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LITERATURE REVIEW

# Factors Associated With Pneumonia Severity in Children: A Systematic Review

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Community-acquired pneumonia in children is associated with significant morbidity and mortality; however, data are limited in predicting which children will have negative outcomes, including clinical deterioration, severe disease, or development of complications. The Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) pediatric pneumonia guideline includes criteria that were modified from adult criteria and define pneumonia severity to assist with resource allocation and site-of-care decision-making. However, the PIDS/IDSA criteria have not been formally developed or validated in children. Definitions for mild, moderate, and severe pneumonia also vary across the literature, further complicating the development of standardized severity criteria. This systematic review summarizes (1) the current state of the evidence for defining and predicting pneumonia severity in children as well as (2) emerging evidence focused on risk stratification of children with pneumonia.

**Keywords:** children; pneumonia; risk stratification; severity.

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in children worldwide [1]. In the United States, CAP is one of the most frequent and costly reasons for childhood hospitalization [2, 3]. Despite its impact, significant variation exists in the diagnosis and management of children with pneumonia [4–6]. Although practice guidelines can assist with clinical decision making [1, 7, 8], no validated severity criteria exist for children with CAP. The objective of this systematic review is to summarize the current state of evidence for defining and predicting pneumonia severity in children.

## PNEUMONIA SEVERITY SCORES

Numerous severity scores have been developed in adults with CAP (Table 1) [9–14]. They have been shown to reduce hospitalizations and administration of broad-spectrum antibiotics [15, 16], but they predict other outcomes with varied success.

The World Health Organization (WHO) defines "pneumonia" in children as presence of cough or difficulty breathing associated with fast breathing or chest indrawing in children 2–59 months of age, whereas "severe pneumonia" is defined as pneumonia plus inability to drink, persistent vomiting, convulsions, lethargy, stridor, or severe malnutrition [1]. These criteria were developed for use in countries with limited resources, and they are highly sensitive at the cost of specificity.

In the developed world, pediatric CAP guidelines include severity criteria intended to assist site-of-care decision making. The British Thoracic Society (BTS) [8] and the Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) [7] criteria were developed by author consensus (Table 2) and have not been formally derived and validated in children. A recent study found that >50% of children who met PIDS/IDSA severity criteria were safely discharged home from the emergency department (ED) [17].

There are few severity scoring systems developed in children with CAP. A 2016, large-scale, multicenter, prospective cohort study developed a prediction model for severe outcomes (defined as death or need for mechanical ventilation or vasoactive medications) in children hospitalized with CAP [18]. Age extremes, vital signs, chest indrawing, and radiographic infiltrate pattern were the most important predictors. Given its derivation in hospitalized children, its applicability to the ED or clinic is currently unknown.

In a developing nation, Araya et al [19] developed a scoring system (based on age, comorbidities, hypoxemia, hypotension, bacteremia, multilobar/complicated pneumonia, kidney/liver failure, and acute respiratory distress syndrome) to predict mortality in children hospitalized with pneumonia. The application of this system in developed nations is limited.

## METHODS

We conducted a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [20].

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**Table 1. Summary of Existing Pneumonia Severity Scores[a]**

| Severity Score | Components | Area Under the Receiver Operator Characteristic Curve |
|---|---|---|
| PSI [10] | Age, Nursing Home, Comorbidities, AMS, Tachypnea, Hypotension, Hypo- or Hyperthermia, Tachycardia, pH <7.35, BUN ≥30, Na <130, Glucose ≥250, Hematocrit <30%, Partial pressure of arterial oxygen <60 mmHg, Pleural Effusion | 30-day Mortality: 0.70–0.89<br>CAP Complications: 0.58–0.85 |
| CURB-65 [11] | Confusion, Urea ≥7 mmol/L, Tachypnea, Hypotension and Age ≥65 | 30-day Mortality: 0.73–0.87<br>CAP Complications: 0.60–0.78 |
| IDSA/ATS 2007 [14] | Minor Criteria: Tachypnea, PaO2/FiO2 ≤250, Multilobar Infiltrates, Confusion, BUN ≥20, WBC ≤4000, Platelets ≤100 000, Hypothermia, Hypotension<br>Major Criteria: Invasive Mechanical Ventilation, Need for Vasopressors | 30-day Mortality: 0.63–0.67<br>CAP Complications: 0.85–0.88 |
| SMART-COP [9] | Hypotension, Multilobar Infiltrates, Albumin <3.5 g/dL, Tachypnea, Tachycardia, Confusion, Hypoxemia and Arterial pH <7.35 | 30-day Mortality: Not assessed<br>CAP Complications: 0.83–0.87 |
| SCAP [12] | Major Criteria: pH <7.30, Hypotension<br>Minor Criteria: Confusion, Urea >30 mg/dL, Tachypnea, Multilobar Infiltrates, Hypoxemia, Age ≥80 | 30-day Mortality: Not assessed<br>CAP Complications: 0.75–0.83 |
| Williams et al [18] (Pediatric) | Age[R,E], Sex[E], Race[E], Comorbidities[R], Household smoke exposure, Season, Symptom Duration, Vomiting/feeding refusal, Hypo/Hyperthermia[E], Tachypnea[R,E], Tachycardia[R,E], Hypotension[R,E], Hypoxemia[R,E], AMS[R], Chest Indrawing[R], Asymmetric breath sounds, Wheezing, White blood cell count[E], Infiltrate Pattern[R], Pleural Effusion[R] | Death or CAP Complications: 0.78–0.81 |
| Araya et al [19] (Pediatric) | Age, Comorbidities, Hypoxemia, Hypotension, Bacteremia, Multilobar/Complicated Pneumonia, Kidney/Liver Failure and Acute Respiratory Distress Syndrome | Death: 0.94 |

Abbreviations: AMS, altered mental status; CAP, community-acquired pneumonia; [E], components of electronic health record-based variable model; IDSA/ATS, Infectious Diseases Society of America/Amercan Thoracic Society; PSI, pneumonia severity index; [R], components of reduced variable model; SCAP, severe CAP.

