RESPIRATORY INFECTIONS

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Mortality Predictive Scores for Community-Acquired Pneumonia in Children

Antonio Arbo [1,2,3] · Dolores Lovera [2,3] · Celia Martínez-Cuellar [2,3]

Abstract

Purpose of Review The use of severity score for the staging of pneumonias has emerged as a necessity for the physician caring for this disease. Although there are several established prognostic scoring systems for community-acquired pneumonia in adults, the availability for children are scarce.

Recent Findings Recently, scoring system for risk stratification of children with pneumonia were developed in low- and middle-income countries. They use clinical variables that represent known risk factors for severe outcomes of respiratory illness in children, such as hypoxemia, chest indrawing, refusal to feed, malnutrition, age, and stage of HIV disease among others factors. Although they showed good discriminating power and are very useful in low-resource settings, the characteristics of the patients, the local epidemiology of concurrent diseases, the social conditions, and the facilities of the hospitals make them not applicable to developed countries. A new prognostic scale for estimating mortality based on the modified PIRO scale used in adults with pneumonia can be useful for developed countries.

Summary Although several scoring systems for the estimation of mortality in childhood CAP were developed in the last years, most of them come from developing countries and the results are not applicable to patients with pneumonia in developed countries. Prospective studies applying scores adapted to the reality of the developed countries are needed.

Keywords Community-acquired pneumonia · Children · Scoring system · Mortality

Introduction

Respiratory infections represent one of the main causes of mortality in pediatrics [1]. It is estimated that one million of the six million deaths that occur annually in children under 5 years of age are caused by respiratory infections [2]. Severe pneumonias are responsible for > 75% of these deaths, with two thirds occurring in infants [3]. Around 96% of episodes of pneumonia, and 99% of deaths from pneumonia, take place in low- and middle-income countries (LMICs) [4, 5•].

Pneumonia is an acute disease of respiratory system that compromises the lower respiratory tract and that can affect the

lobes or the pulmonary interstitium, translating into consolidation in chest radiography. This article discusses community-acquired pneumonia (CAP). Pneumonia is considered acquired in the community when it occurs in a patient who has not been admitted to a hospital in the last 14 days [6].

CAP can be caused by bacterial, viral, or parasitic infections. In some cases, a similar clinical picture may be caused by noninfectious agents [6]. Most severe cases of pneumonia are caused by bacteria, of which the most important are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (in infants not vaccinated with the anti-Hib vaccine), and *Staphylococcus aureus* [7]. It is estimated that 10–60% of cases of pneumonia in children can be severe enough to require hospitalization, and in some cases hospitalization in intensive care units (ICU) [8•].

Global Burden of Pneumonia

Of the 156 million of cases of pneumonia that occur annually around the world, it is estimated that 7–13% might progress to severe disease and warrant hospital admission. In 2015, the

This article is part of the Topical Collection on *Respiratory Infections*

✉ Antonio Arbo
antonioarbo@hotmail.com

1 Department of Pediatric, Instituto de Medicina Tropical, Avda. Venezuela y Florida, Asunción, Paraguay

2 Institute of Tropical Medicine, Asunción, Paraguay

3 National University of Asuncion, San Lorenzo, Paraguay

WHO estimated that CAP accounted for 920,136 deaths in children of all ages and 16% of deaths in children younger than 5 years of age globally [2]. The majority of these deaths were in the LMICs of Southeast Asia and Africa [2], and less in Latin America. Studies from these countries show that only 60% of child caregivers seek appropriate care for suspected pneumonia, and proper antibiotic treatment is given only in about one third of pneumonia cases [9].

In developed countries, such as the USA, pneumonia is the most common serious infection in children, accounting for 1–4% of all pediatric emergency department (ED) visits [10]. Although most children are treated as outpatients, the proportion of children presenting to the ED with pneumonia who are then hospitalized varies, ranging from 19 to 69% [8, 11–13]. This makes pneumonia one of the most important causes of hospitalization among children in developed countries, with medical costs in the USA estimated at almost $1 billion in 2009 [14]. Annual pneumonia incidence rates in < 5-year-olds across developed countries are between 34 and 40 per 1000 child-years, with the highest rates among children under 5 years of age [15] decreasing to 11–16 episodes/1000 children and year in children from 5 to 14 years of age [16•]. Despite this high morbidity, mortality from CAP in previously healthy children in developed countries it is very low, unlike adults, in which mortality for hospitalized patients could be more higher (up to 14%) [17, 18].

