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REVIEW ARTICLE

Community-acquired pneumonia among children: the latest evidence for an updated management☆

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KEYWORDS
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Abstract
Objective: To provide cutting-edge information for the management of community-acquired pneumonia in children under 5 years, based on the latest evidence published in the literature.
Data source: A comprehensive search was conducted in PubMed, by using the expressions: ''community-acquired pneumonia'' AND ''child'' AND ''etiology'' OR ''diagnosis'' OR ''severity'' OR ''antibiotic''. All articles retrieved had the title and the abstract read, when the papers reporting the latest evidence on each subject were identified and downloaded for complete reading.
Data synthesis: In the era of largely implemented bacterial conjugate vaccines and widespread use of amplification nucleic acid techniques, respiratory viruses have been identified as the most frequent causative agents of community-acquired pneumonia in patients under 5 years. Hypoxemia (oxygen saturation $\leq$96%) and increased work of breathing are signs most associated with community-acquired pneumonia. Wheezing detected on physical examination independently predicts viral infection and the negative predictive value (95% confidence interval) of normal chest X-ray and serum procalcitonin <0.25 ng/dL was 92% (77–98%) and 93% (90–99%), respectively. Inability to drink/feed, vomiting everything, convulsions, lower chest indrawing, central cyanosis, lethargy, nasal flaring, grunting, head nodding, and oxygen saturation <90% are predictors of death and can be used as indicators for hospitalization. Moderate/large pleural effusions and multilobar infiltrates are predictors of severe disease. Orally administered amoxicillin is the first line outpatient treatment, while ampicillin, aqueous penicillin G, or amoxicillin (initiated initially by intravenous route) are the first line options to treat inpatients.
Conclusions: Distinct aspects of childhood community-acquired pneumonia have changed during the last three decades.

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PALAVRAS-CHAVE
Criança;
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Tratamento

Pneumonia adquirida na comunidade em crianças: as evidências mais recentes para um manejo atualizado

Resumo

Objetivo: Fornecer informações de ponta para o manejo de crianças menores de cinco anos com pneumonia adquirida na comunidade, com base nas evidências mais recentes publicadas na literatura.

Fonte de dados: Uma pesquisa abrangente foi feita no PubMed, com as expressões: ''*community-acquired pneumonia*'' + ''*child*'' + ''*etiology*'' ou ''*diagnosis*'' ou ''*severity*'' ou ''*antibiotic*''. Todos os artigos encontrados tiveram o título e o resumo lidos e os artigos que relatavam as evidências mais recentes sobre cada assunto foram identificados e recuperados para leitura completa.

Síntese dos dados: Na era das vacinas bacterianas conjugadas amplamente usadas e do uso difundido de técnicas de amplificação de ácidos nucléicos, os vírus respiratórios foram identificados como os agentes causadores mais frequentes de pneumonia adquirida na comunidade em pacientes com menos de cinco anos. A hipoxemia (saturação de oxigênio $\leq$ 96%) e o aumento do esforço respiratório são os sinais mais associados à pneumonia adquirida na comunidade. A sibilância detectada ao exame físico prediz de forma independente a infecção viral e o valor preditivo negativo (intervalo de confiança de 95%) da radiografia de tórax normal e a procalcitonina sérica <0,25 ng/dL foi de 92% (77–98%) e 93% (90–99%), respectivamente. Incapacidade de beber e se alimentar, vomitar todo o alimento, convulsões, retração torácica subcostal, cianose central, letargia, aleteo nasal, estridor e saturação de oxigênio <90% são preditores de óbito e podem ser usados como indicadores de hospitalização. Derrames pleurais moderados/grandes e infiltrados multilobulares são preditores de doença grave. A amoxicilina administrada por via oral é a opção de primeira linha para tratar pacientes ambulatoriais e a ampicilina ou penicilina cristalina G ou amoxicilina (administrada inicialmente por via intravenosa) são as opções de primeira linha para tratar pacientes hospitalizados.

Conclusões: Aspectos distintos da pneumonia adquirida na comunidade durante a infância mudaram durante as últimas três décadas.

