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Community acquired pneumonia in children: Outpatient treatment and prevention☆

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Abstract There have been significant changes in community acquired pneumonia (CAP) in children in the last decade. These changes are related to epidemiology and clinical presentation. Resistance to antibiotics is also a changing issue. These all have to be considered when treating

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Children;
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Vaccines

Community acquired pneumonia (CAP). In this document, two of the main Spanish pediatric societies involved in the treatment of CAP in children, propose a consensus concerning therapeutic approach. These societies are the Spanish Society of Paediatric Infectious Diseases and the Spanish Society of Paediatric Chest Diseases. The Advisory Committee on Vaccines of the Spanish Association of Paediatrics (CAV-AEP) has also been involved in the prevention of CAP. An attempt is made to provide up-to-date guidelines to all paediatricians. The first part of the statement presents the approach to ambulatory, previously healthy children. We also review the prevention with currently available vaccines. In a second part, special situations and complicated forms will be addressed.

PALABRAS CLAVE
Neumonía adquirida en la comunidad;
Niños;
Tratamiento;
Prevención;
Streptococcus pneumoniae;
Resistencias;
Vacunas

Neumonía adquirida en la comunidad: tratamiento ambulatorio y prevención

Resumen La neumonía adquirida en la comunidad (NAC) en la edad pediátrica ha sufrido, en la última década, una serie de cambios epidemiológicos, clínicos, etiológicos y de resistencias a antibióticos, que obligan a replantear su abordaje terapéutico. En este documento, dos de las principales sociedades de especialidades pediátricas involucradas en el diagnóstico y tratamiento de esta entidad, como son la Sociedad Española de Infectología Pediátrica y la Sociedad Española de Neumología Pediátrica, así como el Comité Asesor de Vacunas de la AEP, proponen unas pautas consensuadas de tratamiento y prevención, con el fin de proporcionar a todos los pediatras una guía actualizada. En esta primera parte del consenso, se aborda el tratamiento de los pacientes sin enfermedades de base relevantes con NAC que no precisan ingreso hospitalario, así como la prevención global de esta patología con vacunas. En un siguiente documento se expondrá el abordaje terapéutico tanto de aquellos pacientes en situaciones especiales como de las formas complicadas de la enfermedad.

Introduction

Community acquired pneumonia (CAP) is the single main cause of child mortality worldwide. It is estimated to be responsible for 1.2 annual million deaths in children under 5 years of age, which accounts for 18% of all deaths at this age, 99% of them in developing countries.[1]

In developed countries and regions, such as North America, Europe, Oceania and Japan, there are estimated to be up to 2.6 million annual cases of CAP in children under 5 years of age, causing 1.5 million hospitalisations and, approximately, 3000 deaths,[2] more than the number of deaths for meningitis.

In the last decade, the aetiology, clinical presentation and evolution of CAP in the paediatric population have changed significantly with the introduction of vaccines against pathogens involved in its aetiology (such as *Haemophilus influenzae* [*H. influenzae*] type b and *Streptococcus pneumoniae* [*S. pneumoniae*]), the better use of antibiotics, as well as other factors which have not yet been explained but are probably associated with independent epidemiological trends.

As already explained in the document on the aetiology and diagnosis of CAP agreed by these two paediatric associations,[3] the main aetiological agents are viruses and *S. pneumoniae*. Viruses affect mainly children under 4–5 years of age, while *S. pneumoniae* affects children of any age. However, in the last 10–15 years the incidence of complicated pneumonias, manifesting as either pleural effusion or necrotising pneumonia, has steadily increased. Changes have also been observed in the age of onset of complicated pneumonias. Where previously it was more frequent in children under the age of 2–3 years, it now predominates in children 2–5 years of age. There has also been a slight increase in the number of cases caused by *Staphylococcus aureus* (*S. aureus*), some caused by strains produced by certain virus factors which make them more serious.

