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Management of Lower Respiratory Tract Illnesses in Developing Countries: A Narrative Review

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ABSTRACT

Pneumonia is the leading cause of mortality in young children worldwide. Early diagnosis and empiric antibacterial therapy is an important strategy to improve outcome. The World Health Organization has developed case management guidelines to reduce pneumonia-related deaths through early diagnosis and antibiotic treatment. For management purpose, pneumonia is subclassified by its severity. Children with simple pneumonia, pneumonia with chest wall in-drawing or pneumonia with danger signs (convulsion, cyanosis, inability to drink, abnormal sleepiness). Pneumonia with danger signs requires hospitalization and parenteral antibiotics, whereas children who only have fast breathing (tachypnea) can be treated at home with oral antibiotics. Later, these strategies were incorporated into the Integrated Management of Childhood Illnesses, and the protocol was adopted by several developing countries. Despite the proven benefit of this program in reducing pneumonia-related deaths, there has been some concern about the specificity of the World Health Organization and the Integrated Management of Childhood Illnesses guidelines, leading to unnecessary use of antibiotic for children with tachypnea, which were categorized as pneumonia. There is a necessity to improve the Integrated Management of Childhood Illnesses case management of childhood pneumonia because of overlap with other lower respiratory tract illnesses. This review outlines current guidelines for childhood pneumonia management in developing countries and identifies challenges for improvement in management in a variety of settings.

Introduction

According to world health organization (WHO) estimates, more than 150 million episodes of community-acquired pneumonia and 2 million pneumonia – related deaths

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occurred in the year 2008 among children under five years of age in developing countries. Of all pneumonia cases 7 - 13% were sever enough to be life – threatening and required hospitalization.[1]

To reduce the morbidity and mortality caused by pneumonia in children younger than five years in resource-poor countries the WHO has developed a standard case – management strategy of acute respiratory infection (ARI) in the 1980s through early diagnosis of pneumonia and empirical antibacterial therapy. [2] The basis for the case-management program was that almost all ARI-related death was caused by bacterial pneumonia. According to the protocol, pneumonia could be distinguished from other respiratory illnesses by trained paramedical health care providers using simple clinical signs- in primary health facilities.[2-7] The WHO incorporated the ARI case- management guidelines into the clinical protocols of "The Integrated Management of Childhood Illnesses (IMCI)" and the program had been adopted by many developing countries including Iran.[8-12] These guidelines included recommendations for the case–management of acute childhood illnesses and guidance when referral to higher levels of care is required. They specify appropriate anti-bacterial treatment and preventive interventions against the leading causes of childhood mortality.[8-12] This approach has been effective in reducing ARI- related mortality in children younger than five years in developing countries.[13,14] Over time, to increase the specificity of the guidelines, the programs have evolved.[15-27] Our objectives in this narrative review are: to define and diagnose pneumonia and its subtypes based on the WHO criteria, to specify the most appropriate antibacterial agent for different settings of illnesses "simple versus sever and very sever pneumonia", to diagnose and discuss the most appropriate approaches to cases with treatment failure, and finally to define patients who have benefited from other therapies.

Epidemiology of Acute Lower Respiratory Tract Infections

Acute respiratory infections are the most common infection in children and include a wide spectrum of illnesses from colds, pharyngitis and influenza, to lower respiratory infections. Clinically, acute lower respiratory tract infections (ALRTI) can be divided into pneumonias and bronchiolitis.[28,29] Differences between these two conditions can be particularly difficult in young children. [30,31]Although the frequency of ARI is similar in both developed and developing countries, [30] morbidity and mortality due to ARI is 10-15 times higher in developing nations. [18,32-35] The annual incidence of pneumonia in children younger than five years in developing countries is not only more common: 7-40 versus 2-4 cases/100 children respectively, but also is more severe compared to what occurs in developed countries.[18,32-35] In 2010, more than 11.9 million episodes of severe pneumonia, 3 million cases of very severe pneumonia and 1.4 million deaths occurred in young children worldwide, resulting in a substantial burden on care systems.[34,35] Despite the inadequacy of research into the epidemiological causes of pneumonia, certain risk factors have been identified. Younger age, low birth weight, overcrowding and large family size, malnutrition, and early childhood respiratory damage due to indoor air pollution were the main significant factors for development of pneumonia.[33,34] Also, risk factors associated with increased mortality in cases with ALRTI were investigated and the age less than one year, inability to feed,

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severe malnutrition and those with loose stools during an acute episode were found to be at higher risk of deaths.[36]

