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Journal

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Publication Date

DOI

Peer reviewed

Developing Consensus on Clinical Outcomes for Children with Mild Pneumonia: A Delphi Study

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Background: The absence of consensus for outcomes in pediatric antibiotic trials is a major barrier to research harmonization and clinical translation. We sought to develop expert consensus on study outcomes for clinical trials of children with mild community-acquired pneumonia (CAP).

Methods: Applying the Delphi method, a multispecialty expert panel ranked the importance of various components of clinical response and treatment failure outcomes in children with mild CAP for use in research. During Round 1, panelists suggested additional outcomes in open-ended responses that were added to subsequent rounds of consensus building. For Rounds 2 and 3, panelists were provided their own prior responses and summary statistics for each item in the previous round. The consensus was defined by >70% agreement.

Results: The expert panel determined that response to and failure of treatment should be addressed at a median of 3 days after initiation. Complete or substantial improvement in fever, work of breathing, dyspnea, tachypnea when afebrile, oral intake, and activity should be included as components of adequate clinical response outcomes. Clinical signs and symptoms including persistent or worsening fever, work of breathing, and reduced oral intake should be included in treatment failure outcomes. Interventions including receipt of parenteral fluids, supplemental oxygen, need for high-flow nasal cannula oxygen therapy, and change in prescription of antibiotics should also be considered in treatment failure outcomes.

Conclusions: Clinical response and treatment failure outcomes determined by the consensus of this multidisciplinary expert panel can be used for pediatric CAP studies to provide objective data translatable to clinical practice.

Key words. antibiotics; clinical trials; Delphi; outcomes; pneumonia.

INTRODUCTION

Community-acquired pneumonia (CAP) is the most frequent cause of death in young children worldwide [1, 2]. Although

most deaths from CAP occur in lower-income nations, CAP remains a significant cause of morbidity in the United States. The annual incidence of CAP requiring hospitalization in the United States is approximately 15.7 per 10,000 children [3], making it the second most common reason for pediatric hospitalization [4]. Fortunately, most CAP in children is mild and can be managed in outpatient settings [5].

Despite its prevalence and importance, there have been few clinical trials of therapeutics for children with CAP. There is also substantial variability in the outcomes assessed in observational studies and clinical trials of pediatric CAP. Commonly used outcomes are often non-specific, such as hospital length of stay or revisit rates, or occur in a very small proportion of

children, such as sepsis or death. In addition, no study that we are aware of considers the impact of either the degree of improvement or relative importance of a factor on the outcomes of symptom response and treatment failure. The need for objective outcome measures is highlighted as a critical area for future research by the Pediatric Infectious Diseases Society/Infectious Diseases Society of America national guideline for the management of pneumonia in children [1]. Yet, no consensus exists on ideal outcome measures for pediatric CAP. The absence of consensus for case definitions and outcomes in pediatric antibiotic clinical trials is a major barrier to harmonization in research and translation into clinical practice [6]. There is thus a critical need to gain consensus around CAP outcomes, both patient-centered and clinician-focused, for pediatric trials of CAP therapies.

To fill this important gap, we aimed to develop expert consensus around outcomes, including adequate symptom resolution and treatment failure, for use in clinical trials evaluating therapies for children with mild CAP. We chose to develop these outcomes for mild pneumonia, as not only is most pneumonia in children mild, but there is also great variability in outcomes definitions in outpatient pediatric pneumonia trials. Thus, there is a need to develop consistent definitions for use across studies for children with mild (i.e., outpatient) CAP.

METHODS

We conducted a three-round, electronic modified Delphi survey between February and April 2021 to gain consensus on the components of adequate clinical response and treatment failure outcomes in trials of young children with mild CAP, defined as being well enough to be managed as an outpatient. We selected young children as the focus of this work, as most mild CAP occurs in children younger than 6 years old and this work was part of a planning process for future antibiotic trials in younger children. This study was deemed exempt by the institutional review board at Ann and Robert H. Lurie Children's Hospital of Chicago.

