Antimicrobials Use in Community Acquired Respiratory Tract Infections

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Opening Remarks on Antimicrobial Use

Not just a step-by-step set of instructions, the purpose of this Chapter is rather to update the reader on the characteristics of the causing *Community Acquired Respiratory Tract Infections* (CARTI) in Brazil. We will review some aspects of the resistance profiles of these agents and the principles guiding the use of antimicrobials in our daily practice, particularly for dealing with otitis, pharyngotonsillitis and sinusitis.

For example, with regard to acute otitis media (AOM)[1], we highlight data from an interesting publication that identified this clinical condition as being the main cause of visits to doctors and antimicrobial prescriptions in Europe for infants and toddlers during the first two years of life, resulting in an average of 42 to 49 days of taking antibiotics each year. In other words, European infants take antibiotics for an average of almost two months over the first two years of life. This information spotlights the burden imposed by this disease in the daily practices of ENT specialists and pediatricians.

With regard to sinusitis[2-3], this may well be over-diagnosed by emergency care clinics in situations that often involve newly-appeared acute infections with viral etiologies that are mistakenly identified as bacterial sinus diseases, very frequently treated with antimicrobials. According to data published in the *Pediatrics* journal in June 2013 [3], 60% of bacterial sinusitis (and otitis) at all ages in the USA is caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.* It is also clear that the more antibiotics are used, the higher the expectations of surging bacterial resistance rates in the community, as shown in **Figure 1** below[4-5].

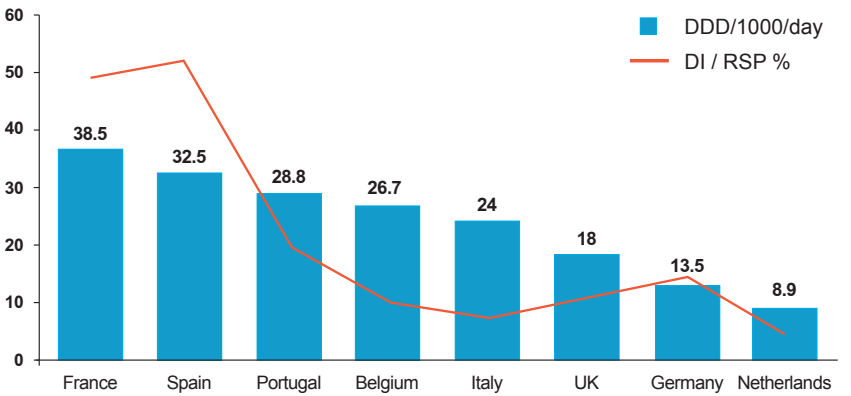

Figure 1. Penicillin-resistant pneumococci colonization rates by days of antibiotic use each year in Europe.

The more days that antimicrobial medications are taken each year in some European countries, the higher the levels of penicillin-resistant pneumococci found in the nasopharinx of these patients. In countries that have managed to impose firm constraints on the abusive use of antimicrobials, lower pneumococcal resistance rates are found today. It is clear that the abusive use of antimicrobial medications is boosting the prevalence of resistant strains, thus hampering treatment. [4-5]

Antibiotic use and pneumococcal resistance to penicillin in Europe

Particularly noteworthy among the risk factors of pneumococci colonization rates in children[6] are: young age (especially the under-twos); going to day-care centers and kindergartens; recent viral respiratory infections; absence of breast feeding; and malnutrition. Recent use of antimicrobial medications plays a leading role in boosting antimicrobial resistance rates in bacteria causing CARTI. (**Figure 2**).

