National Academy of Clinical Biochemistry (NACB)

Laboratory Medicine Practice Guidelines (LMPG):

Infectious Disease

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Infectious Disease Subgroup

- Members
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  - Geraldine Hall, Ph.D. (Cleveland Clinic, OH)
  - William D. LeBar, M.S. (Hospital Consolidated Laboratories-Providence Hospital), Southfield, MI
  - Wallace Greene, Ph.D. (Pennsylvania State University, Hershey Medical Center, Pa and Pan American Society for Clinical Virology)
  - James T. Rudrik, Ph.D. (Michigan Dept. of Health)
  - Barbara Russell, MHE, MT(ASCP)SH (Medical College of Georgia)
  - Robert Sautter, Ph.D. (Pinnacle Health System, Harrisburg, PA)

Tests for Review

- **Bioterrorism agents- Geri Hall**
- ***Clostridium difficile*- Barbara Russell**
- **Chlamydia and GC- Bill LeBar**
- **Group A streptococci- Joe Campos**
- **Group B streptococci- Bob Sautter**
- ***H. Pylori*- Jim Rudrik**
- **HIV- Sheldon Campbell**
- **Influenza and RSV- Wallace Greene**
- **Mono- Barbara Russell**
- **Provider Performed Microscopy (BV)- Geri Hall and Bob Sautter**

Protocol for Review

- Assignments of tests
- Development of clinical questions
- Systematic searches (Pub Med or OVID)
- Classification of articles
- Review of CDC recommendations if any
- Develop recommendations of group
- Share with consultant members (AAFP, IDSA, private reviewers)

Bioterrorism Agents

- Clinical Question: Are there POC tests available for bioterrorism agents?
- Recommendation: No recommendation can be made for or against routinely providing POCT for bioterrorism agents as there is no data to support such a claim.
- Only opinions of authorities that POCT would aid in investigations of potential bioterrorism events.

Bioterrorism Agents

- Documentation: Classification of literature as C III.
- Kiratisin, P. et. al. JCM 40: 3012-3016, 2002. Large scale screening of nasal swabs for *B. anthracis*: descriptive summary and discussion of NIH's experience.
- Anderson A and JF Eisoid. Anthrax attack at the U.S. Capital. Front Line thoughts. AAOHN Journal 50: 170-173, 2002.
- Bryne, KM et.al. Expert Rev of Molec Diagn 3: 759-768, 2003

Bioterrorism, What is available? Laboratory Response Network wants < 10 spore Detection

- Anthrax BioThreat Alert (BTA) from Tetracore, Gaithesburg, MD. - Detects ≥ 10(6) spores with a specificity of 100%. Can be used in the field- 15 minutes to result. Claim, ricin, bot, tularemia, etc.
- Biowarfare Agent Detection Devises, Osborne Scientific, Lakeside, AZ. Similar to above for spores. Also products for ricin, bot at 250 nanograms/ test- They market themselves as "we don't need no stinking readers!"
- Response Biomedical Corporation (RBM)- RAMP Anthrax Test- detection level of 10 (4). 15 minute assay, 100% specificity. Also, smallpox, monkeypox, cowpox, ricin and bot toxins.
- HandyLab, Inc. Ann Arbor Mich. "lab-on-a-chip" 2"X2" square handheld reader- no product on market- first will be dection of antrhrax spores.

One article evaluating lateral flow devises : JCM 41:3454-5, 2003

Mononucleosis

- Clinical Question: **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?**

Infectious Mono Recommendations

- -Most of the recent literature available compares the Epstein-Barr (EBV) specific serologic markers to clinical disease
- -There are a few recent studies (past 10 years) that compare heterophile antibodies (HA) to the EBV specific serologies
- *HA tests are most frequently used at the point of care -With both types of testing (HA and EBV specific serologies) no literature found where POCT personnel had performed the testing during the study

- -Recommendation
- Research needs to be performed that compares the tests results received by POCT personnel to the clinical outcomes of the patient

