

Systemic antibiotic treatment in upper and lower respiratory tract infections: official French guidelines

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INTRODUCTION

These guidelines concerning the best use of antibiotics for the treatment of upper and lower respiratory tract infections, common cold, pharyngitis, acute sinusitis, acute otitis media, community-acquired pneumonia, acute bronchitis and bronchiolitis rely on evidence-based medicine. They represent a consensus among French experts, and the goal of this publication is to make their recommendations available to others countries in Europe.

The prescription of antibiotics should be limited to clinical situations in which their efficacy has been proved to reduce the increasing incidence of bacterial resistance and adverse events. The emergence of resistant bacterial strains is mainly due to the massive prescription of antibiotics, which explains the high level of resistance in France to antibiotics of two community-acquired bacteria responsible for respiratory tract infections: *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*. It has been demonstrated that regulated antibiotic consumption, which can be achieved by educating both physicians and patients, leads to a decrease in resistance. In this context, the French Health Products Safety Agency (Afssaps) has established recommendations concerning the use of systemic antibiotic treatment in upper and lower respiratory tract infections. These recommendations do not take into account immunocompromised patients [patients receiving systemic corticoid therapy, immunosuppressant treatment or chemotherapy for periods longer than 6 months, patients who have undergone splenectomy and patients presenting with HIV infection (CD4 < 200/mm³, AIDS or cachexia, etc.)].

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Methods

These recommendations were drafted by a multi-disciplinary working group, taking into account published data and official French records. The bibliographical search was made using Medline. The text has been read, discussed and evaluated critically by a group that includes 91 skilled experts outside the working group. It was then submitted for approval to the Afssaps medical reference Validation Committee. The full-length, discussed and referenced French text is available on the Afssaps website: <http://www.afssaps.sante.fr>. The proposed recommendations were graded A, B or C depending on the level of reliability of the data on which they were based. When the published data were inadequate or incomplete, the recommendations were based on a consistent professional consensus (Table 1).

Working group

Recommendations on common cold, pharyngitis and lower respiratory tract infections in adults

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Recommendations on Acute sinusitis in children and in adults, exacerbations of chronic bronchitis and lower respiratory tract infections in children

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Table 1 Strength of recommendations

Level of scientific evidences of studies	Grade
Level 1 Comparative, high-powered, randomised studies Meta-analysis of comparative, randomised studies Decision analysis based on well-conducted studies	A, High-level, strong scientific evidence
Level 2 Comparative but low-powered, randomised studies Comparative, non-randomised but conscientious studies Cohort studies	B, Intermediate-level scientific evidence
Level 3 Case-control studies	C, Low-level, evidence of limited credibility
Level 4 Comparative studies involving major bias Retrospective studies Series of cases Descriptive, epidemiological studies (transverse, longitudinal)	C, Low-level, evidence of limited credibility

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COMMON COLD

Common cold is defined as an inflammatory syndrome of the upper part of the pharynx (cavum) associated with varying levels of nose inflammation. Acute common cold develops mainly in children and is usually of viral origin. It is a mild illness that generally disappears in 7–10 days.

Antibiotic treatment is not justified in noncomplicated acute common cold, either in adults or in children (*Grade B*). It has not been shown to effect the duration of symptoms nor prevent complications, even when risk factors were present. In noncomplicated colds, treatment addresses the symptoms (antipyretics, nose blowing), and the patients, as well as their parents in the case of children, should be informed of the viral origin of the illness, the median duration of symptoms, the usually favorable outcome of this self-limited infection, and also of the suggestive signs of possible complications (*Professional consensus*).

Antibiotics are recommended only in the case of complications, presumably of bacterial origin,

such as acute otitis media or sinusitis (*Grade A*). Acute otitis media usually occurs in children between 6 months and 2 years of age. Acute ethmoiditis is a rare affection in infants and maxillary sinusitis usually occurs in children over 3 years of age. Lower respiratory tract infections such as bronchitis, bronchiolitis or pneumonia, are not considered to be a complication or superinfection of the common cold (in this case, a cold is a premonitory symptom or one of the associated signs). The patients, especially those at risk of complications (e.g. children prone to otitis or otitis media with effusion) should be asked to contact their physician whenever signs suggesting a bacterial complication occur (*Professional consensus*) (Figure 1). Purulent nasal discharge and fever (within the normal duration of the cold) are not usually associated with bacterial infection and should not be considered as risk factors for complications (*Professional consensus*). In common cold, the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) at anti-inflammatory doses or oral corticoids has not yet been demonstrated.

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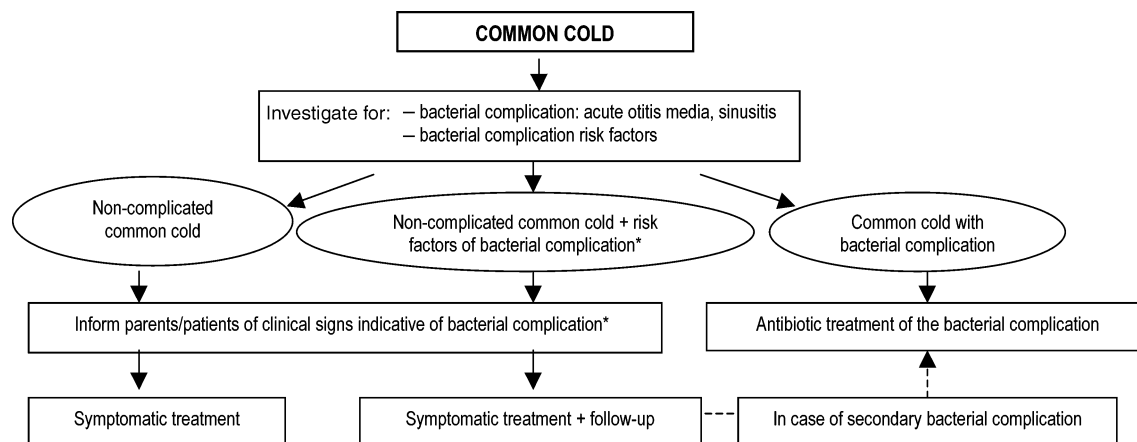


Figure 1 Current approach to treating common cold. *Respiratory discomfort, fever persisting more than 3 days or occurring after this period, persistence of the other symptoms (cough, rhinorrhoea, nasal obstruction) after 10 days with no signs of improvement, irritability, nocturnal awakening, otalgia, otorrhoea, purulent conjunctivitis, palpebral oedema, gastrointestinal disorders (anorexia, vomiting, diarrhoea) and skin rash.