Introduction

Community-acquired pneumonia (CAP) is still a leading cause of death among children aged less than 5 years worldwide, with an estimate of 0.921 million deaths in 2015. Indeed, CAP was second only to preterm birth complications, being the leading cause of death in countries with high under-5 mortality rate, yet important in medium high, and medium child mortality countries.[1] Furthermore, CAP imposes a substantial burden on health services and is a major cause of hospital referral and admission. According to the last estimate, in 2010, roughly 265,000 deaths due to CAP took place in hospitals, 99% of them in developing countries.[2] Therefore, it is possible to observe that 81% of deaths happened outside hospitals,[2] particularly in Sub-Saharan Africa and Southern Asia countries.[1] In Brazil, during 2017, 1,117,779 hospital admissions occurred among children under 5 years, and the most frequent causes of admission were respiratory disease (351,763; 31.5%), perinatal complications (277,212; 23.5%), and infectious/parasitic illnesses (163,958; 14.7%).[3] Regarding mortality, 2,349 deaths due to respiratory disease were registered in the same age range, in Brazil, in 2017, *i.e.*, 0.7% of the cases hospitalized died (case fatality rate).[3] These figures are in agreement with the findings of mortality and morbidity according to the economic development of the countries,[1] as Brazil is an upper middle income country.[4] That is, although CAP is not a frequent cause of death, it is a major cause of hospital admission in Brazil. Due to its impact on childhood morbidity and mortality, in health care assistance, it is paramount to be updated in diagnosing and treating children with CAP. Thus, this study aimed to provide cutting-edge information for the management of CAP patients under 5 years, based on the latest evidence published in the literature.

Etiology

Up to the 1990's, bacterial infections were the main concern about CAP etiology, particularly pneumococcal infection. Besides being a classical concept in medicine, derived from the available bacteriological assays that were routinely used to investigate CAP etiology, this concept was highlighted by the finding that death due to CAP was mainly secondary to bacterial infection.[5] Based on this finding, the World Health Organization (WHO) launched a program with guidelines aiming to identify children at risk of having CAP, who should receive empiric antibiotic treatment promptly.[6] As a matter of fact, this program was quickly deemed to have a substantial effect on child mortality.[7]

Between the end of the last century and the beginning of the current one, significant changes occurred in the childhood CAP scenario. Firstly, the progressive implementation of bacterial conjugate vaccines, specifically the *Haemophilus influenzae* type b (Hib) vaccine and the pneumococcal conjugate vaccines (PCVs),[8] the most frequent bacterial causative agents of CAP among children under 5 so far.[9] It has been recognized that the widespread use of Hib vaccine and PCV in countries with high child mortality has been associated with reductions in Hib and pneumococcal cases and deaths.[8] Secondly, the successively widespread use of amplification nucleic acid techniques (PCRs) has been impacting on the estimation of the proportion of respiratory virus infections in childhood CAP.[10]

In an American study conducted in 2,219 children (<18-years-old) hospitalized due to CAP, between 2010 and 2012, respiratory viruses were detected in 1,627 (73.3%), out of which 1,472 (90.5%) had only viruses detected.[11] In a Swedish study conducted at the pediatric emergency room or inpatient wards between 2011 and 2014, 121 cases with radiographic evidence of CAP and 240 healthy controls were enrolled, out of which 81% and 56%, respectively, had viruses found; the authors reported that influenza, human metapneumovirus (HMPV) and respiratory syncytial virus (RSV) were detected in 60% of cases and were significantly associated with CAP with odds ratios >10.[12] In an Australian study carried out in 230 children (<18-years-old) hospitalized with CAP and 230 healthy controls, between 2015 and 2017, respiratory viruses, particularly RSV and HMPV, were major contributors for CAP etiology.[13] The authors estimated that RSV, HMPV, influenza, adenovirus, and *Mycoplasma pneumoniae* were responsible for 20.2% (95% CI: 14.6–25.5), 9.8% (5.6%–13.7%), 6.2% (2.5%–9.7%), 4% (1.1%–7.1%), and 7.2% (3.5%–10.8%) of hospitalizations, respectively.[13] In turn, in a multi-center study conducted in eight developing countries (Cambodia, China, Haiti, India, Madagascar, Mali, Mongolia, and Paraguay), between 2010 and 2014 (the GABRIEL study), 888 cases hospitalized with radiologically confirmed CAP and 870 healthy controls were recruited; at least one microorganism was detected in 93% of the cases and in 74.4% of the controls. *Streptococcus pneumoniae*, *M. pneumoniae*, HMPV, rhinovirus, RSV, parainfluenza virus 1, 3, and 4, and influenza virus A and B were independently associated with pneumonia and the authors speculate that increasing *S. pneumoniae* vaccination coverage may substantially reduce the burden of CAP among children in developing countries.[14] In addition to that, another multi-center study conducted in Bangladash, Gambia, Kenya, Mali, South Africa, Thailand, and Zambia, all developing countries, between 2011 and 2014 (the PERCH study), 1,769 non-HIV cases with positive chest X-ray, hospitalized with severe CAP, aged 1–59 months, and 5,119 community controls were enrolled; detection of RSV, parainfluenza virus, HMPV, influenza virus, *S. pneumoniae*, Hib, *H. influenzae* non-type b, and *Pneumocystis jirovecii* in nasopharyngeal and oropharyngeal specimens was associated with case status. The etiology analysis estimated that viruses accounted for 61.4% (95% confidence interval [CI]: 57.3–65.6) of causes, whereas bacteria accounted for 27.3% (23.3–31.6) and *Mycobacterium tuberculosis* for 5.9% (3.9–8.3). RSV had the greatest etiological fraction (31.1%, 95% CI: 28.4–34.2) of all pathogens.[15]