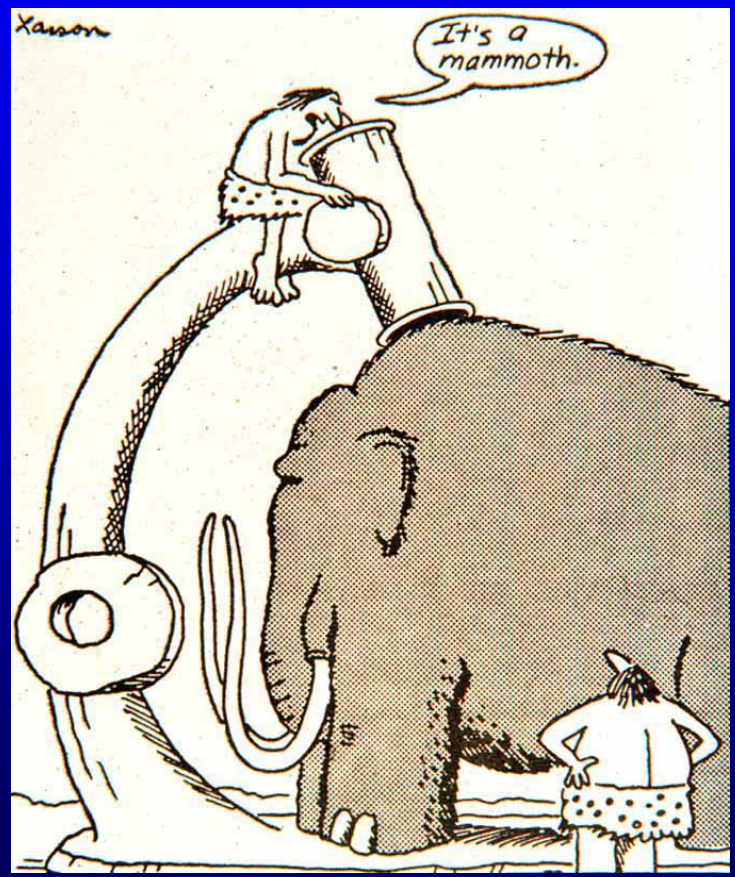
Grading of Literature Mono

Aggregate Internal Validity	Aggregate External Validity	Coherence Consistency	Overall Link to POCT Outcome	Patient Benefit
GOOD	GOOD	GOOD	POOR*	FAIR

* POCT personnel did not perform testing

Provider Performed Microscopy(PPM)

- Tests included:
  - Wet mount- *Trichomonas vaginalis*, Cellular agents, sperm, post coital testing, etc.
  - KOH preparation- yeast, hyphae, pseudohyphae
  - KOH preparation- Other, skin, nail (fungi, parasites)
  - Scotch tape Mount- Pin worm preparation

