# *Acute Otitis Media: Can We Predict Severity of Disease?*

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**Introduction**

Acute otitis media (AOM) is the most common infection of the upper respiratory tract in childhood [1]. Evidence to date suggests that AOM may not be a pure bacterial disease, but rather a polymicrobial disease, in which both bacteria and respiratory viruses participate and interact in its pathogenesis. In most cases, a viral upper respiratory tract infection (URI) occurs before and/or concurrently with AOM [2, 3]. It has also been shown that about one-third of children with viral URI developed AOM within 4 weeks of its onset. Of note, tympanic membrane (TM) changes in AOM can be observed as early as the first day of symptomatic viral URI [4].the advent of important vaccines, i.e., influenza vaccine and the pneumococcal conjugate vaccines (PCVs), into many national childhood immunization programs worldwide, dramatically changed the microbiology of AOM, when compared to the pre-vaccine era [5, 6]. The clinician's assessment of AOM severity is an important step for decision-making purposes, when treatment or watchful waiting are considered.

Retrospective studies in unvaccinated children identified specific indicators which were associated with a severe, prolonged and complicated AOM course, such as leukocytosis, high temperature, and more intensely yellow/red and bulging TMs on otoscopy [7-9]. These studies aimed to predict the presence of *Streptococcus pneumoniae* (Sp) in the middle ear as the offending pathogen in AOM, and to distinguish its infection from with other otopathogens. Other prospective studies, in both vaccinated and unvaccinated children, utilized designated clinical scoring systems, and relied on the parents' report on the child's condition, mimics of the child's face on exam and TM appearance on otoscopy [10-12]. They also failed to foresee a severe AOM episode, based on the initial observations/scores. Also, much of these variables are not in use in real-life, daily practice. Instead, the pragmatic integration of signs, symptoms and TM otoscopy findings are sufficient for the subjective evaluation and judgement of the treating physician.

**Factors influencing AOM severity**

**Host-Related Factors**

To date, host-related factors that are associated with severe AOM course include age <2 years, pacifier use, males, otitis-prone parents, short duration of breastfeeding, presence of adenoid hypertrophy, high levels of pro-inflammatory mediators (such as interleukin-10), high levels of lactate dehydrogenase, and being in an at-risk population, such as Aboriginal origin ("First Nations") [13]. Bilateral AOM seems to be a clinically more severe than unilateral AOM [14]. Antibiotic therapy within the last month, and any diagnosis of AOM within the last month are

both indicators for a more severe course and higher rate of treatment failure. Children presenting with recurrent AOM (defined as >3 episodes in the last 6 months, or >4 in the last 12 months, with one recent episode) are prone to a more severe disease, as children who had their the first of episode of AOM prior to the age of ~7 months [15].

**Infectious-Related Factors**

Infectious-related factors include pneumococcal infections (and especially with serotypes not covered in PCV7, such as 19A[16]), unvaccinated children, biofilm formation in the middle ear cavity (in particular *Haemophilus influenzae*)[17], bacterial non-susceptibility to penicillin, and high respiratory viral loads and multi-virus detection in nasopharyngeal secretions during AOM course [18, 19].

Environmental-Related Factors

Environmental-related risk factors include the winter season (when the flu activity is high), passive smoke exposure, daycare attendance, and presence of other siblings in the family. A lower socioeconomic status is a key factor influencing AOM severity, through promoting other risk factors. Of note, factors that adversely affected parental quality of life include increased parental perception of AOM severity, younger child age and multiple AOM episodes.

**Severity of *Streptococcus pneumoniae* - AOM caused**

In the past, several reports tried to link the severity of an AOM episode to the presence of *Sp,* an important otopathogen. Coffey *et al*. reported an association of Sp with bullous myringitis [20]. Other reports, by Howie *et al.* showed that children presenting with Sp-caused AOM were prone to present with both high fever and increased pain levels [9], and Rodriguez *et al.* described higher temperature and an intensely yellow/red and bulging tympanic membrane in Sp-caused AOM [21]. These reports instigated similar studies by many AOM researchers of scores predicting AOM severity, as previously described.

Shaikh *et al.* constructed an AOM symptoms score called the "AOM severity of symptoms score" (AOM SOS Score) [22]. This score indicated the severity of 7 directly observable behaviors of the child with AOM: ear tugging, crying, fussiness, disturbed sleep, decreased play, decreased appetite and fever. The authors noted that children with Sp-caused AOM presented with higher scores.

