



SPANISH ASSOCIATION OF PAEDIATRICS

Community acquired pneumonia in children: Treatment of complicated cases and risk patients. Consensus statement by the Spanish Society of Paediatric Infectious Diseases (SEIP) and the Spanish Society of Paediatric Chest Diseases (SENP)^{☆,☆☆}



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Abstract The incidence of community-acquired pneumonia complications has increased during the last decade. According to the records from several countries, empyema and necrotising pneumonia became more frequent during the last few years. The optimal therapeutic approach

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^{☆☆} The names of the members of the association are listed in the [Appendix](#).

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for such conditions is still controversial. Both pharmacological management (antimicrobials and fibrinolysis), and surgical management (pleural drainage and video-assisted thoracoscopic surgery), are the subject of continuous assessment. In this paper, the Spanish Society of Paediatric Infectious Diseases and the Spanish Society of Paediatric Chest Diseases have reviewed the available evidence. Consensus treatment guidelines are proposed for complications of community-acquired pneumonia in children, focusing on parapneumonic pleural effusion. Recommendations are also provided for the increasing population of patients with underlying diseases and immunosuppression.

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Neumonía adquirida en la comunidad: tratamiento de los casos complicados y en situaciones especiales. Documento de consenso de la Sociedad Española de Infectología Pediátrica (SEIP) y Sociedad Española de Neumología Pediátrica (SENP)

Resumen Desde hace más de una década, los casos complicados de neumonía adquirida en la comunidad, fundamentalmente con empiema pleural o formas necrosantes, comenzaron a ser más frecuentes en niños, según la amplia documentación procedente de numerosos países. El abordaje terapéutico óptimo de estos casos, tanto desde el punto de vista médico (antibióticos, fibrinolíticos) como técnico-quirúrgico, (drenaje pleural, videotoracosopia) continúa siendo controvertido. En este documento, la Sociedad Española de Infectología Pediátrica y la Sociedad Española de Neumología Pediátrica revisan la evidencia científica y proponen unas pautas consensuadas de tratamiento de estos casos, fundamentalmente para el abordaje del derrame pleural paraneumónico en niños, así como la actuación en situaciones especiales, sobre todo en la cada vez más frecuente población pediátrica con enfermedades de base o inmunodepresión. © 2014 Asociación Española de Pediatría. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

In the late 1990s there was a progressive increase in the number of complicated cases of community-acquired pneumonia (CAP), and particularly of cases complicated by pleural effusion.^{1,2} The trend continued over the following decade, with striking incidences of pleural empyema and necrotising forms of disease, especially of pneumococcal aetiology, in children older than 2 years.³⁻⁵ This epidemiological change was probably due to multiple factors, including the serotype shift in the nasopharyngeal carriage of pneumococcal strains due to the pressure of the 7-valent pneumococcal conjugate vaccine, although the trend was already apparent before the vaccine was introduced.^{1,2} This new situation mostly involved the emergence of several pneumococcal serogroups, such as 1, 3, 5 and 19A.³ However, it seems that the increasing trend has been partially curbed since the introduction in 2010 of new pneumococcal vaccines that cover the emerging serotypes, especially the 13-valent vaccine.^{6,7}

Meanwhile, disease caused by *Staphylococcus aureus* (*S. aureus*) has been increasing at a slow pace, including disease by methicillin-resistant strains (MRSA) and strains that produce specific virulence factors, such as Panton-Valentine leukocidin (PVL), that can increase clinical severity, while the prevalence of other causative agents, such as *Streptococcus pyogenes* (*S. pyogenes*), continues to be low.⁸

This consensus document has been developed by the Sociedad Española de Infectología Pediátrica (Spanish Society of Paediatric Infectious Medicine [SEIP]) and the Sociedad Española de Neumología Pediátrica (Spanish Society of Paediatric Chest Diseases [SENP]), and it proposes guidelines for the treatment of complicated CAP and for the management of special circumstances, concluding the documents previously published in this journal on the diagnosis,⁸ treatment of uncomplicated cases, and prevention of CAP.⁹

The criteria for admitting children with CAP to the hospital may vary from one facility to another. This consensus offers recommendations approved by the authors of this document and supported by international guidelines,^{10,11} which can be consulted in [Table 1](#).

While there is broader consensus on first-line antibiotic treatment, its choice should be determined on a case-by-case basis in a certain group of at-risk patients. There is greater controversy surrounding the best approach to the management of complicated cases with pleural effusion, both from a medical and a technical-surgical standpoint, which we will therefore analyse here.

