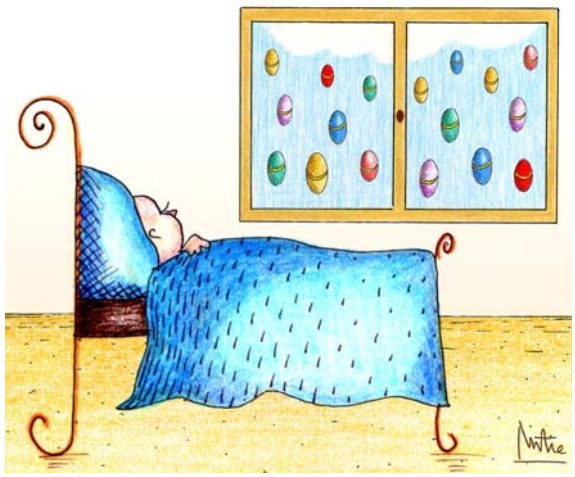
ACUTE OTITIS MEDIA AND PHARYNGITIS IN CHILDREN
Antibiotic - when and how?

Upper respiratory infections are among the most frequent cause of paediatric consultation, and according to international[1] and national[2] data they are responsible for around two-thirds of prescriptions of medicines.
It has been shown that excessive use of antibiotics, in general and in particular during upper respiratory infections, increases:

- consultation for subsequent infections; prescribing antibiotics, in fact, reinforces the parents' believe that for every illness of the child, even a mild one, it is necessary to visit the doctor immediately to get an antibiotic prescription;[3]
- resistance to antibiotics, both at community [4, 5] and at individual level;[6]
- drug side effects (variable in severity from diarrhea to anaphylaxis);[7]
- cost of drugs for the National Health System.[8]

It is also shown that administration of antibiotics during upper respiratory infections due to viruses does not prevent bacterial superinfection (bacterial pneumonia).[9]
Several randomized controlled trials, some systematic reviews and various guidelines have been published on the management of children with upper respiratory infections; however, it is worth exploring in greater detail some aspects relevant to clinical practice.



The aim of this Information Package is to provide evidence-based information on some of these aspects, in particular:

- the "wait and see" strategy in acute otitis media;
- the role of rapid antigen detection (RAD) tests in the management of pharyngotonsillitis;
- the management of *S. pyogenes* carrier;
- relevant aspects to consider when choosing the treatment: local pattern of antibiotic consumption, local level of antibiotic resistance of common pathogens causing upper respiratory infections, and kinetics of antibiotics.

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SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena
CeVEAS Centre for the Evaluation of the Effectiveness of Health Care

ACUTE OTITIS MEDIA

Should we start the antibiotic immediately, or can we wait ?

Results of randomized controlled trials (RCT) published in the last 5 years on benefits and risks of the "wait and see" strategy are reported below.

The "wait and see" strategy

The experience in the ambulatory setting

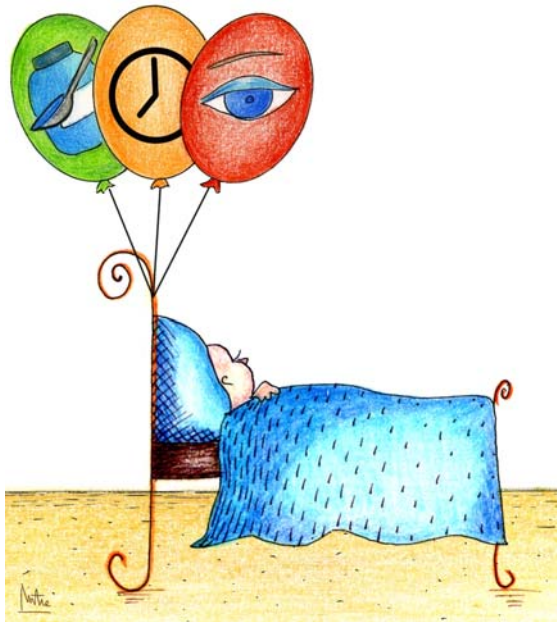
Two RCTs conducted in ambulatory setting involving children with non-severe Acute Otitis Media (AOM) compared the **wait and see strategy** *(for the definitions see box on page* 3) with **immediate antibiotic prescription.**[10, 11]

The first RCT was conducted in the United Kingdom by general practitioners and involved 315 children (aged 6 months to 10 years): 76% of the children **in the wait and see group was cured (no pain or fever) without taking the antibiotic.** No statistically significant difference was found between the two groups in resolution of pain at day 3. Children in the wait and see group had on average 1/2 days' more pain, they consumed slightly more paracetamol (1/2 spoonfuls a day) and had a reduced risk of developing diarrhea (absolute risk reduction 9.2%; *number needed to harm* -NNH- 11, i.e. every 11 children treated with the wait and see strategy there was one child less with diarrhea).[10] Follow-up after 3-12 months showed that there was no statistically significant difference in the onset of earache, incidence of hearing and language impairments and in the development of social relations.[12]

The second RCT conducted in the USA involved 223 children (aged 6 months to 12 years) with AOM assessed in the pediatric outpatients' department of a university hospital: **66%** of the children **in the wait and see group was cured without assuming the antibiotic.** No statistically significant difference was found in the rates of therapeutic failures and/or recurrences, in the number of emergency visits, outpatient visits, telephone calls to the doctor, in the number of days lost at school or work, and in the degree of parents' satisfaction. Among the children that had assumed an antibiotic in the 30 days prior to enrolment, the risk of treatment failure and/or recurrence of AOM was higher: NNH 3 (i.e. every three children that had assumed an antibiotic in the 30 days before the enrolment there was one child more with failure or recurrence).

