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Review

The principles of curative antibiotic treatments

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ABSTRACT

Knowledge of infectious diseases and their treatments is constantly evolving. New infectious agents are regularly discovered, due mainly to improvement of identification techniques, especially the development of molecular biology and mass spectrometry. While changes in the epidemiology of infectious diseases are not always predictable or readily understood, several factors regularly enter into consideration, such as not only the natural history of diseases and the impact of vaccinations, but also the excessive and irrational use of antibiotics. Antibiotic resistance is now recognized as one of the major challenges for humanity, especially since few new molecules have been put on the market in recent years. These molecules are reserved for serious infections caused by bacteria resistant to other antibiotics and should be prescribed only by infectious disease specialists trained in their use. Rationalization of antibiotic therapy is therefore one of the keys to reducing antibiotic resistance and the spread of resistant bacteria.

In this guide, with regard to each clinical situation, the bacterial target(s) of antibiotic treatment, the preferred antibiotic choice, and the therapeutic alternatives will be specified. Comments on diagnosis and treatment of the infection will be added if necessary.

1. Introduction

Infectious diseases and their treatments are constantly evolving for many reasons. New infectious agents are regularly discovered, mainly due to the evolution of identification techniques, especially through the development of molecular biology (PCR, sequencing, metagenomics) and mass spectrometry. As recently as 15 years ago, who was aware of the role of *Kingella kingae* in osteoarticular infections of infants and young children, or of the richness of microbiota and the importance of their variations in different pathologies? While changes in the epidemiology of infectious diseases cannot always be explained, three factors undoubtedly predominate: changes in climate, ecology and lifestyle, the impact of vaccinations and, finally, the consequences of widespread and often inappropriate prescription of antibiotics.

A parallel can be drawn between global warming and antibiotic resistance. Both phenomena are worsening rapidly and the known measures that would allow us to control them have not been taken or, in any case, are not being applied rigorously enough, while the two situations could become catastrophic for humanity in the coming years. More specifically, antibiotic resistance has become one of the main causes of worldwide mortality and one of the major challenges for humanity [1,2]. If the appearance of antibiotic-resistant strains is an inevitable and therefore expected phenomenon in the bacterial world, their increased number and widespread diffusion are directly linked to antibiotic misuse. Unfortunately, few new molecules have come onto the market in recent years, rendering the situation even more complicated. The rationalization of antibiotic therapy is therefore key to the reduction of antibiotic resistance.

The French pediatric antibiotic prescription guide was first published in 2016 [3], and needed updating. This new version incorporates the latest recommendations, consensus conferences and opinions of learned societies: Groupe de Pathologie Infectieuse

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Pédiatrique (GPIP) of the Société Française de Pédiatrie, Société de Pathologie Infectieuse de Langue Française (SPILF) and official state health agencies: Agence Nationale de Sécurité Sanitaire (ANSM), Haute Autorité de Santé (HAS) [4]. It also addresses new topics such as the introduction of new antibiotics for serious infections due to antibiotic-resistant species; the notion of antibiotics "critical" to the evolution of bacterial resistance; the disappearance of old antibiotics, mainly because they are not profitable enough for manufacturers due to relatively low prescriptions; and improved awareness of their adverse effects.

The purpose of this guide is to assist clinicians in their selection and use of antibiotics in view of optimizing the management of infectious bacterial diseases of infants and children. Ideally, the choice of an antibiotic in a given clinical situation should be the result of evidence-based medicine, i.e., randomized studies demonstrating the superiority (or, at least, the non-inferiority) of a therapeutic regimen in terms of efficacy and/or tolerance. In reality, these studies are rarely available, particularly in pediatrics, or only marginally relevant due to the evolution of epidemiological knowledge and, more particularly, bacterial resistance. In the absence of these data, other factors are to be taken into account, notably pharmacokinetic-pharmacodynamic parameters, safety and, increasingly, the ecological impact. These parameters are often the main determinants of antibiotic choices in this guide's recommendations.

For each clinical situation, the bacterial target(s) for antibiotic treatment (an essential prerequisite for any decision), the preferred antibiotic choice, the therapeutic alternatives, and pertinent comments on diagnosis and treatment are indicated. Therapeutic alternatives are viewed not equivalent treatments to be proposed in case of failure, but rather as acceptable second-choice possibilities to consider in case of contraindication, intolerance or recognized or strongly suspected allergy to the preferred treatment.

2. Antibiotic resistance

Multi-resistant bacteria, especially extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing bacteria, have become a public health emergency, especially as a result of careless and abusive management of our antibiotic resources [5,6]. The situation calls for a massive reduction in antibiotic prescriptions and the implementation of monitoring tools to follow the evolution of resistances, the objective being to adapt diagnostic and therapeutic strategies as soon as possible.

The main possibilities for reducing antibiotic prescriptions consist in:

- Strict limitation of their use to clinical situations in which antibacterial treatment is necessary and of proven effectiveness.
- Minimizing diagnostic uncertainty through rigorous clinical analysis and rapid diagnostic tests, taking into account pre-test probability, likelihood ratios and post-test probability (Box 1) [7].

Today, a massive antibiotic prescription reduction must also be associated with urgent systematic reflection and rationalization of our choices, avoiding the use of antibiotic classes with the highest risk of selection of multi-resistant bacteria, especially in the fecal flora. Means of counteracting "ecological emergencies" include:

- Reduction in the use of 2nd and 3rd generation cephalosporins (2GC and 3GC) and quinolones in an effort to curb the increase in ESBL Enterobacterales;
- Rigorous use of penems to limit the emergence of Gram-negative bacillus resistant to all antibiotics, and close monitoring of their consumption.

3. Criteria for choosing antibiotics

The general rules for prescribing antibiotics remain and should be known by all prescribers. The majority of antibiotic prescriptions are made empirically prior to isolation of the causative pathogen and determination of the result of the antibiogram. The choice depends on:

- the bacterial species most often responsible for the infection, and their usual antibiotic susceptibility profiles: one must always "name the bacterium" that will be the main target of the prescribed antibiotic,
- the disease, especially the site of infection,
- the patient, taking into account his age, a possible allergy, a physiological condition (pregnancy, prematurity...) or underlying conditions,
- the severity of the infection and its expected spontaneous evolution (risk of complication, rate of recovery without antibiotics),
- the compound: side effects, ecological impact, ease of administration, and its mechanism of action and pharmacokinetic-pharmacodynamic profile,
- and finally, the cost of the treatment and the cost-effectiveness ratio.

4. Steps in the reasoning process

There are 4 of them:

Identify the bacterial species most commonly responsible for infection at this site (*name the bacterium*).

Select the first-choice antibiotic theoretically effective against the presumed causative bacterium and its spread at the site of infection; it is usually among those indicated in the official recommendations.

Systematically *re-evaluate* the indication of antibiotic therapy at 48–72 h and eventually modify the initial choice: discontinue or change, according to clinical, biological and bacteriological data (antibiogram...), possibly after seeking advice from an infectious disease specialist.

Specify the expected *duration* of antibiotic therapy. Too often, antibiotic therapy is prescribed for an overly extended long period. For all the clinical situations described in the guide, the optimal duration of treatment is specified, in accordance with the HAS recommendations (3). For hospitalized patients, it is advisable to note on the daily prescription and in the patient's medical record the expected duration of antibiotic therapy. (Box 2).

Box 1
Recommendations for fever without source.

- Apart from at-risk populations (neonates, aplastic anemia patients...), do not prescribe antibiotics for simple fever without clinical signs of distress: an antibiotic is neither an antipyretic (for the patient) nor an anxiolytic (for the parents or the physician)!
- Identify the bacterial agent responsible for the infection: blood cultures, urine cytobacteriology if the urine dipstick is positive, local samples (discharge, puncture, surgical site) according to the clinical situation.

Box 2
Criteria for good antibiotic use.

- Systematically re-evaluate the indication and modalities of antibiotic therapy between 24 and 72 h of treatment and record them in the medical file.
- For hospitalized patients, continue antibiotic therapy beyond 3–4 days only after confirmation by a senior physician.
- In case of combination of antibiotics, justify in the medical record its maintenance beyond 3 days.
- When initiating treatment, record the expected duration of treatment in the file.
- Systematically adapt antibiotic therapy to the microbiological data and prescribe de-escalation in most cases (otherwise justify the decision in the file).
- Do not exceed 8 days of antibiotic therapy without justification.

5. The concept of critical antibiotics [8,9]

The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts. Antibiotics are classified into three groups, Access, Watch and Reserve, taking into account their impact on antimicrobial resistance, thereby underlining the importance of their being used appropriately. The 2021 update of this classification includes an additional 78 antibiotics. It helps to monitor antibiotic consumption, defining targets and assessing the effects of stewardship in view of optimizing antibiotic use and curbing antimicrobial resistance.

In 2022, the SPILF published an update of the list of critical antibiotics available in France for outpatients and hospitalized patients; they are classified into two categories:

On the one hand, antibiotics that are particularly at risk, either because their concentrations are close to the MICs, because of a long half-life leading to prolonged exposure of bacteria, or because of their strong impact on the normal flora, particularly the digestive microbiota.

On the other hand, antibiotics of last resort, used in clinical situations with few therapeutic alternatives.

Several examples can be cited:

- 3GC and 2CG lead to the emergence of ESBL-producing enterobacterales, leading to resistance, not only to all cephalosporins, but also to almost all forms of penicillin. This is the main reason that in 2011, the GPIP and the SPILF established recommendations in regarding ENT infections, thereby for the first time considering ecological impact as a major determinant of choice [10]. These recommendations were taken up by the HAS in 2021 [11].
- Quinolones favor the emergence of bacterial species resistant not only to this class of antibiotics, but also to 3GC.
- Penems, which are the reference treatment for infections caused by bacteria resistant to 3GC, favor the emergence of Gram-negative bacteria resistant to all ß-lactams.
- Azithromycin, because of its prolonged half-life, despite a short treatment duration, favors the emergence of gram-positive cocci (notably pneumococci) resistant not only to macrolides, but also to penicillin (Box 1).
- Finally, the combination of amoxicillin + clavulanate, which has a very broad spectrum including anaerobes, induces major disturbances of the digestive microbiome.

The available antibiotics can consequently be classified as follows:

- Class 1: molecules with preferential use.
- Class 2: molecules with restricted indications due to their impact on bacterial resistance.
- Class 3: molecules reserved, especially in hospitals, to preserve their effectiveness, used in serious infections for which few if any therapeutic alternatives exist.

The class of a given antibiotic can depend on whether it is prescribed for an outpatient or an inpatient. Hospitalized patients may obviously be in serious condition, have underlying pathologies rendering them fragile, and/or have a higher risk of bacterial resistance.

In our opinion, a number of so-called "critical" class 2 or class 3 antibiotics should be prescribed only by practitioners qualified in infectious disease treatment or, at the very least, should presuppose up-to-date training of prescribers, acquainting them with tools to reduce diagnostic uncertainty.

For pediatric outpatients:

- Class 1 includes amoxicillin, first-generation cephalosporins (1GC), cotrimoxazole, macrolides (excluding azithromycin), and doxycycline.
- Class 2, to be avoided whenever possible, includes 2GC and 3GC, azithromycin, and amoxicillin-clavulanate.

In pediatric hospital practice, however, amoxicillin-clavulanate and 2GC and 3CG are included in class 1 molecules, as they are likely to avoid the prescription of piperacillin-tazobactam or penems.

Aminoglycosides (mainly amikacin) remain active on the vast majority of ESBL-producing enterobacteria. They constitute a particular class, because of their possible use in monotherapy for urinary tract infections, and due to their very low digestive passage, which limits selection of antibiotic-resistant strains.

6. The disappearance of many antibiotics

Since 2016, several antibiotics are no longer available. We have seen some disappear without experiencing regret, but for others, the situation is worrisome:

- Even though injectable amoxicillin is likely to disappear, it can be replaced by injectable ampicillin without loss of chance for patients.
- Virtually all pediatric oral C1Gs have disappeared, including cefadroxil. While cefaclor remains available, its activity against Gram-positive cocci, particularly staphylococci and pneumococci, is insufficient. Likewise available, Cefalexin has a better PK/PD profile on Gram-positive cocci and could be useful in treatment of skin and soft tissue infections and as a relay treatment for all methicillin-susceptible *S. aureus* infections.
- Cefamandole (2GC), which was proposed for the initial IV treatment of bone infections, has disappeared. It can be replaced by cefuroxime without loss of chance for patients.
- Among the macrolides utilized in pediatrics, only azithromycin and clarithromycin remain available in France. Azithromycin is to be avoided as often as possible because of its long half-life, which generates more resistance than the other macrolides. Of note, its activity on pneumococcus is suboptimal.

7. Improved knowledge of adverse effects

Two points should be emphasized: improved knowledge of the adverse effects of quinolones, and the gradual lifting of the contraindication of doxycycline for children under 8 years of age for certain infections and for duration shorter than 3 weeks.

- Quinolones are now rarely used in pediatrics, but the list of adverse (cardiac...) effects has grown and, above all, their frequency now appears to be much greater than was estimated in the early years of their use [12]. In pediatrics, their use should be limited to infections generally documented bacteriologically and after consulting a pediatric infectiologist.
- The use of tetracyclines has historically been limited due to possible permanent tooth discoloration in children under 8 years of age, as their breakdown products are incorporated into the tooth enamel. Doxycycline binds less readily to calcium than other tetracyclines, but because of concerns about a class effect, up until now its use has been limited to patients at least eight years old. However, recent data from the United States and Europe suggest that doxycycline does not cause permanent visible tooth discoloration or enamel hypoplasia in children under 8 years of age. These reassuring data support the AAP's recommendation that doxycycline can be administered for short durations (i.e., 21 days or less) regardless of patient age [13]. Due to the photosensitivity associated with doxycycline, patients should nonetheless avoid excessive sun exposure.
- Penems (imipenem and meropenem) should be limited due to the risk of emergence of resistant strains. In pediatrics, meropenem should be the most frequently used: very similar its spectrum is similar to that of imipenem, its PK/PD profile is often better, as are tolerance and ease of use.

8. Antibiotic combinations

France is one of the developed countries in which antibiotic combinations are the most frequently used, although there is no clear evidence of their advantage [14], except in specific situations (*Helicobacter pylori* infections, tuberculosis...). Before prescribing a combination, it is essential to specify one's objectives and to verify that the clinical situation meets one of the three recognized indications:

- The first is to *broaden the spectrum*. Sometimes, the infection is severe (surgery, Intensive Care Unit ICU) and caused by several bacteria that cannot be treated with a single antibiotic; for example, in a digestive perforation, both enterobacterales and anaerobic germs resistant to 3GC may be feared.
- The second is to prevent the emergence of resistance under treatment. This is recommended mainly for bacteria such as *Pseudomonas aeruginosa, Acinetobacter, Enterobacter, Serratia, Citrobacter, Providencia, Morganella* (*B. cepacia, S. maltophilia),* for which it is initially necessary to broaden the spectrum of coverage to the least sensitive strains. However, as soon as the resistance profile is known, the initial combination must be discontinued in favor of monotherapy with an *in vitro* active ß-lactam, which generally (the one exception is Acinetobacter). However, given the risk of rapid emergence of resistance under treatment, certain antibiotics should never be prescribed alone: fusidic acid, colimycin, fosfomycin, rifampicin.
- The third is to obtain synergy and more rapid bactericidal effect. This was the main theoretical objective when combining a beta-lactam with an aminoglycoside for 2 to 5 days in severe infections. In reality, the number of situations in which this benefit has been clinically demonstrated is extremely low (endocarditis, deep neutropenia...).

