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Review Article

Rational Use of Antibiotics in Childhood Pneumonia: A review

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Abstract:

Inappropriate antibiotic treatment in childhood pneumonia may lead to greater expense, antibiotic resistance, toxic side effects, or even death. Important risk factors are infant and young children, low birth weight, nonexclusive breastfeeding, malnutrition, vitamin A deficiency, incomplete immunization and exposure to polluted air. Common organisms involved in pneumonia in neonatal periods are gram negative rods, group B streptococcus and staphylococcus. Beyond the neonatal period S. pneumoniae, H. influenzae, staphylococcus and mycoplasma are common. MRSA, gram negative rods and Legionella spp are commonly involved in nosocomial pneumonia.

Rational use of antibiotic for bacterial pneumonia is based on probable organism, age, vaccination and clinical status of the child. Children who do not require hospitalization should have high doses of amoxicillin 90 mg/kg/day orally divided twice daily, alternatives include cefuroxime and amoxicillin/clavulanate. For school-aged children when mycoplasma is suspected, azithromycin is generally preferred, alternatives clarithromycin can be given.

Fully immunized against H. influenzae type b and S. pneumoniae children who are not severely ill should give ampicillin or penicillin G. For children who do not meet these criteria: ceftriaxone or cefotaxime should be given. If clinical features suggest staphylococcal pneumonia (pneumatocele or empyema), then include oxacillin or vancomycin. Vancomycin and meropenem are the initial treatment of choice for nosocomial pneumonia.

Pneumonia in neonatal period should have ampicillin plus gentamicin or ceftazidime plus amikacin. Antibiotics should be continued until the patient has been afebrile for 72 hours, and the total duration should be 10 days.

Selection of appropriate antibiotic in childhood pneumonia considering age of the child, risk factor, probable organism, immunization status and clinical severity are paramount important.

Keywords: *Childhood Pneumonia, Rational Use of Antibiotics, Antibiotic resistance.*

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Introduction

Pneumonia is the single largest infectious cause of death in children worldwide which accounting for 14% of all deaths of under 5 children. Pneumonia has been the leading cause of morbidity and mortality among children under 5 for more than 3 decades.[1] Pneumonia affects children and families everywhere, but deaths are highest in southern Asia and sub-Saharan Africa. Pneumonia is caused by several infectious agents, including viruses, bacteria and fungi. The most common are the following. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children. *Haemophilus influenzae* type b (Hib) is the second most common cause of bacterial pneumonia. Respiratory syncytial virus is the most common viral cause of pneumonia. This is a preventable and treatable illness via vaccines, antibiotic treatment, and improved sanitation.[2]

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The annual incidence of *M. pneumoniae* was1.4/10,000 and of *S. pneumoniae* was 0.5/10,000. Less commonly, severe infection is caused by *Staphylococcus aureus*, especially following influenza. Fungal infection by *Pneumocystis jiroveci* (PJP) is particularly important in young children with AIDS. Viruses commonly associated with CAP are respiratory syncytial virus (RSV), para- influenza and influenza. Other viruses isolated in children with pneumonia include adenovirus, rhinovirus, herpes simplex virus, enteroviruses, human meta-pneumovirus, human bocavirus and coronavirus. Overall, viruses account for 30–67% of childhood CAP and are more frequently identified in children aged <1 year than in those aged >2 years.[3]

Nosocomial infections, or hospital-acquired infections (HAI), are among the most significant causes of morbidity and mortality in healthcare settings throughout the world Prevention of hospital-acquired infections (HAI) is central to providing safe and high-quality healthcare. Transmission of infection between patients by health workers, and the irrational use of antibiotics have been identified as preventable aetiological factors for HAIs. Whether antibiotic use was rational or inappropriate was assessed at the time of study entry in every patient with a community acquired infection and was treated with antibiotics, and each day during their hospital admission. The standards for empirical antibiotic prescribing for community-acquired infections were based on the recommendations contained in the WHO Pocket Book of Hospital Care for Children.[4]