The experience in the emergency department

A recent RCT conducted in USA involved 283 patients (aged 6 months to 12 years) attending the emergency department for AOM. In this specific setting it is probable that the wait and see strategy is applied also in children with severe AOM.[13] Nevertheless **62% of children in the wait and see group were cured without taking the antibiotic.** No statistically significant difference was found in fever duration, earache frequency, number of subsequent outpatient visits. The absolute risk reduction of developing diarrhea was 15.7% in the wait and see group, NNH 6 (i.e. for every 6 children treated with the wait and see strategy there was one child less with diarrhea)[13].



… more from a metanalysis

A metanalysis[14] published in 2006, that also included the trials above described, quantified the advantage of antibiotic treatment compared to no treatment in cases of AOM. Among the main results it emerged that **it is necessary to treat 20 children to have one less child with fever and 10 children to have one child less with pain** (outcomes measured 3-7 days after first appearance of the symptoms).

ACUTE OTITIS MEDIA

The "wait and see" strategy

Evidence from placebo controlled trials

A Cochrane **systematic review** comparing the efficacy of **antibiotics** versus **placebo** in 2287 children (aged 6 months to 15 years) with AOM, shows that:[15]

- antibiotic administration does not increase pain resolution. **61.5% of children in both groups recovered from pain after 24 hours;**
- there is no statistically significant differences between the two groups in the frequency of complications (perforation, development of contralateral otitis, late recurrences);
- there is a reduction of vomiting, skin rash and diarrhea in the placebo group, absolute risk reduction 6%, NNH 16 (i.e. for every 16 children who did not take antibiotic there was one less child with vomiting, skin rash or diarrhea).

Is the "wait and see" strategy applicable in Italy?

An observational prospective study, conducted by 169 family pediatricians evenly distributed on the whole country belonging to the ACP (Cultural Association of Pediatricians), evaluated the applicability of the wait and see strategy in Italy.
Each pediatrician studied 11 consecutive cases of AOM within 24-36 hours of the onset of the symptoms. Enrollment criteria were: age 1 to 14 years, fever and or earache and/or irritability plus one or more of the following sings: marked redness, bulging, dullness, and perforation of the tympanic membrane were evaluated.
The treatment proposed was:

- symptomatic treatment (paracetamol and nasal lavage) for all children enrolled;
- immediate antibiotic treatment (**amoxicillin in 3 doses for at least 5 days)** in case of otorrhoea or recurrent AOM (≥ 3 episodes in 6 months or ≥ 4 episodes in 12 months);
- wait and see strategy in the remaining cases, followed by antibiotic treatment if, after 48-72 hours, symptoms persisted.

The study showed that **67.6% of 1277 children enrolled were cured (no fever or pain) without taking the antibiotic.** No major complications were recorded. In addition 81.2% of 356 children treated with antibiotic received amoxicillin; instead children with previous treatment failures with amoxicillin or with history of allergy received a macrolide or cephalosporin.

DEFINITIONS

THE WAIT AND SEE STRATEGY IN CHILDREN WITH AOM

Delayed antibiotic treatment for 48-72 hours after the diagnosis if the child is:

- at least six months old
- has no otorrhea
- has no severe chronic diseases (e.g. craniofacial malformations, immunodepression, diabetes mellitus, cystic fibrosis, Down's syndrome)

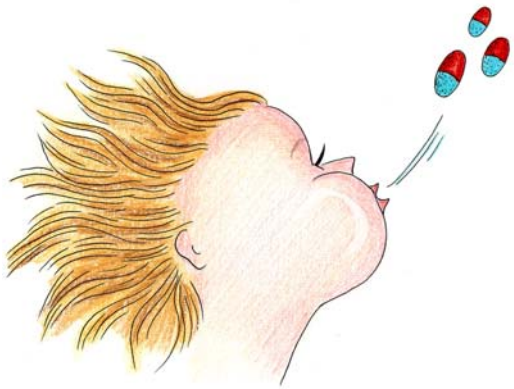
Administration of analgesics and **clear explanation** to the parents, also using printed informative material.
Administration of antibiotic if the symptoms worsen or persist beyond 48-72 hours after diagnosis.

TREATMENT FAILURE

The child returns to visit with earache and impaired tympanic membrane within 12 days from the first examination.

RECURRENCE

The child returns to visit with earache and impaired tympanic membrane after 13-30 days from the first examination.



IN PRACTICE

The "wait and see" strategy has been proved to be useful in children with AOM without serious baseline conditions. This strategy was seen to be applicable also in the Italian setting. The inappropriate prescription of antibiotic increases both the risk of treatment failures and unjustified recourse to the pediatrician when subsequent infectious episodes occur.

ACUTE OTITIS MEDIA

In case of treatment, which antibiotic is better to use ?

Most cases of AOM resolve without antibiotic treatment, since they are due to viruses or are caused by bacteria with a high rate of spontaneous clearance (i.e. that recover without treatment). The three germs most commonly isolated during the course of AOM in children (*M. catarrhalis, H. influenzae, S. pneumoniae)* show the following spontaneous eradication rate[17] :

- *M. catarrhalis* 80%,
- *H. influenzae* 50%,
- *S. pneumoniae* 10% (see figure 1).