To summarize, the indications for antibiotic combinations are very limited.

9. Aminoglycosides

Aside from urinary tract infections, aminoglycosides should generally be used as part of a combination of antibiotics as detailed above.

They should always be administered as a slow daily intravenous (IV) injection (recommended duration: 30 minutes), except in cases of endocarditis, for which two administrations per day are recommended. Two exceptions require a longer interval between injections: prematurity and renal failure.

Serum assays should be performed:

- At peak, to assess efficacy (from the first dose in case of suspicion of a germ with high minimum inhibitory concentration (MIC), cystic fibrosis and for patients in intensive care).
- In residual, to assess and reduce the risk of toxicity, mainly in renal failure or in treatment exceeding 5 days.

Lastly, the choice of aminoglycosides must be reasoned:

- Gentamicin is the most common prescribed aminoglycoside, as it is the most active (best pharmacokinetic-pharmacodynamic parameters) against Gram-positive cocci.
- Amikacin is prescribed in cases of nosocomial infection or suspected infections due to ESBL-producing pathogens (particularly BGN).
- Tobramycin is the preferred aminoglycoside for proven or suspected *P. aeruginosa* infection.

10. Injectable 3GC (Box 3)

Cefotaxime and ceftriaxone present similar microbiological activity profiles but very different pharmacokinetics. Ceftriaxone has several specific pharmacokinetic characteristics compared to other ß-lactams:

- A very long half-life (>7 h) allowing a single daily administration.
- Very strong binding to plasma proteins (95%), contraindicating it in newborns, especially in jaundice.
- Mainly biliary elimination, justifying its privileged choice in biliary or digestive infection (salmonellosis or shigellosis) but also having a major and prolonged ecological impact on the digestive flora.
- Modest pharmacokinetic and pharmacodynamic performance on methicillin-susceptible *S. aureus* and limited scope for dose escalation beyond the usual doses.

For these reasons, cefotaxime is often preferred in this guide, not only for neonates, but also for hospitalized patients when an IV approach is warranted.

Box 3
Antibiotic dosing.

Antibiotic assays are used to reduce the risk of toxicity and to predict their efficacy. Two families of antibiotics are frequently measured in clinical practice: glycopeptides (vancomycin in particular) and aminoglycosides.

Vancomycin

- Very high inter-individual pharmacokinetic variability.
- Renal toxicity dependent on other associated nephrotoxic treatments and the medical background (pre-existing renal insufficiency).
- Dosages are recommended as soon as the treatment period exceeds 2 days.Expected serum levels are:
- In the absence of bacterial species (and/or MIC) knowledge:
  - o 20 to 30 mg/L in case of continuous administration (to be measured after 24 h).
  - o 8 to 15 mg/l as residual level in case of discontinuous administration (to be determined before the 6th dose).
- When a bacterial species is isolated:
  - o 10 to 20 times the MIC in case of continuous administration (to be measured after 24 h).
  - o 5 to 10 times the MIC in residual rate in case of discontinuous administration (to be measured before the 6^{th} dose).

Aminoglycosides

Generally, dosage are not necessary unless the expected duration of treatment is 3 days or less. If an assay is needed:

- Determination of peak plasma concentration (C°max) to assess efficacy:
  - o Recommended after the first injection in severe situations in intensive care.
    Performed 30′ after completion of the end of a 30′ infusion.
  - o The objective is to obtain a concentration $\geq$ 10 times the MIC when a strain is isolated.
- Determination of residual concentration (C°min) predictive of renal and auditive toxicity:
  - o Only if the duration of treatment is > 5 days or in case of renal insufficiency.
  - o Performed just before the next injection.
  - o **Repeat dosage twice a week.**
  - o **Always associated with renal function monitoring.**

After a single daily dose	Target Cmax at peak (mg/L)	Cmin target in residual (mg/L)
Gentamycin, Tobramycin, Netilmicin	30 to 40	<0,5
Amikacin	60 to 80	<2,5

11. Oral route

For non-hospitalized patients, the oral route is the rule. For hospitalized patients, it should be preferred whenever possible because of the risks associated with injections (pain, extravenous toxicity, nosocomial infection...) and in order to shorten hospitalization stays. In the absence of serious infection, it should be used immediately or secondarily as a relay to initial parenteral antibiotic therapy, as soon as the infection is under control (generally after 48–72 h following clear improvement in clinical symptoms and, if applicable, of inflammatory markers) and in the absence of digestive disorders that interfere with the taking or absorption of medication.

The orally available antibiotics with IV/per os bioequivalence are: fluoroquinolones, metronidazole, cotrimoxazole, linezolid, azole antifungals (fluconazole, voriconazole) and, to a lesser degree, amoxicillin. For this molecule, the maximum doses compatible with oral administration are generally not sufficient to treat meningitis, cerebral abscess or endocarditis, except in exceptional cases, subsequent to the advice of a pediatric infectious disease specialist.

12. Allergy to penicillin [15]

Penicillin, in particular amoxicillin (and the combination amoxicillin-clavulanic acid) is the most frequently prescribed antibiotic in pediatrics. Although very often reported, the notion of allergy to penicillin rarely leads to authentication of a true allergy, and in many cases constitutes a real loss of chance for patients. Being "labelled" as allergic to a penicillin antibiotic is associated not only with avoidance of the antibiotic in question, but also with broader avoidance (other penicillin, cephalosporins, carbapenems...). Symptoms classified as "low risk" should clearly lead to reconsider this diagnosis; they include delayed (several days) urticarial or non-urticarial rashes, pruritus, diarrhea, vomiting, rhinorrhea, nausea, cough, headache, dizziness, and a family history of penicillin allergy. For high-risk immediate (<1 hour) allergic manifestations (anaphylactic shock, facial edema, angioedema, labial edema, airway edema, respiratory discomfort, wheezing), and severe phlyctenular or bullous lesions, and systemic symptoms, the diagnosis must be confirmed or refuted, in a majority of cases, by an allergist.

The ß-lactams are composed of a ß-lactam core, the structure of which is conserved among the different ß-lactams, and of side chains, which vary from one molecule to another. The main carriers of allergic reactions are side chains. Cross-allergies should be considered only between certain antibiotics whose side chains are identical or have strong similarities. As a matter of fact, the side chains of penicillin, particularly amoxicillin (by far the most prescribed molecule), differ from the main 3GCs (cefotaxime, ceftriaxone, cefpodoxime, cefixime), but have similarities with those of certain 1GCs (excluding cefalotin) and 2GCs (excluding cefuroxime). In case of a true allergy to penicillin, the risk of cross-reaction concerns 1GCs (except for cefalotin, the molecule most commonly used by the IV route for antibiotic prophylaxis in surgery and as a treatment for methicillin-susceptible *Staphylococcus aureus* infections) and 2GCs (except for cefuroxime), which indeed have similar side chains, but do not concern 3GCs, which can therefore be prescribed. In the rare cases of proven allergy or strong suspicion of allergy to penicillin, these cephalosporins (cefotaxime, ceftriaxone, cefpodoxime, cefixime, cefuroxime, cefalotin) represent the best alternative in terms of efficacy and safety. They are frequently indicated according to the clinical picture and the targeted bacteria.

13. Antibiotic treatment duration [16]

For over 30 years, shortened antibiotic treatment duration has been considered a priority for several reasons: compliance, side effects, cost, and ecological impact. For common respiratory infections, numerous studies have been published. The choice of treatment duration p for each molecule and each clinical situation has been guided more by cost (and often by the packaging of the antibiotic) than by scientific reasons. However, few studies have compared the same compound, at the same dosage, over different treatment durations. That said, the cornerstone for antibiotic treatment duration should be the results from prospective, comparative studies using the same molecule in two groups and double-blinded when the effectiveness criteria are far from robust (pain alleviation, reduced fever duration, otoscope...). Non-double-blinded studies could be useful in cases with robust evaluation criteria (bacteriological eradication...). The others critical points in the treatment duration concern the selection of relevant inclusion and effectiveness criteria and calculation of the necessary number of subjects, taking into consideration the proportion of spontaneous recoveries, which frequently occur in community-acquired infections. For example, 6-day treatment duration with amoxicillin for Group A pharyngitis has been driven by packaging for adults and children (one box versus 2 boxes); however, no study has been published with regard to 4 or 5 days of treatment.

14. Antibiotic supply shortages

Drug manufacturing chains, especially for antibiotics, are complex and international in view of reducing production costs and ecological impact. As a result, most active ingredients are manufactured in China and/or modified in India.

In recent years, prolonged stock-outs of many antibiotics (IV penicillin M, IV fosfomycin, cefepime, piperacillin-tazobactam, IV amoxicillin, ceftolozane-tazobactam, IV pediatric formula of amoxicillin-clavulanic acid, aztreonam…) have been observed. For each shortage, an alternative treatment has been found. Fortunately, due to their relatively small therapeutic targets, the prescription volumes for these antibiotics have been sufficiently modest to avoid a "domino effect". The same cannot be said for current supply difficulties, especially shortages of amoxicillin and amoxicillin-clavulanic acid; a pronounced domino effect affecting almost all second-line antibiotics is likely to occur.

Different scenarios are possible:

If the deficit does not exceed 40 to 50%, strict application of the guidelines should be sufficient insofar as nearly 40% of pediatric antibiotic treatments in France are prescribed for presumed viral infections (bronchitis, rhinitis, bronchiolitis, fever without source…) and could be strongly reduced without fearing any damage [17].

If the shortage is more severe, transitional changes in recommendations for the most common conditions that previously warranted antibiotics will be necessary in order to continue treating the most serious conditions, those for which antibiotics are essential. Otitis and tonsillitis account for more than 80% of the current recommended prescriptions for ambulatory patients and the changes to be proposed could consist in:

- shortened treatment duration,
- transitional adoption of protocols recommended in several Northern European countries, which prescribe fewer antibiotics, namely:
  - o for acute otitis media, treat with first-line antibiotics only infants under 6 months of age and, at any age, all complicated otitis. In older patients with uncomplicated otitis media, antibiotics should be prescribed only secondarily if no improvement is observed in 36 to 48 h under analgesic treatment alone [18],
  - o for sore throats, treat only the most severe cases, even if group A streptococcus is involved [19].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Definitions and implications of the pharmacokinetic-pharmacodynamic parameters of antibiotics in pediatric clinical practice

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ABSTRACT

Knowledge of infectious diseases and their treatments is constantly evolving. New infectious agents are regularly discovered, mainly due to improvement of identification techniques, especially the development of molecular biology and mass spectrometry. While changes in the epidemiology of infectious diseases are not always predictable or readily understood, several factors regularly enter into consideration, such as not only the natural history of diseases, the impact of vaccinations, but also the excessive and irrational use of antibiotics. Antibiotic resistance is now recognized as one of the major challenges for humanity, especially since few new molecules have been put on the market in recent years. These molecules are reserved for serious infections caused by bacteria resistant to other antibiotics and should only be prescribed by infectious diseases specialists trained in their use. Rationalization of antibiotic therapy is therefore one of the keys to reducing antibiotic resistance and the spread of resistant bacteria.

In this guide, for each clinical situation, the bacterial target(s) of antibiotic treatment, the preferred antibiotic choice, and the therapeutic alternatives will be specified. Comments on the diagnosis and treatment of the infection will be added if necessary.

1. Introduction

For almost half a century, numerous studies have demonstrated the value of serum pharmacokinetic/pharmacodynamic (PK/PD) parameters in predicting bacterial eradication or therapeutic success, first in animal models and then in humans [1,2]. These parameters are now the cornerstone in the pre-clinical development of antibiotics, helping to determine the dosage and interval of administration, as well as the establishment of critical MICs enabling the classification of strains in the sensitive or resistant zone with regard to a given antibiotic [3,4]. The initial studies that led to the determination of predictive PK/PD parameters used animal models in which the MICs of the antibiotics against the infecting strain were known, as were the serum concentrations at different times after administration. In all of these models, the free form of the antibiotic, which most often corresponds to the active form, appeared to more closely correlate with efficacy than total concentration. Since then, the data provided by these animal models have been confirmed in various infections encountered in clinical practice: upper and lower respiratory infections, bacteremia, skin and soft tissue infections, intra-abdominal infections, community-acquired bone and joint infections. For other infections (bone or upper urinary tract), which have yet to obtain the same level of evidence, it seems essential to consider serum PK/PD parameters. In infections of tissues in which antibiotics are poorly diffused (cerebrospinal fluid, eye…) and prosthetic infection, local PK/PD parameters are the most predictive. The choice of antibiotics, as well as the daily doses and frequency of administration, are largely influenced by the relevant PK/PD parameters. They need to be recognized by infectious disease specialists and by pediatricians in critical care departments so as to achieve optimal management of patients infected with less susceptible bacterial strains or those with characteristics likely to modify drug PK (cystic fibrosis, sickle cell disease, renal insufficiency, severe infections…). When

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the infection involves antibiotic-resistant strains, due to the relative rarity of these situations, prescription cannot be based on evidence-based medicine alone. Lastly, prescribers must take into account the PK/PD characteristics of the molecules administered.

To ensure optimal efficacy, PK/PD parameters facilitate identification of antibiotic concentrations that prevent the multiplication of resistant bacterial subpopulations, thereby helping the clinician to maintain serum concentrations sufficient to prevent this risk (concentrations $\geq$ 4 to 7 times the MIC) [5,6]. These PK/PD targets are higher than those classically associated with clinical efficacy or bacterial eradication. This has been amply demonstrated with quinolones, and appears to be particularly pronounced for bacterial species such as *Pseudomonas aeruginosa* and certain enterobacterales (*Enterobacter, Serratia*, etc.).

2. Definition of the main serum PK/PD parameters predictive of efficacy

Fig. 1 defines the main serum PK/PD parameters predictive of antibiotic efficacy: ratio of the peak serum concentration to the MIC for the target bacterial strain (P/MIC), percentage of time where the serum concentration remains above the MIC (fT > MIC), and area under the curve of the serum concentration of the antibiotic above the MIC (AUC/MIC). The differences between the predictive parameters of the different families of antibiotics can be explained not only (albeit primarily) by the type of bactericidal effect obtained (concentration or time-dependent activity), but also by the presence and duration of a persistent antibacterial effect (particularly a post-antibiotic effect). However, it should be noted that regarding the oldest antibiotics, PK data are frequently scarce, these compounds were marketed before the importance of these PK/PD parameters was known [7].