The World Health Organization (WHO) developed a pneumonia case management strategy which included the use of antibiotics for both primary and hospital-based care.[1] The commonly used antibiotics in Bangladesh were ampicillin, gentamicin, amoxicillin, cloxacillin, azithromycin, ciprofloxacin and ceftriaxone for treating pneumonia and diarrhea for all the pediatric age groups which might be influenced by physicians' personal choice and limited experience. Antibiotic use is influenced by the personal preference of hospital physicians, limited experi-ence, availability of antibiotics, and the potential effects of marketing by pharmaceutical industries.[5] It has been shown that ceftriaxone, cefotaxime, amikacin, cefuroxime, and ceftazidime with or without combination were commonly used for the treatment of pneumonia after hospital admission. It also appeared that physicians in primary health care in that country have antibiotic preference for the cephalosporin and carbapenem group.[6]

These antibiotics prescribed by qualified physicians or drug sellers prior to hospitalization may have an influence on antibiotic practices in the inpatient depart-ment of hospitals after admission. the use of injectable antibiotics was high in the private hospital which did not follow the WHO standard treatment guidelines.[7]

At present, antibiotics are the most commonly sold drugs in the developing countries. The rampant and excessive use of antibiotics for any and every condition has escalated the problem of antibiotic resistance. Overall, in this study it was found that misconceptions exist about the use and indications of antibiotics. Lack of knowledge regarding antibiotic resistance was prevalent.[8,9]

There was no difference in outcome of uncomplicated CAP in previously healthy children <36 months of age be-tween those treated and not treated with antibiotics. Additional tools are needed to facilitate identification of viral CAP in young children and decrease unnecessary antibiotic use. The rational use of antibiotics not only concerns the actions of providers, in ensuring patients receive appropriate treatment for their condition, at the right dose and duration, but also those of patients, in adhering to the treatment regimens prescribed, completing the full course and not sharing or storing medicines for future use.[10] The important reasons of irrational use of antibiotics in childhood pneumonia are difficult microbiological diagnosis and non-availability drug resistance profile along with unrestricted use of antibiotics by the physicians, poor public awareness and management of pneumonia on the basis of fast breathing.

Risk factors and common pathogens involved in Childhood pneumonia

Common risk factors for childhood pneumonia are infant and young children, low birth weight, no or nonexclusive breastfeeding, malnutrition, vitamin A deficiency, Incomplete basic immunization, overcrowded and exposure to polluted air.[11]

Aetiology is further complicated by limited microbiological work-up in the community, seasonality, mixed infections and viruses and commensal bacteria in samples.[12]

Table I

Pathogens commonly associated with pneumonia in children.[13]

Age group	Bacteria	Viruses
Birth to 3 weeks	Group B streptococcus, *Escherichia coli,* other Gram-negative bacilli, *Listeria monocytogenes* *Streptococcus pneumoniae,* *Haemophilus influenzae* (type b, nontypeable)	
3 wks to 3 mo	*S. pneumoniae, H. influenzae* (type b, nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus)
4 mo to 4 yrs	*S. pneumoniae, H. influenzae* (type b, nontypeable), *Mycoplasma pneumoniae,* group A streptococcus	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus)
≥5 yrs	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b, nontypeable), *Legionella pneumophila*	Influenza viruses, adenovirus, other respiratory viruses, Human corona virus

Streptococcus pneumoniae (pneumococcus) is the most common bacterial pathogen in children 3 week to 4 years of age whereas, Mycoplasma pneumoniae and Chlamydophila pneumoniae are the most frequent bacterial pathogens in children age 5 years and older. Mixed Anaerobes in aspiration pneumonia and parasites (Ascaris, Strongyloidiasis) in eosinophilic pneumonia are common pathogen.

Table II

Infectious agents and clinical implication of childhood pneumonia.[13]

Organisms	Clinical implication
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
Staphylococcus aureus	Pneumatoceles, empyema; infants; nosocomial pneumonia
Mycoplasma pneumoniae	Adolescents; summer–fall epidemics
Chlamydophila pneumoniae	Adolescents
Chlamydia trachomatis	Neonate
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
H. influenzae type b	Unimmunized
Legionella species	Exposure to contaminated water; nosocomial

Selection of antibiotics

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on local epidemiology, the immunization status of the child, and the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae*, children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime may beused. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin. Moreover, if infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic should be included in the treatment regimen (Table 3). If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for preschool-aged patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens.

