Top Recent Articles from Infectious Disease Perspective

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Disclosure

❖ I have no relevant financial relationships with the manufacturers of any commercial products or provider of commercial services discussed in this CME activity
❖ I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation
Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

❖ ACIP and Tdap with pregnancy
❖ 2006 - administer Tdap in the immediate postpartum period
❖ 2011 - Tdap during pregnancy for those who had not previously received Tdap
❖ 2013 - Tdap during every pregnancy, preferably between 27-36 weeks gestation

Retrospective cohort study of full term infants born at Kaiser Permanente Northern California from 2010 to 2015
❖ Mothers born before 1996 so that all mothers had received whole-cell rather than acellular pertussis
❖ Cases of pertussis were defined as being PCR positive
❖ Infants followed from birth to 12 months of age
❖ Vaccine efficacy determined for 0-2 months of age and 0-12 months of age
Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

❖ Percentage of mothers who received Tdap during pregnancy increased from <1% in 2006-2008 to 11.9% in 2010 and to 87.4% by 2015
❖ The percentage of mothers who received the Tdap vaccine during postpartum days 0-14 peaked at 31.7% for infants born in 2010 and declined thereafter to 1.8% for infants born in 2015

Study population consisted of 148,981 infants born from 2010, when KPNC began recommending Tdap vaccination in pregnancy, through 2015
❖ Mothers of 45.8% of the study population received Tdap vaccine during pregnancy at least 8 days before birth
❖ 17 infants (11.4 per 100,000 infants) tested positive for pertussis by 2 months of age
❖ 110 infants (73.8 per 100,000 infants) tested positive by 1 year of age
❖ 103 included in the analyses after restricting to infants who followed the recommended DTaP schedule
Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis

- Maternal Tdap vaccination during pregnancy reduced pertussis risk by an estimated 91.4% during the first two months of life
- Pertussis risk reduced by 69.0% during the entire first year of life
- No evidence for interference of Tdap during pregnancy with infant DTaP vaccination
- Maternal Tdap after pregnancy (cocooning) did not significantly reduce pertussis risk

<table>
<thead>
<tr>
<th>VE % (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tdap During Pregnancy Infant 0 DTaP</td>
<td>87.9 (42.4-97.5)</td>
</tr>
<tr>
<td>Tdap During Pregnancy Infant 1 DTaP</td>
<td>81.4 (42.5-94.0)</td>
</tr>
<tr>
<td>Tdap During Pregnancy Infant 2 DTaP</td>
<td>6.4 (-165.1-66.9)</td>
</tr>
<tr>
<td>Tdap During Pregnancy Infant 3 DTaP</td>
<td>65.9 (4.5-87.8)</td>
</tr>
<tr>
<td>Tdap After Pregnancy</td>
<td>24.1 (-28.5-55.1)</td>
</tr>
<tr>
<td>Tdap Before Pregnancy</td>
<td>35.6 (20.1-75.4)</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

* Systematic review of the literature in December 2015
  * any study design reporting nonoperative treatment (NOT) for acute uncomplicated appendicitis (AUA)
  * NOT = antibiotic therapy without surgery
  * limited to studies of children (<18 years) and articles published in English
  * excluded studies that report NOT for complicated appendicitis (such as perforated or ruptured appendicitis, appendicitis with an abscess, or appendix mass)

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Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

* 727 records screened
* 20 full-text articles assessed for eligibility
* Ten articles (7 prospective, 3 retrospective) reporting NOT for AUA were included
  * Six, including one randomized controlled trial, compared NOT to appendectomy
  * Four reported outcomes of children receiving NOT without a comparison group
  * 413 children were either randomized to or selected for NOT

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No study reported any adverse events related to NOT or concern over the safety of NOT.

NOT was successful as initial treatment in 97% (95% CI 95.5-98.7).

Adjusted incidence of recurrent appendicitis was 14% (95% CI 7-21).

The long-term efficacy of NOT (those children who did not have an appendectomy by the final follow-up) was 82% (95% CI 77-87).

In the six studies that compared NOT with appendectomy, duration of initial hospital stay was reported in 4 studies.

Duration of hospital stay for children who had an appendectomy was shorter by a mean of 0.5 days (95% CI 0.2-0.8) compared to children who had NOT.