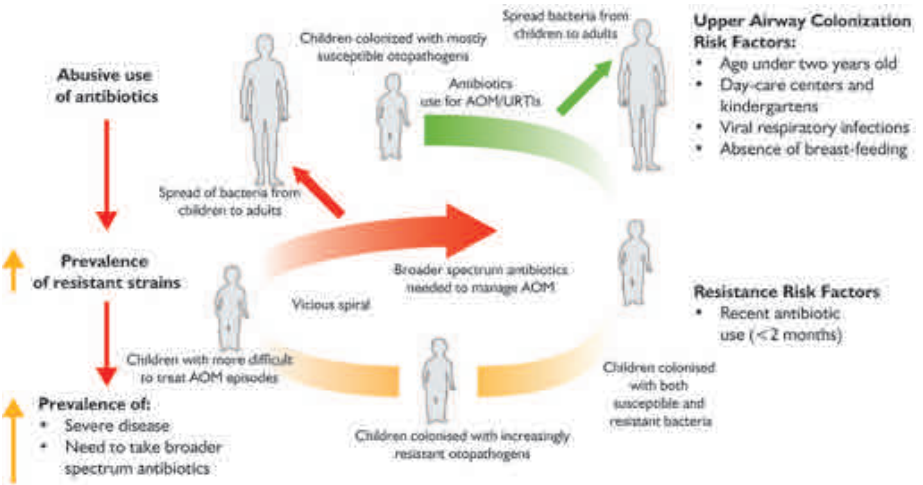

Figure 2. Antibiotic Resistance Cycle

Pharyngotonsillitis (pharyngotonsillitis)

In clinical practice, there is a widespread belief that the presence of pus in the throat is an indication of bacterial pharyngotonsillitis, thus justifying the use of an antibiotic. There is an anthological comment on this topic:

"If you are entirely comfortable selecting which pharyngotonsillitis patients to treat for ten days with penicillin, perhaps you don't understand the situation."

(Stillerman and Bernstein, 1961)

This phrase was written 54 years ago! In practice, many physicians think like this: "Pus in the throat is bacterial pharyngotonsillitis, so I will prescribe an antibiotic."

Even for the most experienced physicians, there are many situations where it is really difficult to identify patients who should take antimicrobial medications. An example is the treatment of streptococcal pharyngotonsillitis, which is virtually the only type of pharyngotonsillitis seen in clinical practice in Brazil with a routine indication for prescribing antimicrobial medications[6-7].

An important point that many guidelines recommend is when a physician has the possibility of using diagnostic tests, they should be ordered. Should the physician have workplace access to the Quick test for *Streptococcus pyogenes* (Quick Strep A Test), this is a test that contributes significantly to enhancing the positive and negative predictive values that indicate whether or not to prescribe antimicrobial medications for treating patients with suspected streptococcal pharyngotonsillitis. Clinical parameters should obviously also be used in the presence of conjunctivitis, cough, runny nose, and systemic indications such as diarrhea, as these conditions are generally associated with viral etiology (**Figure 3**).

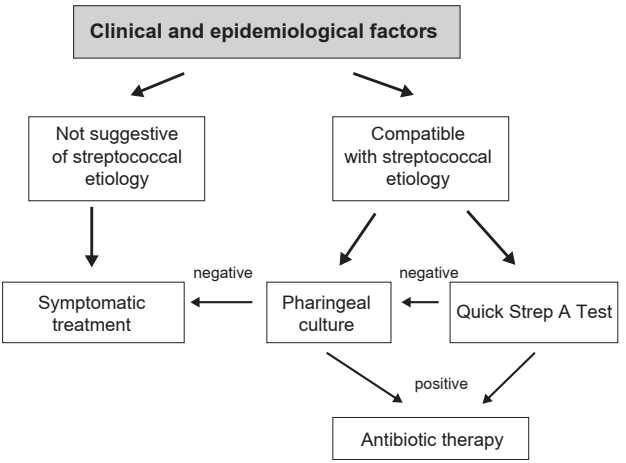

Figure 3. Algorithm for treating pharyngotonsillitis in children

When the pharyngotonsillitis is caused by *Streptococcus pyogenes*, penicillin will be the antimicrobial of choice [6-7]. In Brazil, the resistance situation of *Streptococcus pyogenes* is no different to that found anywhere else in the world. There is no resistance for *Streptococcus pyogenes* to the ß-lactam antimicrobial medications. There is no resistance to penicillin, which is thus the antibiotic of choice for pharyngotonsillitis caused by this bacterial agent. In clinical practice, this is replaced by amoxicillin, due to its palatability, easy dosing scheme, etc. Consequently, amoxicillin becomes the antimicrobial of choice for treating these situations involving streptococcal pharyngotonsillitis [6-7].

