New Penicillin MIC for Streptococcus pneumoniae

The Clinical and Laboratory Standards Institute (CLSI) is the organization that provides microbiology laboratories with standards for interpreting susceptibility tests. New standards for the year 2008 include changes in the way penicillin susceptibilities should be reported.

The new standards include separate penicillin MIC breakpoints for meningitis and non-meningitis isolates of Streptococcus pneumoniae. The new standard arose due to the recognition that effectiveness of antibiotic therapy is dependent upon the site of infection, and is analogous to the change in reporting for ceftriaxone that was made in 2002.

Effective immediately, all susceptibility reports for S. pneumoniae isolated from sources other than CSF will include interpretations for penicillin that are appropriate for treatment of both non-meningitis (penicillin not CSF) and meningitis (penicillin CSF). All susceptibility reports for S. pneumoniae isolated from CSF will include an interpretation for penicillin that is appropriate for the treatment of meningitis.

Anti-CCP Antibodies for Rheumatoid Arthritis

The current standard for diagnosing rheumatoid arthritis is based on the 1987 American College of Rheumatology criteria, which include:

1. Morning stiffness
2. Arthritis of 3 or more joints
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Positive serum rheumatoid factor
7. Radiographic changes

Five of the criteria are related to clinical assessment, 1 to radiographic examination of the hand and wrist and 1 to the presence or absence of rheumatoid factor. At least 4 of the 7 criteria must be present to diagnose rheumatoid arthritis. Because irreversible joint destruction can be prevented by intervention during the first months of disease, early diagnosis of rheumatoid arthritis is important.

Rheumatoid factor (RF) is an antibody directed against the Fc region of IgG. Although it is included as one of the diagnostic criteria, it is not very sensitive or specific for rheumatoid arthritis. Approximately 3% of the general population has low level RF. The incidence increases with age, up to 20% in persons over 65 years old. High titered RF is present in other autoimmune diseases such as Sjogren's syndrome and essential mixed cryoglobulinemia. RF is present in low titers in a variety of chronic infections and inflammatory disorders that are associated with intense stimulation of the immune system and hypergammaglobulinemia.

For more than 20 years, anti-keratin antibodies have been known to be specifically associated with rheumatoid arthritis. Subsequent research demonstrated that the antigen for anti-keratin antibody is the epithelial protein filaggrin. More recent studies determined that filaggrin is rich in the amino acid, arginine. The oxidation that occurs in an inflamed joint results in the deamidation of arginine to form citrulline, which is responsible for the antigenicity of filaggrin. Citrullinated peptides are also present in inflamed synovial tissues of non-RA patients, but they do not stimulate production of anti-citrullinated peptide antibodies. An aberrant immune response in RA is most likely responsible for the production of these auto-antibodies.

Three generations of assays for cyclic citrullinated peptide (CCP) antibody have been developed. The first generation (CCP1) used synthetic peptides that were based on filaggrin, while the second generation assay (CCP2) used synthetic cyclic citrullinated peptides that had higher specificity than RF. The third generation (CCP3) incorporated additional citrullinate epitopes to increase sensitivity.

A recent meta-analysis compared the sensitivities, specificities, and positive and negative likelihood
ratios (LR) from 37 studies of first and second generation anti-CCP antibody and 50 studies of RF (Ann Inter Med 2007;146:797-808).

<table>
<thead>
<tr>
<th>Pooled Data</th>
<th>CCP1 or 2</th>
<th>RF</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Specificity</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>Positive LR</td>
<td>12.46</td>
<td>4.86</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.36</td>
<td>0.38</td>
</tr>
</tbody>
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Anti-CCP antibodies were more specific than RF for diagnosing rheumatoid arthritis. CCP antibody was more often negative in patients with Sjogren’s syndrome, systemic lupus erythematosus with erosive arthritis, polymyalgia rheumatica and hepatitis C infection presenting with joint complaints than RF.

Another conclusion of the meta-analysis was that the risk for radiographic progression was greater with anti-CCP antibody positivity than with RF positivity. The authors concluded that positivity for anti-CCP antibodies should be added to the American College of Rheumatology criteria for diagnosis of rheumatoid arthritis.

Currently, most rheumatologists measure both anti-CCP antibody and RF to comply with American College of Rheumatology guidelines and to maximize sensitivity. However, RF may become obsolete in the future if the anti-CCP antibody is added to the diagnostic guidelines and the third generation anti-CCP antibody assay is confirmed to have higher sensitivity than RF.

*Helicobacter pylori* Treatment and Improvement of Chronic ITP

A recent study in Blood (2007;10:3833-3841) suggests that eradication of *Helicobacter pylori* may lead to a significant and persistently increased platelet count in patients with chronic immune thrombocytopenic purpura (ITP). In this study, 75 patients with ITP were screened for infection with *H. pylori*. Active *H. pylori* infection was found in 38 (51%) of these patients and effectively eradicated in 34 (89%) patients. The urease breath test was used to assess eradication 4 to 6 weeks following treatment.

Platelet counts were then monitored at regular intervals; 2 weeks for the first 2 months, monthly for the next 4 months, and every 6 months thereafter. The average baseline platelet count in *H. pylori* infected ITP patients was $40.6 \times 10^9/L \pm 25.0 \times 10^9/L$. The authors defined platelet responses as follows:

- **Complete response (CR):** normal platelet count for at least 3 months after eradication.
- **Partial response (PR):** platelet count not >$149 \times 10^9/L$ or a doubling of the initial count above $40 \times 10^9/L$.
- **No response (NR):** platelet count less than or equal to $40 \times 10^9/L$, even if the initial count doubled.

Five patients without *H. pylori* but with ITP were also given eradication treatment to act as control subjects.

After a median follow-up time of 60 months post treatment, 23 (68%) of the 34 patients with eradicated *H. pylori* infection showed a significant and persistent increase in their platelet count. Sixteen (46%) patients achieved CR, 7 (20%) achieved PR and 12 (34%) showed no response. Only 1 patient who was refractory to eradication treatment showed a response during follow-up. No *H. pylori*-negative patients experienced a platelet response. Overall, 55% of the *H. pylori*-positive patients with ITP who underwent eradication treatment were disease free at 60 months.

With an average follow-up time of 60 months, the results of this study demonstrated that *H. pylori* eradication treatment may lead to a sustained improvement in the platelet count and possibly long-term cure in patients with chronic ITP. Therefore, the authors suggest that because the eradication of *H. pylori* is a simple, safe, effective and inexpensive approach, all patients with ITP should be screened for *H. pylori* at diagnosis and treated with *H. pylori* eradication therapy prior to starting or in conjunction with other treatments for ITP.