the patient's visit changes clinical outcome. However in another critical aspect of diabetes management, when hemoglobin A1c results are available at the time of the patient's visit, patients achieve better glycemic control evidenced by subsequently lower hemoglobin A1c values (97-102). POCT for microalbuminuria has been utilized in research studies (181-183) and general practice settings (184) and its performance has been found to be reasonably user-friendly.

Table 2 provides ranges recommended for the interpretation of albumin excretion (143). When the routine urine dipstick is positive, clinical (overt) proteinuria is present.

The American Diabetes Association (ADA) recommends that patients with type 2 diabetes mellitus should be examined for albuminuria at diagnosis, whereas patients with type 1 diabetes mellitus should be examined after 5 years of disease (143). Patients are then tested yearly. Because of the gradual, often subtle onset of type 2 diabetes mellitus and the frequent delay in the diagnosis of type 2 diabetes mellitus, based on the recognition of symptoms alone, many patients have had long periods of unrecognized diabetes that can contribute to type 2 diabetes mellitus subjects already having significant albuminuria at disease diagnosis (185).

To reduce the cost of testing for albuminuria, many laboratories will screen all urines submitted for microalbumin testing by initial dipstick screening. If the dipstick is positive, macroproteinuria, by definition, is present. In this case with the routine dipstick being positive

for protein, a 24 hour urine should be collected for measurement of protein excretion and calculation of creatinine clearance. A repeatedly positive routine dipstick for protein indicates stage IV, clinical (overt) nephropathy (see below).

If the routine dipstick is negative, albuminuria is sought by any of the 3 accepted approaches outlined above. According to the ADA, if the albumin excretion rate is normal, the test should be repeated in one year. If increased minimal albumin excretion is detected, the test should be repeated to confirm the finding in the next 3 to 6 months. If minimal albumin excretion is identified in two out of three tests, microalbuminuria is diagnosed consistent with incipient nephropathy.

In a report (No. 84) from the Agency for Healthcare Research and Quality (AHRQ), the clinical relevance of elevated urinary albumin excretion was linked to increased risk of progression to ESRD, increased cardiovascular morbidity, increased cardiovascular mortality and increased total mortality (86). Furthermore, this AHRQ publication reported that the risks associated with microalbuminuria are graded: higher levels of urine albumin excretion are associated with greater degrees of declining renal function and faster rates of declining renal function. Higher levels of urine albumin excretion are associated with a greater magnitude of risk for cardiovascular morbidity, cardiovascular mortality and total mortality.

When microalbuminuria is confirmed, therapy to delay or prevent progression of nephropathy should be instituted. According to the ADA 2004 Clinical Practice Guidelines (143), the key interventions are 1) improve glycemic control, 2) initiate of anti-hypertensive therapy in

normotensive and hypertensive patients using either angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB), and 3) restrict dietary protein (0.8 g/kg/day).

There is strong evidence that anti-hypertensive treatment decreases the likelihood of progression from incipient nephropathy to more severe forms of nephropathy (186-188). The drug class of first choice is the angiotensin-converting enzyme inhibitors. In addition, benefit has been shown in type 2 diabetes mellitus patients treated with angiotensin-receptor blockers (189). If these drugs are not tolerated, non-dihydropyridine calcium channel blockers (NDCCB), beta-blockers or diuretics should be therapeutically considered.

Stage IV nephropathy [ie., clinical (overt) diabetic nephropathy] displays dipstick-detectable albuminuria and albumin excretion increased above minimal levels (Table 1). Stage IV nephropathy occurs after an average duration of diabetes of 15 to 17 years with a range of 10 to 30 years. Decreasing renal function is observed as a declining GFR. Hypertension is routinely present. There is increased risk for coronary heart disease and mortality with a 100 fold increased risk. Retinopathy is almost always present. Progression to stage V nephropathy is observed in ~75 to 100% of stage IV type 1 diabetes mellitus patients.

With persistent proteinuria (stage IV), the 5 year survival rate is 65%, the 10 year survival rate is 28% and median survival is 10 years. Death usually results within 20 years from renal or cardiovascular causes. In summary, stage IV diabetic nephropathy is a clinical syndrome of

sustained, high-level albuminuria (proteinuria), hypertension and progressive renal insufficiency when action is not taken to halt nephropathy.

Stage IV nephropathy histologically is characterized by progressive glomerulosclerosis. Diabetic glomerulosclerosis is characterized by thickened GBMs and mesangial expansion. Over time, diffuse diabetic glomerulosclerosis evolves into nodular diabetic glomerulosclerosis. Nodular lesions within the glomeruli are referred to as Kimmelstiel-Wilson nodules or lesions. Tubulointerstitial disease is also possible in cases of diabetic nephropathy noted by the presence of hyperkalemia and a type IV renal tubular acidosis.

The value of annual microalbumin measurements following the diagnosis of incipient nephropathy and the institution of therapy is controversial. Serial GFR measurements should be obtained to assess glomerular function in patients with diabetic nephropathy (178). Transient elevations in albumin excretion can follow short-term hyperglycemia, exercise, urinary tract infection, marked hypertension, heart failure and with acute febrile illnesses. Microalbuminuria is best sought when these conditions are absent or are under control to avoid false positive tests for microalbuminuria.

Stage V nephropathy is characterized by the development of ESRD. Azotemia (e.g., the retention of nitrogenous wastes with an elevated BUN level) prestage uremia and oliguria. Uremia is the clinical syndrome that results from renal failure that includes increased fatigability, headache, anorexia, nausea and vomiting, diarrhea, hiccups, restless and depression. The signs of uremia encompass epistaxis (nose bleeds), melena (blood in the stools), dyspnea (shortness of breath),

irregular start-stop breathing, halitosis, dehydration, muscle twitching, seizures and delirium. Biochemical findings in addition to elevated blood urea nitrogen (BUN) and creatinine (in an approximate 10:1 ratio) include systemic acidosis (low serum CO₂), hyperkalemia, hyperphosphatemia, hypocalcemia, normocytic normochromic anemia and urine specific gravity usually <1.010 to <1.012. Untreated, uremia progresses to coma and death.

ESRD eventually requires dialysis or transplantation. Stage V nephropathy is reached after 20 to 40 years of diabetes and usually develops 5 to 7 years after the onset of stage IV nephropathy. Ultimately, 75% of ESRD cases occur within 10 years of dipstick positive proteinuria.

New methodologies are being developed for the determination of urinary albumin (190). Earlier markers of progressive nephropathy are being sought. Elevations in nocturnal blood pressure appear to precede the appearance of microalbuminuria (191). As well, albumin excretion measured by HPLC has demonstrated higher rates of microalbuminuria and earlier onset of microalbuminuria in diabetes than immunologically-measured albumin determinations (192-194). Thus HPLC can detect both non-immunoreactive as well as immuno-reactive albumin. This is a developing field that bears review.

The field of microalbumin testing and diabetic nephropathy is not without controversy. One recent paper reported a high frequency of renal insufficiency in type 2 diabetes in the absence of albuminuria (195) whereas another paper reported that microalbuminuria frequently does not progress to more severe degrees of renal impairment (196).

Finally, up to at least 2001, “no controlled trials of screening to prevent progression to nephropathy or that compared sequential repeated screening strategies were identified” (188). A search of PubMed (see Literature Search 45) and selected recent review articles did not reveal any controlled trials of screening to prevent progression to nephropathy.

Does the provision of the urine albumin result at the point of care (i.e. secondary care setting) in the management of diabetes (i.e early detection of diabetic nephropathy) lead to an economic benefit, when compared with central laboratory testing? (Literature Search 45)

Guideline 80: *From the one available study, POCT for microalbuminuria with central laboratory confirmation of microalbuminuria is more expensive than testing alone, recognising that this only takes into account the marginal cost of testing.*

Strength/consensus of recommendation: I

Level of evidence: II (evidence from well designed case control study)

It is only a possible postulate in the absence of any formal trials that there will be an economic benefit to be obtained from POCT for microalbuminuria, although it is assumed that clinician and patient benefit will result in some economic benefit

Does patient self-testing for urine albumin (i.e. primary care setting) lead to an improved patient (clinical) outcome, when compared with central laboratory testing? (Literature Search 45)

Guideline 81: *in the absence of data on self testing for microalbuminuria, there is no basis to recommend for or against this practice.*

Strength/consensus of recommendation: I

There is no evidence of studies investigating the use of self-monitoring of albuminuria and therefore it is not possible to provide an answer to this question.

What is the optimal frequency of urine albumin testing? Does more frequent testing lead to better outcomes? (Literature Search 45)

Guideline 82: *In the absence of any data on the frequency of POCT for microalbuminuria it is not possible to make any recommendation on this point, and that guidance should be sought from the guidelines documents that have been published on testing for microalbuminuria in diabetics*

Strength/consensus of recommendation: I

Level of evidence: III (opinions of respected authorities based on clinical experience)

It has been suggested that type 1 diabetics should be screened on an annual basis starting about five years after initial diagnosis. In the case of type 2 diabetes screening should begin immediately after diagnosis. In the event of an abnormal result being found then two further tests should be undertaken and if two of the results are found to be abnormal then a 24 hour collection should be undertaken to confirm microalbuminuria. These guidelines have been devised with POCT in mind.

In drawing together the conclusions from this review of the evidence on point of care testing in the diagnosis and management of diabetes mellitus the reader is referred back to an observation made at the commencement of this discussion, namely that *'absence of evidence of effect does not constitute evidence of absence of effect'*. It has been acknowledged on many occasions in the literature, that generating data on the outcomes from the use of 'diagnostic tests' with robust

study design can be extremely challenging. This is particularly true in the case of a complex condition such as diabetes mellitus, where, in the management of the condition, the test and the intervention are intimately linked and it is the combined use of test and intervention that yields an improved health outcome. In addition, it is also recognised that it can be difficult to design studies that minimise the risk of bias in the study results, as with the use of a randomised controlled trial. Thus as has been suggested in earlier systematic reviews of aspects of diabetes care (e.g. ref 5), that it may be necessary to look at other types of study design e.g. observational studies. This effectively looks at a package of care, and measures taken to involve the patient in managing their own health care. In this respect it is worthy of note that many of the current guidelines on the management of diabetes mellitus indicate the use of ‘diagnostic tests’ as part of an ‘integrated package of care and ‘taking account of patient’s needs and expectations’. Further research is needed on the use of point of care testing, as part of an integrated package of care in the management of diabetes mellitus.

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Public Comments:

No public comments were received on the guidelines.

Table 1. The Five Proposed Stages of Diabetic Nephropathy in type 1 diabetes mellitus

Stage	GFR	MA (UAE)	Dipstick Proteinuria	BP
I: Hypertrophy-hyperfunction	Incr.	NI	Transient	NI
II: Glomerular lesions				
without clinical disease	NI	NI	Negative	NI
III: Incipient DN	NI	Incr.	Negative	+/- Incr.
IV: Overt DN	Decr.	----	Positive	Incr.
V: ESRD	Very Decr	----	Positive	Incr.

UAE: Urinary albumin excretion; ESRD: End stage renal disease; Incr.:increased; NI:normal;
+/-: possibly; Decr:decreased

Table 2: Albuminuria: definitions

	Nephropathy Stage	24H		Spot
		Timed collection		Alb/Cr
		ug/min	mg/24H	ug/mg
Normal	---	<20	<30	<30
MAU*	III	20-199	30-299	30-299
Clinical Albuminuria**	IV	=>200	=>300	=>300

* Microalbuminuria (ie., minimal albumin excretion)

** aka: overt (clinical) diabetic nephropathy; dipstick (+)

Chapter 7: Drugs and Ethanol

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Detecting substance abuse using point of care testing (POCT) is a multi-million dollar business. Generally, such testing is performed using urine as the sample and targets the more commonly abused substances. The purported flexibility and ease of use makes these devices attractive for use in a variety of settings and by an equally varied range of users. These guidelines will focus on the use of POCT for drugs of abuse in medical and non-medical settings. Issues of training, quality control, economics, and accuracy will be addressed, as will limitations. As will be emphasized throughout this document, these devices are designed to screen for the presence of

designated drugs or groups of drugs. None are intended to serve as confirmation tests. The document will not address the broader issues or questions of urine drug screening; however those interested may find some of the issues associated with such testing in the medical setting discussed in the Emergency Toxicology LMPG.

After the initial questions were agreed upon, we found it necessary to perform a broad literature search in order to identify a sufficient number of papers for review. Pairs of members assessed the papers on the basis of the abstract to identify 100 manuscripts for full review. Additional papers referenced in the reviewed papers were identified and read. All reviewed papers were rated for relevance to particular questions. Members also consulted their personal manuscript collections. The search strategy used is presented in Literature Search 46.

For many settings, the availability of POCT devices designed to detect abused drugs in urine is an attractive alternative to collection, transport and subsequent laboratory analysis. POCT devices are available in a range of formats from dipsticks to cup devices, cards or plastic cassettes. The amount of sample needed for testing ranges from a few drops of urine to ~30 mL. Currently, all devices are immunoassay based and, as such, designed to screen for the presence of defined drugs of abuse. Devices are available for the detection of a single drug or drug class, as well as for the detection of groups of drugs, i.e., cannabinoids and cocaine and amphetamines. As with laboratory-based methods, most are designed to detect drug metabolites instead of the parent drug. Following practices stemming from workplace drug testing, a positive result is obtained when the drug(s) or metabolite of interest is present at or above a designated concentration, i.e., the cut-off.

Unlike the automated immunoassay-based laboratory methods for serum/plasma, where primary tube sampling is applicable, though urine may need to be transferred, most of the steps for POCT require operator intervention: these include sample application (and if required, subsequent transfer of the sample to another portion of the device), timing of the reaction, reading/interpreting the visual endpoint, and recording/documenting the result. Turnaround times from initial sample application to a result are 15 minutes or less. The visual endpoint derived is dependent upon the technological approach and will be discussed shortly. Currently, there is only one commercially available system that provides a semi-automated assay and a printable report or record of the result(s). For other devices the operator is responsible for all manipulations of the sample, reagent application, timing as well as interpretation and recording of the results, including quality control indicators.

Although the devices can be classified as those utilizing agglutination reactions, chromogenic antibodies, fluorogenic or chromogenic drug-conjugates, it is more common to see the devices separated according to the visual indicator generated when drug is present at or above the designated cut-off. Unlike for other qualitative POCT applications, most POCT devices for drugs of abuse give a negative visual sign when the drug of interest is at or above the defined threshold. In other words, the absence of a line or color means the test result is positive while the development of a line or color indicates the drug is below the threshold. At this time, there is one device that indicates the presence of the drug of interest with the appearance of a line.

Sample preparation and testing: The simplest devices combine the collection and testing device; but for most devices, the operator must perform multiple steps in handling and transferring the sample. Freshly collected urine with no evidence of turbidity and sediment appears optimal for these devices. Samples containing sediment or that are visibly turbid are poorly absorbed into the testing area. (1,2). For such samples, pre-centrifugation may be necessary for proper sample application.(1,2) In one study, poor absorption was felt to contribute to the occurrence of false negative results (1).

Generally, the literature is dominated by method validations or evaluations (1,3-18). In these, urine samples were tested using the POCT device(s) and the result(s) compared to those results obtained using an instrument-based immunoassay. For many of the studies, the practice of pre-screening samples to assure the inclusion of a range of drugs and drug levels automatically induced a selection bias. The outcomes on which the comparisons were made included concordance between devices or with the comparator immunoassay methods, sensitivity, specificity, efficiency, and ease of operation. These studies were usually designed to include confirmation of the presence of the drug of interest using gas chromatography/mass spectrometry or high-performance liquid chromatography. However, in the majority of studies, only discordant samples were evaluated in this manner. Very few studies confirmed the absence of drug or did so only randomly. Generally, testing was performed using trained laboratory personnel under laboratory settings with only a few studies using non-laboratory analysts in non-laboratory settings.

No POCT device yielded 100% concordance with the comparator method. Disagreement between methods was highest for samples near the designated thresholds. In some multi-device evaluations, different devices used different thresholds or cut-offs making comparisons difficult. There was limited discussion or recognition of variability in antibody specificity. Antibody specificity appeared to have the greatest impact when testing for amphetamines, opiates and benzodiazepines; i.e. classes containing multiple drugs or compounds of interest. For the amphetamine and opiate classes, confirmation was usually based upon NIDA (SAMHSA) criteria using specified target analytes and concentrations with no evaluation of other amphetamine compounds (ephedra, MDMA, etc) or opioids (hydrocodone, oxycodone, etc). Disagreement also depended upon the use of synthetic samples as opposed to human-derived samples containing metabolites or related, cross-reacting compounds. We found 5 prospective studies conducted in non-laboratory settings. Three were conducted in medical settings and included evaluations of patients presenting to a pain clinic, (10) an obstetrics service, (19) and an emergency department. (20) Two were conducted in law enforcement settings evaluating drivers suspected of intoxication and driving under the influence (5,21).

Are there significant differences between POCT devices?

Guideline 83: *The currently available POCT devices for screening urine samples for drugs of abuse differ from each other in terms of sensitivity and specificity. Once the potential need for POCT is established, a careful evaluation should be conducted by the staff in the environment in which the devices are to be used and on the relevant population.*

Strength/consensus of recommendation: A

Level of evidence: II

The majority of literature concerning POCT for drugs and ethanol are simple comparisons between POCT and laboratory methods. Differences in analytical performance, ease of use, accuracy and reproducibility abound (4-7,9,10,15,16,18,22-30) with the more recently developed devices generally comparing more favourably with laboratory based methods.

When a site is considering implementing such testing, it is important that the evaluations be conducted using the staff who will perform the testing and under the conditions in which the testing will be performed (10); this advice is often ignored in evaluations so that laboratory staff perform the evaluations, but nursing or others perform the routine testing.

What analytical accuracy issues impact the use of POCT devices?

Guideline 84: *Users of POCT devices should understand any limitations of the devices. This should include the statistical and analytical sensitivity, specificity and nomenclature of the devices to facilitate their appropriate use.*

Strength/consensus of recommendation: A

Level of evidence: I

Initial screening techniques, even in a controlled laboratory environment, may give rise to both false positive results and false negative results (31). These findings have been reproduced in the evaluation studies of several POCT devices for urine (6,16,22,32) and saliva (33).

The efficiency of drug detection by POCT devices has been shown to vary according to the drug being monitored (32), or the specific device being used (6,16,22). It has been concluded that POCT device sensitivity may be the most important parameter governing their use (22) but

discrepancies exist between claims and performance of POCT devices (16), and their effectiveness in detecting illicit drug use has been questioned (6).

What knowledge of cross-reactivity of POCT devices is required for their use?

Guideline 85: *Users of POCT devices need to be aware of any known interferences from drugs or metabolites that could impact results interpretation.*

Strength/consensus of recommendation: A

Level of evidence: I

POCT devices for drugs are based on immunoassay technologies, and it is vital that users understand their strengths, weaknesses, and limitations to facilitate accurate results interpretation (34). This is especially true in the case of false positive results arising from cross-reactivity with foods, over-the-counter preparations, commonly prescribed drugs, and/or their metabolites that may also be present in the specimen being screened (35). If such limitations are not recognized, then the potential for inaccurate or inappropriate interpretation increases significantly. This is exacerbated where misleading nomenclature is used by manufacturers of POCT devices, causing false positive reports (6).

What are the chief quality issues associated with POCT?

Guideline 86: *Purchasers of POCT devices should ensure users are correctly trained in their use, application and interpretation. This training should include quality issues and recognition of any device limitations.*

Strength/consensus of recommendation: A

Level of evidence: I

The ever-increasing demand for more rapid results availability in certain clinical, employment, and urgent medical situations has resulted in the increased use of POCT devices (36). There are several important quality aspects surrounding the use of POCT technology that need to be taken into account. These include:

- 1) The accuracy (in terms of analytical sensitivity and specificity) of the POCT technique
- 2) The cross-reactivity of POCT assays with drugs and metabolites not under investigation
- 3) The impact of chemical interference or adulteration on POCT devices
- 4) The issues of quality assurance and quality control
- 5) The appropriate interpretation of POCT technique results
- 6) The impact of physiological variables
- 7) Use of acceptable confirmatory methods

What knowledge of adulteration is required for the use of POCT devices?

Guideline 87: *Users of POCT devices need to be aware of any known interferences from chemicals and other methods of adulteration/manipulation that could impact results interpretation. Procedures need to be adopted within a protocol framework to ensure specimens are tamper-free. In critical situations the type of POCT chosen should enable the tester to detect manipulation by the donor.*

Strength/consensus of recommendation: A

Level of evidence: II

Not only do staff using POCT devices need to be aware of the potential problems raised by cross-reactivity to drugs and metabolites, chemical adulterants can render the test devices inaccurate (37-41) A recent study demonstrated the impact of potential interferents in breath that

could give rise to false positive alcohol results on the evidential infrared-based breath testing device, the Intoxilyzer-5000 (37).

With regard to urine screening, the use of nitrites has been demonstrated to have little or no marked impact on the results generated by POCT devices, but could render the GC-MS assay used to confirm the screening results inaccurate, leading to the assumption that the POCT device had produced false positive screening results. This is especially true for cannabinoids (39,40). The adulterant “Stealth” has been shown to cause negative results in samples spiked with the carboxylic acid metabolite of cannabis, LSD, and morphine at between 125% and 150% of analytical cutoff (38).

A survey of 50 urine specimens submitted for workplace drug testing under chain-of-custody conditions found that 2 specimens contained another product, pyridinium chlorochromate or “Urine Luck” designed to invalidate urine drug screening assays (41). Other manipulations include dilution by drinking excess water, sample substitution and claims of legally obtainable substances that would give positive results e.g. the poppy seeds causing positive opiates. Devices such as TesTcup aid collection, by the incorporation of a thermometer cup that can be used to monitor that the sample is close to body temperature at the time of collection (19).

Are there significant differences between POCT and Central Laboratory Testing?

Guideline 88: *POCT for DOA or ethanol may provide adequate information for clinical intervention. Where a definitive penal or legal action is to be taken, laboratory confirmation is mandatory.*

Strength/consensus of recommendation: A

Level of evidence: I

Are there significant differences between POCT and Central Laboratory Testing?

Guideline 89: *POCT screening can be effective provided quality and data recording issues are addressed. The cost/economic impact needs consideration prior to introduction. Recording of data is vital and a legally defensible approach is advised.*

Strength/consensus of recommendation: A

Level of evidence: III

Are there significant differences between POCT and Central Laboratory Testing?

Guideline 90: *There is insufficient evidence for or against specimen stability as a justification for testing location.*

Strength/consensus of recommendation: I

Level of evidence: III

In answering this question it must be recognized that no POCT device is designed to serve a confirmatory role. These devices are designed to be used in a screening role and can only be compared to similar immunoassay based systems in the central laboratory. When comparisons are based on methods with similar analytical performance in terms of specificity and sensitivity, there is little difference.

The main difference between central laboratory testing and POCT is the reduction of time involved between sample collection and testing completion. However this is not an acceptable justification for POCT if the quality of results is compromised (10,24). Unfortunately, there is evidence that in the non-laboratory settings, the performance of quality control and quality assurance practices fall short of central laboratory standards (24,25). Data recording from typical POCT devices must usually be performed manually and is poor (10) in contrast to central laboratory testing where data are typically captured on a laboratory computer system. Devices are reaching the market-place that are read by meter and may be interfaceable to an information system.

An additional consideration is cost. POCT devices have a fixed unit cost, which often considerably exceeds those using laboratory-based methods at full costing. Thus the economic/clinical/penal/liability relevance of POCT should be carefully established and frequently reviewed. There is surprisingly little evidence on the economics of POCT for drugs and ethanol although cost and economic issues are central to any decision on POCT use.

While early studies suggested that POCT could supplant laboratory testing, many authors and manufacturers advise performing GC/MS confirmation prior to taking definitive or punitive actions (e.g. child protection issues) (27).

Is there an evidence base to confirm that POCT devices perform adequately at detection limits/cut-offs?

Guideline 91: *The cut-off(s) should be considered in the selection of a device as these will*

impact the number of samples requiring confirmation. The statistical likelihood of obtaining a negative result for a sample containing drug near the cut-off should be defined by the manufacturer and presented so that the user who is not a laboratorian can understand the implication of false negative results. Validation studies during selection and implementation should include testing of the defined cut-off.

Strength/consensus of recommendation: A

Level of evidence: III

Unlike for most other analytical tests, the cut-offs used in DOA testing vary. Some are based upon the analytical performance of the method but others are determined by governmental or regulatory agencies. Some POCT devices were found to be comparable in terms of the performance near the stated cut-offs (5), while others did not perform adequately. (4,16,20,24). Another issue was the lack of data to support continued performance over several lots of devices.

What is the impact of quality assurance and quality control on POCT screening?

Guideline 92: *All users of POCT devices must use QC material and participate in EQA proficiency schemes.*

Strength/consensus of recommendation: A

Level of evidence: I

The error rates (false positive and negative results) associated with all immunoassay techniques, including POCT devices, results in the recommendation of participation in external quality assurance (EQA) programs (31) regardless of the setting and requirements. As testing for drugs of abuse in urine may have medical and legal implications, false positive results must be

identified. Continuous participation in EQA programs enables this process (42). It is only by demonstrating continued accuracy and competence through such programs that the results obtained from the analytical testing system can withstand legal scrutiny (43).

There have been several reports from EQA scheme organizers illustrating the level of false positive and false negative results obtained from the testing of submitted urine specimens (44-47). These audit reports have commented on the improvement in accuracy with time, and the fact that some of the false positive results could have a marked impact on the diagnosis and treatment of individuals.

In addition to EQA participation, there will also be the need for local quality control (QC) of POCT testing devices to ensure they are fit for purpose and produce accurate results in the hands of the individuals using them. This must occur before applying them to the analysis of urine from patients or employees. However, this may prove difficult when the POCT site is remote from any source of QC material or advice on its interpretation (36). This aspect of assay validation typically requires local laboratory involvement and control.

Guideline 93: *The decision to use POCT should be a formal Corporate decision following a formal evaluation process of the options to ensure fitness-for purpose. Only authorized, trained, competency assessed staff should be allowed to perform POCT within agreed governance arrangement.*

Strength/consensus of recommendation: A

Level of evidence: III

Although often missed, it should be remembered that it becomes the responsibility of the POCT device user to generate an analytically appropriate test result. This takes the responsibility away from the Laboratory and places it firmly on the shoulders of the POCT user. It can therefore be seen that the single most important quality issue surrounding POCT devices is the initial and on-going training of the individual(s) performing the testing to maintain competency. Therefore there is both a corporate and a personal liability arising from the use of POCT. Corporate procedures for governance ensuring initial and continuing application and training and fitness-for-purpose must be established and be clear.

Are there specific quality issues around interpretation of results obtained from POCT devices?

Guideline 94: *Procedures must be agreed and in place to ensure only those recognised by the organization as being competent to interpret POCT results do so. The consequences to the patient/client, analyst and corporation must be recognised*

Strength/soncensus of recommendation: A

Level of evidence III

Formal studies on this issue are lacking. However users of devices have to be aware of specificity issues; they cannot judge the degree of positivity, or negativity, nor can one determine if someone has re-used a drug. This is particularly true for substances with slowly eliminated metabolites. Physiological variation in the concentration of urine or pH may result in a positive result following a negative without re-use. Inappropriate interpretation may carry penalties just as much as an incorrectly performed analysis.

Are there specific quality issues for POCT versus central laboratory testing (CLT)?

Guideline 95: *All analyses, whether POCT or CLT must be subject to quality control and quality assurance. This should encompass a quality system that includes effective training, record keeping and review.*

Strength/consensus of recommendation: A

Level of Evidence: II

While anecdotal evidence of poor POCT practice and result utilization abound, there is little systematic evidence. Poor training of POCT testers is a common theme, (5) (18) and though there may be significant differences in skill levels in different countries, (48) some users find the analytical aspect of POCT acceptable, but dislike the quality and record-keeping aspects. (10) CLT staff are often highly trained and therefore a more robust and consistent performance can be anticipated.

There are no systematic evidence-based studies on the quality of POCT for drugs of abuse; regrettably few users of POCT devices participate in external quality assessment schemes, so long term assessment of performance ‘in-use’ is not available.

Use of POCT for Drugs of Abuse in the Clinical Setting

What is the effect on outcome of rapid drug screening in emergency departments?

Guideline 96: *While immediacy of POCT drug testing results is generally thought to be useful in an ED, this has not been systematically documented in outcome studies. Therefore no*

recommendation can be made at this time.

Strength/consensus of recommendation: C

Level of evidence: I (randomized controlled trials)

The value of drug testing in emergency departments is controversial and has been addressed previously in an NACB Evidence-Based Laboratory Medicine Practice Guideline, available at http://www.nacb.org/lmpg/emtox_lmpg.stm. Although several studies assumed or hypothesized that the availability of a more rapid result would improve patient care by reducing the time for clinical decision and implementation of therapy, no study actually tested the hypothesis using any measurable outcome (20,27). It should be noted in this context that as clinical intervention is the goal, confirmation by GC-MS is not required.

In a pediatric emergency department (ED) cocaine detection showed higher concentrations in older children (>13 years) and lower concentrations in younger children (< 7 years) probably due to passive exposure. While advocating the use of POCT for better disposition from the ED, and even referral to Child Protection Services, none of these outcomes were tested or observed (20). Other similar studies make assumptions about the impact of drug abuse, but do not test these hypotheses against outcome (27).

Guideline 97: *There is little cumulated outcome literature to support POCT for drugs of abuse in out-patient clinic and out-reach clinical settings. While there are situations where utilization of POCT may enable faster decision making regarding patient disposition, as in an Addiction Clinic, there is little evidence to support this, and therefore introduction and use should be*

circumspect.

Strength/consensus of recommendation: I

Level of evidence: III

Is POC drug testing useful in maternal-fetal medicine?

Issues in obstetrics include the impact of abused substances on the physical development of the fetus, teratogenic effects, and the risk to fetal integrity and/or physical risks to the mother. In the latter, identification of drug using mothers enables referral for treatment and an opportunity to intervene to improve outcome for mother and fetus. Subsequently, a successful live birth may require detoxification of the baby.

Guideline 98: *There currently no evidence base for the benefit of POCT for drugs of abuse in obstetric and pain clinics.*

Strength/consensus of recommendation: I

Level of evidence: III

Is POC drug testing useful in pain management?

In a pain management clinic testing is required to both assure compliance and to identify abuse of non-prescribed drugs. Drugs of interest in these clinical setting include benzodiazepines, and opioids such as oxycodone, methadone, hydrocodone, hydromorphone, and morphine. There were no studies identified that addressed the use of POCT in this setting, nor is its use in this setting common practice.

Is POCT drug testing useful in detoxification clinics?

Testing in such clinics has a two-fold goal: To determine what substances an individual is using (this can be a check on their veracity) in order to confirm the completeness of abstinence from drug abuse, and to confirm compliance with prescribed therapy. Diversion of prescribed medications such as methadone or oxycodone from the individual prescribed the medication to another is a public health problem. Testing to detect diversion is difficult using screening techniques. Confirmatory testing is often necessary to attain the specificity and sensitivity needed.

Guideline 99: *In settings where testing is for the purpose of monitoring compliance, the user must be aware of the possibility of sample adulteration/manipulation.*

Strength/consensus of recommendation: I

Level of evidence: III

There is insufficient evidence upon which to base a recommendation for or against the use of POCT devices for detecting drugs of abuse in the above outpatient clinical settings. While much of the literature describing method evaluations makes assumptions about the benefits of using POCT devices, there is no evidence supporting a difference in pregnancy outcome or referral for treatment (in obstetric clinics), or compliance in pain management clinics and addiction medicine/drug treatment programs. (6,49)

We identified one study comparing POC testing for drugs of abuse in an inpatient drug treatment detoxification, unit. (10) Concordance for results generated by nursing staff with those determined in laboratory was 82% for cocaine and THC. The nursing staff considered the quality

control and record keeping to be too time consuming, and had the opinion that on-site testing in this environment had no advantage in improved patient care.

One study addressed alcohol testing in a short (6-8 h) stay detoxification unit comparing tests using blood, breath, urine, and saliva. The investigators reported that some highly intoxicated subjects had difficulty producing a sufficient saliva specimen. Quantitative saliva ethanol concentrations did not correlate well with blood alcohol, especially at high concentrations ($r=0.75$). Results of alcohol testing did not alter patient management. (50)

One issue not addressed was that of adulteration, a well-recognised phenomenon in some settings. As POCT devices are immunoassay based, they are susceptible to many of the same interferences as laboratory based immunoassays and false negatives are possible.

What is the evidence from the literature on the need for confirmation from different population groups?

Guideline 100: *Clear guidelines should be developed regarding the need to confirm positive test results using a more sensitive and specific laboratory method particularly for situations where definitive punitive action will be taken based on the result. In clinical settings where treatment may be based upon non-confirmed results, staff using the data should be educated with respect to the limitations of the testing.*

Strength/consensus of recommendation: A

Level of evidence: I

In clinical practice the identification of the ingested drug by class may be sufficient to enable appropriate intervention. Using POCT theoretically allows more rapid actions. In some situations, including those in which the patient/client acknowledges use, action or response may be acceptable without confirmation. However, where there is likelihood of a legal/penal action—*e.g.* referral to Child protection agencies, loss of employment, imprisonment, etc. —then confirmation is strongly recommended, as is typically stated in the POCT device manufacturers' literature. As discussed previously, these screening devices suffer from the same limitations as the central laboratory immunoassay-based screening methods: antibody specificity is not 100%. It is surprising that some authors do not understand the limitations of POCT devices and the potential legal pitfalls (51), though some do (2,6,7,9,12,16,25,52).

Urine versus alternative matrices

Does the matrix (blood/serum/plasma, saliva, sweat, urine, meconium) affect acceptability for POCT for drugs and what is the evidence supporting this recommendation?

Guideline 101: *Urine is the best established matrix for POCT. Cut-off levels, interferences and interactions have been established and studied more in urine than in testing with other matrices.*

Strength/consensus of recommendation: A

Level of evidence: I

Guideline 102: *If alternate matrices are to be used for POCT, the antibodies and cut-offs must be optimized to detect the parent drug or metabolite most abundant in that matrix. Evidence of*

accuracy and precision must be documented. Sample sites and collection methods for oral fluid, sweat and breath must be standardized. Sweat sample contamination issues must be resolved before sweat can be considered an acceptable testing matrix.

Strength/consensus of recommendation: I

Level of evidence: II

Guideline 103: *Reports using oral fluid for drug screening by POCT demonstrate unsatisfactory results for certain drugs, especially for opiates, THC and benzodiazepine detection. There is a lack of evidence regarding limitations of oral fluid testing.*

Strength/consensus of recommendation: C

Level of evidence: II

Until recently, screening to detect the use of drugs of abuse has focused primarily on the use of urine as the sample for testing. In some settings, adulteration/manipulation of the sample by users to circumvent positive results (13,38,39,41,53) is a major issue. A number of issues, such as invasion of privacy, many methods of manipulation, cross-reactions *etc.*, have led to interest in alternative matrices.

