A PRACTICAL GUIDE FOR THE DIAGNOSIS AND TREATMENT OF PEDIATRIC PNEUMONIA

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Abstract

Introduction: Age is the best predictor of the cause of pediatric pneumonia, viral pneumonia being most common during the first 2 years of life. The absence of a symptom cluster of respiratory distress, tachypnea, crackles and decreased breath sounds accurately excludes the presence of pneumonia (level II evidence). Bacterial cultures of samples from the nasopharynx and throat have no predictive value; however, Gram staining and culture of sputum from older children and adolescents are useful (level III evidence). Oral antimicrobial therapy will provide adequate coverage for most mild to moderate forms of pneumonia in children (level III evidence). Parenteral therapy is typically reserved for neonates and patients with severe pneumonia admitted to hospital (level III evidence).

Objectives: To develop guidelines for the diagnosis and management of community- acquired pediatric pneumonia. They are the only guidelines to address antimicrobial treatment from an age-related, etiologic perspective.

Patients and methods: The patients are tipically in pediatric age. The methods to evaluate studies on treatment are considered well-conducted randomized placebo-controlled trials as level I (strong) evidence, well-designed controlled studies without randomization (including cohort and case–control studies) as level II (fair) evidence and expert opinion, case studies and before–after studies as level III (poor) evidence.

Conclusions: Increased awareness of the causes of pneumonia, accurate diagnosis and prompt treatment should reduce costs associated with unnecessary investigations and complications due to inappropriate treatment.

Key words: Clinical assessment, empirical antimicrobial therapy, laboratory testing and radiography.

Introduction

Pneumonia occurs more often in early childhood than at any other age. Identifying the cause of pneumonia in children is difficult because of the lack of rapid, commercially available, accurate laboratory tests for most pathogens. Thus, empirical therapy is the common course in most cases. Children had previously been excluded from treatment guidelines (1,2) because of differences between adults and children in frequency and type of underlying illness and causative pathogens. A hierarchical evaluation of the strength of evidence modified from the methods of the Canadian Task Force on the Periodic Health Examination (4) was used. To evaluate studies on treatment, the consensus group considered well-conducted randomized placebo-controlled trials as level I (strong) evidence, well-designed controlled studies without randomization (including cohort and case–control studies) as level II (fair) evidence and expert opinion, case studies and before–after studies as level III (poor) evidence. The choice of antibiotics on the basis of various organisms' susceptibility to antimicrobial agents and the generalization of experience from another clinical condition involving the same organism also constituted level III evidence. For studies examining other aspects of pediatric pneumonia (e.g., epidemiologic features, and clinical and laboratory evaluation), the application of such a hierarchy of evidence was not feasible or appropriate. Different criteria were used instead. For epidemiologic studies, evidence derived from a population-based sample was considered superior to results from a hospital-based sample. In addition, studies that followed a population prospectively were preferred over cross-sectional surveys. Several "viralwatch studies" — involving the enrolment of neonates and their families and follow-up over the first few years of life with both telephone calls and office visits—provided incidence data in a well-defined denominator population and thus were considered superior to poorer quality studies. Analogous to the hierarchical criteria for evidence on treatment, cohort studies were preferred over crosssectional studies or descriptive studies. For the review of studies of clinical and laboratory diagnosis, the diagnostic test and "gold standard" had to be determined independently. A spectrum of illness severity was preferred. When possible, a discussion of interrater or intrarater reproducibility is included. Thus, cohort studies (level II evidence) form the basis of review of the epidemiology and diagnosis sections. These study designs usually constitute the highest quality

evidence for such aspects of a topic. Unfortunately, few studies have been conducted involving children in developed countries, and many of these have been limited by poor power and inappropriate choice of antibiotic alternatives. Thus, the consensus group developed antibiotic recommendations on the basis of available clinical trials, however few, and the spectrum of activity against the most frequent pathogens in each age group. The members selected the least expensive antibiotic with the narrowest antibacterial spectrum unless an agent with a broader spectrum was felt necessary. They also considered minimization of side effects and maximization of compliance as important factors in recommending specific agents.