Etiology of ALRTI

Multiple microbes predominantly viruses and bacteria cause ALRTI in infants and children. Establishing a microbial diagnosis for pneumonia is difficult. Identification or prediction of the likely organism causing ALRTI is the most important step in selecting appropriate therapy. The limited available data indicated that the respiratory viruses including respiratory syncytial virus (RSV),influenza virus (FLU) and bacteria such as streptococcus pneumonia (Spn) and homophiles influenza type B (Hib) are the most common microbial agents causing pneumonia in children. The relative distribution of these pathogens varied with disease severity with Spn and Hib being the most important microbial agents in the cases with severe disease. [34, 37-44] In a hospital based study in Pakistan, RSV was identified in 33% with Spn and Hib in 9.9% and 4.6%, respectively of hospitalized patients with WHO defined severe and very severe pneumonia[38]. In a study in India, viruses were detected in 49% of patients with ALRTI and RSV was the commonest agent[41]. During a one year study conducted in Iran, one or more respiratory viruses were identified from 54% of hospitalized patients with ALRTI. Parainfluenza viruses in 15.8% and RSV in 12.9% were the most common agents.[43,44] In another study which consisted of 14 Asian countries isolates from lung aspirate of hospitalized children were analyzed, and Spn was found as the commonest isolate followed by Hib. Mixed viral and bacterial infections occurred frequently.[39]

Pneumonia definition and diagnosis of ALRTI

The definitions of pneumonia vary widely. Acute pneumonia is generally defined as an infection of the alveoli and interstitial tissues of the lung that is marked by symptoms of acute infection such as fever, cough and dyspnea, and is typically associated with abnormal auscultatory findings (eg; rales, altered breath sounds) or the presence of infiltrate on chest imaging. The WHO has defined pneumonia solely on the basis of clinical findings obtained by visual inspection and timing of respiratory rate. Definitions are a particular problem in small infants, because pneumonia and bronchiolitis are both common, and the features of these two diseases often overlap.[30,31]

The WHO diagnoses pneumonia as an acute episode with cough or difficult breathing accompanied by fast breathing (tachypnea).

According to the protocol for a child younger than 5 years, simple (non-severe) pneumonia is indicated by a respiratory rate of $\geq$50 breath per minute in a child <12 month of age, and a respiratory rate $\geq$40 breaths per minute in those aged 12-59 months. Patients with pneumonia and chest wall in drawing are categorized as severe pneumonia. When pneumonia is accompanied by danger signs (inability to drink, excessive sleepiness, central cyanosis, convulsion, severe malnutrition or persistent vomiting) it is considered as very severe pneumonia. Because of the increased risk of higher mortality in infants younger than 2 months of age the cut-off values for diagnosing pneumonia is $\geq$60 breath/minute, and this is categorized as severe pneumonia needing immediate referral for in-patient care.[3-5,45] This classification correlate well with disease severity and the category of severe pneumonia is highly specific for lower respiratory infections. Several studies have shown that in children<5 years of age the WHO defined tachypnea had the highest sensitivity and specificity with radio-logically confirmed pneumonia.[6-12] A clinical

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study was conducted to investigate the reliability of age appropriate respiratory rate and other clinical signs and symptoms in the diagnosis of pneumonia in children <5 years of age. Chest radiography was used as the diagnostic standard. Rapid breathing was a better predictor of pneumonia than rales (PPV 75% vs 66.9%). Nasal flaring, chest wall in drawing and cyanosis had PPV>80% but were observed only in a small proportion of patients.[6]

Treatment (management) of ALRTI

Early diagnosis and prompt establishment of empiric antibacterial therapy is the mainstay of the WHO/IMCI/ARI case-management guidelines to reduce pneumonia related mortality in developing countries. According to protocol any patient with severe and/or very severe pneumonia requires hospital admission for parenteral medications, whereas those with simple pneumonia (cases only with tachypnea) could be treated at home with an oral first–line antibacterial agent. The guidelines also recommended that all infants younger than 2 month of age with pneumonia should be hospitalized as a severe case and treated with parenteral antibiotics.[3-5,45]

The first-line antibiotics should be directed primarily at the two treatable pathogens. However, the first-line antibacterial agents should be effective, reliable, widely available and affordable in resource-poor countries. For the empiric treatment of non- severe pneumonia at a first –level health facility, technical update of the WHO/IMCI guidelines published in 2005 recommended oral Amoxycillin (Amx) (50 mg/kg/day in two divided dose) or Co-trimoxazole (Co-tr) (8 mg/kg/day of trimethoprim in two divided dose) as the first –line therapy because of their low cost and wide-spectrum coverage.[45-47] An approach that targets the two predominant bacterial agents, Snp and Hib, has been repeatedly shown to be effective in reducing pneumonia mortality through studies and clinical experience over the past two decades.[13,14,33-35]

Treatment failure

In cases with simple pneumonia, specific empiric antibacterial treatment should result in reduction of respiratory rates and improvement in the general conditions within 48 hours of therapy.[48,49] Development of chest-wall in- drawing or occurrence of danger signs at any time during therapy are defined as treatment failure. In this situation, for further evaluation and inpatient care immediate referral is required.[37,45,50]