Supportive care

In addition to antibiotic treatment, children admitted with CAP require supportive care, a subject that was partly

Table 1 Criteria proposed for hospital and PICU admission of children with community-acquired pneumonia.**Criteria for hospital admission***Clinical criteria*

- Septic appearance
- Poor general health status
- Moderate to severe tachypnoea
- Retractions—use of accessory respiratory muscles (of any degree), suprasternal, intercostal or subcostal; grunting
- Apnoeas
- Sustained SaO₂ below 92% with environmental air
- Dehydration and/or significant electrolyte imbalance
- Fatigue-somnolence
- Cannot tolerate enteral nutrition
- Oral antibiotherapy cannot be administered (vomiting, family cannot cooperate with treatment...)
- Lack of response to appropriate empiric oral treatment 48 h after initiation

Radiological criteria

- Multifocal involvement in typical CAP
- Lung abscess
- Pneumatoceles
- Significant pleural involvement
- Severe interstitial lung pattern
- Radiological images suggestive of an atypical microorganism

Risk factors to consider

- Age <6–12 months
- Underlying disease, including:
 - Malnutrition
 - Immunodeficiency
 - Cystic fibrosis
 - Bronchiectasis
 - Bronchopulmonary dysplasia associated with preterm birth
 - Cardiac disease
 - Renal disease
 - Diabetes
- Inadequate hygiene-social environment. Inadequate supervision in the household

Criteria for admission to the paediatric intensive care unit

- Shock
- Severe breathing difficulty or respiratory muscle fatigue, in spite of supplementary oxygen
- Frequent apnoeas
- Hypoxaemia (SaO₂ ≤ 90%) despite oxygen therapy with con FiO₂ ≥ 0.5
- Progressive hypercapnia (pCO₂ ≥ 65–70, capillary or venous)
- Rapidly progressing radiological findings
- Pneumothorax
- Severe metabolic abnormalities
- Changes in level of consciousness

FiO₂, fraction of inspired oxygen; pCO₂, partial pressure of carbon dioxide; PICU, paediatric intensive care unit; SaO₂, oxygen saturation.

addressed in the previous consensus document⁹ and that we proceed to complete in this one.

Monitoring

Pulse oximetry, which can be continuous. If the condition is serious, pCO₂ should be measured, as hypercapnia is a sign of impending respiratory failure.¹²

Respiratory support

(A) *Oxygen therapy*: with nasal cannulae, masks or face tents if the basal oxygen saturation (SaO₂) is equal or lower than 92%, to achieve a FiO₂ of up to 40% with the prongs or up to 50% with Venturi masks. If this were not

sufficient, high-flow cannulae or non-rebreather masks with 100% oxygen should be used, assessing the need for intensive care unit admission in the following hours (Table 1) except in cases with limitation of therapeutic effort.

(B) *Respiratory support*: in exceptional cases, patients with CAP require mechanical ventilation. There is growing evidence of the advantages of non-invasive ventilation.¹³

Fluid and electrolyte management

Baseline requirements must be met by either the oral or, when necessary, the intravenous route. Patients with

Table 2 Antibiotic treatment of children hospitalised with typical community-acquired pneumonia (with a suspected or confirmed pneumococcal aetiology), depending on the presence of parapneumonic pleural effusion.

	Recommended antibiotic treatment
Without parapneumonic pleural effusion	Equally valid options: – Ampicillin IV: 150–200 mg/kg/day, every 6 h (maximum 12 g/day) – Penicillin G sodium IV: 250 000–300 000 IU/kg/day, every 4 h (maximum 24 million IU/day)
With parapneumonic pleural effusion	Equally valid options: – Ampicillin IV: 250–300 mg/kg/day, every 6 h (maximum 12 g/day) – Penicillin G sodium IV: 300 000–400 000 IU/kg/day, every 4 h (maximum 24 million IU/day)

clinically significant heart disease may require fluid restriction (2/3) and diuretics.

A third of the patients may have hyponatraemia (<135 mEq/L),¹⁴ which has shown a stronger association with lobar forms of CAP and higher degrees of severity.^{14,15} Hyponatraemia is usually due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH), although secretion may be appropriate in hypovolemic children. Similarly, there is evidence of increased atrial natriuretic peptide levels in children with CAP and SIADH. The administration of isotonic fluids is recommended in children admitted with CAP to prevent the development of hyponatraemia.

Respiratory physiotherapy

The available data is scarce. A supported sitting position is recommended to help lung expansion.¹⁰

Nutrition

Malnutrition carries a poorer prognosis. Patients unable to tolerate enteral nutrition may require nasogastric tube feeding.¹⁰

Corticosteroids

Corticosteroids seem to shorten the duration of disease in adults.¹⁶ Two small trials on children, one on patients with severe CAP and another in patients with CAP caused by *Mycoplasma*, showed that corticosteroid treatment shortened the duration of disease,^{17,18} even at high-doses for the treatment of refractory cases.¹⁹ Clinical trials are currently being developed to analyse their usefulness in the treatment of CAP and parapneumonic pleural effusion.

Antibiotic therapy

Antibiotic therapy in hospitalised children with no underlying disease

Typical community-acquired pneumonia with a suspected or confirmed pneumococcal aetiology

The most frequent causative agent in typical forms of CAP continues to be *Streptococcus pneumoniae*, which at present has an excellent susceptibility profile to

beta-lactams such as penicillin, amoxicillin and ampicillin.²⁰ Thus, the first-line antibiotic for the treatment of children older than 3 months with typical CAP that requires hospital admission (Table 1) with a suspected or confirmed pneumococcal aetiology is ampicillin or penicillin G sodium, administered intravenously at high doses, given its excellent tolerability.¹¹ Both choices are equally appropriate, although ampicillin has the advantage of requiring fewer doses a day and having a slightly lower cost. Table 2 shows the dosage for these antibiotics.