[a]Table adapted from Pereira JM, Paiva JA, Rello J. Assessing severity of patients with community-acquired pneumonia. *Semin Respir Crit Care Med.* 2012;33:272. CAP complications defined as need for intensive care unit admission, need for mechanical ventilation, or need for vasopressor support.

### Literature Search

We searched PubMed, Embase, EBM Reviews, CINAHL, and SCOPUS in February 2018. We limited our search to English language articles in children over the past 20 years. We excluded studies in which a high percentage of subjects had wheezing or diarrhea, use of WHO-definitions of pneumonia without requiring focality on exam or chest x-ray confirmation, or if severe comorbidities (ie, human immunodeficiency virus [HIV] or malaria) affected generalizability. Our search strategy and results are listed in Figure 1. Included studies are listed in Table 3.

**Table 2. Summary of BTS and PIDS/IDSA Criteria for Severe Pneumonia**

| British Thoracic Society [8] | Pediatric Infectious Diseases Society/Infectious Diseases Society of America [7] |
|---|---|
| Temperature >38.5°C | Major Criteria: |
| Respiratory rate | Invasive mechanical ventilation |
| • >70 in infants | Fluid refractory shock |
| • >50 in older children | Acute need for noninvasive positive pressure ventilation |
| Moderate/severe recession in infants | Hypoxemia requiring $FiO_2$ at a higher concentration or flow feasible in general care area |
| Severe difficulty in breathing in children | Minor Criteria: |
| Not feeding in infants | Tachypnea for age: |
| Nasal flaring | • 0–2 months: respiratory rate >60 |
| Cyanosis | • 2–12 months: respiratory rate >50 |
| Apnea | • 1–5 years: respiratory rate >40 |
| Grunting | • >5 years: respiratory rate >20 |
| Tachycardia | Apnea |
| Signs of dehydration | Increased work of breathing |
| Capillary refill ≥2 seconds | $PaO_2/FiO_2$ <250 |
| | Multilobar infiltrates |
| | Pediatric Early Warning Score >6 |
| | Altered mental status |
| | Hypotension |
| | Pleural effusion |
| | Comorbid conditions |
| | Unexplained metabolic acidosis |

Abbreviations: BTS, British Thoracic Society; $FiO_2$, fraction of inspired oxygen; IDSA, Infectious Diseases Society of America; $PaO_2$, oxygen partial pressure; PIDS, Pediatric Infectious Diseases Society.

## CLINICAL FACTORS

### Hypoxemia

The PIDS/IDSA guideline recommends that children who require a fraction of inspired oxygen ($FiO_2$) of ≥0.50 to maintain an oxygen saturation of >92%, or those with an arterial oxygen partial pressure ($PaO_2$)/$FiO_2$ <250, should be admitted to the intensive care unit (ICU) or a unit with continuous cardiorespiratory monitoring [7]. Hypoxemia is also a component of the Pediatric Early Warning Score (PEWS), a validated general early warning score to predict need for ICU care in children [21]. Although the association with hypoxemia with severe outcomes is well recognized, exact thresholds for defining hypoxemia are variable (BTS <92%, PIDS/IDSA <90%) [7, 8].

Numerous studies in developing countries show a consistent association between hypoxemia and mortality in childhood pneumonia [19, 22–25]. In the developed world, supplemental oxygen requirement was the most significant determinant in predicting time to clinical stability in hospitalized children with CAP [26]. The PF ratio has also been shown to be the factor most strongly associated with severe outcomes [18].

### Age

The PIDS/IDSA guideline states that infants and young children are at highest risk for severe disease [7]. In the developed world, 1-year-olds have increased odds of severe disease compared with 2-year-olds [18], and infants are more likely to have pneumonia-specific readmissions (adjusted odds ratio [aOR], 1.36; 95%

