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GCRC Residents Rotation

IRB PROTOCOL

Post Prevnar: Changes in Pneumococcal Acute Otitis Media Incidence and in Rates of Penicillin Resistant Pneumococcal Acute Otitis Media.

A. Statement of Study Rationale and Purpose:

The current study is a retrospective chart review that will evaluate existing data for children undergoing tympanocentesis for acute otitis media (AOM). The study aims are two-fold: 1) to appreciate a difference in the overall incidence rate of pneumococcal AOM before and after the 2000 introduction of Prevnar (the heptavalent conjugated pneumococcal vaccine approved in 2000) and 2) to monitor for a change in the incidence of penicillin resistant AOM before and after the introduction of Prevnar.

B. Background and Hypothesis

Acute otitis media serves as the most frequent diagnosis in sick children visiting the physician's office. It is estimated that over 7,000,000 cases of AOM occur each ear with most of these infections affecting children between 6-24 months. Approximately 60-80 percent of children will have otitis by 12 months (Klein JO et al 2006). Among a multitude of risk factors, young children are at a higher risk than the adult and older child population due to incompletely developed eustachian tubes, immature immunity, exposure to tobacco smoke, frequent first time exposures to new pathogens (often in the setting of daycare), and pacifier use (possibly creates backflow of nasopharyngeal contents into the eustachian tubes and middle ear). Causal pathogens include Streptococcus pneumoniae (35% of cases), non-typable Haemophilus influenzae (~20%), and Moraxella catarrhalis (~15%), other bacteria (25%), respiratory viruses (~15%) (note numbers add to more than 100% as isolates may contain more than one pathogen, Klein JO 2001). Of these organisms, only H. influenzae has a vaccine that is given for its type B serotype (of note, since its introduction rates of H. influenzae infections secondary to type B serotypes have fallen dramatically). For S. pneumoniae there has been a vaccine developed termed Pneumovax (23- valence unconjugate polysaccharide vaccine). Unfortunately, the vaccine does not generate a T-Cell response and cannot induce lasting immunogenicity in young children. The immune response for Pneumovax is typically of the IgM subtype and short-lived. In contrast, Prevnar (7- valence conjugated vaccine that contains pneumococcal capsular saccharides conjugated to a diphtheria protein) does generate a T-Cell response and can induce lasting immunogenicity in young children. Prevnar's immune response is of the IgG subtype and typically long lasting. Prevnar gained its FDA approval in 2000 for all children below age 2 and for high-risk children between 2-5 years of age. That same year, the American Academy of Family Physicians, the American Academy of Pediatrics, and the Advisory Committee on Immunization Practices recommended Prevnar be used in these age groups. Following vaccination, a large scale double blinded clinical trial out of Finland documented a reduction in the

number of episodes of acute otitis media from any cause by 6% and also noted a decrease in the incidence of culture-confirmed pneumococcal episodes by 34% (Eskola et al 2001). Additionally, between 1999 (pre-vaccination) and 2004 (post-vaccination) the proportion of cases that were penicillin resistant declined by 80% in children less than 2 years of age (Kyaw et al 2006). Similarly, a 49% decrease was also demonstrated in adults greater than 65 years of age during this same period (Kyaw et al 2006). These isolates were, however, typically grown from the blood of bacteremic patients. As such, the purpose of the proposed study is to compare pre-vaccination and post-vaccination time periods and to re-document the finding by the made by the 2001 Finish which notes a decrease in the overall incidence of pneumococcal AOM and to also look for drop in penicillin resistance in pneumococcal AOM in the post-vaccination period. This last effort is unique because the prior study documented predominantly blood isolates whereas our study will document only isolates taken directly from the middle ear by tympanocentesis.

C. Study Design and Analysis:

This is a retrospective chart review of 486 patients (243 will be selected that have not received the Prevnar vaccine and 243 patients will be selected that have either documentation of Prevnar vaccination or were born after the year 2003). Patients that will be reviewed were initially recruited for a study (Haddad et al 1999) that documented the proportion of children with acute otitis media (AOM) who were infected with non-susceptible streptococcus pneumoniae. Additionally, investigators aimed to determine the susceptibility of these organisms to penicillins and other antibiotics commonly used to treat AOM. The study came out of a recommendation from the Centers for Disease Control and Prevention that cited the geographic variability of penicillin resistant S. pneumoniae. The report recommended that periodic sampling be performed to evaluate for the incidence of resistant S. pneumoniae and also that susceptibility testing be performed on isolates that might guide effective therapy (MMWR 1997; 46: 297-9: RR-1). As such, secondary to the necessity for periodic sampling and documentation of penicillin resistance the study had patients undergo tympanocentesis prior to commencement of antibiotic resistance in 115 cases between the years 1993 to 1995 (tympanocentesis prior to antibiotic treatment failure is a departure from the recommended treatment protocol). For the purposes of this project, I am assuming that in each of the following two years until the present day, that roughly 115 patients also underwent the same protocol during each respective period.

Sample Size:
To assess for a change in the incidence of pneumococcal AOM:
I applied a Chi-Square Test in my two study groups (with or without Prevnar vaccination) in order to detect a difference in the proportions of a categorical outcome (with or without pneumococcal otitis media).