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PHARYNGITIS

Most cases of pharyngitis are of viral origin. Group A beta-hemolytic streptococcus (GAS) is the main bacterial agent implicated in pharyngitis. GAS-pharyngitis accounts for 25–40% of cases in children and for 10–25% in adults: its incidence peaks between the ages of 5 and 15 years. Even untreated, cases of GAS-pharyngitis generally improve within 3–4 days. However, it may trigger potentially severe poststreptococcal complications, i.e.,

acute rheumatic fever (ARF), acute glomerulonephritis (AGN) and local or systemic septic complications. It should be emphasized that:

- the current risk for ARF is extremely low in industrialized countries (but remains high in developing countries);
- a decrease in this risk had started before antibiotics became available in industrialized countries, reflecting the influence of environmental and social factors as well as therapeutic regimes, and perhaps also changes in the virulence of the strains;
- the incidence of suppurative loco-regional complications has also decreased and remains low in industrialized countries (1%) independent of antibiotic therapy;
- poststreptococcal AGN is rarely the consequence of GAS-pharyngitis, and there is no evidence that antibiotics might prevent the occurrence of AGN.

The efficacy of antibiotics in cases of GAS-pharyngitis has been demonstrated by the rapid disappearance of symptoms (*Grade A*), the eradication or decreased dissemination of GAS (*Grade A*), and the prevention of ARF demonstrated for penicillin G (*Grade A*).

Indications for antibiotic therapy

Given the risks of GAS, especially ARF, and because antibiotics have not proved effective in the management of nonstreptococcal pharyngitis, antibiotic treatment is justified only in patients with GAS-

pharyngitis (apart from the cases of infections due to *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae* and anaerobic microorganisms) (*Grade A*).

The streptococcal origin of pharyngitis cannot be determined by any clinical signs or scores with adequate positive and/or negative predictive value. Only microbiological tests are reliable to confirm the diagnosis of GAS-pharyngitis (*Grade A*). In clinical practice, culture of pharyngeal specimens is not a routine procedure. Rapid antigen tests (RAT) carried out by physicians are recommended. Their specificity is similar to that of cultures and their sensitivity is close to 90%. In children below 3 years of age, RAT is usually not performed as GAS is rarely involved. The following approach is recommended:

- positive RAT confirming GAS etiology justifies antibiotics (*Grade A*);
- a negative RAT with low risk factors for ARF usually requires neither control cultures nor antibiotic therapy (*Professional consensus*). Only a symptomatic treatment (analgesics, antipyretics) is useful in such cases.

Some very rare situations suggest ARF risks:

- individual medical history of ARF;
- age between 5 and 25 years, associated with some environmental conditions (social, hygienic and economic conditions, promiscuity, closed institution);
- particular bacterial epidemics (rheumatogenic strains);
- medical history of recurring GAS-pharyngitis;
- stays in streptococcal-endemic regions (Africa, West Indies, etc.).

In such contexts, a negative RAT could be further investigated by specimen culture (*Professional consensus*). If the culture is positive, an antibiotic therapy will be initiated (*Grade A*).

Recommended antibiotic therapy

Antibiotic treatment should be promptly initiated after confirmation of GAS-pharyngitis. However,

the capacity of antibiotics to prevent ARF lasts only until day 9 after the onset of symptoms.

A 10-day course of Penicillin V is the historical reference treatment (*Grade A*). The first-line treatment of pharyngitis relies on amino-penicillins, or even a cephalosporin, as GAS is still sensitive to the beta-lactam group. Given the increase in resistance of GAS (6–10%), macrolides represent an alternative to beta-lactams, especially in cases of allergy to beta-lactams (*Grade A*). Considering compliance, short-term treatments should be preferred, according to marketing authorizations. Patients should be informed of:

- the advantages of limiting antibiotic treatment to the management of GAS-pharyngitis (apart from rare diphtheric or gonococcal pharyngitis or pharyngitis due to anaerobic microorganisms).
- the necessity of good compliance (*Professional consensus*).

Symptomatic treatments to improve comfort, especially analgesics and antipyretics, are recommended. No data confirm the benefit of NSAIDs at anti-inflammatory dose levels, or of systemic corticosteroids in the treatment of acute pharyngitis whereas considerable risks are involved (Figure 2).

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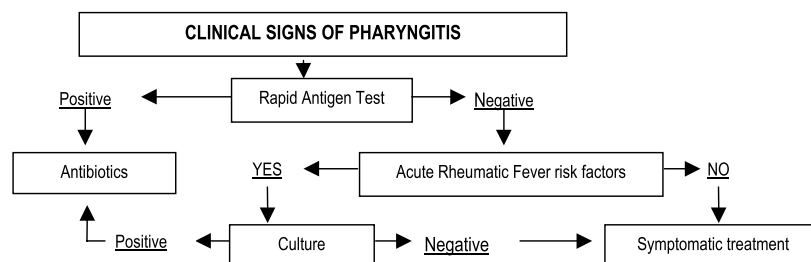


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ACUTE SINUSITIS IN ADULTS

Acute purulent sinusitis corresponds to the infection of one or more sinus cavities, usually by a bacteria. Acute maxillary sinusitis is the most common version, and the main topic of these recommendations. Clinical examination is usually limited to the observation of purulent rhinorrhea (anterior and/or posterior, often unilateral) and pain upon pressure in the area over the infected sinus cavity. In current practice, examination of the nasal cavity is not always performed. Maxillary sinusitis of dental origin is a particular example. Frontal sinusitis and sinusitis of other sites (ethmoidal, sphenoidal) should be recognized, because of the high risk of complications. Clinical signs suggestive of complicated sinusitis (meningeal syndrome, exophthalmia, palpebral edema, ocular mobility disorders, severe pain) require hospitalization, bacteriological testing and parenteral antibiotic therapy.