In Brazil, two distinct studies thoroughly investigated CAP etiology. In the first one, 184 hospitalized cases with radiologically-confirmed CAP were included, and only viral, only bacterial, and viral-bacterial infections were found in 67 (36%), 34 (18%), and 43 (23%) patients, respectively, being rhinovirus (21%) and *S. pneumoniae* (21%) the most common pathogens.[16] Parainfluenza viruses 1, 2, and 3 (17%), RSV (15%), influenza A and B (9%), human bocavirus (HBoV; 8%), enterovirus (5%), HMPV (4.1%), and adenovirus (3%) infections were diagnosed.[16–18] In the second study, 774 non-hospitalized cases were recruited, out of which 708 (91.5%) had viruses detected, 491 (69.4%) with multiple viruses; rhinovirus (46.1%), adenovirus (38.4%), enterovirus (26.5%), RSV (24.9%), parainfluenza virus 1, 2, 3, and 4 (20.5%), HMPV (12.9%), influenza A and B (8.5%), and coronavirus OC43, NL63, and 229E (8.3%) were found.[19] In this study, all viruses were significantly more frequent among cases with multiple detections, except for RSV and influenza viruses.[19] Furthermore, acute HBoV infection was serologically confirmed in 38 (5.0%) of the 759 cases with available paired serum samples.[20] Typical bacterial infections were also searched for, by employing quantitation of specific IgG titers: out of 690 patients with paired serum samples available for these assays, the rate of antibody responses was 15.4% for at least one pneumococcal protein antigen, 5.8% for *H. influenzae*, and 2.3% for *M. catarrhalis*; the detection rate of significant antibody increase for at least one of these three bacteria was 20.4%.[21] Atypical bacterial infections were also investigated: *M. pneumoniae* acute infection was diagnosed through the detection of specific IgM antibodies in the convalescent serum sample, *Chlamydia pneumoniae* and *Chlamydia trachomatis* acute infections were diagnosed through the detection of specific IgM antibodies or by significant IgG or IgA titer change. Overall, *M. pneumoniae* (86/787; 10.9%), *C. pneumoniae* (79/733; 10.8%), and *C. trachomatis* (3/28; 10.7%) acute infections were diagnosed, and 147 (20.1%) out of 731 patients investigated for these three bacteria had acute infection by at least one of these three bacteria (18 patients had concomitantly positive tests for acute *M. pneumoniae* and acute *C. pneumoniae* infection).[22]

Based on the aforementioned data, it is possible to observe that respiratory viruses have been increasingly implicated in childhood CAP etiology, along with the recognition that viral infections have been more frequent than bacterial infections, even in developing countries.

Diagnosis

The screening of children with complaints of acute respiratory infection to diagnose pneumonia relies initially on clinical aspects. Since the early 1990's, the WHO has recommended the use of quantitative tachypnea (age-specific elevated respiratory rates) to identify children that would require treatment with antibiotics for possible pneumonia.[6] It is necessary to clarify that the WHO respiratory rate criteria were selected based on field, observational studies in target epidemiologic settings due to their high sensitivity, reasonable specificity, and ease of implementation where access to formal medical evaluation was limited. Additionally, the evidence base for establishing these criteria is prior

to the introduction of vaccines against Hib and *S. pneumoniae*, regarded as the two major causes of CAP mortality.[23] It is also necessary to emphasize that the WHO respiratory rate criteria are not a diagnostic approach; instead, it was recommended to be employed as an easy tool to identify, among children under 5 years with acute respiratory infection complaints, those who had chance to have a compromised lower respiratory tract, who could then be at risk of dying. In a recently published systematic review of the accuracy of symptoms and physical examination findings to identify cases with radiographic pneumonia among children younger than 5 years, 23 prospective cohort studies of children were included (eight from North America), among which the prevalence of radiographic pneumonia in North American studies was 19% and 37% outside of North America. The presence of moderate hypoxemia (oxygen saturation $\leq$96%) and increased work of breathing (grunting, flaring, and retractions) were signs most associated with pneumonia, whereas normal oxygenation (oxygen saturation >96%) decreased the likelihood of pneumonia. Curiously, tachypnea (respiratory rate >40 breaths/min) was not strongly associated with pneumonia diagnosis.[24] Indeed, the limitations of respiratory rate-based pneumonia diagnosis also include overdiagnosis, due to the inclusion of cases of asthma and other respiratory ailments that compromise the lower respiratory tract.[25]