3. Pediatric studies

Most drugs - including antibiotics - have been developed in adults, with dosage subsequently extrapolated to children in terms of dose/kg or dose/body surface area. For ethical, practical, and economic reasons, trials demonstrating the real-life efficacy of pediatric antibiotics are rarely conducted. In this context, differences in PK and safety are the primary concerns of pediatric studies. For PK, the objective is to obtain concentrations (P/MIC, T/MIC, AUC/MIC) similar to those observed in adults at the dosages retained in the marketing authorization. To achieve this result, the doses required in infants and children are generally higher (in mg/kg) than in adults [8]. Renal and hepatic functioning in children are highly relevant. The situation is different in neonates, particularly premature infants, who combine increased drug dilution space with glomerular immaturity; while unit doses are often increased, the spacing between doses must be wider. Of note, children have developmental and maturation peculiarities, which may contribute to sizable PK variability. These alterations are further enhanced by non-maturational factors related to the disease itself: severity, inflammatory state, increased renal clearance by glomerular hyperfiltration, and ICU stays potentially leading to underexposure. In these patients, clinical integration of antibiotic dosages may help to optimize dosages and frequency of administration [9].

4. The predictive PK/PD parameters of different antibiotic families

For different families of antibiotics, Table 1 displays the main predictive efficacy parameters. In animal models having contributed to the determination of PK/PD parameters predictive of efficacy, the MIC of the antibiotic used for the infecting bacterium and the inoculum are well-known. By contrast, this is not the case in real life, where the MICs are often unknown, as is the inoculum. It is for these reasons and because PK variations are in children particularly wide-ranging that it is necessary to ensure safety margins.

While the predictive PK/PD parameters depend mainly on the antibiotic family, other factors enter into consideration: the patient's immune status (e.g., whether or not he or she is neutropenic), the severity of the infection (e.g., patients in intensive care), the site of infection, and the bacterial species implicated [1,2,5]. For severe infections or those occurring in immunocompromised patients, the immune system cannot be relied upon to contribute to recovery, and treatment should be aimed at heightening PK/PD parameters. In these situations, PK often varies, usually tending towards shortened half-life and increased volume of distribution, factors leading to underexposure (regardless of PK/PD goals) and tending to decrease antibiotic efficacy; for these patients, unit doses of antibiotics are often higher, time between doses is decreased, and/or infusion time is increased (possibly to the point of continuous infusion), the objective being to maximize exposure.

The desired PK/PD parameters also have an influence when an assay is requested to predict the efficacy of an antibiotic [1,2,7].

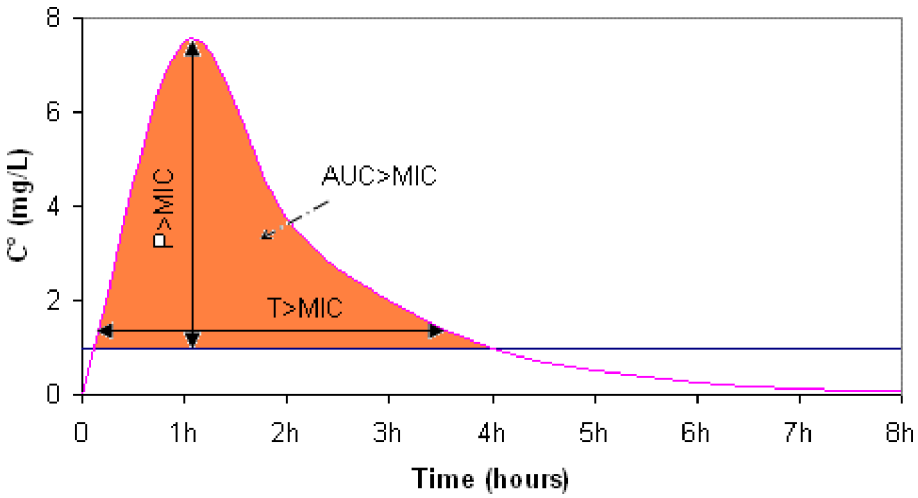

Fig. 1. Definitions of pharmacokinetic/pharmacodynamic parameters. Abbreviations: C°, concentration; P, peak; MIC, minimum inhibitory concentration, AUC, area under the curve; T, time.

Table 1
Predictive PK/PD criteria of efficacy for different antibiotic families

Antibiotic family	Type of bactericidal activity	Post antibiotic effect	Main criterion PK/PD predictive of efficiency	Dosage to be requested in clinical practice to assess efficacy
ß-lactams	Time-dependent	GNB: No GPB: Yes (short duration)	**T>MIC** 40% for common infections100% for sepsis, intensive care, infections and meningitis	Exceptionally necessary Only serious infections (resuscitation) or bacteria with high MICs
Macrolides & related	Time-dependent	Yes	**AUC >CMI T>MIC** 40% common infections	Exceptionally necessary
Aminosides	Concentration-dependent	Yes	**P>CMI**	Rarely necessary except for patients in intensive care Determination at the peak of the first dose (objective: rate > 8-10 times the MIC of the responsible bacterium or, failing that, of the critical MIC) Residual concentrations are used to assess toxicity (prolonged treatment or renal failure)
Glycopeptides	Time-dependent	Yes	**AUC>CMI**	Determination of the residual concentration (or plateau concentration if continuous administration) useful as soon as a bacterium is isolated (effective rate: at least 10 times the MIC)
Quinolones	Concentration-dependent	Yes	**AUC>CMI P/CMI**	Exceptionally necessary
Imidazoles	Concentration-dependent	Yes	**AUC>CMI P/CMI**	Exceptionally necessary
Cotrimoxazole	Time-dependent	Yes	**AUC>CMI T>MIC**	Exceptionally necessary
Linezolid	Time-dependent	Yes	**AUC>CMI**	Exceptionally necessary
Colimycin	Concentration-dependent	Yes	**AUC>CMI P/CMI**	Always useful as well as the determination of the MIC of the responsible bacteria
Daptomycin	Concentration-dependent	Yes	**AUC>CMI P/CMI**	Always useful as well as the determination of the MIC of the responsible bacteria

Abbreviations: C°, concentration; P, peak; MIC, minimum inhibitory concentration, AUC, aera under the curve; T, time; GNB, Gram-negative bacilli; GPB, Gram-posittive bacilli.

5. Some practical examples

If we consider the MIC 50 of susceptible strains (for resistant or intermediate strains, by definition, the predictive PK/PD parameters are never reached), the free forms of the antibiotics, and their average PK, several facts appear:

- While intravenous (IV) penicillin M achieves excellent PK/PD parameters, the *f*T > MIC of oral forms for *S. aureus* is always < 20%, explaining why oral penicillin M is no longer recommended, even for the treatment of susceptible Gram-positive infections. This is not surprising insofar as serum concentrations are 50 to 100 times lower by the oral route than in the IV forms.
- The same applies to IV cefuroxime and oral cefuroxime-axetil.
- On *E. coli* strains sensitive to amoxicillin, by oral route and even at high doses, this compound does not exceed 20 to 30% of the time above the MIC.
- The main family of antibiotics used in human therapeutics is that of the ß-lactams, for which the parameter of efficacy is prolonged time above MIC. To extend this time, increasing the doses is of little interest, whereas extending the time of administration of the molecules or offering them in continuous administration makes sense. For example, extending administration time of the antibiotic from 30′ to 3 hours has been proposed for meropenem and cefiderocol.
- In addition to practical difficulties, continuous administration often comes up against the fact that many of these molecules are not stable in infusion solutions. Clinicians can rely on guidelines for optimal maximum antibiotic concentration, dilution solute, stability, and administration modality [10].

6. Switch from the IV route to the oral route

Some antibiotics (quinolones, metronidazole, cotrimoxazole, clindamycin, linezolid) reach comparable serum concentrations or area under the curve when administered orally or by IV. The transition from intravenous to oral form does not pose any problem of delay. On the contrary, other antibiotic (penicillin M…) have concentrations 20 to 50 times lower by the oral route. In this case, oral administration is incompatible with PK-PD objectives, and actually represents a disguised cessation of treatment after parenteral administration, which is usually sufficiently prolonged. Other antibiotics, such as the combination of amoxicillin-clavulanate or some first-generation oral cephalosporins, can reach acceptable PK/PD performances compared to IV administration. For these antibiotics, a switch to the oral route is allowable in some controlled infectious situations to complete the treatment.

7. Conclusion

Understanding of antibiotics' mechanisms of action has made it possible to determine PK/PD parameters, which are highly predictive of their efficacy. These parameters significantly contribute to the determination of unit doses, dosing schedules and the optimal time to switch from IV to oral administration. They should be considered in the selection of antibiotic therapy, particularly in patients infected with resistant bacteria and in those with characteristics likely to alter the pharmacokinetics of antibiotics.

Conflicts of interest

None.

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Review

Antimicrobial treatment of ENT infections

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ABSTRACT

Ear, nose and throat (ENT) or upper respiratory tract infections (URTI) are the most common infections in children and the leading causes of antibiotic prescriptions. In most cases, these infections are due to (or are triggered by) viruses and even when bacterial species are implicated, recovery is usually spontaneous. The first imperative is to refrain from prescribing antibiotics in a large number of URTIs: common cold, most cases of sore throat, laryngitis, congestive otitis, and otitis media with effusion. On the contrary, a decision to treat sore throats with antibiotics is based primarily on the positivity of the Group A Streptococcus (GAS) rapid antigen diagnostic tests. For ear infections, only (a) purulent acute otitis media in children under 2 years of age and (b) complicated or symptomatic forms of purulent acute otitis media (PAOM) in older children should be treated with antibiotics. Amoxicillin is the first-line treatment in the most cases of ambulatory ENT justifying antibiotics. Severe ENT infections (mastoiditis, epiglottitis, retro- and parapharyngeal abscesses, ethmoiditis) are therapeutic emergencies necessitating hospitalization and initial intravenous antibiotic therapy.

ENT infections are the most frequent infections in children and in many countries the leading reasons for antibiotic prescriptions [1,2]. The vast majority are viral in origin or triggered by viruses. Furthermore, even if bacterial species are implicated, most are self-limited diseases [3–5]. This explains why antibiotics are most often unnecessary, except in the most severe forms, for which diagnosis and treatment must begin at an early stage. The first message in the recommendations of the *Groupe de Pathologie Infectieuse Pédiatrique de la Société Française de Pédiatrie* (GPIP-SFP) and the *Société de Pathologie Infectieuse de Langue Française* (SPILF), which were included in the 2021 Haute Autorité de Santé (HAS) guidelines, is that antibiotics should not be prescribed in cases of common cold, non-streptococcal tonsillopharyngitis, laryngitis, congestive acute otitis media or otitis media with effusion [6,7]. The second message is that in most cases, prescription of "critical antibiotics" ("watch" and "reserve" antibiotics in the WHO classification) should be avoided. They include:

- 2nd and 3rd generation cephalosporins, which favor the emergence of extended-spectrum ß-lactamase-producing enterobacterales,
- amoxicillin-clavulanate (amox/clav), of which the spectrum is unnecessarily broad,
- azithromycin, with half-life inducing prolonged selective pressure [8,9].

A decision to treat sore throat with antibiotics is based mainly on the results of rapid diagnostic antigen tests (RADT) for group A streptococcus (CAS). While positive GAS-RADT justifies antibiotic prescription, negative GAS-RADT most often does not [6,7]. With regard to otitis, only purulent acute otitis media (PAOM) in children under 2 years of age and symptomatic or complicated forms of PAOM in older children should be treated with antibiotics [6,7].

Decreased antibiotic resistance largely ascribable to pneumococcal conjugate vaccines and reduced antibiotic prescriptions for the two most frequently involved bacterial species (*S. pneumoniae* and *H. influenzae)* explain why antibiotic choices have been restricted in recent years and, more specifically why, in most cases, amoxicillin is now the first-line treatment [6–8]. However,

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Table 1
Antibiotic therapy for outpatient ENT and stomatological infections.

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contra-indicated preferred treatment)	Comments
Common cold	No antibiotics		Viral infection.No demonstrated efficacy of antibiotic treatment
Congestive acute otitis media	No antibiotics		Viral infection.No demonstrated efficacy of antibiotic treatment
Otitis media with effusion	No antibiotics		No proven medium or long-term effectiveness of antibiotics
Purulent acute otitis media ***Main targets of antibiotic treatment*** *S. pneumoniae* *H. influenzae*	**Amoxicillin** (oral) 80–100 mg/kg/day in 2 divided doses (maximum 3 g/day)	**Cefpodoxime** (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day)	Properly diagnosed purulent AOM should be treated with antibiotics until the age of 2 years.From the age of 2, only the most severe forms (high fever, intense otalgia) or complicated forms (otorrhea, recurrent otitis…) should be treated with antibiotics.
Other bacteria – *M. catarrhalis* – *S. pyogenes*	Treatment duration – 5 days for children older than 2 years – 10 days for children under 2 years and after this age, only for • otitis-prone children (recurrent AOM) • otitis media with otorrhea	Treatment duration – 5 days for children older than 2 years – 10 days for children under 2 years and after this age, only for • otitis-prone children (recurrent AOM) • otitis media with otorrhea	For other conditions, a wait-and-see attitude is recommended. Antibiotics are indicated in case of persistent symptoms (over 48 hours). In 2022, in France, fewer than 7% of pneumococcal strains and fewer than 20% of *H. influenzae* strains isolated from the nasopharynx of children with ear infections were resistant to amoxicillin (ACTIV data). Reserve ceftriaxone for exceptional situations of digestive intolerance or strong suspicion of resistant pneumococcus.
Otitis + conjunctivitis syndrome ***Main target of antibiotic treatment*** *H. influenzae*	**Amoxicillin** (oral) 80–100 mg/kg/day in 2 divided doses (maximum 3 g/day) or **Amox/clav** (oral) 80 mg/kg/day in 2 divided doses (maximum 3 g/day) Treatment duration – 5 days for children older than 2 years – 10 days for children under 2 years and after this age only for • otitis-prone children (recurrent AOM) • otitis media with otorrhea	**Cefpodoxime** (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day) Treatment duration – 5 days for children older than 2 years – 10 days for children under 2 years and after this age only for • otitis-prone children (recurrent AOM) • otitis media with otorrhea	Decreased resistance to amoxicillin due to the production of *H. influenzae* ß-lactamases in recent years support the use of amoxicillin, even for otitis-conjunctivitis syndrome. Ceftriaxone is reseved for exceptional situations of digestive intolerance or strong suspicion of resistant pneumococcus.
Otitis with otorrhea ***Main target of antibiotic treatment*** *H. influenzae* *S. pyogenes* *S. pneumoniae*	**RADT +** **Amoxicillin** (oral) 50 mg/kg/day in 2 divided doses (maximum 3 g/day)	**Cefpodoxime** (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day)	Before the age of 3 years, the most frequent bacterial species is *H. influenzae*. It is often involved in recurrent otorrhea [13]. After 3 years of age, GAS is the first species found [13].
	RADT - **Amoxicillin** (oral) 80–100 mg/kg/day in 2 divided doses (maximum 3 g/day) or **Amox/clav** (oral) 80 mg/kg/day in 2 divided doses (maximum 3 g/day)	**Cefpodoxime** (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day)	After relaxation of NPIs imposed by COVID-19 pandemic, GAS has increased, including in children under 3 years old [17]. Because GAS remains susceptible to all ß-lactams, GAS-RADT could help to guide antibiotic treatment. Furthermore, the low MICs of amoxicillin for GAS allow lower doses than *H. influenzae*
	Duration of treatment 10 days regardless of age	Duration of treatment 10 days regardless of age	The sensitivity and specificity of these tests in this situation is close to 100%. In addition, GAS is rarely associated with other bacteria in ear infections.