Urine

POCT, or near patient testing, for drugs of abuse has evolved over the past 30 years with urine as the best established sample matrix for devices now in use. Urine DAU cassette devices are available with sensitivities and specificities similar to enzyme immunoassays used in central

laboratory urine screening. The cut-offs used in POCT devices can be configured to match those used by the central laboratory and to reflect the needs of the testing site. As previously discussed, the antibodies used in the devices target the same drug and/or metabolites detected with urine laboratory screens. The labelling of these devices with respect to what is measured or detected is perhaps even more important since many users may not fully understand that most of these tests are designed to detect classes or groups of drugs. The POCT devices sometimes are inappropriately labelled as detecting a specific drug when actually detecting a class of drugs. This mislabeling may lead to interpretational false positives or negatives when testing personnel do not understand the specificity. For example, a test claiming to detect morphine, e.g., RapiTest MOP (One Step Morphine Test, Morwell Diagnostics, Zurich, Switzerland), may actually detect other opiates, so that a result is read as positive for morphine when codeine is present. (9)

There have been reports showing differences in interpretation of POCT results when experienced laboratory personnel read the results versus when the interpretation was performed by non-laboratory personnel (8) Certain devices have been reported as more difficult to read with an increase in false positive results shown by confirmatory methods (24,54) As with laboratory screening results, published results from POCT devices show that screening results should be followed up by confirmation testing if the result could be used for medico-legal processes. (16,52)

Oral Fluid (Saliva)

Saliva, or oral fluid, as an alternate POCT matrix has reported advantages and disadvantages. Oral fluid collection is regarded as easy, non-invasive and the specimen is less likely to be

adulterated. Justification for use of oral fluid because of ease of collection may be offset by the fact that oral fluid is potentially more infectious than urine. Immunoassays developed for urine are not directed to the optimum parent drug or metabolite in oral fluid and alternative cut-offs have been advised by SAMHSA with the proposed cut-offs being considerably lower than in urine, presenting a significant analytical challenge. In addition, for many of the drugs of interest, it is the parent drug that is usually detected with the compound typically present at higher concentration levels relative to its or its metabolite(s) concentration in urine. As a result, most devices designed for detecting the urinary metabolites will not be useful for oral fluid testing. For roadside testing in law enforcement, an advantage of oral fluid is that drug detection relates more directly to levels of drug in blood, and hence impairment, than does the presence of drug in urine.

Collection procedures and devices for collection are not standardized and drug concentration can differ depending on collection method (55). Stimulation of saliva flow has been used. Basal pH is around 6.5, whereas stimulated flow has a pH around 8, so any drug with a pKa around these values will be substantially affected and may lead to decreased drug concentration (24).

Adsorption by the drug of interest to the collection device (to the filters or absorbent material contained in some devices) is also an issue. Oral fluid specimens have shorter, but earlier detection times than urine. The sample volume of saliva necessary for laboratory testing and POC testing is difficult to obtain (1,50). In one study interference from foods, drinks, poppy seeds (n=1) and mouthwash were assessed as not compromising test results based on an unclear number of samples (56). Results were reported to correlate well with urine results from samples collected at the same time as the saliva samples. The detection time after drug use for oral fluid

was 3 days for opiates and cocaine and 1 day for THC. Methamphetamine detection time after drug use was not determined.

While some criticise saliva as a medium, (57) the evidence suggests that saliva is a viable alternative and an aesthetically more acceptable matrix than urine. However the shortened time-window for detection, the lack of evidence on interferences, oral drug residues and other issues of manipulation currently require some circumspection in the general applicability of this matrix to addressing the question of drug usage.

One study comparing POCT oral fluid testing to GC/MS results showed “good” correlation results for opiates and methadone (15% error rate) (27). In a small study (N=15) using saliva with the Drugwipe device, (58) results obtained by law enforcement officers correlated well with laboratory results for cocaine and amphetamines. The oral fluid POCT was shown to lack sufficient sensitivity to demonstrate heroin abuse. THC detection was unsatisfactory because the antibody is more sensitive to THC-COOH than to THC, which is the major analyte in saliva (58,59). The immunochromatographic test strip used with the Drugwipe system in these studies is based on the Frontline urine test strip (Roche). Another study concluded that oral fluid was not adequate for detection of THC and benzodiazepines. (25) This study also reported differences in results based on experience of the analyst. In comparing saliva testing to urinalysis, Yacoubain *et al.* (60) found satisfactory correlation for cocaine, “heroin” and marijuana.

Saliva strips have been used for quick assessment of ethanol ingestion at POCT (61). The authors concluded that the strips were useful for “rule-out” of ethanol use, but not for “rule-in.” The

Q.E.D. TMA-150 test (STC Technologies, Inc., Bethlehem, PA) demonstrated poor correlation between blood ethanol and oral fluid ethanol ($r=0.75$; $N=36$) with increasing differences at higher concentrations (50). Oral fluid specimens have shorter but earlier detection times compared to urine. The sample volume of saliva necessary for laboratory testing and POCT testing is difficult to obtain. (1,50), some drugs inhibit saliva production resulting in difficult to manipulate viscous fluid, making transfer to an on-site device difficult.

Breath

As with oral fluid specimens, obtaining adequate sample with breath alcohol testing is a constant issue, (50) especially with very intoxicated individuals. With proper sampling, good correlation between blood alcohol and breath ($r=0.97$; $N=52$) was demonstrated.

In a study comparing arterial blood, venous blood, urine and breath (end-expired air) for ethanol monitoring, (23) the breath ethanol showed the worst bias and precision compared to arterial blood ethanol measured by GC. The breath analysis was affected by body temperature and breathing patterns at time of sample collection. Wide under- and over-estimation of ethanol by breath analysis was demonstrated compared to arterial blood ethanol measured by GC. Others cite the convenience of breath testing in the emergency department for early results, although adequate record keeping was an issue. (62) In contrast, Soderstrom, *et al.* (63) examined alcohol testing in U.S. trauma centers and reported that only 63.7% of Level I trauma centers routinely perform alcohol analysis. They reported that the primary reasons given for trauma centers not routinely performing alcohols were that results are considered “clinically not important” or legal

concerns. Alcohol POCT results in drug treatment centers might facilitate immediate confrontation and/or counselling of the patient.

Sweat

There are two different approaches to sweat collection. One is a sweat patch worn by the subject for a period of time, resulting in an integrated collection of drugs in sweat over a period of time. In the other, the skin is wiped (Drugwipe) and has been used in road-side testing. Sampling of this matrix is not standardized.

Findings similar to those from oral fluid have been published with laboratory-tested sweat samples (59;64) with the parent drug predominating. The elimination of a drug through the skin is reported to be delayed for many days and drugs may bind to various skin fractions (65). Drug concentrations in sweat did not correlate with dose or to time of use. Drugs in sweat were found to be present in a wide concentration range requiring laboratory analytical techniques (65).

Collection of sufficient sample is an issue, making POCT impractical. Sweat patches need to be worn for prolonged periods to collect enough sample.

An alternate sweat collection device, Drugwipes, (Securetec, Germany), has been used for sweat collection in Europe. Sweat is prone to external contamination of the skin, such as passive exposure to smoke (66). Sweat concentration of several drugs differ according to the collection site (58). Time intervals between drug administration and excretion of the drug in sweat are variable and have not been extensively studied. Good correlation has been shown between sweat

samples collected using Drugwipes and blood and urine tested in a central laboratory for MDMA (67).

Other Matrices

Other matrices of interest are hair, nails and meconium. At present, none of these matrices can be tested using POCT due to the extensive preparation that is required before analysis.

Confirmation of POCT results by laboratory methods is necessary to eliminate many false positive and false negative screening results. Ease of use and proper training of testing personnel are obvious recommendations. Manufacturers should design POCT devices to facilitate the required regulatory agency documentation and retrieval of data, including quality control data.

POCT devices have been used in post-mortem situations. The logic of this application of POCT technology is unclear, but decomposition products can interfere in some assays: *e.g.* falsely positive detection of amphetamines may occur in the presence of tyramine (2).

Non-clinical applications of POCT for drugs of abuse and ethanol

Drug testing for non-clinical purposes is very common, but higher price and concerns about legal defensibility of results have limited the applications of point of care devices for drug of abuse testing in non-clinical settings. Since none of the POCT devices currently available—with the exception of breath alcohol analyzers—are sufficiently specific to be considered a confirmatory test, application of point of care devices in these settings require additional confirmatory testing

at a laboratory facility. Therefore, the advantage of expediency is often lost when positive tests must be confirmed. However, there may be some benefit to immediate negative results: In one study of the US Postal Service, 1/3 of applicants were lost between the time of the interview and when the drug test results were available. POCT drug testing, which may allow immediate hiring of applicants who tested negative, may reduce that attrition rate.

Point of care drug testing may offer another advantage in non-clinical applications. At worksites involving operation of machinery or handling of materials that may pose a threat to workers and public safety if an employee is impaired, screening on site is an efficient way to provide the employer with some assurance that workers are drug-free. In this type of setting, the consequences of a false positive are not necessarily severe, as long as a confirmatory test is required. An occasional day or two off work until the results of the confirmatory test are available seems to be an acceptable trade for the assurance that negative results provide. Clearly, screening in a central laboratory does not provide the same measure of assurance, since results inevitably are delayed by several hours, if not a day or more, and an impaired employee may present a danger or liability in the interim.

Non-clinical point of care testing for alcohol is quite common, as most States have implied consent laws that compel licensed motorists to submit to breath alcohol analysis. A critical assessment of the literature pertaining to standards of practice for evidentiary breath alcohol analysis is moot, since statutory authority directs the use of these devices. Beyond the scope of the implied consent statutes are workplace and other non-clinical settings where alcohol intoxication may be of concern.

In this review, we assess the use of point of care devices for drugs of abuse and alcohol testing in non-clinical settings. While there is extensive data in the literature regarding the analytical performance of various point of care devices designed to test for drugs of abuse, few studies have examined the overall benefit of these devices compared to conventional laboratory testing.

What is the effect of POCT devices on the outcome of drug testing in non-clinical settings?

Guideline 104: *Although drug testing in non-clinical settings may have an overall positive effect of identifying and discouraging drug abuse, there is no evidence that point of care drug testing offers any incremental benefit towards those outcomes when compared to conventional testing in a referral laboratory. There may be logistical, and perhaps economic, advantages to point of care drug testing, but these benefits are not generalizable.*

Strength/consensus of recommendation: I

Level of evidence: II

The appropriate outcome measure to assess the value of a laboratory test in a non-clinical setting is not always apparent. In clinical settings, there is a rich variety of positive outcomes—success of treatment, length of stay, cost of diagnosis, frequency and severity of adverse events, patient satisfaction, to name just a few—against which the use of new laboratory methods can be evaluated, but the success of non-clinical drug testing rarely pivots on the welfare of the subject. Most would accept without serious debate the notion that prevention of drug abuse, either by identifying abusers and taking appropriate action to remove potential risks that result from their impairment, or from the deterrent effect of surveillance programs, is a benefit to society, but this outcome is difficult to quantify. French, *et al.* (68) reviewed the available literature estimating

the societal costs of drug abuse, and assessed direct expenses associated with drug abuse in several categories, including premature births, aid to families with dependent children (AFDC) and food stamp benefits, acquired immune deficiency syndrome (AIDS), various crimes, foster care, sexually-transmitted diseases, and prosecutorial costs. Their estimates, however, apply only as long as drug use is prevented and therefore do not directly accrue from drug testing programs. Consequently, there are few data in the literature that addresses the question of whether drug testing, in the most general sense, correlates with positive outcomes (increased efficiency, reduction in accidents, fewer healthcare claims, etc.). Whether the logistical advantages of point of care testing translate into an incremental added benefit is even less clear.

One study (51) compared the cost of point of care urine drug screening in a large manufacturing company with the cost of drug testing in a Department of Health and Human Services (DHHS) certified reference laboratory. A total of 1,101 employees were screened by the food and Drug Administration (FDA) approved point of care device, and urine specimens from 56 employees were sent to the referral laboratory for screening. All positive screens were confirmed by GC/MS. The principal difference between the point of care screening and offsite lab is related to the elimination of administrative expenses associated with processing negative screens, which at the point of care were not subject to the same intensity of review as in the offsite lab. The detailed variable cost analysis includes factors representing the labor associated with collecting, processing, and reviewing negative results, and these factors principally account for the cost differential between onsite and offsite drug testing. More specifically, the authors point out that the bulk of the cost savings was due to employee time lost when subjects travelled to offsite

collection centers, rather than submitting a specimen at a designated onsite location. There is no indication that the laboratory charge was different for pre-screened specimens.

Are POCT devices reliable for non-clinical applications?

Guideline 105: *Although generally reliable in comparison to automated screening methods for drugs of abuse, point of care devices do not have sufficient specificity to be used for non-clinical applications and results may be subject to legal challenge unless positive results are confirmed by a definitive method.*

Strength/consensus of recommendation: A

Level of evidence: I

In a medical setting, laboratory results are interpreted by licensed medical professionals, most often physicians. For the vast majority of laboratory tests, a clinically trained gatekeeper mitigates the potential for patient harm when the laboratory result has the potential to prompt an intervention that is otherwise inconsistent with medical management based on clinical indications. Such safeguards do not ordinarily exist for non-clinical drug testing except for regulated drug testing programs that require a Medical Review Officer. Therefore, non-clinical drug testing demands a higher standard of reliability than is customary for laboratory applications that are used in conjunction with diagnostic medical services.

Among the SAMHSA-regulated drugs of abuse, the specificity of POCT devices varies according to the individual target drug. Cannabinoids, benzoylecgonine and PCP are the most specific, while amphetamine and opiate assays cross-react significantly with congeners. Benzodiazepine and barbiturate assays variably detect the many drugs within those

classifications. Screening devices that differ significantly in the degree of cross-reactivity with drugs within a particular classification introduce ambiguities that may create opportunities for legal challenge.

Studies in Europe (64) and Canada (69) assessed the results of POCT drug-testing programs directed at impaired drivers and inmates on conditional release, respectively. In the former study, positive results of the roadside test were used only to give police additional information when drug use was already suspected, and all specimens were submitted for subsequent GC/MS analysis. There is no mention of whether the roadside testing had any impact on the legal proceedings that followed. In the Canadian study, positive screening results were likewise confirmed by GC/MS, but regrettably, no data are given concerning falsely positive screens. A recent field study of point of care drug testing of impaired drivers (5), however, compared the results obtained by police officers with parallel analyses on the same devices performed by trained technologists, and overall, the police officers had a greater than three-fold higher error rate than technologists. A Finnish study (25) also found significant differences between point of care tests performed by trained and untrained staff, and this disparity has been demonstrated in clinical settings, as well (10). So in addition to the limited analytical specificity of point of care drug screening tests, non-clinical applications of these devices may introduce a higher frequency of analytical errors.

How well do non-laboratory personnel use POCT devices for drugs of abuse in urine for definitive actions in non-clinical settings?

Guideline 106: *When used by trained laboratory personnel, there is evidence that the current*

POCT devices for urine drug screening produce results that are comparable to laboratory based screening methods. When used by trained, non-laboratory personnel, results are poorer. Policy makers need to decide the acceptable benefit/risk ratio they seek in taking definitive actions; advice from laboratorians should be sought.

Strength/consensus of recommendation: A

Level of evidence: II

In the study by Brookoff *et al.* (21) initial screening was exclusively performed on-site by a trained law enforcement officer. This study was conducted over 46 consecutive 7-h night shifts, using one device to screen for cocaine and marijuana. Samples giving a positive result were retested on-site. Those remaining positive were submitted for re-screening (EMIT) and confirmation (GC/MS). 150 of 175 subjects stopped for reckless driving underwent screening; and of these, 59% were positive for either or both drugs. Of those that screened negative for cocaine or marijuana, none were subsequently found to contain cocaine using GC/MS. There were 10 found positive for THCCOOH, but using a cut-off of 50 ng/mL. All of the 38 cocaine positive samples were confirmed, while 70% of the THC positive samples confirmed. The results of the confirmed analyses were successfully used in prosecuting the subjects.

In the study by Crouch *et al.*, (5) 5 different devices were compared at two sites. Though the settings were not described, samples were collected from suspected drivers on Friday and Saturday nights (10pm to 6am) over a 9-12 month period. The devices were tested in a rotating sequence with the first screen performed by the participating officers and all subsequent ones by a technologist; it is not clear if the technologist was on-site, this individual tested each sample

using the remaining 4 devices. Results were compared between devices and were confirmed using GC/MS (all positive results were confirmed, 5% of all negatives were confirmed and any discrepant results were confirmed). The error rates reported for the officers were 2.5% (total) compared to 0.8% for the technologists. The lowest error rates were reported using the TesTcup and TesTstik devices. The 800 specimens collected yielded a positive rate of 36% for at least one drug class. The overall performance of the devices was good with few false positives and negatives observed using any of the devices. The highest false positive rate for THCCOOH occurred using the AccuSign device with 2 non-confirmed samples out of 172 samples. The greatest numbers of “false-positive” results were obtained for the amphetamine and opiates classes and for PCP. One of the strengths of this study was that for amphetamines and opiates, effort was made to identify other drugs of the class present in the samples that had potentially contributed to the positive response in addition to target analytes (amphetamine/methamphetamine, morphine). These data are perhaps the most interesting in that they demonstrate the presence of drugs not sought by some laboratories e.g. 39 positive amphetamine samples: six had measurable amphetamine, methamphetamine or phentermine (the target analytes), while 17 of the samples were found to contain MDMA. Pseudoephedrine, phenylpropanolamine and ephedrine were also found in samples yielding positive screening results using the Triage panel. Similar data are seen with the opiates in that of the 38 samples screening positive using one or more of the devices for opiates, only 19 contained measurable amounts of morphine or codeine while all but two of the remaining positive samples were found to contain hydrocodone and /or hydromorphone.

Collectively, these studies suggested higher discrepancy rates for the non-laboratory personnel. Efficiency rates of pain clinic nurses (10) were 82.9% (THC), 82.3% (COC), 100% (OPI) compared to laboratory technologists 100% (THC), 98.1% (COC), and 98.4% (OPI). Though this study suggested that increased errors were more frequent with multi-drug panels, details were not clearly presented. When trained law enforcement officers were compared to laboratory personnel on site and using multi-drug panel devices, the over-all comparison of error rates was 0.8%(27/3200 analyses) by the technologists compared to 2.5% (20/800 analyses) for the officers. In a study involving a pain clinic, the noise and distraction level of the clinic was considered as contributing to the error rate.

Other issues

Are POCT panels of drugs preferred over single tests?

Guideline 107: *If opting to use POCT panels, consider the prevalence of use in you're the population to be tested for all the drug types on the panel, consider the benefits of single POCT devices in terms of flexibility and cost. Balance this against the breadth of testing available from a central laboratory.*

Strength/consensus of recommendation: I

Level of evidence: III

There is little evidence to indicate the best panel combinations and selection should be based upon the needs of the testing setting. Some authors indicate that testers can become confused using panel devices (10). However in the Roadside Testing evaluation (70), police officers

clearly preferred panel tests. The same combination of tests performed singly may be more expensive than a device containing a panel of drugs

Is there evidence for an economic impact of POCT for drugs of abuse and ethanol in any context?

Guideline 108: *Independent studies to assess the economic value of POCT for drug testing are urgently needed, particularly given the multi-million dollar nature of the market.*

Strength/consensus of recommendation: I

Level of evidence: III

There are no studies of the economics of POCT drug and alcohol testing vs laboratory testing in any environment.

In summary, the introduction and use of POCT for drugs of abuse is a corporate policy issue for an organization. POCT should be used within a clearly defined framework. The objective of testing should be clear, and the benefits and risks recognized. Policies regarding confirmatory testing must be understood as part of an overall use strategy. Involving laboratory professionals in the decision-making process is advised and essential where definitive punitive action may result. Quality issues, maintenance, record-keeping and cost/benefit also require consideration. The development of interfaceable devices with unequivocal recording of patient/client identification is needed and are still generally lacking. Collaboration between manufacturers, laboratory personnel, end-users and managers requires a more informed and balanced approach.

In the future, there is need for evaluation of the economic impact of immediacy of POCT testing for Drugs and Ethanol in a variety of clinical and non-clinical situations. Best practices for the use of POCT and CLT need to be established based on evidence. There needs to be further independent investigation as to the benefits of urine versus saliva [oral fluid] testing.

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Public Comments:

No public comments were received on the guidelines.

Chapter 8: Infectious Disease

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A constant in an ever-changing healthcare environment is the need for fast, accurate and reliable diagnostic testing. Point of care testing (POCT) technology is a relatively new science that is focused on meeting the demands for faster testing and better patient care and outcomes. Point of care is rapid testing done on site or at the bedside by trained personal such as nurses, nursing assistants, medical assistants as well as patients. There are a variety of POC tests available for home use as well as clinical setting ranging from rapid testing for glucose, cholesterol, prothrombin time, screening for streptococcal throat and human immunodeficiency virus (HIV).

As the number of rapid tests has increased so has the number of situations that POC testing could apply. The development and implementation of POC testing for infectious disease would have a huge impact not only on public health concerns but also for “routine” clinical situations.

Reliable and accurate POC testing may improve patient outcomes as well as reduce inappropriate antibiotic therapy. The purpose of this manuscript is to evaluate the available literature concerning several infectious disease tests and determine whether or not the current literature supports the use of POC, near patient, testing.

Bioterrorism

The need to worry about the use of bioterrorism agents in the U.S. did not seem a reality before 2001, however since the fall of 2001, the need for guidelines for the diagnosis and treatment of potential agents such as *Bacillus anthracis* or the virus smallpox, and the need for methods to quickly recognize the agents involved in a potential bioterrorist threat is apparent. During the events in the fall of 2001, health departments on their own or with the assistance of local hospitals and health-care facilities, attempted to screen potential exposed individuals and many thousands of environmental substances for the presence of the spores of *B. anthracis*. Not many rapid methods were available for such screening, although molecular tools, such as polymerase chain reaction (PCR), were used to provide more rapid testing than would be available with more traditional culture methods. Traditionally, POCT is performed on patients, however in this section tests are reviewed that are used by governmental agencies to screen the environment for select agents. The reader should be aware that select agents are currently screened in approved sentinel laboratories and referred for confirmation. Some tests discussed here are done so to inform the reader what is available on the market.

Are there tests for the detection of *B. anthracis* spores as agents of bioterrorism that are or will be available for use as POCT? Are these needed for “field” or POCT testing?

Guideline 109: *No recommendation can be made for or against routinely providing POCT because there is no data to support the fact that routine nasal swabs in each office or lab would provide information that would aid in determining cause or presence of a bioterrorism agent, in particular anthrax. There is no good literature with randomized studies that would allow for one to determine if the need for testing these nasal swabs at POCT would aid in the investigation.*

Strength/consensus of recommendation: I

Since 2001, there have been reports of assays that are or are being developed to detect *B. anthracis* spores as well as assays to rapidly detect other potential agents, such as *C. botulinum* or *F. tularensis*. The Anthrax BioThreat from Tetracore (Gaithersburg, MD) was shown to detect $> 10^6$ spores with a specificity of 100%. As a POCT, the claim is that the detection of anthrax spores can be done within 15 minutes in the field. BioWarfare Agent Detection Devices (Osborne Scientific, Lakeside, AZ) claims a similar rapid test without any instrument requirements, hence also touted as a potential “in the field” test. Response Biomedical Corporation (RBM) has developed a RAMP Anthrax test that can detect at a level of 10^4 spores in 15 minutes with 100% specificity. Assays for smallpox, monkeypox, cowpox, ricin, and botulinum toxins are also promised. Lastly, HandyLab, Inc (Ann Arbor MI) have a “lab-on-a-chip” in development using a small handheld reader that can be taken “in the field” and the first assay will be for detection of anthrax spores. In addition, three of the commercially available lateral flow devices have been evaluated in the literature to be used in detection of spores of *B.*

anthracis (1). Recently, a report in the MMWR (June 4, 2004, Responding to Detection of Aerosolized *Bacillus anthracis* by Autonomous Detection Systems in the Workplace) details the advantages of early detection of a release of Anthrax spores. These devices are being deployed in postal offices and etc. It is clear that this is the technology of the future and may soon be available to the clinical laboratorian. So clearly the technological marketplace is responding to the potential need for such products. Whether any of these are needed for POCT testing in patient areas is the question posed.

The literature would be graded as III, following the opinions of authorities as follows. In a reference by Kiratisin, P. et al. (2) the results of large scale screening of nasal swabs for *B. anthracis* in the midst of the Fall 2001 threats were presented. A descriptive summary of the culture methods used to screen 689 individuals from Capitol Hill and another 3247 from the Brentwood Post Office facility is given. There were a few positive cultures for *Bacillus* sp., none of which proved to be *B. anthracis*. The authors concluded that the screening was perhaps not the most effective way to detect the organism, if present, in these exposed individuals, but they suggest that time from exposure until processing may greatly affect recovery. Rapid testing was performed in this study, but results were not available for quite some time due to the incubation of the media and need for confirmation of suspect isolates. The authors do not speculate, however, if a more rapid test might have been more effective nor provided more efficient outcomes, since all individuals were offered and/or given prophylaxis, regardless of the culture results.

In a report by Anderson and Eisoid (3) summarizing the events of October 15, 2001 and subsequent days of the anthrax investigations, communications was seen to be the key factor to controlling the situation; comments were made by the authors that health care workers should make the decisions as to who gets screened and how but do not further comment on need for rapidity of testing. Byrne, KM et al. (4) comment on the use of an automated aerosol collection system for constant surveillance of the environment rather than relying on collection of samples by individuals as being much more efficient, constant and reproducible.

The need for rapid screening if another attack occurs would seem probable, however, there is no literature nor outcome studies to provide information that use of such “in the field” tests would contain any outbreak nor reduce the incidence of exposure or infection. Such assays will probably continue to be investigated, however, and should be with studies done to indicate their efficacy. A rapid molecular PCR product by GeneOhm Sciences (Beckton, Dickinson & Company) that can be performed on Cepheid’s Smart Cycler does have an application for detection of *B. anthracis* in post offices presently. This might be considered “at the place” or point of care, although no patients are involved directly in this type of testing. “Rapid” molecular tests are or will become available and the use of these assays as point-of-care-tests may be possible (5-7). Currently, you have to be a “certified” facility in order to identify and work with agents of bioterrorism. If the methods involve handling of potentially dangerous agents, then one would think that there would be restrictions on use of any of these assays, except by “certified” labs and individuals. Thus, use of any of these potential tests would have to be performed by laboratories which have been certified to handle agents of bioterrorism, and not done in most labs, that are considered Level A or sentinel laboratories. There are risks in

employing a test which might become available for agents of bioterrorism. Some of these agents might be involved in non-terrorist activities and inappropriate alarms may sound if one of these assays is performed without benefit of determining the “bioterrorism” nature of the incident. On the other hand, handling of any of the bioterrorism agents by untrained individuals may unduly expose them and others at point of care to the hazards of the agent in question.

Clostridium difficile

Clostridium difficile is the causative agent of pseudomembranous colitis. The syndrome is most often associated with antibiotic use. The organism produces two main toxins which are associated with the disease. Toxin A, a potent enterotoxin with minimal cytotoxic capabilities, involves the erosion of the intestinal mucosa and then a fluid response in the intestine. The second, cytotoxin B, is a heat labile toxin that causes a decrease in protein synthesis, disorganization of actin filaments and loss of intracellular potassium.

The cytotoxin B assay has been the “gold standard” for the determination of *Clostridium difficile* disease. However many hospitals elect not to perform the assay. This choice is often made since the test is technically difficult to perform, is difficult to transport due to its sensitivity to heat, and the time required detecting a negative sample. For these reasons, many laboratories have elected to assay for toxin A. Toxin A assays utilize a same day enzyme immunoassay. In addition to these tests toxin A/B tests and antigen tests [glutamate dehydrogenase] have been used for same day results.

Is there research available evaluating the clinical outcomes of rapid tests for *Clostridium difficile* toxin performed at the point-of-care?

Guideline 110: *There is fair evidence against point of care testing for C. difficile toxin at this time.*

Strength/consensus of recommendation: C

Level of evidence: II

There are no data available to evaluate *C. difficile* tests at the point of care. Many of the rapid tests utilized for the detection of *C. difficile* toxin involve multiple sample preparation steps such as dilutions, vortexing, centrifugation, washing.(8,9) The multiple steps required of the procedures would make this type of testing difficult to perform at the point-of-care. In addition, an important piece that is missing in all of the rapid testing articles is the fact that the testing was not performed by individuals that typically are involved in point-of-care testing.(8,9) For *C. difficile* testing to be brought to the point-of-care the number of procedural steps of the test would need to be reduced and studies would need to be performed comparing the POCT result to the laboratory result and ultimately to the clinical outcome.

Infectious Mononucleosis

Infectious mononucleosis testing performed in physician office laboratories is widespread since there is a need to clinically differentiate this syndrome from other entities. Rapid card tests that detect heterophile antibodies (HA) have been available for a long time. However, the majority of research performed on the laboratory tests for the diagnosis of infectious mononucleosis (IM) during the past 10 years has focused on specific serologies for Epstein-Barr virus. Commercially

available EIA tests for IgM and IgG antibodies to the viral capsid antigen (Anti-VCA-IgM, Anti-VCA-IgG), antibody to the nuclear antigen (Anti-EBNA), and antibody to early antigen (Anti-EA-IgG) have been compared to the gold standard method utilizing indirect immunofluorescence assays. A few studies within the past ten years have compared EBV-specific serologies to the commercially available heterophile antibody (HA) tests.

Have patient outcome studies been performed on the rapid tests that are available to screen for Infectious mononucleosis at the POCT site, and have the studies been performed by the POCT personnel?

Guideline 111: *Recommend POCT for heterophile antibody testing in patients greater than 12-years old, fair evidence to support procedure. However, some individuals do not produce heterophile antibodies in infectious mononucleosis, and if a negative test is obtained EBV-specific serologies should be performed before ruling out infectious mononucleosis.*

Strength/consensus of recommendation: B

Level of evidence: II

Guideline 112: *Recommend against POCT for heterophile antibody testing in children less than 13-years old, fair evidence against procedure. It is well documented in the literature that a large portion of children do not produce heterophile antibodies. In these patients, EBV-specific serologies should be performed before ruling out infectious mononucleosis.*

Strength/consensus of recommendation: C

Level of evidence: II

Gartner et al. tested 264 samples with four commercially available EIAs and compared these results to an IFA reference method (10). Rea, Russo, and Buchwald collected 380 samples for analysis by ELISA to detect EBV specific serologies and compared these to results obtained by using IFA methods (11). Fung et al. compared a single EIA test to an IFA test in 152 patient samples (12). Studies performed utilizing only the EBV-specific serologies are not used at this time at the point of care.

Other studies have compared the commercially available tests for EIA and IFA EBV specific serologies along with the commercially available heterophile antibody tests. Gomez, Nieto, and Escribano found that three rapid IM tests for heterophile antibody when compared to EBV-specific serology had low sensitivity, 15-33% in children under 13 years old and 59-81% in patients greater than 13 years old. The specificities ranged from 86-100% in both age groups. The researchers recommended that EBV-specific serologies should be performed on all heterophile antibody-negative cases in adults and on all children (13). Bruu et al. compared twelve commercially available tests for the diagnosis of infectious mononucleosis (six were tests for EBV specific serologies and six were tests for heterophile antibodies). Samples from six groups of individuals were used in the study. Group A included samples from patients with recent primary EBV infection. Group B consisted of serial dilutions of samples from patients with recent primary IM. Group C samples were from immunocompromised patients. Group D samples were from healthy blood donors and Group E contained sera from patients with no previous EBV infection. The researchers recommended four of the six tests for heterophile antibodies (14). Elgh and Linderholm compared six heterophile antibody tests with EBV specific serology. The researchers found that the sensitivity for the rapid tests was 70-92% and the

specificity was 96-100%. They recommended five of the six tests for confirmation of EBV-associated IM (15). Gerber, Shapiro, Ryan, and Bell compared four HA tests and one ELISA EBV-specific serology test to EBV specific serology by IFA. The sensitivities for the HA tests ranged from 78% to 84% with specificities of 89% to 100% (16). These HA tests are being utilized at the point-of-care as a diagnostic test for infectious mononucleosis.

Research has been performed that compared the results of tests for heterophile antibodies only. Schwartz studied the congruence of three rapid HA tests. He found that only 9 out of 135 specimens were incongruent among the three tests (17). Rogers, Windust, and Gregory compared a new dry latex preparation HA test to three other commercially available HA tests. Through this comparison the authors found that the new test had a sensitivity of 87% and a specificity of 98.7% (18).

The research studies listed above were comparative studies. Little if any research has been performed in regards to the downstream effects of the correct or incorrect diagnosis of infectious mononucleosis when utilizing tests for heterophile antibodies at the point of care. Research needs to be performed that considers the outcomes of utilizing tests to detect the presence of heterophile antibodies at the point of care site. (Data such as number of clinic visits or reduction of length of stay in the ED, reduction in the number of contraindicated drugs or therapies, length of time to recovery, or days of work/school lost needs to be collected). In addition, research needs to be performed that studies the feasibility of performing EBV-specific serologies on all children less than 13 years old in place of the heterophile antibody test. Also, research that compares the accuracy of infectious mononucleosis testing at the point of care site by point of

care personnel to the accuracy of the test performed in a CLIA approved laboratory by certified Medical Technologists is essential to investigate the true outcomes of point of care testing.

Chlamydia trachomatis and Neisseria gonorrhoeae

Will direct examinations for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, delivered as point of care tests, achieve high enough sensitivity for routine care?

Guideline 113: *Point of care Chlamydia tests should only be used while the patient is present for treatment and follow up. If the results are not available until after the patient leaves, do not use point of care tests. The Gram stain may be used as a point of care test for symptomatic males with urethral discharge.*

Strength/consensus of recommendation: A

Level of evidence: II (small analytic studies and opinions of respected authorities)

Most tests currently available for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* must be performed in a laboratory and results are usually not available prior to the patient's departure.(19-25) This delay may lead to patients not returning for treatment and further disease transmission. Twenty percent of patients with positive tests fail to return in 30 days and 30% fail to return in two weeks following notification of test results. This can lead to the spread of the disease and ultimately may result in increase cases of PID in women. As 30% of untreated cases of Chlamydia result in PID this may result in as much as \$4,000 in future medical costs. In a recent study (Swain et.al.) it was determined that using a decision analysis scheme including clinical criteria and POC (near patient) test could increase the number of patients treated from 48.6% of those women assessed by clinical criteria to as high as 79.1% using a DFA method in

the POC and 78.4% using a POC OIA method. However, the results of the Swain study and other studies of the performance of point-of care *C. trachomatis* tests have shown that these products have reduced sensitivity when compared to culture or nonamplified chlamydia methods. Many studies have been assessed using culture as the “gold standard”, however, it is anticipated that this disparity would be even greater if point of care tests were compared to nucleic acid amplification tests or to an infected patient standard. The best overall strategy for therapy in the above mentioned study was using a presumptive treatment protocol along with selective NAAT testing (12.8% untreated patients) versus OIA POC tests and the same presumptive protocol (21.6% untreated patients). A clear need for testing does occur since using only the presumptive treatment and not laboratory testing resulted in 51.4% of patients with disease untreated. Using universal NAAT testing with no presumptive treatment resulted in 23.6% of patients left untreated. Clearly, clinical criteria and laboratory testing is required. A proposed model including the prevalence of the disease in the population, clinical risk assessment, and the probability of infection coupled with laboratory testing might be the most prudent method of STD evaluation for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The National Chlamydia Laboratory Committee, Association of Public Health Laboratories ‘recommendation that Point of care tests should only be used when the patient is available for treatment and or follow-up or in specific situations such as in high risk patients who are unlikely to return, criminal intake facilities where individuals are released within hours after detention, homeless or in method evaluations and projects should be followed.

The 2002 MMWR (25) states that the Gram stain is the most reliable point of care test for the presumptive identification of *N. gonorrhoeae* from urethral exudates in symptomatic males.

Gram stain is not recommended for testing for infection in women.

More research and development are needed with POC tests that have increased accuracy and reliability at the point-of-care for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. With this increased reliability there may be a change in the recommendations for their routine use in screening populations.

Group A Streptococcal Antigen Tests

In acute care settings, Group A streptococcus (GAS) antigen testing has become a routine point of care (POC) test.(26-60) Overall performance of the test has varied with regard to sensitivity.

It is common practice to perform rapid antigen testing since approximately 20-30% of office visits are concerned with the diagnosis of pharyngitis. This evaluation details the available published literature to determine whether there is enough evidenced based research in the literature to support the use of rapid antigen tests for the diagnosis of GAS pharyngitis at the point of care.

Are rapid tests for Group A streptococcal antigen performed at the point of care useful for diagnosis of Group A streptococcal infections? Is there research available evaluating the clinical outcomes of rapid tests for Group A streptococcal antigen performed at the point of care?