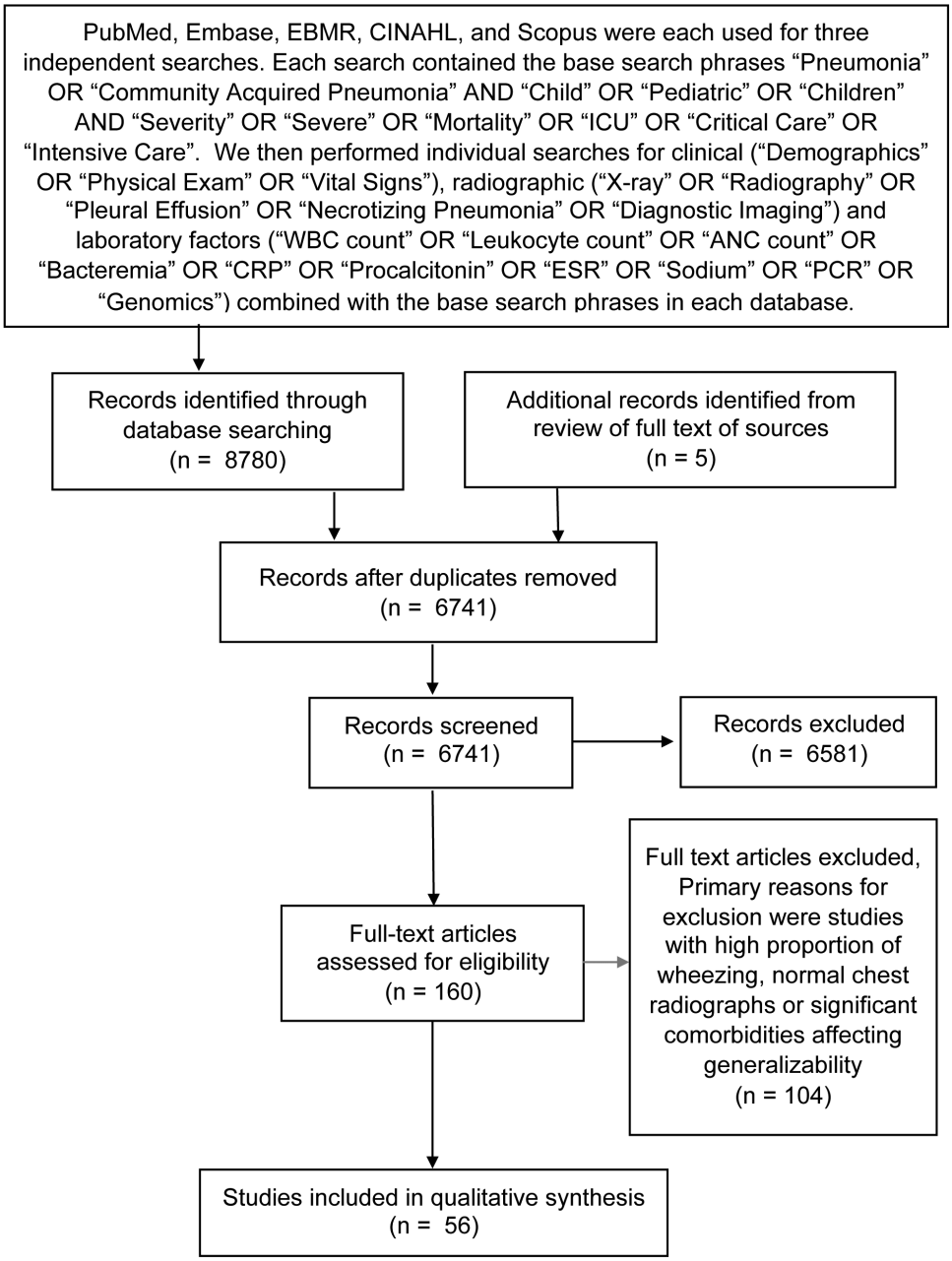


**Figure 1.** Results from literature search.

confidence interval [CI], 1.14–1.61) [27]. In children hospitalized with pneumonia in the developing world, age <6 months was the strongest factor associated with enteral treatment failure (aOR, 5.15; 95% CI, 2.94–9.02) among children 3–59 months [28], age <4 months was associated with mortality (relative risk [RR], 3.5; 95% CI, 3.0–4.2) among children <24 months [23], and age <6 months was associated with mortality (OR, 2.2; 95% CI, 1.1–4.2) among children <15 years [19].

#### Tachypnea

Tachypnea is included in the WHO definition, the BTS and PIDS/IDSA severity criteria, and in PEWS [21]. In the developing world, WHO-defined tachypnea-for-age is associated with mortality [19]. In the developed world, studies found tachypnea-for-age was not associated with severe disease in infants but showed increasing association as children got older (aOR = 0.99–1.53, depending on age) [18].

The use of tachypnea as a severity sign has important limitations, including association with fever, dehydration, and acidosis [29]; physician impression of tachypnea has only fair interrater reliability (kappa 0.42) [30]; and age-based respiratory rate thresholds vary, including conflicting definitions from WHO [1], Pediatric Advanced Life Support [31], and Advanced Pediatric Life Support [32] (Table 4). Recent studies