A different reality is observed in LMICs. Although the incidence rates of pneumonia in children less than 5 years of age varied greatly between studies, the reported incidence in this age group in the Western Pacific region is 110 per 1000 person-years [19•], being this figure in Bangladesh of 510 episodes per 1000 child-year [20]. In Latin America and the Caribbean, more than 80,000 children aged under 5 years die every year secondary to lower respiratory tract infections, being the incidence of an intermedium level if compared to developed countries [21, 22].

Although hospital admission is a common outcome in developed countries in children with CAP, requirement of ICU care, although not rare, is less frequent. There are challenges in interpreting the incidence of ICU requirement in CAP cases probably related to differences in the denominator used. While some use only cases of pneumonia with radiographic documentation of consolidation for the calculation of cases that require hospitalization in the ICU, others use all cases of suspected pneumonia seen in the emergency department. If only radiographic pneumonia is considered, the hospitalization percentage can be as high as 21% [16•]. Florin TA et al. [19•] report an ICU admission rate of 5% among pneumonia cases diagnosed in the emergency department and 11% in those already hospitalized. Berg AS [23] in Norway reports an ICU admission rate of 3% in CAP cases. However, CAP cases appear to be more severe in developing countries. In our institution, of 860 cases of hospitalized pneumonia between 2004 and 2013, 12% required ICU care [24•].

Risk Factors for Mortality in Pneumonia

Although CAP mortality in previously healthy children is rare in developed countries (≤ 0.6), globally the mortality is higher (2.3–6.1%) [25•, 26]. A different situation is what happens with children with pneumonia hospitalized in the ICU. Despite advances in critical care management and antimicrobial therapy, morbidity and mortality in patients with pneumonia that require ICU admission remain high. However, the mortality is clearly different between developed countries and low-resource countries. While CAP mortality in children hospitalized in ICU in these latter countries ranges from 10 to 80% [27–29], in developed countries, the mortality in this subgroup of patients, although higher compared to the total cases of pneumonia, is not more than 1% [16•].

Several characteristics have been identified as risk factors for increased mortality among children diagnosed with CAP. Some of these factors are related to the child (e.g., age, nutritional status, underlying diseases), others to the disease (e.g., pneumonia caused by S. aureus), others may be related to the environment, to the socioeconomic status of the family, or to the health system (availability of ICU) [9, 30, 31].

The risk factors associated to mortality are different in cases occurring in developed countries vs. countries with less resources. In very poor regions, female sex, age < 2 months, inadequate breastfeeding practices, prematurity, severe malnutrition, chronic disease comorbidity with conditions such as HIV/AIDS, and a previous episode of acute lower respiratory infections are known risk factors to increase the severity of pneumonia [32–37]. Also, comorbidity with malaria, diarrhea, or measles increase the chance of acquiring severe pneumonia and/or dying from it [9]. All of these risk factors are seen in developed countries, but the incidence is much smaller. In a recent study conducted at three children's hospitals in Memphis, TN, Nashville, TN, and Salt Lake City, in the USA, the presence of altered mental status, chest indrawing, and multilobar or nonlobar (e.g., interstitial) infiltrates were identified as risk factors for severe pneumonia [8•].

