Annotated Bibliography—GABHS Pharyngitis Testing
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Abbreviations:
AAFP—American Academy of Family Physicians
AAP—American Academy of Pediatrics
ACP—American College of Physicians
ASIM—American Society of Internal Medicine
CDC—Centers for Disease Control and Prevention
GABHS—Group A beta-hemolytic streptococcus
IDSA—Infectious Diseases Society of America
RADT—rapid antigen diagnostic test

I. Practice Guideline Statements

A. CDC—Children and Adults
Although the CDC endorsed the original ACP-ABIM-AAFP statement of 2001, it is obvious to me that they have moved on, and now support the IDSA & AAP guidelines which strongly favor performance of GABHS RADT/culture before antibiotic prescription, rather than use of clinical scoring systems. This is best seen by the material available on the CDC Get Smart: Know When Antibiotics Work web site [http://www.cdc.gov/getsmart/index.html, Info for Healthcare Professionals link]—the 2 statements on Careful Antibiotic Use in Children, and Adults, as well as 2 statements on Pharyngitis in Children and Adults. Each states that the diagnosis of GABHS should be made on clinical and laboratory [RADT/culture] grounds, and that antibiotic treatment is appropriate only for those with laboratory evidence of GABHS. Clinical findings alone may suggest a viral etiology [i.e., exclude GABHS] but does not serve to diagnose GABHS—in both children and adults. Web pages [most recent access date 6/8/14]:
B. **AAP--Children**

In the “**Clinical Report: Principles of Judicious Antibiotic Prescribing for URTIs in Pediatrics**”, published in *Pediatrics* 2013;132:1146-1154 [and also available at the AAP website], AAP states in Principal 1: Determine the Likelihood of a Bacterial Infection, that clinical scoring systems such as the McIssac or Modified Centor system can assist in identifying who should be tested with RADT/culture test—which is precisely congruous to what is suggested by CDC above. “Patients with 2 or more of the following features should undergo testing: 1) absence of cough; 2) presence of tonsillar exudates or swelling; 3) history of fever; 4) presence of swollen and tender anterior cervical lymph nodes; and 5) age <15 years.” Note that this defines a McIssac/Modified Centor score of >2. AAP proceeds to state [and discusses why], “GABHS should not be diagnosed in the absence of testing, even among patients with all of the aforementioned clinical criteria, with rare exceptions (eg, symptomatic and household contact with confirmed GABHS pharyngitis).”

C. **IDSA—Children and Adults**

The “**Clinical Practice Guideline for the Diagnosis and Management of GABHS Pharyngitis: 2012 Update by the IDSA**”, available at the idsociety.org web site and published in *Clin Infect Dis* 2012; 55:e86-e102, make recommendations for both children and adults. The IDSA evaluated all available evidence using the GRADE system, and concluded [Recommendations I-1 and I-2] that “Swabbing the throat and testing for GABHS pharyngitis by RADT and/or culture should be performed because the clinical features alone do not reliably discriminate between GABHS and viral pharyngitis except when overt viral features...are present...In children and adolescents, negative RADT tests should be backed up by a throat culture...Positive RADTs do not necessitate a backup culture. Routine use of back-up throat cultures for those with a negative RADT is not necessary for adults in usual circumstances, because of the low incidence of GABHS pharyngitis in adults and because the risk of subsequent acute rheumatic fever is generally exceptionally low in adults with pharyngitis...Physicians who wish to ensure ...maximal sensitivity...may continue to...back up negative RADTs with a culture.”

IDSA specifically commented on the ACP-ASIM approach from the Cooper et al article below, stating that the scoring system proposed [Centor score] had “…an accuracy of only 32%-56%, resulting in treatment of an unacceptably large number of adults with non-streptococcal pharyngitis...The generally high specificity of the RADT should minimize over-prescription of antimicrobials for treatment of adults. The latter point is of particular importance in view of national data indicating that antibiotics....are prescribed for approximately three-quarters of adults who consult community primary care physicians because of a sore throat.”
D. ACP-ASIM Guideline of 2001, endorsed by AAFP, CDC [at that time] but notably, NOT co-endorsed by IDSA

In 2001, 2 articles summarizing the “Principles of Appropriate Antibiotic Use for Acute Pharyngitis in Adults” were published—the Background document by Cooper RJ et al, Ann Intern Med 2001;134:509-517, is the most extensive and most cited [the other part was the summary, Snow V et al, Ann Intern Med 2001;134:506-508]. As noted above, it is my belief that CDC has moved away from this position; IDSA and the American Heart Association did not co-endorse it [see the Letter to the Editor by Bisno AL, Kaplan EL, Ann Intern Med 2002;136;489-490.]

In this Guideline, the Centor scoring system for adults was reviewed as having a positive predictive value of 40%-60% for scores of 3-4, and a negative predictive value of 80% for scores ≤2. The recommendations were made that those with Centor scores of 0-1 should not be treated [evidence grade A]; those with scores of 2,3, or 4 could be tested with an RADT and those with a positive test be treated with antibiotics [evidence grade D]. An alternative was suggested, again with evidence grade D, of RADT testing for adults with scores of 2 or 3, treating those with positive RADTs, and also simply treating those with all 4 of 4 Centor criteria. A final alternative was to treat only those with 3 or 4 Centor criteria. However, the authors noted that prospective studies were required to compare relevant outcomes and costs when using these strategies; the estimated antibiotic prescription rates for adults presenting with a complaint of sore throat using the 3 strategies would be 10.6%, 25%, and 33%, respectively. More recent study data are discussed below.