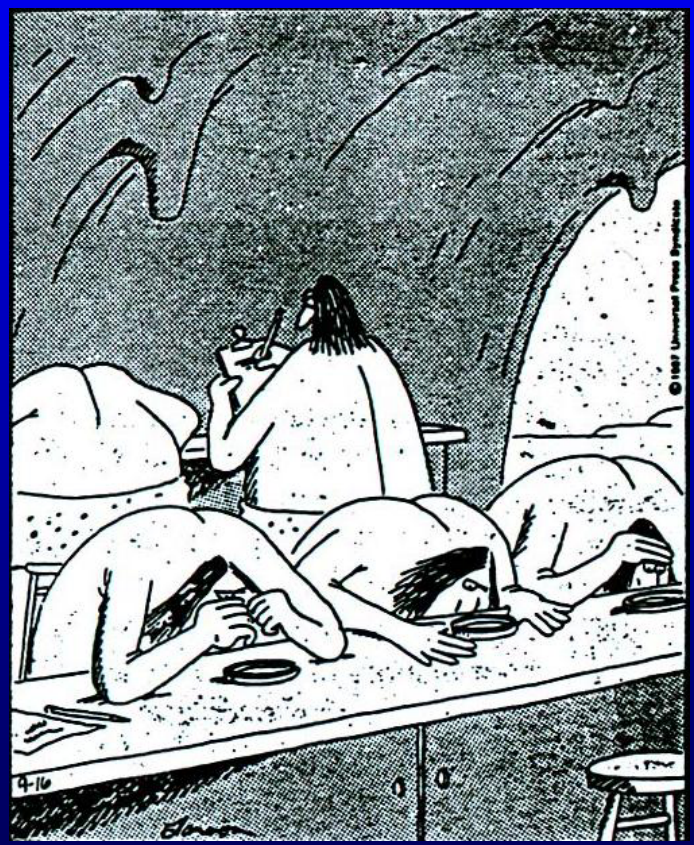


Provider Performed Microscopy

- Testing cont.
  - Fern Testing (reproduction sub group)
  - Nasal smear for eosinophils
  - Smear for leukocytes
  - Wet prep, cervical mucus, post coital testing

THE RAPID DIAGNOSIS OF BACTERIAL VAGINOSIS: WHAT IS AVAILABLE?

- Wet mounts
  - pH, clue cells; “whiff” test
- Scored Gram Stain
- Clinical Criteria alone or with above
- AFFIRM DNA Probe Test
- FEM Card
  - West B. et al. Sex Transm Dis. 2003 Jun;30(6):483-9



Wet Prep BV

- Clinical Question: Will direct examinations for agents of vaginitis, delivered in POCT, achieve high enough sensitivity for routine care?
- Recommendation: Wet mount testing for BV is an insensitive procedure used alone. Newer methods have been developed for point of service that may result in better outcomes.

WET MOUNT VS SCORED GRAM STAIN FOR DIAGNOSIS OF BV

- "Standard" lab method has become the "scored gram stain of Nugent" performed primarily in laboratories and not as POCT
  - Felt to be superior to wet mount examination for clue cells (Tam MT et al.,Infect Dis Obstet Gynecol. 1998;6(5):204-8.)
- Suggest that wet mount scoring with phase contrast microscopy is superior to "standard" scored gram stain (Schmidt H, Hansen JGAPMIS. 2001 Sep;109(9):589-94.)

DNA Probe for BV Diagnosis at POCT

- Becton Dickinson distributes the AFFIRM II for identification of the agents of vaginitis (Candida, Trichomonas and Bacterial Vaginosis)
  - 45 minute probe test after collection of specimen and the latter could be self-collected
- References on its good performance as compared to high levels of *Gardnerella vaginalis* in the specimens as marker of BV:
  - Witt AJ et al. Clin Microbiol. 2002 Aug;40(8):3057-9
  - Briselden AM, Hillier SL. **6** J Clin Microbiol. 1994 Jan;32(1):148-52

Significance of rapid testing for BV at POCT?

- Correlation of presence of bacterial vaginosis and complications of pregnancy such as PROM and preterm birth
  - Swedberg JA. Compr Ther. 1989 Aug;15(8):47-53
- There is some controversy about this association but a review article concluded that the literature does support detection of BV in pregnancy and its treatment as a method to reduce pre term birth rate.
  - Tebes CC et al. Infect Dis Obstet Gynecol. 2003;11(2):123-9
- Some literature suggests diagnosis of BV may be indicator of other STD's
  - Steinhandler L et al. Obstet Gynecol. 2002 Apr;99(4):603-7.

Wet Prep Trichomonas

- Clinical Question: Will direct examinations for agents of vaginitis, delivered in POCT, achieve high enough sensitivity for routine care?
- Recommendation: Wet mount testing for *Trichomonas vaginalis* is an insensitive procedure compared to other methods. Newer methods have been developed for point of service that may result in better outcomes.
- Additionally, outcome data will need to be based upon more sensitive tests, ex. Association of preterm labor- not significant as predicted by wet mount, IS significant as predicted by culture.

Wet Preparation- Trichomonas (TR)

- Background: Wet mounts for TR have a sensitivity of between 33%-70% compared to culture and other methods. Controversy exists on long term sequelae associated with TR. Studies based upon wet mount have shown that pre-mature rupture of membranes are not associated with TR, but is associated with BV. Recent studies have shown that TR assessed by culture is associated with pre-mature delivery. However, other studies have shown that treatment of gravid females positive for TR with metronidazole results adverse outcomes for babies.