This recommendation is mostly based on the expert recommendations documented in clinical guidelines. There have been no clinical trials that compared the efficacy of these antibiotics with that of broader-spectrum antibiotics, although there are retrospective studies that suggest the results are comparable.²¹

Hospitalised patients usually improve and can be switched to oral amoxicillin when they have remained afebrile for 24–48 h. We recommend a course of treatment lasting 7–10 days.

There is a high and unwarranted use of third-generation cephalosporins in hospitalised children with CAP. Thus, a multicentric study conducted in Spain showed that up to 34% of them received initial empirical treatment with these agents.²²

Typical community-acquired pneumonia associated with other pathogens

Table 3 presents various situations in which treatment with other antibiotics is recommended.

Amoxicillin/clavulanic acid is recommended in children that have not been vaccinated against *Haemophilus influenzae* (*H. influenzae*) type b and children less than 6 months of age, except for children younger than 3 months, in whom the recommended treatment is ampicillin–cefotaxime.

In certain situations, and especially in severe cases, other bacteria should be considered, such as *S. aureus* and *S. pyogenes*, requiring different antibiotic treatment (Table 3). The recommended empirical treatment for necrotising forms, which amount to 0.8% of CAP cases (and 6% of hospitalised patients with CAP) and in Spain are usually associated with *S. aureus* (usually methicillin-susceptible but PVL-producing) followed by *S. pneumoniae*,⁵ consists of a cefotaxime and clindamycin regimen for a minimum of 14–21 days.

Table 3 Empirical antibiotic treatment in special cases of typical community-acquired pneumonia, with or without parapneumonic pleural effusion (use the upper limit of the doses in cases with pleural effusion).

	Recommended antibiotic treatment
Younger than 6 months	<ul style="list-style-type: none"> – Younger than 3 months: ampicillin IV (200 mg/kg/day, every 6 h) + cefotaxime IV (200 mg/kg/day, every 6 h) – 3 to 6 months: amoxicillin–clavulanic acid IV (proportion, 10:1): 150 mg/kg/day, every 6 h
Children not vaccinated against <i>Haemophilus influenzae</i> type b	Options: <ul style="list-style-type: none"> – Amoxicillin–clavulanic acid IV (proportion, 10:1): 150 mg/kg/day, every 6 h (maximum 2 g every 6 h) – Cefuroxime IV: 150 mg/kg/day, every 6–8 h
Suspicion of <i>Streptococcus pyogenes</i> ^a	Penicillin G sodium IV (250 000 IU/kg/day, every 4 h) + clindamycin IV (30–40 mg/kg/day, every 6 h)
Suspicion of methicillin-susceptible <i>Staphylococcus aureus</i> ^b	Options: <ul style="list-style-type: none"> – Cloxacillin IV (150–200 mg/kg/day, every 6 h) + cefotaxime IV (200 mg/kg/day, every 4–6 h) – Amoxicillin–clavulanic acid IV (proportion, 10:1): 150 mg/kg/day, every 6 h (maximum 2 g every 6 h) – Cefuroxime IV: 150 mg/kg/day, every 6–8 h
Pulmonary abscess and necrotising pneumonia ^c	Cefotaxime IV (200 mg/kg/day, every 6 h) + clindamycin IV (30–40 mg/kg/day, every 6–8 h)
Suspected aspiration pneumonia	Amoxicillin–clavulanic acid (proportion, 10:1) IV: 150 mg/kg/day, every 6 h (maximum 2 g every 6 h)
Allergic to beta-lactam antibiotics	Allergy, not anaphylaxis: cephalosporins, preferably cefuroxime, oral or IV Anaphylaxis: <ul style="list-style-type: none"> – Mild-moderate CAP: levofloxacin or glycopeptides antibiotics^d – Severe CAP: glycopeptides + levofloxacin or macrolides

^a Circumstances that suggest the likelihood of *S. pyogenes*: varicella, pleural fluid negative for pneumococcal antigen; scarlatiniform rash; pharyngeal swab positive for this bacterium; sepsis, poor general health status.

^b Circumstances that suggest the likelihood of *S. aureus*: necrotising pneumonia and/or pneumatoceles; microbiological findings such as pleural fluid negative for pneumococcal antigen, suspicious Gram-positive cocci in pleural fluid, blood culture positive for this bacterium; previous skin or soft-tissue staphylococcal infection; children less than 2–3 years of age that respond poorly to appropriate antibiotic therapy; septic condition; poor general health status.

^c Aetiology: *S. aureus* (including MRSA), *S. pneumoniae*, other (*S. pyogenes*, *Nocardia* in immunosuppressed patients), Gram-negative bacteria (*Haemophilus*, *E. coli*, *Klebsiella*, *Pseudomonas*), anaerobic bacteria, fungi (*Candida*, *Aspergillus* in immunosuppressed patients).

^d Teicoplanin can be administered by the intramuscular or the intravenous route.

In children with CAP associated with influenza,¹⁰ usually caused by *S. pneumoniae* or less frequently by *S. aureus*, *S. pyogenes* or *H. influenzae*^{5,23}, empirical treatment with amoxicillin–clavulanic acid as opposed to amoxicillin or ampicillin is recommended.