Guideline 114: *Rapid tests for diagnosis of GAS pharyngitis in general provide clinically useful, financially justified results; these tests also have utility for testing nonpharyngeal specimens. The*

recommendation of the American Academy of Pediatrics to confirm negative rapid GAS antigen detection results of pharyngeal specimens from children should be followed; the Infectious Diseases Society of America recommendation to perform laboratory tests (either throat culture or rapid antigen detection) on specimens from adults with clinical evidence of pharyngitis should be followed.

Strength/consensus of recommendation: B

Level of evidence: III

Group B Streptococci

By 1996, the clinical data was well documented and the CDC along with other public health officials published guidelines for the prevention of perinatal group B streptococcal disease (61). At that time, the CDC offered two different prevention systems; a risk-based approach or a culture based screening method. The risk based method used the following criteria: delivery at or less than 37 weeks gestation, maternal temperature of greater than 100.4 degrees F, rupture of membranes without progressing labor of greater than 18 hours. The CDC recommendations of 1996 helped raise awareness of GBS and provided effective guidelines for prenatal screening thereby reducing the number of neonates born with early onset disease. “Before active prevention was initiated, an estimated 7,500 cases of neonatal GBS disease occurred annually, [costing \$294 million in direct medical costs annually]. The rate of early-onset infection has decreased from 1.7 cases per 1,000 live births (1993) to 0.5 cases per 1,000 live births (2000) (62). The CDC continued to monitor prenatal screening for GBS and found overwhelming evidence that culture-based screening was substantially more effective than the earlier suggested

risk-based approach (63). As a result, several recommendations and updates were published in 2002 to help meet the needs of each of the different groups that are affected by GBS; obstetrics, pediatric care, laboratory, public health authorities, as well as expectant parents. The use of evidence based practice as well as consulting a wide spectrum of stakeholders established a more comprehensive approach for prevention of GBS.

There are several recommendations that remain the same as well as some major differences when comparing the 1996 and 2002 CDC report (61,62). Penicillin remains the antibiotic of choice with ampicillin as an acceptable alternative. Women whose culture results are not known at delivery should be managed as before, using the risk-based approach. The most notable difference is the 2002 recommendation is replacing the risk based assessment for universal prenatal culture-based screening. The CDC recommends culture screen of the vagina/rectum of all pregnant women at 35-37 weeks gestation. The CDC no longer suggests using risk-based assessment as a means to prevent GBS unless the patient has not received prenatal care or if the culture results are not known at delivery. POC testing would be extremely useful to the clinician in this scenario which may reduce inappropriate use of antibiotics. The updated guidelines specifically include recommendations against the use of antibiotics for GBS-colonized women undergoing planned cesarean deliveries where there is no rupture of membranes and labor has not begun (62) There are also detailed instructions on collection as well as expanded methods of GBS culture processing, including instructions on susceptibility testing. Currently, no POC device is recommended to be used as a screen only for GBS.

There are many factors that contribute to the accuracy of laboratory test results. Whether the sample is a blood test, or culture it is important to collect, label, and process the specimen properly. It is essential for clinicians to follow the recommended CDC guidelines for collection to improve isolation and to ensure reliability. Both the 1996 and 2002 CDC guidelines recommend collecting lower vaginal and rectal cultures at 35-37 weeks' gestation. A single swab may be used for the vagina followed by insertion into the rectum through the anal sphincter. It is also acceptable to use two different swabs; however both swabs should be processed in the same broth. It is important to note that the presence of GBS is what is important not the site of GBS colonization. The collection of "vaginal/rectal swabs improves GBS isolation by 40% compared to use of vaginal specimens alone," and yet there are still clinicians that collect only vaginal swabs (63). The CDC also specifically states that collecting cervical specimens and using a speculum are not recommended. There is documentation to support the CDC's claim that cervical collection yields 40% fewer positive cultures than single vaginal swabs. Yet, 6% of laboratories accept cervical specimens (63). Since GBS colonization may be transient, proper timing of collection at 35-37 weeks gestation is recommended to improve sensitivity and specificity and to give more reliable results. Laboratory processing of the specimen according to CDC guidelines is equally important for isolation and identification of GBS. The vagina and rectum are colonized with heavy normal flora which can make isolation of GBS challenging. The 1996 and 2002 CDC guidelines for clinical laboratories recommend two different media for GBS isolation; plate media and selective broth (61,62). The plate media suggested is trypticase soy agar with 5% sheep's blood known as TSA, or CNA. There are two selective broths suggested; Todd-Hewitt or LIM broth which are supplemented with antibiotics to suppress normal flora and allow GBS to grow. The synergist effects of using both plate and

selective media improve GBS isolation. The use of plate media alone without selective broth will miss 50% of women who are GBS carriers and will give false-negative results (62). “A survey of clinical laboratories in selected counties of three states in 1997-1998 found that only a proportion of laboratories were using the recommended selective broth media to process GBS cultures (Georgia, 39% of laboratories; Minnesota, 42%; Connecticut, 62%) suggesting that this may be an area in need of improvement.” (62) A follow up report was published in 2003 to determine if clinical laboratory improvements had been made using the 2002 CDC guidelines.

Is there research available evaluating the clinical outcomes of rapid tests for group B streptococcus? Are rapid test kits reliable and should they or should they not be used for Point of Care testing?

Guideline 115: *There is insufficient evidence to recommend POCT for group B Streptococcus. There was no literature found demonstrating a link to POC testing for Group B Streptococcus and outcomes data.*

Strength/consensus of recommendation: I

Rapid detection of Group B Streptococcus is well documented using Latex particle agglutination (LPA), enzyme immunoassay (EIA), and DNA testing (64-77). Review of published data shows that rapid testing of LPA and EIA are not sensitive for low colonization of Group B Streptococcus and therefore are not reliable for replacing the current standard of culture. Molecular testing is very sensitive for detection of low to high colonization of Group B Streptococcus, but may be cost prohibitive as compared to the low cost of culture. There is no information about outcomes of POCT. Research is needed to determine if POC testing using newer molecular approaches would further decrease the incidence of neonatal meningitis and

sepsis as a result of Group B Streptococcus disease in the newborn, as a result of time of delivery detection of Group B detection in the mother. Molecular tests have been marketed for the detection of Group B streptococci and are currently in development as a POC test.

H. pylori

Peptic ulcer disease causes chronic inflammation of the stomach and duodenum that may affect as many as 10% of all Americans at some time in their lives. Potent anti-ulcer medications may eliminate symptoms, but recurrence rates remain high. Approximately 80% of patients with gastric or duodenal ulcers without other predisposing factors such as NSAID (nonsteroidal anti-inflammatory drug) use are infected with *Helicobacter pylori*. Eradication of infection results in the resolution of gastritis and a marked decrease in the recurrence rate of ulcers (78-89).

Is there research available evaluating the clinical outcomes of rapid tests for *Helicobacter pylori* at the point-of-care?

Guideline 116: *There appear to be tests available for sensitive and specific testing at POC for Helicobacter pylori, but as yet no studies have been done to determine if such POC testing would have favorable clinical outcomes. Since tests including stool antigen tests, and urea breath tests have proven comparable in overall detection of H. pylori at the POC, studies should be conducted to determine their utility in early detection and treatment of dyspepsia associated H. pylori disease.*

Strength/consensus of recommendation: I

Influenza Virus Infection

Influenza infections occur in large numbers every year, and are associated with increased morbidity and mortality. These infections produce a broad range of symptoms, ranging from asymptomatic infections to fulminant viral pneumonia making diagnosis based solely on clinical presentation difficult, especially during non-peak periods. There are numerous studies demonstrating the benefits of rapid diagnostic assays for influenza, both in directing appropriate use of antiviral drugs, and in the reduction of unnecessary diagnostic tests (90-92). With the availability of CLIA waived assays for influenza, their use as point of care tests needs to be addressed. Specifically, how does the sensitivity, specificity, and positive and negative predictive values of these rapid tests determine their clinical usefulness in the POCT setting?

Are there studies available for evaluating the clinical outcomes of rapid tests for influenza virus performed at the point-of-care?

Guideline 117: *We found that the literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of influenza virus infection. Therefore, additional testing, including POCT may be useful. These tests should only be used for POCT when the virus is prevalent in the community, and negative results should not be used to rule out influenza virus infections. Only nasopharyngeal swabs, aspirates or washings should be used with these assays. The sensitivities of the tests using throat swabs are 60% or less. During the peak of an outbreak, not every single patient with flu symptoms needs to be tested, unless a positive result will result in the with-holding of antibiotics. The greatest cost-benefit is achieved when unnecessary antibiotics are not prescribed for patients with positive influenza virus test results. If treating with antivirals is being considered, the patient must be treated within the first 48*

hours of onset of symptoms for even a minimal effect to be achieved.

Strength/consensus of recommendation: B

Level of evidence: I and III

One study addressed the use of a rapid influenza assay in a point-of-care setting using non-laboratory personnel to perform the testing at a pediatric hospital emergency department (93). They studied 391 patients between 2 months and 21 years presenting with fever, cough, coryza, myalgias, and headache. They were randomized into 2 groups: 1) physician received the rapid flu result prior to seeing the patient; or 2) physician did not have the result of the rapid test. The two influenza-positive groups were compared for laboratory and radiographic studies, and their associated patient charges, prescriptions and length of stay in the ED. There were significant reductions in unnecessary tests prescriptions, and increase in antiviral prescriptions, and a significant reduction in time spent in the emergency department and in the mean charge. A telephone follow-up revealed no differences between the two groups for return visits to the primary physician or ED, new prescriptions, length of time patient missed school or day care, and the length of time primary caregiver missed work. These recommendations are in agreement with the recommendations of the World Health Organization for the use of rapid diagnostic tests for the detection of influenza virus (94).

Respiratory Syncytial Virus

Respiratory syncytial virus is an important viral pathogen most commonly seen in young children less than one year of age. Serious respiratory infections may also occur in elderly and immunocompromised adults. Diagnosis of RSV infections based on clinical presentation is

difficult (sensitivity 72.8%, specificity 73.2%) (95). RSV is also a significant nosocomial pathogen making rapid diagnosis of these infections useful for infection control. RSV may be grown in cell culture, however this usually required four or more days, which reduces the clinical usefulness of this method. Rapid diagnostic methods include direct fluorescent antibody staining, and several rapid antigen detection kits. The reported sensitivity values range from 62% up to 96%. This wide range is due to multiple factors, including the age of the patients (these assays perform very poorly in adults, 10-23% sensitivity) (96), the specimen type being tested (throat swabs perform poorly), and the assay used as the “gold-standard” (culture or molecular amplification) to which the rapid test is being compared. The use of rapid diagnostic assays for RSV by the laboratory has been documented to reduce the length of hospital stay, antibiotic use, and other tests (97, 98). Reductions in nosocomial infections in a newborn nursery were reported, when combined with cohorting, visitation restrictions, and gowns, gloves and masks (99).

Are there studies available for evaluating the clinical outcomes of rapid tests for respiratory syncytial virus performed at the point of care?

Guideline 118: *The literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of respiratory syncytial virus infection, therefore additional testing, including POCT, may be useful when used appropriately. Tests for RSV suitable for POCT have a broad range of sensitivity and specificity, and their positive and negative predictive values vary greatly, depending on the prevalence of the virus in the community. Because of these performance characteristics, these tests should only be used for POCT when the virus is prevalent in the community, and negative results should not be used to rule out RSV infections.*

Only nasopharyngeal swabs, aspirates or washings should be used with these assays. The sensitivities of the tests using throat swabs are 60% or less. The greatest cost-benefit is achieved when unnecessary antibiotics are not prescribed for patients with positive RSV test results.

Strength/consensus of recommendation: B

Level of evidence: I and III

One study addresses the use of a rapid RSV assay in a point-of-care setting using non-laboratory personnel to perform the testing at a large pediatric hospital emergency department. They reported a reduction of needless antibiotic use, and a reduction in hospital-acquired RSV infections (100).

HIV Testing

The prevalence of HIV infection is increasing in the US, and many persons at risk are unaware that they are infected (101). CDC goals for HIV prevention include making HIV testing a routine part of medical care, and recent publications suggest that expanded screening for HIV is a cost-effective health intervention (102-104). Unfortunately, many at-risk persons have limited access to the healthcare system, and approaches to hard-to-reach populations have been limited by the logistics of conventional HIV testing, which require a follow-up visit before results of testing are available, even for seronegative patients. In addition, conventional HIV testing protocols fall short when an immediate result would optimize patient care, for example in assessment of the source-patient in occupational blood and body fluid exposures, and in labor and delivery settings with women of unknown HIV serostatus.

To address these issues, rapid HIV tests have been under development and being assessed in active use for over a decade (105,106). Utilized both in clinical laboratories and at the point-of-care, rapid HIV tests promise to enhance our ability to assess HIV status in situations where rapid action is necessary, and to expand HIV testing to previously difficult populations and situations.

Four rapid HIV antibody tests were available as of April 2005; the Abbott Oraquick and Trinity Uni-gold Recombigen; both with ‘waived’ status, and MedMira Reveal and Bio-Rad Multispot HIV-1/HIV-2, which are non-waived. Other tests are in development; and an older kit, Abbott’s Single Use Diagnostic System HIV-1 (SUDS), has been removed from the market, but not before extensive experience was gained with its use.

Do rapid HIV antibody tests perform as well as laboratory-based methods a) in validation studies and b) in field studies? Are there sources of analytic variation unique to rapid/POC HIV test kits?

Guideline 119: *Under validation conditions, currently available HIV antibody tests perform with comparable sensitivity and specificity to laboratory-based ELISA methods in patient populations which are suitable for rapid testing.*

Strength/consensus of recommendation: B

Level of evidence: I (at least one randomized controlled trial)

Guideline 120: *In field studies, currently available HIV antibody tests perform with comparable sensitivity and specificity to laboratory-based ELISA methods.*

Strength/consensus of recommendation: B

Level of evidence: I (at least one randomized controlled trial)

Guideline 121: *Rapid/POC tests for HIV should be used by personnel well-trained in the method, with ongoing quality control and performance improvement programs.*

Strength/consensus of recommendation: A

Level of evidence: II and III (small studies and opinions of respected authorities)

Guideline 122: *Rapid/POC tests should be used with caution, if at all, to follow exposed persons who are heavily anti-retroviral therapy (ART) treated.*

Strength/consensus of recommendation: B

Level of evidence: II (dramatic results in uncontrolled experiments)

In FDA data supporting the approval of all four current methods, the rapid tests appear to have comparable sensitivity to conventional EIA methods, using seroconversion panels, low-titer panels, high-and low-risk unknown panels, and known positive and negative specimens. Occasional false-positive and false-negative results were seen in large panels, but never in numbers sufficient to discriminate between different kits in a significant manner. The kits vary in the number of conventional EIA methods used in the comparisons, and the particular conventional EIA method is rarely specified. Uniquely, the Multispot allows discrimination between HIV-1 and HIV-2 reactivity. (107-110)

Numerous published studies support the manufacturer's validation data suggesting that rapid tests perform similarly to lab-based EIA methods when performed by skilled staff. In the largest such study, the MIRIAD trial, HIV testing with Oraquick at POC had equal sensitivity to lab-based ELISA and had fewer false-positives (111). The Oraquick has also been studied in a region with transmission of multiple HIV subtypes, and performs as well as a lab-based EIA in this setting as well (112). Other rapid tests have also been evaluated in patients with non-B subtypes (113), but the existing data is limited relative to the large number of HIV subtypes in the world.

In addition to the four currently approved methods, numerous other tests are being studied and, presumably, in the process of approval. As an expanding number of methods become available, careful post-marketing surveillance of test performance and problems will be essential.

One publication explored the rate of performance-related errors in use of rapid HIV tests by non-laboratorians. The rate of errors decreased when the procedure was demonstrated to the users, and the authors concluded that careful training and ongoing performance assessment is important in POC HIV-testing programs. Significant levels of errors related to sample handling, inoculation, and record-keeping were observed (114). CDC has issued extensive performance and quality assurance guidelines for use of rapid HIV tests which are recommended for all health care organizations performing testing (115). The labeling of the rapid tests includes language stating that they are to be sold only to agents of a clinical laboratory – what this means in practice is not entirely clear.

The rapid HIV antibody tests have comparatively small antigen suites. In theory, this should limit sensitivity in some patients. A report has been published of a series of patients who were treated with HAART early after a known HIV exposure. These patients developed HIV infection with low viral loads and a declining gp 41 antibody response which was not detected by the Oraquick method (116). While this is not a patient population for which rapid testing would be appropriate currently, this report points to a potential problem with rapid tests, particularly if used for two-stage confirmatory testing (see below). The tests with both gp 41 and gp 120 (Table 1) might be less susceptible to this effect, but have not been tested.

The performance of rapid HIV tests at point of care under actual field conditions is still difficult to determine. The potential for substandard performance of the tests is significant, caused by human errors, kits storage problems, environmental issues in non-laboratory testing environments, and other variables. Authors of studies which examine the use of rapid HIV tests at the point of care should be encouraged to provide details of the type and training of personnel performing POC HIV testing, the location and environment in which the testing was performed, and any other information relevant to evaluating the factors affecting practical performance of rapid HIV tests. Additional studies of the quality of testing under actual conditions of routine use are difficult to perform; one of the desirable properties of the rapid tests is ease of sampling compared with conventional testing, which makes comparative studies awkward; but highly desirable.

Does HIV testing at POC improve rates and timing of ART for HIV-infected women in labor?

Guideline 123: *Rapid HIV testing in the peripartum period; laboratory-based or POC; improves antiretroviral prophylaxis, and most likely reduces peripartum transmission of HIV, provided*

systems are in place to utilize the information therapeutically.

Strength/consensus of recommendation: A

Level of evidence: II

Multiple trials have now established that rapid testing protocols can provide information to support provision of antiretroviral therapy during the perinatal period. In an uncontrolled intervention trial in Lima, Peru, 3543 women were tested with both oral fluid and blood-based rapid methods and 27 were positive with one or both. ART was provided prior to delivery for 17/19 women whose delivery records were available. Two of the 27 positive tests failed to confirm with a lab EIA, but no parallel testing was performed, making it difficult to assess the quality of the rapid HIV test results (117).

In a study in Nairobi, rapid testing increased the rate of notification of pregnant women of their HIV serostatus, but did not impact the (low) rate of antiretroviral prophylaxis. Rapid testing protocols must be coupled with effective post-test strategies for provision of care to be effective in impacting health (118). A similar protocol in Cote d'Ivoire led to just 26.2% of HIV-infected women entering the preventative program. Entry into preventative care was adversely affected by illiteracy and by living with a partner, again demonstrating the limitations of rapid testing in addressing systemic problems in provision of care (119).

One study compared the availability of HIV test results between institutions using SUDS and using conventional ELISA methods, and within a single institution before and after conversion from ELISA to SUDS. The use of SUDs significantly decreased time-to-report, but there were

major differences between institutions using the rapid test, emphasizing the need for comprehensive systems to facilitate rapid testing and utilization of results (120)

In the MIRIAD trial, rapid testing was performed for 4849 women who presented to labor-and-delivery units in a multi-center trial. Of these, 34 were positive by a rapid test; in these women, zidovudine was started prior to delivery in 18, and all HIV-exposed infants received zidovudine after delivery. Of the 32 infants who were available for follow-up, three were HIV-infected, two DNA-positive at birth and one negative at birth but positive at 6 weeks of age. In historical studies, the rate of transmission of HIV in the absence of prophylaxis is 14-33% (121). There was no control arm of this study; either standard care without rapid testing, or with risk-based provision of ART (111)

A cautionary note was sounded by the observation that of 69 patients with a positive rapid EIA (of 9,781 women tested peripartum), only 26 were confirmed as HIV-infected by Western blot, yielding a positive predictive value for the rapid test of only 37.7%; 9.8% in Hispanic women. The authors suggested that in very-low-risk populations, the routine disclosure of rapid intrapartum HIV results should be avoided prior to confirmatory testing (122).

No systematic study has compared laboratory-based and POC use of rapid HIV tests in the peripartum period.

The comparative value, accuracy, and operational efficiency of point-of-care versus laboratory-based rapid HIV testing, both in the peripartum and other settings, has not been determined.

Results from any such study may be difficult to generalize to different settings because of differences in institutional organization and resources. Despite the limitations of the MIRIAD trial, it will be difficult to ethically justify a truly controlled trial of rapid testing versus no or conventional testing, unless a large fraction of patients in the ‘no testing’ or ‘conventional testing’ arm of the study receive prophylaxis. Research is also needed on the cost-effectiveness of rapid testing in highly resource-limited environments such as the less developed countries.

Does HIV testing at POC provide benefits for blood and body-fluid exposed employees?

Guideline 124: *Strongly recommend rapid testing of the source-patient for employee exposures.*

Strength/consensus of recommendation: A

Level of evidence: II

Guideline 125: *No recommendation regarding testing at POC.*

Strength/consensus of recommendation: I (insufficient evidence)

In a controlled study, the use of rapid HIV testing decreased costs and self-reported stress among blood-and-body-fluid exposed healthcare workers. The rapid test was performed by nursing staff of the emergency unit, who also performed the clinical evaluation of the exposed workers. The rapid test, GENIE-II, is not available in the US, but performed identically to the conventional EIA (123).

The impact of rapid testing was assessed in a retrospective review format, estimating the costs that would have been incurred had conventional testing been performed instead. The authors

estimated that over \$5,000 was saved in treating 17 patients by the use of the rapid test. The costs used in the model included medication costs, lost work time, labor, and testing costs (124). Another, similar study in Brazil estimated a savings of nearly \$3,000 in 109 cases (125).

In Italy, implementation of a rapid HIV test, the Capillus HIV-1/HIV-2 (not currently available in the US) in two hospitals produced a dramatic reduction in use of ART and a significant reduction in the number of source-patients who remained untested. At Hospital A, of 567 workers exposed in the pre-rapid era 90 received ART; Only 6 source-patients tested HIV-positive. After implementation of the rapid test, only 3 exposed workers out of 628 received ART, and 3 source-patients were HIV-positive. A similarly dramatic reduction in prophylaxis was seen at hospital B. The incremental cost of rapid versus conventional testing was similar to the cost of the doses of antiretroviral drugs saved. There was also an increase in the number of exposures reported at Hospital B; the authors speculate that rapid testing protocols might make reporting more likely by decreasing the likelihood of unnecessary prophylactic therapy (126).

While the available data are limited, the magnitude of the effect is impressive.

Further studies of the impact of rapid testing versus risk-based protocols, even historical studies, would be useful. As in many areas, comparison of lab-based and POC rapid testing are desirable, though the results may be difficult to generalize.

Does HIV testing at POC improve HIV case-finding, entry into comprehensive HIV care programs, or facilitate changes in risky behaviors?

Guideline 126: *No strong recommendation for rapid/POC testing in outreach settings can be supported by current literature, but there is reason to expect that certain populations could be better served by POC screening.*

Strength/consensus of recommendation: I

Level of evidence: II

Analytically, conventional HIV tests perform superbly; outside of the seroconversion ‘window period’ and other defined area of physiological ambiguity (e.g. the neonatal period), the sensitivity and specificity of laboratory-based testing with an EIA and confirmatory Western blot approach 100%. In many settings, however, preanalytical and postanalytical issues sharply limit the achievable performance of HIV/AIDS testing. When significant numbers of at-risk persons lack access to testing, or fail to return for results after samples are drawn for off-site testing, the analytical performance of the test is irrelevant. In 1998, when 1.9 million publicly funded HIV tests were performed in the US, 48% of those tested failed to receive post-test counseling (127). Thus, there is a compelling rationale for rapid and point of care testing strategies.

In a controlled trial in public clinics, the use of an early rapid test (SUDS) increased the number of patients learning their serostatus versus conventional testing in both an anonymous testing clinic and an STD clinic. Eighty-eight percent of patients who had previously been HIV tested using a conventional protocol preferred the rapid test. In the year following the testing, clients tested with rapid and standard methods were equally likely to return with a new STD (128).

A study assessing the value of offering HIV testing routinely in the ER incidentally assessed the use of rapid HIV versus conventional testing. Using the SUDS test, 467 patients tested in the rapid arm of the study, compared with 981 tested conventionally. Rapid tests were performed both in the main lab and in a satellite lab next to the ED. Follow-up was better for seropositive patients in the rapid test group, but the difference was not statistically significant. Turnaround time was faster in the ED satellite laboratory than in the main lab (107 \pm 52 min versus 48 \pm 37min), and more patients received their results before leaving the ED with satellite lab testing (80% versus 45%). The interpretation of these results is limited by an extremely complex 4-phase protocol in which enrollment procedures changed with each phase (129).

An uncontrolled descriptive study in an STD clinic enrolled 1581 patients, of whom 1357 had same-visit results and posttest counseling, while 209 refused rapid testing and preferred conventional testing. The test used was the SUDS assay. Of the 1357 patients who received same-visit testing and counseling, 37 were HIV-positive, and 36 of these attended their first HIV clinic visit; the other patient died of HIV-related complications prior to the first visit. There were 6 false-positive and one false-negative SUDS result. In this setting, rapid testing was highly preferred by patients, and even discordant results were handled well by the recipients (130).

Several studies of patient acceptance of rapid HIV testing suggest that rapid tests will be well-received by the target population. A focus-group study at an inner-city hospital showed overwhelming preference for rapid testing, provided concerns about accuracy were addressed, and provided the rapid testing did not prolong already long clinic waiting times (131). A survey

of persons aged 12-24 showed a preference for oral sampling and for rapid testing versus blood or longer times to result (132). Women in Northern Thailand preferred rapid testing (133). Journal and newsletter articles (134-137) indicate considerable interest in HIV care providers and target populations in rapid HIV testing, tempered by concerns about how rapid testing will be handled, and availability of anti-retroviral therapy for newly-identified patients.

Studies of rapid testing in outreach settings (gay bathhouses) showed an increase from 74% to 99% of clients receiving their test results over conventional testing. There was also an increase in the number of patients who returned for partner notification and early treatment counseling after result confirmation. The rapid test was more cost-effective. The authors noted, however, the potential problems inherent in performing testing in a dim, crowded space, including the phrase 'In places where lighting is poor we recommend having a flashlight on hand to read the test results;' which suggests that a more systematic approach to quality assurance would benefit these programs. Other issues identified were the bathhouse owner's level of comfort with the impact of a screening program, and of giving positive results on the social atmosphere of the facility, and the availability of a CLIA-certified lab to oversee the testing (138,139).

A randomized trial in needle exchange and bathhouse outreach testing showed that client acceptability increased both with oral fluid testing (using an off-site laboratory for oral fluid testing) and with rapid testing relative to traditional testing. Testing strategies were randomized by offering different strategies on randomly determined shifts. Although the largest proportion of clients accepted oral fluid testing, rapid testing was preferred over traditional testing, and more persons received results with rapid testing than with traditional or oral fluid testing. Fewer

than half those who agreed to be tested with the rapid test in the needle exchange environment received their results, pointing out the limitations of even rapid tests in difficult-to-reach populations (140).

More trials, preferably controlled trials with careful description of testing procedures and environments, would help to assess the settings in which rapid HIV testing can be usefully performed, the performance of the tests under field conditions, the relative value of on-site laboratory-based versus POC testing, for settings in which that is applicable, and the impact of rapid testing on behavior change, both as it impacts on HIV risk and on transmission of other sexually-transmitted or blood-borne diseases. Quality assurance is likely to be essential to effective outreach programs; what is the role of clinical laboratories in outreach testing? How will the results of outreach testing be entered into and maintained in the medical record?

What algorithms for confirmatory testing should be used with POC HIV tests?

Guideline 127: *Confirmatory testing should go directly to Western blot/IFA, bypassing a second EIA step.*

Strength/consensus of recommendation: A

Level of evidence: III

Guideline 128: *In some resource-limited settings, a second, different rapid test is used for confirmation; this has not been carefully studied but is promising.*

Strength/consensus of recommendation: I

Level of evidence: III

Given the overall good performance of rapid HIV tests, CDC recommends that a second screening EIA NOT be performed prior to confirmation by IFA or Western blot. Requiring a second positive EIA could harm the sensitivity of the overall testing scheme; a positive rapid or POC EIA should be considered equivalent to a laboratory-based EIA as a screening test. This recommendation is not based on direct trials but on the operational characteristics of the rapid tests as sufficiently similar to existing conventional EIAs to be treated as equivalent for the purpose of confirmatory testing (141,142)

There is significant interest in the use of a second, different rapid test as a sufficient confirmatory method in some settings. Such a scheme has been modeled for cost-effectiveness, even recommended, but not extensively studied in practice (143-145). Results of pilot projects using varying strategies for accelerated confirmatory testing have been encouraging (146-148).

Ideally, a strategy for confirmatory testing should employ rapid tests with different antigen coverage. Currently approved methods use similar antigen mixes (Table 1). The Trinity Unigold and MedMira Reveal add gp 120 to the gp 41 used by Oraquick and Multispot. No study has examined confirmatory testing using currently-approved methods.

The use of a second, independent rapid test for confirmation should be assessed in systematic controlled trials. The value of rapid confirmation will vary with the prevalence of the disease in the target population.

***Trichomonas vaginalis* Vaginitis**

Trichomonas vaginalis is a protozoan parasite that is one of the three most common etiologies of infectious vaginitis. The most commonly used diagnostic tool has been observation of motile trophozoites of this parasite in vaginal discharge, however there is ample literature that this method is not very sensitive and is thoroughly dependent upon the viability of the organism. The trophozoites are very fragile and will no longer be motile within 1-2 hours or less, hence necessitating a point of care test. However, it is not a very sensitive assay. Culture is the gold standard, however, this is not a rapid, nor point of care test. Most recently there have been some additions to the testing marketplace of assays for the detection of *Trichomonas vaginalis* along with assays for Bacterial vaginosis and *Candida*, the other two agents of vaginitis. The Affirm probe (Becton Dickinson, Sparks, MD) can be used to detect all three entities with very high sensitivity in about 1 hour after specimen collection. It however is a moderately complex test and not readily performed in every office situation. Immunochromatographic assays that do lend themselves easily to POC testing are becoming available for the detection of *Trichomonas vaginalis*.

Is there a clinical need for POC testing for the presence of *Trichomonas vaginalis* in the diagnosis of vaginitis? Will direct examinations for agents of vaginitis, delivered in POC format, achieve high enough sensitivity for routine care?

Guideline 129: *We would recommend POCT given the fair evidence to support the procedure.*

*Wet mount examination of vaginal discharge for the presence of *Trichomonas vaginalis* is an insensitive procedure and should be replaced with newer methods that provide a higher level of sensitivity. Newer methods have been developed for point of care that may result in better*

outcomes. Additionally, outcome data will need to be based upon more sensitive tests that are used in pregnancy to establish an association with preterm labor/delivery and low birth weight deliveries.

Strength/consensus of recommendation: B

Level of evidence: III

The literature remains controversial about the association of *Trichomonas vaginalis* with complications of pregnancy, including lower birth weight and premature labor and delivery. However the sensitivity of the methods used to document the infection in part limit the results obtained in some studies and explain the lack of consensus on any association. The literature demonstrates a 49-89% sensitivity of the wet mount examination in detection of *Trichomonas vaginalis*. Only a 15-20 minute survival time has been documented when specimens are sent to laboratories on swabs. Unless the specimen can be examined immediately, the sensitivity is even lower. In studies that include more sensitive methods, such as culture for detection, the association of *T. vaginalis* with preterm labor is significant; with wet mount, the association is not always proven to be significant. There is some clinical evidence that treatment of *Trichomonas vaginalis* with metronidazole during pregnancy may have worse outcomes than not treating, however, the antibiotic appears to be the reason for this and not the elimination of the parasite.

More recently there has been an association of *T. vaginalis* and HIV as well as increasing reports of possible associations of *T. vaginalis* and cervical cancer. These are also in the area of controversial correlations that will require better methods of detection and more outcomes studies to confirm any relationships (149-179).

Candida Vulvovaginitis

There are three infectious agents responsible for over 95% of the infectious causes of vaginitis. One of these is the yeast *Candida*, most often *Candida albicans*. Yeast vaginitis is usually diagnosed clinically by the presence of a distinctive discharge, which tends to be very thick and “cheesy” in appearance and is seen in women in whom symptoms of extreme pruritis, following use of antibiotics, or other agents that would change the normal vaginal flora and increase colonization of the yeast. Laboratory or office diagnosis of yeast vaginitis is usually made by means of examination of a wet mount preparation of the discharge. Many authors, such as Handa, VL et al (180) have however cautioned against the use of a wet mount alone because of its low sensitivity, about 61%. They and others suggest that culture is needed for a definitive diagnosis. The latter of course is not a rapid test. Plourd et al (181) reported a 50-70% sensitivity of wet mount examinations in the diagnosis of yeast vaginitis. The Affirm probe test (BD Microbiology Systems, Sparks, MD) does afford a 45 minute test for the detection of the three most common agents of vaginitis, including *Candida albicans*. In a recent study, 11% of samples tested were positive by the Affirm probe as compared to only 7% by wet mount observation; however this is ranked as a moderately to highly complex test and probably not appropriate for point-of-care testing (182).

Are there point of care tests that are available for the detection of yeasts in vaginal samples as cause of vaginitis and are these tests necessary for good patient outcomes?

Guideline 130: *No recommendation for or against the need for a POC test for the detection of yeast in a vaginal specimen. This is because there are no good studies that provide information that a rapid test for the diagnosis that is more sensitive than the wet mount tests presently*

available would provide a better clinical outcome than what is presently obtained.

Strength/consensus of recommendation: I

Level of evidence: III

There is an article in 2003 by Watson MC et al (183) that attempts to address the need for rapid and correct diagnosis of yeast in cases of vaginitis so that appropriate antibiotics are used. It is not truly an outcomes study, but comes closest to this.

Bacterial Vaginosis

There are three main infectious disease etiologies for the clinical syndrome of vaginitis: *Candida sp.*, *Trichomonas vaginalis* and the entity referred to as bacterial vaginosis. The diagnosis of all three is often made with a combination of clinical criteria and observations of a wet mount preparation of the vaginal discharge for the presence of yeast (representative of *Candida sp.*), motile trichomonads (*T. vaginalis*), and/or the presence of “clue cells”. The latter are epithelial cells that are studded with coccobacillary bacteria, suggestive of organisms including *Gardnerella vaginalis* or *Mobiluncus sp.* Bacterial vaginosis is a result of a change in the normal vaginal flora from one of predominantly *Lactobacillus sp.* to one in which anaerobic gram negative curved rods (*Mobiluncus sp.*) and other anaerobes predominate. *G. vaginalis*, long considered the cause of bacterial vaginosis is now known to be possibly involved, but not the single cause. Consequently, culture specifically for the presence of *G. vaginalis* should not be used as a method of diagnosis. What is used is what is referred to as a “scored gram stain” of the vaginal discharge to discern the “flora” that is present in the vagina of the patient. This scored gram stain (184) in combination with clinical criteria (185) has become widely used. The gram stain is read and quantities of organisms consistent with *Lactobacillus*, curved rods and

coccobacillary organisms are tabulated. Points are designated for each and a “score” of 1-3 (no curved rods or coccobacillary organisms and mainly *Lactobacillus* sp seen) is interpreted as consistent with normal vaginal flora; scores above 7 are considered consistent with bacterial vaginosis. Scores of 4, 5 and 6 are in an intermediate category, representing a wide variety of conditions, one of which may be a transitional time before bacterial vaginosis. Tam et al (186,187) found that use of this method provided a rapid and cost-effective approach to the screening of bacterial vaginosis patients. The sensitivity of this method in a group of 51 pregnant women was 91% vs. clinical criteria alone that had a 46% sensitivity in the first study and in the second study, out of 74 examinations, bacterial vaginosis was diagnosed in 31% by the scored gram stain as compared to 28% by the clinical criteria. The scored grams stain was felt to be more objective and rapid even if the differences were not dramatic. Inter-observer reliability was confirmed by Joesoef et al in a study in 1991 using the scored grams stain as the method of diagnosis on 225 pairs of duplicate gram stained slides in Jakarta, Indonesia and the University of Washington, Seattle (188). Correct slide preparation was emphasized for maximally good results. Experience of the individuals who read the scored gram stains is most beneficial to the effectiveness of the results. Whether this could be considered as a POCT is a question that needs to be answered.

