Challenges of Empirical Antibiotic Therapy for Community-Acquired Pneumonia in Children

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally, responsible for more than 14% of deaths in children younger than 5 years of age. Due to difficulties with pathogen identification and diagnostics of CAP in children, targeted antimicrobial therapy is not possible, hence the widespread use of empirical antibiotics, in particular penicillins, cephalosporin, and macrolides.

Objectives: This review aimed to address medical, societal, and political issues associated with the widespread use of empirical antibiotics for CAP in the United Kingdom, India, and Nigeria.

Methods: A literature review was performed identifying the challenges pertaining to the use of widespread empirical antibiotics for CAP in children. A qualitative analysis of included studies identified relevant themes. Empirical guidance was based on guidelines from the World Health Organization, British Thoracic Society, and Infectious Diseases Society of America, used in both industrialized and resource-poor settings.

Results: In the United Kingdom there was poor adherence to antibiotics guidelines. There was developing antibiotic resistance to penicillins and macrolides in both developing and industrialized regions. There were difficulties accessing the care and treatment when needed in Nigeria. Prevention strategies with vaccination against *Streptococcus pneumonia, Haemophilus influenza,* and measles are particularly important in these regions.

Conclusions: Effective and timely treatment is required for CAP and empirical antibiotics are evidence-based and appropriate in most settings. However, better diagnostics and education to target treatment may help to prevent antibiotic resistance. Ensuring the secure financing of clean food and water, sanitation, and public health infrastructure are also required to reduce the burden of disease in children in developing countries.

Introduction

In 2016, community-acquired pneumonia (CAP) remained an important cause of morbidity and mortality in both industrialized and developing countries.[1] Between 2000 and 2010, pneumonia caused 14.1% (n = 1,071,000) of all deaths worldwide in children aged 1 month to 5 years, making it the single most significant disease.[2] There are many factors that influence CAP incidence and disproportionately affect children in developing countries, including access to health care, vaccine implementation, living conditions, and nutrition (Table I). However, CAP remains a globally problematic disease and the barriers to overcoming its influences are multifactorial and varied across different regions of the world.

Why do we need empirical antibiotics for CAP?

The use of empirical antibiotics is inevitable due to the challenges of accurately diagnosing CAP and identifying the causative organism. Current guidelines for the management of CAP in children have been produced by the World Health Organization (WHO),[3] British Thoracic Society (BTS),[4] and Infectious Diseases Society of America[5] (this discussion will not include the treatment of neonates, immunocompromised patients, or those with underlying respiratory conditions). These guidelines have

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Table I
Estimated incidence of community-acquired pneumonia in industrialized and developing regions of the world. Estimated incidence of community-acquired pneumonia in industrialised and developing regions of the world, reported by the World Health Organisation.[1]

Region	Incidence (episodes per child-year)	Number of new cases per year (millions)
Southeast Asia	0.36	60.95
Africa	0.33	35.13
East Mediterranean	0.28	19.67
Western Pacific	0.22	29.07
Americas	0.10	7.84
Europe	0.06	3.03

been written by clinicians and academics in the fields of respiratory medicine, infectious diseases, microbiology, and epidemiology, with substantial review of the literature. Further Cochrane systematic reviews have also extensively reviewed the body of evidence to optimize empirical guidance.[6–9] They recognize the literature in both industrialized and developing countries is lacking and in need of good epidemiologic data and large, multicenter, randomized controlled trials (RCTs).

The consensus recommendations from these guidelines suggest first-line antibiotics (eg, amoxicillin and cephalosporins) for CAP and severe CAP based on the most frequently identified bacteria (ie, *Streptococcus pneumonia*) and the use of oral antibiotics in preference to intravenous (IV) unless there is severe pneumonia or the child is unable to tolerate oral antibiotics, is vomiting, or has complications.[3] Therefore, the severity of CAP must be assessed to decide whether or not the child needs treatment and if so the most suitable mode of antibiotic administration.