Indications for antibiotic therapy

Acute purulent maxillary sinusitis

When the diagnosis of acute, purulent maxillary sinusitis is established, antibiotic therapy is indicated (*Grade B*). First-line antibiotic therapy is not indicated when nasal symptoms remain diffuse, bilateral and of moderate intensity, are compounded by congestion with serous or plain puriform discharge, occurring in an epidemic context. A reassessment is necessary in the case of abnormal persistence or worsening of symptoms under symptomatic treatment (*Professional consensus*). Antibiotic therapy is indicated if the initial symptomatic treatment fails or if complications occur (*Professional consensus*). It is also indicated in the particular case of unilateral maxillary sinusitis associated with an upper unilateral dental infection (*Professional consensus*). The clinical signs suggestive of complicated sinusitis are: meningeal syndrome, exophthalmos, palpebral edema, ocular mobility disorders, pain preventing sleep.

Other types of sinusitis

Antibiotic therapy is definitely indicated in the case of frontal, ethmoidal or sphenoidal sinusitis.

Recommended antibiotic therapy

The most frequent bacteria implicated in sinusitis are *H. influenzae* and *S. pneumoniae*, with a high proportion of strains resistant to antibiotics. Given

Table 2 Site and first-line treatment of acute sinusitis

Site	Symptoms	First-line antibiotic therapy
Maxillary	Unilateral or bilateral infraorbital pain which increases if the head is bent forwards; sometimes pulsatile and peaking in the early evening and at night	Amoxicillin-clavulanate, 2nd and 3rd generation cephalosporins (except cefixime): cefuroxime-axetil, cefpodoxime-proxetil, pristinamycin, cefotiam-hexetil
Frontal	Supraorbital headache	As above, or fluoroquinolone active on pneumococci (levofloxacin, moxifloxacin)
Fronto-Ethmoidal	Filling of the inner angle of the eye, palpebral oedema. Retro-orbital headache	As above, or fluoroquinolone active on pneumococci (levofloxacin, moxifloxacin)
Sphenoidal	Permanent retro-orbital headache, radiating to the vertex, which focus, intensity and permanence may simulate the pain caused by intracranial hypertension. Purulent discharge on the posterior pharyngeal wall.	As above, or fluoroquinolone active on pneumococcus (levofloxacin, moxifloxacin)

the increasing bacterial resistance, first-line oral antibiotic therapy includes one of the following:

- amoxicillin-clavulanate,
- second generation oral cephalosporins (cefuroxime-axetil) and some third generation oral cephalosporins (cefpodoxime-proxetil, cefotiam-hexetil);
- pristinamycin, particularly in case of allergy to beta-lactams.

(Professional consensus)

The fluoroquinolones active against pneumococci (levofloxacin, moxifloxacin) should be reserved for situations where major complications are likely, such as frontal, fronto-ethmoidal or sphenoidal sinusitis, or the failure of first-line antibiotic therapy in maxillary sinusitis, after bacteriological and/or radiological investigations.

The duration of treatment is usually 7–10 days (Grade C). Cefuroxime-axetil and cefpodoxime-proxetil have been shown to be effective in 5 days. The efficacy of NSAIDs at anti-inflammatory doses has not been demonstrated. Corticosteroids may be of use if given for a short period, as adjuvant therapy in acute hyperalgetic sinusitis (Table 2).

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ACUTE SINUSITIS IN CHILDREN

Acute sinusitis is usually of viral origin, but the possibility of bacterial superinfection means that antibiotic therapy must be considered, especially

when the infection occurs in certain sites. Acute ethmoiditis (fever associated with painful edema of the internal upper eyelid) affects young children. It is rare, with a serious prognosis. The same applies to infections of the sphenoidal sinus (intense and permanent retro-orbital headache), which affects older children. These sites must be identified by the practitioner so that parenteral antibiotic therapy may be rapidly administered in hospital, as is necessary in most cases. Frontal sinusitis in older children does not differ from that seen in adults (see 'Acute sinusitis in adults'). Maxillary sinusitis is the most common form and is only observed in children aged 3 years or older. It is essential to distinguish it from sinus inflammation (congestive rhinosinusitis), which may accompany or follow viral rhinopharyngitis, and which does not require antibiotic therapy (see 'Common cold').

Indications for antibiotic therapy

Immediate antibiotic therapy is indicated in severe acute forms of purulent maxillary sinusitis (*Grade C*). The benefits of antibiotic therapy are controversial in subacute forms. Two approaches are reasonable: follow-up during symptomatic treatment with further reassessment, or prescription of antibiotics.

In subacute forms, immediate antibiotic therapy is recommended in children with risk factors such as asthma, heart disease or drepanocytosis, or in the case of symptomatic treatment failure (*Professional consensus*).

Recommended antibiotic therapy

The antibiotics recommended as first-line treatment are:

- amoxicillin-clavulanate (80 mg/kg/day in three doses, not exceeding 3 g/day);
- cefpodoxime-proxetil (8 mg/kg/day in two doses).

(*Professional consensus*)

The standard duration of treatment is 7–10 days (*Professional consensus*). Because of the prevalence of resistance, amino-penicillins, macrolides, first generation cephalosporins and cotrimoxazole are no longer recommended.

In sinusitis, the efficacy of NSAIDs at anti-inflammatory doses has not been demonstrated. Corticosteroids may be of use if given for a short period, as adjuvant therapy in acute hyperalgeic sinusitis.

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EXACERBATIONS OF CHRONIC BRONCHITIS

Antibiotic therapy is often used in standard practice to treat exacerbations of chronic bronchitis, although the results of comparisons with placebo are contradictory. Exacerbations may be of bacterial, viral or noninfectious origin. If they are of bacterial origin, the benefit of antibiotic therapy is usually limited to patients suffering from an obstructive syndrome. The choice of the antibiotic is based on respiratory status and frequency of exacerbations. Other bronchial pathology (asthma, bronchiectasis) should be identified and not mistaken for chronic bronchitis. They should be considered particularly in nonsmoking subjects. The present recommendation does not apply to either paroxysmal asthma or early chronic asthma (for which there is no indication for antibiotic therapy), or to bronchiectasis. It may apply to late-stage chronic asthma, which presents considerable similarities with obstructive chronic bronchitis (Table 3).