The severity of pneumonia and need for ICU admission may be defined in part by the etiology. One of the main determinants of the prognosis of pneumonia and, therefore, mortality is the etiological agent. Different microorganisms (mainly bacteria and viruses and less frequently fungi and parasites) can be a cause of acute pneumonia acquired in the community. However, in the vast majority of cases, three bacterial agents are responsible for most of the severe cases of CAP: S. pneumoniae, H. influenzae type b, and S. aureus [16•, 38]. In some studies, S. pyogenes and gram-negative enteric bacteria are also described [7, 16•, 38, 39•]. With the widespread introduction of the anti-Hib vaccine in the 1980s, and the pneumococcal vaccine from the 2000s, cases of CAP by these microorganisms have decreased. Data from the Pediatric Multicenter Pneumococcal Surveillance Study Group in the

USA show a substantial reduction in the rate of hospitalization for pneumococcal pneumonia after the introduction of the PCV13 vaccine (from 53.6 to 23.3 per 100,000 admissions) [40]. Similar observations were reported in Brazil and Finland, where the introduction of the 10-valent pneumococcal conjugate vaccine (PCV10) was associated with a 13.1–25.4% reduction of clinical and X-ray confirmed pneumonia in Brazil [41] and 23% among hospital-treated primary pneumonia in Finland [42]. However, severe pneumonia due to strains of pneumococcus not included in the vaccine, as well as those caused by *S. aureus*, currently are emerging as the main cause of severe pneumonias. In the Cincinnati series, 30% of children with pneumococcal pneumonia had moderate or severe pneumonia, whereas 83% of those with *S. aureus* and 75% with *S. pyogenes* had moderate or severe pneumonia [19•]. In two retrospective case series of pediatric patients, CA-MRSA pneumonia has been shown to have a high incidence of necrotizing pneumonia, a need for ICU care, and associated high mortality [43, 44].

Even though *Mycoplasma pneumoniae*, *Chlamidophila pneumonaie* (important causes of disease in preschool and school-age children), and *C. trachomatis* (in newborns and infants) are important and frequent etiological agents of pneumonia, they are usually severe in only a few cases [45, 46]. Viruses are the most common etiological agents of pneumonia, especially in children under age 5 [16•], and the great majority of cases are mild to moderate in the immunocompetent host. Moreover, viral and bacterial coinfections can be detected in > 20% of children with pneumonia [47]. Viral-bacterial coinfection, however, can worsen the prognosis of pneumonia [48–50]. In a retrospective review of children admitted to a pediatric tertiary care center with invasive pneumococcal infection, those with concurrently positive viral studies (influenza, rhinovirus, adenovirus, RSV), were admitted to pediatric ICU more frequently and found to have longer pediatric ICU stays [50]. Further, viral pneumonias, even without bacterial coinfections, may cause severe pneumonia, requiring ICU admission, particularly influenza (H1N1 strain and lately, the H3N2 strain), RSV, or adenovirus [51, 52].

Family conditions, mainly socioeconomic status and education, may predispose to a greater severity of pneumonia; since in these cases, there may be a delay in seeking medical care or there may be poor compliance with medical prescriptions which may allow for the progression of the disease [34]. The non-availability of hospitals with an ICU is a deficiency in many parts of the world. In cases of pneumonia with respiratory insufficiency, the absence of intensive care support will undoubtedly impact mortality.

Staging Pneumonia Severity

Several criteria have been proposed to define severe CAP. The use of severity score for the staging of pneumonias has emerged as a necessity for the physician caring for this disease in order to differentiate between patients who can be safely managed at home and those who require hospitalization. However, most of the information on this topic comes from studies of pneumonia in adults [53•, 54, 55–63]. In Table 1 are shown the components of the main scoring systems that can be applied to adult population with CAP. In general, they include demographic variables, physical findings, and laboratory data. Each of these tools has advantages, and limitations, and have been extensively studied and repeatedly validated. In general, the PSI and CURB-65 (and its modified form A-DROP) systems were designed to predict CAP mortality; however, they are less effective to predict intensive care requirement as compared to Smart-COP system.