**Table 3. Studies Included in Systematic Review**

| Study, Year | Region, Setting | Study Design | Age | n | Limitations and Potential Biases |
|---|---|---|---|---|---|
| Florin et al [17], 2018 | Single center, US, ED | Retrospective | 3 months–18 years old | 518 | Single center, use of ICD coding may have introduced misclassification bias |
| Williams et al [18], 2016 | Multicenter, US, inpatient | Prospective | <18 years old | 2319 | Definition of mild, moderate, and severe pneumonia based on author opinion, limited to hospitalized patients |
| Araya et al [19], 2016 | Single center, Paraguay, inpatient | Retrospective | <15 years old | 860 | Single center, retrospective, exclusively inpatient, significant rates of comorbidities |
| Duke et al [22], 2001 | Single center, Papua New Guinea, inpatient | Prospective | 28 days–5 years old | 703 | High rates of malnourished children, lack of invasive interventions available, elevation of 1600 m, use of WHO severity criteria |
| Djelantik et al [23], 2003 | Single center, Indonesia, inpatient | Retrospective | <24 months | 4531 | Possible selection bias, high rates of malnourishment, lack of invasive interventions, use of WHO severity criteria |
| Nantanda et al [24], 2008 | Single Center, US, ICU and General Wards | Retrospective | 2–59 months | 157 | Retrospective, single center, developing nation with high rates of malnourishment limiting generalizability, used WHO-definitions but required either CXR confirmation or excluded children with wheezing with negative CXR |
| Reed et al [25], 2012 | Single center, South Africa, inpatient | Retrospective | <24 months | 4148 | Limited to young infants, high rates of malnourished children |
| Wolf et al [26], 2015 | Single center, US, inpatient | Post hoc analysis of prospective population-based study | <18 years old | 336 | Single-site analysis of a multicenter study introducing possible selection bias |
| Neuman et al [27], 2012 | Large-scale Multicenter, US, inpatient | Retrospective | <18 years old | 82 566 | Children may have been readmitted at nonincluded facility, admission decisions can show great variation between institutions |
| Mamtani et al [28], 2009 | Multicenter, 8 developing countries, inpatient | Post hoc analysis of previous RCT | 3–59 months | 889 | Developing countries, use of WHO severity criteria, treatment dose of amoxicillin 45 mg/kg per day, did not comment on percentage of children with wheezing (bronchiolitis, reactive airway disease) or HIV status |
| Tiewsoh et al [34], 2009 | Single center, India, inpatient | Prospective | 2–60 months | 200 | Use of WHO severity criteria, high rates of malnourishment and overcrowding, high proportion of children had wheezing, possible recall bias |
| Basnet et al [35], 2006 | Single center, Nepal, outpatient/ED | Retrospective | 2–60 months | 250 | Use of WHO severity criteria, developing country, 1300+m above sea level likely influencing degree of hypoxemia |
| Kuti et al [36], 2013 | Single center, Gambia, inpatient | Prospective | 2–59 months | 420 | Used WHO definitions for pneumonia diagnosis and severity, and did not require CXR confirmation (however, did exclude children with wheezing or cough for >2 weeks), single center and developing nation limiting generalizability |
| Demers et al [37], 2000 | Single center, Central African Republic, inpatient | Prospective | <5 years old | 395 | Developing nation with limited resources and high rates of malnourishment, possible observer bias as "alteration of general status" based on physician opinion and not validated scoring system, possible selection bias (significant proportion of patients absconded due to military uncertainty during the study, and not all patients had CXR performed) |
| Chisti et al [38], 2013 | Single center, Bangladesh, ICU | Retrospective | <5 years old | 140 | Developing nation, high rates of malnourishment, retrospective, limited to ICU |
| Hsu et al [41], 2015 | Multicenter, Taiwan, ICU | Retrospective | <18 years old | 12 577 | Retrospective, dependent upon ICD-9 coding, only ICU setting limiting generalizability |
| Hirsch et al [42], 2016 | Multicenter, US, inpatient | Retrospective | Children | 12 097 | Retrospective, used administrative database relying on ICD coding, all sites are tertiary care referral centers limiting generalizability |
| Champatiray et al [43], 2017 | Single center, India, inpatient | Prospective | 2 months– 5 years old | 141 | Single center, exclusively inpatient, use of WHO definitions, CXR were obtained on admission, but study does not mention whether cases were radiographically confirmed, study did not comment on rate of wheezing, history of present illness/social history subject to recall bias, much longer LOS (8–9 days) and much higher mortality rate (22%) than US studies |
| Muszynski et al [44], 2011 | Single Center, US, ICU | Retrospective | <18 years old | 23 | Retrospective, single center, small n, limited to ICU setting |
| Grafakou et al [48], 2004 | Single center, Greece, inpatient | Retrospective | 1–14 years old | 167 | Single center and only inpatient limiting generalizability, markers for severity were duration of fever and LOS |
| Kin et al [49], 2009 | Single center, Brazil, inpatient | Prospective | <5 years old | 113 | Single center, excluded bilateral pulmonary infiltrates that could present with more severe disease, severity criteria were WHO and BTS guidelines that are not validated, CXR interpreted by single radiologist |

**Table 3. Continued**

| Study, Year | Region, Setting | Study Design | Age | n | Limitations and Potential Biases |
|---|---|---|---|---|---|
| Patria et al [50], 2013 | Single center, Italy, ED | Retrospective | <14 years old | 335 | Single center, not all children with CAP during the study period had CXR performed introducing possible selection bias for more severe disease, CXR interpreted by single radiologist, higher than expected mean age (7.5 years old) |
| Mclain et al [51], 2014 | Multicenter, US, inpatient | Retrospective | 60 days–18 years old | 406 | Retrospective, CXR interpreted by single radiologist, potential selection bias as this was a sampling of a larger cohort |
| Ferrero et al [52], 2010 | Multicenter, Developing nations, inpatient | Prospective | 3–59 months | 2536 | Exclusively inpatient, use of WHO severity criteria, patients not vaccinated against pneumococcus significantly limiting generalizability, each CXR interpreted by 1 reviewer (possible interobserver bias) |
| Tapisiz et al [53], 2011 | Single center, Turkey, inpatient | Retrospective | <18 years old | 501 | Single center, retrospective, pre- pneumococcal and *Haemophilus* vaccination era in this region |
| Erlichman et al [56], 2017 | Multicenter, Jerusalem, inpatient | Retrospective | <18 years old | 144 | Retrospective, demographics limit generalizability |
| Langley et al [57], 2008 | Multicenter, Canada, inpatient | Retrospective | <18 years old | 251 | Retrospective, reliant upon chart review and ICD-coding, did not require specific WBC cutoff in pleural fluid to verify diagnosis of empyema |
| Goldbart et al [58], 2009 | Single center, Israel, inpatient | Retrospective | ≤8 years old | 112 | Retrospective, single center, and patients not vaccinated against pneumococcus significantly limiting generalizability, each CXR interpreted by 1 reviewer (possible interobserver bias) |
| Sawicki et al [61], 2008 | Single center, US, inpatient | Retrospective | Children | 80 | Single-center and retrospective design limit generalizability |
| Bender et al [62], 2008 | Single center, US, inpatient | Retrospective | <18 years old | 33 | Small n, single-center and retrospective design limit generalizability |
| Krenke et al [63], 2015 | Single center, Poland, inpatient | Retrospective | 1 months–18 years old | 32 | Small n, single-center and retrospective design limit generalizability |
| Donnelly et al [64], 1998 | Single center, US, inpatient | Retrospective | 6 months–16 years old | 17 | Very small n, single center, retrospective |
| Hacimustafaoglu et al [65], 2004 | Singe center, Turkey, inpatient | Prospective | 6 months–14 years old | 108 | Single center, each radiographic study interpreted by 1 reviewer (possible interobserver bias) |
| Hsiesh et al [66], 2011 | Single center, Taiwan, inpatient | Retrospective | <18 years old | 112 | Retrospective, single center, relatively few number of cases with BPF (18) |
| Hsiesh et al [67], 2015 | Multicenter, Taiwan, inpatient | Prospective | <18 years old | 94 | All cases limited to 1 region, images were not independently reviewed by 2 pediatric radiologists |
| Chen et al [70], 2017 | Single center, Taiwan, inpatient | Retrospective | 6 months–18 years old | 142 | Single center, retrospective, exclusively inpatient, not all patients during study had an ultrasound performed introducing possible selection bias, intrinsic limitation of ultrasound is that quality of images are operator-dependent (significant number of cases were excluded due to suboptimal images) |
| Lai et al [71], 2015 | Single center, Taiwan, inpatient | Retrospective | Children | 236 | Retrospective, single center, potential selection bias as children who had lung ultrasound were likely to have more severe pneumonia, ultrasound inherently is operator-dependent |
| Williams et al [72], 2015 | Multicenter, US, inpatient | Retrospective | <18 years old | 153 | Sampling from larger cohort that only included patients that had CRP and WBC performed thus introducing possible selection bias, retrospective |
| Don et al [74], 2009 | Single center, Italy, ED | Prospective | Children | 100 | Used hospital admission (institutional and provider differences can play a role) and alveolar infiltrate (vs interstitial) as markers for severity, single center |
| Prat et al [75], 2003 | Single center, Spain, ED | Prospective | 6 months–10 years old | 85 | Primarily studied PCT, ESR, and WBC's ability to predict etiology of CAP; however, secondary analyses revealed no association between WBC and bacteremic patients, which may indicate a more severe disease course, limitations include a relatively small n at a single center limiting generalizability |
| Wu et al [76], 2015 | Single center, China, inpatient | Retrospective | Children | 865 | Use of WHO definition and severity criteria that are not specific, single center, no mention of exclusion criteria, no mention of how many patients had CXR and what the results of those potential imaging studies may have been, no mention of additional outcomes of cases (ie, mortality, ICU admission, invasive interventions) |