Paediatricians treating children with CAP[4] have access to a huge range of therapies, and in many countries clinical guidelines are not followed.[5,6] Therefore, one of the most ambitious goals of this consensus is to harmonise therapeutic measures against this disease in Spain and improve control measures.[7] In this document, based on the scientific information available and the experience of the authors, initial measures are proposed which we believe are more adequate for the therapeutic treatment of CAP. Also, the prevention measures available against CAP in the population of children are summarised. In another document, soon to be published in this journal the therapeutic approach to complicated cases and special circumstances will be presented.

Current status of resistances to antimicrobial drugs

Drug-resistant bacteria that can potentially cause CAP include *S. pneumoniae*, *S. aureus*, *Streptococcus pyogenes* (*S. pyogenes*) and *H. influenzae* type b. In Spain, other causal agents of CAP, such as *Mycoplasma pneumoniae* (*M. pneumoniae*) or *Chlamydophila pneumoniae* (*C. pneumoniae*), or viruses, are not drug-resistant. *M. pneumoniae* and *C. pneumoniae* are usually sensitive to macrolides and the only virus to be treated with antiviral drugs, the flu virus, so far does not present resistance to oseltamivir in our area.

The most reliable data on the drug-resistance of the main respiratory pathogens in our area are periodically provided by the multi-centre study known as Sensitivity to Antibiotic Drugs Used in the Community in Spain (SAUCE in Spanish). The latest, published in 2010 as the SAUCE-4 study,[8] offers results on sensitivity and resistance according to official cutoff points (*CLSI cutoff points*). It contains a total of 2559 isolations of *S. pneumoniae*, 2287 of *S. pyogenes* and 2287 of *H. influenzae*, and these are compared to those recorded in the previous 11 years. In summary, the most relevant data are described in Table 1. For *S. pneumoniae*, as regards sensitivity to β-lactams, currently almost all strains circulating in Spain are sensitive to oral amoxicillin and intravenous penicillin and ampicillin, and also cefuroxime, if we wish to broaden the spectrum. They are all sensitive to cephotaxime. In recent years, the percentage of penicillin-resistant strains (intermediate sensitivity or total resistance) have risen from 60.0% to 22.9%. The proportion of strains with total resistance to oral penicillin (MIC $\geq$ 2) has decreased drastically from 36.5% to 0.9%. Also, 0% presents total resistance (MIC $\geq$ 8) for parenteral penicillin and only 0.2% intermediate sensitivity (MIC $\geq$ 4). There are still high rates of resistance to macrolides (21–25%).

Table 1 Sensitivity of the main bacteria causing CAP in Spain (data from the SAUCE-4 study).

Bacteria	Type of antibiotics	Percentage pf sensitive strains
Streptococcus pneumoniae, in infections outside the central nervous system	β-Lactams	Amoxicillin (at high doses): 98.8%
		Ampicillin: 93.4%
		Parenteral penicillin: 99.8%
		Cephotaxime: 99.6%
		Oral cefuroxime: 94.5%
		Parenteral cefuroxime: 99.3%
	Macrolides	Erythromycin, clarithromycin, azithromycin: 75–79%
	Quinolones	Levofloxacin: 97.7%
Haemophilus influenzae	β-Lactams	Amoxicillin, ampicillin, penicillin: 85%
	Macrolides	100%
Streptococcus pyogenes	β-lactams	100%
	Macrolides	Erythromycin, clarithromycin, azithromycin: 65%

Adapted from Pérez-Trallero et al.[8]

For *H. influenzae*, 15.7% are producers of β-lactamases and, therefore, resistant to penicillin, ampicillin or amoxicillin. This percentage has decreased, from the previous level of 25.7%.

These data, based on samples from children and adults taken 6–7 years ago, can be combined with the findings of a recent study by Heracles in the Community of Madrid (May 2011–April 2013),[9,10] where 100% of *S. pneumoniae* strains isolated in children under 15 years old with invasive pneumococci disease outside the central nervous system—including bacteraemia pneumonias and empyema—are sensitive to penicillin and cephotaxime.