Table III

Selection of Antimicrobial Therapy for Specific Pathogens[13]

Pathogen	Parenteral Therapy	Oral therapy (step-down Therapy or mild infection)
Streptococcus pneumoniae with MICs forpenicillin ≤ 2.0μg/mL	**Preferred:** ampicillin (150-200 mg/kg/day every 6 hr) or penicillin (200,000-250,000U/kg/day every 4-6 hr); **Alternatives:** ceftriaxone (50-100 mg/kg/day every 12-24 hr) (preferred for parenteral outpatient therapy); may also be effective: clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	**Preferred:** amoxicillin (90 mg/kg/day in 2 doses or 45 mg/kg/day in 3 doses); **Alternatives:** second- or third generationce phalosporin (cefpodoxime, cefixime, cefprozil); oral levofloxacin, if susceptible (16-20mg/kg/day in 2 doses for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg) or oral linezolid (30 mg/kg/day in 3 doses for children <12 yr old and 20 mg/kg/day in 2 doses for children ≥12 yr old)
S. pneumoniae resistant to penicillin, with MICs ≤4.0 μg/mL	**Preferred:** ceftriaxone (100 mg/kg/day every12-24 hr); **Alternatives:** ampicillin (300-400 mg/kg/day every 6 hr), levofloxacin (16-20 mg/kg/day every 12 hr for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg), orlinezolid (30 mg/kg/day every 8 hr for children <12 yr old and 20 mg/kg/day every12 hr for children ≥12 yr old); may also be effective: clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	**Preferred:** oral levofloxacin (16-20 mg/kg/day) in 2 doses for children 6 mo to 5 yr and 8-10 mg/kg/day once daily for children 5-16 yr, maximum daily dose, 750 mg), if susceptible, or oral linezolid (30 mg/kg/day in 3 doses for children <12 yr and 20 mg/kg/day in 2 doses for children ≥12 yr); **Alternative:** oral clindamycin (30-40mg/kg/day in 3 doses)
Group A streptococcus	**Preferred:** intravenous penicillin (100,000–250,000 U/kg/day every 4-6 hr) or ampicillin(200 mg/kg/day every 6 hr); **Alternatives:** ceftriaxone (50-100 mg/kg/day every 12-24 hr); may also be effective: clindamycin, if susceptible (40 mg/kg/day every 6-8 hr) or vancomycin (40-60mg/kg/day every 6-8 hr)	**Preferred:** amoxicillin (50-75mg/kg/day in 2 doses), or penicillin V(50-75 mg/kg/day in 3 or 4 doses); **Alternative:** oral clindamycin (40mg/kg/day in 3 doses)

Table III (Cont'd)