Selection of Participants
Invited multidisciplinary panelists were clinical stakeholders in the outpatient management of children with CAP [7]. Panelists met predefined criteria, including relevant knowledge, experience, and willingness to participate [8]. Additional criteria for panelists included: (1) physicians with expertise in general/primary care pediatrics, general emergency medicine, pediatric emergency medicine, or pediatric infectious diseases; (2) in practice as a board-certified clinician for at least 5 years; and (3) specific expertise in lower respiratory tract infections, infectious diseases, antimicrobial stewardship, or clinical practice relevant to the management of children with CAP. Selection

intentionally ensured diversity of specialty, practice location, sex, and years in practice. Based on prior studies examining the stability of Delphi panel results, we set a threshold of 15 to 25 panelists to produce statistically reliable results [9].
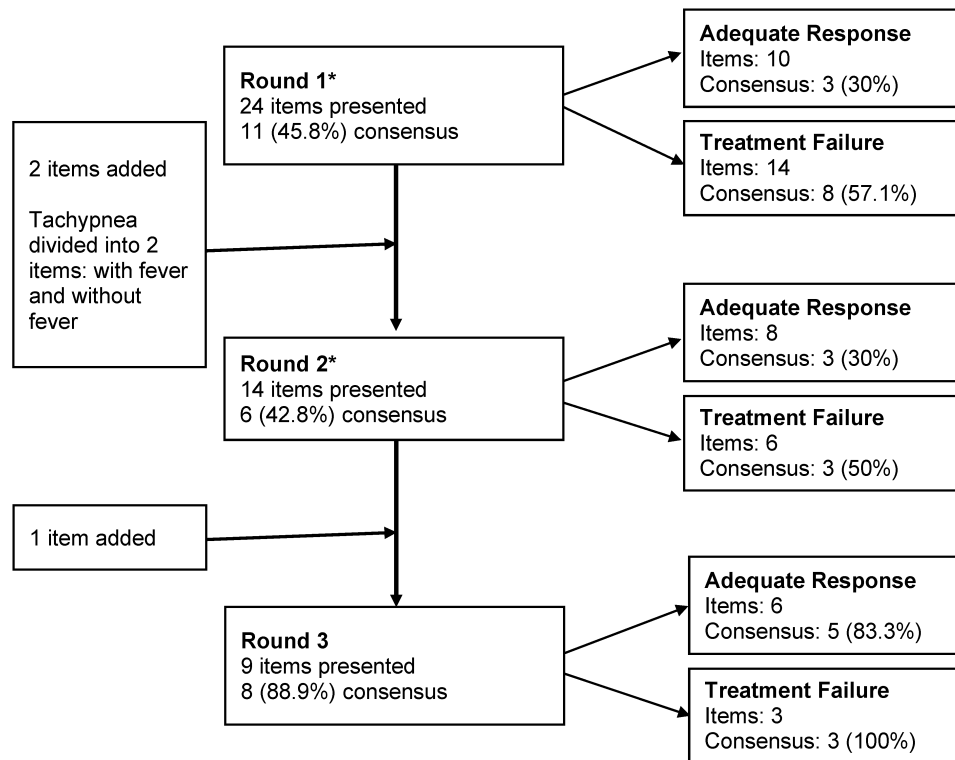
Delphi Survey
Electronic surveys were created in Qualtrics (Qualtrics; Provo, UT) for distribution to the panelists. The surveys were designed to be completed anonymously. Panelists did not know the identity of the other panelists throughout the entire Delphi process. Three rounds of surveys were planned. The first-round survey was developed based on a literature review and was pilot-tested and iteratively refined by several authors (T.A.F., N.K., J.G., R.R., M.G., and J.M.) prior to distribution to panelists. The survey did not include items that clearly would indicate response or treatment failure to most clinicians and researchers. For example, the survey did not ask whether the subsequent need for a chest drainage procedure after initial discharge should be considered a treatment failure, as this is widely recognized as a failure of initial treatment.

The survey consisted of features used to define adequate clinical response (9 items) and treatment failure (14 items) for use in clinical trials of young children with mild CAP, which was defined as being well enough to be managed as an outpatient. For each symptom or sign defining "adequate symptom response," panelists were asked to rank if the feature was not important to gauging treatment response, or if mild improvement, substantial improvement, or complete resolution from baseline presentation was necessary to be considered an "adequate" response. Panelists were then asked at how many days after initiation of treatment for mild CAP a patient would be considered to have "failed treatment," assuming full adherence to the treatment plan. Panelists ranked whether certain interventions or outcomes were (1) not important, (2) important but not critical, or (3) critical to include in a definition of treatment failure.

During Round 1, panelists could add items not included in the survey in open-ended responses. These items were then included in Round 2 of the Delphi survey. The second and third survey rounds were distributed after data analysis of prior rounds. Items that reached consensus were not presented during subsequent rounds. Rounds 2 and 3 included descriptive statistics for each item, including the overall distribution of panelist responses and their individual responses on the prior round, as feedback to the panelists to inform subsequent responses.