With regard to macrolides, there is a possibility of resistance in *Streptococcus pyogenes* to this group of antimicrobial medications. This resistance is directly related to the frequency with which macrolides are taken in the community. Consequently, the macrolides must be saved for specific situations, substituting penicillin and the other ß-lactam antibiotics only in situations where patients really have a proven history of allergies to this group of drugs, being an Immunoglobulin E (IgE) mediated allergy. It is important to recall that for other types of penicillin allergies that are not IgE mediated, the cephalosporins, especially first generation, may replace penicillin as they induce less resistance than those in the second and third generations [6-8].

The US Guideline published in the Clinical Infectious Diseases Journal in 2012 (**Table 1**), also issues a recommendation (as mentioned here), stipulating that when amoxicillin allergies are present, cephalexin should be the first choice, avoiding other second and third generation cephalosporins, and more specifically keeping the macrolides in reserve for situations of allergy or Type 1 hypersensitivity to penicillin[6].

Table 1. Recommended doses of antibiotics for treating pharyngotonsillitis.

Drug, Route	Dose or Dosage	Duration or Quantity	Recommendation Strength, Quality
For individuals without penicilin allergy			
Penicillin V. oral	Children: 250 mg twice daily or 3 times daily; adolescents and adults: 250 mg 4 times daily or 500 mg twice daily	10d	Strong, high
Amoxicillin, oral	50 mg/kg once daily (max = 1000 mg) alternate: 25 mg/kg (max = 500 mg) twice daily	10d	Strong, high
Benzathine penicillin G. intramuscular	<27 kg: 6000.000 U; ≥ 27 kg: 1.200.000 U	1 dose	Strong, high
For individuals with penicillin allergy			
Cephalexin, oral	20 mg/kg/dose twice daily (max =500 mg/ dose)	10d	Strong, high
Cefadroxil, oral	30 mg/kg once daily (max = 1g)	10d	Strong, high
Clindamycin, oral	7 mg/kg/dose 3 times daily (max = 300 mg/ dose)	10d	Strong, moderate
Azithromycin, oral	12 mg/kg once daily (max = 500 mg)	5d	Strong, moderate
Clarithromycin, oral	7.5 mg/kg/dose twice daily (max = 250 mg/ dose)	10d	Strong, moderate

Principles for the use of antimicrobial medications for otitis

Some principles must be reviewed [9-10]. When taking into account the etiology of bacterial acute otitis media (AOM), two agents (*Haemophilus influenzae* and *Streptococcus pneumoniae)* stand out from the others. What are the basic resistance mechanisms of these two microorganisms? Strains of *Haemophilus influenzae* and *Moraxella catarrhalis* may produce an enzyme - ß-lactamase - that hampers or disables the action of the beta-lactam antibiotic, thus requiring the inclusion of a beta-lactamase inhibitor on some occasions. There are other *H. influenzae* resistance mechanisms, meaning that this is not the only one, but it is generally the most important associated with this bacteria [9-10].

With regard to *Streptococcus pneumoniae*, the resistance mechanism is different, but not for ß-lactamase production, and it is very important that this is quite clear to general practitioners. The use of ß-lactamase inhibitors does not help in treating infections by resistant pneumococci. Unfortunately, this is a frequent mistake that should not be made. *Streptococcus pneumoniae* Resistance Mechanisms are associated with alterations in penicillin binding proteins, known as PBPs.

Group: under 12 months					
Serotype	n	ß- lactamase			
		Positive		Negative	
		n	%	n	%
a	9	0	0,0	9	100,0
b	9	2	22,2	7	77,8
e	1	1	100,0	0	0,0
NT*	16	7	43,8	9	56,3
Total	**35**	**10**	**28,6**	**25**	**71,4**

Group: 12 - 23 months					
Serotype	n	ß- lactamase			
		Positive		Negative	
		n	%	n	%
a	5	0	0,0	5	100
b	1	0	0,0	1	100
e	1	1	100,0	0	0,0
NT*	10	3	30,0	7	70
Total	**17**	**4**	**23,5**	**13**	**76,5**

Group: 24 - 59 months					
Serotype	n	ß- lactamase			
		Positive		Negative	
		n	%	n	%
a	10	0	0,0	10	100,0
b	4	1	25,0	3	75,0
e	1	0	0,0	1	100.0
NT*	5	0	0,0	5	100,0
Total	**20**	**1**	**5,0**	**19**	**95,0**