The presence of at least two of the three Anthonisen triad criteria is suggestive of bacterial origin:

Table 3 Definition of the stages of chronic bronchitis

	Simple chronic bronchitis	Obstructive chronic bronchitis	Obstructive chronic bronchitis with chronic respiratory insufficiency
Clinical (and paraclinical) definition	Daily expectoration for at least 3 consecutive months during at least 2 consecutive years	Chronic bronchitis with persistent obstruction of the minor airways, associated or not with partial reversibility (under betamimetics, anti-cholinergics, corticosteroids), bronchial hypersecretion or pulmonary emphysema	Obstructive chronic bronchitis associated with hypoxemia at rest outside exacerbations.
In practice	Chronic cough and expectoration without dyspnea, FEV1 > 80%	Exertional dyspnea and/or FEV1 between 35% and 80% and no hypoxemia at rest	Dyspnea at rest and/or FEV1 < 35% and hypoxemia at rest (PaO ₂ < 60 mmHg or 8 kPa).

increase in volume and purulence of expectoration, increase in dyspnea (*Grade B*). Fever suggests an infectious origin. Inconsistent in cases of infection, it does not enable a distinction to be made between viral and bacterial causes. Its intensity does not necessarily indicate bacterial origin. However, its persistence after more than 3 days suggests a bacterial infection (bronchial superinfection or pneumonia). The presence of associated ENT signs (rhinorrhea, obstruction of the upper airways, etc.) suggests a viral infection.

Indications for antibiotic therapy

It is often difficult to diagnose correctly a condition requiring antibiotic therapy at an early first visit. Clinical follow-up is essential, with reassessment during the following 2 or 3 days.

Different therapeutic approaches are recommended below.

Exacerbation of simple chronic bronchitis

Immediate antibiotic therapy is not recommended, even if fever is present (*Grade B*). During reassessment 2 or 3 days later (or during a late first visit), antibiotic therapy is only recommended if fever (>38 °C) persists for more than 3 days (*Grade C*).

Exacerbation of chronic obstructive bronchitis (i.e. exertional dyspnea and/or FEV1 between 35% and 80%, outside the period of exacerbation)

Immediate antibiotic therapy is only recommended if at least two of the three criteria in the Anthonisen triad are present (*Grade B*). During reassessment (or during a late first consultation), antibiotic therapy is only recommended if fever (>38 °C) persists for more than 3 days (*Grade C*) or, if there is no fever, when at least two of the three Anthonisen criteria are present (*Grade B*).

Exacerbation of chronic obstructive bronchitis with chronic respiratory insufficiency (i.e. dyspnea at rest and/or FEV1 < 35% and hypoxemia at rest outside the period of exacerbation)

Immediate antibiotic therapy is recommended (*Grade B*).

Recommended antibiotic therapy

Antibiotic therapy for an exacerbation of chronic bronchitis suspected to be of bacterial origin should be active principally on *S. pneumoniae*, *H. influenzae* and *Branhamella catarrhalis* (*Moraxella catarrhalis*).

First-line antibiotics

First-line antibiotics may be used for infrequent exacerbations (≤3 within the past year) in subjects with FEV1 ≥ 35% at baseline (*Professional consensus*). Amoxicillin remains the reference compound. First generation cephalosporins are an alternative. Macrolides, pristinamycin and doxycycline are other possible alternatives, particularly in the case of allergy to beta-lactams. Cotrimoxazole is a poor choice, because of its inconsistent activity on pneumococci and its poor benefit/risk ratio.

Second-line antibiotics

Second-line antibiotics may be used in the case of failure of first-line antibiotics or as first treatment in the case of frequent exacerbations (≥4 within the past year), or if baseline FEV1 (outside exacerbations) is <35% (*Professional consensus*). Amoxicillin-clavulanate remains the reference antibiotic therapy. Second generation (cefuroxime-axetil) or third generation (cefpodoxime-proxetil, cefotiam-hexetil) oral cephalosporins and fluoroquinolones active on pneumococci (levofloxacin,

moxifloxacin) remain possible alternatives. Fluoroquinolones inactive on pneumococci (ofloxacin, ciprofloxacin) and cefixime (3rd generation oral cephalosporin, but inactive on pneumococci with decreased susceptibility to penicillin) are not recommended. Ciprofloxacin should be reserved for the treatment of infections in which Gram-negative bacilli, and most particularly *Pseudomonas aeruginosa*, are implicated or strongly suspected.

Duration of antibiotic therapy

The classic duration of treatment is 7–10 days (Grade C). However, some antibiotics have proved to be effective with duration of treatment reduced to 5 days (Grade B) (Table 4).

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ACUTE OTITIS MEDIA

Acute otitis media (AOM) is usually a bacterial superinfection, with purulent or mucopurulent middle ear fluid. This recommendation only relates to AOM in children over 3 months of age. In adults, AOM is rare; the bacteria involved are the same as those observed in children and the therapeutic choices do not differ. Recommended treatments are: amoxicillin-clavulanate, cefurox-

Table 4 Indications for antibiotic therapy in exacerbations of chronic bronchitis

	Simple chronic bronchitis*	Obstructive chronic bronchitis†	Obstructive chronic bronchitis with chronic respiratory insufficiency‡
Indication for immediate antibiotic therapy	No	At least 2 of the 3 Anthonisen criteria	Yes
Indication of antibiotic therapy during reassessment (or late, first consultation)	Fever >38°C after more than 3 days	Fever >38°C more than 3 days At least 2 of 3 Anthonisen criteria	
Type of antibiotic	First-line antibiotics amoxicillin First generation cephalosporins macrolides pristinamycin doxycycline	First-line antibiotics Infrequent exacerbations Second-line antibiotics Failure of first-line treatment or frequent exacerbations (≥4 within past year)	Second-line antibiotics amoxicillin-clavulanate cefuroxime-axetil cefpodoxime-proxetil, cefotiam-hexetil levofloxacin, moxifloxacin

*cough, chronic expectoration, no dyspnea, FEV1 >80%; †exertional dyspnea and/or FEV1 between 35 and 80%, absence of hypoxemia at rest; ‡dyspnea at rest and/or FEV1 <35%, hypoxemia at rest.

ime-axetil, cefpodoxime-proxetil, cefotiam-hexetil and pristinamycin particularly in case of allergy to beta-lactams.