Total duration of hospital stay including during follow-up (initial plus readmissions) was similar between children initially treated with NOT and appendectomy with a weighted mean difference of 1.1 days (95% CI -1.2 to 3.5; P=.34).
Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis

❖ Total complications were reported in 5 of the 6 comparative studies
❖ Risk of complications was similar
❖ Risk difference 2% (95% CI 0-1; P=.1)
❖ 1/175 with NOT (surgical site infection in child who failed initial NOT and had appendectomy)
❖ 9/239 with appendectomy

Related Study

❖ Prospective nonrandomized study of NOT for acute appendicitis with appendicolith compared to appendectomy
❖ Recruitment of the study was halted after enrollment of 14 patients (5 nonoperative, 9 surgery) due to high failure rate (3/5) in the nonoperative group
Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Multicenter retrospective cohort study with propensity score modeling and matching
- Children ≥2 months and <18 years discharged with complicated pneumonia (pleural effusion, empyema) between 2009 and 2012
- Used data from the Pediatric Health Information System (PHIS) affiliated with the Children’s Hospital Association

Main exposure variable was PICC or oral discharge antibiotic administration and primary outcome was treatment failure
- Treatment failure was defined as an ED revisit or rehospitalization that resulted in extension or change of antibiotic therapy or performance of pleural drainage
- Propensity score matching incorporated age, race, insurance, length of stay in days, blood culture results (negative or positive), ICU admission, and timing and route of pleural drainage
Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- 2123 subjects in final cohort from 36 hospitals
  - 1842 received oral antibiotics and 281 received antibiotics via PICC
  - PICC use post discharge varied across hospitals, ranging from 0% to 71%
- Pleural fluid drainage was performed in 43.9% of children
- Pathogen was identified in blood or pleural fluid culture in 305 (N=14.4%) of children
  - 175 Streptococcus pneumoniae, 77 Staphylococcus aureus (56 MRSA, 72.7%), 21 Streptococcus pyogenes, 9 Streptococcus milleri group

### TABLE 1 Study Population Characteristics Pre- and Postmatch

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prematch Oral</th>
<th>PICC</th>
<th>Postmatch Oral</th>
<th>PICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;5 y</td>
<td>1842</td>
<td>281</td>
<td>1842</td>
<td>281</td>
</tr>
<tr>
<td>White race</td>
<td>15.7</td>
<td>15.5</td>
<td>15.7</td>
<td>15.5</td>
</tr>
<tr>
<td>Government payer</td>
<td>70.3</td>
<td>65.5</td>
<td>58.5</td>
<td>65.5</td>
</tr>
<tr>
<td>Length of stay</td>
<td>11.7</td>
<td>15.3</td>
<td>14.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Culture positive</td>
<td>12.4</td>
<td>24.6</td>
<td>23.0</td>
<td>24.6</td>
</tr>
<tr>
<td>ICU admission</td>
<td>18.1</td>
<td>28.2</td>
<td>27.0</td>
<td>28.2</td>
</tr>
<tr>
<td>No drainage</td>
<td>63.8</td>
<td>24.6</td>
<td>64.5</td>
<td>24.6</td>
</tr>
<tr>
<td>Late surgical drainage</td>
<td>11.7</td>
<td>15.3</td>
<td>14.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Early surgical drainage</td>
<td>14.6</td>
<td>18.2</td>
<td>21.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Late chest tube drainage</td>
<td>4.6</td>
<td>15.3</td>
<td>12.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Early chest tube drainage</td>
<td>7.8</td>
<td>25.6</td>
<td>27.2</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Values presented as percentages except for length of stay, for which mean values are presented.

Percentages are weighted.
Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

- Treatment failure before matching occurred in 57 (2.7%) overall
- 3.2% with PICC antibiotic and 2.6% with oral (P>0.2)
- No treatment failures among the 77 patients with Staph aureus
- Among children discharged with oral therapy for culture-negative infection, treatment failure occurred in 1.4% discharged with amoxicillin and 1.9% of those discharged anti-MRSA antibiotics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted Rates</th>
<th>Matched OR (95% CI)</th>
<th>Matched Rates</th>
<th>Matched Risk Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All complications</td>
<td>1.8% (0.5 to 2.9)</td>
<td>1.8% (1.0 to 3.3)</td>
<td>1.2% (1.0 to 2.3)</td>
<td>0.71 (0.45 to 1.12)</td>
<td></td>
</tr>
<tr>
<td>PICC complications</td>
<td>2.8%</td>
<td>2.8%</td>
<td>2.8%</td>
<td>1.00 (0.59 to 1.68)</td>
<td></td>
</tr>
<tr>
<td>PICC readmission</td>
<td>2.8%</td>
<td>2.8%</td>
<td>2.8%</td>
<td>1.00 (0.59 to 1.68)</td>
<td></td>
</tr>
<tr>
<td>PICC treatment-related complications</td>
<td>2.8%</td>
<td>2.8%</td>
<td>2.8%</td>
<td>1.00 (0.59 to 1.68)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, insurance, and hospital.