Figure 4. Resistance data on *Haemophilus influenzae* strains (SIREVA, 2012)

It is important to acknowledge that we unfortunately do not have data available in Brazil on isolated mid-ear pathogen resistance. The available resistance data for strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* available from the SIREVA Project [11] (focused on Improving Surveillance and Characterization of Meningococcal Disease in Latin America and the Caribbean Region) are for strains isolated from patients with invasive diseases, taken from samples drawn from the blood, the pleural liquid and CSF and not necessarily representing the profiles of strains causing otitis and sinusitis. Addressing strains isolated in 2012, the last SIREVA publication showed that some 20% to 30% of *Haemophilus influenzae* strains in Brazil are ß-lactamase producers. With regard to nontypable *Haemophilus influenzae*, these rates may well be even higher, reaching 30% to 40% [11]. Consequently, it is now expected that 20% to 40% of *Haemophilus influenzae* strains are ß-lactamase producers (**Figure 4**).

***Streptococcus pneumoniae* Resistance Mechanisms**

As mentioned, *Streptococcus pneumoniae* resistance mechanisms may be illustrated in the following didactic manner: in order to have an effect, the ß-lactam antibiotic (penicillin, amoxicillin or cephalosporin) with its ring must bind to a specific location on the bacteria, known as the Penicillin-Binding Protein (PBP) [12-13]. As its name indicates, this will bind to the ß-lactam ring of the antibiotic, allowing it to perform its function. However, bacteria may build up resistance, altering their configuration, meaning the ß-lactam ring that formerly bonded seamlessly to the protein, is no longer able to bind firmly to it in this new configuration, thus hampering the action of the antibiotic. It is clear that the level of this resistance varies greatly, which defines the greater or lesser susceptibility of *Streptococcus pneumoniae* to penicillin and the other ß-lactam antibiotics [12].

Pharmacokinetics (PK) and Pharmacodynamics (PD)

The concepts of pharmacokinetics (PK) and pharmacodynamics (PD) are fundamental for a better understanding of the mechanisms of action of the antibiotics (**Figure 5**) [14-16]. For the ß-lactam antibiotics (**Figure 6 a**) their concentrations must be above the Minimal Inhibitory Concentration (MIC) for at least 40% of the time between one dose and the next, in order to eradicate the bacteria causing the infection. In brief, this is the secret of success: if an antibiotic is used at a dosage that results in a concentration higher than the MIC for more than 40% of the time between one dose and the next, it will successfully eradicate the bacteria [13-16].

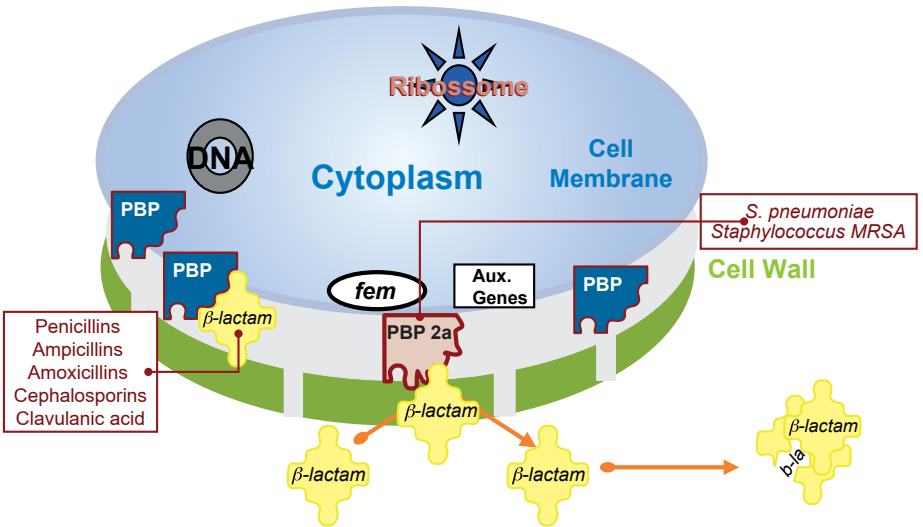

Figure 5: *Streptococcus pneumoniae* resistance mechanism.