Chi Square Test (proportions in two groups):

N (in each group) = $8\ ((p_1q_1 + p_2q_2)/\ effect^2) + 2/\ effect + 2$

p_1= proportion of children developing pneumococcal AOM prior to the implementation of the Prevnar vaccine. I designated p_1 as 0.35, a value that is consistent with prior studies of pneumoccocal AOM (Klein, JO 2001).

p_2= proportion of children developing acute otitis media after the implementation of the Prevnar vaccine. I designated p_2 as 0.23, a value that reflects a 34% decrease in pneumococcal incidence following Prevnar vaccination. This value is consistent with the results obtained from the Finnish Otitis Media Trial, a Randomized Controlled Trial of 1662 infants randomized to placebo (Hep B vaccine) or Prevnar (Eskola et al 2001).

N = 243 patients in each study arm

To assess for a change in the incidence of penicillin resistant pneumococcal AOM:
I applied a Chi-Square Test in my two study groups (with or without Prevnar vaccination) in order to detect a difference in the proportions of a categorical outcome (with or without resistant pneumococcal otitis media).

Chi Square Test (proportions in two groups):

N (in each group) = $8 ((p_1q_1 + p_2q_2)/ \text{effect}^2) + 2/ \text{effect} + 2$

p_1= proportion of children developing penicillin resistant pneumococcal acute otitis media prior to the implementation of the Prevnar vaccine. I designated p_1 as **0.084** with the following conclusions:

- Incidence Rate of S. pneumonia in General Cases of AOM: 0.35
- Proportion of Cases of S. pneumoniae that are Penicillin Resistant: 0.24 (Doern et al 1996).
- Incidence Rate of resistant S. pneumoniae in General Cases of AOM: 0.35 x 0.24 = 0.084.

p_2= proportion of children developing penicillin resistant pneumococcal acute otitis media after the implementation of the Pneuomvax vaccine. I designated p_2 as **0.01104** with the following conclusions:

- Incidence Rate of S. pneumonia in General Cases of AOM: 0.23 (consistent with prior expected decrease in cases of pneumococcal AOM).
- Proportion of Cases that are penicillin resistant would decline by 80% as estimated by the NEJM article (Kyaw et al 2006). As such, as before if pneumococcus was resistant 24% of the time prior to the vaccination, but following the vaccination it is reduced by 80% than we can multiply 0.24 x 0.20 (number of isolates are still resistant) than we can attain our new hypothesized percentage of pneumococcal isolates that resistant to penicillin as 4.8% or 0.048.
    - Of note: the 80% decrease in penicillin-nonsusceptible strains was for children under 2 years of age treated with the Prevnar at appropriate intervals.

    - Also of note: a 49% decrease was observed in pts 65 years of age or older. It appears that the incidence penicillin- nonsusceptible strains may be between these two figures in vaccinated children that are older than 2 years of age.
- Incidence Rate of Resistant S. pneumoniae in General Cases of AOM during the post vaccination period: 0.23 x 0.048 = 0.01104

N = 161 in each study arm

Analysis:
Following receipt of data a simple chi-squared test will be performed on the proportion of each group that develops pneumococcal AOM and for those that develop penicillin resistant pneumococcal AOM. I will also make a graph of the prevalence that will compare the incidence of rates before and after vaccination for the overall incidence of pneumococcal AOM and for the resistant pneumococcal AOM.

D. Study Procedures:

The study is retrospective, there will be no procedures performed upon patients for the study.

E. Study Drugs:

There will be no drugs given.

F. Medical Device

None

G. Study Questionnaire:

None

H. Study Subjects:

Inclusion Criteria For Pre-vaccination Arm:

- Less than 2 years of age when tympanocentesis was performed.
- Born prior to 1998
- No documented history of receiving Prevnar vaccine
- Prior to development of AOM patients were healthy children without a specific risk factor for AOM or resistant organisms.
- Previously undergone tympanocentesis as a part of ongoing 1999 Haddad trial.
- Patients did not receive antibiotics for at least one week prior to tympanocentesis.

Inclusion Criteria For Post- vaccination Arm:

- Less than 2 years of age when tympanocentesis was performed.

- With either: 1) Documentation of at least 3 doses of Prevnar or 2) Were born after June 2002.
- Prior to development of AOM patients were healthy children without a specific risk factor for AOM or resistant organisms.
- Previously undergone tympanocentesis as a part of ongoing 1999 Haddad trial.
- Patients did not receive antibiotics for at least one week prior to tympanocentesis.

I. Recruitment of Subjects:
Recruitment of subjects will be performed through a webcis using a documented list of patients that have participated in the ongoing 1999 Haddad trial.

J. Potential Conflicts of Interest:
None

K. Location of Study:
Study is computer based and on a chart review basis.

L. Potential Risks:
None

M. Potential Benefits:
Benefits include, characterizing the efficacy of the Prevnar vaccine to reduce the overall incidence of pneumococcal AOM as well as penicillin resistant pneumococcal AOM.

N. Alternative Therapies:
N/A

O. Compensation to Subject:
None

P. Costs to the Subject:
None

Q. Minors as Research Subjects:
Approval from the Department of Pediatrics Committee on Human Investigation will be required prior to IRB approval

R. Radiation or Radioactive Substances
None

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