How accurate is the diagnosis of bacterial vaginosis using clinical criteria alone and/or with a wet mount observation?

Guideline 131: *We would suggest that the literature supports the lack of sensitivity and accuracy of clinical criteria alone for the diagnosis of bacterial vaginosis. Therefore additional testing, including POCT may be necessary to investigate in the future.*

Strength/consensus of recommendation: B

Level of evidence: III

What is the association of bacterial vaginosis with complications of pregnancy, such as preterm birth?

Guideline 132: *We would recommend that clinicians routinely provide POCT for pregnant patients for the rapid diagnosis of bacterial vaginosis because of its association with preterm birth.*

Strength/consensus of recommendation: A

Level of evidence: I

Can a POCT that involves no wet mount observation be used to detect BV?

Guideline 133: *It would be of benefit to have other assays available that do not rely on direct wet mount or gram stain evaluations of vaginal discharge. These would potentially provide assays that could be used as POCT especially in the pregnant woman. Some literature is available to support the use of non wet-mount examination tests to make a laboratory diagnosis of BV. However, there are no outcomes studies using any other assays other than direct observational examination tests such as wet mounts or gram stains.*

Strength/consensus of recommendation: B

Level of Evidence: II

In 2002, a review of the literature since 1976 was published by the CDC Bacterial Vaginosis (BV) working group evaluating outcomes of treatment in BV positive pregnant women (189). The suggestion in the review was that there appeared to be a causal association between prematurity and BV and the group felt that there was sufficient evidence to support the treatment of BV in order to prevent BV-associated preterm births. In addition, Hillier et al detected a higher rate of preterm births in women who were detected positive for BV at 23-26 weeks gestation compared to women that were negative for BV (190). There are opposing views about whether there is an association between BV and preterm births. A British study in 2004 has not found any relationship (191). Kekki et al tried to determine a risk-benefit to screening and treating pregnant women at low risk for BV. Their study did not uncover a cost-benefit to early screening programs, but they concluded that overall health care was improved when the women were screened and appropriate treatment for BV was administered (192).

A new rapid diagnostic kit called FemExam was examined in Gambia and results have been published. The Fem Cards had a sensitivity of > 90% as compared to clinical criteria for the diagnosis of BV. This test may afford a rapid POCT test that is less subjective than wet mount preparations (193). Use of the AFFIRM VP III assay, a probe assay for the detection of *Candida* sp., *Trichomonas vaginalis* and the entity bacterial vaginosis has been reviewed in the literature. For the diagnosis of BV, detection of high levels of *Gardnerella vaginalis* DNA appears to provide a rapid test that correlates well with scored gram stain and other methods to detect BV (194,195). It is listed as a moderately to highly complex assay and as such would require expertise and quality control monitoring as any such assay in order to be used as a POCT assay. Newer EIA or lateral flow assays for the detection of BV have only recently been

introduced into the clinical microbiology arena and it will be some time before any outcome studies are done to determine their true efficacy and value in making a rapid diagnosis of BV.

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Public Comments:

No public comments were received on the guidelines.

Table 1

Test	Antigens represented		Approved for HIV Types
	HIV-1	HIV-2	
Abbot/Orasure Oraquick Advance Rapid HIV ½	gp 41	gp 36	HIV-1 & 2
Bio-Rad Multispot HIV-1/HIV-2 Rapid	Recombinant & synthetic gp41	gp36	HIV-1 & 2, separate result for each
Trinity Unigold Recombigen HIV	gp 41, gp 120	?	HIV-1
MedMira Reveal Rapid HIV-1 Antibody	gp 41, gp 120	?	HIV-1

Chapter 9: Occult Blood

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This document summarizes our review of the literature on fecal occult blood and gastric occult blood. Occult blood is the unexpected presence of non-visible blood in the stool or other body fluids. A daily loss of 2 – 3 mL of blood is generally considered the lower limit for abnormal bleeding that may be indicative of gastrointestinal pathology. Increased sensitivity of fecal occult blood tests (FOBT) beyond this limit is associated with higher rates of false positives and decreased test specificity. Fecal occult blood testing is commonly utilized in outpatient settings to screen for colorectal neoplasia in asymptomatic individuals. FOBT has also been employed to monitor gastrointestinal bleeding in high risk hospitalized patients and to detect upper gastrointestinal bleeding. In emergency department settings, FOBT can indicate bleeding due to trauma or other conditions. Three methodologies are currently employed for FOBT including chemical or peroxidase-based methods, heme-porphyrin assays and immunological methods. FOBT is not reliable for detecting occult blood in gastric fluid, so other methods such as gastroccult have been developed for this purpose. These guidelines will focus on the use of FOBT for detecting colorectal neoplasia and other gastrointestinal lesions. We will also review data concerning the preferred methodology for FOBT in these settings. The utility of gastroccult

testing in an inpatient setting will be addressed. The literature search performed for occult blood testing is seen in Literature Search 61.

Does annual or biennial guaiac-based FOBT, in the average risk asymptomatic outpatient population over 50 years old (no family history or other risk factors for colorectal cancer), reduce mortality from colorectal cancer compared to no FOBT screening?

Guideline 134: *We strongly recommend that clinicians routinely provide guaiac-based FOBT for asymptomatic individuals older than 50 years at least biennially to reduce mortality from colorectal cancer. Three large randomized control trials have illustrated a 15-33% reduction in mortality from annual or biennial FOBT. FOBT is easy, inexpensive and poses no risk to the patient.*

Strength/consensus of recommendation: A

Level of evidence: I and II (randomized control trials and case-control studies)

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States with over 570,000 new cases per year. The lifetime incidence in the US population is approximately 6%, a rate that justifies mass screening. Colorectal carcinoma has a well-defined natural progression and survival correlates strongly with the stage of the tumor. Screening can change the overall prognosis and outcome in patients with early disease. FOBT detects blood loss in the stool arising from colorectal neoplasms and has become a standard practice to screen for CRC. However, the optimal approach for the prevention of CRC remains uncertain (1-4).

Three randomized control trials, Minnesota Colon Cancer Control Study, Nottingham, United Kingdom and Funen, Denmark, enrolled over 250,000 participants and demonstrated a 15-33%

reduction in mortality from annual or biennial FOBT (5-14). The Minnesota Colon Cancer Control Study enrolled 46,551 volunteers aged 50-80 years randomized to annual FOBT, biennial FOBT or control (no intervention) (5). Participants were asked to submit six guaiac-impregnated paper slides (slides contained two smears from each of three consecutive stools). Dietary restrictions, such as avoidance of aspirin, red meat and vitamin C, were in place, but were not verified. The Hemoccult II method, with rehydration for most samples, was employed in the hospital laboratory. All volunteers with positive results were encouraged to obtain a full examination and colonoscopy. After a 13 year follow up the volunteers receiving annual FOBT had a 33% reduction in mortality compared to controls. This remained unchanged after 18 years. The volunteers receiving biennial FOBT for 13 years had a 6% reduction in mortality compared to controls. The results in the biennial group were not significant after 13 years, however; after an 18 year follow up the mortality reduction in the biennial group was statistically significant at 21% (6).

The European studies were similar in design to the Minnesota study with a few exceptions. The Nottingham, United Kingdom trial recruited 152,850 people aged 45-74 who lived in Nottingham between 1981 and 1991 (7). The participants were randomly assigned to biennial FOBT or no screening. No dietary restrictions were utilized except in cases of borderline results. Participants received the original Hemoccult home test kit (single slide rather than triple slides) with instructions from their primary care physician. The specimens were shipped to the medical center and results analyzed without rehydration by one of three investigators. A 15% reduction in cumulative CRC mortality was found in participants who received biennial screening with a median follow up of 7.8 years. This mortality reduction was still apparent after an 11 year

follow up (8). In Funen, Denmark 140,000 people aged 45-75 who lived in Funen were allocated to biennial FOBT or no screening (9). The Hemoccult II assay was employed with dietary restrictions, but without rehydration. Biennial screening for 10 years decreased CRC mortality by 18%. Further delineation in this study illustrated that the mortality reduction was most pronounced in patients with lesions above the sigmoid colon (10). The Denmark study is still in progress.

The conclusions in the three randomized trials were similar, although the magnitude of mortality reduction differed. These differences have been attributed to multiple factors including variations in compliance rates, study population, test sensitivity and length of follow up. Compliance is a major impediment to FOBT and it has been estimated that less than 25% of the population undergoes FOBT despite aggressive publicity (15). The European trials may have better external validity because they enrolled all eligible members of the population as opposed to volunteers. The Minnesota study has also been criticized for rehydrating test samples, which increases test sensitivity (16,17). In the Minnesota study 28-38% of the volunteers in the test group received colonoscopy, while only 4% of the participants in the European trials underwent colonoscopy for a positive fecal occult blood result. Both annual and biennial screening techniques were employed. Although annual testing in the Minnesota trial, further decreased mortality compared with biennial testing, it occurred at the expense of additional testing (1). The follow up periods were also not consistent between trials.

The randomized studies have also shown that patients who receive annual or biennial FOBT have both a longer survival time than patients who are not screened or are at an earlier stage of

CRC upon detection (5-10,13,14). However, these conclusions are made with caution due to lead-time bias. The increased survival may be due to the detection of cancer at an earlier stage.

Other studies corroborate the results of the three randomized control trials. A recent large controlled trial including 91,999 individuals aged 45-74 years was performed in Burgundy, France (18). Individuals received either biennial FOBT using a guaiac-based method (without diet restriction or rehydration) or no screening. The population was followed for eleven years. CRC mortality was 33% lower in the population that had at least one FOBT screening than in the control group. O'Leary et al. (19) examined the efficacy as well as the cost effectiveness of FOBT compared to more invasive methods. Colonoscopy averted the greatest number of deaths from CRC (31%), followed by annual FOBT (29%), flexible sigmoidoscopy (21%) and biennial FOBT (19%). However, flexible sigmoidoscopy was the most cost-effective. Several case control studies have confirmed the ability of annual or biennial FOBT to lower mortality from CRC by 25-80% (20-25). These studies typically compared patients who died from CRC to age and sex-matched controls and retrospectively determined whether they had received FOBT. Case-control studies provide direct estimates of efficacy of screening uninfluenced by noncompliance, however; screened patients may differ from nonscreened patients in terms of CRC risks. A recent abstract at the Digestive Disease of the Week (DDW) by Bampton et al. (26) illustrated that screening patients with an immunoassay for hemoglobin (InSure, Enterix, NJ), after an initial colonoscopy, detected additional pathology.

The utility of FOBT in combination with sigmoidoscopy for the detection of CRC has been examined by several studies, including two randomized control trials (11,27,28). One study

randomized 24,465 volunteers to either 16 years of biennial Hemocult II testing or a single flexible sigmoidoscopy and Hemocult II test (11). Screening with Hemocult II biennially for 16 years detected more CRCs than single screening, but the difference in length of follow up makes mortality rates difficult to compare. At thirteen Veteran's Administration centers 2885 asymptomatic individuals aged 50-75 received a colonoscopy to detect neoplasia in addition to flexible sigmoidoscopy and FOBT (27). In those patients with CRC, a combination of flexible sigmoidoscopy and FOBT identified 75.8% of the cancers. FOBT detected 5% of cancers that were not seen on flexible sigmoidoscopy. In the Colon Project, Winawer et al. enrolled 21,756 patients aged 40 or older to either a study group (annual rigid sigmoidoscopy and FOBT) or control group (annual sigmoidoscopy alone) (28). They found an increased survival in the study group but no significant effect on mortality. More studies with similar designs will be necessary to determine if the addition of flexible sigmoidoscopy to FOBT is warranted. Although the evidence is not clear, based on currently available studies, the American Gastroenterological Association (AGA) recommends combining the tests and performing FOBT every year and sigmoidoscopy every five years (29). FOBT should be performed first because a positive test warrants a colonoscopy and sigmoidoscopy can be avoided.

Two randomized control studies showed no reduction in mortality from CRC screening. Kewenter et al. reported a study of 68,308 participants in Goteborg, Sweden randomized into screening or control groups (12). More CRCs were detected in the screened group, but no significant differences in mortality rate were found. These participants were only followed for 2-7 years, which may not have been long enough to detect a statistical difference in mortality rates. In another study, all residents of Jiashan County, China, aged 30 years or older were enrolled in a

randomized control trial to screen for CRC (30). The screening method was immunological FOBT. The study showed a reduction in mortality from rectal cancer, but no reduction in mortality from colon cancer. These results may differ from other randomized control trials because of the study population, screening method or other disparities in the study design.

Most studies illustrate that FOBT reduces CRC mortality at minimal risk to the patient (1-14). Studies performed in the UK, using the knowledge gained from the Nottingham trial, also illustrated that screening for CRC with FOBT can be successfully implemented in a population between 50 to 69 years old (31,32). The 2003 AGA guidelines recommend yearly FOBT of two samples from each of three consecutive stools in all average risk men and women starting at age 50. Currently the AGA recommends against rehydration because it substantially increases the false positive rate. Either an immunochemical test without dietary restrictions or guaiac-based tests with dietary restriction are advocated (29). In contrast to the AGA, there is one meta-analysis showing that dietary restriction does not significantly affect the positivity rate for non-rehydrated guaiac-based FOBT and advises against dietary restriction (33).

Although there is strong evidence to support FOBT for colorectal screening, studies have not addressed several key points. No trials have shown the preferred methodology for FOBT screening in CRC including whether the guaiac-based assays should be rehydrated or non-rehydrated. Other issues include the need for dietary restrictions, the recommended length of follow up, the most beneficial frequency of screening and the strategy for follow up of positive fecal occult blood results.

Does annual or biennial guaiac-based FOBT, in the asymptomatic population over 50 years old, significantly decrease the incidence of colorectal cancer?

Guideline 135: *We cannot currently recommend for or against the use of guaiac-based FOBT to reduce the incidence of colorectal cancer. Randomized control studies addressing this question are conflicting, however; the differences in length of follow up make it difficult to draw direct comparisons. More studies need to be performed to resolve this question. or biennial FOBT. FOBT is easy, inexpensive and poses no risk to the patient.*

Strength/consensus of recommendation: I

Level of evidence: I and II (randomized control trials and case-control studies)

The concept that FOBT may lower the incidence of CRC has been debated. Some experts have postulated that screening for CRC with FOBT will decrease the incidence of cancer. Patients with positive fecal occult blood results may receive colonoscopy and in a percentage of cases precursor lesions (i.e. adenomatous polyps and villous adenomas) will be detected and removed preventing cancer from developing. On the other hand, small benign adenomatous polyps are less likely to bleed than carcinomas and they may not be efficiently detected by mass screening. In many cases, FOBT will discover early stage cancers without necessarily decreasing the incidence of disease but rather only the rate of mortality (1,2,4).

The three randomized control trials addressing the use of FOBT made different conclusions concerning the effect of FOBT on the incidence of CRC (5,7,9). The Minnesota Colon Cancer Control Study involved 46,551 volunteers tested annually or biennially for fecal occult blood. This study found a decreased incidence of CRC in both screened groups at 13 and 18 years of

follow up (34). After eighteen years the number of cases of CRC was 417, 435 and 507 in the annual, biennial and control groups, respectively. In the Nottingham, United Kingdom study 4.3% more cancers were detected in the biennially screened population after 7.8 years of follow up (7). In the Funen, Denmark trial an equal number of cancers were seen in the screened and control populations, which included a 10 year follow up period (9). The different conclusions in the three studies have been attributed to the variation in length of follow up (7.8 years in UK, 10 years in Denmark and 18 years in Minnesota). The Denmark trial, which is still ongoing, may answer this question. In addition, hydrated fecal occult blood samples were utilized in the Minnesota trial, which increases test sensitivity and may help detect more precursor lesions. The design of the Minnesota study may actually have underestimated the true effect on the incidence of CRC in each group (34). The subjects in the control group were not prevented from undergoing screening through their personal physicians. Compliance with the protocol was also not optimal and may have attenuated the true effect. Finally a hiatus occurred in the screening program (4.5 years for the annual group and 3.6 years for the biennial group), which may have masked the true incidence.

Other studies investigating the effect of FOBT on the incidence of CRC are also conflicting. A randomized controlled trial was performed on 27,000 inhabitants of Goteberg, Sweden aged 60-64 (35). After the original randomized control trial was completed (12) a subsequent study determined the incidence of CRC in the test and control group during a seven year follow up. The control group had more colorectal neoplasms than the test group with the greatest effect during the first two years. However, if the entire length of screening and follow up was included, the incidence of CRC in the two groups was similar. The increased incidence of cancer

in the control group during rescreening may have been due to a lead-time effect. Niv et al. (36) did not find any difference in the incidence of CRC in screened versus non-screened volunteers during a three year screening and 8 year follow up period. A similar incidence of CRC in the screened and control group was also found in a study done in Burgundy, France (18). In contrast, a case control study done on 357 patients with advanced CRC and age and sex-matched controls strongly suggested that screening reduced the incidence of advanced CRC (37).

In conclusion, although randomized control trials have been performed to determine whether FOBT decreases the incidence of CRC, the results to date are unclear. Ongoing studies with longer lengths of follow up may clarify this issue.

Should FOBT be performed in the central laboratory or at the point-of-care for asymptomatic patients who require screening for colorectal cancer?

Guideline 136: *We cannot recommend for or against the use of point of care testing to screen for colorectal cancer in asymptomatic patients. Experts suggest that home collection of specimens with analysis either in the physician office or laboratory is recommended over traditional point of care testing for occult blood by digital rectal examination. In addition, the randomized control trials illustrating colorectal cancer mortality reduction utilized the central laboratory to perform FOBT. However, no trials have compared these methodologies and addressed the benefits of point of care testing, which include convenience and an increase in compliance.*

Strength/consensus of recommendation: I

Level of evidence: III (retrospective trial, expert opinion)

The validity of testing for occult blood at the point-of-care versus the central laboratory has not been adequately addressed. Specimens for FOBT may be obtained at home, by the patient, or in association with a digital rectal examination (DRE). Specimens can then be mailed to a central laboratory for testing, delivered to an outpatient clinic for analysis, or collected at the bedside during examination for immediate FOBT. Home collection of samples with physician office analysis is neither traditional point of care testing (POCT) (i.e. immediate collection with prompt results at the bedside) nor central laboratory testing. Categorization of non-traditional POCT techniques is controversial.

The AGA and other experts imply that traditional FOBT at point of care is not recommended due to lack of sensitivity (29,38). The significance of a single positive FOBT obtained during DRE compared to the recommended home collection of six specimens has also not been evaluated. In addition, specimens received by DRE may be affected by the lack of dietary and medication restrictions in these patients. In a study by Fisher et al. (39), published as an abstract in the DDW, only 5% of patients with significant pathology by colonoscopy had a positive FOBT by DRE. Some clinicians believe that induced rectal trauma at the time of digital exam leads to a high false positive rate. However, Eisner et al. (40) performed a retrospective study on 270 patients who underwent colonoscopy for any positive FOBT. The frequency of colonic abnormalities was similar with both collection methods, which argues against a high false positive rate with DRE. Many clinicians perform DRE as part of a routine physical or hospital admission, in part because it may be the only opportunity to screen for CRC in certain patients. However, no large prospective trials have compared the accuracy of central laboratory testing to non-traditional or traditional POCT.

Which FOBT method, guaiac-based, heme-porphyrin assay or immunological, is the most accurate (sensitivity, specificity, positive predictive value) in an outpatient setting for the detection of colorectal cancer in asymptomatic individuals over 50 years old?

Guideline 137: *We cannot currently recommend an ideal fecal occult blood method for the detection of colorectal cancer based on the current literature and available methodology.*

Although guaiac-based testing is not extremely sensitive, it is reasonably specific, cheap, easy to use, and poses no risk to the patient. In addition, three large randomized control trials utilized guaiac-based methods to illustrate a reduction in colorectal cancer mortality. Even though guaiac-based methods are widely used in the United States, there is insufficient evidence to recommend guaiac-based methods over other types of assays.

Strength/consensus of recommendation: I

Level of evidence: II and III (prospective comparative trials, descriptive studies and opinion)

Three main categories of FOBT are available in the United States, guaiac-based/chemical methods, immunological assays and heme-porphyrin methods (38). Guaiac-based methods such as the Hemoccult II (HO) detect pseudoperoxidase activity in hemoglobin. The pseudoperoxidase present in hemoglobin interacts with guaiac, impregnated in a card, producing a blue color. False positives results can occur in patients on certain medication or in patients who consume rare red meat, turnips and horseradish, which contain peroxidase. High doses of vitamin C can produce false negative results. The sample utilized for guaiac-based methods can be rehydrated to increase sensitivity at the expense of specificity and positive predictive value (17). The Hemoccult SENS(A) (HOS) (SmithKline Diagnostics, Inc.) is also a guaiac-based method with acceptable sensitivity and specificity and fewer false positives than the rehydrated

HO. Guaiac-based methods are inexpensive, easy to perform and can be interpreted in the physician's office (POCT). However, dietary and drug restrictions are required, and there will still be a delay in processing the test if rehydration is performed (1,3,15).

The immunological and heme-porphyrin methods were developed to improve sensitivity. Immunological methods include the HemeSelect (HSeI), which uses reverse passive hemagglutination and detects intact hemoglobin and globin. It was designed to specifically detect colonic lesions (but not upper gastrointestinal bleeding). These methods are more expensive than guaiac-based methods and require more involved interpretation. The Hemoquant (HQ) is a heme-porphyrin test, which detects porphyrin. Patients with CRC generally have fecal hemoglobin concentrations greater than 2 mg/g feces. The test has a high sensitivity for bleeding both from upper and lower gastrointestinal sources, but this compromises its specificity for CRC (1,3,15).

A large study was done on 8104 asymptomatic patients scheduled for routine physicals at Kaiser Permanent Medical Center to compare the ability of HO, HSeI, HOS and a combination of HOS and HSeI to detect CRC (41). Each patient received all three testing methods. Dietary restrictions were in place, but not confirmed and no rehydration of samples was performed. Patients with positive results by any testing method received a colonoscopy and all patients were followed for two years. The HOS had the highest sensitivity for the detection of CRC at 79.4%, but the lowest specificity at 86.7%. HO had the highest specificity (97.7%), but a poor sensitivity (37.1%). The HSeI was neither the most sensitive nor the most specific. All had positive predictive values (PPV) less than 9.0%. Combination testing was also performed. If a

positive HOS result was obtained by screening, it was confirmed with the HSeI method. This resulted in a sensitivity of 65.6%, a specificity of 97.3% and a PPV of 9.0%. The value of combination testing in an outpatient setting beyond this study is uncertain.

Several other studies have been performed to determine the accuracy of FOBT methods in asymptomatic individuals eligible for CRC screening (16,41-50). A wide range for sensitivities, specificities and PPVs are obtained when the results of different studies are compiled. The variations could be the result of differences in study population, age of participants, dietary requirements, preparation of specimens (i.e. rehydration), endpoints measured, screening intervals and years of follow up. The large discrepancies in the ranges for sensitivity, specificity and PPV make the data in the literature difficult to interpret. Immunological methods (i.e. Hemeselect) are generally more sensitive and less specific, but interpretation of the available literature suggests that the differences are not striking. Guaiac-based methods such as HO are more specific and for their convenience tend to be the method of choice. All methods have poor PPVs due to the relatively low prevalence of CRC in the asymptomatic screened population.

A few articles have examined the accuracy of FOBT in symptomatic or high-risk patients with family histories of CRC (51-54). Similar to the studies done with asymptomatic patients, these studies are also not consistent. Four studies on symptomatic patients compared HO to the heme porphyrin method, HQ (51-54). Barber et al. (52) compared the HQ and HO method in 184 patients with bleeding secondary to iron deficiency and concluded that the HQ had an overall better performance for detecting gastrointestinal lesions. On the other hand, St. John et al. (54) reported that HO was more sensitive than HQ for the detection of CRC in a cross-sectional

study. The range of sensitivities for the detection of CRC or gastrointestinal lesions was between 26-89.5% for HO and 26-74.2% for HQ. Specificities ranged from 32.4-99.3% for HO and 81-94.7% for HQ. Most of the authors question the added benefit of quantitative HQ especially due to the increased cost and inconvenience (51,52,54). Ahlquist et al. (51) suggests that neither HO nor HQ is optimal for screening high-risk patients.

Patient and physician compliance is a major obstacle in FOBT. Averages from the literature estimate that only 50% of the eligible population undergoes FOBT for CRC screening, but in reality the numbers may be less than 25% (15). Cole et al. (55) performed a study on 1818 residents between 50 and 69 years to determine compliance rates with different FOBT methodologies. Participation was higher with immunological methods that involve more convenient sampling and remove the need for dietary and drug restrictions. By contrast a meta-analysis found that moderate dietary restrictions did not affect completion rates (33). In addition to providing optimal sensitivity and specificity, the preferred methodology for FOBT should maximize patient participation.

The literature does not demonstrate that any one FOBT method is superior for the detection of CRC. After a review of the literature, Young et al. (56) also concluded that no FOBT method fulfills the needs of all target populations. This study recommends using the patient population and colonoscopy resources to determine the most reliable method. No studies incorporated a cost analysis into their study design to aid in the differentiation of methodologies. In general, guaiac-based methods are utilized clinically because they are easy to use, inexpensive and have been shown to decrease mortality from CRC in at least three randomized control trials. The

AGA recommends either guaiac-based testing with dietary restriction or an immunochemical method (29).

Is FOBT useful in symptomatic patients to differentiate bleeding due to upper gastrointestinal lesions (including gastroesophageal cancer) from bleeding due to lower gastrointestinal lesions?

Guideline 138: *We cannot currently recommend FOBT to differentiate upper from lower sources of gastrointestinal bleeding. A limited number of cohort and case-control studies have demonstrated that FOBT can detect bleeding due to upper gastrointestinal lesions, but there is no evidence to support that guaiac-based FOBT can determine the origin of bleeding.*

Strength/consensus of recommendation: I

Level of evidence: II (case-control and cohort studies)

Both upper and lower gastrointestinal lesions can result in positive fecal occult blood tests.

Traditionally, guaiac-based FOBT was designed to detect lower gastrointestinal sources of bleeding by monitoring intact hemoglobin. In the case of upper gastrointestinal bleeding, hemoglobin undergoes degradation by intestinal enzymes as it passes through the gastrointestinal tract, which frequently causes a false negative result using guaiac-based tests. However, in patients with significant bleeding (5-10 mL per day) from an upper gastrointestinal source intact hemoglobin can still be detected in the stool. The ability of guaiac-based tests to detect bleeding is variable and depends on anatomic, physiologic and dietary factors. Immunochemical tests are very sensitive for colonic bleeding but do not detect blood from the upper gastrointestinal tract.

In contrast, the heme-porphyrin test, which measures porphyrin, the breakdown product of hemoglobin, can quantitate bleeding from any gastrointestinal source. However, most immunological and porphyrin methods require laboratory processing (38).

Studies have shown that guaiac-based FOBT can detect upper GI sources of bleeding (57,58). However, these studies do not suggest that FOBT can differentiate the source of bleeding and have questioned the utility of FOBT for detecting bleeding due to gastric or esophageal lesions. A prospective study was published using 248 patients with positive guaiac-based fecal occult blood tests (Hemoccult II) (58). All of the patients were referred for further evaluation (colonoscopy or upper endoscopy). Of all patients, 48% had gastrointestinal lesions identified. 21.8% were colonic and 28.6% were upper gastrointestinal, illustrating that guaiac-based FOBT can detect bleeding throughout the gastrointestinal tract, but without discrimination. A study done in high risk inpatient pediatric patients with known upper and lower gastrointestinal sources of bleeding suggested the use of highly sensitive guaiac-based methods for suspected upper gastrointestinal bleeding in children. However, the authors did not suggest that this method may be used to differentiate the source of bleeding (59). In 178 patients starting dialysis, guaiac-based FOBT detected more CRCs than upper gastrointestinal tumors (57).

Heme-porphyrin methods have also been shown to detect bleeding from upper gastrointestinal sources. Harewood et al. (60) tested 56 patients with known upper gastrointestinal lesions and found that heme-porphyrin methods detected upper gastrointestinal blood loss more frequently than guaiac-based or immunological based assays. Another study compared guaiac-based methods with heme-porphyrin methods in 106 healthy volunteers, 170 patients with gastrointestinal symptoms, 44 patients with gastrointestinal cancer, 75 patients with benign polyps and 374 patients with other benign gastrointestinal lesions (61). The heme-porphyrin

based method was more sensitive for gastrointestinal bleeding and was better in detecting bleeding from proximal lesions.

Immunological FOBT are insensitive for upper gastrointestinal sources of bleeding (62,63).

Nakama et al. performed two studies (62,63) using patients with documented upper and lower digestive tract diseases and healthy controls. In one study immunological FOBT was performed on 226 subjects (124 with upper gastrointestinal disease, 34 with CRC and 68 healthy controls) (63). The sensitivity for upper digestive tract disease was only 19%. In the other study immunological FOBT was performed on 150 patients with gastric cancer, 150 patients with CRC and 300 healthy volunteers (62). FOBT was positive in 8% of patients with gastric cancer and 7% of patients without gastric cancer. In these studies immunochemical occult blood tests could detect only a low percentage of patients with upper gastrointestinal bleeding. These studies recommended against the use immunological FOBT to screen for suspected upper gastrointestinal lesions.

In a paper by Rockey et al. (64) groups of 10 healthy volunteers drank blood mixed with tomato juice for three consecutive days and were tested for fecal occult blood by a variety of methodologies. The highly sensitive guaiac-based method (HOS) detected blood in all subjects after ingestion of 20 mL of blood and in 50% of subjects after ingestion of 10 mL and was more sensitive than the Hemoccult II for detecting upper gastrointestinal bleeding. Immunochemical assays did not detect occult blood in any of the subjects. This data raised “the possibility that a combination of a highly sensitive guaiac-based FOB test plus an immunochemical method could aid in differentiating occult upper from lower GI bleeding.”

Evidence supports the fact that upper gastrointestinal bleeding can be detected by FOBT, but no in vivo human studies have addressed the ability of FOBT to differentiate the source of bleeding. Although clinicians would find a rapid, easy to use, sensitive method to differentiate upper from lower sources of gastrointestinal bleeding useful, there is no evidence to suggest that the guaiac-based FOBT can make this distinction.

Can guaiac-based FOBT be utilized in patients on therapeutic anticoagulation to predict if a patient is at high risk for gastrointestinal bleeding?

Guideline 139: *We cannot currently recommend for or against the use of guaiac-based FOBT to predict gastrointestinal bleeding in patients on anticoagulation. Although the current literature is sparse, it suggests that positive fecal occult blood results do not correlate with the level of anticoagulation. From this data it can be extrapolated that FOBT would not be predictive of bleeding risk. More studies need to be done to directly address this issue.*

Strength/consensus of recommendation: I

Level of evidence: II and III (prospective trials and expert opinion)

Many inpatients and outpatients receive anticoagulation for cardiovascular-related events.

Bleeding is a significant risk for patients on anticoagulation. A few studies have investigated the effects of anticoagulants on FOBT results. A prospective crossover study of 100 patients over 40 years old was done (65). Patients were assigned to groups taking no aspirin or warfarin, daily aspirin (81 mg or 325 mg), or warfarin, but no aspirin. Each patient collected stool at home and occult blood testing was done in the central laboratory by the HQ and/or HO methods. No increase in the rate of positive FOBT was seen in the patients taking warfarin. In addition the

international normalized ratio (INR) level, which is used to monitor anticoagulation therapy, was not associated with occult blood by HQ. A small dose-dependent increase in gastrointestinal blood loss was seen in patients taking aspirin, however; the quantity detected was still within the normal limits of 2 mg hemoglobin per gram of stool.

A study by Blackshear et al. (66) investigated 117 patients on anticoagulation for atrial fibrillation. The patients received either standard warfarin (INR 2-3), warfarin (INR <1.5) and 325 mg of aspirin, or aspirin alone. After one month of therapy the patients mailed specimens to the laboratory for HQ FOBT. The patients taking warfarin and aspirin had slightly more fecal hemoglobin than those taking standard warfarin. None of the results were significantly different from the reference population without atrial fibrillation. In a prospective study, 256 patients on anticoagulation were screened with HO with no rehydration (67). The positive rate was higher in the patients on anticoagulation (12% versus 3%), but the patients with positive results had previously undiagnosed lesions of the gastrointestinal tract. This study postulated that anticoagulants might unmask bleeding from preexisting lesions.

The few trials examining FOBT on anticoagulated patients are consistent. Fecal blood level in patients treated with anticoagulation or low dose aspirin are normal or minimally elevated compared to controls (38,65-68). Some recommendations suggest stopping aspirin before FOBT is performed, but Greenberg et al. (65) suggests that aspirin and warfarin do not compromise the accuracy of FOBT and that the cardiovascular disadvantages of discontinuing anticoagulation outweigh the minimal FOBT benefits. In addition the INR does not correlate with positive FOBT results (65-67). These studies conclude that a positive FOBT should not be attributed

solely to anticoagulation therapy and should lead to a formal evaluation. Whether qualitative or quantitative hemoglobin monitoring in the stool may predict bleeding events is not known, but the studies described imply otherwise. FOBT can be done at the point-of-care (i.e. DRE at inpatient bedside) or by home collection (i.e. presumably in outpatients). No study has described the effect of anticoagulation on guaiac-based FOBT results done on inpatients after DRE.

Although clinicians utilize FOBT at the point of care to predict gastrointestinal (GI) bleeding in inpatients or outpatients on anticoagulation this practice cannot be substantiated by the literature.

Can gastroccult testing of gastric fluid from a nasogastric tube be used to detect gastrointestinal bleeding in high-risk intensive care unit patients receiving antacid prophylaxis?

Guideline 140: *We cannot currently recommend for or against the use of gastroccult to detect gastric bleeding in intensive care unit patients receiving antacid prophylaxis. Only one study to our knowledge has indirectly addressed this issue. No randomized controlled trials have been performed.*

Strength/consensus of recommendation: I

Level of evidence: III (small study and clinical evidence)

FOBT should not be used to measure occult blood in gastric fluid because of interferences from low pH, certain medications (antacids and vitamin C lead to false negative results) and metal ions (iron and copper salts lead to false positive results). The presence or absence of occult blood in gastric fluid is useful in emergency department or intensive care unit settings for the detection of bleeding due to trauma or a deteriorating gastric condition (stress ulcer syndrome). Gastroccult tests are employed for this purpose. The pseudoperoxidase in hemoglobin reacts with guaiac and a buffered, stabilized hydrogen peroxide solution producing a blue color in the

presence of blood. Two in-vitro studies have illustrated that gastrocult is a simple, rapid and convenient method for the evaluation of patients with suspected occult blood in gastric fluid. Gastrocult, unlike Hemocult, is not influenced by pH or sucralfate (69,70).

Derrida et al. (71) used gastrocult every four hours to identify blood in gastric juice of 41 ICU patients at risk for gastrointestinal bleeding (patients with overt gastrointestinal bleeding were excluded) and receiving antacid prophylaxis. 27% (14/41) had at least one positive gastrocult reading and received an upper endoscopy. No endoscopy was performed in patients with negative gastrocult findings. In 13/14 patients a source of gastric bleeding was detected. This study suggests that gastrocult testing may aid in detecting occult bleeding in critically ill patients. However, this small study did not perform upper endoscopy on negative patients, which would have documented the false negative results obtained with the gastrocult test.

Current data is insufficient to recommend the use of gastrocult for ICU patients to detect upper gastrointestinal bleeding. Although this practice is widespread, more studies will be necessary to document the utility of gastrocult testing for this application.