These findings triggered other researchers to seek for symptoms indicating AOM severity, such as the AOM facies score by Friedman *et al.* [12]. This score, graded 7 facial expression of infants with AOM and tried to find the correlation of these grimaces to AOM severity. In this study, no correlation was found between facial scoring and Sp-caused AOM. A study by McCormick *et al.*(10) pooled parental grading of 5 items; fever (0 ≤38°C, 4 = 38-39°C, or 7 ≥39°C), ear ache (tugging) (0 = none, 4 = occasional or 7 = frequent), irritability (0 = none, 4 = occasional, or 7 = frequent), feeding (0 = feeds well, 4 = mild decrease in appetite or 7 = very poor appetite) and sleeping (0 = normal sleep, 4 = somewhat restless sleep or 7 = very poor sleep). The authors tried to prove a correlation between the symptoms score and bacterial pathogens of AOM, but a clear-cut correlation could not be demonstrated.

Because symptoms did not seem to suffice as indicators of AOM severity, Freidman *et al.* decided to add an important physical examination sign: assessment of the TM. They named their score the "otologic system-8" (OS-8) [12]. This score includes several stages of TM changes in the evolution of AOM: 0 = normal, or effusion without erythema, 1 = erythema only, no effusion, 2 = erythema, air fluid level, clear fluid, 3 = erythema, complete effusion, no opacification, 4 = erythema, opacification with air-fluid level or air bubble(s), no bulging, 5 = erythema, complete effusion, opacification and no bulging, 6 = erythema, bulging rounded doughnut appearance of the tympanic membrane and 7 = erythema, bulging, complete effusion and opacification with bulla formation. The authors concluded that, in the presence of erythema, complete effusion and opacification (grade 5 or above) physicians were more likely to diagnose and treat with antibiotics. Furthermore, physical examination rather than history had a major influence on AOM management decisions.

McCormick *et al.* [10] showed the relationship between the presence of a bulging TM and Sp-AOM. They concluded that a bulging TM was highly associated with the isolation of bacterial pathogens or bacterial/viral combinations, as compared with pure viral or negative cultures ($P = 0.01$). More so, they stated that the finding of a bulging TM predicted a bacterial AOM with a positive predictive value of 74% and a negative predictive value of 45%. Bulging TMs were also noted somewhat more often in ears infected with Sp.

To conclude, findings regarding the possible prediction of AOM severity or Sp-caused AOM are somewhat ambiguous; risk factors- do not differentiate, parental scoring systems- do not differentiate, facial expressions- do not differentiate, symptoms and signs scores- do not differentiate. Only otoscopic findings, such as TM bulging may indicate to a certain extent AOM severity or Sp-induced AOM.

**Laboratory findings and AOM severity**

A different, more pragmatic approach was to look for laboratory findings in all-caused, and more specifically Sp-caused AOM. The ability to rely on laboratory findings may be of interest and can be realistic for decision-making purposes, particularly in order to differentiate pneumococcal and non-pneumococcal AOM in an emergency-care setting.

In a study dating from the pre-PCV era, Polachek *et al* found significantly higher white blood cell (WBC) counts and absolute neutrophil count (ANC) in Sp-caused AOM cases, when compared to *Haemophilus influenza* positive or in culture-negative AOM cases [23]. Another finding was that high CRP levels were more frequently associated with AOM caused by a bacterial origin than viral origin.

In order to ascertain that these findings were also valid in the post-PCV era, Ovnat Tamir *et al.* [24] recently published a study examining the correlation between common laboratory findings and the causative agent(s) of AOM in a subset of young children presenting with 'severe' AOM episodes, in an era when PCVs have been gradually implemented in Israel. They found that WBC counts (and particularly ANCs) and C-reactive protein (CRP) levels were significantly elevated in pneumococcal versus non-pneumococcal AOM episodes. In the pneumococcal AOM group, WBC counts were higher in 'PCV-unimmunized' children, when

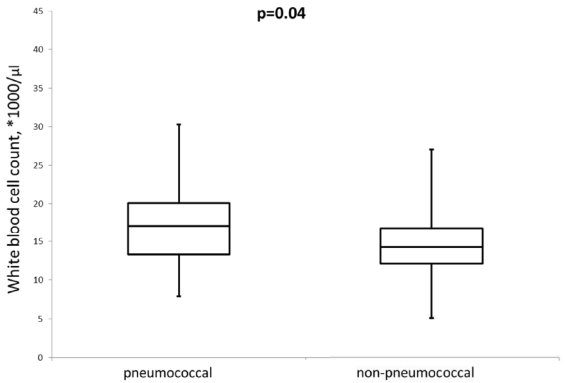
compared to 'PCV7/PCV13-immunized' children (**Figure 1**). Differences in CRP levels between the three patient groups presenting with pneumococcal AOM were slight and non-significant (**Figure 2**). The current results indicate that with the changing pathogens of AOM, relying on laboratory findings may become more complex and not reliable anymore (**Figure 3**).

