Community-Acquired Pneumonia

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Definition

Community-acquired pneumonia (CAP) is an infection of the distal part of the breathing airway and the pulmonary parenchyma in the extra-hospital environment.

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Epidemiology

In spite of the development of new antibiotics and vaccines, community-acquired pneumonia is still a frequently occurring disease, which usually presents in children under 5 years of age. It is one of the main causes of mortality annually worldwide, especially in developing countries: 2 million deaths, of which 20% correspond to children. In Chile, it is the main cause of pediatric hospital-

ization during winter and spring, corresponding to 52% of hospital admissions to the hospital in the first 2 years of life. It is the first cause of late infant mortality, with a 0.18/1000 ratio in children under 1 year old (2010), although it has experimented a dramatic decrease since 1990, when the mortality rate of community-acquired pneumonia was 60% (see Minsal 2013). Currently, the infection caused by the human immunodeficiency virus (HIV) has increased the number of deaths caused by pneumonia (with a risk six times higher in comparison to those not infected), particularly in underdeveloped countries.

Etiology

The biggest challenge in pneumonia is to determine the causative agent. The identification depends on such factors as age, disease severity, immunological condition, geographic location, year season, epidemiological situation, and immunizations. Therefore, identification of the causative agent varies between 10% and 85%, depending on the method used.

Etiology differs according to the patient's age. In newborns, group B *Streptococcus* and gram-negative bacteria are the most common agents; in infants, the most common agent is usually a virus, corresponding to 50% to 60% in Chile, for example, whereas in developed countries this percentage increases to 80%. Among the viral agents, respiratory syncytial virus (RSV) is the most frequent agent, and adenovirus causes the most serious disease (B7h serotype). Among common etiological agents, we can mention influenza, parainfluenza, and metapneumovirus: human metapneumovirus (hMPV) causes about

7% to 20% of lower respiratory infections in this age group. In past years, rhinovirus and coronavirus have also been described as causing community-acquired pneumonia.

Bacterial etiology increases with age: as many as 50% of hospitalized children are older than 5 years. *Streptococcus pneumoniae* causes the most common bacterial infection at any age, about 20–30%. It is predominant during winter and spring times. Other bacteria include *Haemophilus influenzae*, which is a rare causative agent because of mandatory vaccination, although nontypified serotypes can cause serious presentations: *Staphylococcus aureus*, which has a quick and serious progression, but currently is exceptional; and *Streptococcus pyogenes*, which has a variable clinical course, but may cause serious disease with shock and pulmonary suppuration.

Other less frequent agents include *Chlamydia trachomatis*, which is an infection acquired through the birth canal, with a clinical onset between 2 to 12 weeks of life. It does not include fever, but it does involve tachypnea, rhinitis, conjunctivitis, and coughing fits. A hemogram shows eosinophilia, and the chest X-ray is unspecific, but shows interstitial pattern predominance. *Bordetella pertussis* causes a whooping cough clinical syndrome and mainly interstitial pulmonary compromise. Atypical agents such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are common causes agents in children between the ages of 5 and 10 years, respectively (Table 31.1).

Coinfection with different pathogens is possible. The most frequent combinations are RSV or influenza virus with *Streptococcus pneumoniae*, in 30% of the cases, and *Mycoplasma pneumoniae* with *Streptococcus pneumoniae* or *Chlamydia pneumoniae* in 15% of cases (Table 31.2).

Table 31.1 Etiological orientation for pneumonia

Etiology	Bacterial	Viral	Mycoplasma
Age	Any	<2 years	5–15 years
Season	All year	Winter	All year
Presentation	Sudden	Variable	Insidious
Fever	High	Variable	Low
Tachypnea	Common	Common	Infrequent
Coughing	+	++	+++
Related symptoms	Chest pain	Acute rhinitis, conjunctivitis	Pharyngitis