In a study conducted in three rural hospitals in Rwanda between May 2011 and April 2012, 147 cases were analyzed and 58% had radiologist-diagnosed pneumonia; the accuracy for diagnosing radiologically-confirmed pneumonia was assessed in 31 historical, clinical, and laboratory signs. Oxygen saturation was the best clinical predictor; its area under the receiver operating characteristic (ROC) curve (0.675 [95% CI: 0.581–0.769]; p = 0.001) was higher than that of the respiratory rate (0.528 [95% CI: 0.428–0.627]; p = 0.588).[26] In Malawi, between 2012 and 2014, 13,266 children aged 2–59 months with clinically-diagnosed pneumonia were evaluated; those authors demonstrated that oximetry increased the referral rate for severely hypoxemic children without chest indrawing or danger signs.[27] Indeed, when oximetry data were excluded, retrospective application of the guidelines published by WHO in 2014[28] failed to identify a considerable proportion of severely hypoxemic children eligible only via oximetry.[27] Furthermore, it had been shown that pulse oximetry can not only significantly increase the incidence of correctly treated severe cases but also reduce the incidence of incorrect treatment with antibiotics.[29]

The gold standard usually considered in the investigation of predictive signs of pneumonia is radiologically-confirmed pneumonia. Radiologic findings consistent with pneumonia include pulmonary infiltrate, either alveolar or interstitial; alveolar infiltrate is characterized as a dense or fluffy opacity that occupies a portion or the entire lobe, or even the entire lung, which may or may not contain air-bronchogram, and interstitial infiltrate is defined as linear and patchy densities in a lacy pattern.[30] Interestingly, it had been demonstrated that the sensitivity (95% CI) of radiologically-confirmed pneumonia for pneumococcal infection was 93% (80%–98%); conversely, the negative predictive value (95% CI) of normal chest X-ray was 92% (77%–98%).[31] These findings were detected among hospitalized[31] and non-hospitalized children.[32] Thus, the findings of radiologically-confirmed pneumonia are actually predictors of bacterial pneumonia. Moreover, if the frequency of bacterial pneumonia is decreasing due to the wide implementation of the conjugate vaccines (Hib and PCVs), the accuracy of those predictors may change over time and among different settings, depending on vaccines coverage. From a practical standpoint, bacterial pneumonia should be the target as children with typical bacterial infections, alone or complicated by a viral infection, have worse outcomes than those infected with a virus alone.[11]

In a prospective cross-sectional study that investigated CAP etiology (11 viruses and eight bacteria) in hospitalized children under 5 years, the frequency of signs and symptoms was assessed in patients with viral or exclusively bacterial infection; 188 patients had a probable etiology established as only viral (51.6%), mixed viral-bacterial (30.9%), and only bacterial infection (17.5%). Asthma was observed in 21.4%. In the multivariable analysis, viral infection (AdjOR [95% CI]: 9.6; 95% CI: 2.7–34.0), asthma (AdjOR [95% CI]: 4.6; 95% CI: 1.9–11.0), and age (AdjOR [95% CI]: 0.95; 95% CI: 0.92-0.97) were independently associated with wheezing on physical examination. The positive predictive value of detected wheezing for viral infection was 96.3% (95% CI: 90.4–99.1%). The authors concluded that wheezing detected on physical examination is an independent predictor of viral infection.[33] However, wheezing does not rule out bacterial infection. As in practice it is not only necessary to identify children with CAP, but mainly those with probable bacterial infection, it is possible that the combination of normal chest X-ray, detection of wheezing upon physical examination, and pulse oximetry may be useful for this goal. This is a potential issue for future research.