Several risk factors increase the incidence or severity of pneumonia in children: prematurity, malnutrition, low socioeconomic status, passive exposure to smoke and attendance at day-care centres (10). Underlying disease, especially that affecting the cardiopulmonary, immune or nervous systems, also increases the risk of severe pneumonia; however, the consensus group focused on otherwise healthy children with community-acquired pneumonia.

Causes

In most studies the specific cause of pneumonia could not be identified in 40% to 60% of cases (5,6,7,8),(10,11,12,13,14,15,16,17,18,19,20). Most of the difficulty is in differentiating between viral and bacterial infections. Early studies required a positive blood culture result for proven bacterial pneumonia 5,6,7,8). More recently, detection of a bacterial antigen or a convalescent antibody response to bacterial antigens has been used to implicate *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), nontypable *H. influenzae* (NTHI) and *Moraxella catarrhalis* (12,13,14, 15,16, 17,18,19). The best predictor of the cause of pediatric pneumonia is age (Table nr.1). During the first 2 years of a child's life viruses are most frequently implicated (5,6,7,8). As age increases, and the incidence of pneumonia decreases, bacterial pathogens, including *S. pneumoniae* and *Mycoplasma pneumoniae*, become more prevalent.

Infants and toddlers (1–24 months)

Pneumonitis syndrome: Infants (1–3 months) may present with a characteristic syndrome of cough, tachypnea, progressive respiratory distress and radiologic evidence of bilateral diffuse pulmonary infiltrates with air trapping. Most are afebrile. Stagno and associates[11] found a single pathogen in 70 patients (76%) of 104 patients and multiple

pathogens in the remaining 25 patients (24%). The presence of more than one pathogen was significantly associated with more frequent requirements for oxygen and mechanical ventilation. The most common pathogens included *Chlamydia trachomatis* and respiratory viruses. A recent study involving Canadian infants admitted to hospital with bronchiolitis or pneumonia confirmed the importance of *C. trachomatis* as a cause of afebrile pneumonitis syndrome (20). *Ureaplasma urealyticum* was also isolated; however, its role is not entirely clear (20,21) *Bordetella pertussis* may also be considered in the differential diagnosis of this syndrome. *Mild and moderate pneumonia:* Respiratory syncytial virus, parainfluenza, influenza and adenovirus account for most lower respiratory tract infections, including pneumonia, in infants and toddlers (level II evidence) (7,8,12,13,15). Less frequently isolated viruses include rhinovirus, coronavirus and enterovirus (7,8). A single viral pathogen has been isolated in 31 patients (30%) to 60% of cases, and multiple viruses or a combination of viruses and bacteria have been found in 7 patients (7%) to 30% (7,8). In most cases illness begins as an upper respiratory tract infection and progresses gradually over several days, with increasing cough and respiratory distress. Scandinavian investigators (13,16,17) have implicated *S. pneumoniae* and, less often, Hib and NTHI in 4 patients (4%) to 20% of cases. *Severe pneumonia:* Bacterial pneumonia due to *S. pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus* or Hib must be considered in severely ill infants and toddlers with one of the following: rapid onset and progression of symptoms, radiographic evidence of lobar or diffuse infiltrates, large pleural effusion or lung abscess (level II evidence) (8,15,16,17).

Table nr.1 Age-specific causes of pneumonia in otherwise healthy Children

Age group	Pathogen (in order of frequency)
1–3 mo	Pneumonitis syndrome, usually afebrile: *Chlamydia trachomatis*, respiratory syncytial virus (RSV), other respiratory viruses, *Bordetella pertussis*
1–24 mo	Mild to moderate pneumonia: RSV, other respiratory viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), nontypable *H. influenzae* (NTHI), *C. trachomatis*, *Mycoplasma pneumoniae*
2–5 yr	Respiratory viruses, *S. pneumoniae*, Hib, NTHI, *M. pneumoniae*, *Chlamydia pneumoniae*
6–18 yr	*M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, NTHI, influenza A or B, adenovirus, other respiratory viruses
All ages	Severe pneumonia requiring admission to ICU: *S. pneumoniae*, *Staphylococcus aureus*, group A streptococci, Hib, *M. pneumoniae*, adenovirus

Preschool children (2–5 years)
The frequency of viral pneumonia is decreased among children in this age group. The predominant bacterial pathogen is *S. pneumoniae*. Others include Hib, NTHI, group A streptococci and *Staph. Aureus* (6,7,12,13,15) *M. pneumoniae* has been found more frequently in recent studies (22,23).