Table 31.2 Etiological agents according to age

	RN	1–3 months	4–24 months	Preschool	School
Virus					
RSV	+	+++	++++	++	–
ADV	–	+	++	+	–
Influenza	–	–	+	++	+++
Parainfluenza	–	+	+	+	–
Metapneumovirus	–	+	+	+	–
Bacteria					
<i>Streptococcus pneumoniae</i>	+	+	++	++++	++++
<i>Mycoplasma pneumoniae</i>	–	–	+	++	++++
<i>Haemophilus influenzae</i>	–	+	+	–	–
<i>Staphylococcus aureus</i>	+	+	+	+	+
<i>Streptococcus agalactiae</i>	+++	+	–	–	–
<i>Escherichia coli</i> and other gram-negative bacilli	++	+	–	–	–
<i>Chlamydia trachomatis</i>	–	–	–	+	+
<i>Chlamydia pneumoniae</i>	–	–	+	+	++
<i>Streptococcus pyogenes</i>	–	–	–	+	+

Physiopathology

The following factors protect the respiratory system from infections:

1. *Mechanics*: nasal filter of inhaled air, gag reflex, cough reflex, and mucociliary clearance
2. *Immunological*, involving: alveolar macrophages, immunoglobulins, local inflammatory response, complement, cytokines, antiproteases, lysozyme, fibronectins
3. *Immune cellular response*.

Under normal circumstances, mucociliary clearance removes efficiently inhaled agents; however, if the inoculum is big, the agent is especially aggressive, or the defense mechanisms are altered, the pulmonary parenchyma will develop an infection. The inhalation of infectious agents (virus or bacteria), or the aspiration of germs through the mouth and upper airway (bacteria), is common. Contiguous hematogenous spread or endogenous reactivation, as in tuberculosis, is rare.

Bacteria cause alveolar damage accompanied by inflammatory exudate, edema, fibrin, and afterward, invasion of polymorphonuclear leukocytes. General resolution is complete almost

always, with no functional compromise. Virus cause epithelial damage which may progress to necrosis and diffuse alveolar damage in varying degrees. There is evidence suggesting that the virus could be a factor for the increase of bacterial infections, because it may take advantage of the alterations of the mechanical or immunological barrier of the host.

Clinical Manifestations

The clinical picture fluctuates in seriousness and depends on age, etiological agent, and extension. The classic triad is fever, cough, and respiratory distress. Nevertheless, cough may appear later, because there are a few receptors in the lower airways that are only irritated when cellular lysis and inflammatory exudate appear.

In the newborn, when there is a history of premature membrane rupture related to respiratory distress during the first hours of life, along with cardiovascular collapse, group B *Streptococcus* must be suspected. Infants under 3 months old frequently present with tachypnea, usually above 60 breaths per minute, along with a retraction of the soft chest structures. This is frequently associated to unspecific symptoms such as hypothermia, hyperthermia, fatigue food intolerance,

somnolence, diarrhea, or apnea. High fever must alert the clinician to rule out septic shock secondary to a respiratory infection.

In older infants, there is usually a history of upper airway symptoms with coughing and rhinorrhea. Soon after, fever, tachypnea ($>50/\text{min}$), general status deterioration, and grunting and nasal flaring appear. High fever, especially in those under 2 years old, can be related to the seriousness of the disease, although it is not a sign that can be used to determine a specific etiology. Preschool and school-age children present with high fever, accompanied by shivers, coughing, and chest pain (pain resembling a side stitch). Abdominal pain may be present when there is compromise of the inferior lobules, and often acute appendicitis must be ruled out, particularly in school-age children. Pain in the shoulder area suggests pleural compromise. Dry or productive cough, rhinorrhea, general discomfort, headache, myalgia, and abdominal pain are nonspecific signs that may or may not accompany bacterial and viral infections. Physical examination results vary and fluctuate depending on the age of the patient. Tachypnea is a very sensitive sign in patients under 5 years old. Younger infants and newborns present with reduced breath sounds but only a few crackles. Condensation syndrome—bronchophony, dullness when percussing, bronchial murmur, and fine crackles—is frequently present in children over 2 years of age. Crackles have a sensitivity of 75% and specificity less than 60%. Wheezing may be present in infants

with viral pneumonia or, in children over 5 years old with atypical pneumonia agents such as *Mycoplasma pneumoniae*. A normal respiratory examination does not rule out pneumonia, especially during the first 48 h, named the “silent period.”

Diagnostic Approach

Diagnosis suspicion is mainly clinical.

Chest X-ray

No routine chest X-rays are needed for the diagnosis in the ambulatory setting, and administration of treatment must not be delayed. However, the chest X-ray is considered the gold standard to confirm the diagnosis of community-acquired pneumonia, except when acquired very early (24 h) in the clinical progression when sensibility is low.