The use of blood inflammatory biomarkers to distinguish bacterial from viral CAP has been investigated. Procalcitonin (PCT) and C-reactive protein (CRP) have shown some value in the identification of bacterial infections[34,35] but it has not been established yet a relevant clinical cut-off point for their use.[36] For instance, in an Italian randomized clinical trial, children with non-severe CAP were admitted at the hospital specifically to be included in this PCT investigation: 155 received antibiotics if the mean serum PCT upon admission was $\geq$0.25 ng/mL and the remaining 155 children received antibiotics based on the clinical evaluation of the attending physician. Antibiotics were prescribed to 133 children (85.8%) from the first group and 155 children (100%) from the second group, (p < 0.05). The length of antibiotics use was lower (5.37 *vs.* 10.96; p < 0.05) as well as the frequency of adverse events related to antibiotics use (3.9% *vs.* 10.96%; p < 0.05) in the group that had serum PCT measured. It is necessary to emphasize that none of the patients who did not receive antibiotics worsened or needed antibiotics afterwards.[37] A Brazilian study described that serum PCT upon admission below 0.25 ng/dL had high negative predictive value for pneumococcal infection (93%; 95% CI:90–99%).[38] It is important to highlight that, in both studies, patients had radiologically-confirmed pneumonia and, for that reason, even with a chest's radiograph that confirms CAP diagnostics, it appears to be possible to identify those children who will not benefit from antibiotic use, for example, considering the serum PCT level <0.25 ng/mL. Additionally, IL-6 was independently associated with pneumococcal infection, having a high neg-

ative predictive value among children under 5 years of age hospitalized with CAP.[39] To date, there is lack of this information in non-hospitalized children in this age range. Moreover, a combination of biomarkers (tumor necrosis factor-related apoptosis-inducing ligand, C-reactive protein, and interferon μ-induced protein) was described to be useful in distinguishing bacterial from viral infections in hospitalized children; however, less than 200 children were investigated.[40,41] A common pitfall in this kind of study is how children without bacterial CAP are identified. For example, in a recently published study from Australia, definite bacterial infection was described as clinical empyema and/or bacteria detected in blood or pleural effusion, while presumed viral pneumonia comprised at least one virus detected in the nasopharyngeal swab without criteria for definite bacterial pneumonia.[42] In fact, by using these definitions, the authors grouped cases in two subgroups: the first with invasive bacterial infection and the second without invasive bacterial infection and possible viral infection. The great challenge in grouping CAP cases with bacterial infection is the diagnosis of non-invasive bacterial infection.[43] When the methods employed do not diagnose non-invasive bacterial infection, these patients are mislabeled as cases without bacterial infection. Undoubtedly, the identification and validation of tools to reliably distinguish, among children with CAP, those with viral infection from those with bacterial infection is a priority in the childhood CAP research field.

Hospital admission

Clinical management requires assessment for defining whether the patient requires hospitalization. By reviewing seven distinct childhood CAP country representative guidelines, it was possible to observe that the criteria recommended for hospital admission differ between developed and developing countries.[44] In the United States, Canada, the United Kingdom, and Japan, signs of respiratory distress including tachypnea are indicators for hospitalization, whereas in Brazil, South Africa, and in the WHO guidelines, tachypnea alone is regarded as an indicator for starting antibiotics on an ambulatory basis.[44] In 2012, the WHO made a considerable change in its guideline: for patients with tachypnea and chest indrawing, to whom the formal recommendation was hospitalization, were indicated oral antibiotic outpatient treatment from 2012 onwards.[45]

Figures for developed countries prior to the introduction of PCV estimated approximately 2.6 million episodes of CAP, including 1.5 million (58%) children hospitalized for their illness, annually, among children aged <5 years.[46] In contrast, estimates for developing countries were 151 million new episodes annually, 9% of which were associated with hospitalization.[47] It is possible to observe that the proportion of CAP cases associated with hospitalization was 6.4-fold greater in children from developed (58%) when compared with those from developing countries (9%). The difference in proportion of CAP cases that are hospitalized in developing and developed countries likely reflects a combination of physician differences in management, limited access to health care, and differences on healthcare seeking behavior among parents for children, rather than less severe disease among children in developing countries.[44] Furthermore, the health care system structure differs between developing and developed countries.[44] In reality, no published studies from developed countries have systematically compared outcomes of children treated as outpatients with those of hospitalized children according to varying degrees of respiratory distress.[48] Current recommendations from developed countries are based on the assumption that children have reasonable access to healthcare, including evaluation by a doctor. The attending physician's overall assessment of the child's clinical status and the anticipated clinical course are used to determine whether hospitalization is required.[48,49]