References:
- Stockmann et al found that while low overall, occurred more among those receiving parenteral antibiotics.
- No treatment failures among the 77 patients with Staph aureus.
- Treatment failure before matching occurred in 57 (2.7%) overall.
- 3.2% with PICC antibiotic and 2.6% with oral (P>0.2).
- Among children discharged with oral therapy for culture-negative infection, treatment failure occurred in 1.4% discharged with amoxicillin and 1.9% of those discharged anti-MRSA antibiotics.
Intravenous Versus Oral Antibiotics for Postdischarge Treatment of Complicated Pneumonia

❖ Conclusions
❖ Treatment failure rates did not differ between PICC and oral postdischarge antibiotic administration
❖ Adverse events were more frequent with PICC
❖ Children with complicated pneumonia should preferentially be discharged with an oral antibiotic

Quinolone Ear Drops After Tympanostomy Tubes and the Risk of Eardrum Perforation: A Retrospective Cohort Study

❖ A cell culture study showed that treatment of TM fibroblasts with ciprofloxacin led to marked cytotoxicity and depression in collagen synthesis
❖ Retrospective cohort study using Medicaid encounter and pharmacy billing data from 29 US states between 1999 and 2006.
❖ Children <18 years old without predisposing factors for perforation requiring tympanoplasty entered the cohort after TT placement and first dispensing of antibiotic ear drops (within one year of TT placement).
❖ Included ear drops were quinolones (ofloxacin, ciprofloxacin plus hydrocortisone, or ciprofloxacin plus dexamethasone) or neomycin plus hydrocortisone
❖ Analysis adjusted for age, sex, race, adenoidectomy, TT reinsertion, calendar year of tube insertion, number of ear drop prescriptions, and time to first ear drop initiation
Quinolone Ear Drops After Tympanostomy Tubes and the Risk of Eardrum Perforation: A Retrospective Cohort Study

- 96,595 children entered the study cohort
  - 18,320 received neomycin
  - 78,275 received quinolone
- Each year increase in patient’s age was associated with a 21% increase in the hazard of perforation (95% CI 18%-24%)
- An increased frequency of ear drop prescriptions was also associated with higher risk of perforation (HR 1.14; 95% CI 1.11-1.17)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No. of Patients</th>
<th>No. of Cases</th>
<th>Incidence per 10,000 person-years</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin</td>
<td>18320</td>
<td>42</td>
<td>11.4</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>All Quinolones</td>
<td>78275</td>
<td>322</td>
<td>17.3</td>
<td>1.44 (1.04-2.00)</td>
<td>1.61 (1.15-2.26)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>50163</td>
<td>207</td>
<td>16.3</td>
<td>1.35 (0.96-1.90)</td>
<td>1.49 (1.07-2.09)</td>
</tr>
<tr>
<td>Cipro/HC</td>
<td>11649</td>
<td>79</td>
<td>25.2</td>
<td>2.17 (1.46-3.16)</td>
<td>1.94 (1.32-2.85)</td>
</tr>
<tr>
<td>Cipro/Dex</td>
<td>16463</td>
<td>36</td>
<td>12.7</td>
<td>0.87 (0.55-1.39)</td>
<td>2.00 (1.18-3.41)</td>
</tr>
</tbody>
</table>
Quality of Life after Surgery for Recurrent Otitis Media in a Randomized Controlled Trial

- Evaluated the effect of tympanostomy tubes (TT) with and without adenoidectomy for improving the quality of life (QOL) in young children with recurrent acute otitis media (RAOM).
- Myringotomy with tympanostomy tube placement is the most common ambulatory surgery performed on children in the United States.
- 667,000 children <15 years of age underwent TT placement in 2006.

- Part of a larger study looking at reduction in episodes of AOM for children undergoing tympanostomy tubes, tympanostomy tubes plus adenoidectomy, or neither that was published in 2012.
- Children aged between 10 months and 2 years of age who had at least 3 AOM episodes in the previous 6 months and had been referred to Otolaryngology Dept.
- A disease-specific QOL questionnaire (Otitis Media-6) completed by the principal caregiver at entry (time of surgery or no surgery) and 4 and 12 months later.
- Divided into 6 subsets of physical suffering, emotional distress, caregiver concern, activity limitations, hearing loss, and speech impairment.
159 children were randomized and 123 completed the study and analyzed:

- 42 TT, 46 TT with adenoidectomy, 35 no surgery
- No significant differences in baseline characteristics (e.g., age, number of episodes of AOM, age of first AOM episode, daycare, duration of breastfeeding)

A remarkable improvement in ear-related QOL between entry and 12-month followup was seen in all 3 groups, with no difference between groups.