II. Relevant Recent Clinical Trials

A. Children


The study, performed in 6 community pediatric practices in Chicago and Cincinnati and the hospital laboratories of Children’s Memorial Hospital/Northwestern University Medical Center & Cincinnati Children’s Hospital Medical Center, examined the performance characteristics of RADT, office blood agar plate throat culture, and hospital microbiology lab blood agar plate throat culture [gold standard] among 1848 children ages 3-18y of age with acute pharyngitis [prevalence of GABHS=30%], each of whom had 2 throat swabs to enable testing. McIsaac scores [=modified Centor criteria] were recorded for each child as well. The mean sensitivity of the RADT was 70% (range 61%-80% across the offices) and the mean specificity 98% (range 98%-99.5%). The study confirmed the presence of spectrum bias among RADTs [sensitivity of the test increases with increased likelihood of disease; this is distinct from the routine Bayesian effect that
the PPV increases with prevalence of the disease. The McIsaac score was not
discriminative enough by itself to allow accurate diagnosis. Selected results:

Children with McIsaac scores:

0-2: RADT sensitivity 49.4%, RADT/culture backup sensitivity 70.5%
3-5: RADT sensitivity 77.7%; RADT/culture backup sensitivity 90.9%

PPV of McIsaac scores:

<table>
<thead>
<tr>
<th>Score</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7%</td>
</tr>
<tr>
<td>1</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>45%</td>
</tr>
<tr>
<td>5</td>
<td>62%</td>
</tr>
</tbody>
</table>

Scores of 3-5: 38% PPV for group; the NPV of scores 0-2 was high, at 81%

Although the odds ratio of a positive RADT when the McIsaac score was >2 [ie, scores of 3-5] looked promising [OR=3.00, 95% CI 3.08-5.18] receiver-operating characteristic analyses did not find a clinical score that discriminated well enough to be used alone [AUC only 0.65-0.70]. The authors concluded that “In areas with low rates of GABHS complications, such as North America and Western Europe, the diagnostic paradigm for pharyngitis should emphasize selective swabbing to avoid testing of patients who are unlikely to have GABHS pharyngitis and avoidance of antimicrobial overuse through treatment only of patients with positive results.”

B. **Children and Adults**


In this article, McIsaac [the creator of Modified Centor=McIsaac scores!] and colleagues actually put to the test each of the Guideline suggestions discussed above, utilizing 787 children and adults 3-69 years of age with acute sore throat and McIsaac/McIsaac scores >1 seen in a family medicine clinic in Calgary Alberta over 3 years. They examined the sensitivity and specificity, and the total and unnecessary antibiotic prescriptions generated, for the IDSA, ACP-ASIM recommended algorithms. This work is the best I could find to actually meld diagnostic accuracy with antibiotic overuse, along with the important caveat that pediatric pharyngitis is very different than adult pharyngitis [different prevalence of GABHS, which will affect PPV by Bayes theorem; different McIsaac or Centor scores, which can affect spectrum bias; and higher complication rate of suppurative and nonsuppurative [ARF] complications in children, which affects severity of misdiagnosis]. They concluded that “…recommendations for the selective use of throat cultures but antibiotic treatment based only on positive RADT or throat culture results can reduce unnecessary use of antibiotics for treatment of
pharyngitis. However, empirical treatment of adults having a Centor score of 3 or 4 is associated with a high rate of unnecessary antibiotic use.”

*Their data included the following; the BEST compromise between test turnaround time, sensitivity, specificity, and least unnecessary antibiotic Rx, across the whole of children and adults, is the IDSA [=new CDC/AAP] algorithm [results below in bold], which was indeed included in the original 2001 ACP-ASIM article.*

*Note the high unnecessary antibiotic Rx rates when modified Centor scoring is used to predict who will have GABHS pharyngitis [in bold]; the positive predictiveness is not as useful as the negative predictiveness [Centor score of 0-1 indicates no GABHS, don’t test]. This is reminiscent of the Rochester criteria for sepsis in young infants; one can accurately predict who DOES NOT have sepsis, but NOT who DOES.*

*My conclusion is that the best practice remains that of RADT with culture backup for children with acute pharyngitis, and RADT for adults [with or without culture backup as the office desires for ease of protocols]. Those with low Centor scores of 0 or 1 [ie, likely viral disease] should not even be tested.*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>First no. = Children</th>
<th>Second no. = Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional: Culture all, tx only if positive</td>
<td>100/100</td>
<td>100/100</td>
</tr>
<tr>
<td>IDSA [=AAP/new CDC also] [=ACP/ASIM 1]: RADT/culture backup for all children; RADT only [no backup] for adults; tx children and adults only if positive</td>
<td>100/76.7</td>
<td>99.0/99.2</td>
</tr>
<tr>
<td>ACP/ASIM 2: Use IDSA algorithm for children; adults do RADT on Centor scores of 2-3, tx if positive; adults with Centor 4, just treat empirically</td>
<td>100/78.1</td>
<td>99.0/95.8</td>
</tr>
<tr>
<td>ACP/ASIM 3: Use IDSA algorithm for children; test no adults, but if Centor 3-4, just treat them empirically</td>
<td>100/76.7</td>
<td>99.0/43.8</td>
</tr>
<tr>
<td>Modified Centor &amp; culture for all: Culture only children &amp; adults with mod Centor 2-3, tx if pos; for mod Centor 4 or 5, just treat [no RADT at all]</td>
<td>100/100</td>
<td>90.3/96.5</td>
</tr>
<tr>
<td>RADT for all: no culture</td>
<td>85.8/76.7</td>
<td>99.0/99.2</td>
</tr>
<tr>
<td>backup, tx only if RADT positive</td>
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<td></td>
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