Chest X-rays do not differentiate among bacterial, viral, or atypical agents, but a lobar condensation pattern suggests bacterial infection and an interstitial pattern suggests viral or atypical agent infection (Figs. 31.1 and 31.2). Chest X-rays are best when used to rule out pneumonial complications such as empyema or abscess. When the clinical picture shows a persistent fever after starting antibiotic treatment and/or dullness

Fig. 31.1 Consolidated pneumonia

Fig. 31.2 Interstitial pneumonia

Fig. 31.3 Rounded pneumonia

when percussing the chest, which can be presented as an acute respiratory difficulty syndrome, accompanied by hypoxemia, and/or hemodynamic instability, a chest X-ray is mandatory. This test also must be considered in patients with no response to treatment, lobar atelectasis, round-shaped consolidation, persistent symptoms, and complicated pneumonia.

A chest X-ray follow-up at 4 weeks must be done in cases of recurrent pneumonia, lobar atelectasis, suspicion of malformation, or slow-resolution pneumonia (Fig. 31.3). Chest

echography is useful when there is a suspicion of effusion to evaluate the amount and presence of septa or recollection areas.

Basic Laboratory Analysis

White cell blood count, neutrophil count, C-reactive protein, sedimentation rate, and procalcitonin are not useful to identify the etiology. Several prospective studies have proven that acute-phase reactants have a low sensitivity and

specificity when it comes to distinguishing between a viral or bacterial infection.

Microbiology

Microbiological identification does not have any clinical impact for most children with community-acquired pneumonia. Nevertheless, for patients undergoing the most serious course and/or hospitalized, etiological investigation is important. When facing the possibility of a viral etiology, direct immunofluorescence (DIF) or ELISA tests are useful, although it must be considered that for adenovirus the sensitivity is not greater than 50% in most cases. DIF on incubated cells (shell-vial technique) yields better results. It is advisable to request this technique in cases having negative results with a high clinical suspicion. Currently, the amplification of specific viral genome fragments has a high sensitivity and specificity. It uses minimum quantities of DNA, with the simultaneous detection of multiple virus; it is easy to standardize, with quick results (8 h), and therefore it is very useful in hospitalized patients. When facing the possibility of a bacterial infection, hematic cultures have a low positive rate, so they are considered only for patients who show poor clinical response. In infants, hematic culture yields poorly (around 2%) but it is similar in older children (about 10%). In patients with pleural effusion, direct pleural space, Gram stain, and culture are less than 30% positive. Nevertheless, cytochemical analysis can help to precisely locate an empyema. In older children, Gram stain and expectoration culture may be useful when there are agents that differ from those that usually colonize the upper airway, particularly when its intracellular location corresponds to macrophages or polymorphonuclear leukocytes. To validate the sample, it is necessary to have at least 25 white blood cells and fewer than 25 epithelial cells per field. Serum antigen detection for *Streptococcus pneumoniae* and *Haemophilus influenzae* in blood, urine, or pleural effusion liquid has a low specificity and sensitivity, yielding false-positives in nasopharyngeal colonization or in patients who have recently received immunization, and therefore they are not recommended. The combination of

urine antigen with acute-phase reactants may be a good predictor for bacterial pneumonia. The effectiveness of the immune complex for *Streptococcus pneumoniae* has shown better specificity and sensitivity to diagnose *Mycoplasma pneumoniae*, and for *Chlamydia pneumoniae* serum tests such as IgM are used. They have the limitation of allowing the diagnosis only after the first week, and therefore they are not useful for early diagnosis.

Protein chain reaction (PCR) technique has a 73% sensitivity and a specificity of 94%, so the diagnosis can be done early and rapidly within the progression of the disease. Invasive methods such as bronchoalveolar lavage (BAL) may have better results, but their indication for community-acquired pneumonia is restricted to patients with a complicated course, generally with a poor response to empirical treatments, and when serological or fast microbiological methods (PCR, ELISA, DIF) have failed to yield a diagnosis. These observations are especially true for immunocompromised patients presenting with feverish neutropenia, lymphopenia, AIDS, or bone marrow or another organ transplant. When treating these patients, especially those in whom *Pneumocystis jirovecii* is suspected, it is suggested to obtain an induced sputum sample, which can be a noninvasive method that may be effective and secure in relationship to bronchoalveolar lavage.