If within 72 hours of therapy, the patient general conditions dose not deteriorate and persistent tachypnea is still observed (respiratory rate is not decreased by $\geq$ 5 breaths/minute), before referral and/or changing antibiotic, a brief but systematic evaluation by the primary health care provider is required to assess possible causes of unresponsiveness to treatment (Figure 1).[50]

If the assessment indicates incorrect use of the antibiotic, and presence of wheezing, HIV, and TB are unlikely and referral is not warranted, a second-line antibacterial agent with broader coverage is recommended. In this situation, high dose Amoxycillin (80-100 mg/kg/day) with Clavulanic acid (co-Amx) for 5 days, or if patient is older than 3 years an affordable macrolide/azalide should be added to the existing Amx. If the initial therapy was with Co-tr changing to the standard dose of Amx for 5 day is recommended.[37,45,50]

For cases with severe and/or very severe illness

In-hospital care management, the second–line antibacterial agents should ensure coverage of resistant organisms and cover a

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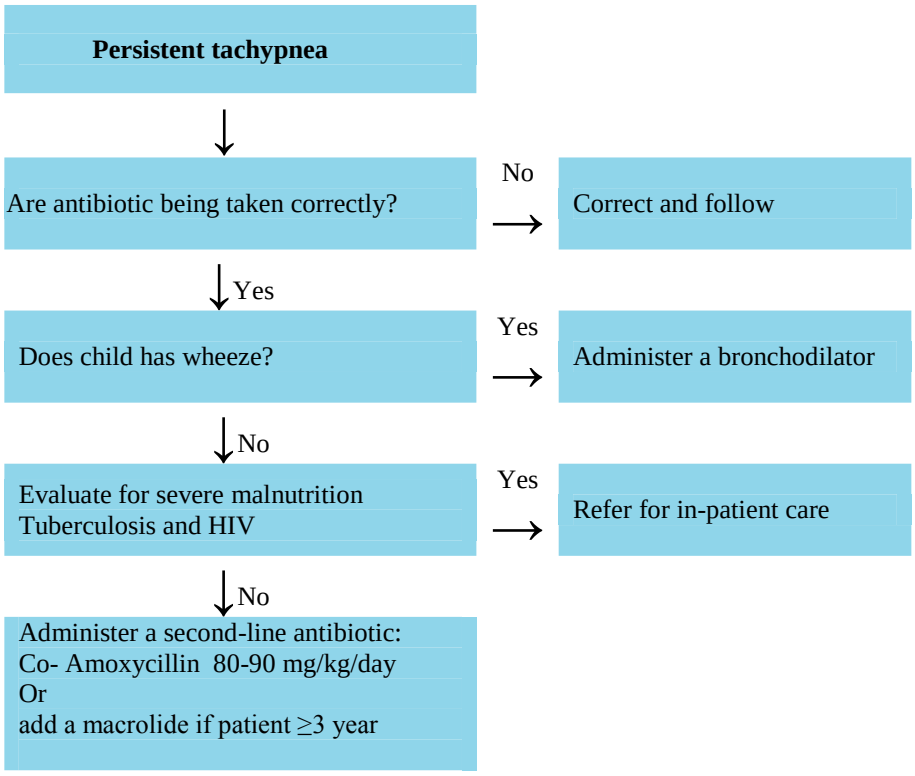

Figure 1. Algorithm of systematic management in children 2 to 59 months of age with non-severe pneumonia and persistent tachypnea 48-72 hours after initiation of antibacterial therapy

broader range of organisms that would not be treated with typical first-line agents. Of those, cost of treatment was thought to be the next most important factor. The guidelines recommended antibiotics included parenteral intravenous chloramphenicol (100mg/ kg/day divided every 6 hours) or benzyl-penicillin (200000 unit/kg/day divided every 6 hours) combined with gentamicin (7.5 mg/kg/day divided every 12 hours).[45] If a child meets criteria for referral but this is impossible, the child should be treated with the same antibiotics. In addition to administration, and bronchodilators antibacterial therapy, the WHO guidelines include intravenous fluid therapy, O_2 as clinically indicated based on severity of the disease.[45]

Discussion

Using the IMCI guidelines to treat pneumonia in developing counties has helped to reduce pneumonia-related mortality significantly.[13,14] However, nearly 20-30% of cases fulfilling the WHO criteria for non-severe pneumonia receive unnecessary antibiotics for possible non-severe lower respiratory infections.[51] Studies from Asia reported that a large proportion of antibacterial treatment failure for pneumonia occurred in children with wheeze who were misclassified as pneumonia.[15]