In children with varicella that have CAP of a suspected bacterial aetiology, the recommended treatment is antibiotics covering *S. pyogenes* and *S. aureus*, such as cefuroxime, or in more severe cases, penicillin G or cefotaxime combined with clindamycin, especially in cases of necrotising pneumonia or with signs of toxic shock syndrome.²⁴

Community-acquired pneumonia complicated by parapneumonic pleural effusion

The same antibiotics used in CAP without pleural effusion (ampicillin or penicillin) are recommended (Table 2), save for exceptional cases detailed in Table 3,^{10,11} although they should be administered at higher doses to achieve adequate pleural fluid concentrations.²⁵

It is recommended that administration is switched to the oral route once the patient has remained afebrile for 48 h, for a total course lasting 2–4 weeks depending on the causative agent, although treatment could be extended for a few more days in prolonged or severe cases.

Atypical community-acquired pneumonia

These cases are most frequently caused by viral infections, especially in children younger than 4 or 5 years, and they do not usually require admission to the hospital or antibiotic treatment. In children older than 4 or 5 years, in whom disease is more frequently caused by *Mycoplasma pneumoniae* and to a much lesser degree by *Chlamydia pneumoniae*, treatment with macrolides is recommended, by the oral route whenever possible and otherwise intravenously.¹¹

Clarithromycin and azithromycin are the two most commonly used antibiotics, at the same doses for both the oral and the intravenous preparations, with azithromycin being better tolerated¹¹ (Table 4). The use of erythromycin has waned due to its adverse effects, including phlebototoxicity

Table 4 Atypical community-acquired pneumonia with confirmation or high suspicion of *Mycoplasma* or *Chlamydomphila*. Most commonly used macrolides (same dosage for oral and intravenous routes).

Name	Dosage	Duration
Azithromycin	10 mg/kg every 24 h (maximum dose: 500 mg/day) ^a	3 days
Clarithromycin	15 mg/kg/day, every 12 h (maximum dose: 1 g/day)	7 days

^a In the United States, the same total dosage is used, but it is distributed over five days (day 1, 10 mg/kg, to a maximum of 500 mg; days 2–5, 5 mg/kg every 24 h, to a maximum of 250 mg/day), as this is the dosage approved by the FDA, but it does not have any advantages over the 3-day course approved by the European Medicines Agency (EMA).

when administered intravenously, and its complicated dosage (every 6 h for 10–14 days).

Influenza can be treated with antivirals, and there are no oseltamivir-resistant strains in Spain. There are reasonable doubts concerning the effectiveness of oseltamivir in hospitalised patients with no risk factors,²⁶ so its use should be restricted to hypoxaemic or seriously ill patients, especially those with significant underlying disease.

Severe community-acquired pneumonia that requires admission to the Paediatric Intensive Care Unit

The aetiological spectrum is broader: *S. pneumoniae*, *S. aureus*, *S. pyogenes*, and others. This consensus recommends cefotaxime, possibly in combination with an antibiotic with antistaphylococcal activity such as cloxacillin (Table 5). Considering the association of *S. aureus*, including MRSA, and influenza, it would be appropriate to use clindamycin (or vancomycin, depending on local data on susceptibility) combined with a cephalosporin (cefuroxime or cefotaxime).

In adults, combination treatment with a macrolide results in reduced mortality,²⁷ but there are no data on this subject for children. A study of children more than 5 years of age hospitalized with CAP of varying severity found that they had shorter lengths of stay.²⁸

Antibiotic treatment in patients with underlying disease

Although cases of pneumonia in these patients are usually community-acquired, they may have special characteristics: a great variety of potentially involved microorganisms, frequent coinfections, a broad range of clinical findings and a potentially greater severity. These circumstances lead to a greater number of diagnostic tests and more aggressive treatments.

The probable aetiological agents depend on the underlying disease (Table 6) and the characteristics of radiographic findings. Usual pathogens such as respiratory viruses and *S. pneumoniae* should be generally considered, as well as non-typeable *H. influenzae*.¹²

In patients that are not severely immunosuppressed, most of the panel would recommend initiating empiric treatment with amoxicillin–clavulanic acid, cefuroxime or cefotaxime, with the possibility of adding a neuraminidase inhibitor (oseltamivir) if influenza virus is detected. In patients with a higher degree of immunosuppression, a macrolide should be added if there are diffuse pulmonary infiltrates, and even cotrimoxazol if *Pneumocystis pneumonia* is suspected.

Treatment failure

It is defined as the development of respiratory failure or the persistence of tachypnoea 72 h after the onset of disease, or as persistence of fever or of poor general health status 48–72 h following admission.¹⁰ However, in the latter case, if the patient shows improvement and the levels of acute phase reactants (especially of C reactive protein) decrease, antibiotic treatment has probably not failed.

If treatment is considered to have failed 48–72 h after initiation, a clinical, radiological and laboratory re-evaluation should be performed, assessing for the most frequent causes of failure (Table 7).^{10,29}

Pleural drainage

Approximately 20–40% of children admitted with CAP will have pleural effusion, and up to 0.6% will progress to empyema.³⁰

About half of the cases of parapneumonic pleural effusion resolve with antibiotic treatment and do not require invasive interventions.³⁰ The patient's clinical condition (especially breathing difficulty) and the extent of the effusion are key in decision-making. Fig. 1 presents the recommended care protocol for parapneumonic pleural effusion.