Differential Diagnosis

It is difficult to make an etiological differential diagnosis in pneumonia. For some recurrent events, other diseases may explain its origin (Table 31.3).

Table 31.3 Pneumonia differential diagnosis

Recurrent pneumonia: same location	Foreign body aspiration
	Pulmonary malformation
Recurrent pneumonia: different location	Cystic fibrosis
	Chronic aspiration
	Immunosuppression
Noninfectious pneumonia	Gastric content aspiration
	Hydrocarbon aspiration
	Lipid aspiration
Pneumonia in immunodeficient patients	Noncommon agents

Treatment

Outpatient

General Measures

Most patients will respond to outpatient treatment. For infants, medical monitoring is recommended at 24 h, and for preschoolers this can be up to 48 h. Monitoring must be foreseen for worsening of the condition caused by food rejection, medication intolerance, increase in respiratory difficulty, irritability (persistent crying), or compromised consciousness. The use of antipyretics and analgesics is indicated to keep the child in better condition and to reduce the metabolic and oxygen requirements. The physician must insist that the caregivers look for medical advice in case of symptom worsening, axillary fever greater than 38.5°C for longer than 3 days, respiratory difficulty (tachypnea, cyanosis, rib retraction), food rejection, or notable weakness.

Kinetic Therapy

Kinesiotherapy is not indicated for pneumonia management. It does not accelerate the recovery process and may delay symptom progression. Cough assistance techniques, postural drainage, diaphragmatic reeducation, and early mobilization may help to expand poorly ventilated areas and improve symptoms of respiratory distress to achieve these objectives.

Antibiotics

Antibiotic treatment is empirical, and given the difficulty in isolating the etiological agent, it should be based on the best possible etiology, depending on the patient's age and the epidemiological timing. In children under 5 years old, antibiotics should not be routinely indicated, because in most cases the disease will be caused by a virus. If bacterial etiology is suspected, amoxicillin should be prescribed at 80–100 mg/kg/day, fractioned every 12 h during 5 to 7 days (using a maximum of 2 g/day). In children who are over 5 years old, amoxicillin can be prescribed at 50–80 mg/kg/day. If there is poor oral tolerance, sodium penicillin

should be used as follows: 200,000 U/kg/day IV every 12 h (maximum of 4 million U/day) until tolerance is recovered, and continue with oral amoxicillin. The use of macrolides is considered for older children who are suspected of having *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae*, or penicillin allergy: azitromycin 10 mg/kg/day on a daily dosage, without food, for 5 days (maximum 500 mg/day); claritromycin 15 mg/kg/day every 12 h for 10 days (maximum 1 g/day); or erythromycin 50 mg/kg/day divided into four doses, for 10 days (maximum 2 g/day). As an alternative to macrolides use, quinolones can be indicated: daily levofloxacin in 10 mg/kg doses for 10 days. In epidemic episodes, influenza A virus must be ruled out, and early treatment with antivirals (oseltamivir) must be started.

In Hospital

Hospitalization Criteria

- No clinical response to outpatient therapy
- Vomiting and dehydration, which may make oral treatment difficult
- Total or partial respiratory insufficiency: transcutaneous saturation <93%
- Under 3 months of age, because of apnea and risk of cardiorespiratory arrest
- Relevant comorbidity: cardiac, pulmonary, neuromuscular, immunological
- Complicated pneumonia: effusion, excavated lesions
- Serious disease: Hemodynamic instability, alteration of consciousness, seizures, toxic presentation

General Measures

Oxygen for patients whose saturation is less than 93 mmHg in environment air.

Avoid prolonged fasting, especially in infants who are under 1 year old. Because of this, it is recommended to administer fractionated feeding, feeding in small volumes, or through a small nasogastric tube, to avoid worsening the respiratory difficulty.