Indications for antibiotic therapy

Acute otitis media

In the case of AOM in children below 2 years of age, antibiotic therapy is recommended (*Grade A*). For children over 2 years of age, abstinence is reasonable, except in the case of marked symptoms (high fever, intense earache) (*Grade B*). Abstinence must be followed by reassessment after 48–72 h of symptomatic therapy (*Grade B*).

Redness of tympanic membrane

Isolated redness of the tympanic membrane, with normal landmarks, is not an indication for antibiotic therapy. The child should be reassessed if the symptoms persist for more than 3 days (*Professional consensus*).

Otitis media with effusion

Antibiotics are not indicated, except in cases of AOM that continue beyond 3 months. In the case of a prolonged course and hearing loss it is recommended to refer the patient to an ENT specialist (*Grade B*).

Difficulties in assessing the tympanic membrane

Adequate visualization of the tympanic membrane is often impaired by the cerumen and because of difficult conditions of examination, particularly in infants. Antibiotic therapy should not be prescribed in such cases without further examination. Where it is difficult to clean the external ear canal, referral to an ENT specialist should be considered. In children over 2 years of age, without presence of earache, the diagnosis of AOM is highly improbable. Faced with symptoms suggestive of otitis in children less than 2 years of age, it is necessary to visualize the tympanic membranes, and reference to an ENT specialist should be considered.

Recommended antibiotic therapy

In children over 3 months of age, the most frequent bacteria involved in AOM are *S. pneumoniae*, *H. influenzae* and *Branhamella catarrhalis* (*Moraxella catarrhalis*). Oral antibiotic therapy is usually recommended. Concerns are raised due to the increased antibiotic resistance of these bacteria.

The clinical symptoms may suggest a particular causal bacterium.

In the case of otitis associated with purulent conjunctivitis, there is a strong probability of *H. influenzae* infection; in such cases cefixime, cefpodoxime-proxetil, amoxicillin-clavulanate or cefuroxime-axetil are indicated.

In the case of febrile painful otitis, there is a high probability of pneumococcal infection, but the possibility of infection due to *H. influenzae* should also be taken into account; in such cases amoxicillin, cefuroxime-axetil or cefpodoxime-proxetil may be prescribed.

If no bacteriological markers are available, amoxicillin-clavulanate, cefpodoxime-proxetil or cefuroxime-axetil have the most suitable profile. Erythromycin-sulfafurazole is an alternative in case of allergy to beta-lactams. The use of IM injections of ceftriaxone should be used only in exceptional circumstances, and must comply with the conditions of the marketing authorization (*Grade B*). The treatment duration is 8–10 days below 2 years of age and 5 days for older children (*Grade A*).

Failures of antibiotic therapy are defined as:

- worsening of the patient's condition;
- persistence of symptoms for more than 48 h after the initiation of antibiotic therapy;
- recurrence of functional and systemic signs, associated with otoscopic signs of purulent AOM, within the 4 days following treatment discontinuation.

This possibility, which is to be feared particularly in infants below 2 years of age, justifies paracentesis with the collection of a bacteriological specimen, followed by a change to antibiotic therapy considering the first agent prescribed and the bacteria isolated (*Grade B*).

In cases of acute otitis media, the efficacy of NSAIDs at anti-inflammatory doses and of corticosteroids has not been demonstrated.

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COMMUNITY-ACQUIRED PNEUMONIA AND ACUTE BRONCHITIS IN ADULTS

Lower respiratory tract infections are frequent and their incidence increases with age. They represent one of the leading causes of medical visits and prescription of antibiotics.

Indications for antibiotic therapy

There is a distinction between lower respiratory tract infections involving the parenchyma (pneumonia) and those not affecting parenchyma (acute bronchitis). Given the predominant bacterial etiology and the potential mortality (2–15%) associated with pneumococcal pneumonia, antibiotics are justified in the treatment of this disease. However, this does not apply to acute bronchitis of mainly viral origin in healthy subjects, which requires no antibiotic treatment. This distinction may be difficult in practice. Some clinical signs or symptoms may suggest a diagnosis (Table 5).

Community-acquired pneumonia

The choice of the treatment takes into account the *in vitro* activity of the antibiotics. In France, the incidence of penicillin intermediate-resistant *S. pneumoniae* (MIC > 0.1 mg/L) collected from the lower respiratory tract is high (close to 35% in adults) and is still rising. Thirty to 50 percent of the strains with a decreased susceptibility are resistant (MIC > 1 mg/L) to penicillin. Clinical criteria likely to predict infection due to pneumococci with decreased susceptibility to penicillin include: age over 65 years, prior prescription of

Table 5 Signs and symptoms suggestive of lower respiratory tract infections

Signs suggestive of lower respiratory tract infection
Combination or succession of:
cough, frequently loose
At least one functional or physical sign of lower respiratory tract involvement: dyspnoea, chest pain, wheezing, diffuse or focal signs at auscultation
At least one general sign suggesting infection: fever, sweating, headache, joint pain, pharyngitis, common cold
Signs suggestive of pneumonia
Fever >37.8°C
Tachycardia >100 bpm
Polypnoea >25/min
Chest pain
No infection of the upper respiratory tract
Overall impression of severity
Focal signs on auscultation (crepitations, rales)
X-ray examination confirms the diagnosis
Signs suggestive of acute bronchitis
Inconstant fever, generally slightly raised
Retrosternal burning sensation
Cough sometimes preceded by infection of the upper respiratory tract
Normal auscultation or diffuse bronchial rales

beta-lactams, hospitalization within the last 3 months, presence of a chronic disease (chronic bronchopathy, cancer, splenectomy, HIV infection), nosocomial origin of the pneumonia and its initial severity. *S. pneumoniae* is also often resistant to macrolides (30–40%) and is often associated with a resistance to beta-lactams. Both resistances are observed three times out of four in infections due to *S. pneumoniae*. It should be considered in subjects at risk of carrying such a strain with decreased susceptibility to penicillin. The 'atypical' bacteria are naturally resistant to beta-lactams and susceptible to macrolides.