While *M. catarrhalis* does not cause complications, and similarly to *H. influenzae* has a good spontaneous clearance, *S. pneumoniae* (pneumococcus), at the contrary, has the lowest spontaneous eradication rate and can cause severe complications. Therefore, **in case of persistence of symptoms after the "wait and see" period (that is the first step in managing AOM anyway), the antibiotic chosen empirically must be effective against pneumococcus.**

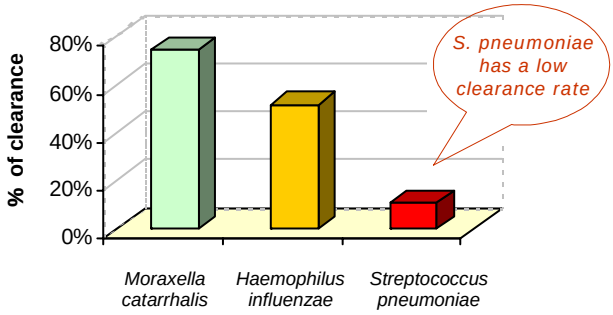


Figure 1. *Percentage of spontaneous eradication of germs isolated from the middle ear during AOM.*[17]

DEFINITIONS

In the antibiogram, each germ is defined as:

- susceptible (S)
- intermediate (I)
- resistant (R)

to the antibiotics tested, based on the minimum concentration of antibiotic necessary to inhibit the growth of the germ in vitro (MIC) in relation to the drug plasmatic concentrations that can be reached with the doses normally used.[18]

Resistance of S. pneumoniae in Emilia-Romagna

The table below confirms the very low resistance level of *S. pneumoniae* to amoxicillin and the high resistance level to macrolides in Emilia-Romagna (2005 data). The bacteria were isolated from respiratory tract's samples of 208 patients (for the most part outpatients) aged < 15 years.

	Antibiotics	Patients N°	Resistant %	Resistant (R) + Intermediate (I) %
S. pneumoniae	penicillin G	194	1.0	10.8
	amoxicillin ampicillin	162	0.0 *	0.6 **
	cephotaxime ceftriaxone	92	0.0	1.1
	clyndamycin	115	30.4	30.4
	co-trimoxazole	131	16.8	64.1
	erythromycin	203	36.0	38.9

Modified from: Gagliotti C.[20]

(*) Resistant to amoxicillin: MIC ≥ 8 µg/ml

(**) Total resistant to amoxicillin: includes both resistant germs (MIC ≥ 8 µg/ml) and those with intermediate sensitivity: (MIC = 4 µg/ml)

Pneumococci do not produce ß lactamase

- The resistance of *S. pneumoniae* to ß lactamics is not due to the production of ß lactamase, but to the selection of bacterial strains with mutations of the penicillin binding proteins.[19] **The addition of clavulanic acid therefore does not increase the probability of eradicating the pneumococcus**
- In case of pneumococcal infection, administering amoxicillin + clavulanate every 12 hours (compared to amoxicillin every 8 hours) **may reduce the likelihood of recovery**, due to the inappropriate administration interval (*see page 10)*.

In addition to in vitro susceptibility, pharmacokinetics tells us that…

According to a study[21] **amoxicillin at a standard dosage** of 40-50 mg/kg/day in three divided doses **is sufficient** to stay above MIC_{90} for a sufficient length of time either in presence of *S. pneumoniae* strains susceptible or resistant to penicillin G.

On the other hand, **none** of the **oral cephalosporins,** is above the MIC level of *S. pneumoniae* for a sufficient length of time (*see pages 10-11).*

IN PRACTICE

- If it has been decided to start an antibiotic treatment, the drug chosen empirically must cover *S. pneumoniae.*
- ***S. pneumoniae*** isolated in the Emilia-Romagna Region **are susceptible to amoxicillin.** On the other hand, they are frequently resistant to macrolides.
- The resistance of pneumococci to penicillins is not due to the production of β lactamase.

ACUTE OTITIS MEDIA

Antibiotic: doses and length of treatment

How much of the drug?

Guidelines: agreement on the drug, not on the dose

The three main guidelines (GLs) [22-24] selected on the basis of their quality using a standardized method [25] recommend **amoxicillin** as the first choice drug for AOM that need antibiotic treatment.

The US guideline advise to use high doses of amoxicillin (90mg/kg/day); the Scottish [23] and the Spanish [24] guidelines instead, that refer to an epidemiological situations similar to the Italian one, recommend to use the standard doses (40-50 mg/kg/day).

All the GLs agree on the need to administer amoxicillin every 8 hours.

High or standard dose? The RCTs tell us...

The only double blind RCT, published after the guidelines [22-24], that has compared high versus standard doses of amoxicillin in children over 3 months of age with AOM, did not find any difference between the two dosages used in terms of efficacy and tolerability.[26]

162 children aged >3 months with AOM

Amoxicillin 40-45 mg/kg/day in 3 doses	Amoxicillin 80-90 mg/kg/day in 3 doses	Difference
Failures: 10.5%	Failures: 12%	**1,5 %** Not statistically significant
Not severe side effects: Skin rashes 14.7% Diarrhea 29.7%	Not severe side effects: Skin rashes 11.7% Diarrhea 32.9%	**3 %** (rash) **3,2 %** (diarrhea) Not statistically significant

For how long?

A Cochrane **systematic review** evaluated the efficacy of a short course of antibiotics (≤ 5 days) compared to a longer one (8-10 days) in treating AOM. The review included 32 studies involving over 3500 patients under 18 years and using different antibiotic molecules.[27] The review concluded that:

- treatment failure rate after 8-19 days from diagnosis were slightly more frequent (absolute difference 6%) in the group treated with short course of antibiotics. This difference, however, disappeared when the statistical analysis took into consideration the problem of heterogeneity of the studies included and their timing, too short from the end of the treatment to correctly evaluate the failures and the recurrences (evaluation bias);
- treatment failure rate after 20-30 days from diagnosis did not differ between the two groups;
- treatment failure rate after one month from diagnosis did not differ between the two groups even when only children aged < 2 years were taken into consideration;
- side effects were less frequent in the short course antibiotic group (absolute difference 6%). This difference disappeared when the studies that used amoxicillin plus clavulanic acid were excluded.

A subsequent **systematic review** (2001) concluded that there is no evidence in favour of a particular antibiotic regimen in terms of dose used and length of treatment.[28]

What do 'the others' say?