Adjuvant support treatment

In children with CAP, antibiotic therapy at times needs to be complemented with other strategies, although this is less frequent in patients not requiring hospitalisation.

Children with pneumonia usually feel associated pain (pleuritic, abdominal, headache) and discomfort or pain due to inflammation of upper airways (otalgia, odynophagia). Analgesia is recommended for relief, especially in cases of pleuritic pain, because it interferes with coughing and breathing.[11,12] Paracetamol can be used (15 mg/kg/6 h; up to a maximum of 75 mg/kg/day) or ibuprofen (5–10 mg/kg/6–8 h). Fever must be controlled with these same agents, as oxygen requirements increase. There is insufficient evidence that mucolytic and cough suppressants are beneficial, and in theory, medications with codeine or antihistamines should not be used in young children.[13]

Increased effort of breathing and fever increase the requirement for fluids. The ideal way to provide them is orally, in small amounts and frequently.

Ambulatory treatment of non-complicated CAP with antibiotics

Indication for the use of antibiotics

Empirical treatment of CAP is based on the pathogens most frequently involved. However, one of the most important problems is correct distinction between probable viral aetiology and probable bacterial aetiology. Clinicians tend, mistakenly, to use antibiotics in excess, which leads to an increase in antimicrobial resistances. In patients aged less than 2 years, with mild clinical lower airway manifestations and a history of correct immunisation according to age against *H. influenzae* type b and *S. pneumoniae* bacterial aetiology is unlikely.[14]

Antibiotics are indicated in typical CAP where bacterial aetiology is suspected. In cases of atypical CAP they should only be used in children over 4–5 years old and in certain younger patients if the infection is serious.

For treatment under special circumstances (allergy to β-lactams, base disease, immunodepressed, etc.), or patients requiring hospitalisation, more information will be available in the specific document that will be published in a subsequent issue of this journal.

Selection of the antibiotic, route, dosage and duration

Typical CAP

If it has been decided to initiate ambulatory antibiotic treatment in typical CAP with no criteria for hospital admission, considering that most are caused by pneumococci and that, currently, almost all are sensitive to penicillin and amoxicillin,[8] the antibiotic of choice is 80–90 mg/kg/day oral amoxicillin, every 8 h (Table 2). This recommendation is consistent with current international guidelines.[12,15] The maximum recommended dose, according to the package leaflet, is 2 g every 8 h, given the good tolerance of this antibiotic.

There may be some controversy regarding the recommended dose. Given the good absorption of this drug and its good penetration at a pulmonary level, as well as the low rates of resistances of *S. pneumoniae*, doses of 40–50 mg/kg/day will suffice in most cases. This consensus recommends, however, higher doses (80–90 mg/kg/day) due to the following reasons:[16]

- The use of low doses (40–50 mg/kg/day) may lead to reappearance of resistant strains.
- Children with respiratory infections frequently vomit, which may cause infradosage scenarios, especially if low doses are used.
- In pneumococcal infections of the upper airways (acute otitis media and sinusitis), it is necessary to continue to use high doses due to lower penetration of drugs in these locations. It is preferable to harmonise the dosage of this oral antibiotic for all pneumococcal infections, for the purpose of minimising prescription errors.

Table 2 Ambulatory antibiotic treatment for children with CAP who do not need hospitalisation.

Typical CAP (with suspected or confirmed aetiology)		
Name	Posology	Current duration
Oral amoxicillin	80–90 mg/kg/day, divided into 3 doses (every 8 h)[a]	7 days
Atypical CAP with confirmed aetiology or high suspicion of *Mycoplasma* or *Chlamydia*. Most used macrolides		
Name	Posology	Duration
Oral azithromycin	10 mg/kg every 24 h (maximum: 500 mg/day)[b]	3 days
Oral clarithromycin	15 mg/kg/day, every 12 h (maximum dose: 1 g/day)	7 days

[a] The maximum recommended dose for children is 2 g every 8 h (6 g/day), according to the data sheet.