Acute bronchitis in healthy adults

The following bacteria are, on very rare occasion, involved in acute bronchitis in healthy adults: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Bordetella pertussis*. Given the lack of specificity of the clinical picture, another possible diagnosis (pneumonia, exacerbation of chronic bronchitis) or underlying disorders with predominant bacterial etiology requiring a different therapeutic approach, should not be overlooked. The clinical course is generally spontaneously favorable after about 10 days, although the cough may persist for a longer period. Colonization of the upper and lower airways by pathogenic bacteria, enhanced by the viral infection of the respiratory tracts, has not been shown to be responsible for bacterial superinfection in healthy subjects. The onset of a purulent sputum during acute bronchitis in healthy adults is not associated with bacterial superinfection. Fever persisting more than 7 days would be indicative of bacterial superinfection (*Professional consensus*). The benefit of antibiotic therapy on the clinical course of the disease or on the occurrence of complications has not been confirmed in clinical trials vs. placebo (*Grade B*).

There is no evidence that antibiotic therapy prevents superinfection. As a rule, antibiotics should not be prescribed in the treatment of acute bronchitis in healthy adults. The prescription of NSAIDs at an anti-inflammatory dose level or of systemic corticosteroids is not justified.

Recommended antibiotic therapy in community-acquired pneumonia

In adults with no risk factor and no sign of severity the initial recommended treatment is one of either below (Figures 3 and 4):

- Oral amoxicillin 3 g/day, in cases of suspected pneumococcal origin (especially in adults over 40 years of age with or without underlying disease). The administration of higher dosages is not usually indicated.
- Oral macrolides, which remain the reference treatment for pneumonia supposedly due to 'atypical' bacteria in adults under 40 years of age with no underlying disease, and within no epidemic context).

Telithromycin represents an alternative to these two treatments, which are recommended as first-line therapy.

At present, the systematic use of parenteral beta-lactams is not justified unless changes in the resistance of *S. pneumoniae* occur (*Professional consensus*). Taking into account the causative agents, there is no justification for associating aminopenicillin with a beta-lactamase inhibitor (*Professional consensus*). Cyclins, trimethoprim-sulfamethoxazole and first generation oral cephalosporins, are not recommended either because of their inadequate activity against penicillin, abnormal susceptibility to *S. pneumoniae* (to be considered in cases of patients at high risk of carrying *S. pneumoniae* with decreased susceptibility to

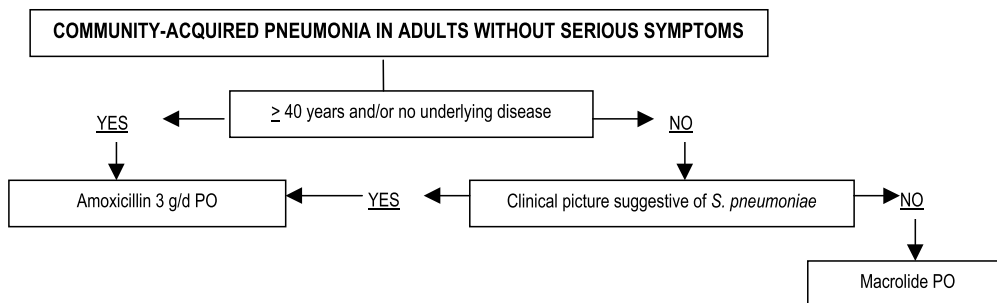


Figure 3 Initial therapeutic strategy in community-acquired pneumonia (without risk factor and without serious symptoms).

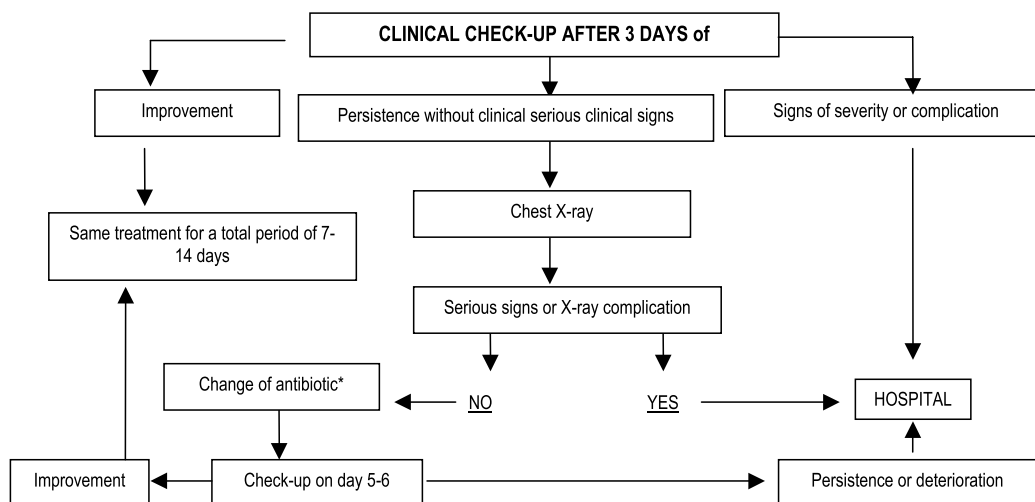


Figure 4 Secondary therapeutic strategy in community-acquired pneumonia (without risk factor or serious symptoms). *amoxicillin macrolides; more rarely : either amoxicillin + macrolide, either : telithromycin or fluoroquinolone active against pneumococcus.

penicillin) or because of their absence of activity against atypical microorganisms (cephalosporins, trimethoprim-sulfamethoxazole). Second and third generation oral cephalosporins, active in vitro against *S. pneumoniae* with intermediate susceptibility to penicillin, are not recommended, however, mainly because they are not active against penicillin-resistant *S. pneumoniae*. Among fluoroquinolones, only those active against pneumococcus can be used (levofloxacin, moxifloxacin). However, they are not recommended as first-line therapy, given their tolerance profile and impact on resistance. In healthy subjects, there is no justification for initial combined therapy, prescribed simply in order to extend the therapeutic spectrum of activity (*Professional consensus*). Antibiotic therapy should be initiated immediately. The proposed duration of treatment is 7–14 days (*Grade B*). Therapeutic efficacy should be assessed after 3 days of treatment. Symptoms decrease within 48–72 h of effective treatment, therefore treatment should not be changed within the first 72 h unless the patient's clinical state worsens, possibly requiring hospitalization or extended antibiotic therapy. A clinical and radiological evaluation (especially if X-ray has not been performed at the onset) should be performed after 3 days of closely monitored treatment if no improvement occurs or if the clinical state worsens. This evaluation may result in a change in the antibiotic therapy when the lack of improvement is attributed to inappropriate initial antibiotic treat-