In summary, FOBT is rapid, inexpensive, easy to use and useful in a variety of practice settings to assist clinicians in detecting gastrointestinal bleeding and to guide the selection of appropriate follow up testing. Annual or biennial FOBT on two samples from each of three consecutive stools is recommended for all average risk men and women beginning at age 50 to reduce mortality from CRC. Most experts agree that FOBT, while reducing CRC mortality, does not affect the incidence of CRC. This issue remains controversial because the literature conclusions

are not consistent. Although FOBT is inexpensive and poses minimal risk to the patient, many patients with no pathology will require the discomfort, cost and risk of colonoscopy if a positive result is obtained. Despite consensus among expert groups that FOBT reduces mortality from CRC, the screening rates remain low and the follow up of positive FOBT is inadequate. The medical community should not only optimize the clinical utility of FOBT, but also should improve patient and physician compliance and enforce regular FOBT to maximize the benefit for patients. No studies have investigated the role of FOBT, if any, in the management of patients with CRC.

The use of FOBT at the point of care cannot be advocated due to lack of medical evidence, although it's convenience and the opportunity for greater compliance is appealing. The randomized control trials performed FOBT in the central laboratory and no clinical trials have investigated the role of POCT versus the central laboratory.

Currently no specific FOBT methodology can be recommended. However, the most recent AGA recommendation suggests either yearly guaiac-based tests with dietary restriction or an immunochemical test without dietary restriction. The AGA also recommended against rehydrating FOBT because it leads to substantially higher false positive rates. Guidelines on the preferred methodology in specific settings, including a cost analysis, need to be published.

The use of FOBT in hospitalized patients has not been thoroughly explored. Studies suggest that FOBT results do not correlate with the level of anticoagulation, however; the utility of FOBT to monitor anticoagulation has not been addressed. According to current evidence, the use of

FOBT to differentiate upper and lower gastrointestinal lesions also cannot be advocated.

Furthermore, the role of occult blood testing on non-gastrointestinal specimens such as nipple discharge and sputum is unknown. The small numbers of studies that have examined the role of occult blood in nipple discharge or sputum for the diagnosis of breast or lung cancer have shown that occult blood testing is neither a sensitive nor specific method (72-75).

Gastrocult is frequently used in inpatient setting to detect blood in gastric fluid or vomitus.

Studies on gastrocult testing are sparse and no definitive guidelines on the clinical utility of gastrocult at the point-of-care can be determined from the literature.

Finally, new methodology has recently been developed to detect DNA mutations in the stool that are associated with CRC. Studies are currently in progress that compare FOBT to DNA-based methods.

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Public Comments:

- 1) Received during the AACC presentation – Can you address the utility of digital rectal exam for point of care fecal occult blood? *We added a recommendation addressing*

- the use of FOBT in the central laboratory or at the point of care. This recommendation states that although most experts advise against testing for occult blood by DRE, the evidence to support this is insufficient.*
- 2) Dr. Callum G Fraser wrote a letter suggesting that several points and references be added to the discussion. – *We added discussions pertaining to the following references (31-33,38,55,56) that can be found throughout the guidelines.*
 - 3) Dr. Gary Lee Utz wrote that “The POC issue in FOBT does not appear to be adequately addressed in the draft guidelines.” – *In response to his comment we added a separate recommendation discussing the utility of FOBT at the point of care versus the central laboratory. Evidence to recommend FOBT at the point of care is insufficient.*
 - 4) Brenda L.M. Franks asked “Do you have any plans to address FOB testing for patients on intensive anti-coagulant therapy?” – *We added a recommendation on the use of FOBT in patients on therapeutic anticoagulation. The evidence was insufficient to recommend for or against the use of FOBT to predict gastrointestinal bleeding in patients on anticoagulation.*

Chapter 10: Intraoperative Parathyroid Hormone Testing

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In the late 1980s, intact parathyroid hormone (PTH) was proposed as an intraoperative monitor to the already successful surgery for primary hyperparathyroidism to provide guidance regarding extent of neck exploration and removal of parathyroid tissue (1). The utility of PTH lies in its specificity to the parathyroid glands and a half-life of the intact 84-residue molecule of less than 5 minutes. Modifications to intact PTH assays allowed for results available in 15 minutes or less and commercialization of assays in the mid 1990s expanded the application of the intact PTH assay to allow for real-time testing during parathyroid surgery. Although PTH may not be thought of as a typical point-of-care test or analyte, measurement in the operating and angiography suites qualifies it as such. Detailed reviews providing background on intraoperative

PTH testing have been published previously (2-4). This document will explore clinical questions on the applications of the rapid PTH assay and the impact of the assay on patient health, operational, and financial outcomes. Development of practice guidelines was based on literature searched from the PubMed database (1966-November week 2, 2003) and was limited to articles in English and those with abstracts (Literature Searches 62 - 75).

Primary Hyperparathyroidism

- Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the accuracy of identifying multiglandular disease compared to bilateral exploratory surgery?
- Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with: Primary Hyperparathyroidism?
- Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve morbidity or complication rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism?
- Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve the use of local or regional anesthesia or extent of exploration (unilateral vs. bilateral) compared to standard bilateral exploration?
- Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve use of

frozen sections compared to standard bilateral exploration?

- Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve operating room time, operating room fees, overall hospital costs, or length of stay compared to standard bilateral exploration?
- Does the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve incision size/cosmetic result or patient satisfaction/pain compared to standard bilateral exploration?

Guideline 141: *Based on evidence for improved patient health, operational, and economic outcomes, we recommend routine use of intraoperative parathyroid hormone testing for patients undergoing surgery for primary hyperparathyroidism and strongly recommend routine use in minimally invasive or directed procedures.*

Strength/consensus of recommendation: A/B

Level of evidence: I, II, and III (randomized controlled trials, controlled trials, cohort study, case series, models and simulations, opinion)

Literature Search 62 investigated the following questions: 1) Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the accuracy of identifying multiglandular disease compared to bilateral exploratory surgery? and 2) Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism?

Of the greater than 200 publications on intraoperative PTH, fewer than 10 have any type of control group for comparison. The idealized randomized controlled trial with blinding to patient and surgeon may not be applicable to all surgical procedures. Also, as techniques become well known it is difficult to perform prospectively controlled trials (5). This may be the case for intraoperative PTH where in a discussion of study design it was noted “the fact that quick parathormone early on was so useful . . . it seemed a disservice to limit the use of the technique (6).” The limited controlled studies on intraoperative PTH have typically compared different operative strategies of which intraoperative PTH was a component. In these studies cure rates were uniformly very high in all of the studies in both the control and experimental groups (Table 1).

Two studies employed a prospective randomized design (7,8). In the study by Bergenfelz et al, 91 patients undergoing first time exploration for primary hyperparathyroidism were randomized to either the experimental unilateral group with limited exploration, preoperative localization with sestamibi scintigraphy radiologic scans, and intraoperative PTH testing with sampling at, before, and 5 and 15 minutes after gland excision (n=47) or the control bilateral group with no preoperative localization, bilateral exploration with four gland visualization and frozen section (n=44) (7). Groups were equivalent with respect to age, sex distribution, preoperative lab values, clinical signs and symptoms, and, at surgery, the incidence of multiglandular disease. The overall cure rate was 97% based on normocalcemia one year postsurgery with two patients with persistent disease in the unilateral group and one in the bilateral group. With respect to intraoperative PTH, there was one false positive result and one true negative result for the operative failures. A false positive result is defined as a 50% decrease in PTH concentrations

from baseline in a patient who is not cured while a true negative result is an appropriate lack of a 50% decrease in PTH concentrations from baseline due to existing hyperfunctioning tissue.

In the second study, forty-eight patients with primary hyperparathyroidism were evaluated for video-assisted parathyroidectomy (VAP) based on clinical history and preoperative ultrasonography suggestive of a solitary parathyroid adenoma (8). Thirty-eight patients were eligible for the study and patients were randomized through the flip of a coin. Gender distribution was similar although the mean age in the control group (n=18) was 60 ± 14 (mean \pm SD) years compared to 48 ± 13 years in the experimental group (n=20). Preoperative serum calcium and intact PTH concentrations, and location and size of adenoma based on preoperative findings were similar between the two groups. At six months, all patients were normocalcemic regardless of surgical approach. In a prospective longitudinal cohort study, Carty et al compared the palpation method for selective unilateral exploration (n=61) to use of preoperative ^{99m}Tc sestamibi single photon emission computed tomography (SPECT, n=67) with intraoperative PTH monitoring in 128 consecutive patients over a 19 month period (6). Ninety-five percent of patients in the control group and 96.9% of all patients were deemed to have a successful outcome using a criterion of normocalcemia at 6 months post-surgery.

Several studies have evaluated intraoperative PTH testing with comparisons to historical control groups (5,9-11). A potential confounder of this type of control group may be an effect on surgical outcome as a result of surgical experience. Henry et al (5) performed a case control study comparing endoscopic VAP modified via a lateral approach in 68 patients with sporadic primary hyperparathyroidism and a single adenoma suggested by ultrasonography and sestamibi

scan. The control group consisted of 68 patients matched for age and sex who underwent conventional parathyroidectomy with bilateral exploration and general anesthesia. The study was conducted over a two year period. A rapid intact PTH assay, method not described, was used during surgery on the VAP group. All patients were biochemically cured 1 year after surgery.

In another study by Johnson et al, the experimental group consisted of 49 patients with primary hyperparathyroidism who underwent preoperative imaging with ^{99m}Tc -sestamibi scanning and in whom the IMMULITE turbo PTH was performed in the central laboratory. The control group was made up of 55 historical cases who underwent parathyroidectomy prior to the introduction of these two technologies (9). There was no statistical difference between groups in the outcome measure, postoperative calcium concentrations.

In a study by Chen et al, an outpatient minimally invasive parathyroidectomy technique (MIP) consisting of preoperative sestamibi-SPECT imaging, surgeon administered local or regional anesthesia, exploration through small incisions of 1 to 4 cm, and intraoperative PTH measurements at 5 to 10 minutes after parathyroid resection was used in 33 consecutive patients with primary hyperparathyroidism (10). The control group consisted of 184 consecutive patients who underwent bilateral exploration with general anesthesia. The MIP patients and control patients were similar with respect to age, preoperative calcium and parathyroid hormone levels, cause of primary hyperparathyroidism, and weight of resected glands. Patient outcomes were also similar with respect to cure rates of 100% and 97.3%, respectively (p not significant). Surgical cure was indicated by a serum calcium concentration of 8.4-10.5 mg/dL four months postoperatively with follow-up to 6 months when possible. This series has recently been

expanded to 656 consecutive parathyroid explorations by a single surgeon over an 11 year period (11). Of the 656 patients explored for primary hyperparathyroidism, 61% were performed employing the standard technique and 39% were selected for MIP. The success rate for the entire series was 98% with no significant difference between the two techniques (97% standard, 99% MIP).

In Canada, a Consensus Development Task Force on Diagnosis and Management of Asymptomatic Hyperparathyroidism (12) stated in their recommendations that intraoperative PTH assays are necessary for patients undergoing MIP. Finally operative failure rates were examined in 447 consecutive cases of primary hyperparathyroidism over a 30 year period (13). Rates were 5% (14/275, 1969-89), 10% (4/39, 1990-1993), and 1.5% (2/133, 1993-1998) with operative approaches of bilateral neck exploration with excision of large glands and biopsy of normal glands, bilateral neck exploration with excision of large glands with intraoperative PTH, and limited dissection with preoperative localization and intraoperative PTH, respectively. The failure rate significantly decreased from 6% to 1.5% ($p < 0.05$) in the last 5 years.

Approximately 50 case series, both retrospective and prospective, have examined the use of intraoperative PTH in patients operated on for primary hyperparathyroidism (1,14-58). Studies where assay results were utilized in real-time to guide the operation have in general found the assay to be useful in cases of uniglandular disease. Accuracy in detecting multiglandular disease is more controversial. In the most focused study, Gauger et al (59) retrospectively looked at 20 patients from two institutions undergoing conventional parathyroidectomy who had exactly two glands excised based principally on size greater than an estimated 70 mg. Specimens were taken

post-induction, and at 5 and 10 minutes after removal of the first gland, however PTH values were not used to guide exploration. Nine of 20 patients had a true negative result with PTH values failing to fall below the 50% threshold. The false positive rate with PTH values falling greater than 50% compared to baseline was 55%. It has been questioned however in patients with double adenomas, whether the second gland is hyperfunctioning with one parathyroid functionally dominant and other enlarged gland relatively quiescent (60), or whether the larger gland can suppress smaller yet abnormal glands that could become hypersecretory if not removed (25).

In a similarly designed study where PTH measurements were not utilized in real time, Weber et al found 15 false positives in 112 patients undergoing conventional parathyroid exploration, specifically 1 of 71 single adenomas, 4 of 6 double adenomas, 7 of 15 primary hyperplasias and 3 of 17 tertiary hyperplasias (60). Gordon et al also used morphologic criteria, not intraoperative PTH values to guide tissue resection (25). Twenty-four percent of the 72 patients with primary hyperparathyroidism had multiglandular disease. Utilizing intraoperative PTH, six percent would have had extended explorations and six percent may have required reoperation for unidentified multiglandular disease. The authors concluded the results validated the accuracy of the intraoperative PTH assay. False positive rates of 50% in primary hyperparathyroidism were observed in very small series when intraoperative PTH was used in real time (35,61). Persistent hypercalcemia was present in one study (61) and the other morphologically abnormal glands were found during contralateral thyroidectomy (35). In contrast, in several additional studies in primary hyperparathyroidism the intraoperative PTH assay was accurate in correctly identifying multiglandular disease (53,56).

The incidence of multiglandular disease has been used as an argument that parathyroid glands excised based on morphologic criteria may be non-functioning and therefore not identified biochemically. For example, in contrast to the overall frequency of multiglandular disease in reported series of 8-33%, Molinari et al (62) found an incidence of multiglandular disease in primary hyperparathyroidism of 5% using intraoperative PTH in 105 consecutive patients. In another study (63), the multiglandular disease rate was 15% with bilateral exploration and 0% with focal neck exploration in patients with sporadic primary hyperparathyroidism with one gland identified preoperatively. Intraoperative PTH was measured in both groups.

A concern in excising hyperfunctioning glands determined by intraoperative PTH without visualizing remaining glands is there will be a higher late recurrence rate (64). This was addressed in two studies (56,64). The accuracy of intraoperative PTH measurements to predict late postoperative normocalcemia was 95% in 80 patients followed for five years following primary exploration (56). In the second study, 320 consecutive patients with primary hyperparathyroidism were followed 6 to 313 months after successful parathyroidectomy (64). The experimental group (n=144) had glands excised based on intraoperative PTH measurements and the historical control group (n=176) had bilateral neck exploration with excision of enlarged glands. The number of patients with more than one gland excised in the control group was three times higher than in the experimental group ($p<0.05$). However, there was no significant difference in the incidence of recurrent hyperfunctioning glands between the 2 operative approaches.

Literature Search 63 addressed if the addition of intraoperative PTH measurements to surgery for parathyroid disease improve morbidity or complication rate compared to bilateral exploratory surgery alone in patients with primary hyperparathyroidism.

In general, in the small number of studies in which surgeries were performed with and without intraoperative testing, morbidity and complication rates were similar to or lower than the rate for the control group. Eleven percent of patients in the bilateral group and 4% of patients in the unilateral group had a significant complication in the randomized study by Bergenfelz (7) ($p=0.27$), while in the subset of patients with a solitary adenoma, patients operated on with a unilateral approach consumed less oral calcium during the first four postoperative days and had less incidence and severity of symptomatic and biochemical hypocalcemia ($p=0.04$).

Complications totaled 1 out of 68 patients (inferior laryngeal nerve palsy) for the VAP procedure and 4 out of 68 patients with conventional parathyroidectomy (transient systematic hypocalcemia, $n=3$; wound hematoma, $n=1$) which was not statistically significant (5). Concise parathyroidectomy with intraoperative PTH and preoperative imaging (6) had less frequent minor morbidity compared to controls ($p<0.00001$) with no major morbidity such as permanent vocal cord injury as observed in the controls ($n=1$). Morbidity was equally low for MIP (0%, $n=33$) versus bilateral exploration (2.2%, $n=184$, p value, not significant) (10). Complications in the larger patient group (11) were similarly low at 3.0% and 1.2% for standard and MIP explorations, respectively as was the incidence of ipsilateral recurrent laryngeal nerve injury in both groups ($<1\%$).

Literature Search 64 addressed if the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve use of local or regional anesthesia or extent of exploration (unilateral vs. bilateral) compared to standard bilateral exploration.

In the study by Johnson et al described previously, the impact of intraoperative PTH in conjunction with preoperative imaging and concise parathyroidectomy on use of local versus general anesthesia and unilateral versus bilateral neck explorations was evaluated (9). There was significantly increased use of local anesthesia in the experimental group compared to the control group (33% versus 0%, $p < 0.001$) as well as increased unilateral exploration (65% versus 0%, $p < 0.001$). Carty et al also saw increased unilateral exploration in a prospective cohort study comparing the palpation method for selective unilateral exploration ($n=61$) to use of preoperative ^{99m}Tc sestamibi single photon emission computed tomography (SPECT, $n=67$) with the intraoperative PTH assay (6). Unilateral exploration was possible in 41% of patients using the first strategy and in 63% of patients with the operative technique including intraoperative PTH ($p=0.014$). In this study, a modification of the Nichols ICMA assay with a sensitivity of 40 pg/mL was performed in the operating room with a total turnaround time of less than 15 minutes. Unilateral exploration has been described as the major advantage of intraoperative PTH measurements (15).

Literature Search 65 investigated if the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve use of frozen sections compared to standard bilateral exploration.

Two studies have examined the effect of intraoperative PTH on frozen section use in comparison to historical control groups of patients undergoing parathyroidectomy prior to the introduction of the technique. In one study (51) comparing 2 groups of patients undergoing parathyroidectomy with bilateral exploration, an average of 3.4 (range 1-9) frozen sections were sent in the group of patients prior to introduction of the assay and 2.0 frozen sections sent (range 0-6, $p < 0.01$) in the patients in whom the PTH assay was used on the operating room. In patients undergoing reoperation ($n=2$), 3.0 (mean) frozen sections sent were in the group without PTH measurements and 2.12 frozen sections sent in the group with PTH measurements ($n=8$) although statistical significance was not reached in this small sample set. In this study, operative times were similar as were cure rates. Costs were not directly examined.

In the second study (9), the experimental group consisted of 49 patients who underwent preoperative imaging with ^{99m}Tc -sestamibi scanning and in which intraoperative PTH was used while the control group was made up of 55 historical cases operated on consecutively using a concise, minimally invasive approach. Frozen section use was significantly greater ($p < 0.0001$) in the control group with a mean of 2.5 sections (range 1-7) and all patients had a least one frozen section. The mean in the experimental group was 1.4 (range 0-6) and 10 out of the 49 patients had no frozen sections sent. Based on a cost of \$203 per frozen section, it was estimated there was an average savings of $> \$200$ in surgical pathology costs. The authors speculated in this 2001 report, that as surgeons become more accustomed to the intraoperative PTH assay, frozen section use will almost disappear when expected falls in PTH values are achieved (9).

A novel application for the rapid PTH assay as a substitute for tissue frozen section has been suggested in one report (65). In this retrospective study, intraoperative parathyroid aspirates from histologically confirmed parathyroid adenomas were compared to thyroid and other non-parathyroid tissue aspirates. A sensitivity and specificity of 100% was achieved using a cutoff of >1500 pg/mL, the upper limit of the QuiCk-Intraoperative Intact PTH assay.

Literature Search 66 investigated if the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improve operating room time, operating room fees, overall hospital costs, or length of stay compared to standard bilateral exploration.

The majority of evidence suggests financial savings to the institution as a result of utilization of intraoperative PTH, often incorporated with other techniques and surgical approaches. Most evidence incorporates historical controls for comparison, however. Outcomes examined include operating room time and fees, hospital lengths of stay, and overall hospital charges or costs. In one of the first studies combining preoperative localization of parathyroid tumors via ^{99m}Tc sestamibi (MIBI) scintigraphy with a rapid PTH assay, cost-effectiveness was evaluated by comparing operating times in 18 patients with primary hyperparathyroidism to operating time in patients not subjected to these procedures (33). Operative times decreased to an average of 36 minutes from 90 minutes. In a subsequent prospective study by the same surgeon in a consecutive series of 85 patients (34), the mean operative time was 55 minutes (range, 21-130 min) utilizing intraoperative PTH. In 42 of 57 patients eligible for surgery in an ambulatory setting, same-day discharge was possible. At that institution, parathyroidectomy performed in an

ambulatory setting was charged at a rate 39% less than the rate for patients requiring an overnight admission.

In two studies of VAP compared to conventional parathyroidectomy (5,8), operative time was shorter in the randomized study (57 versus 70 min, $p<0.05$) (8) and similar in the case control study with 64.9 min for the VAP group and 67.5 min for the standard operation (5).

Unfamiliarity with the new technique was an explanation. Operative time directly affected the cost per procedure charge in the first study (\$1720 versus \$1910) since other costs for anesthesia and frozen section or intraoperative assays were similar between the VAP and bilateral neck exploration procedures (8). Operative times and surgical procedure costs were not different between the unilateral (with intraoperative PTH) and bilateral groups in the randomized prospective trial by Bergenfelz (7) for all 88 patients, however when patients with only a solitary parathyroid adenoma were compared, mean operative times were significantly shorter in the unilateral group (62 ± 29 min, $n=41$) compared to the bilateral group (84 ± 38 min, $n=40$, $p<0.01$). Similarly, in a subset analysis comparing directed operations using the intraoperative PTH assay ($n=30$) to conventional bilateral explorations ($n=31$) in a case series, total hospital costs were similar (\$3847 versus \$3949) as was the mean length of hospitalization (1 day) while mean operating times tended to be shorter at 72 versus 97 minutes (66).

In a cohort study comparing two methods for selective unilateral exploration for sporadic primary hyperparathyroidism, one of which included intraoperative PTH and preoperative imaging, operative times were similar (6). This was explained by the study protocol requiring biopsy of a normal parathyroid gland post adenoma excision. Perioperative costs also did not

differ, however the mean length of hospital stay was significantly shorter in the intraoperative PTH group (1.07 ± 0.82 days versus 1.9 ± 0.94 days, $p < 0.00001$). Similarly, Johnson et al (9) observed more same day surgeries (35%) and fewer overnight stays (59%) and stays ≥ 48 hours (6%) in the intraoperative PTH/imaging experimental group than in the control group ($p < 0.0001$) which had 87% of patients stay overnight and 13% stay ≥ 48 hours.

The ability to perform parathyroidectomy on an outpatient basis with a minimally invasive approach incorporating intraoperative PTH resulted in shorter operative times and accounted for the significant decrease in length of hospital stay and therefore decreased hospital charges compared to patients who underwent bilateral parathyroid exploration in the study by Chen et al (10). Lengths of stay were: MIP (n=33): 0.3 ± 0.2 days, controls (n=184): 1.8 ± 0.1 days, $p < 0.001$ while hospital charges in 1998 were: MIP: $\$3174 \pm \386 , controls: $\$6328 \pm \292 ($p < 0.001$). In an expansion of this series of patients operated on by a single surgeon over an 11 year period comparing MIP with conventional bilateral exploration, durations of surgery (1.3 hr versus 2.4 hr, $p < 0.001$) and anesthesia (1.6 hr versus 3.1 hr, $p < 0.001$) were lower as again were lengths of stay (0.24 days versus 1.64 days, $p < 0.0001$)(11). There was a significant overall mean savings of $\$2,693$ which represented 49% of the total hospital charges ($p < 0.0001$). When stratified by new or redo procedures, lengths of stay and hospital charge outcomes followed the same significant pattern.

Flynn et al compared charges for minimally invasive radioguided parathyroidectomy (MIRP) with discharge within 23 hours to a historical standard neck exploration group with 23 hour admission (24). Operating room time (83 min. versus 128 min.), operating room charges ($\$1,612$

versus \$2,486) and anesthesia charges (\$868 versus \$1,165) were less in the MIRP group and frozen sections were eliminated. However, overall savings of \$965 (\$7,451 versus \$8,416) with the outpatient procedure was characterized as modest by the authors. Wilkinson et al reported an analysis of hospital expenses for consecutive parathyroidectomies performed in 1994 without intraoperative PTH testing (n=40), surgeries performed during 1997 to 1998 in hospitalized patients with intraoperative PTH and preoperative imaging studies (n=20), and surgeries performed on an outpatient basis with both imaging and PTH studies (n=20) (67). Average costs were \$5,830, \$4,061, and \$3,420, respectively.

Fahy (68) performed a cost-benefit analysis of localizing strategies including intraoperative PTH and other techniques by developing a clinical outcome model to simulate the surgical management of primary hyperparathyroidism based on charges from their surgical practice and the literature. Average total charges for bilateral neck exploration were \$17,358 while charges for a limited neck exploration with intraoperative PTH were \$14,962, and charges combining intraoperative PTH and preoperative technecium 99mTc sestamibi scanning were \$13,854. Another study defined cost-effectiveness as the true cost of avoiding a failed operation as opposed to the cost of performing one test (69). Their model was based on a study in 88 patients who underwent minimally invasive parathyroidectomy with intraoperative PTH, although values were not used intraoperatively, but only used as part of the study in comparison to short term serum calcium concentrations up to three months post surgery. They calculated a cost of \$19,801 to avoid a failed operation based on seven patients who would be converted to a bilateral exploration procedure. Use of same day routine PTH and calcium measurements instead would cost \$625 although cost to repeat the operation was not included.

Literature Search 67 investigated if the use of intraoperative PTH measurements alone or in combination with a unilateral or minimally invasive surgical procedure for primary hyperparathyroidism improves incision size/cosmetic result or patient satisfaction/pain compared to standard bilateral exploration.

Several studies of varying design have examined the impact of intraoperative PTH on patient reported aspects of parathyroid surgery including postoperative pain, cosmetic result, and other patient satisfaction issues. In the prospective randomized control trial by Miccoli (8), postoperative pain assessed using a visual analog scale was significantly less in the VAP with intraoperative PTH group during the 48 hours post-operative period ($p < 0.03$) with a score approximately half that in the control group. The authors attributed the decreased pain to a shorter skin incision as well as decreased neck hyperextension. Patients were also asked to complete a questionnaire at 1, 3, and 6 months post-surgery describing time to return to normal activities and personal opinion on esthetics of the scar using a 10 point score. The post-operative inactivity period was significantly shorter in the experimental group (12 ± 5.5 days vs. 16 ± 6 days, mean \pm SD). Personal satisfaction was also greater in the experimental group with respect to cosmetic result with a score averaging approximately 3 points higher ($p < 0.03$).

In the case control study by Henry et al (5), patients in the VAP experimental group with a 12 mm skin incision were paired with patients who had a classic transverse cervicotomy. Patients in the control group required analgesic (paracetamol) administration during the postoperative period an average of 1.66 times compared to 0.46 times for the VAP group ($p < 0.05$). Satisfaction

with the cosmetic results was slightly but significantly higher in the VAP group ($p < 0.05$) as assessed during telephone questioning. Follow-up was obtained in 89% of patients with a shorter mean follow-up of 9.2 ± 6.3 months in the VAP group compared to 23.2 ± 13.5 months in the control group. In a final study in which patient satisfaction was assessed by telephone, Burkey et al (66) found no difference in overall satisfaction, satisfaction with anesthesia, length of stay, pain after discharge, and scar among patients in a prospective study utilizing a gamma probe, intraoperative PTH, or neither. Patients in all 3 groups were explored through a collar incision ranging from 3-6 cm. Follow-up surveys were attempted in only 50% of patients ($n=75$). A limitation to the study was lack of uniform treatment protocols as described by the authors.

Other Parathyroid Diseases

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with secondary or tertiary hyperparathyroidism? (Literature Search 68)

Guideline 142: *Numerous case series suggest a role for intraoperative PTH in secondary or tertiary hyperparathyroidism, yet no studies compared outcomes to surgical procedures where intraoperative PTH testing was not used. In addition, criteria for expected changes in PTH concentrations following total or sub-total parathyroidectomy require further study. Therefore we make no recommendation for or against routinely providing intraoperative PTH testing for this application.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series, opinion)

In contrast to primary hyperparathyroidism, the use of intraoperative PTH to ensure adequacy of resection in secondary (compensatory hyperplasia due to low calcium concentrations primarily due to renal failure) and tertiary (autonomous PTH production in the presence of corrected calcium levels which usually follows secondary disease) hyperparathyroidism has been less frequently studied. Existing studies primarily consist of observational case series. The first study to address use of intraoperative PTH was published in 1997 (70) and retrospectively looked at 13 consecutive patients with secondary hyperparathyroidism undergoing total parathyroidectomy with autotransplantation or subtotal parathyroidectomy. PTH concentrations decreased an average of 84.6% after resection of 3½ or 4 glands compared to the highest of 2 baselines. In limited early follow-up, symptoms were improved in all patients and PTH concentrations were below preoperative values. The authors speculated use of a 50% guideline similar to primary hyperparathyroidism may not be adequate because at minimum, subtotal parathyroidectomy is required for successful treatment. Differing rates of decline between renal and non-renal hyperparathyroidism may also play a role. The authors also stated long-term follow-up and increasing number of patients would be crucial to define the role of the PTH assay in this setting. A decline of 50% in PTH values at 20 minutes after resection was highly predictive of cure in a large series of consecutive patients undergoing neck exploration for renal hyperparathyroidism (73 secondary, 7 tertiary) where cure was defined as the absence of hypercalcemia and a PTH concentration less than four times normal. The positive predictive value was 93% and sensitivity was 96% in that study (71). The authors also determined a decrease in PTH values of less than 40% compared to baseline suggested a missed or hyperfunctioning supernumerary gland and is predictive of failure with a decrease between 40% and 50% representative of variability in PTH

half-life among patients. The seven patients with tertiary hyperparathyroidism demonstrated declines in PTH similar to patients with primary hyperparathyroidism.

Pellitteri (45) retrospectively investigated 346 patients over a 7 year period in which all patients had intraoperative PTH measurements with the study hypothesis to evaluate a directed exploration protocol. In that group, 13 of 16 patients with secondary hyperparathyroidism and 3 of 3 patients with tertiary hyperparathyroidism had therapeutic success as determined by normocalcemia or resolution of symptoms postoperatively. Three other studies (40,72,73) that specifically studied a series of patients with secondary or tertiary hyperparathyroidism found relevant decreases in PTH concentrations similar to those previously documented in patients with primary hyperparathyroidism. Although, one report stated addition of the assay seemed to change the operative procedure very little (72). The intraoperative PTH was accurate and a useful aid in a number of studies where secondary and tertiary hyperparathyroid patients were studied as part of a larger series of patients, however numbers of patients were typically ten or fewer and follow-up was less than 6 months (30,44,49,50,52,74) with the exception of one study where median follow-up was 8 months (53). In a similarly designed retrospective study of 107 consecutive parathyroidectomies, eleven patients with secondary or tertiary hyperparathyroidism were included(46). There were two late operative failures in dialysis-dependent patients with post-operative hypercalcemia at 18 and 34 months, respectively following a period of normocalcemia. Postexcision PTH concentrations in these patients fell 84% and 86%, respectively. Failures were theorized to be attributed to small nonfunctional or hypofunctional supernumerary parathyroid glands which became hyperfunctional after seemingly definitive surgery.

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with reoperative disease? (Literature Search 69)

Guideline 143: *Evidence with respect to successful surgical outcome shows utility of intraoperative PTH in patients undergoing reoperation and therefore we recommend that the assay be used routinely in this patient population.*

Strength/consensus of recommendation: B

Level of evidence: II and III (controlled trials, multiple case series)

The recommendation for use of intraoperative PTH is based on evidence from studies where reoperative cases were specifically studied as well as studies in which these cases were part of a larger series of primarily new cases. Reoperations may be necessary as the result of persistent or recurrent parathyroid disease or patients may have had previous neck surgery for thyroid disease. Fibrosis and scarring from initial procedures makes subsequent surgeries more difficult, thus repeat procedures for primary hyperparathyroidism have higher complication rates and lower success rates compared to initial explorations. A study by Irvin et al investigated reoperative parathyroidectomy with (n=33) and without (n=17) intraoperative PTH in 50 consecutive patients with persistent or recurrent primary hyperparathyroidism (75). Groups were similar in age and symptoms although the controls preceded the cases in time. A successful outcome was defined in the controls as a serum calcium concentration <11 mg/dL for six months or longer while in the intraoperative PTH group successful outcome was defined as a return to a calcium level of 10.2 mg/dL or less. The success rate was 76% in the control group and 94% in the

intraoperative PTH group where the assay was also used in 42% of cases to lateralize the hypersecreting gland via direct venous sampling.

The large consecutive series of primary hyperparathyroid patients by Udelsman (11), comparing bilateral cervical exploration to MIP with intraoperative PTH, included 72 redo cases in the standard operation group (18% of total) and 12 redo cases in the MIP group (5% of total). In this subgroup, cure rates were favorable and indistinguishable comparing new and redo explorations. Reoperative surgeries were 100% successful in another prospective group of 11 patients with primary hyperparathyroidism previously operated on one to three times using a directed surgical approach consisting of preoperative imaging, intraoperative technecium 99m sestamibi scanning, and intraoperative PTH with normocalcemia at three to six weeks post-operation (76).

Thompson et al (77) performed a retrospective study of 124 patients with primary hyperparathyroidism undergoing reoperative parathyroid surgery, in whom sixteen were monitored intraoperatively with parathyroid hormone testing. Curative results were confirmed with PTH in five patients with suspected single gland disease and nine of eleven patients with multigland disease using a criterion of a 50% decrease at 20 minutes post-excision and curative results in all patients with a 70% guideline. This compared to sensitivities of 75-90% using various pre-operative imaging techniques in the entire 124 patient group. A number of other case series included reoperative patients in their studies, but did not perform subgroup analyses (16,17,22,24,31,35,40,71,78). Primary hyperparathyroid patients were principally studied, although patients with secondary/tertiary disease, and patients with previous neck surgery for thyroid disease were also included. In studies in which subgroup analyses were performed in

both reoperative primary hyperparathyroidism and secondary/tertiary hyperparathyroidism, cure rates were equal to or greater than cure rates in initial surgeries (39,49,50,52).

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in patients with multiple endocrine neoplasia (MEN) I? (Literature Search 70)

Guideline 144: *We make no recommendation for use of intraoperative PTH testing in patients with MEN I since results, although positive in several case studies and several larger retrospective series, control groups were lacking.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series)

Over a six year period Tonelli et al (79) used intraoperative PTH measurements with a modified IRMA in sixteen patients with MEN I who underwent total parathyroidectomy with autotransplantation for their multi-glandular hyperplasia. MEN I is one of a family of genetic disorders which results in multiple endocrine gland neoplasias. Bilateral exploration is required in these patients (80). In the Tonelli study, PTH values decreased in a stepwise fashion after the removal of each gland with an average PTH 22.3% of baseline two minutes after removal of the last gland with values below the upper limit of the reference range. No patients were hypercalcemic after an average of 35 months follow-up. Patterns of PTH decay differed between a comparison group of 20 patients who had a single adenoma resected compared to removal of the first gland in these MEN I patients with declines of 21% and 74% of baseline at 10 minutes post excision, respectively (79).

In another series of 20 patients with MEN I, a subset of a larger group operated on over a 29 year period, intraoperative PTH was employed with a criterion of a 50% decrease at 5 minutes following subtotal parathyroidectomy with thymectomy (81). Cure, defined as eu- or hypoparathyroid with a mean follow-up of 13±11 months, was predicted with a sensitivity of 95% and an accuracy of 95%. It has been suggested (22,81) that in these patients an 80% decrease overall is more reasonable as a target and that final PTH concentrations should be within the reference range or barely detectable. Several case studies have also found positive results with intraoperative PTH monitoring in this population of patients (12,22,30,47).