**Table 3. Continued**

| Study, Year | Region, Setting | Study Design | Age | n | Limitations and Potential Biases |
|---|---|---|---|---|---|
| Agnello et al [78], 2015 | Single center, Italy, inpatient | Retrospective | 1–14 years old | 119 | Single center, excluded patients who were hospitalized for more than 48 hours introducing selection bias against more severe cases, clinical markers for severity were hypoxemia ($SpO_2$ <92%), dyspnea and tachycardia but not more severe markers or outcomes |
| Stockmann et al [79], 2017 | Multicenter, US, inpatient | Post hoc analysis of prospective study | <18 years old | 532 | Possible selection bias as only those with residual serum available for analysis were included (patients in the ICU were more likely to have residual serum), median time during admission PCT obtained was 1 day, thus limiting applicability to risk stratification on initial presentation |
| Yadav et al [80], 2015 | Single center, India, inpatient | Prospective | 2 months–5 years old | 50 | Single center, small n |
| Korppi et al [81], 2003 | Multicenter, Finland, Primary Care | Retrospective | ≤15 years old | 190 | Retrospective, serum samples run for PCT over 15 years after they were collected, pre-pneumococcal and *Haemophilus* vaccination era, performed in 1 region of Finland limiting generalizability |
| Singhi et al [82], 1992 | Single center, India, inpatient | Prospective | Children | 264 | Single-center study in a developing nation during the pre-routine vaccination era significantly limiting generalizability, LOS much longer than average LOSs in current studies in the developed world |
| Wrotek et al [83], 2013 | Single center, Poland, inpatient | Retrospective | <18 years old | 312 | Significant number of patients did not have sodium measured introducing possible selection bias, retrospective, single center, severity assessment based on clinical factors and inflammatory markers but did not evaluate for more severe outcomes, average hospitalization length (8–9 days), significantly longer than other current studies in the developed world |
| Don et al [84], 2008 | Single center, Italy, ED | Prospective | Children | 108 | Small percentage of patients did not have sodium samples introducing possible selection bias, single center, severity assessment based on clinical factors and inflammatory markers but did not evaluate for more severe outcomes |
| Wang et al [85], 2013 | Single center, Taiwan, inpatient | Retrospective | <18 years old | 84 | Single center, retrospective, pre- pneumococcal and *Haemophilus* vaccination era |
| Shah et al [86], 2011 | Multicenter, US, ED | Retrospective | ≤18 years old | 291 | Few number of bacteremic patients (6) limits statistical power of assessment of severity |
| Neuman et al [88], 2017 | Multicenter, US, ED | Retrospective | 3 months–18 years old | 2568 | Retrospective, wide variation between sites in rates of obtaining blood cultures, which introduces possible selection bias, primary objective of study was to evaluate rate of bacteremia in hospitalized children with CAP and determine susceptibility of pathogens to standard care, evaluation of +blood culture impact on severity came via rates of +cultures in complicated vs noncomplicated CAP and did not evaluate for other outcomes |
| Myers at al [90], 2013 | Multicenter, US, inpatient | Retrospective | 60 days–18 years old | 369 | Retrospective, inpatient study limiting generalizability, evaluated severity based on hypoxemia, LOS, ICU admission, and complicated pneumonia including respiratory failure but no mention of assessment on mortality |
| Banerjee et al [91], 2011 | Multicenter, North America, inpatient | Retrospective survey | Children | 37 | Retrospective survey of pediatric infectious disease physicians thus potential for reporting bias with potential preference to report more severe cases |
| Muñoz et al [93], 2011 | Single center, Spain, inpatient | Prospective | <18 years old | 206 | Single center, evaluated severity by LOS and ICU admission but not by other clinical factors or more severe outcomes |
| Shen et al [94], 2011 | Single center, Taiwan, inpatient | Retrospective | Children | 119 | Single center, retrospective, only pneumococcal and exclusively inpatient limiting generalizability, urinary antigen tests may have detected colonization and not acute infection in some cases |
| Pettigrew et al [95], 2016 | Single center, US, inpatient | Retrospective | 6 months to <18 years old | 363 | Single center, retrospective, exclusively inpatient, approximately 50% of children had asthma/reactive airway disease, ethnic distribution not representative of general population, 20% had received antibiotics before sputum collection, limited generalizability |

Abbreviations: BPF, bronchopleural fistulas; BTS, British Thoracic Society; CAP, community-acquired pneumonia; CRP, C-reactive protein; CXR, chest radiographs; ED, emergency department; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; ICU, intensive care unit; LOS, length of stay; PCR, polymerase chain reaction; PCT, procalcitonin; RCT, randomized clinical trial; $SpO_2$, blood oxygen saturation; US, United States; WBC, white blood cells; WHO, World Health Organization.