Pathogen	Parenteral Therapy	Oral therapy (step-downTherapy or mild infection)
Staphylococcus *aureus* , methicillin susceptible	**Preferred:** cefazolin (150 mg/kg/day every 8 hr) or semisynthetic penicillin, e.g., oxacillin (150-200 mg/kg/day every 6-8 hr); **Alternatives:** clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60mg/kg/day every 6-8 hr)	**Preferred:** oral cephalexin (75-100mg/kg/day in 3 or 4 doses); **Alternative:** oral clindamycin (30-40mg/kg/day in 3 or 4 doses)
S. aureus , methicillin resistant, susceptible to clindamycin	**Preferred:** vancomycin (40-60 mg/kg/day every 6-8 hr or dosing to achieve anAUC/MIC ratio of >400) or clindamycin (40mg/kg/day every 6-8 hr); **Alternatives:** linezolid (30 mg/kg/day every 8hr for children <12 yr old and 20 mg/kg/day every 12 hr for children ≥12 yr old)	**Preferred:** oral clindamycin (30-40mg/kg/day in 3 or 4 doses); **Alternatives:** oral linezolid (30mg/kg/day in 3 doses for children <12yr and 20 mg/kg/day in 2 doses for children ≥12 yr)
S. aureus, methicillin resistant, resistant to clindamycin	**Preferred:** vancomycin (40-60 mg/kg/day every 6-8 hr or dosing to achieve anAUC/MIC ratio of >400); **Alternatives:** linezolid (30 mg/kg/day every 8hr for children <12 yr old and 20 mg/kg/day every 12 hr for children ≥12 yr old)	**Preferred:** oral linezolid (30 mg/kg/day in 3 doses for children <12 yr and 20mg/kg/day in 2 doses for children ≥12yr old); **Alternatives:** none; entire treatment course with parenteral therapy may be required
Haemophilus influenza, typeable (A-F) or nontypeable	**Preferred:** intravenous ampicillin (150-200mg/kg/day every 6 hr) if β-lactamase negative,ceftriaxone (50-100 mg/kg/day every 12-24hr) if β-lactamase producing **Alternatives:** intravenous ciprofloxacin (30mg/kg/day every 12 hr) or intravenous levofloxacin (16-20 mg/kg/day every 12 hr for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximumdaily dose, 750 mg)	**Preferred:** amoxicillin (75-100mg/kg/day in 3 doses) if β-lactamase negative, or amoxicillin clavulanate (amoxicillin component, 45 mg/kg/dayin 3 doses or 90 mg/kg/day in 2 doses) if β-lactamase producing; **Alternatives:** cefdinir, cefixime,cefpodoxime, or ceftibuten
Mycoplasma pneumoniae	**Preferred:** intravenous azithromycin (10mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); **Alternatives:** intravenous erythromycin lactobionate (20 mg/kg/day every 6 hr) orlevofloxacin (16-20 mg/kg/day every 12 hr; maximum daily dose, 750 mg)	**Preferred:** azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2-5); **Alternatives**: clarithromycin (15mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 yr old, doxycycline (2-4 mg/kg/day in 2 doses; for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)

Table III (Cont'd)

Pathogen	Parenteral Therapy	Oral therapy (step-downTherapy or mild infection)
Chlamydia *trachomatis* or Chlamydophila pneumoniae	**Preferred:** intravenous azithromycin (10mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); **Alternatives:** intravenous erythromycinlactobionate (20 mg/kg/day every 6 hr) orlevofloxacin (16-20 mg/kg/day in 2 doses for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg)	**Preferred:** azithromycin (10 mg/kg onday 1, followed by 5 mg/kg/day once daily days 2-5); **Alternatives:** clarithromycin (15mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 yr old, doxycycline (2-4 mg/kg/day in 2 doses); for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)
Neonatal pneumonia or Early Neonatal sepsis:*Gram-Ve Rods, Entercoccus, group B Streptococcus*	**First line:** ampicillin plus gentamicin **Second line:** ceftazidime/ cefotaxime plus amikacin as	No
Associated Late onset Neonatal Sepsis or Hospital acquired pneumonia	**First line:** ceftazidime/cefotaxime plus amikacin **Second line:** meropenem + vancomycin/amikacin or piperacillin/ tazobactam, or cefepime as	Yes

Durations of antibiotics

Antibiotics should generally be continued until the patient has been afebrile for 72 hr, and the total duration should not be less than 10 days (or 5 days if azithromycin is used). Shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis, but further study is needed.[13]

The community treatment of non-hypoxaemic children with chest-indrawing pneumonia with 5-day oral amoxicillin by trained, equipped and supervised community level heath workers (CLHWs) is non-inferior to currently recommended facility-based treatment. These findings encourage a review of the existing strategy of community-based management of pneumonia.[14]

Inappropriate duration was defined as antibiotic used for more than 20% longer than the recommended duration in the standard without a documented reason.[15]

However, rational use of antibiotics could be strengthened through improved respiratory rate assessment, and better diagnostic tools. Furthermore, a shorter course of dispersible amoxicillin could potentially improve caregiver adherence, reducing risk of resistance and cost.[4,5]

These data help support current national guidelines from developed countries recommending at least 5 days of antibiotics for children suspected of bacterial pneumonia[6,9,14,1].