Despite the success of the previous two studies with respect to recurrence of disease, rates of recurrence in patients with MEN I are higher than in patients with sporadic hyperparathyroidism which is attributed to inadequate initial surgery, presence of supernumerary and ectopic glands, regrowth of remnant tissue or autograft hyperfunction(82). The utility of intraoperative PTH was explored in fourteen patients as part of a 25 year series (1975-2000) of 94 patients with MEN I reoperated on for hyperparathyroidism (82). With respect to removal of the first gland and an expected decrease of 50%, in twelve cases PTH did not decline and additional glands were resected or PTH did decline and no additional tissue was found. There were two false positive cases as second glands were found. Ninety-three percent of cases had normal calcium and PTH values at a median follow-up of 11 months. The authors commented the potential of the assay in the reoperative MEN I setting was encouraging (82).

Does the addition of intraoperative PTH measurements to surgery for parathyroid disease improve the adequacy of resection or cure rate compared to bilateral exploratory surgery alone in

patients with parathyroid cancer? (Literature Search 71)

Guideline 145: *We conclude the evidence is insufficient to recommend for or against use of intraoperative PTH measurements in patients with parathyroid cancer.*

Strength/consensus of recommendation: I

Level of evidence: III (multiple case series)

Parathyroid cancer is very rare, accounting for 1% of cases of hypercalcemia and hyperparathyroidism. It is usually diagnosed during surgery for hyperparathyroidism although plasma calcium concentrations tend to be higher than in patients with adenomas or hyperplasia (83). Due to the very low prevalence of the disease it is not surprising there are little data on the role of intraoperative PTH in such cases with only one or two patients included in various case series (23,30,39,47,52,63,78,84).

Localization

Does performing intraoperative PTH measurements in the angiography suite aid in identifying PTH gradients and result in a diagnostic study during venous localization compared to performing PTH measurements in the central laboratory? (Literature Search 72)

Guideline 146: *Despite limited evidence, we recommend that intraoperative PTH measurements be considered as a replacement for traditional laboratory measurements of PTH during venous localization in order to provide real-time results to the angiography team to guide sampling.*

Strength/consensus of recommendation: B

Level of evidence: III (case reports and series, and opinion)

Guideline 147: *However, we make no recommendation for use of rapid PTH tests in the operating suite for tumor localization due to conflicting studies. Although this may be a promising application for the rapid assay, additional studies are needed to determine whether this approach is better than more current and improved preoperative scanning techniques and the most appropriate population for use, such as reoperative cases, since routine use is not justified.*

Strength/consensus of recommendation: I

Level of evidence: III (case series)

In patients undergoing repeat exploration for primary hyperparathyroidism, studies to localize abnormal tissue are performed using non-invasive imaging techniques, however these studies will be noninformative in a small number of patients. These patients are referred for selective venous sampling with PTH analysis and arteriography (85). Typically, specimens collected from catheterized veins in the neck and mediastinum are sent to the laboratory and analyzed for PTH in batch. Results are matched to sampling location to potentially determine the general area of the adenoma via a venous gradient. Following introduction of rapid assays for PTH, it was hypothesized by endocrine surgeon Dr. Robert Udelsman that real-time analysis of PTH in the angiography suite would be beneficial to the angiographer and the patient, allowing the angiographer to obtain additional specimens when a subtle gradient in PTH concentrations is detected. This would not be possible using the standard approach. A case report from 2000 in a patient undergoing venous localization for persistent hyperparathyroidism used the rapid PTH assay (QuiCk-Intraoperative Intact PTH assay) in the angiography suite, with comparisons analytically and clinically to samples analyzed as a batch in the clinical laboratory with an IRMA

method (86). The real-time benefits were manifested in this case by the ability to repeat a questionable sample. In this case and in a subsequent series of seven patients, the cure rate was 100% when a venous gradient was demonstrated (86,87). Despite the lack of case controlled studies, it has been noted that angiographic localization may prove to be the most beneficial application of the rapid/intraoperative PTH assay (86).

Several studies (39,88-90) have examined use of the rapid PTH assay in the operating suite for venous localization to aid in locating hyperfunctioning glands by sampling veins on either side of the neck or through tissue massage. In 1996, Saharay (89) studied 15 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism to assess whether a locally increased PTH level during selective venous sampling accurately predicted the site of the adenoma. Using a modification of the Nichols Institute Diagnostics ICMA assay with a turnaround time of 25 minutes, PTH was analyzed in specimens from the superior, middle, and inferior thyroid veins on both sides of the neck. In all 15 patients, the PTH concentration accurately indicated the location of the abnormal parathyroid gland including one case where equivalent results suggested an ectopic location. Although in ten of the cases, the adenoma was identified before the PTH results were available. Post-operative calcium concentrations were normal in all cases. Sensitivity of this approach was superior to ultrasound and thallium/technetium scanning which identified 5 of 15 abnormal parathyroids.

In another study, a lateralizing gradient comparing peripheral and internal jugular veins was found in 63% of 20 consecutive patients with primary hyperparathyroidism (88). Similarly (90), adenomas were correctly lateralized in 76% of primary hyperparathyroid patients (n=23)

compared to 41% for thallium/technetium scanning ($p < 0.02$). In a more recent study (39), localization of the side of the hyperfunctioning tissue was only successful in three of nine patients with negative preoperative sestamibi scans. Although this may be a promising application for the rapid assay, additional studies are needed to determine whether this approach is better than more current and improved preoperative scanning techniques and the most appropriate population for use, such as reoperative cases, since it has been stated that routine use is not justified (88). Therefore we make no recommendation for use of the rapid PTH assay in the operating suite for venous localization.

Secondary Questions

Is there evidence to support use of a specific assay? (Literature Search 73)

Guideline 148: *There is no evidence to suggest superiority of an intraoperative intact PTH assay from a particular manufacturer compared to available assays. We do not recommend the use of a specific assay for intraoperative PTH monitoring. Additional studies comparing bio-intact or whole PTH rapid intraoperative assays to intact rapid intraoperative assays need to be performed to determine whether improved benefit exists.*

Strength/consensus of recommendation: I

Level of evidence: III (comparative studies)

Since the introduction of the first FDA cleared assay in the mid 1990s, several other assays have become commercially available. Assays are available in both automated and manual formats.

PTH assays on traditional immunoassay platforms with appropriately short assay times have also been used successfully. Since the Nichols QuiCk-IntraOperative Intact PTH assay was the first

rapid PTH assay developed, the majority of studies reviewed for these guidelines have employed this assay. Rapid intraoperative assays have been compared to standard length assays as well as to each other analytically in numerous studies, although head-to-head clinical comparisons are sparse. However, clinical studies have been published individually using all commercially available rapid intact PTH assays and there are no results to suggest that assays do not perform in a comparable manner. Two small studies in parathyroidectomy patients, one comparing the Nichols QuiCk-IntraOperative Intact PTH assay and the Immulite *Turbo* Intact PTH assay (n=10) (57) and one comparing the Nichols QuiCk-IntraOperative Intact PTH assay to the Elecsys 1010 Intact PTH assay (n=13) (91) showed complete diagnostic agreement. Models generated using data from minimally invasive surgery in 20 patients with primary hyperparathyroidism showed differences in calculated half-lives and residual PTH concentrations among the Nichols QuiCk-IntraOperative Intact PTH, Immulite *Turbo* Intact PTH, and Roche Elecsys 1010 Intact PTH assays. However, differences were clinically irrelevant (92).

Studies reviewed here have been performed using intact PTH assays that can cross react with amino-terminally truncated PTH fragments in addition to the full length PTH molecule, however an automated Bio-intact (1-84) PTH assay for intraoperative use is now available. Use of a traditional, not rapid, assay for PTH 1-84 was examined for intraoperative use in a simulated study (93). Plasma specimens analyzed from 29 patients with a single adenoma and 7 patients with secondary hyperparathyroidism obtained intraoperatively were frozen at -70°C for subsequent analysis using standard length non-rapid intact and bio-intact PTH IRMAs. Results were similar for all three assays in the single adenoma population. In real-time, the ICMA intact

assay PTH values declined to less than 50% of initial values at 10 minutes post total parathyroidectomy in the secondary hyperparathyroid group as did results with the bio-intact assay. Using the standard intact assay in the frozen samples, three patients had values slightly above the 50% benchmark at 10 minutes with all results <50% of baseline at 15 minutes.

Additional studies comparing bio-intact or whole PTH rapid intraoperative assays to intact rapid intraoperative assays need to be performed to determine whether improved benefit exists.

Is there evidence to support a recommended sampling protocol with respect to timing and number of samples or recommended criteria for interpretation of intraoperative PTH values?

(Literature Search 74)

Guideline 149: *We recommend in patients undergoing parathyroidectomy for primary hyperparathyroidism that baseline samples be obtained pre-operation/exploration and pre-excision of the suspected hyperfunctioning gland. Specimens for PTH should be drawn at 5 and 10 minutes post-resection with a 50% reduction in PTH concentrations from the highest baseline as a criterion. Additional samples may be necessary. Kinetic analyses appear promising, however more work needs to be done to confirm their utility.*

Strength/consensus of recommendation: A

Level of evidence: III (comparative studies and opinion)

Outcomes of studies using PTH intraoperatively in primary hyperparathyroidism can vary depending upon timing of samples and criteria used for expected change in PTH values. Timing and criteria appear to be surgeon dependent. Based on the half-life of intact PTH, a greater than 50% decline in PTH concentrations following removal of the hyperfunctioning parathyroid gland(s) is a generally accepted guideline for the interpretation of PTH levels (33). This was

described at a recent Workshop on Asymptomatic Primary Hyperparathyroidism updating a 1990 Consensus Development panel (94). However, limits of 40% (55), 65% (51), and 75% (specific for the Immulite assay) (36) have been proposed. Using a threshold for decline of 75% at 10 minutes as opposed to 50% resulted in decreased accuracy for uni- and multiglandular disease in one study (25).

Parameters, such as timing and number of samples and sampling location are less clearly defined. Initial baseline samples may be drawn pre-incision and may occur in the pre-op area, in the operating room, and pre-, post- or at introduction of anesthesia. Drawing a second baseline specimen pre-excision, when the affected gland is identified has been recommended (20,31,55,58) to account for any non-specific release of PTH from potential tumor manipulation during surgery. Samples are typically drawn from peripheral veins, although internal jugular veins have also been used intraoperatively. A concern raised with samples obtained from the jugular vein is that the PTH concentration may be influenced by parathyroid tumors up or downstream from the sampling site (56).

The highest baseline value for PTH has been recommended for calculating the % change in PTH concentration. Use of pre-excision samples has been suggested to reduce the number of false-negative results in patients with a single adenoma. Comparing use of the initial baseline instead of the highest pre-excision value would increase the number of false negatives from 2 to 34 in a study of 206 patients (55). Also, PTH concentrations have been observed to increase after general anesthesia (95). A recent protocol has suggested an immediate post gland excision sample may also be useful (58).

Timing of post-excision samples is generally at 5 and/or 10 minutes, although timings of 7, 15, 20 minutes have been used in reported studies (6,44,77). Sensitivity can increase with time (16) as shown in one study where sensitivity, specificity, and accuracy were 86%, 100%, and 85% at 5 minutes and 97%, 100%, and 97%, at 15 minutes, respectively. Sensitivity and accuracy were poorer at 5 versus 10 minutes in a second study (35) although in a third study 10 and 15 minute postexcision operative success results were similar (46). In a small study of reoperative primary hyperparathyroidism it was claimed changing the degree of decline from baseline PTH from 50% to 70% at 20 minutes post-resection increased accuracy for patients with multiglandular disease (77). Whether the post-excision sample should also fall below the lowest baseline or the upper limit of the reference range in addition to a prescribed percentage change has also been debated with a recent study (35) advocating a 50% change from the highest baseline with a result lower than the lowest baseline at any given time point.

A commonly used criteria to predict postoperative calcium concentrations, now termed the Miami QPTH (quick intraoperative PTH assay) criteria, was introduced in the early 1990s by George Irvin, MD an endocrine surgeon who was a leader in the development of the intraoperative PTH assay and its introduction into clinical use (30). Briefly, the Miami criterion is a drop in intraoperative PTH $\geq 50\%$ from the highest of either the pre-incision or the pre-excision level at 10 minutes after gland excision. Irvin's group (96) compared 5 different criteria to the Miami QPTH criteria in 341 consecutive patients with sporadic primary hyperparathyroidism who were followed ≥ 6 months after the operation or recognized as operative failures. Results of this study are shown in Table 2. The Miami criterion was most

accurate at 97% although accuracy was similar at 95% adding the requirement of a fall at 10 minutes below the pre-incision value. All criteria were similar in false positive percentages while the Miami criteria resulted in the lowest false negative rate at 3% compared to 6-24% for the other criteria ($p < 0.05$). Discussion on this paper pointed out that running a 5 minute sample, with the 10 minute sample analyzed if needed, would speed up the operation.

A novel approach was reported by Libutti et al (37) to address inter-individual variability in the half-life of PTH and potential rigid timing of samples. They developed a kinetic algorithm to predict the success of parathyroid surgery based on the rate of PTH decay and found it correctly classified 45 patients with hyperparathyroidism compared to 43 patients correctly classified using a criterion of a 50% drop at 5 minutes. A subsequent study (92) failed to validate this model although a second model was constructed using pre-excision values and 5, 10, and 15 minute timed post-resection samples, concluding the preoperative baseline PTH is necessary to determine cure although insufficient for kinetic calculations which require pre-excision values.

Does performing intraoperative PTH measurements in or adjacent to the operating suite improve turnaround and operative times compared to performing intraoperative PTH measurements in the central laboratory with specimens transported via pneumatic tube or messenger? (Literature Search 75)

Guideline 150: *Evidence is lacking to recommend the location of intraoperative PTH testing either in or adjacent to the operating room or in the central laboratory. Important considerations such as interaction with the surgical team must be weighed in concert with costs and staffing issues. Studies to evaluate turnaround and operative times related to different*

locations have not been explicitly performed. Regardless of specific evidence, external validity may limit applicability to individual institutions.

Strength/consensus of recommendation: I

Level of evidence: III (comparative reports and series, and opinion)

The location of intraoperative testing appears to have come full-circle in the approximately 15 years since its inception. Initial assays were modifications of immunoradiometric (IRMA) assays, thereby limiting testing to locations outside the operating suite such as the central lab due to radioactive tracers. The first assay specifically designed for intraoperative use was introduced and cleared by the FDA in the mid 1990s. The QuiCk-IntraOperative Intact PTH assay (Nichols Institute Diagnostics) was designed to be performed with equipment that fit on a cart that could easily be transported outside the laboratory to the operating room other remote location.

Subsequent assays designed for rapid use have mainly focused on adaptations of assays on traditional immunoassay analyzers such as the DPC Immulite and Nichols Advantage. In a survey conducted by the College of American Pathologists in 2001 (97), out of 92 laboratories performing intraoperative testing, 71% of respondents performed testing in the central laboratory compared to 23% who performed testing in the operating room or surgical suite. Six percent performed testing in a satellite laboratory.

However, little data exists directly comparing testing locations. Wians et al (57) performed a study in 10 patients undergoing parathyroid surgery in which samples were analyzed in the operating room by a medical technologist using the QuiCk-IntraOperative Intact PTH assay and samples were sent to the central lab to be analyzed on the IMMULITE system. Turnaround time

and operative times were not directly addressed in this study although overall costs were reported to be similar (data not shown) comparing both sites. Cost per patient was calculated to be \$360 for central lab PTH testing versus \$760 for operating room testing although the authors' preference was for intraoperative testing. In another comparison reagent costs per test for PTH assays on two automated analyzers (DPC IMMULITE and Roche Elecsys 1010) were calculated to be 12% and 4%, respectively of costs for a manual rapid PTH assay (Nichols QuiCk-IntraOperative Intact PTH). Despite improved costs and efficiency with automated analyzers, the authors recommended direct contact between the surgical and analytical teams to minimize transport time and improve communication (92). Wenk et al (98) calculated a reagent only cost for testing two controls and two patient samples in the central lab with the Immulite assay of \$24. They claimed the overall cost is markedly lower than bedside tests and assays can be done as quickly with equal accuracy.

Although it would seem intuitive that turnaround times would be shorter with testing performed on-site, studies have not been done. Times would also be institution specific depending upon specific assay used, distance from operating suite to the lab, and mode of transportation to the central lab including messenger or pneumatic tube. Distance from the pneumatic tube to the testing location in the central lab as well as the efficiency of transfer also contributes. Whether or not testing location affects operative times may depend upon the complexity of the surgery, such as in patients with renal insufficiency, and the surgical approach. Turnaround time is an important consideration to the surgeon and lab, however there are advantages and disadvantages to testing location (97,99).

The advantages to testing on-site center on the ability of the technologist to interact with the surgical team with direct involvement in preanalytic as well as analytic aspects of testing, increased visibility for the laboratory, and more involvement in patient care for the technologists. Disadvantages to on-site testing for the lab include providing a dedicated technologist as well as potentially dedicated equipment. In the central lab, technologists may perform other testing and use of standard immunoassay analyzers precludes having to acquire new equipment and allows other testing, although perhaps not concurrently. Calibrations are also less frequent on the fully automated systems and results may be more precise and accurate compared to manual methods. Reagent costs are likely to be less as a result of reagent packaging such as for individual patient use. Costs can be an important consideration for the laboratory where in the majority of cases, intraoperative PTH is a low volume test. In 2002, 93% of labs performed testing ten or less times per month while 68% of performed testing five or less times per month (97). In centers where testing volume is high and surgeries are performed by multiple surgeons in multiple locations, such as inpatient and outpatient surgical suites, testing in the central lab allows for that service in addition to efficient use of labor and reagents (97,99).

In summary, based on strong impressions from relatively few controlled studies, intraoperative PTH is recommended for routine use in patients undergoing surgery for primary hyperparathyroidism, particularly in directed surgical approaches (Table 3). This recommendation is based on evidence for improved patient/health, operational, and economic outcomes and applies to initial surgeries and in patients undergoing reoperative procedures. In contrast to the setting of primary hyperparathyroidism, further studies are needed to define the role of intraoperative PTH testing in patients with secondary/tertiary hyperparathyroidism, MEN

I, and parathyroid cancer.

The number of commercial assays available for rapid PTH speaks to the interest in this point of care application. However, none of these assays was deemed superior nor was there a recommendation for testing location. Future studies may serve to refine assay format and specificity, testing location, sampling protocols, and test interpretation although standardization of some of these aspects of intraoperative PTH testing will be limited by institution-specific conditions. In addition to intraoperative monitoring during surgical resection, rapid PTH assays have potential applications in diagnostic localization. The assay is recommended for use in the angiography suite, however additional studies are needed to determine whether or not the assay proves useful in the operating suite. Rapid PTH testing has spawned interest in employing other rapid hormone tests intraoperatively and for tumor localization. Thus, the future is promising for rapid hormones in non-parathyroid disease applications following in the footsteps of the rapid PTH model.

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Public Comments

I was reviewing the NACB LMPG presentations and noticed that calcium measurements for monitoring parathyroid surgery was missing. There was a recent paper describing the benefits of kinetic total calcium levels. This isn't something done at my institution (at least not yet), but may be at others. Here is the reference: Diaz-Aguirregoitia, et al. *J Am Coll Surg* 2004;198:519-524.

Use of serum calcium as an intraoperative monitor for surgery in primary hyperparathyroidism

has been proposed in only a few studies in the literature with mixed results. Randomized controlled trials are needed to determine whether benefit exists.

Table 1. Comparison of cure rates between control and experimental groups in studies using intraoperative PTH in patients with primary hyperparathyroidism.

Study	Design	Control Group		Experimental Group with IO PTH	
		Approach	Cure Rate	Approach	Cure Rate
Bergenfelz, 2002 (<u>7</u>)	RCT	Bilateral (n=44)	98%	Unilateral (n=47)	96%
Miccoli, 1999 (<u>8</u>)	RCT	Bilateral (n=18)	100%	Video-Assisted (n=20)	100%
Carty, 1997 (<u>6</u>)	Cohort	Unilateral w/ palpation (n=61)	95%	Unilateral w/ Preop. Imaging (N=67)	97%
Henry, 2001 (<u>5</u>)	Historical Controls	Bilateral (n=68)	100%	Video-Assisted (n=68)	100%
Chen, 1999 (<u>10</u>)	Historical Controls	Bilateral (n=184)	97%	Minimally Invasive (MIP) (n=33)	100%
Udelsman, 2003 (<u>11</u>)	Historical Controls	Bilateral (n=401)	97%	Minimally Invasive (MIP) (n=255)	99%

Table 2. Comparison of criteria for use of intraoperative PTH (96)

Criteria	False Positives (%)	False Negatives (%)	Accuracy (%)
$\geq 50\%$ from highest baseline at 10 minutes	0.9	2.6	97
$\geq 50\%$ from pre-incision baseline at 10 minutes	0.3	16	86*
$\geq 50\%$ from highest baseline at 10 minutes and within reference range	0.4	24	79*
$\geq 50\%$ from highest baseline at 10 minutes and below pre-incision value	0.6	6	95*
$\geq 50\%$ from highest baseline at 5 minutes	0.6	11	90*
$\geq 50\%$ from pre-excision baseline at 10 minutes	0.6	15	87*

*p<0.05

Table 3. Summary of recommendations for intraoperative PTH

	A Strongly Recommend	B Recommend	C Recommend Against	I Insufficient Evidence
Disease				
Primary Hyperparathyroidism	✓	✓		
Secondary Hyperparathyroidism				✓
Reoperative Hyperparathyroidism		✓		
MEN I				✓
Parathyroid Carcinoma				✓
Venous/Tumor Localization				
Pre-surgery Angiography Suite		✓		
Operating Suite				✓
Implementation				
Specific Assay				✓
Testing Location				✓

Chapter 11: pH Testing

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pH testing is utilized in a variety of medical applications, including critical care blood pH, renal function urine pH, gastric fluid pH to monitor acid suppression therapy, evaluation of ruptured membranes during delivery, diagnosis of bacterial vaginosis, placement of gastrointestinal (GI) feeding tubes, and chemical burn treatment in the emergency room. pH can be determined by electrode and colorimetric litmus paper or dipstick methodologies. These guidelines will focus primarily on the use of pH paper in determining gastric pH, placement of GI feeding tubes and treatment of chemical burns. Guidelines in other sections will focus on blood pH, urine pH, and use of pH during delivery and evaluation of infection.

Does the use of pH paper to diagnose and monitor treatment of chemical exposure in the Emergency Department and Urgent Care patient populations improve length of stay and severity of burn compared to empirical treatment (no monitoring)? (Literature Search 76)

Guideline 151: *We note that pH paper may have utility in monitoring the treatment of chemical exposure in the Emergency Department and Urgent Care patient populations, but there is insufficient evidence to make a strong recommendation for or against its routine use. pH testing*

poses no risk to the patient and the minimal cost of testing have led to its common availability. However, a systematic examination should be conducted to determine if pH testing has an incremental benefit during irrigation therapy after chemical exposure that outweighs the time and expense required to maintain test quality training and documentation.

Strength/consensus of recommendation: I

Level of evidence: III (clinical experience, descriptive studies, case reports and opinion)

Literature Search 76 summarizes the results of our literature search of Medline OVID and AHRQ National Guideline Clearinghouse databases for peer-reviewed manuscripts that address patient outcome from utilizing pH litmus paper in the acute management of chemical exposure. The quality of literature describing the use of pH paper in the treatment of chemical exposure is very poor and does not adequately link patient outcome to the use or failure to use pH paper. Several studies utilize pH testing as a means of monitoring changes during irrigation therapy rather than as the goal or endpoint of that therapy (1-13). In these studies, the change in pH was monitored to note the effects of chemical exposure and washing of the exposed eye or skin area with different irrigation fluids and lengths of time. The recommended duration of irrigation and type of fluid varied, but continuous washing of the affected area as soon as possible after chemical exposure was of utmost importance to prevent permanent tissue damage (3,4,14-16). It was difficult, however, to distinguish whether pH paper had any incremental benefit over the dilutional effects of simply flushing the exposed area with adequate amounts of fluid over a sufficient amount of time after exposure, since patient outcome was not directly compared with and without pH monitoring. Yano et al. exposed rats to alkaline skin injuries and suggested that the pH at the skin surface is important and that irrigation should continue until the pH of the skin

surface returns to normal (5). Amshel et al recommended irrigation of the eyes after anhydrous ammonia burns for at least 20 minutes or until a conjunctival sac pH below 8.5 is achieved (14). A review of chemical eye injuries by Burns and Paterson further indicated, “It is generally accepted that the pH of the external eye should return to normal before discontinuing irrigation. If prolonged irrigation does not return the pH to within the normal range, particulate matter possibly remains.”(17) pH monitoring could thus have a role in determining the endpoint of irrigation therapy or provide the necessary criteria for further treatment. However, these recommendations are based on clinical experience rather than direct comparison of the effects of pH testing in different groups of patients. Additionally, much of the published research on treatment of chemical exposure has been conducted on animals, and animal based conclusions may not be capable of being directly extrapolated to human patients (1-5,8,10,11).

The type of chemical may also be a consideration when using pH paper for monitoring exposure and ingestions. Some chemicals may not alter pH (organic chemicals) or may be so acidic or basic that standard pH paper cannot adequately measure the agent. Krenzelok et al recommends that “a sample of the ingested agent and its original container should be brought with the patient [to the emergency department]. The information obtained from [pH testing] provides objective data regarding the alkalinity of the product and strongly influences the decision to perform endoscopy on each victim” (13). A wide range pH paper of 1 – 12 and also pH paper with an extended range of 12 – 14 is recommended, since some pH paper commonly found in emergency departments has too narrow a pH range to be useful in evaluating caustic substances. Others, however, have noted that pH paper is inaccurate in the assessment of strong acids and strong

bases and biases of 1.7 units or more may inappropriately alter treatment decisions, although patient outcomes have not been thoroughly examined (10).

Of further consideration is the ability to obtain a reliable result from pH paper. pH paper is hygroscopic and susceptible to light and changes in humidity. Storage conditions and operator technique should therefore be monitored to ensure adequate response and interpretation of results. pH paper measures pH in color-coded increments. Accurate paper readings are dependent on sufficient color vision and adequate lighting to discriminate a color change in the presence of interfering paper staining by components such as blood, antacids and bile (18,19). The burden and expense of documenting operator training, competency and quality control of pH paper is not insignificant, yet the cost of the pH paper itself is minimal and pH testing poses virtually no risk to the patient provided proper technique is utilized to collect the sample and perform the test. The pH paper should not be placed in the eye or directly in contact with an exposed area of skin, but should test the tears and irrigation fluid flushing the exposed area. Direct contact can lead to further irritation due to the chemicals in the paper and pH paper is not a sterile medium.

Our literature search also found two other emergent or acute applications of pH testing; prevention of aspiration pneumonia in surgical patients and the differential diagnosis of diarrhea. Aspiration of stomach contents can lead to pulmonary damage due to its acidity, and unconscious or anesthetized patients are at higher aspiration risk. Johnston recommends monitoring the pH of gastric contents as an indicator of the risk of pulmonary aspiration during anesthesia (9). Administration of preoperative cimetidine can block the secretion of acid and

provide protection at intubation or extubation. Wynn notes the critical pH below which severe lung damage occurs varies from species to species, for example, 1.7 for rats and 2.1 to 2.4 for rabbits (20). A critical pH of less than 2.5 has been suggested for humans, but has not been proven. Nevertheless, gastric aspirates have commonly been termed “acidic” at pH values less than 2.5 (20). pH testing may thus have a role in monitoring gastric acidity prior to surgery.

In a separate application, the American Gastroenterological Association suggests that a low fecal pH less than 5.3 is characteristic of diarrhea caused solely by carbohydrate malabsorption, while a pH greater than 5.6 argues for a generalized malabsorption syndrome that involves fecal loss of amino acids and fatty acids in addition to carbohydrate (21). Fecal pH testing may therefore be useful in distinguishing the causes of diarrhea. The use of pH paper is not directly recommended in either of these applications, and a pH meter may be better suited and more capable of distinguishing narrow pH differences, like 5.3 from 5.6, in the presence of gastric or fecal substances that can affect pH color change.

Does continuous gastric pH monitoring, compared to random gastric pH determinations, improve patient symptoms and severity in the management of achlorhydria and gastric reflux in inpatient and endoscopy patients? (Literature Search 77)

Guideline 152: *We recommend against the intermittent use of pH paper on gastric aspirates in the diagnosis of gastric reflux disease in favor of continuous monitoring. The role of pH testing to manage acid suppression therapy is controversial. Although the use of pH testing is common on critical care units, there is a lack of evidence that pH monitoring to adjust drug dosage improves either morbidity or mortality in these patients.*

Strength/consensus of recommendation: C**Level of evidence: II and III** (well designed case controlled, correlation trials and opinion)

Literature Search 77 lists the results of our search for manuscripts that examined patient outcome from the use of pH monitoring in achlorhydria and gastric reflux disease. Continuous pH monitoring is considered the gold standard for the diagnosis of gastroesophageal reflux (GER) (22-24). Ambulatory intraesophageal pH monitoring is regarded as the most accurate, clinically relevant measure of GER available (23) and is useful in measuring gastric pH changes, estimating esophageal acid exposure, and documenting reflux episodes (25). The test involves tiny pH electrodes that are swallowed or passed transesophageal to the depth of the gastric sphincter or into the stomach to sense pH changes at those sites. Data is continuously recorded in a portable data logger that can be wirelessly or manually downloaded after the procedure. Computer software is available for statistical data reduction to determine the cumulative exposure to acid, number of episodes, average duration, number of episodes longer than 5 minutes and the longest episode of pH below 4.0. Continuous pH monitoring demonstrates the highest values of sensitivity (88%) and specificity (98%) (26) for the diagnosis of GER compared with other methods of endoscopy, manometry, barium esophagogram, reflux scintigraphy, cinematography, or reliance on symptoms like heartburn and regurgitation (22,27,28).

Continuous pH monitoring has also provided insight into the various complications of GER. Esophageal damage is more likely to occur with excessive exposure to gastric juice, especially fluids with a pH less than 2.0, and patients with strictures and Barrett's esophagus, a potential

precursor of esophageal carcinoma, have been reported in prolonged exposure to acid of increased concentration (26,29,30). A comprehensive review found pH monitoring alone and in conjunction with motility monitoring to be valuable in the evaluation of patients with a variety of symptoms ranging from non-cardiac chest pain, gastric, pulmonary, laryngeal and dental disease as well as the assessment of medical and surgical reflux therapies (26,27).

Inhibition of acid secretion with H₂ receptor antagonists or neutralization of stomach acid with antacids is frequently used to prevent stress ulcers and bleeding, especially in acutely ill patients. pH monitoring has been utilized to guide antacid and H₂ antagonists with the goal to achieve and maintain a gastric pH greater than 4, and this type of pH monitoring has become the standard of practice on critical care patients, but there is a general lack of supporting evidence that such monitoring improves patient morbidity and mortality (31). As sucralfate therapy does not alter pH, the monitoring of pH is not warranted with this drug (32).

When clinicians do consider monitoring, pH can be tested continuously with gastric electrodes or intermittently on gastric aspirates using either a pH meter or pH paper. pH meters have better accuracy for measuring pH when compared to pH paper (18,33-37), but pH meters may not be practical to maintain at all sites where patients are being monitored. There are mixed reports on the ability of pH paper to adequately estimate gastric pH. Bias has been noted between pH paper and pH meters in the pH range of 2 – 6 that tends to overestimate the patient's gastric pH by litmus paper. While some investigators find this bias to be clinically relevant (18,34), others claim the error bias is smaller than the paper color increments and the use of pH paper is reasonable (37,38). It is important to note that these studies do not recommend implementation

of pH meters for routine monitoring of antacid therapy until further studies specifically evaluate the effects of the pH meter/paper bias on patient outcome (34).

Other studies have compared nasogastric tubes containing a pH electrode capable of continuous monitoring and gastric aspirate pH by litmus paper for assessing antacid therapy (33,36,39).

While general concordance between the methods was found, some discrepancies with pH paper measurement were hypothesized to be the result of aspirated antacid residue (36), the presence of proteins and bile, or simply the heterogeneous nature of gastric contents (35). The timing of gastric aspirates may be critical to the agreement between continuous monitoring and pH paper. Poor correlation was noted for both the median pH values and the percentage of time below pH 3 between 24 hr monitoring and once daily aspirates (40) while better correlation was found with more frequent aspirate measurements (36,41). Intragastric pH measurements may actually be more reflective of the microenvironment surrounding mucosal cells, but could also be registering only the gastric pH in contact with the electrode and differ in various parts of the stomach or gastric contents (19,37,42,43). pH electrodes can measure pH when it is difficult to obtain a sufficient volume of aspirate. This may be important in monitoring intestinal pH where the collection of adequate amounts of aspirate is difficult (19,44). Given the time involved in collecting an aspirate and the potential for various interferences with paper color changes, continuous pH monitoring was judged to be a simpler, safer, faster and more reliable measure of gastric pH when compared to measurement of gastric aspirates with pH paper (19,33,36). However, continuous pH monitoring is expensive and litmus paper might offer a more economical alternative for those clinicians wanting to monitor acid therapies at the bedside (45).

Continuous pH monitoring is not without challenges. The electrodes must be calibrated before each use and the calibration drift monitored after each patient. There is no standard method for calibration or consensus regarding acceptable bias and drift. Calibration is conducted with pH buffers at room temperature, so appropriate correction factors must be factored into the monitor's software to account for differences between body and room temperature (26). Additional corrections may be necessary at very low pH or pH values near 7 where certain types of electrodes may display more bias (26). Internal placement of the electrode will affect the test results. If the electrode is not far enough into the esophagus, the monitor may fail to detect reflux episodes, and if the electrode is placed too far, the test may monitor gastric or duodenal pH changes (26). Drift can be judged by testing of pH buffers before and after patient monitoring. Most studies have limited the examination of data from patients where the electrode did not drift by more than 0.2 – 0.4 pH units over the testing period (25,44,46,47). Despite these limitations, continuous pH monitoring is currently considered the gold standard in diagnosis of GER. Monitoring therapy with pH paper while considered a standard of care in many critical care units, may have a clinical role, but there is a lack of supporting evidence that pH monitoring to guide acid suppression therapies actually lowers patient morbidity and mortality (31). Clinically significant bleeding as opposed to occult bleeding has been suggested as a more appropriate therapeutic endpoint (32).

Does the use of pH paper for assisting the placement of nasogastric tubes, compared to clinical judgement (air, pressure) improve the placement of tubes on inpatient, endoscopy, home care and nursing home patients? (Literature Search 78)

Guideline 153: *We recommend for the use of pH testing to assist in the placement of*

nasogastric tubes. Radiography is considered the gold standard means of determining tube placement, but there is fair evidence that pH testing can predict the position of nasogastric tubes while reducing the number of x-rays and exposure of the patient to additional radiation. The choice of measuring pH with an intragastric electrode or testing tube aspirates with a pH meter or pH paper will depend on consideration of the clinical limitations of each method, and there is conflicting evidence over which method is better.

Strength/consensus of recommendation: B

Level of evidence: II and III (prospective comparative trials and expert opinion)

Fourteen manuscripts were found in our literature search to address our clinical question and have a focus on the use of pH testing for nasogastric tube placement. (Literature Search 78)

Methods to assure correct placement of a nasogastric (NG) or nasointestinal (NI) tubes include careful insertion of an appropriate length of tube, direct visualization of the oropharynx to confirm esophageal entry, auscultation of the gastric area during insufflation of air, aspiration of gastric contents from the tube, irrigation of the tube with 10 to 50 mL of water, abdominal roentgenogram to confirm tube position, and direct palpation of the tube within the stomach during intra-abdominal procedures (48). Radiography is considered the gold standard means of determining tube placement in clinically ambiguous cases, however pH testing may provide a faster, safer and more economical means of screening tube placement prior to considering radiography. Gastric contents are normally more acidic than intestinal or respiratory fluids. Neuman et al noted that an aspirate pH greater than 4 was not useful in predicting malposition of the tube (ie respiratory vs placement in the GI tract), but an aspirate pH of less than 4 can reduce the need for x-ray films and exposure of the patient to additional radiation (positive

predictive value 100%, sensitivity 100%, specificity 88% for N =46 patients and 78 tube placements) (49). As acid inhibitors and antacids increase gastric pH, studies on patients under acid suppression suggest that a higher gastric cutoff of pH 6.0 may provide better discrimination of tube placement and may further be useful in distinguishing gastric from intestinal placements. Over 81% of gastric samples were found to have a pH between 1 and 4, while over 88% of intestinal aspirates had a pH greater than 6 (38,50). Pulmonary fluid has a pH greater than 6.5, confounding the interpretation of aspirates with pH greater than 6 between intestinal and pulmonary placement. Radiography studies may be useful in equivocal cases of aspirated fluid with a pH between 4 and 6. A change of more than 4 pH units, the addition of bilirubin measurement, and the visual characteristics or volume of the aspirate have been suggested as possible ways to improve the prediction of tube placement (51-55). However, the effect of these suggestions on patient outcome remains to be examined.