POC Tests- Trichomonas (TR)

- Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1217-22. Trichomoniasis: trends in diagnosis and management. Lossick JG, Kent HL. Called for more sensitive tests for the diagnosis of TR.
- Reliability of Wet Preparation- Sensitivity range 36- 80% compared to culture and/or PCR. Specificity assumed to be 100%.
- Reliability of Latex agglutination 98.8% and specificity of 92.1%
- Leukocyte esterase in males- symptomatic- 80%/48% sens/ spec respectively. And asymp males - 60 %/ 68%.
- Affirm (possible POC)- 90.5%/ 99.8% for TR

Newer Methods showing Increased Sensitivity for TR

- Adu-Sarkodie Y, Opoku BK, Danso KA, Weiss HA, Mabey D. Comparison of **latex agglutination**, wet preparation, and culture for the detection of *Trichomonas vaginalis*. Sex Transm Infect. 2004

  (Latex) sensitivity 98.8% (95% CI 95.9 to 99.9) and specificity was 92.1 (89.2 to 94.5)
- Kurth A, Whittington WL, Golden MR, Thomas KK, Holmes KK, Schwebke JR. Performance of a New, Rapid Assay for Detection of Trichomonas vaginalis. J Clin Microbiol. 2004 Jul;42(7):2940-3. **(XENOSTRIP) > 70% sensitivity (better than wet prep), > 90% specificity (not as good as wet prep) and > 85% PPV, > 90% NPV.**
- **Genzyme- Capture EIA- literature not available**

Wet preparation for the diagnosis of Candida vaginitis?

- Standard POCT has been a KOH or wet preparation examination for yeast forms with the "gold" standard set at a yeast culture
  - How sensitive is the wet prep: as low as 61% in study by Handa et al (Obstet Gynecol. 2000 Aug;96(2):301-3.)
  - Is specificity of wet prep good enough.
    - only recognizes "yeast" so includes *C. albicans* and other non-albicans yeast which could be resistant to common vaginitis agents.
      - Plourd DM. Medscape Womens Health. 1997 Feb;2(2):2.

Alternatives to wet preparation for POCT diagnosis of Candida vaginitis

- Latex agglutination test for the identification of Candida species in vaginal discharge (Reed BD, and Pierson CLJ Am Board Fam Pract. 1992 Jul-Aug;5(4):375-80.)
  - older literature; not much published recently
  - found to have increased sensitivity over KOH, but less correlation with a positive culture

POCT KOH Preparation

- Routine histological examination for the diagnosis of onychomycosis: an evaluation of sensitivity and specificity (Machler BC et al. Cutis. 1998 Apr;61(4):217-9)
  - superior to KOH of the nails for diagnosis of yeast or dermatophytes
  - probably not a POCT since staining (ie.,PAS) is involved)

POC Tests for Group A streptococci - Clinical Question

- **Is there research available evaluating the clinical outcomes of rapid tests for Group A streptococcal antigen performed at the point-of-care?**

Recommendations

- Rapid tests for diagnosis of GAS pharyngitis in general provide clinically useful, financially justified results; these tests also have utility for testing nonpharyngeal specimens
- Caveats: 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

Grading of Literature GAS

Aggregate Internal Validity	Aggregate External Validity	Coherence Consistency	Overall Link to POCT Outcome	Patient Benefit
GOOD	POOR	FAIR	GOOD	YES

Clinical Question

- Will direct examinations for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, delivered in POCT, achieve high enough sensitivity for routine care?

Background

- 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.
- This delay may lead to:
  - Patients not returning for treatment
  - Further disease transmission

Recommendations

- POC 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 POC tests.

Recommendations

- POC may be appropriate in:
  - High risk patients who are unlikely to return
  - Criminal intake facilities where individuals are released within hours after detention
  - Homeless
  - Evaluations, projects

POCT for Influenza AND RSV

1. Rapid POC assays should ONLY be used when influenza or RSV have been CONFIRMED to be present in the population being tested. The positive predictive value for these assays in periods of low prevalence is very low.
2. 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.

"Don't forget to take a handful of our complementary antibiotics on your way out."