The main aim of antimicrobial agents is to limit progression to severe or very severe CAP and the associated mortality. However, given the ongoing contribution of CAP to global morbidity and mortality, despite global implementation of empirical management strategies, this review aims to analyze the medical, societal, and political challenges facing the widespread use of such guidelines. Region-specific issues with empirical management were evaluated with respect to 3 countries: the United Kingdom representing industrialized regions and India and Nigeria representing the 2 countries with highest estimated incidence of CAP in Asia and Africa, respectively.[2]

Methods

A literature search was performed to address the hypothesis that the challenges with widespread empirical antibiotic use for children with CAP are diverse in the United Kingdom, India, and Nigeria. Literature searches were done using PubMed and Scopus (April 2016) and only included studies published in English (there were no non-English studies identified in the searches). Search terms used included *UK* AND *Children* AND *Community-acquired pneumonia* AND *Antibiotics* (24 results); *India* AND *Children* AND *Community-acquired pneumonia* AND *Antibiotics* (23 results); *Nigeria* AND *Children* AND *Community-acquired pneumonia* AND *Antibiotics* (2 results), *United Kingdom* AND *Pneumonia* AND *Children* AND *Treatment* (391 studies), *India* AND *Pneumonia* AND *Children* AND *Treatment* (369 studies), and *Nigeria* AND *Pneumonia* AND *Children* AND *Treatment* (77 studies). The resulting 886 studies were screened, by title and abstract, for relevance using the following inclusion criteria: CAP national guidelines; antibiotic efficacy; mode of antibiotic administration; and implementation of CAP guidelines or medical, societal, financial, or cultural consequences of using empirical treatment for CAP in children. Exclusion criteria included studies of CAP in adults,

complicated pneumonia; CAP occurring in regions outside of the United Kingdom, India, or Nigeria; and studies not relating to pneumonia. All included studies underwent a qualitative analysis of the complete article and were categorized into the following themes: antibiotic use and efficacy; mode of antibiotic administration; implementation of CAP guidelines; antibiotic resistance; and medical, societal, financial, and cultural influence of empirical CAP management. These themes are discussed according to the 3 countries below.

Results and Discussion

United Kingdom: Vaccination against bacterial pathogens and epidemiology

In the United Kingdom, 7-valent pneumococcal conjugate vaccine (PCV 7) was introduced into the national immunization schedule in September 2006 and replaced by PCV13 in April 2010. During 2012-2013, vaccine coverage in England reached 94.4% for primary immunization course PCV and 92.7% for the booster combined with *Haemophilus influenzae* type b (Hib)/meningococcal C.[10] To identify the common pathogens responsible for CAP, a study of 160 children with clinically or radiologically confirmed CAP were investigated using a combination of blood culture, serology, and molecular methods for bacterial and viral isolation (**Table II**).[11] The BTS guidance was published in 2011 (predated by guidance from 2002) and proposed amoxicillin as the first-line oral antibiotic, which has good efficacy against the most prevalent bacterial pathogens *S pneumoniae* and *H influenzae*.[12] Amoxicillin is also well absorbed from the gut and its side effects are well tolerated.

United Kingdom: Poor adherence to national guidelines

To evaluate implementation, a national audit from 2009-2012 reviewed the management of children older than age 1 year hospitalized with CAP and identified poor adherence to the new BTS guidance. Considering oral antibiotics, there was overuse of macrolides (35.2% of all oral prescriptions) and co-amoxiclav (34.2%) compared with amoxicillin (24.2%) in 2011-2012. The use of IV antibiotics included the most frequent use of co-amoxiclav (39.6%), cefuroxime (17.8%), amoxicillin (7.6%), and cefotaxime

Table II
Distribution of pathogens most frequently identified from studies within the geographic regions of the United Kingdom, India, and Nigeria.* This is not an exhaustive list of microbial population epidemiology. Adapted from references 11, 27, and 34.

	United Kingdom	India	Nigeria
Viral aetiology			
Respiratory syncytial virus	21.2	24.1	30.4
Rhinovirus	8.5	10.5	
Human metapneumovirus	0.7	2.8	
Influenza A and B	7.4	3.5	17.3 (only A)
Bocavirus	3.3		
Adenovirus	6.9	3.7	
Parainfluenza	4.3 (types 1-4)	7.5	19.5 (type 3)
Bacterial aetiology			
Streptococcus pneumoniae	17.4	20.4	5.1
Haemophilus influenzae	2.3	8.2	
Group A *Streptococcus*	10.5		
Staphylococcus aureus	2.3	30.6	37.3
Mycoplasma pneumoniae	9.9	4.3 (serology)	
Moraxella catarrhalis	2.3		
Klebsiella pneumoniae	0.8	12.2	15.3

* Values are presented as %.