Although it does not represent a score, the American Thorax Society has established criteria that, according to its importance, has divided them into major and minor criteria in order to define patient severity [64]. The presence of one of the major criteria (invasive mechanical ventilation or septic shock with need for vasopressors) or the presence of three of the minor criteria would indicate a need for hospitalization in the intensive care unit. Examples of minor criteria include respiratory rate ≥ 30 breaths/min; a PaO2/FiO2 ratio ≤ 250, multilobar infiltrates; confusion/disorientation; uremia (BUN level, ≥ 20 mg/dL); leukopenia (WBC count, < 4000 cells/mm^3); thrombocytopenia (platelet count, < 100,000 cells/mm^3); hypothermia (core temperature, < 36 °C); and hypotension requiring aggressive fluid resuscitation among others. Validation studies show that the criteria of the IDSA/ATS criteria (over other scores such as CURB-65) are better at identifying patients who require mechanical ventilation, vasopressor support, or admission to the ICU [65].

In children, the information is more limited. Children with CAP may present with a range of symptoms and signs such as fever, cough, tachypnea, difficulty in breathing, wheeze, headache, abdominal pain, and chest pain. However, the spectrum of severity of CAP can vary from mild to severe cases. A global assessment of clinical severity and risk factors is crucial in identifying the child likely to require hospital admission or care at ICU level. Features of severe disease in an infant include tachypnea for level of fever, increase in respiratory rate (> 60 for age 0–2 months, > 50 for 2–12 months, > 40 for 1–5 years, and > 20 for age > 5 years); dyspnea; retractions (suprasternal, intercostal, or subcostal); grunting; nasal flaring; apnea; altered mental status; and saturation of oxygen < 92% (pulse oximetry measurement) on room air [66].

For the British Thoracic Society key features that suggest a child requiring transfer to an ICU include failure to maintain oxygen saturation > 92% with a fractional inspired oxygen of > 0.6; shock; rising respiratory and pulse rate with clinical evidence of respiratory distress and exhaustion, with or without a raised arterial carbon dioxide level; and recurrent apnea or slow irregular breathing [66]. The Pediatric Infectious

Table 1   Components of CURB-65, PSI, and Smart-COP scoring system for prognostic of severity of CAP in adults

PSI system	CURB-65 system	A-DROP system	Smart-COP system
Age	Confusion	Age - ≥ 70 years in males - ≥ 75 years in females	Systolic blood pressure - < 90 mmHg
Nursing home	BUN >2 0 mg/dL	BUN ≥ 21 mg/dL or dehydration	Multilobar infiltrates
Presence of comorbidity	Heart rate ≥ 125 beats/min	Hypoxemia - SpO2 $\leq 93\%$ or PaO2 < 60 mmHg	Serum bilirubin level - < 3.5 g/dl
Vital signs: - Mental disorder - RR ≥ 30 breaths/min - Systolic BP < 90 mmHg - Temperature < 35 or ≥ 40 °C - HR ≥ 125 beats/min	Confusion (new onset)	Confusion	Respiratory rate - ≥ 25 (age ≤ 50) - ≥ 30 (age > 50)
Laboratory findings - BUN ≥ 30 mg/dL - Na < 130 mmol/L - Glucose ≥ 250 mg/dL - Htc < 30%	Age ≥ 65 years	Systolic blood pressure - ≤ 90 mmHg	Heart rate ≥ 125 beats/min
Oxygenation - pH < 7.35, 30 - SpO2 < 90%, 10 - PaO2 < 60 mmHg			Confusion (new onset)
Radiology - Pleural fluid			Hypoxemia - SpO2 $\leq 93\%$ or PaO2 < 70 mmHg or PaO2/FiO2 < 333 (age ≤ 50) - SpO2 $\leq 90\%$ or PaO2 < 60 mmHg or PaO2/FiO2 < 250 (age > 50)

Diseases Society and the Infectious Diseases Society of America recommend that a child should be admitted to an ICU if the child requires invasive ventilation via a nonpermanent artificial airway (e.g., endotracheal tube) or noninvasive positive pressure ventilation, if the child has impending respiratory failure, has sustained tachycardia, inadequate blood pressure, or a need for pharmacologic support of blood pressure or perfusion, if the pulse oximetry measurement is < 92% on inspired oxygen of $\geq$ 50% or if the child has altered mental status, whether due to hypercarbia or hypoxemia as a result of pneumonia [67]. Unlike the experience in adults, scoring systems to identify the severity of children with pneumonia are scarce and they come mainly from studies in underdeveloped countries. Due to the characteristics of the population of the countries in which the scoring systems were developed (generally poor socioeconomic conditions, frequency of comorbidities different to that observed in developed countries), coupled with the difficulty in accessing health care, late consultation, and scarce infrastructure of hospitals (e.g., ICU availability); these scores can hardly be very applicable to developed countries.