Data from four developing countries participants in the GABRIEL study showed that, out of 405 cases aged 2–60 months hospitalized with radiologically-confirmed pneumonia, 13 (3.2%) died; hypoxemia and *S. pneumoniae* detection by blood PCR were predictors of death and lower chest indrawing along with cyanosis were predictive of hypoxemia; moreover, HMPV and RSV were independently associated with increased risk of hypoxemia.[50] Furthermore, data from 1,802 children between 1 and 59 months old hospitalized with severe or very severe pneumonia and included in the PERCH study, which was conducted in seven low- and middle-income countries between 2011 and 2014, demonstrated that age <1 year, female sex, ≥three days of illness prior to presentation to hospital, low weight-for-height, unresponsiveness, deep breathing, hypoxemia, grunting, and absence of cough were predictors of death; these authors also pointed out that the chance of dying increased according to the number of WHO danger signs present: no danger sign (1.5%), one danger sign (10%), and ≥two danger signs (33%).[51] Besides that, the number of WHO danger signs at presentation to hospital (c = 0.82) was more accurate than the PERCH-5 stratum score (c = 0.76) or the Respiratory Index of Severity in Children (c = 0.76).[51] Danger signs included central cyanosis or oxygen saturation <90% on pulse oximetry, inability to drink/feed, vomiting everything, convulsions, lethargy (or impaired consciousness), and severe respiratory distress.[51] Severe respiratory distress was defined as nasal flaring, grunting or head nodding (use of auxiliary muscles for breathing) in presence of very labored, fast, or gasping breathing, being the child unable to feed because of respiratory distress and tires easily.[52] All in all, inability to drink/feed, vomiting, convulsions, lower chest indrawing, central cyanosis, lethargy, nasal flaring, grunting, and head nodding have been recognized as reliable and easily detected predictors of death among hospitalized children with CAP, as well as oxygen saturation <90% (hypoxemia). Despite the fact that these findings were based on cases treated in hospital, and therefore it is not possible to infer which cases may have been successfully managed at home, it is possible to recognize that those were evidence-based predictors that can therefore be used in the clinical management of CAP cases across diverse settings, particularly aiding the decision about which patients should be hospitalized for treatment.

Another study, conducted in four hospitals in the United States in 2010, recruited 406 children (<18 years old) hospitalized with clinical and radiographic evidence of pneumonia, aiming to assess whether radiographic findings predict outcomes. Admission radiographs were categorized

as single lobar, unilateral, bilateral multilobar, or interstitial pulmonary infiltrate, as well as with absent, small, or moderate/large pleural effusion. The authors reported that findings of moderate/large pleural effusions and bilateral multilobar infiltrates presented the strongest associations with severe disease, and multilobar (either unilateral or bilateral) and interstitial infiltrate were associated with need for intensive care.[53] Thus, the chest X-ray is a valuable tool that contributes to improve the quality of care and may help predict disease severity.[53]

Treatment

There is a general agreement among distinct international guidelines that orally administered amoxicillin is the first line option to treat outpatients, and ampicillin or aqueous penicillin G or amoxicillin (initiated initially by intravenous route) are the first line options to treat inpatients with CAP in the under-5 years group.[54] Such agreement is based on a general consensus that *S. pneumoniae* is the most common and dreadful bacterial causative agent in childhood CAP among children under 5 years and therefore it should be the target of antibiotic therapy.[55] For example, *S. pneumoniae* detection by blood PCR was recently identified as predictor of hypoxemia among children hospitalized with CAP.[50]

A systematic review published in 2016 analyzed all randomized clinical trials, published until April 2015, where children with CAP were treated with antibiotics and followed up: 54 studies were included, out of which, 13 evaluated the efficacy of amoxicillin in non-severe non-hospitalized patients and eight evaluated the efficacy of amoxicillin in hospitalized patients.[56] Thus, amoxicillin was the most studied antimicrobial, with the best methodological approach and the most reliable evidence. Two different dose regimens were compared in a clinical trial conducted in Salvador, Brazil: 820 children with non-severe CAP were randomly assigned to receive 50 mg/kg/day of amoxicillin either twice or thrice a day; this was a placebo-controlled, randomized, triple-blinded clinical trial that showed equivalence on the efficacy of both regimens.[57] Thus, the most comfortable and convenient dosage (50 mg/kg/day twice daily) can be used based on science evidence. It is important to recall that the key pharmacodynamics parameter for amoxicillin efficacy is length of time over the minimal inhibitory concentration (MIC), which should be $\geq$40%–50% of the dosing interval during treatment of pneumococcal CAP.[58] A pharmacokinetic study compared twice and thrice daily dosing in children receiving 50 mg/kg/day and reported that 91% of the patients had amoxicillin concentrations above 0.5 ug/mL for >50% of the dose interval and 42% had amoxicillin concentrations above 2.0 ug/L for >50% of the dose interval in the twice-daily dose arm.[59] That indicates that the appropriateness of the 50 mg/kg/day dose of amoxicillin needs to be re-evaluated according to the MIC of the pneumococcal strains isolated in the region. For instance, Canadian authors have recently advised against the routine use of higher doses of amoxicillin to treat non-severe CAP cases in Canada, as only 0.6% of pneumococcal strains presented intermediate resistance (MIC = 4 ug/mL) to amoxicillin. Those authors also argued that the unjustified use of higher doses of amoxicillin leads to increases in costs, side effects, and total antibiotic exposure, and the harmful effects on the patients' microbiome should also be considered.[60]