Table 1 (*continued*)

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contra-indicated preferred treatment)	Comments
Acute otitis media after failure of first antibiotic treatment	**Failed after 1er treatment:**	**Second line**	**Definition of failure** Persistence or recurrence of clinical signs during treatment or within 72 hours of discontinuation.
Main target of antibiotic treatment *H. influenzae* *S. pneumoniae*	**Amoxicillin** (oral) →	**Amox/clav** (oral) 80 mg/kg/day in 2 divided doses (maximum 3 g/day) Duration of treatment 10 days	Treatment failures with amoxicillin treatment are mainly due to *H. influenzae.*
		Cefpodoxime (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day) Duration of treatment 10 days	
	Cefpodoxime (oral) →	**Amoxicillin** (oral) 150 mg/kg in 3 divided doses (maximum 3 g/day) Duration of treatment 10 days	Treatment failures with cefpodoxime treatment are due to penicillin-resistant pneumococcus.
	Amox/clav (oral) →	**Ceftriaxone** 50 mg/kg/in 1 dose (IV or IM) (3 days)	Both bacteria can be involved in (very rare) failure of amox-clavulanate. Tympanocentesis for bacterial examination should be considered.
Maxillary or frontal sinusitis	**Amoxicillin** (oral) 80–100 mg/kg/day in 2 divided doses (maximum 3 g/day)	**Cefpodoxime** (oral) 8 mg/kg/day in 2 divided doses (maximum 400 mg/day)	Treatment is indicated: – in frontal sinusitis or in the following situations of maxillary sinusitis: • In the "severe-acute" form, the rarest with fever > 39 °C, headaches, purulent rhinorrhea, evolving > 3–4 days • In any clinical form with risk factors: asthma, heart disease, sickle cell anemia. – Without these risk factors, in both forms of the most common maxillary sinusitis (rhinopharyngeal symptoms lasting more than 10 days with no sign of improvement or secondarily aggravating), treatment should be discussed or delayed according to intensity of symptoms, their duration, and failure of symptomatic treatment.
Main target of antibiotic treatment *S. pneumoniae* *H. influenzae* *M. catarrhalis*	Duration of treatment 10 days	Duration of treatment 10 days	
Tonsillo -pharyngitis			The vast majority of sore throats are viral in origin.The only important bacterial species for ambulatory patients in childhood is GAS. It is no longer acceptable to treat patients with antibiotics without first obtaining positive RDT.
Main target of antibiotic treatment *S. pyogenes* (GAS)	**No antibiotics**	**No antibiotics**	
GAS-RADT -	**Amoxicillin** (oral) 50 mg/kg/day in 2 doses (maximum 2 g/day)	**Cefpodoxime** (oral) 8 mg/kg/day in 2 doses (maximum 400 mg/day) Duration of treatment 5 days or	All GAS strains remain susceptible to ß-lactams. Resistance to macrolides varies depending on the area and the times. Over the last 5 years, the rate of resistance has been very low (less than 5%) in the strains isolated in children with GAS pharyngitis.
GAS-RADT+ *S. pyogenes (GAS)*	Duration of treatment 6 days	**Clarithomycin** (oral) 30 mg/kg/day in 2 divided doses (maximum 500 mg/day) Duration of treatment 5 days	

(*continued on next page*)

Table 1 (*continued*)

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contra-indicated preferred treatment)	Comments
Recurrent GAS Tonsillo-pharyngitis **GAS carrier state** **GAS eradication in invasive GAS infections**	**Cefalexin** (oral) 50 mg/kg/day in 2 divided doses (maximum 2 g/day) For 10 days ———————————————— **Amox/clav** (oral) 50 mg/kg/day in 2 divided doses (maximum 2 g/day) For 10 days ———————————————— **Azithromycin** (oral) In one daily dose 20 mg/kg/day for 3 days ———————————————— **Amoxicillin** (oral) 50 mg/kg/day in 2 doses (maximum 2 g/day) For 10 days **+** **Rifampicin** (oral) 20 mg/kg/day in 2 doses The last 4 days of amoxicillin treatment		For GAS carriage state and GAS eradication in invasive GAS infections, antibiotics are only exceptionally indicated [19].Penicillin V, Penicillin G or amoxicillin are not the optimal treatments. Alternative treatments give better results in terms of GAS eradication. Several hypotheses have been raised to explain these differences (biofilms, internalization, bacterial interferences…) .
Cervical lymphadenitis ***Main target of antibiotic treatment*** *S. pyogenes* *S. aureus (SAMS)*	If GAS-RADT +: **Amoxicillin** (oral) 50 mg/kg/day in 2 doses (maximum 2 g/day) If GAS-RADT -: **Amox/clav** (oral) 80 mg/kg/day in 2 doses (maximum 2–3 g/day) Duration of treatment 10 days	If GAS-RADT + or - **Clarithromycin** (oral) 15 mg/kg/day in 2 divided doses (maximum 500 mg/day) or **Clindamycin** (oral) 30 mg/kg/day in 3 divided doses (after 6 years) (maximum 1.8 g/day) Duration of treatment 10 days	Rapid diagnostic tests for GAS are recommended in cervical adenitis if antibiotic therapy is considered: if positive, an antibiotic targeting this bacterial species may be prescribed [19]. If the infection is severe and hospitalization is indicated, prescribe the same antibiotics as for peri-pharyngeal abscesses, if possible after puncture.
Uncomplicated dental abscess ***Main target of antibiotic treatment*** *Streptococcus viridans and anginosus and other anaerobes*	**Amoxicillin** (oral) 50 mg/kg/day in 2 divided doses (maximum 3 g/day) Duration of treatment days	**Clarithromycin** (oral) 15 mg/kg/day in 2 divided doses (maximum 500 mg/day) Duration of treatment 6 days	
Dental abscess complicated by cellulitis ***Main target of antibiotic treatment*** Cover in addition *Bacteroides species*	**Amox/clav** (oral) 80 mg/kg/day In 2 divided doses (maximum 3 g/day) Duration of treatment 10 days	**Clarithromycin** (oral) 15 mg/kg/day in 2 divided doses (maximum 500 mg/day) **+** **Metronidazole** (oral) 30 mg/kg/day in 2 divided doses, (maximum 1500 mg/day) Duration of treatment 10 days	

Table 1 (*continued*)

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contra-indicated preferred treatment)	Comments
Laryngitis	No antibiotics		Viral infection.No proven effectiveness of antibiotics.
Acute parotitis of bacterial origin (except in neonates)	**Amox/clav** (oral) 80 mg/kg (oral) or 100–150 mg/kg IV in 3 doses (maximum 4 g/day) Duration of treatment 10 days	**Cotrimoxazole** (oral) 30 mg/kg/day of Sulfamethoxazole in 2 divided doses (maximum 1600 mg/day)	Outside of the neonatal period, most parotitis is viral in origin, particularly mumps virus (at over 10 years of age, effectiveness of the vaccine, even after 2 doses, does not exceed 85%), and enterovirus. In a parotitis of bacterial origin, pus is retained at the orifice of Stensen canal, an inflammatory aspect of the parotid gland (suggesting abscessation and high inflammatory biological parameters (CRP and/or PCT). Recurrences are frequent [20].
Main target of antibiotic treatment *S. aureus meti S (SAMS)* Anaerobes		**Clindamycin** (oral) 30–40 mg/kg/day in 3 divided doses (maximum 2,4 g/day) Duration of treatment 10 days	

IV: Intravenous.
IM: Intramuscular.
RADT: Rapid Antigen diagnostic test.
Amox-clavulanate: Amoxicillin-clavulanate combination.

Table 2
Antibiotic therapy for serious ENT and stomatological infections.

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contraindicated preferred treatment)	Comments
Peri-pharyngeal or retropharyngeal abscess **Severe acute suppurative adenitis**	**Amox/clav** (IV) 150 mg/kg/d IV in 3 divided doses (maximum 6 g/day)	**Cefotaxime** (IV) 200 mg/kg In 3 divided doses (maximum 12 g/day) +	Oral relay after the clinical improvement
Essential target of the treatment *S. pyogenes* *SASM* *S. pneumoniae* *Fusobacterium* spp. *Bacteroides* spp.	Duration 10–14 days	**Metronidazol**e 30 mg/kg/d in 2–3 IVL (maximum 1.5 g/day) or **Clindamycin** 40 mg/kg/d in 4 IVL (maximum 2.4 g/day) Duration 10–14 days	
Ethmoiditis ***Essential target of the treatment*** *S. pneumoniae* *H. influenzae* *Peptostreptococcus* *S. aureus* *Fusobacterium Necrophorum*			Even if the bacterial etiologies are identical, antibiotic treatment depends on the severity of the clinical picture and CT imaging. The Chandler-Hubert classification defines 5 stages of increasing severity: Stage 1: Inflammatory eyelid edema, with or without orbital edema.Stage 2: Subperiosteal abscess, (a) with edema of the eyelids and orbit, (b) spread of pus to the eyelids. Stage 3: orbital abscess.Stage 4: orbital cellulitis, (a) severe, (b) mild.

(*continued on next page*)

Table 2 (*continued*)

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contraindicated preferred treatment)	Comments
Minor pre-septal forms (Chandler-Hubert Stage 1) **Ethmoiditis usual forms** (Chandler-Hubert Stages 2 and 3)	**Amox/clav** (oral) 80 mg/kg/d in 3 divided doses (maximum 3 g/day) Duration of treatment 10 days	**Ceftriaxone** (IV or IM) 50 mg/kg/d in 1 daily dose (maximum 2 g/day) Duration of treatment 5 days	Stage 5: Thrombosis of the cavernous sinus. Even if the bacterial etiologies are the same, the use of amoxicillin-amoxicillin in the pre-septal or usual forms is justified by its good microbiological activity and the need to avoid cephalosporins more inductive of extended-spectrum enterobacterales ß-lactamases. However, for stage 4 and 5 forms, the risk of lessened diffusion of clavulanic acid renders preferable the cefotaxime-metronidazole association.
Ethmoiditis (Chandler-Hubert stage 4 and 5) **(Chandler Stage 4 and 5)**	**Amox/clav** (IV) 150 mg/kg/d in 3 divided doses (maximum 4 g/day) or **Cefotaxime** (IV) 200 mg/kg/d 3 or 4 divided doses + **Metronidazole** (IV) 40 mg/kg/d in 3 divided doses Duration of treatment 10 days	**Cefotaxime** (IV) 200 mg/kg/d 3 or 4 divided doses (maximum 12 g/day) + **Metronidazole** (IV) 40 mg/kg/d in 3 divided doses Duration of treatment 10 days	
Acute mastoiditis **Simple form** ***Essential target of the treatment*** *S. pneumoniae* *S. pyogenes*	**Amoxicillin** (IV) 150–200 mg/kg/day in 3 or 4 divided doses (maximum 8 g/day) Duration 10–14 days	**Cefotaxime** (IV) 200 mg/kg/day in 3 or 4 divided doses[6] (maximum 12 g) or **Ceftriaxone** (IV) (75 mg/kg/day) in 1 daily dose (maximum 2 g/day) Duration 10–14 days	The choice of amoxicillin as a first-line treatment is justified by the low proportion of amoxicillin-resistant pneumococci, which was less than 7% in 2022 (ACTIV Data) Duration of treatment must be adapted to clinical and biological evolution.
Acute mastoiditis **Dragging form (>5 days)** **Essential targets of treatment** *S. pneumoniae* *S. pyogenes* *Fusobacterium sp*	**Amox/clav** (IV) 150 mg/kg in 3 or 4 in divided doses (max 4 g/day) Duration 10–14 days	**Cefotaxime** (IV) 200 mg/kg/day in 3 or 4 divided doses (maximum 12 g/day) + **Metronidazole** (IV) 40 mg/kg/d in 3 divided doses (maximum 1.5 g/day) or **Ceftriaxone** (IV) (75 mg/kg/day) in 1 daily dose (maximum 2 g/day) + **Metronidazole** (IV) 40 mg/kg/d in 3 divided doses	
Acute mastoiditis **Complicated form (neurological damage, thrombosis**)	**Cefotaxime** (IV) 200 mg/kg/d 3 or 4 divided doses (max 12 g/day) + **Metronidazole** 40 mg/kg/day in 2–3 IVL (max 1,5 g/day)	Advice on Pediatric Infectious Diseases is required	

Table 2 (*continued*)

Clinical situations and *Bacteriological target*	Recommended regimens	Alternatives (contraindicated preferred treatment)	Comments
Epiglottitis **Essential targets of treatment** *S. pneumoniae* *H. influenzae* serotype b	**Cefotaxime** (IV) 200 mg/kg/d 3 or 4 divided doses Duration 5–7 days (maximum 12 g/day) or **Ceftriaxone** (IV) 50 mg/kg in 1 injection (maximum 2 g/day) Duration 5–7 days	Advice on Pediatric Infectious Diseases is required	
Bacterial laryngotracheobronchitis **Essential targets of treatment** *S. aureus S. pneumoniae* *S. pyogenes*	**Amox/clav** (IV) 100–150 mg/kg in 3 divided doses followed by oral relay	**Cefazolin** (IV) 100 mg/kg in 3 divided doses followed by oral relay	A rare disease, it is an infection of the trachea causing dyspnea and stridor. Most children have symptoms of viral respiratory infection for 1–3 days before severe symptoms appear. Diagnosis is based on clinical, laryngoscopy and/or imaging. In addition to antibiotics, treatment is based on airway control.
Acute bacterial parotitis of the newborn (no meningitis) *Streptococcus agalactiae (Group B Streptococcus)* *SASM*	**Amox-clav** (IV) 100–150 mg/kg in 3 divided doses + **Gentamicin** 5 mg/kg/day in one IV (30 minutes) for 48 hours if **septicemic** form Duration of treatment 10 days		

Table 3
Oral relay according to the molecule initially administered in IV.

Initial antibiotic	Oral relay
– - Amoxicillin: 150–200 mg/kg/day in 3–4 IVL	– - Amoxicillin: 100 mg/kg/day in 3 doses
– Amox/clav: 150 mg/kg/day IV in 3–4 divided doses	– Amox/clav: 80 mg/kg/day in 3 divided doses.
– Cefotaxime: 200 mg/kg/day IV in 3–4 divided doses.	– Amox/clav: 80 mg/kg/day in 3 divided doses
– or Ceftriaxone: 75 mg/kg/day in 1 IVL	– Penicillin allergy: Cefalexin*: 100 mg/kg/day in 3 divided doses Cefpodoxime-proxetil**: 8 mg/kg/day in 2 divided doses**
– Clindamycin: 40 mg/kg/day in 3–4 IVL	– Clindamycin: 30–40 mg/kg/day in 3 divided doses
– Metronidazole: 40 mg/kg/day in 2–3 IVL	– Metronidazole: 40 mg/kg/day in 3 doses.