Antibiotics

Newborns and infants who are under 6 weeks old: ampicillin 100 mg/kg/day every 8 h, IV, plus amikacin 15 mg/kg each 24 h, IV, during 7–10 days to ensure a good coverage for enteric gram-negative bacteria: group B *Streptococcus*, type D *Enterococcus*, and *Listeria monocytogenes*. After the first week of life, as an alternative to amikacin, cefotaxime can be indicated (150 mg/kg/day), given a lower risk of *Listeria monocytogenes*, which may require adding ampicillin to the synergic effect of an aminoglycoside. In patients with progressive worsening, or for whom a resistant *Streptococcus pneumoniae* is suspected, high doses of amoxicillin, of third- or second-generation cephalosporins, or IV ampicillin, should be used. Ampicillin, which is a derivative from penicillin, is a very good choice for patients who are under 24 months of age, and it has a similar efficiency to oral amoxicillin or parenteral cephalosporins, with a significantly lesser cost. The association of macrolides with a beta lactam antibiotic is indicated in hospitalized children when there is a strong suspicion of atypical agents. In the infections caused by *Staphylococcus aureus*, depending on the sensitivity, cloxacillin, clindamycin, or vancomycin is indicated.

Antibiotic Resistance of *Streptococcus*

The appearance of resistant *Streptococcus* is a worldwide concern, and its degree of resistance degree is variable, depending on geographic distribution. The risk of having an invasive disease caused by a resistant *Streptococcus pneumoniae* is related to being 5 years old or younger (specially under 2 years old), use of antibiotics within the precedent month, middle-ear infection, and daycare attendance. Resistance is caused by mutations of penicillin protein-binding (PPB) sites, with a reduction in the protein affinity that binds to the antibiotic. This genetic change is caused by the DNA acquisition from resistant species such as *Streptococcus viridans*. The reduction of the affinity could be countered by increasing the penicillin dosage or with the use of

third-generation cephalosporins. Observations made in patients with community-acquired pneumonia caused by resistant *Streptococcus pneumoniae* who still have a good response to treatment have increased the chosen cutoff points to determine penicillin and cefotaxime resistance (CIM > 8 ug/ml).

Complications

Whenever a patient persists with fever after 48–72 h, the presence of some complication such as effusion, pleural empyema, abscess, pneumatocele, bacterial resistance, or choice of an inadequate antibiotic must be suspected. The presence of some extrapulmonary focus (pericardium, joints, meninges) must be ruled out. Pleural effusion or empyema is a possible complication in up to 40% of hospitalized children.

Prevention

The use of vaccines for *Bordetella pertussis*, measles, *Haemophilus influenzae*, and influenza have reduced the occurrence of community-acquired pneumonia. Important effects have been registered in relation to its prevention and suppurative complications after the incorporation of vaccines for type B *Haemophilus influenzae*. The national rate of invasive disease reported for 2003 was of 2.5/100,000 inhabitants, and the effectivity prevention for the bacterial community-acquired pneumonia and empyema was 80%. It must be considered that 6% to 16% of infections caused by *Haemophilus influenzae* are caused by noncapsulated agents against which the vaccine offers no protection. Influenza vaccine has a double effect: it reduces virus infection rate in high-risk populations, and, as a parallel effect, it decreases bacterial community-acquired pneumonia caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*, related to post-influenza virus infection. In Chile, when mandatory vaccination was introduced in 2000 for risk groups, pneumonia incidence was clearly reduced. For those children under 2 years old, 10- and 13-valent pneumococcal conjugate vaccines are

less effective for preventing pneumonia (30%) than other invasive diseases such as sepsis and meningitis (97%). Both vaccines have a good immunogenicity and herd immunity. The 13-valent vaccine includes 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F serotypes. Premature newborns, with chronic lung damage and other risk factors, must receive monoclonal antibody prophylaxis for syncytial respiratory virus.

Conclusion

Community-acquired pneumonia is still a prevalent disease in children. The etiological diagnosis cannot be done by X-ray studies, hemograms, or acute-phase reactants, so the development of materials for rapid diagnosis is an unmet need required to avoid the indiscriminant use of antibiotics, which is an important factor in the appearance of bacterial resistance. Penicillin derivatives, especially oral amoxicillin, continue to be the treatment of choice when *Streptococcus pneumoniae* is suspected; macrolides are used when a pneumonia caused by atypical agents is suspected, especially in schoolchildren more than 5 years old. Coverage with effective vaccines is important, according to the regional needs, which may contribute to the prevention of the disease. National programs, when systematically applied to have primary care coverage, have contributed to the significant decrease of morbidity and mortality.

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