**Table 4. Respiratory Rate Cutoffs to Define Age-Specific Tachypnea**

| Source | Respiratory Rate Thresholds Defining Tachypnea-for-Age |
|---|---|
| WHO [1] | 0–2 months: >60 |
| | 2–12 months: >50 |
| | 1–5 years: >40 |
| | Older than 5 years: >20 |
| PALS [31] | Infant: >53 |
| | Toddler: >37 |
| | Preschooler: >28 |
| | School-aged child: >25 |
| | Adolescent: >20 |
| APLS [32] | 0–3 months: >50 |
| | 3–6 months: >45 |
| | 6–18 months: >40 |
| | 18–24 months: >35 |
| | 2–8 years: >30 |
| | 8–12 years: >25 |
| | Older than 12 years: >24 |
| Bonafide et al [33][a] | 0–3 months: >62 |
| | 3–6 months: >58 |
| | 6–9 months: >54 |
| | 9–12 months: >51 |
| | 12–18 months: >48 |
| | 18–24 months: >45 |
| | 2–3 years: >42 |
| | 3–4 years: >40 |
| | 4–6 years: >37 |
| | 6–8 years: >35 |
| | 8–12 years: >31 |
| | 12–15 years: >28 |
| | 15–18 years: >26 |

Abbreviations: APLS, Advanced Pediatric Life Support; PALS, Pediatric Advanced Life Support; WHO, World Health Organization.
[a]95th percentile-for-age cutoffs used for study by Bonafide et al [38].

suggest thresholds could be broken down into smaller groupings, because respiratory rate shows significant variation based on age [33].

#### Dyspnea

Examination findings associated with dyspnea include accessory muscle use, retractions, nasal flaring, and grunting. Williams et al [18] found that chest indrawing was associated with severe outcomes (aOR, 2.12; 95% CI, 1.62–2.78). Reed et al [25] found that chest indrawing was an independent predictor of mortality in HIV-negative children <24 months old hospitalized with lower respiratory tract infections (LRTIs) in South Africa (aOR, 4.6; 95% CI, 2.2–9.4). In children hospitalized with WHO-defined severe or very severe pneumonia in a developing nation, head bobbing was associated with mortality (RR, 8.3; 95% CI, 2.71–12.77) and mechanical ventilation (RR, 4.7; 95% CI, 1.50–6.36) [34]. Grunting is associated with hypoxemia [35, 36] and can suggest impending respiratory failure [7]. Retractions have fairly strong interrater reliability (kappa 0.62) among children with suspected CAP; however, nasal flaring, head bobbing, and grunting have only fair reliability (kappa 0.49, 0.25, and 0.33, respectively) [30].

#### Tachycardia

Tachycardia may be due to multiple factors including pain, anxiety/fear, fever, dehydration, and underlying disease processes. Tachycardia is included in PEWS [21] and as a severity marker in the BTS guideline [8]. The PIDS/IDSA guideline recommends admission to the ICU or continuous cardiopulmonary monitoring for sustained tachycardia [7].

Data specifically investigating tachycardia in pediatric pneumonia severity are limited. Although Williams et al [18] found that tachycardia was one of the factors associated with severe pneumonia (aOR = 1.59–2.90, depending on age), Reed et al [25] found that admission heart rate >170 was not associated with mortality (OR, 0.9; 95% CI, 0.3–3.2) in HIV-negative infants <24 months old.

#### Altered Mental Status

Altered mental status (AMS) in children with CAP is often multifactorial, and it can be due to hypercarbia, hypoxemia, severe dehydration, sepsis, or a combination. It is included in the WHO and PIDS/IDSA guidelines [1, 7]. Altered mental status was one of the factors most associated with severe outcomes in the Williams et al [18] study (aOR, 11.9; 95% CI, 6.41–22.23). Araya et al [19] found that a Glasgow Coma Score <13 was the factor most associated with mortality in children admitted with pneumonia (OR, 324; 95% CI, 131–805). In the ED, AMS was highly specific for hospital admission in children with pneumonia (LR+ 10.6) [17]. In children admitted with WHO-defined severe or very severe pneumonia, AMS was associated with mortality (RR, 5.44; 95% CI, 1.34–17.56) [34], and in children admitted with WHO-defined pneumonia in a developing nation, "alteration of general status" based on clinician impression was also associated with mortality (aOR, 3.23; 95% CI, 1.17–8.94) [37].

#### Temperature

Resolution of fever is a common sign of appropriate therapy and is often used to monitor clinical improvement; however, data are limited to suggest an association between height or duration of fever and pneumonia severity. The BTS guideline uses >38.5°C as a marker for severe pneumonia [8]. The PIDS/IDSA and WHO guidelines do not include fever in their severity criteria [1, 7]. Multiple studies in developing nations have found no association between degree of fever and pneumonia severity in children [22, 23, 25]. Hypothermia may be more indicative of severe disease, as Williams et al [18] found that temperature >39°C (aOR, 0.50; 95% CI, 0.39–0.65) was a protective factor against severe outcomes, whereas hypothermia (<35°C) was associated with severity (aOR, 2.0; 95% CI, 1.54–2.59).