In order to address the issue of pneumonia over-categorization and rational use of antibiotics in

children with wheeze the IMCI guidelines and other studies.[16,17,20,21,26, 45]

Recommended giving two cycles of rapid-acting inhaled bronchodilator at 15 minute intervals to patients with a diagnosis of pneumonia but an audible wheeze before

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continuing for antibiotic therapy. If the patient's condition improved and fast breathing and chest retraction resolved after inhaled medication they are reclassified as "no pneumonia" and discharged with an inhaled bronchodilator. However, a large number of infants with wheeze have viral bronchiolitis and do not respond to bronchiodilators.[16,17,20,21]

Because of improvement in socio-economic conditions and vaccination of children against Hib in many developing countries, increased availability of newer antibiotics and the emergence of antibacterial resistance the WHO recently undertook an expert review of the IMCI guidelines for community – acquired pneumonia case- management.[50]

These updated recommendations now identify Amx as the preferred first –line agent. For the treatment of cases with severe and very severe pneumonia in the hospital setting, the third cephalosporins, e.g. ceftriaxone, were recommended as the most appropriate antibiotic against resistant Spn and Hib. It would be acceptable for a second-line agents to be more expensive than first–line drugs. However, the possibility of overuse in developing countries, their use in the out-patient clinics are not recommended. Although, most oral second-and third-generation cephalosporins have improved coverage against beta-lactamase producing Hib, but are not as active as high-dose Co-amx/Amx against Spn, therefore, they are not recommended as an alternative. Beta-lactam antibiotics do not provide coverage against atypical agents causing pneumonia such as *Mycoplasma pneumonia* and *chlamydophila pneumonia*. Macrolides and azalides (erythromycin, clarithromycin, azithromycin) are priced reasonably, but are relatively inactive against Hib and also, there is an increasing resistance against Spn. The most important role of macrolides and azalides is their activity against *Mycoplasma* and *Chlamydia pneumonia*. Therefore, in the cases of first-line treatment failures in children ≥ 3 years, or as the first-line antibiotic in cases older than 5 years these drug are recommended.[50]

Many studies in the world[53-56] and in Iran[57] indicated that between 17% and 90% of children with ARIs are receiving antibiotics, which are inappropriate in the majority of cases. [53-57]

The overuse of antibacterial agents can lead to development of bacterial resistance, adverse effects, and financial cost to both the patient and the community. To rationalize antibiotic prescription, adherence to IMCI/WHO standard ARI case-management guidelines is recommended. Qazi et al[56] compared the extend of antimicrobial therapy before and after the WHO-ARI case management implementation in the Pakistan. The results indicated that although the protocol led to more hospitalization, the strategy contributed to a significant reduction in case fatality and, reduced both antibiotic use and expenditure of drugs.[58]

Iran has adopted the IMCI guidelines for case-management of childhood illnesses since the 1990s. However, there are not uniformly and standardly applied protocol to manage patient with ARIs in the medical universities, public health provider centers, and private clinics in the country. Health care providers in all sectors use various classes of antibiotics in the treatment of cases with ARIs that are strongly promoted by the pharmaceutical industry as better or stronger antibiotics, mostly inappropriately.[57] To reduce overprescription of antibacterial agents, prevent unnecessary hospitalization for pneumonia and ALRTI, and to improve resources for public health, universal

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implementation of the IMCI protocol in the management of cases with ARI seems to be reasonable. Furthermore, to improve the identification of true pneumonia cases in children, who meet the WHO criteria for diagnosing pneumonia cases, appropriate use of clinical findings such as fever,[23] rales, nasal flaring, [6] wheezing[27] and laboratory data such as white blood cell count and polymorphonuclear count, erythrocyte sedimentation rate, C - reactive protein, [31] and finally chest imaging, [25] which are available in most parts of the country are recommended.

Conclusion

The IMCI/ARI case management has been effective in reducing pneumonia related mortality in children< 5 years of age in developing countries. However, this protocol resulted in over use of antibiotics in some cases with ALRTI who were misclassified as pneumonia. To reduce antibiotic over prescription, guidelines recommended administering two cycles of rapid acting bronchodilator inhaler to patients classified as pneumonia and audible wheeze. The protocols had developed overtime. In this reading Amoxycillin was recommended as the first-line therapy with simple pneumonia and third-generation cephalosporin for those with severe/very severe pneumonia in the hospital settings. To rationalize antibiotic prescription, adherence to WHO standard case-management protocols is recommended. Furthermore, to improve the identification of true pneumonia cases in children who met the WHO criteria for diagnosing pneumonia cases appropriate use of other clinical findings such as rales, wheeze, laboratory data such as white blood cell counts and polymorphonuclear cells, erythrocyte sedimentation rate and chest imaging are recommended.

Conflict of Interest

None declared.

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