A common practical question is whether macrolides should be given empirically in the first-line option to treat children with CAP; several attempts have been made to address this question. So far, the strongest evidence has been provided by a Brazilian study: 703 children under 5 years with non-severe CAP were given amoxicillin and were prospectively followed-up; amoxicillin was substituted in 3.5% of children diagnosed with acute infection by *M. pneumoniae* or *C. pneumoniae* and in 2.7% of children without this kind of infection ($p = 0.6$). Three children with acute infection by *C. trachomatis* did not present therapeutic failure and amoxicillin was the antibiotic used through the entire treatment period. The authors concluded that it was not necessary to treat atypical bacterial infection in every child aged between 2 and 59 months with non-severe CAP; on the contrary, macrolide use could be reserved for those rare cases in which amoxicillin was not effective.[22]

A further practical question regards the length of antibiotic therapy. A systematic review published in 2008 evaluated the efficacy of short and long courses of the same antibiotic, in children aged 2–59 months with non-severe CAP, and identified two clinical trials in which three and five days of amoxicillin use were compared (one in India and another in Pakistan) and one clinical trial where three and five days of co-trimoxazole were compared (in Indonesia and Bangladesh): neither study indicated differences in the efficacy per treatment length.[61] It is of utmost importance to notice that all three studies diagnosed CAP patients according with WHO diagnostics criteria: presence of tachypnea. Evidently, cases of asthma, bronchiolitis, and other lower respiratory tract diseases were included, and the CAP diagnostics was erroneously made in children with other respiratory morbidities. That is why results from studies that diagnosed CAP using WHO criteria should only be generalized for those cases diagnosed in clinical practice with the same criteria, once these results might be different in radiologically-confirmed pneumonia or bacterial pneumonia.[25] In this context, the author highlights an Israeli clinical trial published in 2014: children aged 6–59 months, with radiological finding of alveolar infiltrate on the chest radiograph taken upon admission, temperature $\geq$38.5 °C, leucocyte total count $\geq$15.000 mm^3, without dangers signs were followed-up daily. The authors first compared three days of treatment with ten days. Due to 33% rate of therapeutic failure in the first arm against none (0%) in the second arm, a preliminary interim analysis switched the duration of treatment in the first arm to five days. At the end, there were 56 and 59 cases treated either with five or ten days of amoxicillin, respectively, without any therapeutic failure. Authors concluded that five days of amoxicillin are enough to treat CAP with alveolar infiltrate, without danger signs or complications.[62]

Remarkably, the WHO significantly altered its recommendation in 2012: for children with fast breathing and wheezing, but no chest indrawing, danger signs, nor fever (<38 °C), antibiotics should not routinely be recommended, as the cause is most likely viral infection.[45] This was a rupture from the old policy of prescribing antibiotics for any children younger than 5 years old with cough and tachypnea

because of the risk of bacterial infection and death, and is due to the recognition that respiratory viruses are major causes of CAP in children, as well as simple clinical signs such as fever and wheeze may preliminarily screen children who are not prone to have bacterial infection.