**Conclusion**

Differentiating severe AOM or Sp-caused AOM may become more and more complex in the future. The need for research in this area remains enormous, due to the fact that AOM remains one of the most common pediatric infections.

**Figure 1**. Box plots showing WBC counts, according to gender.

(A) Males. Results are shown for 29/39 patients from the pneumococcal group and for 18/22 patients from the non-pneumococcal group who had blood counts.




(B) Females. Results are shown for 20/26 patients from the pneumococcal group and for 13/19 patients from the non-pneumococcal group who had blood counts.

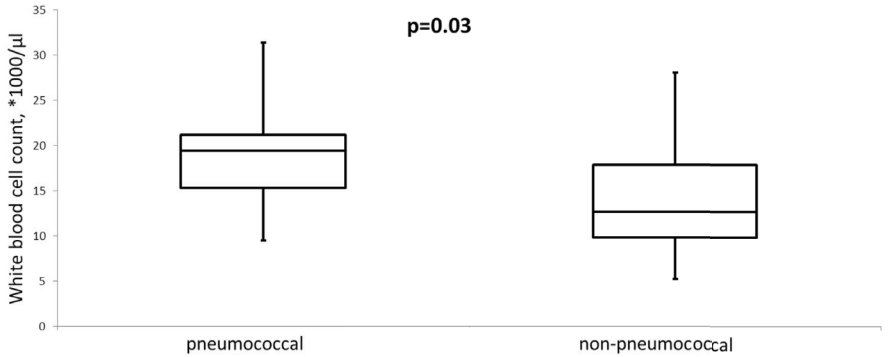
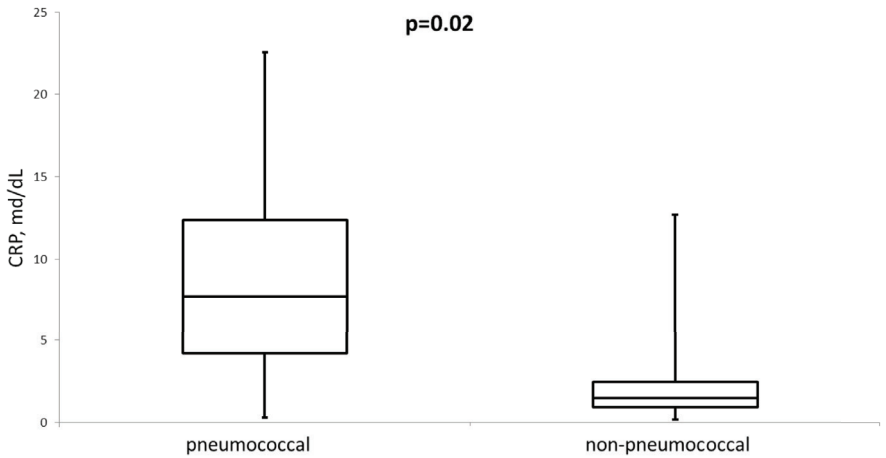


**Figure 2**: Box plots showing CRP levels, according to gender.

(A) Males. Results are shown for 27/39 patients from the pneumococcal group and for 14/22 patients from the non-pneumococcal group who had CRP levels.




(B) Females. Results are shown for 19/26 patients from the pneumococcal group and for 12/19 patients from the non-pneumococcal group who had CRP levels.