On the basis of this evidence one of the most prestigious drug information bulletins - Prescrire - states that a cycle of antibiotic treatment lasting more than 5-7 days does not offer additional benefits for the treatment of AOM in otherwise healthy children.[29]

IN PRACTICE

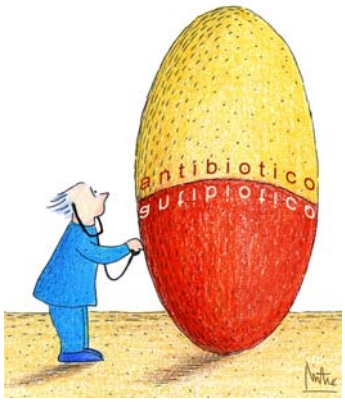
Considering the level of resistance of pneumococcus to ß lactams in Italy and the pharmacokinetics of amoxicillin, it is reasonable to conclude that standard dosage of amoxicillin (40-50 mg/kg/day) in three divided doses during 5-7 days are generally sufficient to treat AOM.

PHARYNGOTONSILLITIS

The clinical evaluation guides the laboratory diagnosis

Can clinical sign predict the need of antibiotic?

As stated in the guidelines[30-32] selected on the basis of their quality using a standardized method,[25] and as confirmed by subsequent studies,[33,34] **individual signs and/or symptoms are not useful in predicting the etiology of pharyngotonsillitis.**
A systematic review that includes **9 prospective studies**, for a total of **5453** among children and adults with sore throat, compared the individual clinical signs/symptoms with the result of the throat culture test. None of the signs/symptoms assessed, taken individually, correlated with the results of the culture; not even tonsillar exudate or palatal petechiae.[33]



The clinical scores (combination of signs and symptoms)

In literature two different methods are described (McIsaac's score[35] and Attia's score[36]) to identify among pediatric patients with sore throat those at highest risk of having a bacterial pharyngitis (*S. pyogenes*). McIsaac's score is the one most widely studied and most commonly used by pediatricians.

MCISAAC'S SCORE

It was developed and validated in Canada, in a general medicine setting, on 167 children aged between 3 and 14 years. The prevalence of *S. pyogenes* in this group of patients was 34.8%.
For low score (0-1), the method showed a low positive likelihood ratio (i.e. infection is unlikely) while for high score (4-5) it showed a rather high positive likelihood ratio (i.e. infection is likely). For intermediate score (2-3), the likelihood ratio does not help define the presence or absence of the infection and it is recommended to recur to a diagnostic test (*see insert on interpretation of diagnostic tests*).
Compared with physician judgment the use of the McIsaac's score, although did not reduced antibiotic prescription or unnecessary antibiotic prescription in children, reduced by around one-third the recourse to laboratory testing.[35]

IN PRACTICE

- The **clinical scores** are **more reliable** than the individual clinical signs in predicting bacterial pharyngitis, but they are **not always sufficient** for an accurate diagnosis.
- **Very low** McIsaac's scores (≤1) can accurately guide the therapeutic decision. In case of **intermediate scores** (2-3), it is better to use a **diagnostic tests (RAD or culture test).** For **very high** scores (≥4), recourse to diagnostic tests is optional.

HOW TO USE THE MCISAAC SCORE

1. Assess the child and look for the following signs

	Score
Temperature (reported or recorded) >38°C	1
Absence of cough	1
Tender anterior cervical adenopathy	1
Tonsillar swelling or exudate	1
Age <15 years	1

2. Calculate the risk of infection from *S. pyogenes*

Score	LR+	Actions suggested by McIsaac
0	0.05	No laboratory test No antibiotic
1	0.52	No laboratory test No antibiotic
2	0.95	Throat swab for culture* Antibiotic if culture +
3	2.5	Throat swab for culture* Antibiotic if culture +
From 4 to 5	4.9	Antibiotic without prior test* *OR* Throat swab for culture* then antibiotic if culture +

LR+ = positive likelihood ratio

(*) As an alternative to the culture test, it also possible to perform a rapid antigen detection test (RAD)

PHARINGOTONSILLITIS

The laboratory diagnosis guides the treatment

Lab: once there was the culture test, is now the time of the rapid test?

The main guidelines recommend as a gold standards for the diagnosis of strep throat the **throat culture**.[30-32] In the 1980s **rapid antigen detection tests (RAD)** were developed that, albeit **less sensitive than the culture**, have the advantage of showing results in short times. Three subsequent generations of RADs have been developed with an increasingly higher sensitivity *(for more details on the sensitivity of a test, see insert*). The tests generally used by italian pediatricians are RAD of second generation, based on immunoenzymatic (EIA) techniques. The latest generation of tests uses immuno-optical (OIA) technology. According to sporadic studies, the OIAs would be as reliable as the culture;[37] use of this type of test is, however, still limited, partly because of the higher cost and difficulty in execution.

Predictive value of RAD (*see insert*)

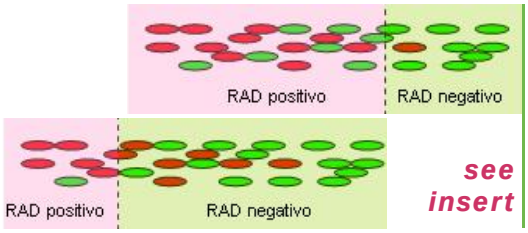
Two reviews of the literature have been identified that summarize the validation studies currently available on rapid tests. The **sensitivity and specificity of RAD depend** on the testing method, on the manufacturer (methods being equal) and on the sample collection method.[37, 38] In general **none** of the RAD studied, unless in sporadic indications, showed a sensitivity higher than 95% (a rate of false negatives < 5% is deemed acceptable). Almost all RAD have a specificity higher than 95% (less than 5% false positives) therefore:[37,38]

- if the RAD is positive an antibiotic treatment should be initiated, given the high specificity of the test (it will rarely be a false positive result);
- If the RAD is negative, on the other hand, the decision to treat should be based on a confirmatory culture given the low sensitivity of the RAD, (it could well be a false negative result).