IV: Intravenous.
* Target spectrum restricted to Gram-positive cocci (SGA, SAMS) possible cross-allergy with penicillin (to be avoided in case of severe allergy and in the absence of allergological exploration).
** No activity on *S. aureus* even meti-S.

it cannot be ruled out that these favorable trends be reversed in the coming years [10,11]. The therapeutic choices proposed in this manuscript are in line with the latest GPIP-SFP-SPILF recommendations, which were adopted in the 2021 HAS guidelines [6,7].

As for PAOM complicated by otorrhea or cervical lymphadenitis, GAS-RADT is recommended. In extra-pharyngeal infections as well, studies have shown excellent sensitivity and specificity and justify GAS-RADT. When antibiotic therapy seems called for, it is possible prescribe a narrow-spectrum compound targeting GAS only [12–14].

The COVID-19 pandemic and the non-pharmaceutical interventions (NPIs) imposed so as to control SARS-CoV-2 spread have had dramatic impacts on epidemiology in many ambulatory pediatric infectious diseases, including URTI (Upper respiratory tract infections). When NPIs were massively applied, sharply decreased URTI frequency was observed, but after the relaxation of COVID-related restrictions, extensive "COVID rebound" was reported [15,16]. The changes concerned not only incidence or frequency, but also the distribution of pathogens in different clinical situations [13,17].

Severe ENT infections (mastoiditis, epiglottitis, retro- and parapharyngeal abscesses, ethmoiditis) represent therapeutic emergencies that most often justify hospitalization and intravenous (IV) antibiotics [14,18]. No data are available on the recommended duration of treatment for these severe forms. That said, total duration of 10–14 days, depending on the initial severity and the rapidity of therapeutic response, seems reasonable by extrapolation from other clinical situations. An oral relay may reduce hospitalization duration when certain conditions are met: clear clinical improvement in fever, pain and local signs; markedly reduced biological inflammatory syndrome. These clinical and biological objectives are generally achieved after 2–5 days of initial IV treatment. If this is not the case, a medical-surgical re-evaluation of the situation must be considered in view of identifying a complication (an abscessed focus…).

As regards ambulatory ENT infections, Table 1 presents, in different clinical situations: the pathogens most often involved (targets of antibiotic treatment), the preferred choice of treatment and the alternatives in case of contra-indication (allergy…).

As regards serious ENT infections requiring hospitalization, Table 2 likewise presents, in different clinical situations: the pathogens most often involved (targets of antibiotic treatment), the preferred choice of treatment and the alternatives in case of contra-indication (allergy, etc.).

Table 3 presents the proposed oral relays according to the compounds initially administered by intravenous (IV) route.

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Review

Antimicrobial treatment of lower respiratory tract infections in children

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ABSTRACT

Lower respiratory tract infections (LRTI) encompass a wide range of clinical syndromes, prominently including bronchiolitis, bronchitis and pneumonia. LRTIs are the second leading cause of antibiotic prescriptions. The vast majority of these infections are due to (or triggered by) viruses and are self-limited diseases. Pneumonia in children is responsible for significant morbidity and mortality worldwide. For clinicians, one of the main difficulties consists in diagnosing pneumonia in febrile children with (or without) cough. The diagnosis is given on the basis of anamnesis, clinical examination and (if necessary) complementary examinations, with chest X-ray or thoracic ultrasound; biological markers are particularly important. Over recent years, since the implementation of PCV13, the bacterial epidemiology of pneumonia and empyema has evolved; involvement in these diseases of pneumococcus has been reduced, and resistance to penicillin has lessened – and remained extremely low. In 2021, according to the National Pneumococcal Reference Center, only 6% of the strains isolated from blood cultures in children are resistant to amoxicillin. The therapeutic choices proposed in this article are in full compliance with the previously published official French recommendations.

Lower respiratory tract infections (LRTIs) are a major cause of outpatient antibiotic treatment in children and adults alike. Between 2015 and 2018, "febrile coughs" (presumed viral respiratory infections) topped the list of antibiotic prescriptions [1]. The vast majority of these are viral in origin (or triggered by viruses) and their natural course most often leads to spontaneous recovery. Non-prescription of antibiotics in cases of bronchitis or bronchiolitis was the initial message of the recommendations published as early as 2005 by the French National Agency for the Safety of Medicines and Health Products (ANSM) [2] and the GPIP antibiotic guide published in 2017 [3]. However, some lung infections call for urgent diagnosis and antibiotic treatment.

Pneumonia is a source of significant morbidity and mortality worldwide. While the number of deaths due to pneumonia in 2015 was estimated at 921,000 children under 5 years of age [4], their overall incidence in children between 2000 and 2015 decreased by one third, and by 22% following the introduction of pneumococcal conjugate vaccines [4]. Utilization starting in 2000 of the 13-valent pneumococcal conjugate vaccine (PCV13) has reduced not only the overall incidence of pneumonia and empyema, but also the role of pneumococci [5,6]. In addition, pneumococcal stains have become less resistant to antibiotics, particularly penicillin and macrolides, a development explaining changes in choices of antibiotics for infections such as pleural empyema [7]. Furthermore, vaccination programs have modified distribution of the agents implicated in pleural empyema and pneumonia.

In addition to the impact of PCV13, non-pharmaceutical interventions (NPIs) coinciding with the Covid-19 pandemic led to dramatically decreased incidence of lower respiratory infections in children, particularly pneumonia [8]. Due to the NPIs necessary to control the pandemic, viral and bacterial respiratory infections

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Table 1
The different clinical situations and the bacterial species most often involved (main targets of antibiotic treatment), the preferred antibiotic choice, and alternatives in case of contra-indications of the first-line antibiotics, mainly due to allergy.

Clinical situation	Preferred antibiotics	Alternatives	Comments
Community-acquired pneumonia Main antibiotic targets: *S. pneumoniae*	**Amoxicillin** (oral) 80 to 100 mg/kg/d in 2 divided doses maximum 3 g/day Duration of treatment 5 days	**Ceftriaxone** (IV or IM) 50 mg/kg/d in 1 injection maximum 2 gr/day Duration of treatment 5 days All oral alternatives to amoxicillin or ceftriaxone induce a loss of chance for the patients whether macrolides (clarithromycin or clindamycin: at least 20% of pneumococcal resistant strains), oral third generation cephalosporins, cotrimoxazole or doxycycline (resistant strains and or unfavorable pharmacokinetic-pharmacodynamic parameters)	Efficacy criteria: rapid apyrexia (≤48 hours). If not, look for a complication (para-pneumonic effusion, abscess, empyema) or an atypical germ infection. Based on data from the National Pneumococcal Reference Center in 2021, 6% of strains isolated from blood cultures in children are resistant to amoxicillin (MIC > 2 mg) At least 4 studies have compared 5 to 10 days of ß-lactam (mainly amoxicillin in 3 or 2 doses per day) validating a duration of 5 days [24,25,26,27]
Atypical community-acquired pneumonia Main antibiotic targets: *Mycoplasma pneumoniae* *Chlamydia pneumoniae*	**Clarithromycin** (oral) 15 mg/kg/day in 2 divided doses maximum 500 mg x2/day Duration of treatment 5 days	**Azithromycin** (oral) if pneumococcus unlikely 20 mg /kg/d in 1 daily dose Duration of treatment 3 days **Doxycycline** (oral) 4 mg /kg/d in 2 divided doses the first day then 2 mg /kg/d in 1 dose for the following 4 days (maximum 200 mg the first day then 100 mg/day for 4 days) Duration of treatment 5 days	Discuss diagnosis when faced with: -Progressive symptom manifestation -Good general condition –No elevation of CRP or pro-calcitonin -Failure of amoxicillin -Absence of pleural effusion Viruses are the most common causes. The etiologic diagnosis of mycoplasma infections is difficult. Apyrexia slower than in pneumococcal pneumonia (3 to 4 days). Cross-allergy between macrolides is rare. Before prescribing clarithromycin: observe contraindications and drug interactions. The only two macrolides currently available in France are Clarithromycin and Azithromycin. Azithromycin is one of the so-called "critical" antibiotics because its very long half-life makes it more likely to induce bacterial resistance. Therefore, except in situations where Azithromycin is essential, clarithromycin is preferred. Tetracyclines, in principle, are contraindicated before the age of 8 years because of the risk of permanent staining of the teeth. Recent data show that this risk is not shared by doxycycline at usual doses and for treatments < 3 weeks.
Swallowing or inhalation pneumonia Main antibiotic targets: *S pneumoniae* Anaerobes (*Fusobacterium, Peptostreptococcus, Bacteroides*)	**Amox-clav** 80 mg/kg/d (oral) 100 mg/kg/d (IV) in 3 divided doses (every 8 hours) maximum 3 to 4 gr/day Duration of treatment 7 days	**Ceftriaxone** 50 mg /kg/d in 1 IV or IM maximum 2 gr/day + **Metronidazole** (IV) 30 mg /kg/d in 3 divided doses Duration of treatment 5 days	If the fever persists, an abscess or empyema should be considered.
Bronchiolitis Viruses (mainly RSV)	**No antibiotics**		
Bronchitis Virus	**No antibiotics**		
Protracted bacterial bronchitis (PBB) Main antibiotic targets: *Haemophilus influenzae* *S. pneumoniae* *Moraxella catarrhalis*	**Amox-clav** (oral) 80 mg /kg/d In 3 divided doses Duration of treatment 2 weeks	**Cotrimoxazole** (oral) 30 mg/kg/d of sulfamethoxazole in 2 divided doses maximum 1.6 gr/day Duration of treatment 2 weeks	Defined by [28,29]: (1) Presence of a continuous chronic wet and/or productive cough (>4 weeks duration) with no tendency to improve. (2) Absence of functional or clinical signs suggestive of another cause. (3) Cough resolving after 2–4 weeks of appropriate oral antibiotic therapy. The clinical respiratory examination is usually normal. Paraclinical investigations should include at least one chest radiograph. The diagnosis of PBB is usually made in young children (<5 years). Daycare and presence of tracheobronchomalacia are risk factors. Some children will have recurrences (>40%). They should receive new courses of antibiotic therapy after a pneumo-pediatric opinion.
Pleural-empyema or Pleuropneumopathy (before microbiological identification without elements of gravity) Main antibiotic targets:	**Amox-clav** (IV) 150 mg/kg/d In 3 divided doses Oral relay and total duration according to clinical evolution 2 to	**Cefotaxime** (IV) 200 mg /kg/d In 3 divided doses Oral relay and total duration according to clinical evolution 2 to 6 weeks	The signs of severity are: - hemoptysis - leukopenia - Toxic signs (rash, necrosis) - septic shock Pleural puncture should be performed whenever

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
S. pneumoniae *S. pyogenes* (or group A streptococcus) *S. aureus* Meti-S (SASM)	6 weeks		possible for bacteriological documentation after a pulmonary ultrasound. Microbiological diagnosis can be made in more than 2/3 of cases if culture, Binax® and/or PCR on pleural fluid are associated. Because of the widespread use of Prevenar 13®, decreased pneumococcal resistance to amoxicillin (<6% in 2021) does not justify C3Gs as first-line therapy.
Pleural empyema due to *S. pneumoniae* *S. pyogenes* (SGA)	**Amoxicillin** (IV) 150–200 mg/kg/d in 3 divided doses Oral relay and total duration according to clinical evolution 2 to 6 weeks	**Cefotaxime** (IV) 200 mg/kg/d in 3 divided doses Oral relay and total duration according to clinical evolution 2 to 6 weeks	Oral Relay: **Amoxicillin** 80 to 100 mg/kg/d in 3 divided doses
Pleural empyema due to *S. aureus* Meti-S (SASM)	**Cloxacillin** (IV) 200 mg/kg/d in 4 divided doses maximum 12 gr/day Oral relay and total duration according to clinical evolution 2 to 6 weeks	**Cefazolin** (IV) 100 mg/kg/d in 3 divided doses maximum 6 g/day Oral relay and total duration according to clinical evolution 2 to 6 weeks or **Cefuroxim**e (IV) 100 mg /kg/d in 3 divided doses maximum 6 g/day Oral relay and total duration according to clinical evolution 2 to 6 weeks	Oral Relay: **Amox-clavulanate** 80 to 100 mg/kg/d in 3 divided doses **Cefalexin** 50 mg/kg/d in 2 divided doses maximum 2 g/day Exceptional cross-allergy between C2G/C3G and amoxicillin
Pleural empyema due to *S. aureus* Meti-R (MRSA)	**Vancomycin** (IV) 60 mg/kg/d* in 4 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses or **Rifampicin** (IV) 30 mg/kg/d in 2 divided doses	**Linezolid** 29d-11 years: 30 mg/kg/d oral or IV in 3 divided doses maximum 600 mg/dose	Use of the new anti-gram positive molecules is contingent on the advice of a pediatric infectious disease specialist: Ceftaroline Tedizolid Dalbavancin Daptomycin
Pneumonia or pleural empyema with signs of severity Before bacteriological documentation Main antibiotic targets: *S. aureus* Meti-S *S. aureus* Meti-R *S. pyogenes* (SGA)	**Amox-clavulanate** (IV) 150 mg /kg/d in 3 divided doses + **Vancomycin** (IV) 60 mg/kg/d* in 4 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses	**Cefotaxime** (IV) 200 mg/kg/d in 3 divided doses + **Vancomycin** (IV) 60 mg/kg/d* in 4 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses	The signs of severity are: - hemoptysis - leukopenia - Toxic signs (rash, necrosis) - septic shock Association with an antibiotic with anti-toxinic action is imperative. Drainage essential if pleural effusion. + Resuscitator and pediatric infectious disease specialist opinion.
Severe Panton and Valentine toxin-secreting *S. aureus* pneumonia or pleuropneumonia (PVL +) Meti-S	**Cloxacillin** (IV) 200 mg/kg/d in 4 divided doses + **Clindamycin** (IV) 40 mg /kg/d in 3 divided doses	**Cefazolin** (IV)100 mg/kg/din 3 divided doses maximum 6 g/day Oral relay and total duration according to clinical evolution 2 to 6 weeks or **Cefuroxim**e (IV)100 mg /kg/din 3 divided doses maximum 6 g/day + **Clindamycin** (IV) 40 mg/kg/d in 4 divided doses OR **Linezolid** 29 days-11 years: 30 mg/kg/d oral or IV in 3 divided doses >12 years: 1200 mg in 2 divided doses maximum 600 mg/dose	Discuss IV Ig (2 g/kg) in case of shock or severe respiratory distress. Association with an antibiotic with anti-toxinic action is imperative. Pediatric infectious disease specialist advice. The use of other anti-Gram positive compound is contingent on the advice of a pediatric infectious disease specialist: Daptomycin Ceftaroline Tedizolid Dalbavancin
Severe pneumonia or pleural empyema (toxin syndrome) caused by *S. pyogenes* (GAS)	**Amoxicillin** (IV) 150–200 mg /kg/d in 3 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses	**Cefotaxime** (IV) 200 mg/kg/day in 3 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses	Discuss IV Immunoglobulines Ig (2 g/kg) in case of uncontrolled toxic shock Pediatric infectious disease specialist advice required.