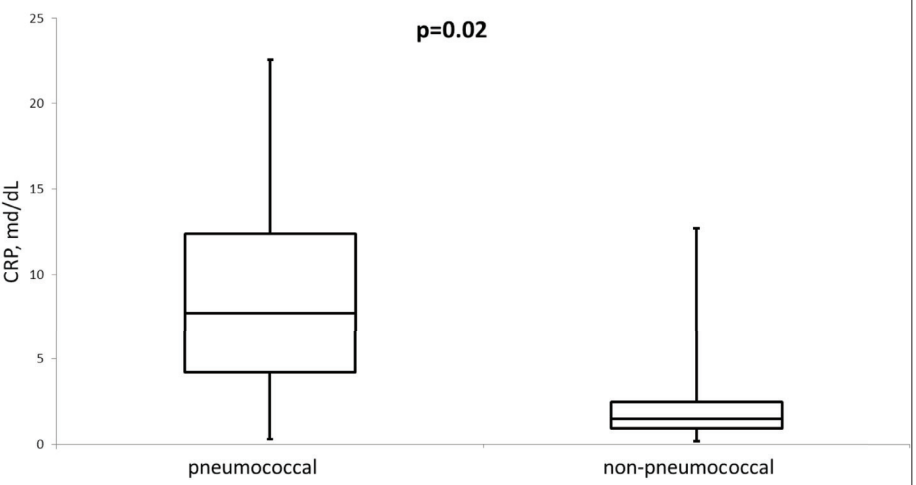
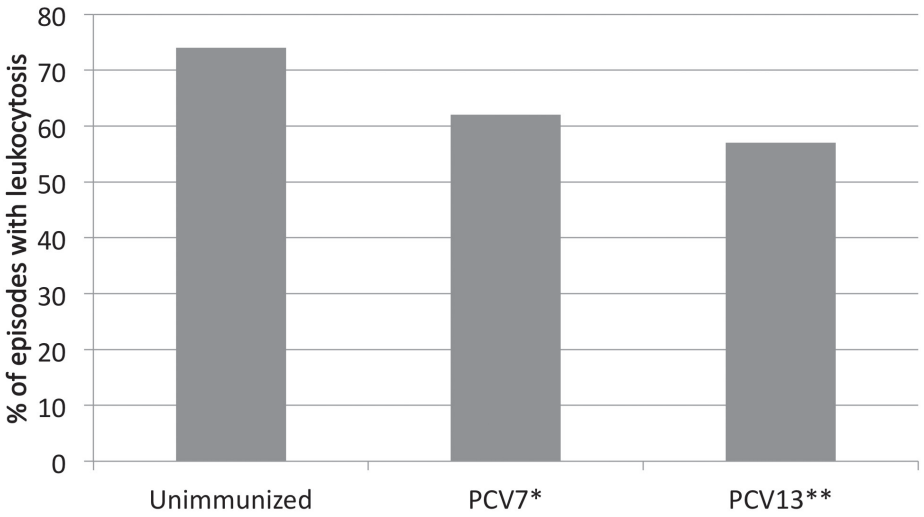
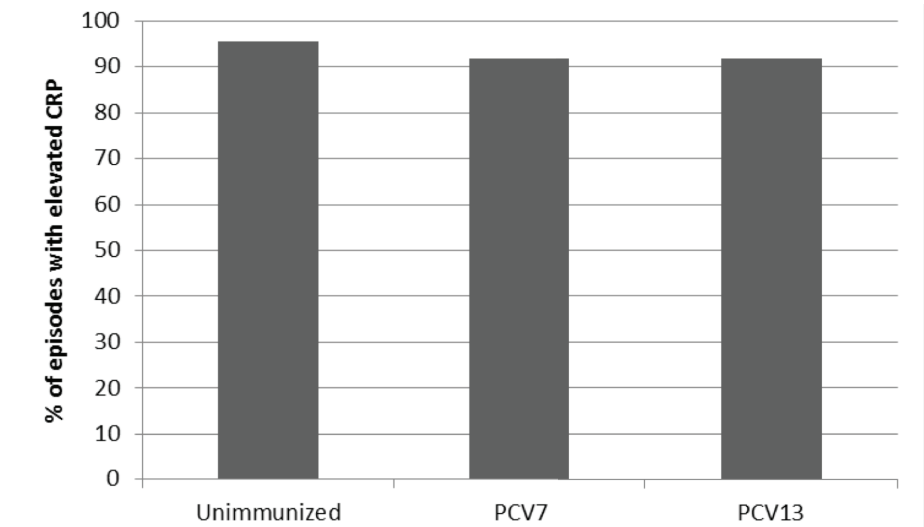


**Figure 3A.** Proportion of pneumococcal AOM episodes with leukocytosis, according to PCV status.




Results are shown for 22/30 patients of the unimmunized group, 15/22 of the PCV7 group and 12/13 patients of the PCV13 group who had blood counts.
*p=0.12 for PCV7 vs. unimmunized
**p=0.04 for PCV13 vs. unimmunized.

**Figure 3B**. Proportion of pneumococcal AOM episodes with elevated CRP, according to PCV status.




Results are shown for 22/30 patients of the unimmunized group, 12/22 of the PCV7 group and 12/13 patients of the PCV13 group who had CRP levels. The differences between the groups were insignificant.

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