[b] In the USA the same total dose is used, but distributed along a period of 5 days (first day 10 mg/kg; 5 mg/kg/24 h from days 2–5), because it is the posology approved by the FDA, but provides no advantage over the 3 days approved by the European Medication Agency (EMA).

The use of clavulanic acid together with amoxicillin in children with typical CAP with no underlying disease and vaccinated against *H. influenzae* type b, is not justified if there is suspicion of probable pneumococci aetiology, since *S. pneumoniae* drug-resistance through the production of β-lactamases is still unclear. Furthermore, their use is associated, relatively frequently, with gastrointestinal symptomatology, particularly diarrhoea, which can decrease absorption of amoxicillin.

Macrolides should not be used for the treatment of typical CAP for many reasons, the most important being current resistance of *S. pneumoniae* to these antibiotics and the risk of bacteraemia in these patients.[17] Despite that, they are often incorrectly prescribed for CAP.[5]

The recommended duration of treatment in a patient with typical CAP with no complications and not requiring admission is 7 days. There are several meta-analyses, based mainly on trials carried out in developing countries, which showed that 3 days of oral amoxicillin will be effective in treating children of 2–59 months of age with CAP that do not require hospitalisation. Although this strategy reduces costs,[18,19] it is associated with a high rate of therapeutic failure, and therefore should not be used in Spain.

Atypical CAP

In the case of atypical CAP in children under 4–5 years old, the aetiology is usually viral, and therefore no antibiotics are prescribed. In children over 4–5 years old, in whom *M. pneumoniae* aetiology is more frequent (up to 40% of CAP in this age group)[20] and, to a lesser extent, *C. pneumoniae*, the use of oral macrolides is recommended,[15,20] although there is no clear evidence of its effectiveness in resolving CAP in this population.[21,22]

The macrolides most used currently (azithromycin and clarithromycin) and their recommended dosage are described in Table 2.[15] Erythromycin is clearly not used due to its adverse effects (mainly gastrointestinal) and complicated dosing regimen (every 6 h, 10–14 days), which limits its effectiveness.

Evolution and follow-up

Once CAP has been diagnosed and treatment has started a clinical assessment by the paediatrician is recommended after 48 h. In non-complicated cases, 90% of patients are afebrile 48–72 h after starting antibiotic treatment, and do not need further blood tests or radiological follow-up.[3]

Only a small proportion need hospital admission. The management of therapeutic failure and the assessment of the hospital admission will be addressed in the second part of this document.

Preventive measures. Vaccines

Vaccination against certain microorganisms has proven to have an impact on the incidence and mortality of CAP worldwide. The aetiological agents for which there are vaccines available are *S. pneumoniae*, *H. influenzae* type b and the flu virus.

Vaccination against *S. pneumoniae*

The release of the heptavalent conjugate vaccine led to a global reduction of invasive pneumococcal disease (IPD) in children, given its effect on nasopharyngeal colonisation by the serotypes included in the vaccine and, consequently, in its clinical forms.[23] However, incidence of IPD has increased in recent years, mainly complicated CAP especially in children over 2 years,[24] produced by serotypes not included in the vaccine.[23] In Spain, the most frequent are: 1, 19A, 7F, 3, 6A, 19F. Serotype 1 mainly affects children over 24 months of age and causes, in particular, bacterial pneumonia and pleural empyema. Serotypes 1, 19A and 3 caused 85% of pleural empyema of children in Spain, before the development of new vaccines, according to a study carried out by Laboratorio Español de Referencia de Neumococo del Instituto Carlos III.[25] Most serotypes noted are uniformly sensitive to penicillin, except serotype 19A, associated more frequently with resistance, including cephotaxime.