(*continued on next page*)

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
Severe Panton and Valentine toxin-secreting *S. aureus* pneumonia or pleuropneumonia (PVL +) Meti-R	**Vancomycin** (IV) 60 mg /kg/d* in 4 divided doses + **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses	**Linezolid** (IV) 29 days-11 years: 30 mg/kg/d in 3 divided doses >12 years: 1200 mg in 2 divided doses maximum 600 mg/dose + **Rifampicin** (IV) 30 mg/kg/d in 2 divided doses	Drainage essential if pleural effusion. The use of other anti-Gram positives is contingent on the advice of a pediatric infectious disease specialist: **Ceftaroline** **Tedizolid** **Dalbavancin**

*Continuous infusion after a loading dose of 15 mg/kg administered intravenously over 30′, or 15 mg/kg every 6 hours administered intravenously over 30′.

became less frequent, leading to "immune debt", with a rebound of these infections, once when these measures were lifted [9]. All told, the introduction and subsequent cessation of NPIs enriched our knowledge of the role of viral and bacterial co-infections in LRTIs, particularly as regards the interactions between pneumococcal infections and those caused by Respiratory Syncytial Virus (RSV), influenza virus or human metapneumovirus [10,11,12]. Lastly, the rise and fall of NPI measures modified the distribution and spectrum of pathogenic agents; more specifically, the relaxation of NPIs was followed by increased respiratory GAS infections, particularly pneumonia and empyema [13]. Monitoring the epidemiology of these infections over upcoming winter periods appears crucial. If in most cases the (difficult) diagnosis of pneumonia in children remains clinical, relevant bacteriological documentation is sparse. Even in cases of genuine pneumococcal pneumonia, blood cultures are rarely positive. Due to false positives associated with frequent nasopharyngeal carriage of pneumococcus in young children, PCR tests specifically targeting pneumococci in the blood are of limited value. Nasopharyngeal multiplex PCR for potential respiratory pathogens is often positive in subjects with no true infections. This is true not only for pneumococcus, but also for mycoplasma and a number of respiratory viruses [14,15]. At present, two main tools are available:

- The first is pulmonary ultrasound, which reinforces a set of diagnostic arguments drawn from case history, clinical examination and biological examinations [16]. This relatively easy, non-irradiating bedside examination has achieved importance in the diagnosis of pneumonia in children [17].
- The second is the rational use of one of the two available biological markers, CRP and PCT [18]. In bacterial infection, PCT increases more rapidly following the onset of symptoms (12 to 24 hours) than CRP (24 to 48 hours), but the latter has the advantage of being performed routinely and, as a micro-method, at a very low cost, and it is now a point-of-care test in several Northern European countries [19,20].

Antibiotic therapy for lower respiratory infections is currently being updated, for the following reasons (Table 1):

- Unavailability of many antibiotics (including most macrolides and oral cephalosporins).
- Emergence of the notion of "critical antibiotics", which are likely to induce bacterial resistance; for respiratory infections, they essentially consist in azithromycin and 2nd and 3rd- generation cephalosporins.
- Disappearance of the contraindication of doxycycline in children undergoing short-term treatment.
- Reduced indication of antibiotic combinations in routine practice.

The therapeutic choices proposed in this article are in line with the previous official French recommendations [3] and those of the 2017 GPIP. Serious pleuropulmonary infections are therapeutic emergencies that more often than not justify hospitalization and intravenous antibiotics [7]. The therapeutic advice set out in this guide takes into close account the epidemiological developments of the bacteria involved, the possible role of toxins when *Streptococcus pyogenes* (pyrogenic exotoxin) or *S. aureus* (Panton and Valentine toxin) are implicated [21,22] and the marketing of recent anti-Gram positive antibiotics. Indications for the latter in the therapeutic arsenal of severe respiratory infections in children remain to be defined [23].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Antimicrobial treatment of urinary tract infections in children

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ABSTRACT

Urinary tract infections are the most frequently proven bacterial infections in pediatrics. The treatment options proposed in this guide are based on recommendations published by the *Groupe de Pathologie Infectieuse de Pédiatrique* (GPIP-SFP). Except in rare situations (newborns, neutropenia, sepsis), a positive urine dipstick for leukocytes and/or nitrites should precede a urine culture examination and any antibiotic therapy. After rising steadily between 2000 and 2012, the proportion of *Escherichia coli* strains resistant to extended-spectrum ß-lactamases (E-ESBL) has remained stable over the last ten years (between 7% and 10% in pediatrics). However, in many cases no oral antibiotic is active on E-ESBL leading either to prolonged parenteral treatment, or to use of a non-orthodox combination such as cefixime + clavulanate. With the aim of avoiding penem antibiotics and encouraging outpatient management, this guide favors initial treatment of febrile urinary tract infections (suspected or actual E-ESBL infection), with amikacin. Amikacin remains active against the majority of E-ESBL strains. It could be prescribed as monotherapy for patients in pediatric emergency departments or otherwise hospitalized patients.

Urinary tract infections (UTIs) are the most frequent proven bacterial infections in children. The prevalence of UTIs is estimated at 7.0% in children under 2 years of age consulting for fever [1]. Usually, a distinction is made between pyelonephritis and cystitis. The former are febrile and/or occur in high-risk patients (neonates, underlying uropathies), expose the patient to complications such as renal scarring, have high biological inflammatory parameters and justify prescription of antibiotics reaching serum pharmacokinetic-pharmacodynamic (PK-PD) parameters enabling treatment of a systemic infection. However, significant proportion of febrile UTIs have normal scans at the time of infection. Nevertheless, all febrile UTIs should be considered "*a priori*" as pyelonephritis and managed as such.

As for cystitis, it typically occurs in girls over 3 years of age, is not accompanied by fever or significant changes in biological inflammatory parameters (if these tests are performed) and does not expose the kidneys to scarring. Even though rare, non-febrile UTIs, with no underlying uropathy and no increase in biological inflammatory parameters, can also occur in boys and girls under the age of 3 years. Unlike febrile UTIs, cystitis requires only antibiotics with urinary concentrations above minimum inhibitory concentrations (MICs). This explains why, for the same antibiotic, breakpoint between febrile and non-febrile UTIs can be different; a strain can be classified on an antibiogram as susceptible for cystitis and intermediate or resistant for pyelonephritis.

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In clinical practice, microscopic analysis with Gram staining and culture should not be performed routinely in febrile infants or children. On the other hand, it should be carried out in those with a underlying condition (newborns, history of underlying uropathy, sepsis neutropenia) and in those with urinary function signs or unexplained fever lasting at least 48 h. A UTI risk calculator from the University of Pittsburgh (Fig. 2), taking into account age, sex, circumcision, duration of fever, history of UTIs and urine dipstick results is available at https://uticalc.pitt.edu/ [2]. In our opinion, it is a very useful tool to select infants for whom a urine cytobacteriological examination is required, and it can even contribute to the choice of urine sampling method.

The diagnosis of UTI may be complex. Pre-test probability varies widely from one child to another [1,2] and the risk of contamination for the least invasive urinary collection methods is high (50–60% for the sterile collection bag and 25% for clean catch midstream versus 10% for urinary catheterization and 1% for suprapubic puncture) [3,4]. Even under optimal sampling conditions, a sterile collection bag may be contaminated by commensal bacteria from the perineum similar to those implicated in UTIs. Aside from special situations (newborns, neutropenia, sepsis. . .), a negative urine dipstick (UD) makes the diagnosis of UTI highly unlikely (negative predictive value >90%) and eliminates the need for UCBE [2,5–7]. A positive UD test (urine dipstick) for leucocytes and/or nitrate) requires confirmation by microscopic analysis with Gram staining and culture.

If the urine sample has been taken from a sterile collection bag, it may need to be checked with another sample, with a lower risk of contamination (clean catch or midstream urine sampling, urinary catheterization or suprapubic puncture), unless the pre-test probability is very high (high positive predictive value if leukocyturia ≥ ++ and nitrites ≥ +). [2,5]. Simple methods such as suprapubic stimulation increase the probability of having midstream urine within 5 min [8,9]. Although rarely used in France, suprapubic puncture is considered the reference method [3,7]. The diagnostic approach must be adapted according to the pre-test probability

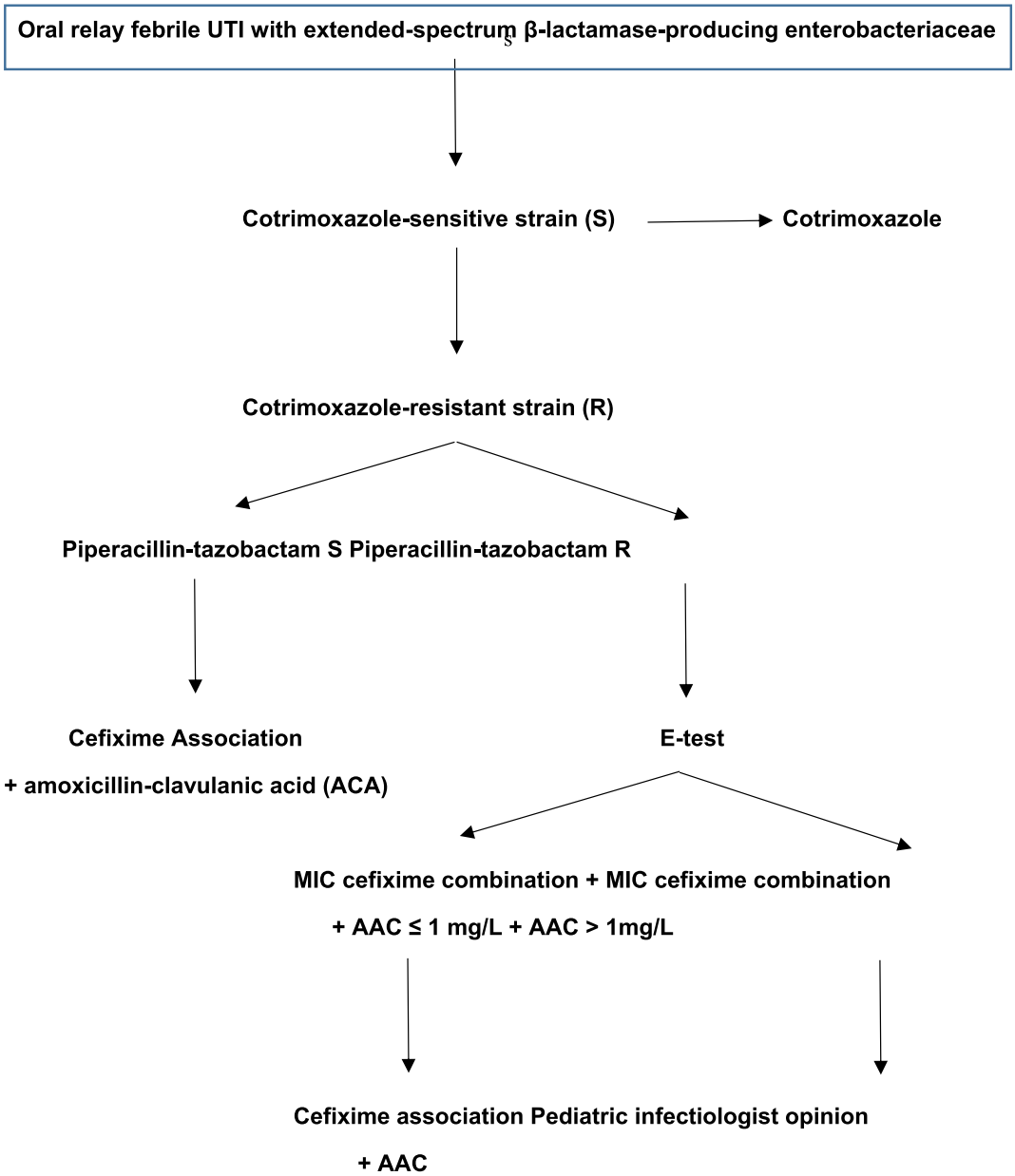

Fig. 1. Decision tree.

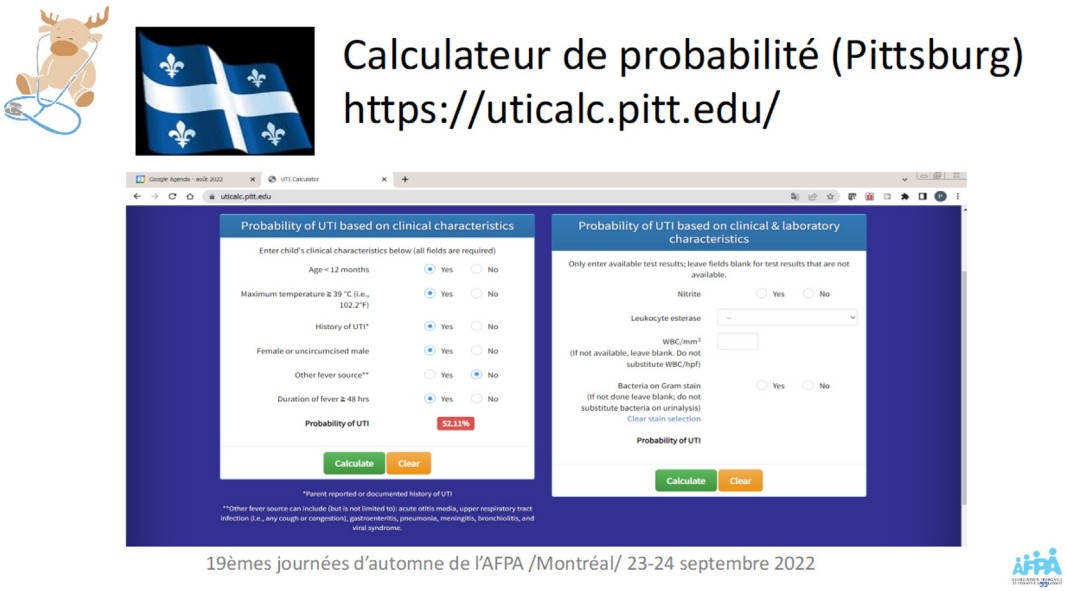

Fig. 2. Probability calculator.

estimate (sex, age, clinical picture, known uropathy, circumcision in boys, history of UTI, existence of a biological inflammatory syndrome…), degree of urgency and local customs [1,2,5]. Antibiotic therapy that is started too quickly can sterilize urine, making it impossible to diagnose UTI with certainty [5]; moreover, the urine sample must be transported rapidly to the laboratory at a suitable storage temperature to avoid the multiplication of contaminating bacteria.

By the oral route, neither amoxicillin nor the amoxicillin-clavulanate (ACA) combination have sufficient PK-PD parameters to consider using them as initial treatment, even on "in vitro" sensitive *E. coli*; the time above MIC does not exceed 20–30%, and an optimal time should be at least 40%. [10]. Some teams use these drugs as a relay treatment when the strain is sensitive.