Whenever there is a moderate to large pleural effusion or there is doubt as to the presence or extent of a small effusion in the radiograph, a thoracic ultrasound should be performed. The extent and sonographic characteristics of the effusion should be determined, along with the optimal puncture site or sites for a potential chest drain, searching for the thickest area that can be accessed most easily, which is usually found between the fifth and the seventh intercostal spaces at the level of the mid-posterior axillary line. Drainage should not be performed in cases of subpulmonic effusion. Effusions smaller than 10 mm should not be performed routinely.¹¹

Thoracocentesis is to be performed in a properly equipped room (anaesthesia, PICU, or operating room), although there may be other equally fitted areas in the emergency department or inpatient wards. We recommend that chest tube insertion be performed in an intensive care unit or operating room.

A chest tube should be placed if the effusion meets one or more of the criteria for pleural empyema or if it causes moderate to severe breathing difficulty. A complicated effusion with septations requires not only tube drainage but also administration of fibrinolytics, and if the patient does not

Table 5 Recommended antibiotic treatment for children with community-acquired pneumonia and severe pleural effusion that required PICU admission.

Typical CAP	<ul style="list-style-type: none"> – Cefotaxime (200–300 mg/kg/day, every 6 h) + one of the following:^a <ul style="list-style-type: none"> – Cloxacillin IV (150–200 mg/kg/day, every 6 h) or – Clindamycin IV (30–40 mg/kg/day, every 6–8 h)^b, or – Vancomycin IV (60 mg/kg/day, every 6 h)^c ± Macrolide IV (erythromycin 40 mg/kg/day every 6 h, or clarithromycin 15 mg/kg/day, every 12 h; or azithromycin 10 mg/kg/day, every 24 h)
Community-acquired interstitial pneumonia	<ul style="list-style-type: none"> – Cefotaxime (200 mg/kg/day) + macrolide IV (erythromycin, clarithromycin or azithromycin) ± – Cotrimoxazol IV (20 mg of trimetoprim/kg/day every 6 h)^d

H, hours; IV, intravenous route; MRSA, methicillin-resistant *Staphylococcus aureus*; PICU, paediatric intensive care unit.

^a This panel did not reach an unanimous consensus for the recommendation of routinely adding an antistaphylococcal agent to the regimen for these cases. Linezolid, which is currently not approved for its use in children, would be the last choice.

^b In cases of necrotising pneumonia or septic shock.

^c If >10% of MRSA circulating in the community, skin and soft-tissue or osteoarticular infections.

^d In cases of severe community-acquired interstitial pneumonia with suspected immunosuppression.

respond favourably, performance of video-assisted thoracoscopic surgery (VATS).

Catheters of variable size may be used. The American Pediatric Surgical Association recommends using 12F catheters.³¹ A recent multicentric study in Spain used 12F–14F catheters,³² although other studies have used 8F–10F tubes.³³ Small-bore catheters (8F–14F) are as effective as large-bore catheters, cause less pain, and shorten the length of stay.³⁴ The use of trocars is discouraged, and it is recommended that soft tubes are used for insertion with the Seldinger technique. Radiography should be used to confirm proper placement of the tube and rule out pneumothorax. The tube has to be connected to a unidirectional flow drainage system that must be kept at a level lower than the patient's chest. The indications for using a drainage system remain unclear, but it seems to improve fluid removal. When these systems are used, a water seal must be used at a pressure of 5–10 cm H₂O.

The drain should be clamped for 1 h once 10 mL/kg have been removed. In older children and adolescents, it is recommended that no more than 1.5 L of fluid are removed at one time, or that larger amounts are drained slowly at a rate of approximately 500 mL per hour.

The drain is usually removed when there is minimal drainage (<40–60 mL/24 h).^{32,33} Some authors recommend keeping the drain until serous fluid drainage amounts to less than 1 mL/kg/day for the previous 12 h. The absence of a significant amount of fluid in ultrasound examination may guide this decision.¹¹ Drain removal does not require previous clamping.

Fibrinolytics

We propose the use of fibrinolytics for the first-line treatment of pleural effusion with septations, either with floating

septa or forming loculations (Fig. 1).^{31,32} Their use has proven to be cost-effective compared to placement of chest drains without fibrinolytics.³⁵ In cases with no sonographic septations but with a lower than expected drainage volume, and especially if the fluid is thick, treatment with fibrinolytics should be considered once other possible causes have been ruled out.

Out of all the available fibrinolytic agents, this panel recommends the use of urokinase because it is the one for which there is the most data for the paediatric age group.