Three scoring systems were developed in South Africa (the respiratory index of severity in children or RISC score) [68]; Kenya (the modified respiratory index of severity in children or mRISC) [69•]; and Malawi (RISC-

Malawi) [70•] respectively. All of these score systems were developed to identify children at greater risk of death from respiratory illness. The RISC score uses a simple set of clinical variables that represent known risk factors for severe outcomes of respiratory illness in children, including hypoxemia, chest indrawing, refusal to feed, malnutrition, age, and stage of HIV disease factors to discriminate between young children with varying risks of death from lower respiratory tract infections (LRTI) [68]. A number of points were assigned to each of the risk factors (Table 2). The RISC scores for children ranged up to 7 points for HIV-infected children and 6 points for non-infected children. When applying this scoring system to 4148 cases of LRTI hospitalizations (including 1502 HIV-infected children, 36%), a direct relationship was observed between the score and the mortality. Thus, the model showed good discrimination (c-statistic = 0.776 for HIV-infected and 0.923 for non-infected children) and calibration (p value for goodness-of-fit = 0.95 for HIV-infected and 0.87 for non-infected children).

The mRISC scoring system was assessed in 5366 children under age five who were hospitalized with a respiratory illness in a government referral hospital in western Kenya, an area endemic for malaria [69•]. This point-based scoring system assigned points to each predictive variable associated with mortality (Table 3). The positive

Table 2 Components of respiratory index of severity in children (RISC) scoring system

HIV non-infected children		
Severity of respiratory signs on physical exam:		
1. Oxygen saturation	If O2 ≤ 90%	3 points
2. Does the child have chest indrawing?	Indrawing	2 points
3. Does the child have wheezing?	Wheezing:	− 2 points
4. Has the child been refusing feedings?	Refusal to feed	1 point
Growth standards:		
5. Weight for age z-score	$z \leq -3$	2 points
	$-2 \leq z \leq -3$	1 point
	$z > 2 - 2$	0 points
	Maximum points	6
HIV-infected children		
1. Oxygen saturation	If O2 ≤ 90%	3 points
2. Does the child have chest indrawing?	Indrawing	2 points
3. Does the child have wheezing?	Wheezing:	− 2 points
4. Has the child been refusing feedings?	Refusal to feed	1 point
5. Age	0–2 months	2 points
	3–12 months	1 points
	> 12 months	0 points
6. HIV clinical classification	C	2 points
	A/B	1 points
	N	0 points
	Maximum points	7

In this scoring system, an increase in the score is directly related to an increase in the probability of death. Adapted from Reed C et al. Development of the respiratory index of severity in children (RISC) score among young children with respiratory infections in South Africa. PLoS ONE 2012; 7:e27793

predictive value (PPV) for mortality increased with increasing mRISC score from 6% at a cut-off score of 0 to 80% for patients with a cut-off score of 6. Of the 176 children who were admitted with an mRISC score of 3 or

more, 70 (40%) died in the hospital; similarly, 31/55 (56%) and 4/5 (80%) of those who were admitted with mRISC scores of ≥ 4 and ≥ 6 respectively, died in the hospital. The mRISC score showed good discriminating power, as measured by the c-statistic of 0.852 in the original dataset and good calibration (goodness-of-fit test $p = 0.4705$).

Researchers from Malawi developed a risk score (RISC-Malawi) for use in children aged 2–59 months that takes into account the degree of hypoxemia, malnutrition severity, level of consciousness, sex, and the presence of wheezing [70•]. This score did not consider HIV status and the points ranged from − 2 to 23, with severe malnutrition and severe hypoxemia contributing 7 points each and unconsciousness contributing 8 points. The study was performed in a total of 14,665 patients and the c-statistic was 0.79 (95% CI, 0.76 ± 0.82), demonstrating a good ability to discriminate between children's risk of mortality. Although all these score can be very useful in low-resource settings, the characteristics of the patients, the local epidemiology of concurrent diseases (malaria, measles, HIV infections among others), the social conditions, and the facilities of the hospitals make them not applicable to developed countries.