Study showed among children responding to initial treatment for outpatient CAP, a 5-day antibiotic strategy was superior to a 10-day strategy.[17] The shortened approach resulted in similar clinical response and antibiotic-associated adverse effects, while reducing antibiotic exposure and resistance.[6,18]

Antibiotic Resistance

Antimicrobial resistance (AMR) is a global public health emergency. Antimicrobial stewardship programmes have been identified as one of the core strategies to tackle AMR. Efforts to prevent antibiotic resistance have been launched both internationally and nationally. Antimicrobial stewardship program

(ASP) in hospitals aims to optimize antimicrobial prescribing to obtain optimal use of antibiotics, prevents the development of antibiotic resistance, improves individual patient care as well as reduce hospital costs, and slows the spread of antimicrobial resistance. To find out the effectiveness of the ASP program, it is necessary to evaluate the use of antibiotics in hospitals.[9,13,19]

Poor knowledge and misunderstanding of antibiotic treatment are also factors in the increased occurrence of resistance.[20]

Study showed blood cultures positive patients of pneumonia was 6% among which 18.5% MDR (ampicillin, gentamicin, ciprofloxacin, and ceftriaxone). Isolated organisms were: Gram-negative pathogens 77% include Pseudomonas, Escherichia coli, Salmonella Typhi, and Klebsiella pneumoniae. Gram-positive pathogens include Pneumococcus and Staphylococcus aureus. 29% pt died blood culture positive and 7% pt died without culture positive pneumonia.[21,22]

The treatment of K. pneumoniae infections has become more difficult due to the emergence of multidrug resistant strains. There are very few therapeutic options for treating MDR Klebsiella pneumoniae.[23]

Table IV

Suggestions for rational use of antibiotics in childhood pneumonia[24]

In general	
Action	Suggestions
Enhanced regulation	• Limit over-the-counter availability of antibiotics; establish strong national policies for appropriate antibiotic regulation;implement measures to ensure compliance• Improved national surveillance of antimicrobial resistance and adherence to treatment guidelines• Regulate agricultural use of antibiotics
Patient/public education	• Increase general awareness of adverse effects associated with excessive antibiotic use• Educate parents, caretakers, politicians & the general community about the benefits of restricted antibiotic use
Universal vaccination	• Maintain high uptake of Hib and PCV as well as other vaccines (e.g. pertussis and measles)
Within hospitals	
Provide information on local drug resistance patterns	• Maintain a network of functional microbiology laboratories, with adequate quality assurance and sharing of information
Establish functional antimicrobial stewardship programs	• Each hospital should have an antimicrobial stewardship program and a Drug and Therapeutics Committee with access to reliable and up-to-date data on antibiotic usage and drug resistance profiles• Each hospital should have regular/annual antibiotic use audits led by pharmacists or infectious disease control personnel
Provide clear guidance	• Develop national/regional consensus treatment guidelines that consider the international evidence base, as well as local disease etiology and drug resistance data
Eliminate perverse incentives	• Delink remuneration from antibiotic prescription • Ban incentives to doctors to provide antibiotics or use specific medical products
Educate medical students and trainees	• Include antimicrobial stewardship in the undergraduate medical, nursing and pharmacy curriculum • Highlight the growing drug resistance problem and need for prudent use

The following aspects should be considered (1) there should be a strong regulation and effective law enforcement to limit excessive use of antibiotics (2) training of health care providers (3) strengthening the laboratory surveillance (4) public awareness program (5) antimicrobial stewardship program.[5,24]

Conclusion:

Pneumonia has significant health impact on the pediatric population. Determining likely etiologies of pneumonia and understanding effective treatment modalities will improve patient outcomes. Rational empiric antibiotic treatment must be started with considering age, vaccination status of the child, clinical status, the most common bacterial causes and local drug resistance profile. Bacteriological isolation with drug sensitivity in childhood pneumonia is important to reduce childhood mortality and prevent the antimicrobial resistance.

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