School-aged children and adolescents (6–18 years)
In this age group the most common causes of community-acquired pneumonia in otherwise healthy children are *M. pneumoniae* and *S. pneumonia* (5,7). Respiratory viruses, primarily influenza A and B, and adenovirus are found in less than 15 patients (15%) of cases.

Impact of recent trends
Universal Hib vaccination of infants
Hib was responsible for 5 patients (5%) to 18% of cases of bacterial pneumonia (7,8,11,12,13,15). Since the introduction of the Hib conjugate vaccine the number of cases of invasive disease has markedly decreased, and Hib is now considered an unlikely cause of bacterial pneumonia in children who have completed a primary series of Hib vaccination. However, the choice of empirical antibiotic therapy for vaccinated children with suspected bacterial pneumonia does not change, because Hib vaccine offers no protection against NTHI.

***Chlamydia pneumoniae*: an emerging pathogen**
Recent studies have shown that *C. pneumoniae* is associated with 15 patients (15%) to 18% of cases of community-acquired pneumonia among children aged 3–12 years (17,19,20,22). An excellent review of *C. pneumoniae* as a respiratory pathogen in children has been recently published (23). Most infections are mild or asymptomatic: only 10 patients (10%) of cases result in clinically apparent pneumonia (23). Patients typically present with fever, malaise, cough and, frequently, headache and pharyngitis (23).

HIV infection
Although the guidelines in this article focus primarily on otherwise healthy children, the first overt sign of HIV infection may be an opportunistic infection such as *Pneumocystis carinii* pneumonia in a previously healthy child. In this AIDS era, the possibility of unusual pathogens must always be considered.

Resurgence of tuberculosis
Children with pulmonary tuberculosis may not differ clinically from those with bacterial or viral pneumonia (24). However, they are more likely to have a history of contact with a person with pulmonary tuberculosis.

Invasive group A streptococcus
A resurgence of virulent group A streptococcus has been associated with outbreaks of rheumatic fever and streptococcal toxic shock syndrome and sporadic cases of invasive disease (25,26,27). Necrotizing fasciitis and pneumonia with empyema are two common clinical presentations.

Clinical assessment
Pneumonia can be defined clinically as the presence of lower respiratory tract dysfunction in association with radiographic opacity. The World Health Organization (WHO) has promoted an algorithm to assess children who present with cough and fever (28). This algorithm, based on the presence of tachypnea, considers an increased respiratory rate (more than 50 breaths/min in infants 11 months of age or less, and more than 40 breaths/min in children over 11 months) to indicate pneumonia. The presence of suprasternal, subcostal or intercostal retractions indicates greater severity. Radiographic confirmation is necessary because there is frequent disagreement between pneumonia diagnosed by clinical examination and that diagnosed by chest roentgenography (29). Radiographic confirmation is considered the gold standard (29). Estimation of respiratory rates can vary depending on the method of measurement (30) Rates are lower when measured by observation than by electronic monitoring, which in turn yields lower rates than auscultation. The duration of measurement also affects the estimation of the rate: rates are lowest when counted for 60 seconds and highest when counted for 15 seconds. Another factor is the child's level of alertness: a sleeping child's respiratory rate is lower than that of a child who is awake and crying. Ideally, the respiratory rate should be measured by observation for 60 seconds when the child is awake and not crying. Measurement of tachypnea has good reproducibility compared with observation of retractions or auscultatory findings of crackles or wheezes (level II evidence) (31,32,33). However, no finding in itself can be used to diagnose or rule out pneumonia. The absence of the symptom cluster of respiratory distress, tachypnea, crackles and decreased breath sounds accurately (100% specificity) excludes the presence of pneumonia (level II evidence) (34,35,36,37). Assessment of oxygenation gives a good indication of the severity of disease (10,38,39). Cyanosis indicates severe hypoxia, but it is usually absent in children with hypoxia (30,40). The respiratory rate is neither sensitive nor specific for identifying hypoxia (level II evidence) (30,32,40,41,42). However, the child's