However, somebody claims that most of the false negatives to RAD are carriers of *S. pyogenes.* Carrier in fact may host a low number of colonies that could not be detected by RAD, but only by throat culture. This theory still has to be confirmed.

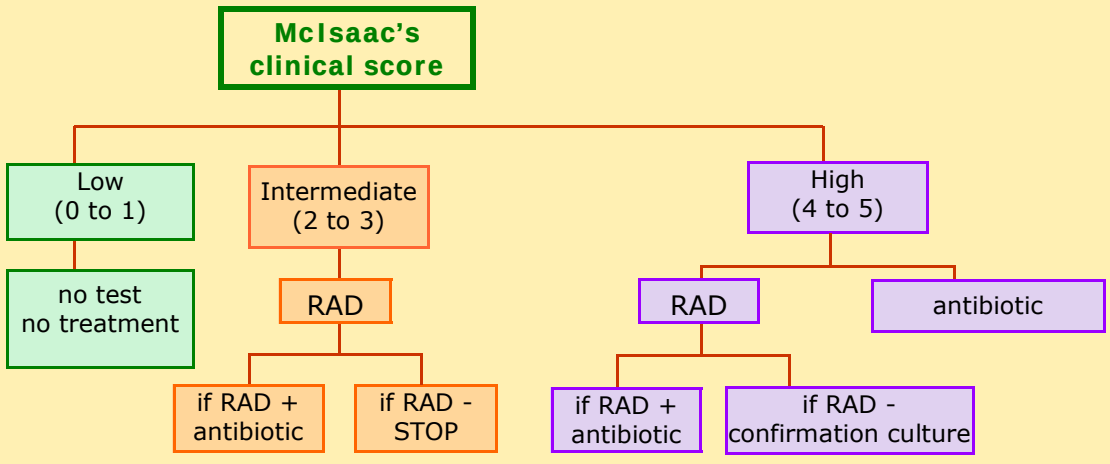
Caution!

The sensitivity of the RADs (*see insert*) is not fixed for a given test, but increases with disease severity (the higher the clinical score the higher the sensitivity). In the absence of typical symptoms for infection from *S. pyogenes*, the sensitivity of the test is low and it is therefore better not to use it. This phenomenon is known as **spectrum bias.**[39]



IN PRACTICE

On the basis of current knowledge, taking into account the italian epidemiological situation and the risk of the individual patient, decision making for the management of sore throat can be summarized with the following flowchart:



PHARINGOTONSILLITIS

Hints for choosing the right treatment

The wait and see strategy in practice

A Cochrane systematic review compared the **immediate antibiotic prescription** (penicillin V in 3-4 doses for 10 days) with the **delayed or no antibiotic prescription**[40] in patients with upper airways infections. Only 4 out of 7 trials included referred to sore throat in a pediatric population. The heterogeneity of the trials made it impossible to obtain an overall result; only 1 of the 4 trials showed, in fact, a difference between the two groups. On day 3, fever was lower (one degree less) in the "immediate treatment" group, an absolute reduction in the risk of pain of 52% and a reduction of malaise of 34.5%. The other **trials showed no difference between the immediate and the delayed antibiotic group in terms of immediate recovery.** Also, 2 of the 4 trials registered a **significant** reduction **in relapses and recurrences in the delayed prescription group.**

Treatment can wait…

In order to prevent the rheumatic complications caused by *S. pyogenes* it is sufficient to start the antibiotic treatment within 9 days from the onset of symptoms.[41]

What about the streptococcus carrier?

A patient with a positive culture test is a carrier if he shows no variations in the antibody titer determined in two subsequent samples, regardless of the presence of clinical symptoms.[32]

How to identify a carrier? The suspicion must arise when a child does not respond promptly (within 24 hours) to antibiotic treatment for sore throat, or when two subsequent episodes of sore throat with positive RAD occur within a short time periods (1 month). In these cases, a RAD must be performed when the child has no symptoms; if the RAD is still positive, the child is a streptococcus carrier.

How frequent is it? According to the North American guideline[32], the percentage of carriers varies from 10 to 25% of the child population, while according to the Scottish guideline[31] it reaches 40%. Two population studies have shown a frequency of 27-32% on children of school age in the USA[42], and 20% in India[43]. No Italian data are available.

What are the risks? The carrier has a low risk of spreading the infection and a very low, if any, risk of developing non-suppurative complications (rheumatic fever, glomerulonephritis).

When it is necessary to treat? According to the guideline, eradication of the streptococcus carrier is indicated for children living with a patient with previous history of rheumatic fever or in case of recurrent cross infections (ping pong spread) within the family.[32]

S. pyogenes: cases of resistance in Emilia-Romagna

The table below shows the pattern of resistance of *S. pyogenes* to some antibiotics in Emilia-Romagna (2005 data). The bacteria were isolated from respiratory tract's samples of 2229 patients (for the most part outpatients) aged <15 years.

	Antibiotics	Patients N°	Resistant %	Resistant (R)+ Intermediate (I) %
S. pyogenes	erythromycin	2228	19.7 *	21.0 **
	clindamycin	2123	10.8 *	11.4 **
	cotrimoxazole ***	596	78.4	81.2
	penicillin G amoxicillin ampicillin	The susceptibilty of *S. pyogenes* to these antibiotics is not tested in the laboratory (resistance have never been reported)		

Modified from: Gagliotti C.[20]

(*) Resistant to erythromycin/clindamycin: MIC ≥1 µg/ml
(**) Total resistant to erythromycin/clindamycin: includes both resistant germs (MIC≥1 µg/ml) and those with intermediate susceptibility (MIC=0.5µg/ml)
(***) Not all microbiological guidelines provide the breakpoint for cotrimoxazole.