Some notes are advised about antibiotic therapy in hospitalized patients for whom ampicillin or aqueous penicillin G or amoxicillin (initiated initially by intravenous route) are the first line options.[54] The American guideline states that the third generation cephalosporins could be the first choice only in those places with high prevalence of pneumococcal resistance to penicillin, that is, with MIC $\geq$4 ug/mL.[48] It has already been demonstrated that patients infected with pneumococcal strains with MIC up to 4 ug/mL present good response when treated with aqueous penicillin G at dosage of 200.000 UI/kg/day.[63] It has also been shown that the daily dosage of 200.000 UI/kg/day has the same efficacy if given every 4 h or every 6 h.[64] When treatment is managed with a larger interval between doses, it is more comfortable for patients and healthcare professionals, which enhances adherence, besides being cheaper for healthcare institutions. It is also relevant to comment on how hospitalized patients with CAP evolve during antibiotic treatment. Another Brazilian study included 154 hospitalized children older than 2 months of age with radiologically-confirmed CAP, all treated with aqueous penicillin G (200.000 UI/kg/day) and penicillin was substituted in 26 (18%) cases due to deterioration of clinical status. Among the 128 remaining cases that received aqueous penicillin G throughout the treatment period, tachypnea, fever and chest indrawing were still present after 48 h of antibiotic therapy in 51.0%, 26.8%, and 10.3% of the cases, respectively; those symptoms were present at 120 h after treatment onset in 33.3%, 10.3%, and 2.2% of the cases, respectively.[65] Notably, all patients presented a full recovery and were discharged from hospital with oral amoxicillin replacing aqueous penicillin G for home completion of antimicrobial therapy. These numbers show that patients may have a slow recovery, suggesting that there is no need of antibiotic replacement if the patient does not present clinical/radiological deterioration. Therefore, the use of ceftriaxone in cases with very severe disease or the association of oxacillin or macrolide should occur in specific situations, where it is possible to assume the presence of high penicillin resistant pneumococcus, or β-lactamase producing *H. influenzae* (ceftriaxone indication), or *Staphylococcus aureus* (oxacillin indication), or even atypical bacteria (macrolide indication).[54]

Patients under 2 months of age should be hospitalized and receive intravenous antibiotics once they have higher chance of dying from CAP, regardless of other factors when compared with children older than 2 months.[66] In this age stratum, group B streptococcus, Gram-negative intestinal bacteria, *Listeria monocytogenes*, and *S. pneumoniae* are potential causative agents.[67,68] Then, antibiotic therapy in this age group includes administration of either intravenous (IV) or intramuscular (IM) ampicillin associated with amynoglycosides throughout the whole treatment and from 1-week-old upwards, it is possible to substitute amynoglycosides for third-generation cephalosporins.[69] If age is <1 month, cefotaxime is the first choice drug, considering hyperbilirubinemia and prematurity. Ceftriaxone increases the risk of kernicterus in these patients, once it has high avidity to serum proteins, especially albumin, which bonds to bilirubin.[70] *C. trachomatis* should be suspected in the presence of conjunctivitis. In this case, the recommended antibiotic choice is erythromycin.[54]

A few comments about corticosteroids as adjunctive therapy should be made. A Spanish study was performed as a multicenter, randomized, double-blinded, parallel-group, placebo-controlled clinical trial. Sixty children, aged from 1 month to 14 years, with CAP and pleural effusion were included. Those authors described faster recovery rate, measured objectively in hours, in the group that received dexamethasone (DXM) 0.15 mg/kg, every 6 h, for 48 h, plus cefotaxime, when compared with the control group. There were no significant differences in adverse events attributable to the study drugs, except for hyperglycemia. Therefore, the authors concluded that DXM appeared to be a safe and effective adjunctive therapy for decreasing the time to recovery in children with parapneumonic pleural effusion.[71] Another study included children with severe CAP: 29 patients received a 5-day methylprednisolone course plus imipenem and 30 patients received imipenem plus placebo. The authors reported that the methylprednisolone group had a faster resolution of symptoms.[72] A recent systematic review identified four randomized controlled trials that included 310 children; corticosteroids reduced early clinical failure rates (RR 0.41 [95% CI: 0.24–0.70]; high-quality evidence) based on two small, clinically heterogeneous trials, and reduced time to clinical cure.[73] To date, the role of corticosteroids in adjunctive chemical therapy of childhood CAP is yet to be established. Further support is needed to recommend the use of corticosteroids in clinical practice across distinct severity subgroups and in association with different antibiotics, especially β-lactams.[54]

Conclusion

CAP is still a major cause of morbidity and mortality among children aged under-5 years, worldwide. Currently, respiratory viruses are being recognized as major causative agents. Hypoxemia (oxygen saturation $\leq$96%) and increased work of breathing are the most associated signs with CAP. In regard to severity assessment, danger signs (inability to drink/feed, vomiting everything, convulsions, lower chest indrawing, central cyanosis, lethargy, nasal flaring, grunting, head nodding, and oxygen saturation <90%) have been recognized as predictors of death and can be used as indicators for hospitalization. The first line option for antibiotic treatment comprises oral amoxicillin for outpatients and ampicillin or aqueous penicillin G or amoxicillin (initiated initially by intravenous route) for inpatients. Future investigations should prioritize the identification and validation of tools to distinguish among children with CAP those with viral infection from those with bacterial infection.

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Conflicts of interest

The author declares no conflicts of interest.

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