Two conjugated antipneumococcal vaccines are currently authorised in children: decavalent vaccine (VNC10) (Synflorix®, GSK), up to 5 years of age, and tridecavalent (VNC13) (Prevenar 13®, Pfizer), authorised in children up to 17 years of age. Systematic antipneumococcal vaccination is still recommended by the Advisory Committee of Vaccines of the Spanish Paediatric Association in its annual immunisation report.[26]

13-valent pneumococcal conjugate vaccine

PCV13 has the 7 serotypes of the VNC7 and the following 6 additional serotypes: 1, 3, 5, 6A, 7F and 19A, and is approved for the prevention of CAP. Currently, PCV13 offers the widest coverage against pneumococcal disease worldwide,[23] including Spain,[9,10,25] and therefore, it is recommended for all children under 5 years of age, both healthy and at risk for disease.[27]

In Madrid, as of July 2012, PCV13 is no longer subsidised, and therefore coverage has decreased to approximately 70%. Still, the data are very good so far, with a decrease in bacterial CAP (87%), pleural pneumococcal empyema (61%) and meningitis (72%), compared with 2007–2010.[9]

In the United Kingdom, one year after starting vaccination, PCV13 was shown to be effective against additional serotypes (1, 3, 5, 6A, 7F and 19A) in over 50% in children under 2 years of age.[28]

In France, where there has been systematic vaccination with PCV13 since 2010 (previously with PCV7) recent studies in children under 15 years of age have shown a 16% decrease in CAP overall, and 63% decrease in pneumococcal CAP. This is in addition to a 53% decrease in cases with pleural effusion.[29]

In the USA, with systematic vaccination with PCV13 since 2010 (previously with PCV7) a 50% overall reduction In IPD has been reported, and a 70% reduction in cases attributed to PCV13, while hospitalisation for CAP in children under 2 years of age fell by 65% in 2012.[30,27]

In Latin America, several countries have published good results after the introduction of PCV13 in their vaccination calendars, including Argentina, with a 41% reduction in cases of CAP in children under 5 years old.[31] In Uruguay, hospitalisation for CAP in the under-14 age group has decreased by 78% overall, and by 92% in cases of pneumococcal origin.[32]

10-valent pneumococcal conjugated vaccine

PCV10 in addition to the serotypes contained in PCV7 incorporates another 3 serotypes: 1, 5 and 7F, and is approved for the prevention of CAP. In a randomised clinical trial (COMPAS study), carried out in approximately 24,000 infants in 3 Latin American countries, a 22% efficacy over typical CAP was reported (95% CI, 7.7–34.2).[33]

In Brazil, a country with low incidence of serotype 19A since the introduction of systematic vaccination with PCV10 there has been a 15% decrease in mortality from pneumonia in children under 24 months.[34]

23-valent pneumococcal polysaccharide vaccine

The 23-valent pneumococcal polysaccharide vaccine is still recommended in children over 2 years of age at risk for infection, although it probably has little impact on the prevention of CAP.

Vaccination against *H. influenzae* type b

Since the introduction of the vaccine against Hib in the late 90s, there has been a drastic decrease of CAP caused by this microorganism. In some reports, a reduction of up to 30% of NACs has radiologically confirmed.[35,36]

Since non-typifiable *H. influenzae* is a very infrequent cause of CAP in previously healthy children, the PCV10 vaccine (due to its non-typifiable Hi component) probably has little impact.

Flu vaccine

The flu virus is a cause *per se* of CAP in the epidemic season. Also, in the cases of bacterial CAP co-infection with this virus is associated with a higher incidence of complicated forms,[37] especially in cases where *S. aureus* is isolated, or no micro-organism is isolated.

According to current guidelines, the flu vaccine is recommended, for patients over 6 months of age with risk factors of complications, or for those living in the same household.[38] Currently, the trivalent inactivated vaccine, which can be administered intramuscularly, is usually used in children. Some countries, such as the USA and the United Kingdom, have introduced the intranasal live attenuated influenza vaccine for children over 2 years of age with no history of bronchialhyperresponsiveness or asthma. This formulation will probably be available in Spain in the 2015–2016 vaccination campaign.

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- JSL has collaborated as a researcher in clinical trials conducted by GlaxoSmithKline and Roche.

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