The resistance of *S. pyogenes* to macrolides can be constitutive or inducible. It has been shown that a reduction in the use of macrolides can lower resistance. In Italy, the level of resistance is high[44] even though variations are observed in neighbouring areas[45].

IN PRACTICE

- In pharyngitis the delayed antibiotic prescription strategy (48-72 hours) reduces the risk of relapses and recurrences, without increasing complications.
- The carrier status is frequent and generally does not need to be treated.
- *S. pyogenes* is always susceptible to amoxicillin. In Italy, however, resistance to macrolides and to cotrimoxazole is frequent.

PHARINGOTONSILLITIS

Antibiotics: doses and length of treatment

Complications: once there were and now no more?

Studies on the efficacy of antibiotics in preventing suppurative (otitis, sinusitis, peritonsillar abscess) and non-suppurative (rheumatic fever, glomerulonephritis) complications of *S. pyogenes* infections are available only for penicillin G (i.v.)[46].
These studies, included in a Cochrane systematic review, were conducted in the '50s and mainly involved young male recruits from the United States air-force. No study published after that was able to evaluate the efficacy of other antibiotics in preventing complications, because of the strong reduction in their incidence: these studies evaluated only the resolving of acute symptoms.

Amoxicillin: the drug of choice

The guidelines continue to recommend penicillin V for 10 days as treatment of choice.[30-32] However, some recent RCTs conducted on children with pharyngotonsillitis due to *S. pyogenes* (clinical + laboratory diagnosis) have evaluated the efficacy of alternative therapeutic schemes. The results of the trials are reported below.

Efficacy

Two RCTs compared **penicillin V** with **amoxicillin.**[47,48] The trials showed that **amoxicillin is more effective** both in terms of clinical cure (17% increase) and bacteriological cure (from 6% to 25% increase).

Length of treatment

In one RCT, conducted on 321 children, **penicillin V** (45 mg/kg/day in 3 divided doses) for **10 days** was compared with **amoxicillin** (50 mg/kg/day in two divided doses) for **6 days**[49]: no differences in the percentage of eradication, relapses, recurrences and side effects were found between the two treatments. In those treated with amoxicillin, a significant increase of compliance (+20%) was found. The efficacy of short-course treatment was confirmed in a subsequent multicenter trial conducted on 517 children[50].

Number of doses

Two RCTs evaluated the efficacy of amoxicillin given in one or two doses per day.
The first one, involving 157 patients, compared **penicillin V** administered every **6-8 hours** with **amoxicillin** (50 mg/kg) in **a single daily dose** for 10 days.[51] The trial showed that:

- there is no difference between the two treatments in percentage of clinical cure;
- in the amoxicillin group, there is a statistically significant difference in term of eradication (6% absolute increase).

The second RCT, involving 652 children, compared the **single daily dose** of **amoxicillin** with **two doses** per day for 10 days.[52] No differences were recorded in the two groups with regard to the percentage of failures, acceptance of the treatment and side effects.

IN PRACTICE

Amoxicillin at the dosage of 40-50 mg/kg/day in two divided doses for 6 days is more effective than the traditional treatment with penicillin V for 10 days in terms of clinical and bacteriological cure.
Moreover, this scheme increases compliance to treatment (greater acceptance).

How ß-lactam antibiotics work

Bactericide activity and time above MIC

To predict the antibacterial efficacy of antibiotics a model based on experimental studies has been develop: it suggests that the **efficacy** of ß-lactam agents **depends on the time** that serum concentrations of the drug are above the minimal inhibitory concentrations (MIC_{90}), i.e the concentration of the drug able to inhibit the growth of 90% of the colony of the pathogen. In case of **ß-lactam agents** it is sufficient that **serum concentration exceed the** time above MIC for 40 to 50% of the dosing interval **to achieve a bacteriological cure of 80-85%.**[21] Little increase in eradication rate is related to further increase of time above MIC.

It has been shown that, in AOM treatment, the time above MIC calculated in serum has the same predictive value as that calculated in the middle ear fluid.[21]

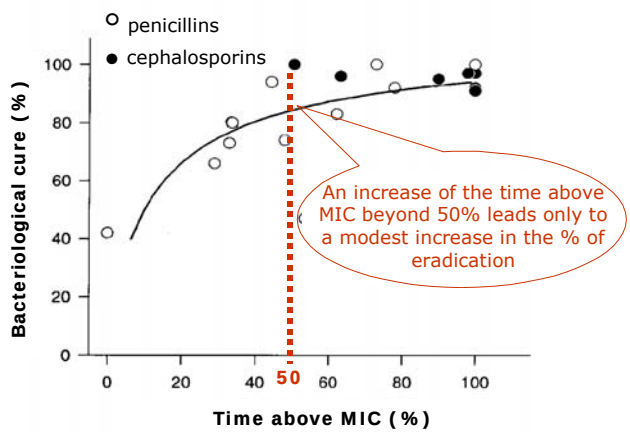
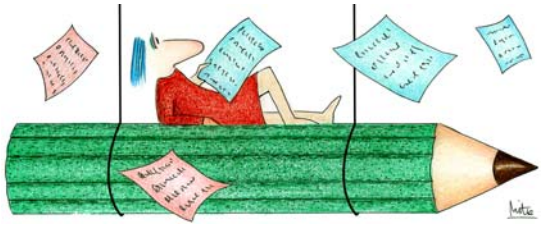


Figure 2. *Correlation between the time above MIC for penicillins and cephalosporins (expressed as % of the interval between two doses) in serum and the % of eradication in patients with AOM due to S. pneumoniae.*



IN SUMMARY

A ß-lactam antibiotic must be considered potentially effective when it has a serum concentration above the MIC of the pathogen to be eradicated for at least 50% of the time that elapses between two doses.