ment. The continuation of a monotherapy or a change of the initial treatment (macrolides–amoxicillin) is recommended in healthy adults with no risk factor, when the usual microorganisms are assumed to be involved (*Professional consensus*). More rarely, an extended therapeutic spectrum of activity may be considered, either by adding a second antibiotic (amoxicillin + macrolide), or by switching to a new broad-spectrum antibiotic: telithromycin (despite its moderate efficacy on *H influenzae*) or a fluoroquinolone active against pneumococci. The failure of an extensive antibiotic treatment should lead to hospitalization. Alternatively, hospitalization may be justified due to severe symptoms or treatment failure associated with complication (empyema), persistence of the initial episode, secondary localization, or an incorrect initial diagnosis. As a general rule, patients should generally be hospitalized if no improvement occurs by day 5–6 despite a change in treatment, as the infection may be due to an unusual microorganism (*M. tuberculosis*, *Pneumocystis carinii*, etc.), or to a particular clinical evolution of the pneumopathy (organized pneumonia).

In adults with risk factor(s) the choice of an antibiotic therapy should be determined on an individual basis.

The nature of the risk factors, the patient's clinical state and the various microorganisms potentially responsible should all be taken into account. Consideration should be given, nevertheless, to infection of pneumococcal origin. The risk

of *S. pneumoniae* with decreased susceptibility to penicillin should always be kept in mind. The antibiotic therapy may comply with the recommendations specified for healthy adults (amoxicillin 3 g/day) or may be extended to a broader spectrum of activity (amoxicillin-clavulanate, parenteral 2nd or 3rd generation cephalosporin, fluoroquinolone active against *S. pneumoniae*) (Figures 3 and 4).

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LOWER RESPIRATORY TRACT INFECTIONS IN CHILDREN

Indication for antibiotic therapy

Diagnosis is based on the symptomatic triad of fever, cough and respiratory distress of varying intensity. A distinction must be made between upper respiratory tract infections (URTI), which occur above the vocal cords, and in which the pulmonary auscultation is normal, and lower respiratory tract infections (LRTI) with cough and/or febrile polypnea. An initial clinical assessment is essential. This allows a distinction to be made between three possible clinical diagnoses: acute bronchiolitis, bronchitis (and/or tracheobronchitis) and pneumonia. Bronchiolitis and bronchitis are very common (90% of LRTI), and are mainly of viral origin. Pneumonia is the expression of parenchymal involvement, therefore a bacterial origin should not be discounted.

Recommended antibiotic therapy

For outpatients, the therapeutic choice of an antibiotic is based on the type of infection. The antibiotic therapy chosen is given orally.

Acute bronchiolitis

First-line antibiotic therapy is of no value because of the low risk of invasive bacterial infection (*Grade C*). In a few situations to be determined on a case-by-case basis, the most appropriate compounds to be used first-line are amoxicillin-clavulanate, cefuroxime-axetil or cefpodoxime-proxetil. This treatment is appropriate in cases of high fever (≥ 38.5 °C) persisting for more than 3 days; in cases of associated purulent acute otitis media (except common congestive otitis); and in cases of pneumonia and/or atelectasis confirmed by chest X-ray.

Acute bronchitis

Acute bronchitis, well-tolerated in a child without any risk factors, does not justify antibiotic therapy (*Professional consensus*). Antibiotic therapy is

recommended in case of fever (≥ 38.5 °C) persisting for more than 3 days. In children under 3 years of age, it is based on beta-lactams (amoxicillin, amoxicillin-clavulanate, cefuroxime-axetil or cefpodoxime-proxetil), and in patients above that age, on macrolides. The duration of treatment is 5–8 days (*Professional consensus*).

Community-acquired acute pneumonia

The decision to initiate antibiotic therapy depends on the pathogens involved. At any age, the greatest risk is infection by *S. pneumoniae*. Amoxicillin is the reference treatment in any clinical and radiological situation suggestive of pneumococcal pneumonia. Age is an important factor used to discriminate pathogens.

- In children below 3 years of age, pneumococcus is the bacterial agent that causes pneumonia most frequently. The initial choice is amoxicillin 80–100 mg/kg/day in three daily intakes for a child weighing less than 30 kg (Grade B). In the case of known allergy to beta-lactams, hospitalization is preferable so that appropriate parenteral antibiotic therapy may be initiated. First, second and third generation cephalosporins, trimethoprim-sulfamethoxazole (cotrimoxazole), tetracyclins and pristinamycin are not recommended (*Professional consensus*).
- In children over 3 years of age, pneumococcus and atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) predominate. Initial antibiotic therapy is based on the clinical and radiological pictures. If these favor a pneumococcal infection, the antibiotic therapy proposed is as described above; if they suggest *M. pneumoniae* or *C. pneumoniae*, the first-line use of a macrolide is reasonable (*Professional consensus*).
- In children below 5 years of age, the only justification for prescription of amoxicillin-clavulanate (80 mg/kg/day amoxicillin), or a second or third generation oral cephalosporin (except cefixime), are absence of or insufficient vaccination (less than three injections) against type b *H. influenzae* and/or the coexistence of a purulent acute otitis media (*Professional consensus*). In a child with no risk factors, initial combination therapy is not justified (*Professional consensus*). It is recommended that pneumococcal pneumonia is treated for 10 days (beta-lactam) and atypical pneumonia for at least 14 days (macrolide). Therapeutic efficacy must be assessed after 2 or 3 days of treatment, or earlier if the initial

clinical picture is serious. The principal assessment criterion is fever. Although apyrexia is often achieved in less than 24 h in case of pneumococcal pneumonia, 2–4 days may be necessary in other etiologies. A cough could last longer. If no improvement is observed, clinical and radiological reassessment is necessary. Hospitalization should be considered in cases of particular radiological observations or suspicion of an underlying diagnosis (inhaled foreign body, tuberculosis, etc.). If these hypotheses do not apply, various therapeutic options may be considered.