Compared to other antibiotic groups, macrolides behave differently, depending on the concentration obtained with their use (**Figure 6 b**). This is why some of these macrolides may be taken once a day. It is far more important for this drug to reach a high concentration at which it will optimize its therapeutic action, allowing more convenient dosing schedules for the macrolides [14].

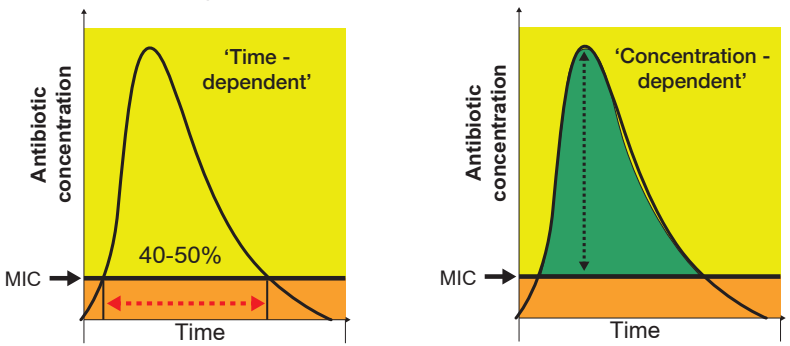

Figure 6. Concentration of (a) time-dependent antibiotics and (b) concentration-dependent antibiotics, by time

A common example in daily practice is a child is brought in with AOM caused by *S. pneumoniae*, whose MIC is 1 µ/mL, treated by amoxicillin prescribed at 50/mg/kg/day every 12 hours, for example. In this situation, it is known that this will result in a concentration of the antibiotic higher than the MIC for more than 40% of the time between each dose of the antibiotic. In other words, the bacteria will be eradicated, generally resulting in clinical success. However, another child is then seen with AOM caused by *S. pneumoniae*, although this time with an MIC of 4 µ/mL. This means that prescribing the same dose of 50/mg/kg will result in the antibiotic remaining above the MIC for only 20% to 30% of the time. In this case, the bacteria will probably not be eradicated and may well not achieve clinical success. Is there any way of overcoming this constraint? Yes. By associating a ß-lactamase inhibitor? No. Because this is the crucial point: for these *S. pneumoniae* strains with higher MICs, high doses of antibiotics are required, using amoxicillin 90/mg/kg in order to obtain an adequate curve (see **Figure 7**). With higher concentrations, this will remain more than 40% of the time above the MIC.

The parameters defining resistance have changed, with new cut-off lines for the use of parenteral penicillin for treating pneumonia, for example [17]. In these clinical situations, where there is no meningitis, a *S. pneumoniae* has an MIC ≤ 2 µ/mL (penicillin-sensible strains), penicillin-intermediate resistant strains with

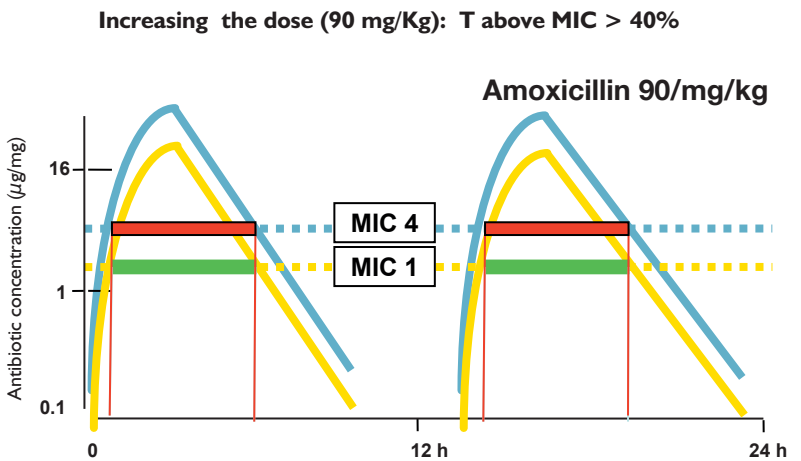

Figure 7. Antibiotic concentration by time.

an MIC of 4 µ/mL and penicillin-resistant strains solely and exclusively for pneumococci with an MIC of ≥8 µ/mL. For oral amoxicillin, these are the exact parameters: sensible ≤ 2 µ/mL; intermediate 4 µ/mL; and resistant ≥8 µ/mL. The parameters that are valid for *S. pneumoniae* strains isolated in the central nervous system remain unchanged, meaning strains with MICs of more than 0.125 are rated as penicillin-resistant for meningitis patients.