#### Dehydration and Decreased Perfusion

In developing countries, clinical dehydration in malnourished children with radiographically confirmed pneumonia admitted to the ICU was associated with death (OR, 9.48; 95% CI, 2.42–37.19) [38]. Delayed capillary refill is one sign that dehydration has progressed to decreased perfusion. It is included in the BTS guideline (≥2 seconds) [8] and in PEWS [21]. Although widely used, the interrater reliability of capillary refill in suspected CAP is fair to poor (kappa 0.18) [30] and is highly variable in assessing dehydration (kappa 0.15–0.64) [39].

#### Hypotension

Age-specific hypotension is the defining factor of uncompensated septic shock [40]. Data examining hypotension specifically in pediatric pneumonia is limited and conflicting. Williams et al [18] found that systolic blood pressure <5th percentile-for-age was not associated with severe outcomes (aOR, 0.95–1.15). In developing nations, Chisti et al [38] found no association between hypotension and CAP severity in children; however, Araya et al [19] found a significant association between mean arterial pressure >2 standard deviation below mean-for-age and mortality in children hospitalized with pneumonia (OR, 48.7; 95% CI, 24.8–95.6).

#### Comorbidities

Araya et al [19] found that significant comorbidities (malnutrition, HIV, congenital heart disease [CHD], asthma, and Down syndrome) were associated with mortality (OR, 4.9–6.2). A retrospective study of children in the ICU with pneumonia found that cerebral palsy, epilepsy, and CHD were associated with mortality (OR, 1.49–2.37), whereas asthma was protective (OR, 0.17; 95% CI, 0.09–0.31) [41]. In a multicenter retrospective study comparing children hospitalized with aspiration pneumonia versus CAP, Hirsch et al [42] found that children with aspiration pneumonia had longer hospital length of stay (LOS) and were more likely to receive ICU care.

#### Duration of Symptoms/Time to Correct Antibiotic Therapy

Champatiray et al [43] found that in Indian children hospitalized with WHO-defined severe/very severe pneumonia, delayed presentation was associated with mortality, although the mortality rate in the study was high overall (22%). Muszynski et al [44] found that in children with pneumonia requiring invasive mechanical ventilation, time to correct antibiotic selection based on bacterial cultures was independently associated with duration of mechanical ventilation, hospital, and ICU LOS.

## RADIOGRAPHIC FACTORS

Despite the widespread use of chest radiographs (CXR), challenges limit their accuracy and utility [45, 46], and clinical factors such as hydration status, degree of atelectasis, and time of presentation can influence interpretation [47]. International single-center studies suggest that various anatomic locations are associated with CAP severity in children (left lung [48], upper lobes [49], bilateral multifocal, and right hilum [50]). These studies evaluated severity based on LOS, duration of fever, dyspnea, tachypnea, and hydration status and did not consider more severe markers [51]. More recently, studies in developing and developed nations (including well powered prospective multicenter studies) have shown multilobar infiltrates are associated with severe outcomes including ICU admission, mechanical ventilation, vasoactive medications, and death [18, 19, 51].

In a recent multicenter cohort, pleural effusions of any size were associated with longer LOS (aOR, 2.6; 95% CI, 1.9–3.6) and duration of supplemental oxygen (aOR, 3.0; 95% CI, 1.4–6.5). Moderate or large effusions were associated with ICU admission (aOR, 3.2; 95% CI, 1.1–8.9) and mechanical ventilation (aOR, 14.8; 95% CI, 9.8–22.4) [51]. In a large multicenter study of children unvaccinated against Streptococcus *pneumoniae* hospitalized with WHO-defined severe pneumonia, Ferrero et al [52] found that pleural effusions were associated with pneumococcal bacteremia (OR, 3.1; 95% CI, 1.23–7.98). In children hospitalized with pneumonia, pleural effusions were the factors most associated with empiric parenteral ampicillin/sulbactam treatment failure (aOR, 5.74; 95% CI, 2.17–15.15) [53]. Complex loculated effusions contribute to treatment failure with conservative measures leading to increased LOS and need for surgical interventions [54, 55].

Empyema is also associated with severity including prolonged hospitalizations, bacteremia, and need for ICU admission, but not mortality [56, 57]. Goldbart et al [58] found that empyema was associated with LOS, ICU admission, and mechanical ventilation compared with children with nonpurulent effusions.

Necrotizing pneumonia is an increasingly recognized complication of CAP, defined by parenchymal liquefaction and necrosis, later replaced by air or fluid-filled cavities. Lung necrosis and abscesses are generally a result of bacterial pathogens, particularly *S pneumoniae* and Staphylococcus *aureus*, the latter of which is associated with a more severe disease course [59, 60]. Retrospective studies suggest that necrotizing pneumonia in children is associated with prolonged hospital stays, ICU admission, and surgical interventions, but not with mortality [56, 61–65]. Necrosis can extend through pleura leading to bronchopleural fistulas (BPF), which are associated with duration of fever, LOS, and mechanical ventilation when compared with culture-proven pneumococcal pneumonia without BPF [66, 67]. Pneumothoraces in children admitted with pneumonia are also associated with mortality (OR, 15; 95% CI, 2.9–76.6) [19].

Emerging evidence suggests that lung ultrasound is highly sensitive and specific for diagnosing pneumonia in children compared with CXR [68, 69]. Evidence of multifocal disease and fluid bronchograms on transthoracic ultrasound are associated

with severity [70]. Lai et al [71] found that degree of impaired perfusion on ultrasound is associated with severity of necrosis and need for resection.

## LABORATORY MARKERS

### Complete Blood Count

Studies have consistently shown that leukocytosis alone is a poor predictor of pneumonia etiology and severity [7, 18, 19, 72–76]; however, Araya et al [19] found that leukopenia (<4000) was associated with mortality (OR, 6.5; 95% CI, 2.7–15.6). The PIDS/IDSA guideline recommends, with low-quality evidence, that a complete blood count should only be performed in severe CAP [7] to evaluate for severe complications such as hemolytic-uremic syndrome (HUS).