Kinetics and MIC

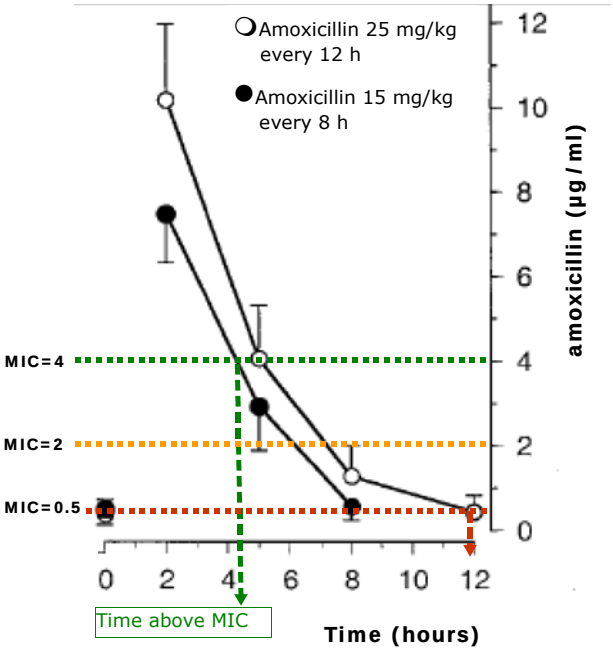


Figure 3: *plasma curves obtained after 3 days of oral administration of amoxicillin at 25 mg/kg every 12 hours or amoxicillin at 15 mg/kg every 8 hours to children aged 3-59 months in relation to different MIC values. The point where the arrow meets the axis of the abscissae defines the time above MIC.*

According to the proposed model, the main factors for keeping the serum concentration above the MIC for at least 50% of the interval between two divided doses, are:

- the pharmacokinetic of the antibiotic
- the MIC of the pathogen to be eradicated.[53]

In figure 3 some possible scenarios are proposed that show the interaction between the real kinetic curves obtained by administering amoxicillin (at two different dosages and administration intervals) and three different value of MIC common in clinical practice.[54]

From the figure it can be seen that the administration interval plays an important role. The serum concentrations when giving amoxicillin every 8 hours are above the highest MIC (green line) for over 4 hours (green arrow), therefore for a period of over 50% of the interval between two doses.

When the MIC is very low (red line), one administration every 12 hours is potentially effective.

IN SUMMARY

As the MIC increases, shorter intervals between the doses increase the likelihood of maintaining effective serum concentrations.

How ß-lactam antibiotics work

Data of regional microbiological laboratories inform us about the MIC of *S. pyogenes*, common cause of bacterial pharyngotonsillitis, and *S. pneumoniae*, the pathogen to treat in case of AOM, commonly circulating in Emilia-Romagna region. Based on these data we can conclude that:

Pathogen and MIC	Treatments
In Emilia-Romagna region, in almost all cases, ***S. pneumoniae*** has a MIC for amoxicillin ≤ 2 mg/ml. Isolation of colonies with MIC = 4 mg/ml (intermediate resistance) is rare.	When treating diseases caused by ***S. pneumoniae*** it should be considered that it is possible (even though it is rare) to find germs for which eradication is necessary to maintain a serum concentrations of amoxicillin between 2 and 4 mg/ml for at least 4-5 hours. This is possible only when giving standard dose of amoxicillin (50 mg/kg/day) divided in three divided doses (i.e.**every 8 hours)**.
The MICs for amoxicillin of ***S. pyogenes*** are, at the contrary, ALWAYS, not only in Emilia-Romagna region, < 0.5 mg/ml.	When treating diseases caused by ***S. pyogenes***, due to low MIC value, it is possible to give standard dose of amoxicillin (50 mg/kg/day) in two divided doses (**every 12 hours)**.

Pneumococcus and ... cephalosporins

A review[21] used the model described[54] to develop kinetic curves of various ß-lactam agents at pediatric dosages, for infections from *S. pneumoniae*, MIC_{50} for amoxicillin = 0.25 mg/ml and MIC_{90} = 1 mg/ml. (MIC_{50} is defined as the serum concentration of antibiotic needed to inhibit the growth of 50% of the colonies; however in clinical practice is better to refer to MIC_{90}).
The data show (see figure 4) that among oral antibiotics, amoxicillin at a dosage of 40 mg/kg/day in three divided doses is the only drug that can reach a satisfactory percentage of bacterial eradication due to its time over MIC_{90}. None of the oral cephalosporins stays above MIC_{90} for at least 50% of the time between doses; only ceftriaxone in IM administration, at the dosage of 50 mg/kg/day, is above the parameters required, but in general IM treatment for AOM is not recommended[21].