In a recent report, we formulated a prognostic scale for estimating mortality, which would be applicable to children with CAP [21]. The study design included patients younger than 15 years with CAP who were hospitalized over a 10-year period in the Institute of Tropical Medicina, from Asunción, Paraguay. This country is among those listed by the Department of Economic and Social Affairs of the United

Table 3 Components of modified respiratory index of severity in children (mRISC) scoring

Variable	Points
History of present illness	
Was the child unconscious?	Yes = 1 point; no = 0 points
Was the child unable to drink/breastfeed?	Yes = 1 point; no = 0 points
Did the child have night sweats?	Yes = 21 point; no = 0 points
On physical examination	
Does the child have chest wall indrawing?	Yes = 1 point; no = 0 points
Is the child alert and awake?	Yes = 0 point; no = 2 points
Comorbidities	
Does the child have malaria?	Yes = 21 points; no = 0 points
Does the child have malaria and chest wall indrawing?	Yes = 1 point; no = 0 points
Is the child dehydrated?	Yes = 1 point; no = 0 points
Weight in kg_____: Age in months_____	
z-score is normal or high (z-score > −2)	0 points
z-score is low or very low (z-score ≤ −2)	1 point
Total points	

Using this scoring system, of the children who were admitted with a score of 3 or more, 40% died in the hospital; among those who reached a score of ≥ 4 and ≥ 6, 56% and 80% died in the hospital (Adapted from Emukule GO, et al. [69•] Predicting Mortality among Hospitalized Children with Respiratory Illness in Western Kenya, 2009–2012. PLoS ONE 2014; 9: e92968)

Nations Secretariat as developing economy with a lower middle income [71]. In the study where 862 patients were included, the severity of pneumonia was stratified using a point-based scoring system based on the modified PIRO scale used in adults with pneumonia [72]. Our modified PIRO score comprised the following variables: predisposition (age < 6 months, comorbidity); insult (hypoxia, O_2 saturation < 90%); hypotension (according to age and bacteremia); response (multilobar or complicated pneumonia); and organ dysfunction (kidney failure, liver failure, and acute respiratory distress syndrome). One point was awarded for each criterion that was present (final points range, 0–10 points). The association between the modified PIRO score and mortality was assessed by stratifying patients into four levels of risk: low (0–2 points); moderate (3–4 points); high (5–6 points); and very high risk (7–10 points). The results showed a significant positive correlation between mortality rates and modified PIRO scores. So, no patient with a modified PIRO score of 0–2 died; but, progressively greater mortality rates were found as the point score rose; 20 (18%) of 112 patients with a score of 3–4 died; 25 (83%) of 30 patients with a score of 5–6 died; all 10 patients (100%) with a score ≥ 7 points died ($P < 0.001$). Thus, this score can predict the probability of mortality in hospitalized children with CAP and may be a reliable tool to select patients for admission to ICU, as well as for its selection for adjunctive therapy in clinical trials.

Conclusions

Although several scoring systems for the estimation of mortality in childhood CAP were developed in the last years, most of them come from developing countries and the results—although useful for low- and middle-income countries—are not applicable to patients with pneumonia in developed countries. Prospective studies applying scores such as the modified PIRO scale in children with CAP from developed countries (in which pediatric pneumonia mortality is rare) are needed to confirm the utility observed in transitional-economy countries.

Compliance with Ethical Standards

Conflict of Interest   Dra. Lovera and Dra. Martínez de Cuellar declare that they have no conflict of interest. Dr. Arbo reports personal fees from Merck and Sanofi.

Human and Animal Rights and Informed Consent   This article does not contain any studies with animal subjects performed by any of the authors. In the studies of the authors mentioned in this article, they were retrospective and approved by the Institutional Ethics Committee. The complete anonymity of the patients involved in it was assured.

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