### Inflammatory Markers

C-reactive protein (CRP) is an acute phase reactant that is associated with disease severity in bacterial infections in children [77]; however, studies have not shown substantial associations between CRP and CAP severity. A single-center cross-sectional study found that elevated CRP was not associated with hypoxemia, dyspnea, or tachycardia [78]. Another retrospective observational study of children admitted with CAP found that admission CRP was minimally associated with LOS and duration of fever (adjusted ratio of means 1.03 and 1.08, respectively) [72]. In children admitted with WHO-defined pneumonia, CRP was not associated with WHO severity criteria (OR, 1.01; 95% CI, 0.99–1.02) [76]. Reed et al [25] found that admission CRP was not associated with mortality in young children hospitalized with LRTIs.

Procalcitonin is a precursor of calcitonin that can increase in bacterial infections and inflammatory states. A multicenter, prospective study found increasing levels of procalcitonin were associated with ICU admission and empyema requiring drainage, and values <0.25 ng/mL were associated with decreased risk of ICU admission [79]. An Indian study found that elevation in admission procalcitonin in radiographically confirmed and WHO-defined severe or very severe pneumonia was associated with increased LOS and pneumonia complications [80]. In a prospective study of children diagnosed with CAP in the ED, Don et al [74] found that elevated procalcitonin was associated with hospitalization, whereas a cross-sectional study of hospitalized children found no association with markers for severity including tachycardia, hypoxemia, and dyspnea [78]. A primary care study found that procalcitonin was not associated with hospitalization in children with radiographically confirmed pneumonia [81]. These conflicting studies are limited by heterogenous populations, study settings, and varied outcomes.

### Electrolytes

Several studies suggest that hyponatremia may be associated with CAP severity in children, although limitations prevent definitive conclusions. In a small-scale, single-center Indian study, hyponatremia was associated with LOS, complications, and mortality, although LOS and mortality rates were high overall [82]. More recently, 2 European studies (a retrospective study of children hospitalized with CAP [83] and a prospective ED-based study [84]) found that hyponatremia was associated with hospitalization, LOS, inflammatory markers, and degree of fever but not with respiratory rate, tachycardia, capillary refill, or defervescence.

### Acidosis

Araya et al [19] found that $HCO_3^-$ <15 was associated with mortality (OR, 26.7; 95% CI, 13–54), and Wang et al [85] found that metabolic acidosis was independently associated with mortality in children hospitalized with pneumonia (aOR, 8.5; 95% CI, 2.82–25.6).

### Bacteremia

In the developed world, bacteremia in childhood pneumonia is uncommon, with rates <1% for outpatients, 2.5% for hospitalized children, and 13% in complicated pneumonia [7, 86–88]. Although blood cultures upon admission are recommended by the PIDS/IDSA guideline, the majority of organisms isolated from blood cultures in children with pneumonia were sensitive to guideline-recommended therapy (ie, penicillin) and rarely changed management [86, 88]. Bacteremia in childhood pneumonia has been associated with hypoxemia, LOS, and complications including effusions and empyema; however, data are limited for more severe measures [86, 89, 90].

### Concern for Hemolytic-Uremic Syndrome

A 2011 survey of pediatric infectious disease physicians found that cases of *S pneumoniae*-associated HUS (diagnosed by microangiopathic hemolytic anemia, renal injury, and platelets <150 000/mL) were associated with severe outcomes including ICU admission, invasive procedures/mechanical ventilation, and dialysis [91].

### Molecular Diagnostics/Genomics

Molecular diagnostic tools are likely to improve severity classification in pediatric CAP. An association has been shown between pneumococcal load and pneumonia severity in adults [92]. In children, plasma pneumococcal load is associated with prolonged hospital stays (aOR, 3.53; 95% CI, 1.43–8.70) [93], and pleural pneumococcal load is associated with worsening necrosis including progression to BPF [67]. Urinary antigen tests have shown promise, and Shen et al [94] found that time to positivity and intensity of band reactions may correlate with pneumococcal CAP severity based on dyspnea, hypoxemia, bacteremia, LOS, and ICU admission. In addition, sputum microbiota profiles using 16S ribosomal ribonucleic acid may

influence pneumonia severity, likely due to complex interactions between bacteria and a child's immune response [95].

## FUTURE DIRECTIONS

This systematic review highlights the current evidence regarding the factors that influence pneumonia severity in children. The current evidence suggests that hypoxemia, AMS, age <3–6 months, dyspnea, multilobar infiltrates, and moderate/large pleural effusions are the factors most predictive of pneumonia severity in children. The development and validation of pediatric pneumonia severity scoring systems for use in settings where site-of-care decisions are made have the potential to improve risk stratification.

Emerging technologies and molecular diagnostics will likely play an increasing role in severity assessment. Quantitative pneumococcal load and pneumococcal urinary antigen tests have shown promise in severity assessment in children [67, 93, 94], although pneumococcal pneumonia represents only one cause of CAP [96]. Gene expression profiling and other -omics approaches will provide new insights into CAP etiology and severity [97]. In nonpneumococcal cases, quantitative urinary metabolites have shown the potential to assess for mortality risk, although further research is still needed [98]. As the use of both rapid viral testing and polymerase chain reaction have become more common, viral coinfections have shown an association with CAP severity in children and may play a role in risk stratification [99, 100]. Assessing for impaired perfusion on lung ultrasound has shown promise in predicting pneumonia complications (necrosis) and may play a larger role in severity assessment going forward [71]. The development of a validated pneumonia severity scoring system across outpatient, ED, and inpatient settings, in combination with emerging technologies, will improve risk stratification and resource allocation.

### Notes

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