general well-being and ability to be consoled indicate normal oxygenation (41). Oximetry should be considered in the assessment of a child with suspected pneumonia and in all children admitted to hospital with pneumonia, because the results correlate well with clinical outcome and length of hospital stay (level II evidence) (38,39,40). Two classic presentations have been described for pneumonia:

• Typical pneumonia: fever, chills, pleuritic chest pain and a productive cough.

• Atypical pneumonia: gradual onset over several days to weeks, dominated by symptoms of headache and malaise, nonproductive cough and low-grade fever. Unfortunately, the overlap of microbial agents responsible for these presentations thwarts identification of the causal pathogen on the basis of clinical presentation (43).

Investigation

Chest radiography

A confirmatory chest radiograph is necessary to diagnose pneumonia. Bronchiolitis and asthma may cause hyperinflation and atelectasis and must be distinguished from pneumonia. Two main patterns of pneumonia are recognized: interstitial and alveolar. However, these patterns cannot be used to identify the cause. Peribronchial thickening, diffuse interstitial infiltrates and hyperinflation tend to be seen with viral infections (level III evidence) (44,45,46,47). Lobar infiltrates, particularly with pneumatoceles and pulmonary abscesses, strongly suggest bacterial pneumonia (44,45,46,47). Half of

patients with bacterial pneumonia will present with a lobar infiltrate. Alveolar infiltrates, however, are also seen in bacterial as well as viral disease and in *Mycoplasma* pneumonia (44,45,46,47). Circular infiltrates are seen in the early stages of pneumococcal pneumonia (44,47). *M. pneumoniae* infection is typically associated with radiologic evidence of diffuse infiltration out of proportion with the clinical findings. Lobar consolidation, plate-like atelectasis, nodular infiltration and hilar adenopathy have also been described with *M. pneumoniae* (level III evidence) (45). Chlamydial pneumonia may be indistinguishable from mycoplasmal pneumonia. *P. carinii* pneumonia is typically associated with a reticulonodular infiltrate that progresses to alveolar infiltrates. Hilar adenopathy strongly suggests tuberculosis, especially if the patient has epidemiologic risk factors. In patients with uncomplicated pneumonia, repeat chest radiographs are unwarranted; however, in patients with circular infiltrates, pleural effusion, pneumatoceles or pulmonary abscess, a repeat chest radiograph should be considered to ensure resolution. Patients with a complicated course or persistent clinical abnormalities should have a repeat chest radiograph after 4 weeks (level III evidence) (48,49). The presence of a foreign body, congenital malformation or asthma should be considered in patients with recurrent pneumonia or atelectasis in the same area of the lung. Recurrences in different areas may suggest aspiration, immunodeficiency or cystic fibrosis.

Table nr.3 Diagnostic tests in children with suspected pneumonia

Test	Physician's Office	Emergency Department	Hospital
Chest radiograph	++	++	++
Complete and differential blood counts	+	+	++
Blood cultures	NR	+	++
Gram staining and culture of sputum†	+	+	+
Antigen detection of Bacteria	NR	NR	NR
Culture of throat Swab	NR	NR	NR
Serologic test for *Mycoplasma Pneumoniae*	NR	NR	+
Culture and antigen detection of viruses	NR	NR	+
Serologic test for Viruses	NR	NR	+
Tuberculin skin test	+	+	+

*++ = strongly recommended, + = recommended, NR = not recommended; level III evidence.
†In patients 6 years of age or more with productive cough.