Clinical trials comparing intrapleural urokinase with VATS in children^{32,33} found no differences between these two interventions. A recent multicentre clinical trial conducted in Spain compared the usefulness of urokinase and VATS in 103 children with fibrinopurulent pleural effusion.³² The results showed that urokinase is as effective as VATS in the treatment of septated pleural empyema, while no differences were found in the length of stay from the time treatment was initiated.³²

These results support the current recommendation of the American Pediatric Surgical Association of using fibrinolytics as the first-line treatment of these patients, given its lower cost and easier implementation, as it does not require surgical intervention.^{31–33,36}

The urokinase doses used in different studies range between 10 000 and 100 000 IU.³⁷ The recommendation in this consensus is the following:³²

- Infants age < 1 year: 10 000 IU in 10 mL of 0.9% saline solution.
- Children age ≥ 1 year: 40 000 IU in 40 mL of 0.9% saline solution.

It is administered through the intrapleural catheter (which is subsequently clamped for 4 h), twice a day for 3

Table 6 Most common causative agents associated with pneumonia in children with severe underlying disease.^a

Underlying disease	Main aetiological agents	Most commonly used treatments
Humoral immunodeficiency	<i>S. pneumoniae</i> , <i>H. influenzae</i> Less common: <i>Salmonella</i> , <i>Pseudomonas</i> , <i>S. aureus</i> Enterovirus	Amoxicillin-clavulanic acid, cefotaxime
Combined immunodeficiency ^b	– Encapsulated bacteria, <i>Listeria</i> , <i>P. aeruginosa</i> , <i>Stenotrophomonas</i> , <i>Burkholderia cepacia</i> , <i>Legionella</i> , <i>Nocardia</i> – VZV, rubella, VHS, CMV, adenovirus, RSV, influenza, parainfluenza, hMPV – MAC, <i>M. fortuitum</i> , BCG, other opportunistic mycobacteria. Reactivation TB – <i>Pneumocystis jirovecii</i> , <i>Aspergillus</i> , <i>C. albicans</i> , <i>Cryptococcus</i>	Cefotaxime, cefepime, cotrimoxazol, acyclovir, antifungals (fluconazole, voriconazole, liposomal amphotericin B)
Phagocytic cell disorders/neutropenia	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Stenotrophomonas</i> , <i>B. cepacia</i> <i>S. marcescens</i> , enterobacteria such as <i>Salmonella</i> , <i>E. coli</i> ^c , <i>Nocardia</i> . BCG, non-tuberculous mycobacteria ^d <i>Aspergillus</i> , <i>Candida</i>	Amoxicillin-clavulanic acid, cefotaxime. Cloxacillin, clindamycin, vancomycin. Cotrimoxazol. Piperacillin-tazobactam, cefepime or meropenem. Antifungals (voriconazole, liposomal amphotericin B)
HIV infection	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i> . <i>Mycobacteria</i> . <i>Pneumocystis</i> . CMV, HSV	Amoxicillin-clavulanic acid, cefotaxime. Cotrimoxazol. Acyclovir
HSCT	Multiple. Depends on the time of the transplantation, presence of GVHD, IS treatment and antimicrobial prophylaxis. Always encapsulated bacteria	Same as for combined immunodeficiency
SOT	Multiple. Depends on the time of the transplantation, IS treatment and antimicrobial prophylaxis. Always encapsulated bacteria	Same as for combined immunodeficiency
Complement deficiency	<i>S. pneumoniae</i> , <i>H. influenzae</i>	Cefotaxime
Sickle cell disease/asplenia	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Salmonella</i> , and other encapsulated bacteria	Cefotaxime
Nephrotic syndrome ^e	<i>S. pneumoniae</i> , <i>H. influenzae</i> , Enterobacteria. Respiratory viruses	Amoxicillin-clavulanic acid, cefuroxime or cefotaxime
Rheumatic or anti-inflammatory disease ^e	<i>S. pneumoniae</i> , <i>H. influenzae</i> and other encapsulated bacteria	Amoxicillin-clavulanic acid, cefuroxime or cefotaxime. Levofloxacin
Cystic fibrosis ^f	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Burkholderia</i> , <i>Stenotrophomonas</i> . <i>H. influenzae</i> . <i>Aspergillus</i> (allergic bronchopulmonary aspergillosis)	Amoxicillin-clavulanic acid ^g Ceftazidime, piperacillin-tazobactam, meropenem, plus an aminoglycoside, or ciprofloxacin. Cloxacillin
Cardiac disease	Common pathogens. Respiratory viruses	Amoxicillin-clavulanic acid, cefuroxime or cefotaxime

BCG, bacillus Calmette-Guérin; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; HSCT, haematopoietic stem cell transplantation; HSV, herpes simplex virus; IS, immunosuppressive; MAC, *Mycobacterium avium* complex; RSV, respiratory syncytial virus; SOT, solid organ transplantation; TB, tuberculosis; VZV, varicella zoster virus.

^a Organisms that cause CAP in healthy children should always be considered, especially respiratory viruses and *S. pneumoniae*, and to a lesser degree *H. influenzae*. The degree of immunosuppression, the immediate history (recent hospitalisation, chemoprophylaxis, recent vaccinations) and the clinical condition should guide the clinician in deciding how aggressive an approach to take to the management of the patient (need for admission, invasive diagnostic and microbiological tests, combination antibiotic treatment, use of antivirals and antifungals).

^b Suppression of cell-mediated immunity could lead to hyperinfection by *Strongyloides stercoralis* (rule out in cases of severe eosinophilia; it is important to know the country of origin of the patient).