3. If antivirals are being considered, the patient must be treated within the first 48 hours for even a minimal effect to be achieved. During the peak of an outbreak, it is more cost effective to treat with amantadine or rimantadine than it is to test first, then treat the positives. At best, the sensitivities of these assays is between 60 and 90%.

4. ONLY nasopharyngeal swabs, aspirates or washings should be used with these assays. The sensitivities of the tests using throat swabs is 60% or less.

5. In seasons where influenza A & B are both circulating, rapid assays that can distinguish between these viruses must be used to guide antiviral therapy, should it be given. Influenza B only responds to the more expensive neuraminidase inhibitors, and not to amantadine or rimantadine.

Proper specimen collection is critical to appropriate test results

Background References TR

- Meis PJ, Goldenberg RL, Mercer B, Moawad A, Das A, McNellis D, Johnson F, Iams JD, Thom E, Andrews WW. The preterm prediction study: significance of vaginal infections. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.. Am J Obstet Gynecol. 1995 Oct;173(4):1231-5. Comment in: Am J Obstet Gynecol. 1996 Sep;175(3 Pt 1):753-4. Am J Obstet Gynecol. 1996 Sep;175(3 Pt 1):754-5.
- Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, Gray RH. Treatment of Trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda.

  Am J Obstet Gynecol. 2003 Nov;189(5):1398-400.
- Cotch MF, Pastorek JG 2nd, Nugent RP, Hillier SL, Gibbs RS, Martin DH, Eschenbach DA, Edelman R, Carey JC, Regan JA, Krohn MA, Klebanoff MA, Rao AV, Rhoads GG. Trichomonas vaginalis associated with low birth weight and preterm delivery. The Vaginal Infections and Prematurity Study Group. Sex Transm Dis. 1997 Jul;24(6):353-60. Comment in:Sex Transm Dis. 1997 Jul;24(6):361-2.

Reference of POC tests for TR

- Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1217-22. Trichomoniasis: trends in diagnosis and management. Lossick JG, Kent HL.
- Briselden AM, Hillier SL Evaluation of affirm VP Microbial Identification Test for Gardnerella vaginalis and Trichomonas vaginalis. J Clin Microbiol. 1994 Jan;32(1):148-52.
- Am J Obstet Gynecol. 1996 Apr;174(4):1339-42. Evaluation of a deoxyribonucleic acid probe for the detection of Trichomonas
- Am J Obstet Gynecol. 1996 Apr;174(4):1339-42. Evaluation of a deoxyribonucleic acid probe for the detection of Trichomonas vaginalis in vaginal secretions. DeMeo LR, Draper DL, McGregor JA, Moore DF, Peter CR, Kapernick PS, McCormack WM.

References- Chlam and GC

- **Mabley D Peeling, RW, Perkins MD. Rapid and simple point of care diagnostics for STIs. Sex Transm Infect 2001; 77:397-401**
- **Mabey, D, Peeling, RW. Rapid diagnostic tests for sexually transmitted infection. IPPF Medical Bulletin. 2002; 36:1-3.**
- **Vickerman P, Watts C, Alary M, MabeyD, Peeling RW. Sensitivity requirements for point of care diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in women. Sex Transm Infect 2003; 79:363-368**
- **Ford CA, Viadro CL, Miller WC. Testing for chlamydial and gonocorrheal infections outside of clinic settings. Sex Transm Dis. 2004; 31:38-51.**

References Chlam and GC

- General consensus from the **National Chlamydia Laboratory Committee, Association of Public Health Laboratories:** ***Recommendations for single use devices for point of care chlamydia tests. URL www.APHL.org\docs\NCCPOC.PDF accessed 7/6/04***
- CDC.Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections- 2002. MMWR 2002; 51(RR15) 1-39

Conclusions

- The laboratory field needs more accurate POC tests for infectious disease.
- Point of Care testing literature has been lacking in outcome studies, however, literature has been published as far back as 1991 calling for more accurate methods. The article below calls for more sensitive methods for wet preparations. We are just now getting around to this endeavor.
- Lossick JG, Kent HL. Trichomoniasis: trends in diagnosis and management. Am J Obstet Gynecol. 1991 Oct;165(4 Pt 2):1217-22.