Laboratory tests

Laboratory tests are performed to identify the causal agent. Unfortunately there are no gold standards. Thus, the utility of most of these laboratory tests are imputed from consensus and expert opinion. The inclusion of these tests in the various settings is based on their availability and feasibility rather than on evidence that they will effect a change in management or follow-up. Complete white blood cell (WBC) and differential counts should be considered in patients with suspected pneumonia (level III evidence) (48,49,50). In cases of bacterial pneumonia, the WBC count is usually increased, with a predominance of polymorphonuclear cells (47,48,49,50). Leukocytosis can occur with infections due to adenovirus and influenza virus or with *Mycoplasma* infections. Leukopenia can also be seen in viral infections; however, its presence in bacterial infections suggests severe or overwhelming infection.51 Blood cultures should be performed in patients with suspected bacterial pneumonia or in those admitted to hospital (47,50) because they may provide definitive proof of the cause. Results will be positive in 10 patients (10%) to 30% of patients with pneumonia (52). Blood cultures do appear to have a low sensitivity, but they are still worth while in order to identify the causative pathogen. In bacterial endocarditis, the organism can be identified after the first 2 cultures (53). With sepsis other than endocarditis, the sensitivity of 1, 2 and 3 cultures is 80%, 89% and 99% respectively (54). Thus, 2 blood cultures should be performed in patients in hospital with pneumonia. Each blood sample should be drawn using aseptic technique from a separate site suitably prepared with a skin disinfectant (55). If a pathogen is isolated, susceptibility testing should be performed and the results used to adjust antimicrobial therapy accordingly. Bacterial cultures of samples from the nasopharynx and throat have no predictive value (13,14). However, Gram staining and culture of sputum from older children and adolescents may be useful (level III evidence) (56). Enzymelinked immunosorbent assay (ELISA) or direct immunofluorescence can be considered in severe cases involving patients at risk of complications or for infection-control surveillance (level III evidence) (47,50). Detection of *Mycoplasma* IgM by ELISA is a sensitive technique and should be considered for children aged 5 or more (47,50).

Management

Two major issues arise in the management of pediatric pneumonia: 1) the difficulty of distinguishing patients with bacterial pneumonia (who would benefit from antibiotics) from those with nonbacterial pneumonia (who would not benefit from antibiotics) and 2) the dearth of randomized controlled trials to guide antibiotic choice. Thus, most guidelines are based on observations of the organism's in vitro susceptibility to the antibiotic rather than on proof of benefit of one antibiotic over another. Where stronger evidence is available, it is provided. However, most randomized trials of pediatric pneumonia have significant flaws or have such limited power that they are not informative (57–67). In general, oral antimicrobial therapy will provide adequate coverage for most mild to moderate forms of pediatric pneumonia (level III evidence) (22,47,50). Parenteral therapy is typically reserved for neonates and patients with pneumonia severe enough to warrant admission to hospital (level III evidence) (68). Indications to consider when contemplating admission to hospital are as follows (47,50):

- Age less than 6 months
- Toxic appearance
- Severe respiratory distress
- Oxygen requirement
- Dehydration
- Vomiting
- No response to appropriate oral antimicrobial therapy
- Immunocompromised host
- Noncompliant parents

These indications are only guidelines. The ultimate decision to admit a patient must be based on the overall clinical picture (68,69). Given the rise in incidence of organisms resistant to antimicrobial agents (70) the prescription of antibiotics for nonbacterial infections should be actively discouraged. The choice of empirical antimicrobial therapy is based on several factors, including the age of the patient, the clinical presentation and the local resistance patterns of predominant bacterial pathogens (68,69,71,72,73). In Canada the prevalence of moderately penicillin-resistant strains of *S. pneumoniae* (minimum inhibitory concentration [MIC] 0.1 to 1.0 g/mL is increasing; however, these strains are rarely associated with treatment failures (57,58,74). Of greater concern are the highly penicillin-resistant pneumococcal strains (MIC greater than 1.0 µg/mL). Vancomycin remains the only agent effective against this organism in vitro; however, high-dose ampicillin and penicillin regimens appear to be effective in cases of pneumonia due to penicillinresistant pneumococci (level II evidence) (58). Table nr.4 summarizes the

empirical antimicrobial agents recommended for patients admitted to hospital and those admitted to the intensive care unit (ICU) (level III evidence) (47,50). In infants with bacterial pneumonia the empirical therapy should be cefuroxime (level III evidence) (69). For infants admitted to the ICU, therapy should include coverage for *Staph. aureus*. Cefuroxime alone or cefotaxime plus cloxacillin is recommended (level III evidence) (69,72).