^c It is important to consider endemic infections in the country of origin; there is evidence that the incidence of TB in adults with blood cancers is very high in the immigrant population.

^d Especially important in IF- γ and IL-12 receptor deficiency, and *Salmonella* and *Listeria* could also be involved.

^e Depends to a great extent on the immunosuppressive treatment given to the patient, who may develop infections by opportunistic pathogens. For example, the administration of anti-TNF drugs and corticosteroids at immunosuppressive doses has been associated with tuberculosis reactivation and infection by *Cryptococcus*, *Aspergillus*, *Listeria*, *Pneumocystis*, HSV, VZV and CMV, among others.

^f It is important to know the previous history of respiratory tract colonisation. A combination of two antibiotics at higher-than-usual doses is recommended. If the patient is colonised by *S. aureus*, this pathogen should always be covered. A saliva sample must always be collected before initiating antibiotherapy.

^g Non-severe condition, no previous colonisation by *Pseudomonas* or *S. aureus*.

Table 7 Most frequent causes of treatment failure in community-acquired pneumonia.

1. Pleural effusion, necrotising pneumonia or pulmonary abscess
2. Non-susceptible microorganism, most commonly viral. The possibility of initiating macrolide treatment can be considered if *Mycoplasma* is suspected. It can also be the first sign of tuberculosis
3. Non-compliance with treatment or insufficient dose
4. Underlying condition in the patient, such as immunosuppression, malnutrition, asthma or cystic fibrosis
5. Alternative diagnosis, such as foreign body aspiration, lung malformation or diaphragmatic hernia