Statistical Analysis
Continuous variables were reported as median and interquartile ranges. Categorical variables were reported as percent agreement for each category. Consensus was defined as 70% or more of panelists agreeing on a given category during each round [10].

```
Round 1*
24 items presented
11 (45.8%) consensus

    → Adequate Response
      Items: 10
      Consensus: 3 (30%)

    → Treatment Failure
      Items: 14
      Consensus: 8 (57.1%)

2 items added

Tachypnea
divided into 2
items: with fever
and without
fever

Round 2*
14 items presented
6 (42.8%) consensus

    → Adequate Response
      Items: 8
      Consensus: 3 (30%)

    → Treatment Failure
      Items: 6
      Consensus: 3 (50%)

1 item added

Round 3
9 items presented
8 (88.9%) consensus

    → Adequate Response
      Items: 6
      Consensus: 5 (83.3%)

    → Treatment Failure
      Items: 3
      Consensus: 3 (100%)
```

*Days to measure treatment response and treatment failure only asked in Round 1

Figure 1. Delphi flow diagram (clinical response and treatment failure).

RESULTS

Invitations were sent to 22 potential panelists by email; three experts declined participation. Of the panelists agreeing to participate, one did not complete, and one partially completed, Round 1; they were not invited for subsequent rounds. Another panelist did not complete Round 2. Thus, 17 panelists completed Round 1 and 16 completed Rounds 2 and 3 (Supplemental Table 1). The flow of responses through the Delphi process is presented in Figure 1. Of the 24 items presented in Round 1, consensus was achieved for 45.8% of items and the average agreement was 68.4%. In Round 2, of 14 items presented, consensus was achieved for 42.8% and the average agreement was 69.5%. In Round 3, of 9 items presented, consensus was achieved for 88.9% and the average agreement was 79.5%.

Adequate Symptom Response

During Round 1, panelists responded that an outcome of "adequate symptom response" should be measured a median of 3 days (interquartile range [IQR] 2–5 days, mean [SD] 4.4 [1.7] days) after initiation of the study treatment to determine if a patient demonstrated clinical response. For adequate symptom response, nine items were considered in Round 1 and consensus was reached on three items (33.3%), including substantial improvement in fever and activity level, and complete resolution

of grunting. Sleep disturbance was added to Round 2 from open-ended comments provided during Round 1. In addition, rather than asking about tachypnea alone, as in Round 1, this item was split into two items, tachypnea with fever and tachypnea without fever, based on panel open-ended input during Round 1. Of eight items presented in Round 2, the consensus was reached for three (37.5%)—substantial improvement in dyspnea, tachypnea without fever, and oral intake. "Able to play" was an open-ended comment from Round 1 that was added as an outcome during Round 2. Of the six items presented during Round 3, consensus was reached on five (83.3%)— mild improvement in cough, tachypnea with fever, and sleep disturbance; and substantial improvement in nasal flaring and chest retractions. After considering a total of 12 items for adequate symptom response over the course of the Delphi process, consensus was reached on 11 (91.7%) (Table 1). Being "able to play" was the only item not to reach consensus during Round 3.

Treatment Failure

During Round 1, panelists responded that an outcome of "treatment failure" should be measured a median of 3 days (IQR 2–3 days, mean (SD) 2.9 (1.0) days) after initiation of the study treatment, including antibiotics or other study medications. Fourteen items were considered in Round 1 and consensus was reached on eight (57.1%). Decreased oral intake

Table 1.   Panel Consensus on Defining Adequate Symptom Response for Children with Mild Community-Acquired Pneumonia

	Degree of Improvement	Percent Agreement (Round Consensus Reached)
Adequate symptom response		
Fever	Substantial	75% (Round 1)
Cough	Mild	87.5% (Round 3)
Grunting	Complete resolution	75% (Round 1)
Nasal flaring	Substantial	100% (Round 3)
Chest retractions	Substantial	87.5% (Round 3)
Dyspnea	Substantial	100% (Round 2)
Oral intake	Substantial	75% (Round 2)
Activity level	Substantial	75% (Round 1)
Tachypnea with fever*	Mild	75% (Round 3)
Tachypnea without fever*	Substantial	75% (Round 2)
Sleep disturbance*	Mild	75% (Round 3)
Able to play**	-	No consensus reached

*Added Round 2.
**Added Round 3.

was added to Round 2 as an open-ended comment provided during Round 1. Of the six items presented in Round 2, consensus was reached for three (50%). Of the three items presented during Round 3, consensus was reached for all items (100%). Persistent or worsening fever, retractions, dyspnea, and decreased oral intake were deemed important symptoms to include as part of a treatment failure definition, while there was agreement that cough should not be included. After considering 14 items for treatment failure over the course of the Delphi process, consensus was reached on all (100%) (Table 2).