The number of AOM episodes did not show any correlation with QOL in any of the OM-6 subsets at entry to the study.

- 12 children in the no surgery group (34%) had a failure of treatment (2 AOM episodes in 2 months or 3 in 6 months)
- 9 failures in the TT group (21%) and 8 in the TT plus adenoidectomy group (17%)
Global ear-related QOL running from 0 (worst possible) to 10 (best possible)

Outcome measures of QOL scale running from 1 (no problem/not present) to 7 (severe problems)
Objective was to compare sleep, cognitive, behavioral, and health outcomes of tonsillectomy vs watchful waiting in children with recurrent throat infections.

Recurrent or severe tonsillitis has been defined as ≥7 episodes of sore throat in the preceding year, or ≥5 episodes in each of the preceding 2 years, or ≥3 episodes in each of the preceding 3 years.


Also hand-searched the reference lists of included articles and recent reviews addressing tonsillectomy in children to identify potentially relevant articles.

Principal outcomes of interest included the number and severity of recurrent throat infections, quality of life, and health care utilization (number of clinician visits or contacts, number of courses of antibiotics).

Significant heterogeneity in outcomes reported precluded meta-analysis.

Synthesized studies qualitatively and reported descriptive statistics in summary tables.

Strength of evidence (insufficient, low, medium, high) was assessed to reflect the confidence in the stability of the treatment effects in the face of future research.
Tonsillectomy versus Watchful Waiting for Recurrent Throat Infection: A Systematic Review

- Seven studies including children with ≥3 infections in the previous 1-3 years were analyzed.
- In studies reporting baseline data, the number of infections/sore throats decreased from baseline in both groups.
  - In the short term (<12 months), there were greater decreases in sore throat days, clinician contacts, diagnosed group A streptococcal infections, and school absences in children who had a tonsillectomy.
  - There were 1.19 fewer mean episodes of sore throat with tonsillectomy compared to no surgery in the first post surgical year based on two RCTs.
  - Benefits did not persist over time.
- Quality of life was not markedly different between groups at any time point (3 studies).
Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, and Adenitis) Syndrome after Tonsillectomy

* Identified children who had tonsillectomy (+/- adenoidectomy) between 1990 and 2007 with a history of regularly recurring fever episodes at least 5 times
* Oulu University Hospital in Finland
* 132 patients met the inclusion criteria and postoperative follow-up data was collected on 119 patients
* divided patients into those who met current diagnostic criteria for PFAPA and those who did not
* Main outcome measure was the effectiveness of tonsillectomy in patients who did and did not meet the current criteria for PFAPA

Table I. Thomas criteria for diagnosis of PFAPA

| I | Regularly recurring fevers with an early age of onset (<5 y of age) |
| II | Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs: Aphthae, Cervical lymphadenitis, Pharyngitis |
| III | Exclusion of cyclic neutropenia |
| IV | Completely asymptomatic interval between episodes |
| V | Normal growth and development |

Incomplete PFAPA

* Patients ≥5 years old at onset of fever episodes, or
* Patients who did not have aphthous stomatitis, cervical lymphadenitis, and pharyngitis at the onset of fever episodes
In 1987, Marshall et al. described a syndrome of periodic fever, pharyngitis, and aphthous stomatitis of unknown etiology. The acronym of PFAPA was introduced 2 years later. It is the most common pediatric inflammatory fever syndrome. The incidence of 2.3 per 10,000 children up to 5 years of age was reported from a Norwegian study. Long-term (12-21 years) follow-up (Wurster VM et al, *Journal of Pediatrics* 2011) showed that 50 of 59 patients had complete resolution with a mean symptom duration of 6.5 years (95% CI, 5.4-7.5 years). Multiple randomized trials and Cochrane systematic review (Burton MJ et al, 2014) have shown the effectiveness of tonsillectomy.

Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, and Adenitis) Syndrome after Tonsillectomy

- Mean age of patients was 2.7 years at the onset of symptoms, 4.3 years at the time of tonsillectomy, and 13.2 years at the time of study visit or telephone interview.
- Data collected 2-20 years (mean 8.9 years) after tonsillectomy.
- The duration of fever episodes and time between fever episodes was similar in the two groups.
In the group that met Thomas criteria for PFAPA, 97% (56/58) had complete resolution of fever episodes after tonsillectomy.

In the group that did not meet Thomas criteria, 50/50 had complete resolution of fever episodes after tonsillectomy.