erythromycin or clarithromycin should be considered (level III evidence) (59,61).
The organisms responsible for community-acquired pneumonia in children aged 6–18 years are the atypical pathogens *M. pneumoniae* and *C. pneumonia* (22,23). Erythromycin or clarithromycin is recommended for initial empirical therapy (level III evidence) (76). Cefuroxime or ampicillin can be added (level III evidence) (76). For children in this age group who are severely ill and require admission

Table nr.4 Empirical antimicrobial therapy for pediatric pneumonia, by age group

Age group	Patients in hospital*	Patients in intensive care unit*	Outpatients†
1–3 mo Pneumonitis syndrome	Erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily (orally) in 2 doses, for 10–14 d	Erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily (orally) in 2 doses, for 10–14 d	Initial outpatient treatment not recommended
Other	Cefuroxime 150 mg/kg daily in 3 doses, for 10–14 d	Cefuroxime 150 mg/kg daily in 3 doses or cefotaxime 200 mg/kg daily in 3 doses, Plus cloxacillin 100–200 mg/kg daily in 4 doses, for 10–14 d	Initial outpatient treatment not recommended
3 mo–5yr	Ampicillin 150 mg/kg daily in 4 doses or cefuroxime 150 mg/kg daily in 3 doses, for 7–10 d	Cefuroxime 150 mg/kg daily in 3 doses, plus either erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily (orally) in 2 doses, for 7–10 d	Amoxicillin 40 mg/kg daily in 3 doses or erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily in 2 doses, for 7–10 d
5–18	Erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily (orally) in 2 doses, for 7 d, with or without cefuroxime 150 mg/kg daily in 3 doses or ampicillin 150 mg/kg daily in 4 doses, for 7–10 d	Cefuroxime 150 mg/kg daily in 3 doses for 7–10 d, plus either erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily (orally) in 2 doses, for 7 d	Erythromycin 40 mg/kg daily in 4 doses or clarithromycin 15 mg/kg daily in 2 doses, for 7 d

In infants with pneumonitis syndrome (typically caused by *C. trachomatis*) the antimicrobial of choice is erythromycin (75). Two randomized trials revealed that clarithromycin has an efficacy similar to that of erythromycin but a lower rate of side effects in an adult and a pediatric population with pneumonia (64,65). Although this suggests that clarithromycin is equivalent to erythromycin for treatment under these circumstances, clarithromycin is significantly more expensive. Most cases of bacterial pneumonia in older children (3 months to 5 years) are caused by *S. pneumoniae* and, occasionally, Hib, NTHI or *S. pyogenes*. Antimicrobial therapy can be initiated with ampicillin or cefuroxime (level III evidence) (76). Children in this age group requiring admission to the ICU should receive cefuroxime, and the addition of either

to the ICU, cefuroxime plus either erythromycin or clarithromycin is recommended (level III evidence) (69). Switching from parenteral therapy to oral therapy is a key management issue. Patients receiving parenteral therapy for 2–4 days can usually be switched to oral therapy provided they are afebrile, can tolerate medication orally, do not have diarrhea and have no relevant complications such as empyema (level II evidence) (59,68). Empirical antimicrobial therapy recommended for the treatment of outpatients with bacterial pneumonia is listed in table nr.4 (level III evidence) (76). Lack of improvement in a patient's condition necessitates admission to hospital as well as appropriate bacterial cultures to identify a resistant organism. Admission to hospital may also be required to drain an empyema and to provide prolonged parenteral

antimicrobial therapy.

Newer macrolide agents, who have fewer gastrointestinal side effects than erythromycin, are substantially more expensive than erythromycin and amoxicillin. Clinical evidence of benefit is necessary in addition to in vitro evidence of greater activity against some of the pathogens. Therefore, randomized trials comparing macrolides with β-lactam agents are urgently needed.

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