The majority of febrile UTIs caused by extended-spectrum ß-lactamase (ESBL)-producing enterobacterales become apyretic even though patients are receiving inactive or weakly active antibiotics [11] despite inadequate serum PK-PD parameters. Nevertheless, even if patients are apyretic, there is a consensus to apply an "*in vitro*" active treatment to the strain responsible for the infection.

In France, the proportion of ESBL enterobacterales (E-ESBLs) in childhood urinary tract infections increased significantly from 2009 until 2011, when it stabilized, with prevalence currently below 5% [11–13]. Similarly, the proportion of E-ESBLs rose steadily between 2000 and 2012, and then stabilized between 7% and 10% in pediatrics (unpublished ACTIV data for rectal carriage of E-ESBL: 8.6% in 2020, 10.1% in 2021 and 9.9% in 2022) [14]. This proportion is higher in children who have recently received antibiotics, been treated for a UTI or been hospitalized [15,16]. Stabilization is probably linked to the significant reduction in cephalosporin prescriptions in France since 2011, following the guidelines (GPIP-SFP-SPILF) for treatment of ENT infections, the leading cause of antibiotic prescriptions. Quite often, no oral antibiotic is active on E-ESBL strains. For these reasons, the antibiotic choices proposed in this guide vary according to age, history and place of care (Table 1). In addition, antibiotic prescribing, particularly of "critical" antibiotics (those that are likely to generate bacterial resistance, or "last resort" antibiotics), must be carefully considered. For example, the use of quinolones, which generate resistance and sometimes severe and long-lasting side-effects, should be avoided whenever possible, particularly when the germ's sensitivity is known and there exists an alternative. [16]. For febrile *E. coli* ESBL UTIs, the aim should be to avoid first-line penems in the first instance. Amikacin monotherapy is the first-line treatment frequently recommended in this guide [8,17–20]. In point of fact, amikacin remains by far the most effective aminoglycoside against ESBL, and a single injection (slow IV) per day is sufficient, allowing outpatient treatment for the majority of patients [12]. The other penem-sparing alternatives (temocillin, cefoxitin, piperacillin-tazobactam) all require several injections a day and hospitalization. Finally, due to their low digestive concentrations, aminoglycosides appear to have a limited impact on the intestinal microbiota. Because of their efficacy and long half-life in renal parenchyma, some teams propose a 5-day treatment without oral relay, but there are no clinical studies confirming the efficacy of this treatment regimen.

E-ESBLs are generally resistant to all parenteral and oral third-generation cephalosporins. For over 10 years, following the first studies carried out in France, the addition of clavulanic acid to cefixime has been shown to restore the activity of this molecule "*in vitro*", at MIC levels comparable to non-ESBL-producing strains. [21]. In the case of UTIs caused by ESBL-producing *E. coli*, various clinical studies have confirmed the efficacy of the combination as a relay treatment [12,22]. Unfortunately, there is no marketed clavulanic acid without amoxicillin (the AAC combination should be prescribed), and there is as yet no randomized prospective study. Given the unconventional nature of the combination, before prescribing this treatment it is advisable to check the sensitivity of the strain using the double E-test technique. Recent data show an excellent correlation with susceptibility to piperacillin-tazobactam [22]. A study carried out at the associate *E. coli* National Reference Center at Robert Debré Hospital on 220 strains of E-EBSLs, showed in 99% of cases a correlation between piperacillin-tazobactam sensitivity and the cefixime + clavulanic acid combination (unpublished data). This study suggests that in cases of proven piperacillin-tazobactam resistance, an E-test should be systematically performed before cefixime + clavulanic acid can be prescribed (25% of strains remain sensitive to cefixime + clavulanic acid, even in cases of piperacillin-tazobactam resistance). Restrictions on the

Table 1
Treatment of urinary tract infections in children (excluding newborns).

Clinical situations	Preferred antibiotics (Initial probabilistic treatment)	Allergy alternatives	Comments
Febrile urinary tract infection (probable pyelonephritis) Target bacteria: *E. coli* Other bacteria - *Proteus* - *Klebsiella* - Enterococcus - *Staphylococcus saprophyticus*	**Hospitalized patients (1)** **Cefotaxime IV** 150 mg/kg/day In 3 divided doses Maximum 6 g/d or **Ceftriaxone** (IV or IM) 50 mg/kg/day in one injection Maximum 2 g/d + **Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d **Outpatients** **Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d or **Ceftriaxone** IV or IM 50 mg/kg/day in one injection Maximum 2 g/d or **Cefixime** oral **(3)** 8 mg/kg/day In 2 divided doses Maximum 400 mg/d **Caution if Gram-positive cocci on direct examination** **Amoxicillin IV** 100 mg/kg/day In 3 divided doses Maximum 3 g/d + **Gentamicin** IV 5 mg/kg/day in one IVL injection (30 minutes) Maximum 320 mg/d	**Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d **Teicoplanin** IV or IM 10 mg/kg every 12 hours 3 times, then 10 mg/kg/d	(1) Hospitalization is recommended for children aged < 3 months or suspected of sepsis, or with known severe uropathy. (2) After verification of normal renal function. (3) Due to a higher percentage of resistance than injectable C3Gs and modest PK-PD performance, initial treatment with cefixime should be reserved for patients at low risk of renal scarring: - Age >3 months - No underlying uropathy - No sepsis - Low PCT level - Good compliance, no vomiting, possibility of reconsulting if necessary Initial treatment is prescribed for a period of 2 to 4 days, which generally corresponds to both apyrexia and antibiotic susceptibility test (AST) results. Total duration of treatment (IV + per os) is 10 days. Before one month of age, prefer cefotaxime. Oral relay should be adapted according to the antibiotic susceptibility with, in order of preference: 1) Cotrimoxazole (>1 month) 30 mg/kg/d sulfamethoxazole, in 2 doses 2) Cefixime 8 mg/kg/d in 2 doses 3) Amoxicillin if infection with sensitive Enterococcus or *Proteus sp.* For *E. coli*, amoxicillin is used by some teams. However, the serum PK-PD performance of amoxicillin on *E. coli*, even when sensitive, is modest (20 to 30% of the time above the MIC). 4) Cefixime + amoxicillin-clavulanic acid combination for cotrimoxazole-resistant E-ESBL (see Fig. 1: decision tree) Quinolones should be avoided whenever possible as initial or follow-up treatment. -If an E-test is not possible, or if the strain is resistant to piperacillin-tazobactam, several options are available (after consulting an infectiologist): ● Oral relay with quinolones if sensitive strain (+sensitive nalidixic acid) ● Amikacin 5 days total ● Temocillin if S strain ● Cefoxitin if S strain For ESBL enterobacterales, some teams use amikacin for 5 days if there is no alternative for an oral relay (due to its long half-life in renal parenchyma and urine).
Non-febrile urinary tract infections (Cystitis) Target bacteria *E. coli* Other bacterial etiologies - *Enterococcus* - *Proteus* - *Klebsiella* - *Staphylococcus saprophyticus*	Before antibiotic susceptibility test **Amox/clav** oral (4) 80 mg/kg/d In 2 divided doses Maximum 3 g/d **(5 j)** If pubescent girl **Fosfomycin (5)** 1 sachet of 3 g 1 single oral dose	**Cotrimoxazole oral** 30 mg/kg/day sulfamethoxazole In 2 divided doses Max 1.6 g/d or **Cefixime** oral 8 mg/kg/day In 2 divided doses Max 400 mg/d **(5 j)**	(4) For Amox/ac. clav, the daily dose should be halved (e.g. for a 15 kg child: 1 and ½ doses every 12 hours). (5) in the absence of underlying uropathy. Hygiene advice must be combined with antibiotic treatment. If the clinical course of Amox/ac.clav is favorable, there is no need to modify the treatment according to the antibiotic suceptibility. High and prolonged concentrations of clavulanic acid in urine, which inhibits the majority of ß-lactamases, explains why critical concentrations for high and low urinary tract infections are different. The same *E. coli* may be classified as sensitive to the amoxicillin-clavulanic acid combination for cystitis and resistant for pyelonephritis. If the disease progresses unfavorably on Amox/ac. clav, the treatment must be modified according to the antibiotic suceptibility test and the order of preference according to sensitivity: - Cotrimoxazole - Cefixime NB: *Staphylococcus saprophyticus is naturally resistant to fosfomycin.*
Urinary tract infections due to - *Pseudomonas sp* - Highly resistant bacteria - Carbapenemase-producing bacteria - Glycopeptide-resistant enterococci Complicated urinary tract infections: abscesses, lithiasis…		Pediatric infectious disease specialist advice required	
Prostatitis		Pediatric infectious diseases specialist advice required	
Urethritis		Refer to adult recommendations	

IV: Intravenous; IM: Intra-muscular; IVL: Intravenous slow; PO: Oral; Amox-ac. clav: Amoxicillin-clavulanic acid combination.

use of quinolones mean that this combination should be prescribed preferentially as a relay treatment in cases of cotrimoxazole-resistant *E. coli* ESBL infection.

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Review

Anti-infective treatment of gastro-intestinal tract infections in children

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ABSTRACT

Gastroenteritis is most often viral in origin and *Rotavirus* and *Norovirus* most frequently implicated in young children. Stool-based multiplex Polymerase Chain Reaction (PCR) can detect bacteria, viruses or parasites that may or may not be responsible for gastroenteritis (colonization). While the etiological profile of these digestive infections has greatly benefited from PCR, in the absence of underlying pathologies the presence of potential pathogens does not justify anti-infectious treatment. Indeed, very few bacterial causes require antibiotic treatment, apart from shigellosis, severe forms of salmonellosis and a few *Campylobacter sp.* infections. The development of antibiotic resistance in *Salmonella* sp., *Shigella* sp. and *Campylobacter* sp. is a cause for concern worldwide, limiting therapeutic options. The antibiotics proposed in this guide are in line with the joint recommendations of *the European Society of Pediatric Infectious Diseases* and *the European Society of Pediatric Gastroenterology and Nutrition*. Azithromycin is preferentially used to treat infections with *Shigella sp.* or *Campylobacter sp.* Ceftriaxone and ciprofloxacin are recommended for salmonellosis requiring antibiotic therapy. Empirical treatments without bacterial identification are not indicated except in cases of severe sepsis or in subjects at risk (e.g., sickle-cell disease). Metronidazole should be prescribed only for acute intestinal amebiasis after microbiological confirmation.

1. Bacterial diarrhea

Gastroenteritis in children is most often of viral origin (mainly *Rotavirus* and *Norovirus*). Children with gastroenteritis generally do not require etiological investigation or antibiotic treatment. However, in particular circumstances, microbiological examinations are necessary for diagnosis and treatment: children suffering from underlying chronic conditions (immunodepression, oncological diseases, inflammatory diseases of the digestive tract…), those whose specific clinical situation (dysenteric syndrome, septic state, return from overseas travel, contact with a confirmed shigellosis, suspicion of collective food poisoning) or those with prolonged symptoms for whom specific treatment is envisaged.

Stool-based multiplex Polymerase Chain Reactions (PCR) detect bacteria, viruses or parasites. While these techniques strongly contribute to etiological diagnosis (ease, speed, specificity), many of the pathogens implicated in gastroenteritis are also found in healthy subjects: results must therefore be interpreted with caution [1]. Among patients suffering from gastroenteritis due to a bacterial species, only those with proven shigellosis should systematically receive antibiotics, even in mild forms, whatever the *Shigella* species, including *S. sonnei* and *S. boydii*, which are considered less severe [2,3].

Patients suffering from typhoid fever (*S. typhi, S. paratyphi* A, B or C) should also receive antibiotics. Infections caused by other Salmonella species, the most common in France, should only be treated in cases of severe disease or in patients (newborns and infants < 3 months, sickle cell disease, congenital or iatrogenic immune deficiency) at risk of developing invasive salmonellosis or secondary foci. Antibiotic treatment, usually parenteral, is

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Table 1
Antibiotic treatment of bacterial gastroenteritis.

Clinical situation	Preferred antibiotics	Alternatives	Comments
Salmonella	Antibiotics usually not necessary		Antibiotics do not shorten carriage or the duration of symptoms. However, bacteremia, prolonged fever or persistent diarrhea may require antibiotic treatment.
Antibiotic therapy recommended if: -*S. typhi* and *paratyphi* - < 3 months - Sepsis - Sickle cell disease or immunodepression - Bacteremia	**Ceftriaxone** (IV or IM) 50 mg/kg/day in one injection Maximum 2 g/d (3 to 5 days)	**Azithromycin** (oral) 20 mg/kg/d in 1 daily dose Max 500 mg / day (3 d) Or **Ciprofloxacin** IV 20 mg/kg/d In 2 divided doses or Oral 30 mg/kg/d In 2 divided doses Max. 1500 mg/d (3 to 5 days)	
Shigella	**Azithromycin** (oral) 20 mg /kg / d in 1 daily dose Max 500 mg / day (3 days)	**Ciprofloxacin** Oral 30 mg/kg/d In 2 divided doses Max. 1500 mg/d (3 days) **Ceftriaxone** (IV or IM) 50 mg/kg/d in one injection Maximum 2 g/d (3 days)	Any diagnosed shigellosis must be treated, even if the diarrhea is apparently trivial.
Campylobacter jejuni	**Azithromycin** (oral) 20 mg /kg /d in 1 daily dose (3 d) Max 500 mg / day (3 days)	**Clarithromycin** (oral) 15 mg/kg/d in 2 divided doses maximum 1000 mg / day Duration of treatment 5 days or **Ciprofloxacin** (oral) 10––15 mg/kg in 2 divided doses Max 1500 mg/d (3 days)	Antibiotics are not indicated if the patient is asymptomatic or pauci-symptomatic at the time of the culture result.In the first 3 days, antibiotics shorten carriage and duration of the disease.
Yersinia enterolytica and pseudo-tuberculosis	**Cotrimoxazole** (oral) 30 mg / kg / day of Sulfamethoxazole in 2 divided doses (maximum 1600 mg / day)	**Ciprofloxacin** (oral) 30 mg/kg/d in 2 divided doses Max 1 000 mg/d OR **Ceftriaxone** (IV) 50 mg/kg/d In one injection OR **Cefotaxime** (IV) 150 mg/kg/d In 3 divided doses OR Doxycycline (oral) 4,4 mg/kg/d In one daily dose	Healthy children with enterocolitis can be treated symptomatically. Even if the clinical benefit of antimicrobial therapy has not been established for immunocompetent patients with enterocolitis, pseudo-appendicitis syndrome, or mesenteric adenitis, treatment helps to decrease the duration of shedding. Neonates, immunocompromised persons and all patients with septicemia or extraintestinal disease require treatment. Parenteral 3GC is appropriate, and evaluation of cerebrospinal fluid should be performed in infected neonates.