An important question arises: what is the real situation in Brazil? Once again, we turn to the SIREVA data [11], recalling that thus information is taken from strains

isolated from invasive infections (**Figure 8**). It is important to acknowledge that there is no resistance data currently available on strains of AOM isolated in Brazil, with no current studies on tympanocentesis providing these data, although we may infer that the strains causing invasive diseases are similar to those causing AOMs and sinusitis.

The following graphic (**Figure 8**) represents the resistance profile for the last ten years of *S. pneumoniae* strains isolated from non-meningeal infections, with the most recent data collected in 2012, showing that 96% of these strains (in yellow) are penicillin-sensible strains (MIC ≤ 2μ/mL), 4% (MIC of 4 μ/mL) with intermediate susceptibility, and 0% resistant strains. This is the context within which the criteria are deployed for this new pneumococci sensitivity cut-off line during the past two years in Brazil, with 0% of pneumococci strains presenting a MIC of ≥8 μ/mL. Transferred this to daily practice, when treating a patient with pneumococcal pneumonia, physicians should feel free to use penicillin IV at doses of 200,000 units per kg. Assuming that strains causing otitis and sinusitis have this same profile, a 50/mg/kg dose is sufficient to treat 96% of AOMs caused by pneumococci, with higher doses of amoxicillin possibly required in 4% of the cases.

An interesting aspect (**Figure 8**) is the recent behavior of the intermediate susceptibility rates. After the introduction in 2010 of the pneumococcal conjugate vaccine with ten *S. pneumoniae* serotypes (PCV-10) in Brazil, these rates are tending to drop. It is thus quite clear that this vaccine encompasses a significant percentage of the serotypes most associated with resistance, clearly indicating that a drop in these resistance rates may be expected, which has in fact been occurring during the past two years since the introduction of this vaccine [11].

For sulfamethoxazole-trimethoprim, there is 6% intermediate resistance and 30% full resistance. For erythromycin, intermediate resistance reaches 11%, with minimal rates for chloranphenicol and zero resistance for vancomycin.

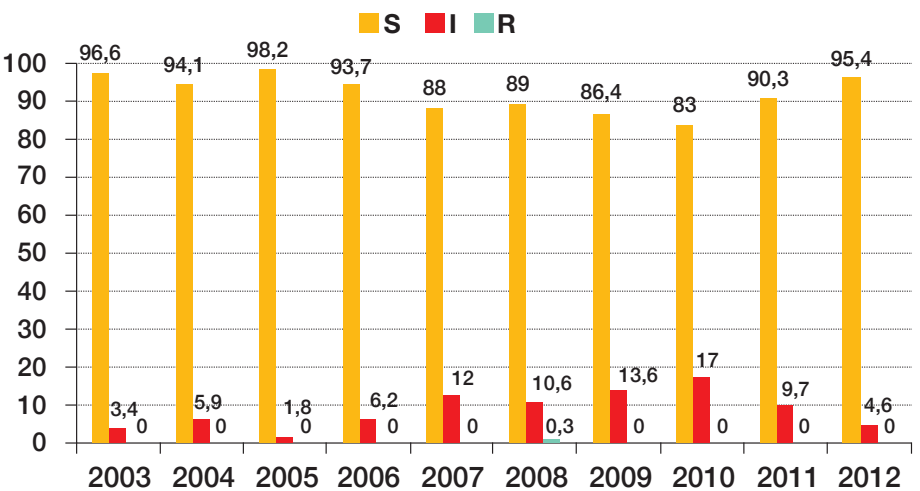

Figure 8. Penicillin susceptibility profiles (2003 - 2012) of *S. pneumoniae* (non-meningeal strains) in Brazil (SIREVA) with the new resistance parameters

When comparing the efficacy of cefuroxime axetil and cefaclor, it was apparent that, these two cephalosporins performed satisfactorily for sensible *S. pneumoniae* strains, although both failed for resistant *S. pneumoniae* strains and those with intermediate susceptibility, with cefaclor failing in more than 60% of the cases and cefuroxime failing in 21% of the cases20. The performance of cefaclor is almost equal to that of a placebo for these strains. For *H. influenzae* strains, the failure rate was also significant for cefaclor at around 40%, meaning that cefaclor is an inappropriate antibiotic for many respiratory tract infections, with cefuroxime being inappropriate for resistant pneumococci and those with intermediate susceptibility[20].