While pH testing is useful in determining tube placement, there is some controversy over which method of monitoring pH is better; use of a continuous intragastric electrode, or measurement of the pH of tube aspirates with a pH meter or pH paper. Intragastric monitoring with a pH probe attached to the end of a feeding tube can assist in both tube placement and monitoring of acid suppression therapy for several hours. These probes are technically simpler, faster and may be more accurate than testing gastric aspirates with pH paper (33,36). Intragastric and aspirate pH monitoring is capable of continuously monitoring pH changes of the gastric contents, but this pH may not reflect the actual pH at the mucosal cell surface (37). Therapy to raise the pH content of gastric contents based on the gastric aspirates may vary significantly from intragastric pH, overestimating the true intragastric acidity and guide therapy changes that may not be

sufficiently protective. This hypothesis is supported by case reports of bleeding and treatment failure while on acid suppression, and significant bleeding as opposed to occult bleeding may be a better endpoint of acid therapy than pH (32).

Testing the pH of aspirated gastric contents with paper or a pH meter also may not provide equivalent pH results. Several studies have noted clinically relevant biases between pH paper and pH meters in the pH range of 2 to 6 that would have led to overestimation of gastric pH in 4 of 51 patients (34), and would have resulted in inappropriate treatment for 28% of the samples tested in another study (18). These biases are believed to be related to the limitations of accurate pH paper assessment in the presence of salts (antacids) and interferences from bile, protein and other substances found in an inhomogeneous sample like gastric fluid (18,56). The patient outcome predicted by the pH paper bias has not been confirmed. Other studies have claimed that the magnitude of the pH bias is smaller than the error of pH paper measurement (typically read in 0.5 – 1.0 pH unit increments) (38). Clearly, pH testing of gastric aspirates has clinical utility in the determination of feeding tube placement, and pH paper can be used to judge the pH of gastric aspirates provided that appropriate consideration is given to its limitations. pH testing in general is not a total replacement for radiography, as gastric fluid is only capable of being aspirated in about 85 – 95% of cases and fluids with pH greater than 6 may not be conclusive for gastric placement (since both intestinal and pulmonary placements can have pH values above 6.0). pH testing can, however, reduce the need for reliance on radiographic confirmation in every tube placement providing efficiency and cost savings in patient management.

Is one brand of pH paper better than another brand in improving patient symptoms and time to

treatment of chemical burns in emergency and urgent care patients, and in improving the accuracy of nasogastric tube placement in inpatient, endoscopy, home care and nursing home patients? (Literature Search 79)

Guideline 154: *There is insufficient evidence to recommend one brand of pH paper over another brand of pH paper for use in the treatment of chemical burns or placement of nasogastric tubes.*

Strength/consensus of recommendation: I

Level of evidence: III (case reports and opinion)

Literature Search 79 summarizes the results of the literature search for studies comparing clinical outcomes from the use of different pH papers. Two studies were found that compared pH results between different brands of pH paper. Brands with multiple color changes were found to be more accurate when compared to pH meter results (57,58). Products providing more than one color change or multiple overlapping scales of colors were found to detect more subtle pH changes and were preferred by nurses and anesthesiologists over those papers with a single color change. The accuracy of single color pH papers ranged from 20 % to 83% depending on the paper (57). Single color pH papers were noted to have major deficiencies discriminating pH 4, while multiple color papers had more difficulty in the low range of pH less than 1 (58). The effects of these inaccuracies on patient outcome were not examined. In light of the age of these studies (1983 and 1987) and variety of pH papers available on the market, there is insufficient evidence to recommend one brand of pH paper over another for monitoring antacid therapy, feeding tube placement or irrigation of chemical burns.

In summary, continuous pH monitoring is recommended for the diagnosis of GER disease, and intermittent testing by pH meter or litmus paper does not have diagnostic utility in this disorder. pH testing seems to have a beneficial clinical role in confirming the placement of feeding tubes. However, the use of pH testing in managing acid suppression therapy and determining the efficacy of wound irrigation after chemical exposure will require further studies that directly examine the effects of pH testing on patient outcome. More importantly, studies are needed to determine the type of monitoring that is most effective and to define when more accurate measurement by pH meter is required or when less precise estimates by pH paper may suffice. pH paper is inexpensive and may be considered inconsequential in patient management, but inaccuracies in pH results can lead to undertreatment with acid inhibitors, inappropriate feeding tube placement, and premature discontinuation of irrigation for chemical burns that has the potential for serious and costly patient consequences. Clinicians are encouraged to thoroughly examine the accuracy, applicability and benefits of any test before implementation in patient care and verify continued outcomes periodically after any change in practice.

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Public Comments:

Received during the AACC Presentation – It seems that your group has left off one of the most important uses of pH testing, Nitrazine paper. Have you looked at nitrazine for women’s health?

In our introduction section, we specifically state, “These guidelines will focus primarily on the use of pH paper in determining gastric pH, placement of GI feeding tubes and treatment of chemical burns. Guidelines in other sections will focus on blood pH, urine pH, and use of pH during delivery and evaluation of infection.” Blood pH can be found in the critical care section grouped with blood gases. Urine pH is addressed in the renal guidelines. Use of nitrazine paper and ruptured membranes is found in the reproduction section. Finally, nitrazine or pH testing for bacterial vaginosis can be found in the infectious disease section.

No other comments have been received.

Chapter 12: Renal Function Testing

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Dipstick urinalysis (DUA) is one of the cornerstones of point of care testing (POCT) – relatively inexpensive, robust, easy to perform, painless to the patient, and available worldwide. Almost since the inception of the Clinistix (Ames Co, Elkhart, IN) in 1956, DUA has been a staple for community health and preoperative screening, and in the work-up of urinary tract and systemic diseases. However, the real clinical utility of DUA is more often assumed than proven. In addition, recent advances in technology have introduced the ability to perform more advanced testing (e.g. quantitation of blood urea nitrogen (BUN), creatinine) at the patient bedside. The guidelines will focus on the use of POCT for renal function or urinalysis in a variety of clinical settings and patient populations. Guidelines in other sections will address urine glucose, ketones or microalbumin (diabetes) and urine dipstick leukocyte esterase and nitrite (infectious disease).

Does measurement of BUN and/or creatinine at the point of care (versus the core lab) result in quicker time to treatment, decreased wait time, or decreased length of stay for inpatient, emergency department (ED), dialysis, cardiovascular diagnostics laboratory (CVDL), or chemotherapy patients? (Literature Search 80)

Guideline 155: *We recommend against routinely providing point of care testing for creatinine or BUN in the ED; we found fair evidence that POCT is ineffective in this environment.*

Strength/consensus of recommendation: C

Level of evidence: II

Guideline 156: *However, we recommend that clinicians routinely provide POCT in the CVDL for creatinine and BUN; we found fair evidence that POCT in this environment improves important patient outcomes and that the benefits outweigh any potential harm.*

Strength/consensus of recommendation: B

Level of evidence: II

We selected 13 papers (1-13) for full-text review (from 77 abstracts), and from these 13 papers, 3 were accepted for grading with respect to the clinical question. The first 2 papers presented studies regarding the use of POCT in the emergency department. Tsai et al (13) conducted a cost-effectiveness study to determine time and labor costs for POCT versus central laboratory testing in an ED setting. The study was conducted over a 4-week period at a teaching hospital in Philadelphia, Pennsylvania and included a cohort of 210 patients presenting to the ED who were triaged at the urgent or emergent level and had blood drawn for a Chem-7 panel (which includes

BUN and creatinine). It should be noted that the POC device was only able to measure BUN. The main outcome measures included test turnaround time (TAT) and cost per test including labor for POCT versus central lab testing. This study found an average TAT of 8 minutes for POCT compared to 59 minutes for central lab testing. When examining cost, depending on testing personnel, the cost for POCT ranged from \$14.37 to \$16.67, while the cost for central lab testing was \$11.14. The authors stated that the cost per test would decrease based on increased testing volume and that the study did not take into account any cost savings due to decreased length of stay (LOS) and increased patient throughput for the ED. Based on these statements, their opinion was that POCT in the ED could be a cost-effective solution.

However, a second study by Parvin et al (7) using a similar device to the previous study examined the relationship of LOS to implementation of POCT in the emergency department. This study defined LOS as the length of time between initial patient interview and discharge; the study examined patient LOS distribution during a 5-week experimental period after implementation of POCT and compared it to the distribution during a 5-week control period prior to implementation and a 3-week control period after POCT use was removed. During the study period, there were approximately 15,000 ED patient visits of which 4985 patients had at least one Na, K, Cl, BUN, or glucose test ordered from the ED (2067 experimental and 2918 control). No decrease in LOS was observed during the study period; median LOS during the experimental period was 209 minutes compared to 201 minutes during the control periods. The authors further analyzed the data by stratification of patients based on presenting condition, discharge/admit status, or presence/absence of other central lab tests, but these results did not reveal a decrease in patient LOS for any patient subgroup during the experimental period. Based

on the increase in cost per test and lack of evidence that LOS is improved or ED throughput increased, we do not see any evidence that POCT for renal function effectively improves patient outcomes.

The third graded paper dealt with utilization of POCT in the CVDL to reduce patient wait times. Nichols et al (4) conducted a study in 4 phases to establish the impact of implementation of POCT for coagulation and renal function testing on the amount of time between when a patient's procedure was scheduled and when it actually occurred. Phase 1 examined overall patient management and workflow in the CVDL. In phase 2, POCT was implemented, but central laboratory results were utilized for patient management. In phase 3, therapeutic decisions were made based on POCT results and in phase 4, the authors worked to optimize workflow around the availability of POCT. In phase 1, the authors demonstrated that 44% of the central laboratory results were not available prior to the scheduled procedure time (n=135). Phase 2 results showed that the mean waiting time for patients who needed renal testing was 188 ± 54 minutes (n=14). For patients needing renal function testing, phases 3 and 4 were combined, and utilization of POCT decreased the mean patient wait time to 141 ± 52 minutes (n=18, p=0.02). The evidence in this paper demonstrates that implementation of POCT in the CVDL led to a statistically significant decrease in wait times for patients needing renal function testing.

Does screening for renal insufficiency by urine pH dipstick at the point of care result in earlier diagnosis of renal insufficiency and fewer adverse events or decreased length of stay for patients compared to screening by core lab urine pH testing? (Literature Search 81)

Guideline 157: *We are unable to recommend for or against routine use of POCT using urine pH dipstick to screen for renal insufficiency.*

Strength/consensus of recommendation: I

While we were able to select three papers (14-16) for full-text review (from 310 abstracts), we were unable to grade any of them based on the fact that either they did not specifically address the clinical question, or they did not contain an evaluation of patient outcomes.

Does screening for metabolic disorders using urine dipstick pH at the point of care result in earlier diagnosis of metabolic disorders, along with fewer adverse events and more rapid time to treatment for patients in outpatient clinics or the NICU/nursery when compared to screening by core lab urine pH testing? (Literature Search 82)

Guideline 158: *We are unable to recommend for or against routine use of urine dipstick pH testing for metabolic disorder screening at the point of care.*

Strength/consensus of recommendation: I

Six papers (16-21) were selected for full-text review (from 310 abstracts), but we were unable to grade the evidence with respect to patient outcomes because they either did not specifically address the clinical question, or they did not contain evidence relating to patient outcomes.

Does measurement of urine specific gravity via dipstick testing at the point of care to evaluate renal function result in decreased patient wait time, quicker time to treatment, fewer adverse events, or decreased length of stay for inpatient, ED, or outpatient clinic patients when compared

to measurement of urine specific gravity in the core lab? (Literature Search 83)

Guideline 159: *We are unable to recommend for or against the routine use of urine dipsticks to measure urine specific gravity at the point of care for evaluation of renal function.*

Strength/consensus of recommendation: I

Of six papers (22-27) that were selected for full-text review (from 21 abstracts), none of them were graded with respect to strength of evidence, because they either did not specifically address the clinical question, or they did not contain evidence relating to patient outcomes.

Does assessment of specimen integrity by measurement of urine specific gravity by dipstick testing at the point of care result in fewer repeat patient visits due to invalid urine specimens in the ED, physician's office lab, or workplace drug testing setting? (Literature Search 84)

Guideline 160: *We cannot recommend for or against the routine use of urine specific gravity by dipstick testing for assessment of urine specimen integrity at the point of care.*

Strength/consensus of recommendation: I

Only one paper (28) was selected from 2 abstracts for full-text review, and it was not graded based on the fact that it did not discuss evidence relating to patient outcomes.

Does determination of hydration status by measurement of plasma, serum, whole blood, or urine osmolality at the point of care result in decreased patient wait time, quicker time to treatment, decreased length of stay, or fewer adverse events for inpatient, ED, or outpatient clinic patients compared to measurement of osmolality in the core lab? (Literature Search 85)

Guideline 161: *We are unable to recommend for or against routine point of care measurement of osmolality – blood or urine – for determination of patient hydration status.*

Strength/consensus of recommendation: I

While three papers (22, 29, 30) were selected for full-text review (from 6 abstracts), we were unable to grade any of the papers because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does screening for proteinuria using urine dipstick testing at the point of care to evaluate renal function result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, or outpatient clinic patients when compared to urine protein screening using a core laboratory method? (Literature Search 86)

Guideline 162: *We recommend against routinely screening for proteinuria using urine dipstick testing at the point of care; we found fair evidence that POCT screening in this environment is ineffective for improving patient outcomes.*

Strength/consensus of recommendation: C

Level of evidence: II

We selected 32 papers (14, 20, 31-60) for full-text review (from 260 abstracts); of these 32 papers, 6 were suitable for grading with respect to the clinical question. The first study by Hermansen et al (14) was performed to evaluate the benefits and costs of routine admission dipstick urinalyses. This study followed 954 pediatric admissions at the authors' institution. Dipstick urinalysis was performed on all admissions, and the results were reviewed between 12 and 36 hours post-admission for the presence of glucosuria, hematuria, and proteinuria. If an

abnormality was found, the chart was reviewed periodically until the abnormality was classified with respect to the clinical diagnosis. After the patient was discharged, the chart was reviewed to determine the costs incurred as a result of the screening effort – no attempt was made to evaluate the effect on LOS. The authors found that the presence of abnormalities and false positive or negative results were comparable to those of non-hospitalized children. Their conclusions pointed to the difficulty in justifying a routine screening dipstick urinalysis on every pediatric hospital admission. A separate study by Shaw et al (53) compared dipstick urinalysis to microscopic examination for diagnosis of urine abnormalities. The results of urinalyses on 1,839 patient samples were evaluated and yielded at 16% false negative rate for dipstick 1+ proteinuria (with trace blood) that improved to 13 % by lowering to trace protein, and improved to 3.3% when using trace protein and adding leukocyte esterase to the dipstick analysis. The study found the test strips to have a sensitivity of 62-70% and specificity of 71-79% for detection of abnormal urine sediment.

Two of the studies focused on comparison of dipstick urinalysis for proteinuria with urine protein/creatinine ratio (P/Cr) analysis performed in the central lab. Ralston et al (54) examined screening for proteinuria in a rheumatology clinic setting. In this study, measurements of protein/creatinine ration in ‘spot’ or random urine samples were compared with central lab testing of 24-hour quantitative proteinuria and dipstick urinalysis in 104 samples from 90 patients presenting consecutively to a rheumatology unit. Significant proteinuria in the study was defined as >300 mg/24 h by core laboratory methods. Compared to the central laboratory method, the false positive rate (positive dipstick results at <300 mg/24 h) was 100% for trace results (n = 15), 76% for 1+ results (n = 46), 38% for 2+ results (n = 21), 15% for 3+ results (n =

15), and 0% for 4+ results (n = 7). Setting the dipstick positive result at 1+ yielded a sensitivity of 100%, but poor specificity due to the high rate of false negatives in the 1+ to 3+ range (48%). In comparison, the P/Cr ratio was able to achieve both specificity and sensitivity of 97% according to the authors. The second study, by Abitbol et al (20), investigates the quantitation of proteinuria with urinary P/Cr ratios compared to random testing with dipsticks in nephritic children. The investigation included 64 children (45 male) with nephritic syndrome that provided 145 timed, 24-hour urine specimens and 150 random urine specimens that were tested by dipstick urinalysis, as well as central laboratory determination of urine P/Cr. Nephrotic-range proteinuria was defined as > 1.0 g/m²/day. Positive results (for nephritic proteinuria) were designated as a ratio of >1.0 for P/Cr, or 3+ and 4+ for dipstick urinalysis. Dipstick urinalysis for proteinuria produced a sensitivity of 70%, specificity of 68 %, and positive predictive value (PPV) and negative predictive value (NPV) of 89 % and 60%, respectively. Using random P/Cr ratios, a sensitivity of 95%, a specificity of 93%, as well as a PPV and NPV of 93% and 100%, respectively were obtained. The authors point out the high negative predictability for urine P/Cr ratio in contrast to the low negative predictability for dipstick urinalysis and assert the random P/Cr ratio to be a better assessment tool for proteinuria in children with nephrosis.

Two of the more recent graded studies presented points of view that screening for dipstick proteinuria exhibits potential to contribute to improved patient outcomes. Craig et al (43) conducted a feasibility study of early detection and treatment of renal disease by mass screening using systematic review and meta-analysis, as well as an evaluation of cost effectiveness. In the study, the authors assert that if screening is implemented solely on the basis of proteinuria, raised serum creatinine, or raised blood pressure, then adverse effects of additional investigations

would be trivial. However, based on their systematic review, it was concluded that the poor specificity of dipsticks would result in a high proportion of the population being recalled for more tests before being declared false positives. The authors state that if screening results in early treatment with ACE inhibitors, then it would be possible that 340 fewer people would develop end-stage renal disease (ESRD) for every 10,000 treated. Based on their assumptions, the study predicts that a dipstick screening program (coupled with early intervention) for men and women aged 50 years and older would prevent 205 cases of ESRD and would result in a net cost savings for the healthcare system despite increased costs incurred by widespread screening. Agarwal et al (39) pose the question as to whether dipstick urinalysis for proteinuria can be used to guide hypertension management. In this study, 332 patients (all male) attending the renal clinic at a VA hospital had urine protein and creatinine levels measured, as well as routine dipstick urinalysis. The investigators were interested in patients with proteinuria greater than 1g/d or greater (corresponds to P/Cr ratio of 1 or greater), because practice guidelines called for lower blood pressure targets in these patients. The authors found that when comparing dipstick urinalysis versus a P/Cr ratio, a dipstick result of 4 gives a 92% chance of having a P/Cr ratio of 1 or greater. Conversely, when the urine dipstick is free of protein, proteinuria with a P/Cr ratio of greater than 1 can be ruled out. Lastly, the authors demonstrated that receiver operator characteristic (ROC) analysis of protein dipsticks with a cutoff value of 3 gives the best combination of sensitivity and specificity (96% and 87%, respectively) in predicting a P/Cr ratio of 1 or greater. While the above studies demonstrate promise for the utilization of dipstick proteinuria analysis, they offer little direct evidence for the improvement of patient outcomes. Based on the studies that were graded, we do not see any evidence that supports improved patient outcomes based on screening for proteinuria using dipstick urinalysis.

Does detection of glomerular dysfunction by evaluation of hematuria using dipstick testing at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, or outpatient clinic patients when compared to evaluation of hematuria using core lab urinalysis? (Literature Search 87)

Guideline 163: *We are unable to recommend for or against dipstick testing for hematuria to evaluate the extent of glomerular dysfunction at the point of care.*

Strength/consensus of recommendation: I

Sixteen papers (27, 48, 53, 61-73) were selected for full-text analysis (from 215 abstracts), but we were unable to grade any of those papers because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does analysis of urine or serum electrolytes at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, or outpatient clinic patients when compared to analysis of electrolytes using the core laboratory? (Literature Search 88)

Guideline 164: *We cannot recommend for or against measurement of urine or serum electrolytes at the point of care.*

Strength/consensus of recommendation: I

While we were able to select 7 papers (1, 2, 8, 28, 74-76) for full-text analysis (from 20 abstracts), we were not able to grade any of those papers because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does evaluation for pregnancy-induced hypertension or pre-eclampsia using urine protein dipstick testing at the point of care result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for ED, outpatient clinic, or labor and delivery patients when compared to urine protein measurement using core laboratory methods?

(Literature Search 89)

Guideline 165: *We recommend against routine use of urine protein dipstick testing at the point of care for antenatal evaluation of hypertension or pre-eclampsia; we found fair evidence that protein dipstick testing in this environment is largely ineffective.*

Strength/consensus of recommendation: C

Level of evidence: II

We selected 17 articles (16, 44, 45, 49, 56, 59, 77-87) for full-text review (from 260 abstracts), and from these 17 articles, 2 were accepted for grading with respect to the clinical question. In a 2001 study, Waugh et al (80) examined the accuracy of urine dipsticks for protein measurement in hypertensive pregnancies. In this study, 24-hour urine specimens were collected from 197 consecutive pregnant women who were at risk for hypertensive pregnancy. Hypertension was defined as a sustained systolic blood pressure of greater than 140 mm Hg, a diastolic blood pressure of greater than 90 mm Hg on two occasions, or a diastolic pressure of greater than 110 mm Hg on a single occasion. The urine specimens were analyzed by dipstick urinalysis and two biochemical assays, the Benzethonium Chloride assay and the Bradford assay. A positive test for proteinuria was defined as a result of 1+ or greater for dipstick urinalysis or a 24-h urinary protein of 0.3g/24h for both biochemical assays. A second analysis was performed for both biochemical assays using a cut-off of 0.3 mg/mL based on the fact that the trace/1+ threshold for

detection of proteinuria in dipstick methodology is set at a protein concentration of 0.3 mg/mL. Using the gold standard definition (0.3 g/24 h) for biochemical assays, the prevalence of proteinuria according to dipstick urinalysis (1+) was 16.2%, compared to a prevalence of 70.1% detected with the Benzethonium Chloride method and 24.9% with the Bradford assay. In comparison to the Benzethonium method, the dipstick analysis yielded a PPV of 96.9% and an NPV of 22.5%; using the Bradford assay as the reference method, dipstick urinalysis gave a PPV of 87.5% and an NPV of 87.3%. Changing the gold standard definition to 0.3 mg/mL for the biochemical assays did not significantly affect the PPV, but did show some improvement for the NPV (increased to 53.9% and 92.1 for the Benzethonium and Bradford assays respectively). It should be noted that both the Bradford assay and urine dipstick methodology are particularly sensitive to albumin and transferrin, while the Benzethonium Chloride assay is sensitive to these proteins and many others (the authors demonstrate this using qualitative gel electrophoresis). Based on this information, the authors assert that Benzethonium Chloride is the preferred gold standard for biochemical assays, and that in comparison to this standard, urine dipsticks produce far too many false negative results in hypertensive pregnant women to be useful – even when employing a similar concentration cut-off rather than the traditional proteinuria definition of 0.3g/24h.

A more recent study by Murray et al (85) examines whether routine urinalysis in the antenatal period facilitates a diagnosis of pre-eclampsia. This study was conducted as a prospective observational study, where 1000 women were enrolled at their first antenatal visit; 913 completed the study. At the first antenatal visit, a urine sample was collected for dipstick urinalysis and central laboratory testing (urine dipsticks were read using a Bayer Clinitek 50).

Of the 913 enrollees, 11 did not have dipstick testing performed at their first visit, 35 women demonstrated dipstick proteinuria (1+), and 867 did not exhibit dipstick proteinuria on the first visit. Out of the 867 patients without dipstick proteinuria, only 338 women developed proteinuria at some time during their pregnancy. Statistically, there were no significant differences in the proportion of women with and without dipstick proteinuria on their first visit that developed hypertension during pregnancy. The authors conclude that while “at-risk” women may benefit from routine dipstick urinalysis for proteinuria, low-risk women do not benefit from routine dipstick proteinuria screening. Based on the above studies, we do not see any evidence that routine screening for proteinuria by dipstick urinalysis leads to improved patient outcomes.

Does the use of urine dipstick pH testing at the point of care to predict renal stone recurrence result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, or outpatient clinic patients compared to core lab urine pH testing? (Literature Search 90)

Guideline 166: *We are not able to recommend for or against routine use of urine dipstick pH testing at the point of care to predict renal stone recurrence.*

Strength/consensus of recommendation: I

Of the 4 papers (25, 57, 88, 89) that were selected for full-text review (from 310 abstracts), none were able to be graded because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does dipstick hematuria testing at the point of care to detect intra-abdominal trauma result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for ED patients compared to evaluation of hematuria using core lab urinalysis? (Literature Search 91)

Guideline 167: *We are unable to recommend for or against dipstick hematuria testing at the point of care to detect intra-abdominal trauma.*

Strength/consensus of recommendation: I

We were able to select 17 papers (63-65, 67, 90-102) for full-text review, but of these papers none were graded because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does measurement of lactate at the point of care to assess or correct lactate buffer replacement in hemodialysis patients result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay? (Literature Search 92)

Guideline 168: *We cannot recommend for or against measurement of lactate at the point of care to assess or correct lactate buffer replacement in hemodialysis patients.*

Strength/consensus of recommendation: I

We pulled 3 papers (100-102) for full text review, but none of the papers were graded because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does detection of myoglobinuria using urine dipstick testing at the point of care as an indicator for possible renal complications of muscle injury result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, and outpatient clinic patients when compared to evaluation of myoglobinuria using core lab urinalysis?

(Literature Search 93)

Guideline 169: *There is not sufficient evidence to recommend for or against urine dipstick testing for myoglobinuria at the point of care as an indicator for possible renal complications of muscle injury.*

Strength/consensus of recommendation: I

Four papers (103-106) were selected for full-text review (from 7 abstracts), however, none of these papers were graded because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

Does measurement of microalbuminuria using dipstick testing at the point of care to assess non-diabetic nephropathy result in decreased wait times, reduced time to treatment, fewer adverse events, and decreased length of stay for inpatient, ED, and outpatient clinic patients when compared to evaluation of microalbuminuria using core lab methods? (Literature Search 94)

Guideline 170: *We are unable to recommend dipstick testing for microalbuminuria at the point of care to assess non-diabetic nephropathy.*

Strength/consensus of recommendation: I

We selected 11 papers (35, 36, 42, 107-114) for full-text review (from 38 abstracts), but we were not able to grade any of the papers because they either did not specifically address the clinical question, or they did not contain evidence pertaining to patient outcomes.

In summary, with respect to most of the clinical questions, there is insufficient evidence to recommend for or against point of care testing (POCT) for renal function evaluation or urinalysis. In the few cases where there is evidence, it does not support the routine use of POCT. We recommend against dipstick urinalysis for proteinuria both for screening and also for evaluation of pregnancy-induced hypertension or pre-eclampsia. We were also unable to recommend POCT for BUN or creatinine with one exception, the cardiovascular diagnostics laboratory setting (CVDL). We were able to find evidence that in a CVDL setting, implementation of renal function testing at the point of care was able to reduce patient wait times for a scheduled procedure (4). Studies are needed that not only address comparison of POCT methods to core lab methods, but also to measure the impact of POCT on specific patient outcomes. These studies are needed to address the variety of settings in which renal POCT is performed, and they should be controlled to address a for specific patient populations (e.g. ED, outpatient). Ideally, studies will be performed in a randomized control format with groups treated based either on POCT or core lab methods.

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Public Comments:

No public comments were received on the guidelines.

Chapter 13: Reproductive Testing

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The use of point of care testing (POCT) for fertility or reproduction-related markers is limited to only a few types of tests. These include urine/serum-based testing as an aid in the early diagnosis of pregnancy, urine-based biochemical tests and bioelectric measurements for predicting ovulation, ferning and pH testing for detection of premature rupture of membranes, and detection of cervicovaginal fetal fibronectin for the prediction of preterm delivery. This chapter will examine the clinical utility of these tests and the effect they have on patient outcomes. There are a number of publications that have examined the ability of the urine-based tests, human chorionic gonadotropin hormone (hCG) and luteinizing hormone (LH), to measure a given amount of antigen (analytical sensitivity). These guidelines do not address studies such as these and focus only on studies that have examined measurable clinical outcomes.

Urine/Serum hCG Testing

Does the use of urine hCG POCT as an aid in the diagnosis of pregnancy improve outcomes (i.e. reduce clinic visits or reduce length of stay (LOS) in ER or reduce number of contraindicated drugs or therapies) compared to serum core laboratory hCG? (Literature Search 95)

Guideline 171: *We note that the use of rapid urine/serum hCG devices may have utility in settings such as the Emergency Department or Urgent Care centers, but remarkably, no studies have been published that examine outcomes such as length of stay, number of clinic visits, or the number of contraindicated drugs or procedures. Therefore, there is not sufficient evidence to make any recommendation for or against the use of rapid urine/serum hCG tests. We note that the use of home urine hCG devices may have utility and reduce adverse social behaviors, but no studies have been published that examine outcomes in this setting either. Therefore, there is not sufficient evidence to make any recommendation for or against the use of home urine hCG tests.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies, clinical experience)

Literature Search 95 summarizes the results of our literature search.

Is the diagnostic accuracy of urine hCG POCT equivalent to serum core laboratory hCG?

(Literature Search 96)

Guideline 172: *Early studies have indicated much brand by brand variation in POC laboratory hCG devices. Recent studies (after 1990) have not been conducted, making a recommendation difficult. Based on the published data available, caution should be used with POC hCG devices.*

Since new novel technologies have significantly enhanced these earlier tests, further studies are needed to determine which devices are most accurate and consistent in performance. POC hCG devices may have utility as an aid in the diagnosis of ectopic pregnancy although this utility has not been adequately compared to the use of in-lab testing. Therefore, there is not sufficient evidence to make any recommendation for or against the use of POC urine hCG devices for the diagnosis of ectopic pregnancy. Studies also indicate brand by brand variation in rapid home hCG devices. However, recent studies (after 1989) have not been conducted, making a recommendation difficult. Based on the published data available, caution should be used with home hCG devices. Further studies are needed to determine which devices are most accurate.

Strength/consensus of recommendation: I

Level of evidence: II (observational and retrospective cohort studies)

Literature Search 96 summarizes the results for our literature search. There are three settings that urine/serum POC testing has been examined: Hospital laboratory for the diagnosis of pregnancy, hospital laboratory for the diagnosis of ectopic pregnancy, and home for the early diagnosis of pregnancy.

Four studies (1979, 1985, 1986 and 1990) have examined the accuracy of POC urine/serum hCG devices in a hospital setting (1-4). All of these studies are more than ten years old. Two of the four reports tested samples that were submitted to the laboratory for hCG testing (2,3). Of the other two reports, one used urine from known pregnant and non-pregnant women (1). The other used urine and serum from women pre- and post-elective abortion (4). A summary of these studies is shown in Table 1. These data demonstrate that even in a hospital setting, there are

significant differences in accuracy for detecting pregnancy between different manufacturer's devices. These findings were consistent for urine and serum samples. Because these studies are all more than fourteen years old, and there have been numerous changes in method technology for these devices since that time, conclusions cannot be drawn to its application today.

Seven studies have been published that examine the accuracy of POC hCG devices to diagnose ectopic pregnancies (2,5-10). Six of the seven papers were published prior to 1989 (2,6-10). As indicated previously, none of these studies examined if patients were treated differently based on the availability of a POC test. These studies examined the ability to accurately detect ectopic pregnancy with a POC hCG device. A summary of the findings are shown in Table 2. These studies show that, with the exception of the first study from 1985 (2), POC hCG devices were able to detect ectopic pregnancies with a sensitivity of >90%. In fact, only one device had a sensitivity of 90%, the remainder were >93% (9). The majority of these studies were conducted during a period of time when STAT quantitative hCG testing was not readily available from the laboratory. Studies need to be performed that compare the sensitivity of POC urine hCG tests to laboratory quantitative hCG tests. The Wong study from 2000 (5) did compare the sensitivity of the POC device to quantification using the Abbott IMx. This study reported sensitivities of 96.9% and 97.4% respectively, suggesting that the POC devices may perform very similar to the laboratory quantitative assays. Further studies are needed to confirm these findings. Furthermore, studies need to be performed that compare treatment differences for those diagnosed with a contemporary POC hCG device vs a contemporary quantitative serum hCG.

Only one paper (in 1989) has been published on the accuracy of home devices (11). This paper compared the accuracy of nine pregnancy devices intended for home use. The urine used was

from non-pregnant women and women who were three months pregnant. No urine was examined from women around the time of the missed menses. The authors noted a big variation in the accuracy between devices (range 69.6 to 97.1%). The accuracy that was measured was lower than the manufacturers' claimed accuracy in all cases (range of claimed accuracies 96-99.5%). Many of the devices (6/9) gave uncertain results. The uncertain results, as a percent of total results for that brand of device, ranged from 0-21%. The authors found similar discrepancies in the sensitivity and specificity for detecting pregnancy as well (measured sensitivity 51.7 to 100%, claimed sensitivity 97.8-99%; measured specificity 60.5 to 100%, claimed specificity 94-100%). These data indicate that there were significant differences in accuracy for detecting pregnancy between home devices. In addition, there were significant differences between manufacturer claims of accuracy and measured accuracy in this one study with early over-the-counter devices. Although this study indicates that these types of analyses are quite valuable, it is the only one that has been done. Because this study is fifteen years old, its application to today's tests is unclear. A recent study by Cole (12) and in Consumer Reports (13) has tried to address such concerns, but these studies use artificially spiked, not real urine samples. Clearly further studies are required to assess the accuracy of the newer rapid home hCG devices.

How early in gestation does urine hCG POCT diagnose pregnancy accurately and how does this compare to serum core laboratory hCG? (Literature Search 97)

Guideline 173: *We note that it is unclear how early all home urine hCG devices can detect pregnancy. It is clear that there are brand by brand differences. Recent studies (after 1989) have not been conducted, making a recommendation difficult. Based on the published data available, caution should be used interpreting home hCG devices early after missed menses. Further*

studies are needed to determine which newer over-the counter devices are best able to detect early pregnancy.

Strength/consensus of recommendation: I

Level of evidence: III (single retrospective cohort studies)

Literature Search 97 summarizes the results for our literature search. Only one paper has examined how early in gestation POCT hCG devices aid in the diagnosis of pregnancy using patient urine. Asch (14) collected urine, on days 7-16 after ovulation, from women trying to get pregnant. He used samples from 35 women who eventually had increasing hCG concentrations and visualization of an intrauterine gestational sac by ultrasound. Three rapid home hCG devices were compared. Testing was performed by laypersons (junior high school students). The results are shown in Table 3. The results demonstrate significant brand by brand variation in the ability to detect pregnancy at various times after ovulation. At the expected day of menses, the three devices were able to detect hCG 70, 88 and 95% of the time. By two days after missed menses, one device detected hCG 100% of the time, but the other two devices detected hCG 75 and 95% of the time. This study was performed in 1988 and clearly the brands and assay formulation have changed since that time. Studies need to be conducted with modern home hCG devices. Recently Cole et al (12) have tried to address this question. However, Cole's study was not included in this analysis because real urine was not used to test the devices. His group determined the concentration of urine in women at various times after missed menses. Then they tested various home hCG devices for the ability to detect urine with hCG added at those concentrations. Cole's group found that, in theory, an analytical sensitivity of 12.5 mIU/mL was needed to detect 95% of pregnancy at the time of the missed menses. They found that only one home pregnancy device

had this sensitivity. This research raises questions about the ability of even modern home pregnancy devices to detect early pregnancy. Clearly, more studies using real urine samples (similar to the Asch study) and modern home pregnancy devices are needed.