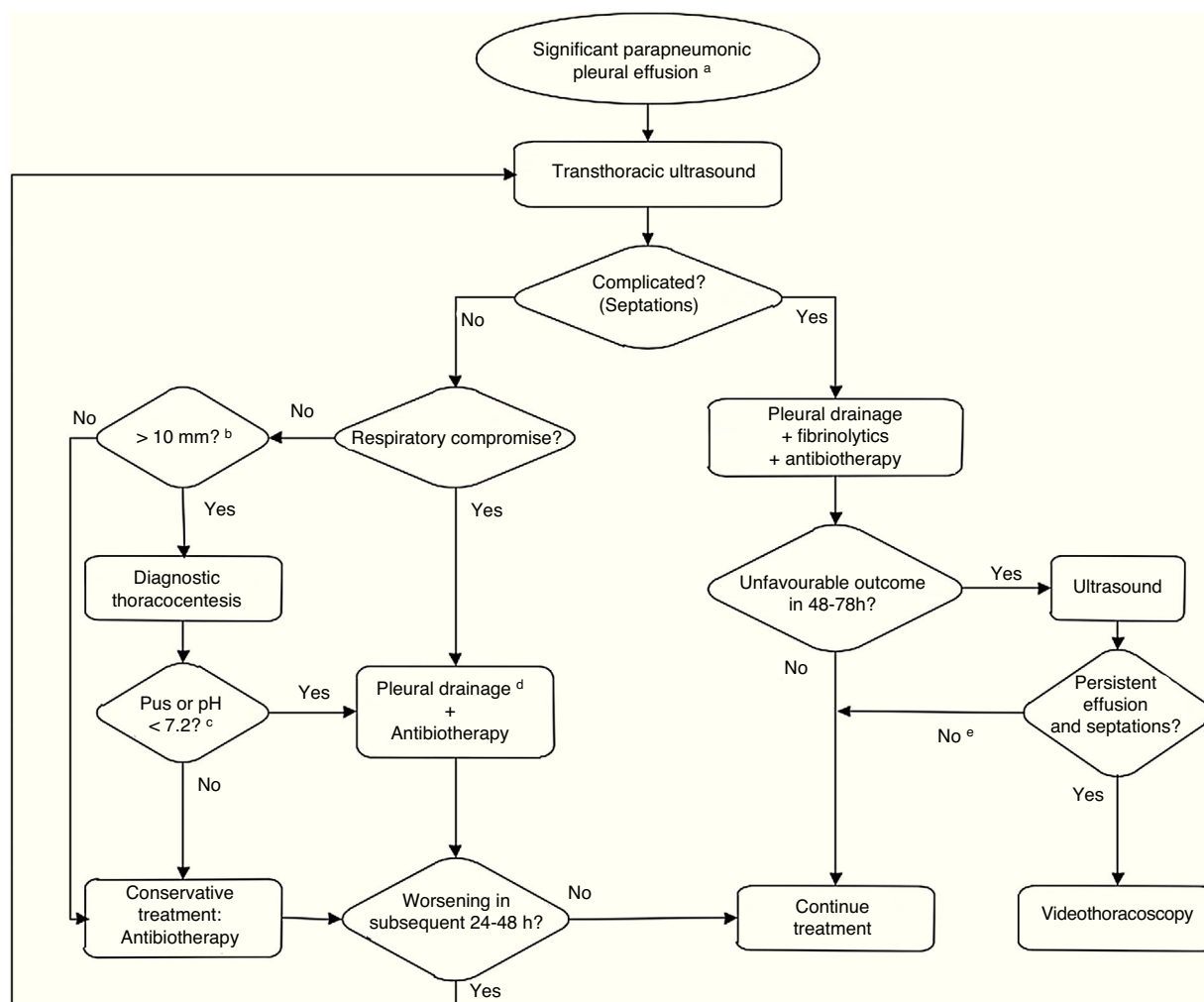


Figure 1 Algorithm for the management of significant parapneumonic pleural effusion. (a) Subclinical pleural effusion (costophrenic angle blunting, minimal volume) will be managed as an uncomplicated pneumonia. (b) In selected cases, a diagnostic thoracocentesis may be performed in cases of small effusion. (c) These findings, which are available quickly, are an indication for immediate pleural drainage during the same procedure. Other findings in the pleural fluid that become available at a later time, such as visualisation of bacteria by Gram staining, positive culture, LDH > 1000 IU/mL, glucose < 40–60 mg/dL, may be indications for pleural drainage *a posteriori*. The use of these biochemical data for the purposes of decision-making is outdated. A positive PCR result for a bacterium or a positive *S. pneumoniae* antigen test (BinaxNow) in pleural fluid will not be used as the sole criteria for chest tube placement. (d) In the absence of empyema, under certain circumstances and in certain patients, if staff trained in the placement and maintenance of a chest drain were not available promptly, a therapeutic thoracocentesis could be performed. (e) Consider other causes for poor outcome: necrotising pneumonia, pulmonary abscess.

days.^{32,33} Additional doses can be used if the patient has not fully responded after the initial six.³⁷

The administration of fibrinolytics through a chest tube may cause discomfort, so it must be accompanied by appro-

priate analgesia. It may also cause light bleeding and, on rare occasions, immediate hypersensitivity reactions.

Fibrinolytic therapy should be discontinued if it is ineffective, which can happen in highly organised effusions, and

should not be considered in patients with bronchopleural fistula when bubbling is observed in the chest tube, as it is suggestive of an air leak. In the latter case, clamping the tube could cause tension pneumothorax. Chest drains should be unclamped immediately if the child develops signs of clinical worsening, such as increased breathing difficulty or chest pain.

Video-assisted thoracoscopic surgery

Video-assisted thoracoscopic surgery can be used to determine the stage of the effusion, break the septations, drain the fibrinopurulent material, reduce the bacterial load in the initial stages, and place the chest drain correctly. Furthermore, it allows the visualisation of the underlying lung, its expansion capacity, and the location of bronchopleural fistulae.

At present, there are two accepted indications for VATS:

- Persistent moderate to massive effusion with respiratory compromise despite treatment with drainage and fibrinolytics for 2–3 days,¹¹ which usually happens in 15% of cases.^{33,36}
- Complications such as bronchopleural fistula.³³

It is also an option for the initial treatment of highly fibrinopurulent and organised effusions in which a thick fibrous peel has developed, or when treatment with fibrinolytics cannot be implemented.^{31,38} Its use as initial treatment must be considered on a case-to-case basis, taking into account the duration and characteristics of the effusion, as well as the availability and surgical experience of the centre for performing VATS. Decortication is not usually necessary in children.

The efficacy of VATS for the treatment of empyema is quite high. Compared to plain drainage without fibrinolysis, VATS significantly reduces the duration of symptoms (fever usually resolves in 24–72 h), the length of stay (reduced to 6–7 days) and the cost of healthcare.^{31,39} On the other hand, its efficacy seems to be similar to that of treatment with drainage and fibrinolytics.^{32,33,36,40} It is estimated that the cost of VATS is higher than that of fibrinolytic treatment,^{33,35,36} although some authors believe that performing VATS early on could be more efficacious and reduce healthcare costs.³⁸

The rate of complications is low (6–7%), including air leaks of persistent pneumothorax, pneumatocele, or bleeding.³⁸

Conflicts of interest

Conflicts of interest of the authors in relation to this document (past five years):

- DMP has collaborated in educational activities funded by GlaxoSmithKline, Pfizer and Sanofi Pasteur MSD, as a researcher in a clinical trial for Novartis, and as a consultant in the Advisory Boards of Astra-Zeneca and Pfizer.
- AAM has no conflicts of interest to declare.
- ATG has collaborated in research activities funded by Pfizer.

- AEM has collaborated in educational activities funded by Novartis, as a researcher in a multicentre study promoted by GlaxoSmithKline and as a consultant in an Advisory Board for Gilead.
- JFM has collaborated in educational activities funded by Gilead and Abbvie.
- JGG has collaborated in educational activities funded by Pfizer and Sanofi Pasteur MSD.
- AMG has participated as a consultant in the Advisory Boards of Abbvie and Gilead, has received institutional research grants from Abbvie and grants for attending scientific conferences from Abbvie, Actelion, Ferrer, GlaxoSmithKline and Novartis.
- CRGL has collaborated in educational activities funded by GlaxoSmithKline, Novartis, Pfizer and Sanofi Pasteur MSD, as a researcher for clinical trials for GlaxoSmithKline and a consultant in the Advisory Boards of Astra-Zeneca, Novartis, GlaxoSmithKline and Pfizer.
- JSL has collaborated as a researcher in clinical trials for GlaxoSmithKline and Roche.

Appendix.

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