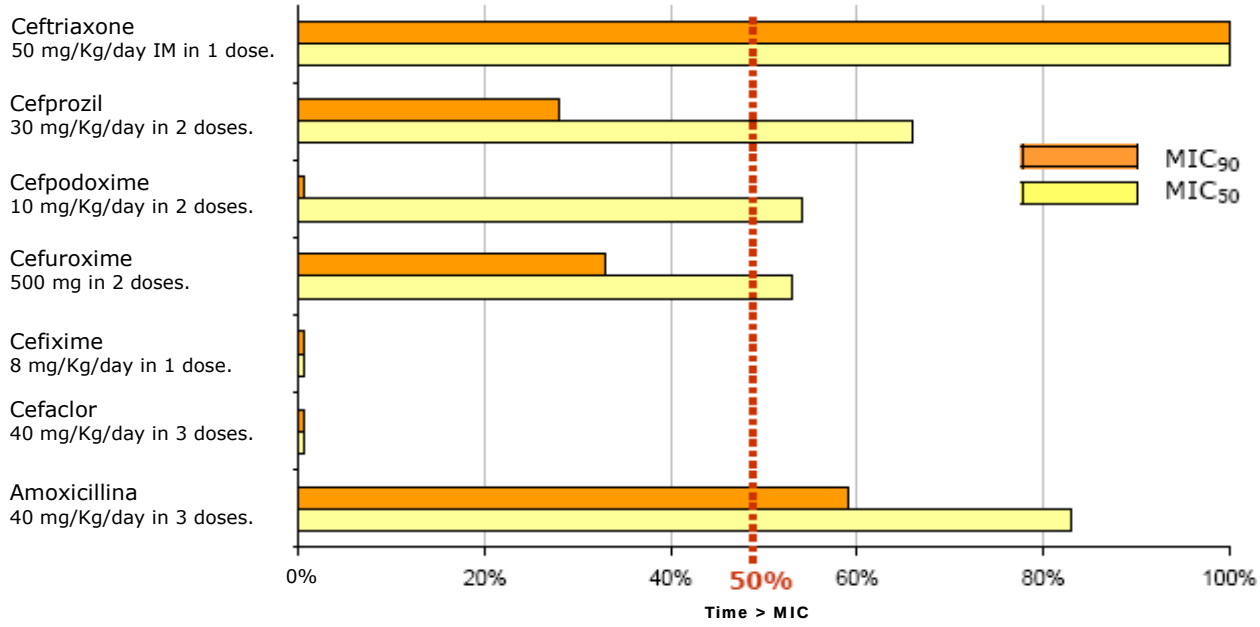


Figure 4. *Percentage of interval between two doses in which the serum concentrations of various ß-lactam remain above the MICs of S. pneumoniae (MIC_{50} for amoxicillin = 0.25 mg/ml, MIC_{90} = 1 mg/ml)*

IN PRACTICE

- When starting an empirical antibiotic treatment, it is important to consider: the suspected pathogen, its local resistance profile and the kinetic of the antibiotic selected.
- If the suspected etiological agent is *S. pneumoniae*, in the actual epidemiological situation of Emilia-Romagna (and in general in Italy), amoxicillin at the standard dose administered every 8 hours must be considered effective. None of the oral cephalosporins meets the criteria of efficacy.
- If the etiological agent is *S. pyogenes*, it is possible to administer a standard dose of amoxicillin every 12 hours.

ACUTE OTITIS MEDIA AND PHARYNGITIS IN CHILDREN

Conclusions

Acute otitis media

- The wait and see strategy (delayed antibiotic prescription for 48-72 hours from diagnosis) is useful and feasible in treating a child with AOM. This approach does not increase the risk of complications, it is well-accepted by the parents and moreover reduces the risk of therapeutic failure and inappropriate recourse to the pediatrician for subsequent infections.
- When antibiotic treatment is needed, it must be chosen to be effective against pneumococcus. Empirical treatment with amoxicillin at the standard dosage of 40-50 mg/kg/day in three divided doses for 5-7 days is the most appropriate (*see page 4).*
- In case of suspected infection from pneumococcus, there is no rational ground in adding clavulanic acid to amoxicillin (*see pages 4 and 10).*
- Oral cephalosporins are not effective in treating AOM, as shown by the pharmacokinetic data.

Pharyngotonsillitis

- Child with sore throat and suspect of pharyngotonsillitis from *S. pyogenes* can be properly investigated applying a clinical score (McIsaac's is the most widely-used) and using a rapid tests (RAD). The throat swab culture may be used when there are doubts about a possible bacterial etiology *(see algorithm on page 7).*
- The wait and see strategy (delayed antibiotic prescription for 48-72 hours from diagnosis) does not increase the risks of complications and reduces the rate of recurrences.
- When antibiotic treatment is indicated, amoxicillin at the dosage of 40-50 mg/kg/day in 2 divided doses for 6 days is be the most appropriate choice. This treatment scheme is more effective than traditional treatment with penicillin V; in addition it gives a higher rate of acceptance (compliance) of the treatment.

Regional prescription data (2000-2004)

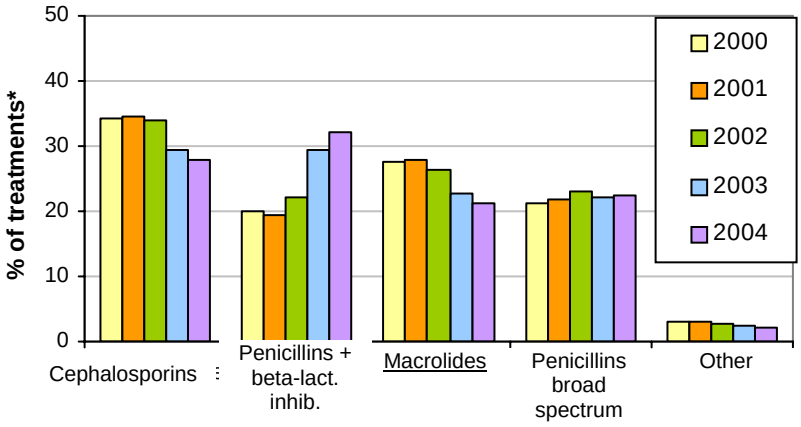


Figure 5. *% of distribution of the various classes of antibiotics prescribed to the child population (0-14 years old) in the Emilia Romagna region between 2000 and 2004. Amended by: Gagliotti C[20]*

A progressive reduction in the prescription of cephalosporins and macrolides was recorded in Emilia-Romagna region in the period between 2000 to 2004 (see fig. 5). It must be noted a sharp and exclusive increase in the prescription of penicillin associated with ß-lactamase inhibitor (the drug most frequently prescribed for children in Italy).

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