DISCUSSION

In this Delphi process, a multidisciplinary panel of experts reached consensus on most components of clinical response and treatment failure outcomes for clinical trials of children with mild CAP. The panel noted that appropriate response and failure of treatment should be addressed a median of 3 days after treatment initiation. Complete or substantial improvement in fever, nasal flaring, chest retractions, dyspnea, tachypnea without fever, oral intake, and activity should be included in outcomes of adequate clinical response. Persistent or worsening fever, dyspnea, retractions, and reduced oral intake should be included in treatment failure outcomes. The panel also defined interventions that are important or critical to include as part of a definition of treatment failure. We synthesized these results into summary outcomes that can be used for clinical trials of young children with mild CAP (Table 3).

Definitions of symptom response and treatment failure in pediatric CAP are varied, as is the decision to use clinical

Table 2.   Panel Consensus on Defining Treatment Failure for Children with Mild Community-Acquired Pneumonia

Treatment Failure	Degree of Improvement/Importance	Percent Agreement (Round Consensus Reached)
Symptoms		
Fever	Persistent or worsening	93.75% (Round 3)
Cough	Not important to include	75% (Round 3)
Retractions	Persistent or worsening	87.5% (Round 1)
Dyspnea	Persistent or worsening	93.8% (Round 1)
Decreased oral intake*	Persistent or worsening	75% (Round 3)
Interventions or new diagnoses		
Initiation of parenteral fluids	Important, not critical	82.4% (Round 1)
Initiation of supplemental oxygen	Critical	100% (Round 1)
New antibiotic started (any reason)	Important, not critical	70.6% (Round 1)
New antibiotic (for persistent or worsening pneumonia)	Important, not critical	75% (Round 2)
New broad-spectrum antibiotic (any reason)	Important, not critical	81.3% (Round 2)
New broad-spectrum antibiotic (for persistent or worsening pneumonia)	Critical	81.3% (Round 2)
New small pleural effusion	Important, not critical	70.6% (Round 1)
New moderate pleural effusion	Critical	82.4% (Round 1)
Need for high-flow nasal cannula	Critical	94.1% (Round 1)

*Added Round 2.

Table 3. Proposed Definitions of "Adequate Symptom Response" and "Treatment Failure" for Clinical Trials of Children with Mild Community-Acquired Pneumonia

Adequate clinical response	Substantial improvement of fever, work of breathing (nasal flaring, dyspnea, retractions), oral intake, and activity level within 3 days of treatment initiation
Treatment failure	1. Persistent or worsening fever, work of breathing (nasal flaring, dyspnea, retractions), or decreased oral intake by 3 days after treatment initiation.
	2. Initiation of parenteral fluids, supplemental oxygen, new antibiotics, or development of complicated pneumonia after treatment initiation within 3 days of treatment initiation.

Note: These proposed definitions were developed based on the consensus findings of the Delphi panel.

improvement versus treatment failure as a primary study outcome. An argument for the use of symptom resolution or clinical improvement is that more rapid improvement provides direct benefit to both the child and parent. On the other hand, using treatment failure focuses on potential harm [11]. A trial comparing 5–10 days of antibiotics for outpatient management of children with mild CAP used a novel outcome called desirability of outcome ranking (DOOR) [12]. DOOR is an ordinal ranking consisting of symptom resolution, adequate clinical response, and adverse events. In that trial, investigators defined "symptom resolution" as absence of fever, tachypnea, or moderate/severe cough. They defined "adequate clinical response" as absence of a visit to an emergency department or outpatient clinic or hospitalization for persistent or worsening pneumonia [12]. Patients were assigned a DOOR rank based on these three outcomes. One potential limitation of DOOR is that its components were derived by study investigators and, to our knowledge, have not been developed, validated, or refined by formal consensus methodology, a gap we sought to fill with our Delphi panel.

Another trial examining short- versus long-course antibiotics in children with CAP demonstrated the challenges of defining a clinical response outcome [13]. That trial initially defined "clinical cure" as improvement (including defervescence) within 4 days of treatment initiation, significant improvement in dyspnea/work of breathing, and no tachypnea by 14–21 days after the study visit, no more than 1 fever spike from days 4–21, and lack of requirement of additional antimicrobials or hospitalization for lower respiratory tract infection. During the trial, however, investigators recognized that participants were being classified as clinical failures that might not be considered as such during routine clinical care (e.g., children with two fever spikes but who were otherwise well). In contrast, our multidisciplinary panel agreed on aspects of response and treatment failure outcomes that can overcome some of these limitations and expand on some of these outcomes. By considering these outcomes in terms of the degree of improvement from baseline

presentation, the overall trajectory of a patient's course is considered, rather than failure because of an isolated fever spike, for example.