- Amoxicillin failure after 48 h suggests atypical bacteria which would justify macrolide monotherapy (*Professional consensus*).
- The absence of marked improvement after a 48-h macrolide therapy does not strictly call into question diagnosis of mycoplasma coinfection, and the patient should be reassessed after a further 48-h period.
- In rare cases (nonspecificity of clinical symptoms and/or lack of improvement under carefully considered monotherapy), combined treatment with amoxicillin and a macrolide may be used. Hospitalization after about 5 days is warranted if no improvement is observed, or if the general condition worsens (Figures 5 and 6).
- In rare cases, combined therapy with amoxicillin plus a macrolide may be used in the event of nonspecific clinical symptoms and/or the absence of appropriate single-drug therapy. A further assessment should then be made after 5 days. The absence of improvement, or a worsening in the patient's condition, would make hospitalization necessary.

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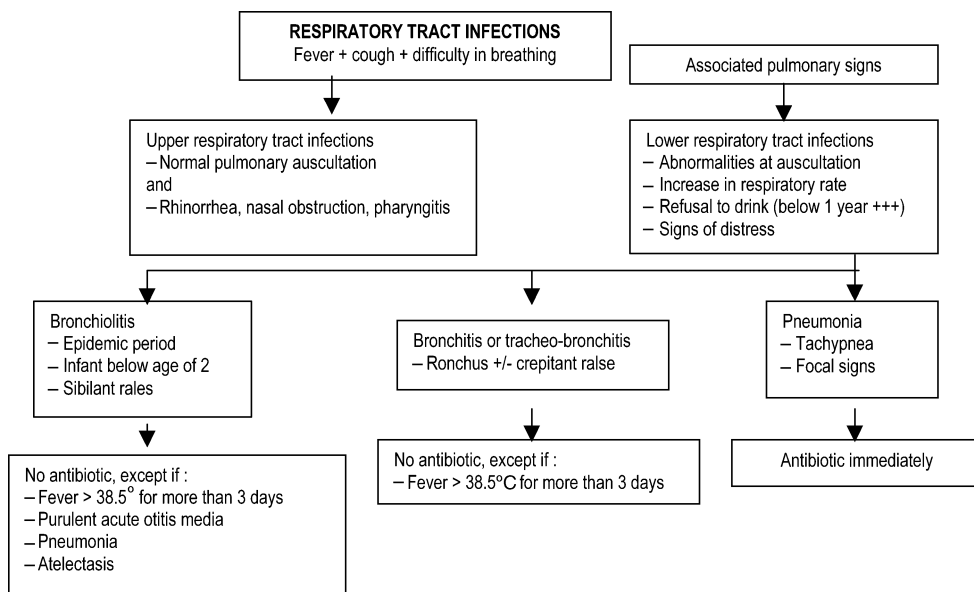


Figure 5 Diagnostic and therapeutic elements of respiratory tract infections in children.

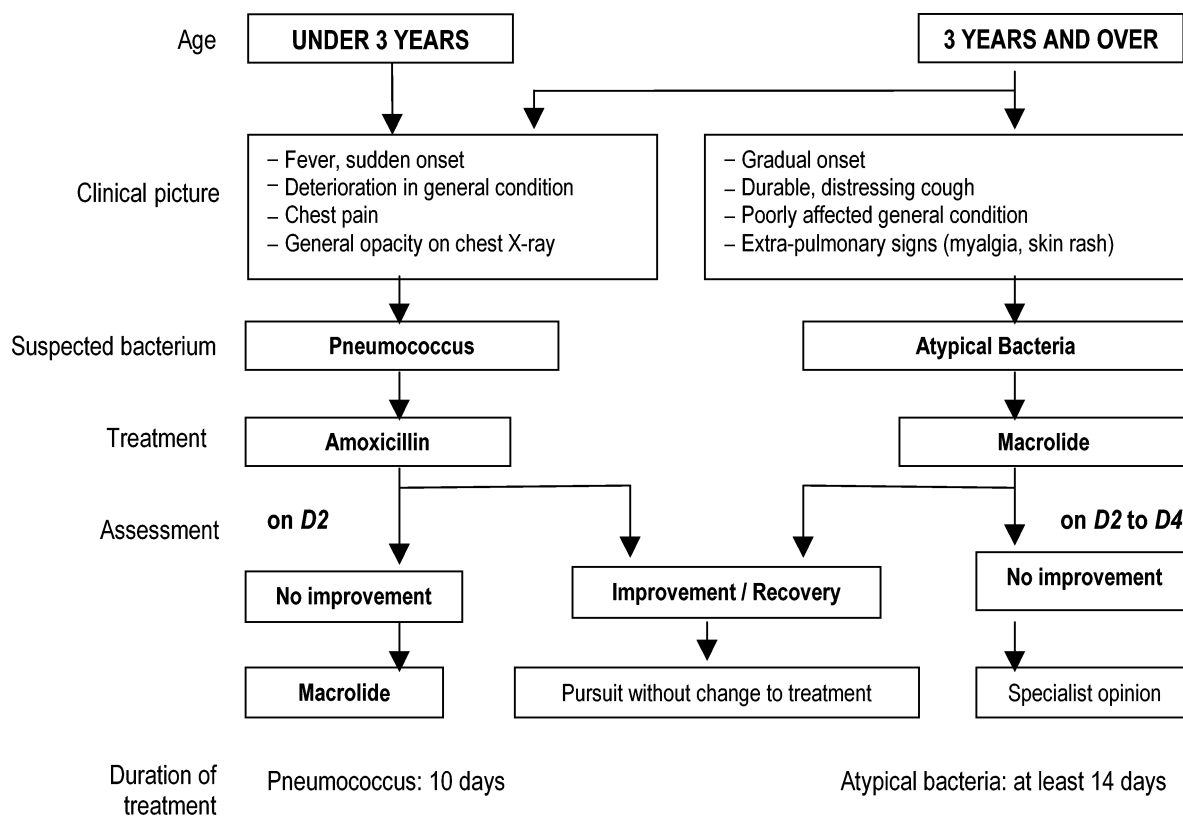


Figure 6 Therapeutic regimen for community-acquired pneumonia in children without risk factors.

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ACKNOWLEDGMENTS

Publication of these guidelines was funded by the Agence Française de Sécurité Sanitaire de Produits de Santé.