With regard to azithromycin, the failure percentage is similar to a placebo for *S. pneumoniae* strains with an MIC of 2 µ/mL, while for *H. influenzae* strains, azithromycin also performs similarly to a placebo. Consequently, the use of these new macrolides is not appropriate for treating AOM, based on these bacteriological data [18-19].

Comparing the efficacy of amoxicillin-clavulanate with azithromycin for children with AOM (**Figure 9**) it is apparent that the performance of amoxicillin-clavulanate for bacteriological eradication and clinical success exceeds that of azithromycin[19].

A study published in the Journal of Antimicrobial Chemotherapy [20] assessed the susceptibility of *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae* strains to various antimicrobial medications, based on pharmacokinetic and pharmacodynamic concepts, finding susceptibility rates for more than 90% of the strains, including oral antibiotics, with just amoxicillin (95%) and with amoxicillin-clavulanate (95% - 97%), in addition to the fluoroquinolones.

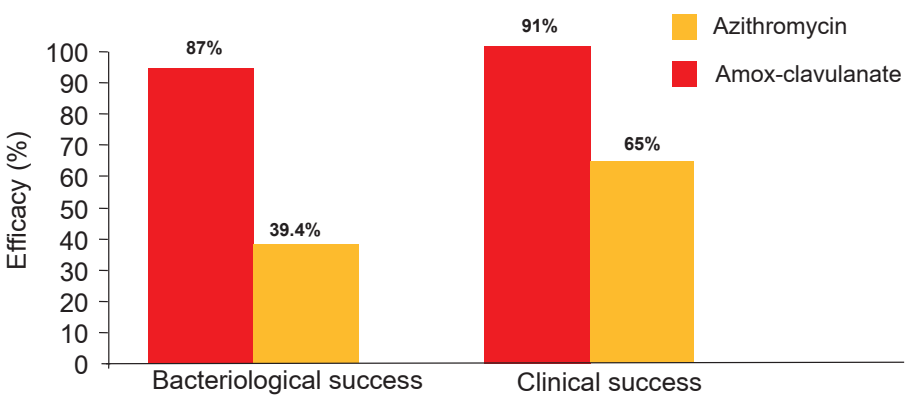

Figure 9. Comparative study of amoxicillin-clavulanate and azithromycin for bacteriological eradication and clinical success in AOM treatment. Bacteriological efficacy versus Clinical Success

Using the PK/PD thresholds, the non-fluoroquinolone agents that were most active against *H. influenzae* and *M. catarrhalis* were ceftriaxone, cefixime and amoxicillin-clavulanate. Both *H. influenzae* and *M. catarrhalis* strains were highly susceptible to fluoroquinolones.

The bacteriological failure rates in double tympanocentesis studies, which were among the studies mentioned, actually show that amoxicillin-clavulanate alone at high doses and ceftriaxone were very effective against *H. influenzae* strains as well as pneumococci with intermediate susceptibility [12-20].

We must also recall that in many situations where infectious processes become chronic, there is a possibility of biofilms being present, when all these pharmacokinetic and pharmacodynamic concepts lose their applicability, as antibiotics are unable to act in the presence of these biofilms[21].

Conclusion

This was the main purpose of this review, offering brief comments on antimicrobials use and recalling that a significant proportion of infections will have spontaneous resolution, due to their self-limiting viral etiology, with no need for antimicrobial medications. When prescribed correctly, these medications may lessen the duration and severity of the symptoms, in addition to reducing the chances of complications for certain bacterial infections of the airways, including sinusitis, otitis and streptococcal pharyngitis. It is worthwhile stressing that strict clinical criteria must be established and used for diagnoses. In the current epidemiological context, amoxicillin and amoxicillin-clavulanate remain the antibiotics of choice for treating otitis and sinusitis in children, due to their safety and efficacy profiles. It should also be recalled that pharmacokinetics and pharmacodynamic concepts are not applicable in cases where biofilm is present.

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