What is the diagnostic accuracy of urine hCG POCT when performed by a layperson compared to the diagnostic accuracy of serum or urine core laboratory hCG? (Literature Search 98)

Guideline 174: *No studies have been published that compare the accuracy of hCG POC devices when performed by a layperson vs the accuracy of a core laboratory. Therefore, there is not sufficient evidence to make any recommendation regarding laypersons and the use of home urine hCG tests.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies, clinical experience)

Literature Search 98 summarizes the results for our literature search.

What is the diagnostic accuracy of urine hCG POCT when performed by a layperson compared to the diagnostic accuracy of urine POCT in a core laboratory? (Literature Search 99)

Guideline 175: *Studies have clearly shown decreased accuracy of urine POCT devices when performed by laypersons. We recommend that manufacturers provide clear concise instructions for use and adequate (easy to interpret) quality control measures to maximize the proper use and interpretation of these devices. We recommend that physicians confirm results with quantitative serum hCG.*

Strength/consensus of recommendation: I

Level of evidence: III (observational cohorts and blind randomized cohort)

Literature Search 99 summarizes the results for our literature search. Three studies have examined the accuracy of POC hCG devices in trained vs untrained individuals (15-17). All three studies were 1993 and earlier. The first study, published in 1977 compared inexperienced individuals, medical technicians with general chemistry knowledge and medical technicians with extensive rapid hCG device experience (17). The researchers found that the inexperienced persons had significantly more false positive and false negative results than both medical technicians with general chemistry knowledge, and medical technicians with extensive experience. This study used a very old hemagglutination assay, so the application of its conclusions to today's devices is inappropriate. The second study was performed in 1986 and compared three brands of home hCG devices (16). Urine samples were obtained from women shortly after missed menses and split in half. One half was tested on three devices by the investigator and one half was returned to the layperson for testing on the same three devices. Unfortunately, the study did not report the accuracy of the layperson specifically. They did examine accuracy in the context of psychological and socioeconomic variables. They found that accuracy in laypersons increased with age and in persons with more education. Income had no effect. Anxiety level (based on if the patient was trying to get pregnant or was unmarried) also had little effect. The final study, from 1993, examined all 27 home-use hCG devices that were currently sold in France (15). First, testing was performed by experienced clinical chemistry technologists. The authors selected eleven devices that had 100% sensitivity and 100% specificity for detecting hCG in samples with no hCG, a low positive adjusted to the claimed detection limit of the kit and a high positive adjusted to twice the claimed detection limit. These devices and urine samples were then given to 631 women ages 14-49. When performed by lay persons, the specificity ranged from 76.9 to 100% (6/11 were <94%; mean 93.4%), the

sensitivity range for the low positive hCG sample was 0-100% (mean 42.1%), and high positive was 20-100% (mean 59.7%). It is clear from this study that results using POC hCG devices vary between trained and untrained personnel. The authors stress the need for rigorous validation of home-pregnancy kits and adequate quality control measures. These data also demonstrate the need for clear concise instructions for laypersons.

Urine LH Ovulation Tests

Is the diagnostic accuracy of urine LH tests sufficient for detecting ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 100)

Guideline 176: *We note that POC tests have excellent diagnostic sensitivity for the detection of ovulation. We can strongly recommend the use of these devices when the purpose of using them is to detect ovulation.*

Strength/consensus of recommendation: A

Level of evidence: II (cohort studies)

Literature Search 100 summarizes the results for our literature search. There is clear and compelling evidence that urine LH POCT devices detect the LH surge. As ovulation frequently occurs between 32 and 38 hours after the LH surge is detected in the plasma, detection of LH in the urine should be an indication that ovulation is approaching and identifies the beginning of peak fertility (18). Table 4 summarizes studies that have investigated the ability of urine LH tests to detect ovulation in normal and clomiphene citrate-stimulated cycles. These studies have reported sensitivities of 85 – 100% (median, 100%). Two studies reported rare instances where urine LH tests failed to identify an LH surge despite evidence of ovulation by gold-standard methods (19,20). The specificity of urine LH POCT for detecting ovulation is difficult to

evaluate as only a few studies have included anovulatory women (21-23). When the data allowed the calculation of diagnostic specificity, the luteinizing unruptured follicle syndrome was often used to explain false-positive results (20,24,25). While this finding is technically a false positive result, the test devices still performed as they were designed: to detect an increased concentration of urinary LH.

Is the diagnostic accuracy of urine LH tests sufficient for predicting ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 101)

Guideline 177: *We recommend the use of urine LH tests to predict ovulation within 48 hours of a positive test.*

Strength/consensus of recommendation: B

Level of evidence: II (cohort studies)

Literature Search 101 summarizes the results for our literature search. The most likely use of urine LH POCT is to predict a time when ovulation is likely to occur in order to potentially increase likelihood of pregnancy. While the studies examined for this report defined this time interval from anywhere between 36 and 72 hours, most considered the 48 hour period prior to ovulation as the optimal time for detection. This is an appropriate time frame as the window for fertilization is brief and introduction of sperm into the female genital tract within two days prior to ovulation has the highest probability of conception (26). In this regard, the sensitivity of urine LH POCT to predict ovulation (defined as the detection of the LH surge within 48 hours prior to ovulation determined by the gold standard), while not as robust as their ability to detect ovulation, ranged from 85-100% (median, 93%) (Table 4).

Does the use of urine LH tests for predicting ovulation in women not treated in a fertility clinic improve outcomes (i.e. increase conception rates; decrease number of clinic visits, or number of unwanted pregnancies) compared to no use of prediction tests? (Literature Search 102)

Guideline 178: *There is insufficient evidence to make any recommendation for or against the use of home urine LH testing to improve conception rates in women not seeking fertility treatments.*

Strength/consensus of recommendation: I

Level of evidence: III

Literature Search 102 summarizes the results for our literature search. No papers have examined the clinical utility of urine LH tests as ovulation predictors in a home setting with women who were not being treated in a fertility clinic. This is precisely the population to which these devices are marketed and such studies would be very useful. While it is logical to assume that the use of these devices would increase conception rates it is also possible that the devices are not needed by this population for whom infertility may not be a problem. Until such data are available these statements are purely speculative.

Does the use of urine LH tests for predicting ovulation in women undergoing fertility treatment improve outcomes (i.e. increase conception rates; decrease number of clinic visits, number of fertility treatment cycles) compared to no use of prediction tests? (Literature Search 103)

Guideline 179: *We can make no recommendation for or against routinely providing urine LH tests to improve outcomes. There is limited data available to adequately assess the utility of the test to improve conception rates, clinic visit frequency, or fertility treatment cycles. While these*

questions are certainly of considerable interest, clear-cut answers remain elusive and additional studies need to be performed.

Strength/consensus of recommendation: I

Level of evidence: I (at least one randomized controlled trial)

Literature Search 103 summarizes the results for our literature search. Of the studies that have examined specific outcomes, most have reported on the ability of urine LH tests to increase conception rates in women undergoing artificial insemination. The data from these studies suggest that the availability of urine LH tests does not have a positive effect on conception rates; however the data are from small studies and are relatively limited. Two studies investigating the ability of urine LH tests to improve pregnancy rates reported that they were worse in the POCT group compared to controls. One reported a 13.7% pregnancy rate in the POCT group (n=346 cycles) which was significantly lower than the 18% rate achieved by patients whose inseminations were timed by a laboratory-performed serum LH test (n=1119 cycles) ($p<0.05$) (27). The second reported that a pregnancy rate of 3.4% was significantly lower in the POCT group (n=174 cycles) compared to the 12.7% rate achieved by a quantitative urine LH group (n=110 cycles) ($p<0.005$) (28).

Five studies reported that POCT offered no benefit over other methods of timing inseminations (29-33). Kossoy, et al reported that pregnancy rates were unaffected by use of POCT with a 13% rate achieved with POCT (n=67 cycles) and 12% without (n=43 cycles) (29). Leader and colleagues reported that pregnancy rates were unaffected by use of POCT in patients with either unexplained infertility (n=110) or for those with partners with male factor infertility (n=50). In women with unexplained infertility, pregnancy rates were 20.4% for those who used POCT LH

tests and 16% for those who did not ($p>0.05$). Likewise, fecundity in women whose partners were infertile was 8% in the POCT group and 11.1% for those who did not use POCT (p not given) (30). Robinson, et al (31) also reported that pregnancy rates were unaffected by the use of POCT (8.1%, $n=123$ cycles) compared to those who used basal body temperature monitoring (BBT) and cervical mucus scoring methods of detection (6.5%, $n=111$ cycles) ($p>0.05$). Another study by Kossoy (32) reported no significant differences in pregnancy rates when POCT was used along with BBT and cervical mucus scoring (13%, $n=26$) compared to just BBT and mucus scoring (11%, $n=94$) (p not given). Lastly, Brook et al (33) reported no significant differences in pregnancy rates when POCT was compared against serum LH, BBT, or cervical mucus scoring for timing of inseminations. Cumulative pregnancy rates in each group were 34% ($n=545$ cycles), 34% ($n=236$ cycles), 31% ($n=405$ cycles), and 37% ($n=209$ cycles), respectively ($p>0.05$).

In addition to fecundity, other outcomes addressed in various studies include the use of urine LH tests to time inseminations, to limit number of clinic visits per treatment cycle, and to investigate the number of inseminations required to achieve pregnancy. Unfortunately, the numbers of studies investigating these other outcomes are also limited in number. Only one study investigated the timing of insemination using urine LH tests and it reported that timing was correctly predicted in 25 patients when POCT urine LH was combined with ultrasound monitoring of follicle size. Insemination was considered to have been correctly timed only if follicle size measured ≥ 18 mm and a detectable LH surge was detected in the urine. This approach predicted all those women who ovulated ($n=20$) and detected unfavorable conditions for insemination in the remaining five (34). Lack of a control group, however, seriously limits

the conclusions of this study.

In a study to investigate the effect of urine LH POCT on the number of clinic visits per treatment cycle, Robinson, et al found that at 1.5 visits/cycle, there were significantly fewer visits to the fertility clinic per cycle for POCT patients (n=123 cycles) compared to the 2.4 visits/cycle observed with a control group that did not use POCT (n=111 cycles) ($p < 0.001$) (31).

Kossoy, et al reported no differences in the number of insemination cycles required to achieve conception when comparing point of care LH testing in addition to BBT and cervical scoring (n=26) to controls using only BBT and cervical scoring (n=94) ($p = 0.79$) (32).

What is the diagnostic accuracy of urine LH POCT ovulation tests when performed/interpreted by a layperson as compared to the diagnostic accuracy of urine LH in a core laboratory (performed by CLIA-approved laboratory staff)? (Literature Search 104)

Guideline 180: *There is insufficient evidence to evaluate the diagnostic accuracy of results obtained from layperson- or laboratory-performed “urine” LH testing.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 104 summarizes the results for our literature search. Only one study was identified and it reported an 89% agreement between layperson-tested and gynecologist-tested (not laboratory-tested) POCT results ($p = 0.5$) (20). Although this outcome was not specifically addressed in other studies, there are studies that comment on large numbers of laypersons that report the performing and reading of POCT urine LH tests confusing. However, this was more

frequently associated with older studies that used older POCT technology and may not be relevant with devices available today.

What is the diagnostic accuracy of urine LH POCT ovulation tests when performed/interpreted by a layperson as compared to the diagnostic accuracy of serum LH in a core laboratory (performed by CLIA-approved laboratory staff)? (Literature Search 105)

Guideline 181: *There is insufficient evidence to evaluate the diagnostic accuracy of results obtained from layperson-performed urine LH tests compared to laboratory-performed “serum” LH testing.*

Strength/consensus of recommendation: I

Level of evidence: III (expert opinion)

Literature Search 105 summarizes the results of our literature search. No studies were identified that examined the performance of layperson performed POCT against serum LH performed by laboratory personnel.

Non-urine Ovulation Tests

Non-urine tests for predicting ovulation include devices that measure electrical admittance (1/impedence) or electrical resistance in saliva, vaginal mucus, or both and the fern test. Although few in number, these devices offer unique methods of ovulation detection and may have broad appeal particularly because they are reusable rather than disposable.

Is the diagnostic accuracy of non-urine POCT ovulation tests sufficient to predict ovulation using progesterone or ultrasound as a gold standard for confirming ovulation? (Literature Search 106)

Guideline 182: *We note that there is limited useful evidence to support the use of non-urine POCT for predicting ovulation and the available evidence is generally of poor quality. We therefore can make no recommendation for or against the use of non-urine POCT for ovulation prediction*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 106 summarizes the results for our literature search. Studies from only two devices that measure electrical admittance or electrical resistance have been reported in the literature: the Ovulon Fertility Monitor and the Cue Ovulation Monitor. While ten studies were identified that investigated the use and performance of these types of devices, only four provided sufficient data to determine their ability to predict ovulation within 48 hours of its occurrence (35-38). Of these four, only one (38) utilized ultrasound of follicular size as the gold standard for detecting ovulation while the other studies utilized urine LH measurements (qualitative or quantitative) or serum LH measurements to confirm ovulation. A study by Moreno, et al compared readings from the Cue Ovulation Monitor to follicle size determined by ultrasound in 29 cycles from 11 normal cycling women. They reported that the monitor produced the expected vaginal nadir signal two days prior to ovulation in 93% of cycles (38). However, because the signal is a nadir it can only be correctly identified retrospectively, making daily interpretation of signals for predicting ovulation challenging if not impossible. The predictive abilities reported

by the other three studies were 74% (37), 52% (35), and 55% (36). However, the lack of a gold standard method for confirming ovulation seriously limits interpretation of these results.

Four studies examined the utility of fern testing performed on saliva or cervical mucus as a predictor of ovulation. Theoretically, a pattern of “ferning” is observed upon examination of dried saliva or cervical mucus that coincides with the fertile period in the female. The ferning or crystallization is caused by alterations in the fluid concentrations of sodium and chloride that cyclically increases under the influence of estrogen. Only two of the four studies utilized ultrasound of follicular size as the gold standard for confirming ovulation and one of these did not report the predictive ability of the fern test. A study by Guida, et al evaluated the efficacy of salivary ferning to detect ovulation (determined by ultrasound) in 125 cycles from 40 normal cycling women (39). They reported that the fern test predicted ovulation one day prior to the event in 21% of cycles and the day after in another 21%. However, 59% of the tests were excluded because they were uninterpretable. Based on this, they concluded that the salivary fern test was a poor method for predicting ovulation. Although the other studies did not include an appropriate gold standard method for confirming ovulation, one report identified ferning patterns throughout the entire menstrual cycle and in salivary specimens collected from males (40).

pH/Nitrazine Tests for Premature Rupture of Membranes

Premature rupture of the membranes (PROM), a common obstetrical problem, refers to amniotic membrane rupture before the start of labor or regular uterine contractions. If it occurs prior to term it is designated as preterm premature rupture of the membranes (PPROM). Because the pH

range of amniotic fluid (pH 7.0 – 7.7) is higher than the normally acidic vagina (pH 3.8 – 4.2), an often-used test in the assessment of a patient with suspected membrane rupture is the analysis of vaginal pH with nitrazine paper (47).

Does the pH/nitrazine test accurately predict preterm premature rupture of membranes?

(Literature Search 107)

Guideline 183: *We note that the evidence is insufficient to recommend for or against providing pH/nitrazine tests for the prediction of preterm premature rupture of membranes.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 107 summarizes our literature search. Only one study for predicting pre-term Prom (PPROM) was identified. This study of 115 patients at high risk for a low-birth weight infant used an indirect method of serially measuring vaginal pH from 23 weeks gestation to delivery and a pH cutoff of >4.5 (48). Sixteen percent of the patients studied developed PPRM although the method of diagnosing PROM was not reported. The use of a mean pH >4.5 produced a 32% positive predictive value and a 90% negative predictive value for PPRM. However, to be clinically useful, pH must be evaluated prospectively and in that regard the study found that any single pH result >4.5 produced positive and negative predictive values of 19% and 89%, respectively. Because the objective of this study was to use vaginal pH to predict PPRM it could be argued that the predictive values may offer an advantage over no prediction method. Considering the limited availability of data, however, no recommendation for using pH to predict preterm PROM can be made at this time.

Does the pH/nitrazine test accurately identify women with ruptured membranes and/or women whose membranes have not ruptured? (Literature Search 108)

Guideline 184: *We note that the pH/nitrazine test is sensitive only when utilized in women for whom membrane status is known. When applied to patients suspected of PROM the test does not appear to be sufficiently sensitive or specific enough for diagnostic determination of premature rupture of membranes. Accordingly, we do not recommend the use of pH/nitrazine testing alone for the detection of premature rupture of membranes.*

Strength/consensus of recommendation: C

Level of evidence: II (case-controlled studies)

Literature Search 108 summarizes our literature search. The evidence indicates that the pH/nitrazine test has high sensitivity when used in populations of women who were definitively known to have either PROM or intact membranes (49-60). Due to lack of a gold standard method of determining PROM, most studies utilized clinical observation and interpretation as the definitive test. However, the diagnostic utility of the test deteriorates when it is applied to populations in whom the test would be used, namely, women in whom PROM is suspected but not known. Table 5 summarizes the data from some of these studies.

The study by Watanabe, et al (53) was well-designed and reported excellent sensitivity (100%) and marginal specificity (79%) when pH was utilized in a population of patients known to have PROM due to amniotomy or obvious leakage of amniotic fluid (n=32) compared to those who did not (n=19). However, when the pH test was used in a group of women in whom PROM was

suspected but not obvious, the test did not perform well producing a sensitivity of 72% and a specificity of 64% (n=40).

Similarly, Garite, et al (54) reported 91% sensitivity and 73% specificity when 23 women with PROM identified by gross pooling of amniotic fluid and 22 with intact membranes were evaluated with vaginal pH. Unfortunately, this study did not evaluate women in whom PROM was uncertain.

A study by Kishida, et al (56) used vaginal or cervical fluid pH to evaluate PROM in women with obvious leakage of amniotic fluid as well as in those with intact membranes and in whom PROM was uncertain (patients with only slight leakage of fluid suspected to be amniotic fluid). However, all the data were combined for analysis to produce an overall sensitivity of 92% and a specificity of 53% (n=103).

Unlike other investigations that noted only marginal specificity, a study of 39 women with intact membranes for whom membrane status was known at the time of testing reported that vaginal pH had excellent specificity (92%) (58). Following amniotomy, the use of vaginal pH was 100% sensitive. As has been noted though, this is not a population that would likely benefit from a test for PROM.

Rochelson, et al (59) reported a sensitivity of 77% and a specificity of 81% in 48 women with PROM identified by clinically evident rupture and 31 with intact membranes when measuring pH from specimens collected from the posterior fornix. The lower sensitivity was attributed to

the prolonged time period (>12 hours) between rupture and specimen collection in 21% of the patients.

Based on these data it is difficult to recommend the use of pH/nitrazine testing alone in evaluating a patient for PROM. The test may better be used as a supportive test in conjunction with other clinical findings.

Does the pH/nitrazine test improve outcomes (number of admissions, use of antibiotics, neonatal morbidity/mortality) compared to the fern test in women suspected to have PROM? (Literature Search 109)

Guideline 185: *We note that the evidence is insufficient to recommend for or against providing pH/nitrazine tests for the prediction of preterm premature rupture of membranes.*

Strength/consensus of recommendation: I

Level of evidence: III (descriptive studies)

Literature Search 109 summarizes our literature search.

Fern Tests for Premature Rupture of Membranes

Another test used frequently to assess a patient with suspected membrane rupture is the fern test.

When fluid from the vagina is smeared onto a glass slide and allowed to dry, amniotic fluid will produce a ferning pattern.

Does the fern test accurately identify women with ruptured membranes and/or women whose membranes have not ruptured? (Literature Search 110)

Guideline 186: *We note that the fern test is neither sensitive nor specific enough for diagnostic determination of premature rupture of membranes. We recommend against routinely providing fern testing alone for the detection of ruptured membranes*

Strength/consensus of recommendation: C

Level of evidence: III (case-controlled studies)

Literature Search 110 summarizes our literature search. There is limited evidence that suggests the fern test has high specificity and sensitivity when utilized in populations of women who were definitively known to have either PROM or intact membranes. Garite, et al (54) reported a sensitivity of 97% and specificity of 100% when they evaluated 23 women with gross pooling of amniotic fluid and 22 with intact membranes. Another study also reported a sensitivity of 62% with 100% specificity in 48 women with obvious amniotic fluid leakage and 31 with intact membranes (59). The lower sensitivity was attributed to the prolonged time period (>12 hours) between rupture and specimen collection in 21% of the patients. When investigating the use of the fern test in 51 women whose membrane status was definitively known, Watanabe et al reported the test to be 84% sensitive and 95% specific (53).

Similar to the pH/nitrazine test, the performance of the fern test deteriorates when applied to a population of women in whom membrane integrity status is uncertain (the very population in whom the test would be used). de Haan et al (61) reported a sensitivity of 51% and specificity of 71% in 100 patients with suspected PROM although the method used to eventually categorize these patients into those with or without PROM was never described. The low sensitivity is particularly concerning as false-negative results might delay appropriate treatments. The study

by Watanabe discussed previously also included 40 women with unknown membrane status and in this population the fern test was only 50% sensitive and 86% specific (53).

Similar to the pH/nitrazine test, the data for the fern test suggest it may better be used as a supportive test in conjunction with other clinical findings.

Fetal Fibronectin (rfFN) testing for Premature Delivery

Does performing a single rapid fFN assay improve outcomes (such as #patient admissions, length of stay (LOS), use of tocolytic medications, cost, neonatal morbidity/mortality, maternal morbidity due to side effects of intervention therapy) compared to cervical dilation, Bishop score, contraction number or cervical length by ultrasound in women with symptoms of preterm labor, intact membranes and cervical dilation less than 3 cm? (Literature Search 111)

Guideline 187: *There are no studies that directly compared rapid fFN to any other method to predict preterm birth. There are several non-comparison studies, but none are available that investigated the role of rapid fFN in decreasing neonatal morbidity or mortality. There are three outcome studies available which investigated length of maternal stay, maternal transfers to a tertiary care facility and need for tocolysis. Two of three studies demonstrated that rapid fFN decreases the need for tocolysis and the need for maternal transfer to a tertiary care facility. It is important to note that these studies utilized historical controls for comparison. The third study, the only investigation that utilized a randomized study design, was not powered to detect a difference in the number of maternal transfers to a tertiary care facility (primary outcome*

measure) and did not demonstrate an overall difference in length of maternal hospitalization in patients with symptoms of preterm labor (secondary outcome measure). Therefore, additional well-designed studies are needed to determine the true efficacy of rfFN testing.

Strength/consensus of recommendation: I

Level of evidence: II (cohort studies)

Literature Search 111 summarizes our literature Search. There is only one study that utilized a randomized control design (62). In this study all patients enrolled had a rapid fFN performed. They were then randomized into two groups, one that allowed providers to know the test results and one group that was blinded to the test results. The primary objective of this study was to look at the number of maternal transports between the two groups. A power analysis with this endpoint suggested that 500 patients needed to be enrolled. The study was terminated due to low enrollment with only 114 patients enrolled. Due to the low numbers the primary outcome comparison could not be performed. The following secondary outcomes comparisons were noted:

1. The overall length of stay was no different between the two groups: fFN unknown 8.1 hours versus fFN known 6.8 hours (p=0.35).
2. Looking at the group that had a least a 6 hour stay (17% of all patients): The mean hospital stay in the fFN unknown group was 37.8 hours versus 22.7 hours in the fFN known group (p=0.04).

Therefore in this study, rapid fFN was only noted to improve care in those patients with a length of stay greater than 6 hours, and only by a hospital stay decrease of 2 hours. The clinical and financial impact of a decrease in length of stay of 2 hours may not support the cost of testing. This study however suffered from low enrollment and the possibility of not finding a difference

due to a Type II error for the other parameters of improved care such as maternal transport, and use of tocolysis is highly possible.

There is another study that explored the utility of rapid fFN in prevention of unnecessary maternal transports to a tertiary care center due to symptoms of preterm labor (63). This investigation looked at the number of maternal transports to a tertiary center before and after rapid fFN was available at the same facility. This investigation noted a 51% decrease in the number of maternal transports after rapid fFN was available. This study used historical cohorts for comparison, thus a change in physician practice patterns over time may also have influenced the decrease in maternal transports.

Only one study examined the value of rapid fFN in the prevention of maternal tocolysis for suspected preterm labor (64). These investigators used historical controls, from the same institution, with symptoms of preterm labor prior to the use of rapid fFN, and then compared them to a group that used a rapid fFN to determine if tocolysis should be utilized. There was a significant difference with 100% of the control group (n=30) receiving tocolysis compared to 20% (n=3) of the group that were screened with a rapid fFN (p=0.0001). However, the use of historical controls is a major study design flaw and may have resulted in selection bias.

Does performing a single rapid fFN assay improve outcomes (such as #patient admissions, LOS, use of tocolytic medications, cost, neonatal morbidity/mortality, maternal morbidity due to side effects of intervention therapy) compared to fFN ELISA in women with symptoms of preterm labor, intact membranes and cervical dilation less than 3 cm? (Literature Search 112)

Guideline 188: *No studies performed a direct comparison of rfFN to the ELISA fFN and reported any of the outcomes of interest. Validation of this test appears to be limited to studies that looked at the sensitivity, specificity, negative and positive predictive value for predicting preterm birth and then compared these results to prior published results of fFN determined by an ELISA microtiter plate. No study used the same sample that was measured using the two different methods. Therefore, there is insufficient evidence to compare clinical outcomes between the rfFN and the ELISA fFN.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies)

Literature Search 112 summarizes our literature search.

Do repeat rapid fFN tests decrease costs and improve clinical outcomes? At what testing interval? (Literature Search 113)

Guideline 189: *There were no studies available that addressed the issue of the utility of repeat rapid fFN testing. In addition, there were no studies available to determine the appropriate time interval between samplings. Therefore, there is insufficient evidence to make recommendations regarding repeat sampling or the appropriate time interval between sampling.*

Strength/consensus of recommendation: I

Level of evidence: III (no studies)

Literature Search 113 summarizes our literature search.

What are rapid fFN PPV and NPV values for preterm delivery? Does rapid fFN reliably identify women at risk of preterm delivery and/or women at no risk of preterm delivery? (Literature Search 114)

Guideline 190: *The major strength of this test is the strong negative predictive value. Studies have clearly demonstrated the high negative predictive value of rapid fFN with negative predictive values greater than 95% to predict preterm birth within 7 days of testing. A negative rapid fFN result in symptomatic patients is a reliable test to place women at low risk of preterm birth within 7 days of testing. However, the positive predictive value of rapid fFN is a poor predictor of preterm birth. Therefore a positive rapid fFN should not be used as the primary guide for therapeutic decisions related to the imminent prevention of preterm birth.*

Strength/consensus of recommendation: I

Level of evidence: II (cohort studies)

Literature Search 114 summarizes our literature search. Since 1998, 4 studies have examined the positive and negative predictive values (PPV and NPV, respectively) of rapid fFN for preterm delivery in symptomatic patients. The data from these four studies is summarized in Tables 6 and Table 7. These studies are difficult to compare directly since they used different end points for the definition of preterm birth. These end points included, delivery within 7 days of testing, 14 days of testing, 21 days of testing, delivery at less than 34 weeks or less than 37 weeks.

An investigation performed in 1998 was retrospective in design (65). The goal of this study was to determine if the results of rFFN as used in clinical practice in patients with symptoms of preterm labor, were comparable to results from prior blinded research investigations. This study

noted that when used in actual clinical practice, the negative predictive value for birth prior to 34 weeks was 98%, compared to a positive predictive value of 45% for birth less than 34 weeks.

Another retrospective study used multiple endpoints for determining preterm birth, including delivery within 7 days of testing, 14 days of testing, delivery at less than 34 weeks or less than 37 weeks (66). The purpose of this study was also to determine if the utility of rapid fFN in actual clinic practice was comparable to that seen in prior investigational studies that kept clinicians blinded to the fFN results. These investigators noted that when delivery within 7 days was used as an endpoint, the positive predictive value was actually greater than reported in prior blinded studies that used the ELISA fFN. The ELISA fFN studies reported a sensitivity between 44-90%, specificity 45-90%, PPV 43-83% and NPV of 63-93% when using preterm birth prior to 37 weeks as a cutoff (67-72). Those ELISA fFN based studies that used delivery within 7 days found a sensitivity between 90-100%, specificity 83-71%, PPV 6-29% and NPV of 99-100% (67-69).

The largest study, involving 501 samples, was also retrospective in design and used delivery at < 7 days, < 14 days, and < 21 days as endpoints for determining the PPV and NPV (11). The negative predictive values obtained for patients that delivered within 7, 14 and 21 days of testing were 96.8%, 93.7% and 93.7% respectively. The authors concluded that this compared well to prior reports that used ELISA based testing systems (as discussed above).

There was only one study that used a prospective study design (62). In this study, all patients that had symptoms of preterm labor had a rapid fFN performed. They were then randomized into a

group in which the providers knew the results of testing and another group in which the providers were blinded to the results of the rapid fFN tests. The primary purpose of this study was to compare treatment decisions in patients with known rapid fFN tests result to a group in which the rapid fFN results are unknown. They then looked at the data to determine the positive and negative predictive value using delivery within 14 days of testing as an endpoint. The positive predictive value was 10% and the negative predictive value was 98%.

In summary, despite that fact that point of care reproductive-related testing represents a huge portion of the over-the-counter testing market and a huge portion of the decentralized hospital testing, very little outcomes-based research has been done on these devices. For rapid urine/serum hCG testing, we found no data that indicate that these devices alter outcomes for patients. The devices do seem to be able to accurately detect hCG in normal and ectopic pregnancies, but we noted great brand to brand variability. We also found decreased accuracy when these devices are used by laypersons. For urine LH testing, we found that these devices detect and predict ovulation well. However, there is little data to suggest that these devices increase pregnancy rates for any women. We also found decreased accuracy when these devices are used by laypersons. There is limited useful evidence for the use of non-urine ovulation tests, and none of these devices are recommended. Despite their common use within hospitals, we found limited evidence to support the use of pH/nitrazine or fern testing to predict or detect PROM. Finally, studies indicate that rapid fFN testing does appear to have a high negative predictive value, but no studies have been done to compare outcomes using the rapid vs ELISA formats. In conclusion, many outcomes-based studies are still needed on point of care reproductive-related testing devices to support their use.

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Public Comments:

No public comments were received on the guidelines.

Table 1. Published studies examining the accuracy of POC hCG devices for detecting pregnancy in a hospital setting

Ref	Year	Population	Sample	% Sens	% Spec	%Accuracy for detecting pregnancy	# of devices
(1)	1979	Known preg/ non preg	Urine	89-100	95-100		7
(2)	1985	Evaluated in ED	Urine	82	97	95	1
(3)	1986	Submitted for hCG	Urine	86.1-98.4	94.6-100	89-99	8
(4)	1990	Pre&post abortion	Urine	70.6-90.6	92.9-100	73.7-91.9	3
(4)	1990	Pre&post abortion	Serum	67.1-94.1	78.6-100	71.7-91.9	3

Table 2. Published studies examining the sensitivity of POC urine hCG devices for detecting ectopic pregnancies

Ref	Year	Population	n	# ectopic	% Sens	# of devices
(2)	1985	Patients eval. For preg in ED	607	N/R	60	1
(10)	1986	Patients eval. For preg (68% ED)	884	27	96	1
(9)	1986	Patients with gynecol emerg	46	30	90-100	7
(8)	1987	Suspected ectopic	909	71	100	1
(7)	1987	Suspected ectopic	107	17	94	1
(6)	1989	Suspected ectopic	51	6	100	1
(5)	2000	Known ectopic pregnancies	207	207	96.9	1

N/R= not reported

Table 3. Percentage of positive hCG results¹

Days after ovulation or follicular aspiration

Device	7	8	9	10	11	12	13	14 ²	15	16
1	0	0	0	10	36	60	75	88	100	100
2	0	0	25	35	65	80	95	95	95	95
3	0	0	5	15	20	30	60	70	75	75

¹Reference (14)²Day 14 is the day of expected menses

Table 4. Studies that have investigated the detection and prediction of ovulation using urine LH POCT.

Ref	Year	Population	n patients/cycles	Sensitivity ¹ (%)	Specificity ² (%)	Predictive value ³ (%)	Comments
(21)	2001	Infertile but ovulatory women	101/101	100	25	85	
(41)	1996	Normally women	26/26	100	ND ⁴	92	
(42)	1994	Infertility patients	145/269	100	0	100	9 false-positives in non-ovulatory patients attributed to LUF ⁵
(24)	1990	Infertile but normally cycling women	50/50	100	0	85	3 false-positives attributed to LUF
(43)	1989	Normally cycling women	33/33	100	ND	91	
(44)	1987	Spontaneous and stimulated cycles	27/30	100	ND	93 & 100	Two different devices evaluated
(22)	1986	Spontaneous and stimulated cycles	55/75	100	100	NA ⁶	
(19)	1990	Normally cycling women	20/20	85	ND	87	
(23)	2000	Normally cycling women	11/11	100	100	100	
(20)	1991	Infertility patients	115/303	99	80	NA	2 false-positives attributed to LUF
(45)	1990	Normally cycling women	55/55	100	ND	100	Predictive value for 36 hours prior to ovulation.
(25)	1988	Infertility patients	15/25	100	0	100	3 false-positives attributed to LUF. Predictive value for 36 hours prior to ovulation.
(46)	1989	Infertility patients	29/29	96	ND	93	

¹Sensitivity to detect ovulation=number of patients who were LH positive/number of patients with confirmed ovulation.

²Specificity to detect absence of ovulation=number of patients who were LH negative /number of patients without confirmed ovulation.

³Predictive value identifies the percentage of ovulations accurately predicted to occur within 48 hours of a positive urine LH POCT.

⁴Not done.

⁵Luteinizing unruptured follicle syndrome.

⁶ Not applicable. Study only investigated ovulation detection, not prediction.

Table 5. Studies that have investigated the use of pH/nitrazine tests for the detection of ruptured membranes.

Reference	Year	Population	n	pH cutoff	Sensitivity (%)	Specificity (%)
(53)	1995	Membrane status known	51	≥7.0	100	79
		Membrane status unknown	40		72	64
(54)	1990	Membrane status known	45	>6.0	91	73
(56)	1995	Membrane status known	103	>6.5	92	53
(58)	1977	Membrane status known	39	Not given	100	92
(59)	1987	Membrane status known	79	≥7.0	77	81
(60)	1995	Membrane status known	30	Not given	100	41

Table 6. Published studies examining the positive predictive value of rFFN for preterm birth in patients with symptoms of preterm labor.

Positive Predictive Value (%)

Author	<i>n</i>	PPV within 7 days	PPV within 14 days	PPV < 34 weeks	PPV < 37 weeks
Luzzi (73)	133	4	6		
Plaut (62)	108		10		
Lopez (66)	85	40	40	55	85
Chuileannain (65)	70			45	

Table 7. Published studies examining the negative predictive value of rfFN for preterm birth in patients with symptoms of preterm labor.

Negative Predictive Value (%)

Author	<i>n</i>	NPV within 7 days	NPV within 14 days	NPV < 34 weeks	NPV < 37 weeks
Luzzi (73)	133	96.8	93.7		
Plaut (62)	108		98		
Lopez (66)	85	98	95	94	52
Chuileannain (65)	70			98	

Appendix B

Supporters:

American Society for Microbiology

College of American Pathologists

IFCC Committee on Evidence-Based Laboratory Medicine

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