Treatment failure is frequently assessed in pediatric pneumonia trials. A placebo-controlled trial of antibiotics in children with fast-breathing pneumonia in Malawi defined treatment failure as any of the following occurring by day 4 after enrollment: persistent fever, severe respiratory distress, hypoxemia, WHO danger signs (stridor, fast breathing, chest wall indrawing, and labored breathing), missing two or more doses of study medication due to vomiting, change in antibiotics, hospitalization for pneumonia, prolonged hospitalization or readmission for pneumonia, or death [14]. A placebo-controlled trial in Pakistan defined treatment failure as death or WHO-defined danger signs or retraction of the lower chest wall, hospitalization, or if the patient's trial regimen was changed owing to new-onset infection or a serious adverse event [15]. In considering outcomes of clinical trials of antimicrobials in children with CAP, guidelines and commentaries note that rate of resolution of infection, vital sign changes, chest radiograph changes, appetite and activity, or return to school should be considered as endpoints; however, scoring systems for resolution of clinical symptoms have not been developed or validated for children with CAP [1]. The results from our Delphi panel help by providing expert consensus on the degree of improvement or importance of a factor to the outcomes of symptom response and treatment failure. In addition, stronger expert support can be seen by those factors that reached a consensus earlier (Rounds 1 and 2) in the process. Important future directions of this work include the incorporation of these components into a formal outcome that is rigorously evaluated.

The panel noted that adequate clinical response and treatment failure should both be evaluated a median of 3 days after study drug initiation. While there is general agreement in the literature that 3 days is likely a reasonable time period to evaluate treatment failure, disagreement exists about the best timing to evaluate clinical response. Studies in adults have found that resolution rates in treated versus untreated patients were maximal at days 3 and 4 after treatment initiation. However, many believe that a durable cure for infection measured at the completion of therapy (or later) is a more appropriate measure of clinical response rather than improvement at an earlier time point [16]. These recommendations, however, have been advocated in the setting of bacterial pneumonia; most mild pneumonias in children are viral. The natural course of typical mild viral illnesses includes improvement by 3–4 days after symptom onset; however, many patients will have lingering symptoms for 1–3 weeks. The symptoms that tend to linger are typically cough and congestion and are less likely to be factors selected by the panel which would largely be expected to be improving in most mild cases of viral pneumonia. There is likely value in incorporating both measures

of early improvement 3–4 days after therapy, as our panel noted, and a longer-term "test of cure" outcome at a time after therapy is completed into trials of children with mild CAP. Regarding the panel-derived outcomes, particularly treatment failure, it may be important to assess before 3 days or give participants clear instructions on contacting study personnel if clinical worsening occurs sooner. We anticipate that this will vary by study.

The Delphi method is subject to several important limitations. First, the output of a Delphi panel is only as robust as the statements evaluated during the process. While we offered participants ample opportunities to respond with open-ended statements and add to the statements offered, there may be other factors that were not captured by this panel. Second, although we rigorously designed this study adhering to the Delphi method [7], these recommendations still represent panelist opinion. We attempted to capture the perspective of all clinicians and investigators who would both treat children with mild CAP or be investigators in a trial of mild pediatric CAP. However, this may have been impacted by our overall small sample size limiting the number of each specialty represented. Third, we did not include auscultatory, laboratory, or imaging findings in our survey (except for the development of complicated pneumonia), as these have not been routinely used to determine clinical resolution or treatment failure in most prior trials. However, some of these may be useful in select cases to assess these outcomes. Finally, we recruited a modest number of panelists. However, a study using bootstrap data expansion compared actual results from 23 panelists to two computer-generated augmented bootstrapped samples of 1000 and 2000 and found similar results in the smaller sample to the bootstrapped larger sample. This suggests that a small expert panel in a well-defined knowledge area can provide effective and reliable results [9]. That said, our panel consisted of 16, and not 23, panelists, and therefore, this exact number of panelists has not been studied.

In conclusion, by applying Delphi consensus methods, our multidisciplinary panel reached agreement on components of the outcomes of adequate clinical response and treatment failure for studies of mild CAP in children. Our panel also had a good agreement on the average time to determine and define such outcomes. As these outcomes do not account for every possible scenario, we anticipate that they will be modified based on each individual trial's study questions and procedures. That said, these consensus outcomes can be used in subsequent studies to evaluate the benefits and harms of existing and novel treatments for pediatric CAP.

Articles Main Point

We determined consensus outcomes of clinical response and treatment failure outcomes using a multidisciplinary expert panel. These outcomes can be used for pediatric pneumonia studies to provide objective data translatable to clinical practice.

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