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
Clostridium difficile (Search for toxins A& B)	**Metronidazole** (oral) 30 mg / kg / day in 3 divided doses Max 1.5 g/d (10 d) Discontinuation of antibiotics having contributed to the episode of *C. difficile infection* whenever possible	**Vancomycin** (oral) 40 mg / kg / day in 4 divided doses (10 d)	Carriage of *C. difficile,* including toxin-secreting strains, is very common in young children. Symptoms are not systematically linked to the presence of this germ. The presence of toxins has no diagnostic value before the age of 2–3 years, except in cases of intestinal obstruction. After this age, interpretation should be based on the clinical context. Asymptomatic patients should not be treated. Stopping anti-microbial trigger treatments is fundamental in the fight against *C. difficile* infections, allowing the intestinal flora to reappear, thereby limiting the development of *C. difficile*. [6,7] Metronidazole is the first- line treatment for moderate forms. Vancomycin is prescribed for more marked forms or in case of non-improvement after 2 or 3 days of treatment. For the most severe forms, metronidazole and vancomycin are prescribed. For recurrent or resistant forms, or in immunocompromised patients, specialized advice is required regarding Fidaxomicin and fecal transplantation.
Moderate forms Severe forms	**Metronidazole + Vancomycin**	Fidaxomicin PO 5 ml (200 mg) × 2 / day from 12.5 kg (before this weight, refer to RCP)	
Helicobacter pylori	**Amoxicillin** 100 mg / kg / day in 2 divided doses **Clarithromycin** 15 à 20 mg / kg / day in 2 divided doses **or** **Metronidazol**e 30 mg / kg / day in 2 divided doses	**Pylera**®* (>12 years) *The Pylera® is a combination of bismuth, tetracycline and metronidazole. In principle, contraindicated before age 12, and always before age 9. Dosage: 3 tablets 4 times a day	Treatment protocol (8): 1) Association with a proton pump inhibitor (PPI) 2) Combination of 2 antibiotics (amoxicillin + one of the other two antibiotics) depending on known or probable sensitivity. Recent treatment with macrolides or resistant strains in close contacts should lead to replacement of clarithromycin by metronidazole. 3) Treatment duration is 14 days. 4) Always check for eradication after treatment (2 to 6 weeks later) and a few months later (respiratory test). In adults with front-off multi-resistant bacteria after several lines of treatment, a simplified treatment combining PPI and high-dose amoxicillin is proposed and is under investigation in children.

essential for *Salmonella* sp. bacteremia. However, antibiotics shorten neither the duration of diarrhea nor the carriage of *Salmonella sp*. In brief, antibiotic treatment in digestive salmonellosis is based above all on clinical diagnosis, in case of poor tolerance of the disease and signs of invasion, or with a terrain at risk of severe forms. Severe *Campylobacter sp.* Infections likewise require treatment, particularly in the initial phase.

The anti-infective choices proposed in this guide (Table 1) are in line with the latest recommendations of *the European Society of Pediatric Infectious Diseases* and *the European Society of Pediatric Gastroenterology and Nutrition* of 2009, updated in 2014 [2]. They also include the pediatric opinions of a working group convened to address indigenous shigellosis in France, taking into account the issue of growing resistance to azithromycin and fluoroquinolones [2]. Azithromycin is the preferred drug for *Shigella sp. and Campylobacter sp*. infections, while ceftriaxone and azithromycin are among the drugs of choice for *Salmonella* infections requiring treatment.

Since 2005, *Shigella* sp. resistance to ampicillin, cotrimoxazole, ciprofloxacin, cephalosporins (ESBL) and azithromycin has increased among both imported and native strains, in 2018 reaching 51%, 85%, 13%, 6% and 20% respectively. [4] In children, resistance to azithromycin appears to be somewhat lower. While gastroenteritis caused by *S. sonnei* or *S. boydii* usually resolves spontaneously, antibiotic therapy can rapidly relieve diarrhea and shorten the duration of bacterial excretion.

Antibiotic resistance affects other species involved in gastroenteritis: *Salmonella* (ampicillin, cotrimoxazole, ciprofloxacin and 3rd-generation cephalosporins) and *Campylobacter* (Fluoroquinolones or ciprofloxacin). Among *Salmonella. spp*. isolated from humans in the European Union, the rate of MDR multidrug resistance is high overall (25.4%), and quite frequently observed in *S. kentucky* (76.6%) and *S. typhimurium* (74.2%) [5].

In severe *Salmonella (*or *Shigella)* infections, It is imperative to take into account antimicrobial susceptibility so as to guide choices of antibiotic therapy. Most *Salmonella* and,to a lesser extent, *Shigella* infections diagnosed in France are autochthonous. Whether or not these are imported pathologies, investigation of the family environment and hygiene measures are essential.

Clostridioides difficile is a Gram-positive, anaerobic bacillus present in normal intestinal flora. Asymptomatic carriage is common in young children (50–70% in infants). The incidence of *C. difficile* infections (often secondary to prior antibiotic therapy) appears to be increasing, but the presence of toxins in stools before the age of 2 is of no diagnostic value (at this age, there is no receptor for the toxin and commensal bacteria of the intestinal microbiota), except in cases of intestinal obstruction [3]. In addition to prior antibiotic therapy, other favorable factors have been identified: proton pump inhibitor treatment, gastrostomy or jejunostomy nutrition, immune deficiency, transplantation and chronic inflammatory bowel disease [6,7].

2. Parasitic diarrhea (Table 2) [8]

Intestinal infection by pathogenic amoebae (*E. histolytica*) most often manifests as dysentery rather than diarrhea. Diagnosis is difficult since microscopic examination of stools cannot differentiate between non-pathogenic *E. dispar and* pathogenic *E. histolytica.* Specialized techniques, including molecular biology, are required. Furthermore, it is possible to be an asymptomatic carrier of *E. histolytica*. Conversely, investigation of digestive disorders may lead to the discovery of non-pathogenic amoebae, which usually do not require treatment. Treatment of intestinal amoebiasis is based on an imidazole, often followed by intra-luminal treatment (most often paromomycin, available only under selective process: Temporary Use Authorization. While *Giardia* infections must systematically be treated, true acute *Giardia* gastroenteritis is rare. In most cases, diarrhea is mild but protracted.

Cryptosporidia can cause diarrhea in immunocompetent children, but often with a spontaneously favorable course. Diagnosis is difficult and requires specific techniques. Severe forms may occur in immunocompromised patients. There is no well-defined treatment. Nitazoxanide is effective but not available in France. Depending on the clinical context, positive PCR results for *Dientamoeba fragilis, Blastocystis hominis* or *Cyclospora cayetanensis* should be taken into account, but anti-parasitic drugs are seldom useful.

Table 2
Treatment of parasitic gastroenteritis [10].

Entamœba histolytica	**Metronidazole** (oral) 30–40 mg / kg / day in 2 or 3 divided doses (7 to 10 days) Maximum 1.5 g/d	**Tinidazole** (oral) 50 mg / kg / day in a single dose (max 1.5 g) (4 to 5 days) or **Ornidazole** (oral) 30 mg / kg/d In 2 divided doses (7 d)	Consider a contact amebicide: Paromomycin ATU 25–30 mg/kg/d in 3 doses (10 d). Always perform stool culture to rule out bacterial causes. In systemic forms of AMOEBIOSIS, METRONIDAZONE is given by IV route
Giardia	**Metronidazole** (oral) 30–40 mg / kg / day in 2 or 3 divided doses (7 to 10 days) Maximum 1.5 g/d	**Tinidazole** (oral) 50 mg / kg / day in a single dose (max 1.5 g) single-shot or **Albendazole** 400 mg/day (5 d) or **Ornidazole** (oral) 30 mg / kg/d In 2 divided doses (5 d)	Repeat treatment if necessary after 10 to 15 days.
Dientamoeba ***Cryptosporidium***	**No treatment**	Nitazoxanide* (ATU)	Immunocompromised* subjects

Table 3
Pediatric intra-abdominal infections [11]. Antibiotic therapy and its duration depend on intraoperative findings.

Acute uncomplicated appendicitis with surgical management	**Amox/ Clavulanate** 50 mg/kg 1 single dose during surgical procedure If preoperative 1 dose > 2 hours, repeat intraoperative dose		
Localized or generalized peritonitis without signs of severity	**Cefotaxime** (IV) 100 mg/kg/day in 3 divided doses for 5 days + **Metronidazole** (IV) 30 mg/kg/day in 3 divided doses for 5 days The duration of treatment is then adjusted according to the severity of the initial symptoms, clinical course and bacteriological results.	**Amox/clav** (IV) 150 mg/kg/d in 3 divided doses for 5 days + **Amikacin** 15 to 30 mg/kg/d 1 IV over 30 min for 2 days The duration of treatment is then adjusted according to the severity of the initial symptoms, clinical course and bacteriological results.	
Appendicitis of delayed diagnosis (false membranes) or Peritonitis with signs of severity or A bscesses/plastrons with surgical management	**Piperacillin-Tazobactam** (IV) 300 mg/kg/day in 4 IV + **Amikacin** (IV) 15 to 30 mg/kg/d IVL over 30 min (in 1 adm/d) for 48 h		
Appendicular abscesses and plastrons without initial surgical management	**Cefotaxime** (IV) 100 mg/kg/day in 3 divided doses for 3 days + **Metronidazole** (IV) 30 mg/kg/day in 3 divided doses for 3 days Followed byAmox/clav (oral) 80 mg/kg/ d in 3 divided doses for 10 to 14 d		Specialized medico-surgical discussion. Hospital follow-up indicated. Compliance with all eligibility criteria and absence of ineligibility criteria. Eligibility criteria: Symptoms > 3 days, mass palpated +/- localized shielding. Abscess and/or plastron on imaging. Ineligibility criteria: Generalized defensiveness, major AEG, hemodynamic disorders, occlusion, poor evolution during follow-up.
Cholecystitis	**Amox/clav** (IV) 150 mg / kg/ day in 3 divided doses max 9 g/d (7 days)		
Angiocholitis	**Ceftriaxone** (IV or IM) 50 mg/kg/day in one injection Maximum 2 g/d + **Metronidazole** (IV) 30 mg/kg/day in 3 divided doses for 5 days **If severe add** + **Amikacin** (IV) 20 mg/kg /d In 30′ infusion for 2 days Total duration 3 days after drainage		

(*continued on next page*)

Table 3 (*continued*)

Acute uncomplicated appendicitis with surgical management	**Amox/ Clavulanate** 50 mg/kg 1 single dose during surgical procedure If preoperative 1 dose > 2 hours, repeat intraoperative dose	
Liver abscess	**Ceftriaxone** (IV or IM) 50 mg/kg/day in one injection Maximum 2 g/d + **Metronidazole** 30 mg/kg/day 3 IVL for 5 days	**Ciprofloxacin** 15 mg/kg/day in 3 IV days + **Metronidazole** If severe + **Amikacin** 20 mg /kg / d In 1 IVL 30 minutes for 2 days

3. Intra-abdominal infections (Table 3) [9]

Most often, these infections complicate an intestinal perforation, bringing the bacteria present in the rich microbiota (enterobacterales and anaerobes, as well as enterococci) into contact with the (normally sterile) peritoneum. The surgical procedure plays a crucial role in the healing process, which explains why studies comparing different therapeutic regimens are usually of limited interest, almost always showing non-inferiority between poorly performing and the most active antibiotics. When antibiotic therapy is indicated, it must be active against both anaerobes and the most common enterobacterales. It can consist in amoxicillin-clavulanate or piperacillin-tazobactam, or else a combination of parenteral 3rd-generation cephalosporin (3GC) associated with metronidazole.

The emergence of extended-spectrum ß-lactamase-producing Enterobacterales (E-ESBL) has remained limited (5–10%), and does not alter therapeutic choices. If an aminoglycoside is indicated, it is preferable to use amikacin according to the activity maintained on most E-ESBLs. However, systematic microbiological sampling (blood cultures, peritoneal fluid) should be performed, the objective being to guide antibiotic therapy in the event of failure.

Each of these therapeutic options has its advantages and drawbacks:

- Amoxicillin-clavulanate has relatively limited activity on Enterobacterales (high minimum inhibitory concentrations and poor PK-PD parameters even on sensitive strains) and should be reserved for less severe infections.
- Piperacillin-tazobactam has extended-spectrum and better PK-PD parameters than amoxicillin-clavulanate. However, for Enterobacterales strains susceptible to 3GC, it is clearly inferior to cephalosporins, leading to the prescription of high doses and, above all, 4 injections per day. Piperacillin-tazobactam remains active on 70 to 80% of E-ESBLs, which is an advantage, but may lead to the emergence of carbapenemase-producing strains.
- Parenteral 3GC, in addition to a lack of activity on enterococci and many anaerobic species (requiring the combination of metronidazole), leads to emergence of E-ESBL.
- Whatever the results of microbiological sampling in community or healthcare-associated peritonitis, the antibiotic spectrum must cover anaerobic bacteria.

The total duration of antibiotic treatment varies widely, ranging from 3 to 15 days according to the clinical picture: initial severity, persistent post-surgery intra-abdominal abscesses...

4. *Helicobacter pylori* infection [10,11]

Several recommendations have been published concerning the management of *Helicobacter pylori (H. pylori*) infection in children [12]. A significant decline in the efficacy of treatment to eradicate this bacterium, due mainly to the emergence of resistant bacterial strains (notably clarithromycin), has led to revision of the previous pediatric recommendations. The new recommendations apply only to subjects under 18 years of age, and only in European and North American countries. To avoid eradication failures and the emergence of bacterial resistance, it is essential to take into account the antimicrobial susceptibility results obtained by culture and/or PC when available, and to insist on good compliance with treatment and post-treatment control of eradication. Satisfactory eradication is achieved only if more than 90% of the prescribed treatment has been taken.

Whole genome sequencing techniques enabling search for the mutations responsible for resistance to antibiotics (clarithromycin, levofloxacin, rifamycin and tetracycline) or for virulence factors (*cagA* gene...) are being developed. In adults, in the presence of when multi-resistant bacteria remain present after several lines of treatment, simplified treatment combining PPI and high-dose amoxicillin is proposed and is under investigation in children.

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Review

Antimicrobial treatment of skin and soft tissue infections

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ABSTRACT

Bacterial skin infections are common in children, and frequently do not require systemic antibiotic therapy, particularly for superficial forms. In these cases, washing (with soap and water) and careful rinsing of the lesion are the key points of treatment. A semiotic analysis must precede any therapeutic decision to assess the appropriateness of antibiotic therapy, need for drainage (which may be spontaneous or surgical) and possible existence of symptoms related to toxin production, which are frequent signs of severity. The bacterial species most frequently implicated in children are *Staphylococcus aureus* and *Streptococcus pyogenes*. Given the low incidence of methicillin-resistant *S. aureus* in France (<10%), the first-line antibiotic treatment is amoxicillin-clavulanate, to which an anti-toxin treatment such as clindamycin may be added for patients with overt toxin signs.

1. Introduction

Skin and soft tissue infections (SSTI) are among the most frequent bacterial infections in children. In 2019, they were the subject of "*Haute Autorité de Santé*" (HAS) guidelines [1]. While the recommendations that follow are in line with these guidelines, they also take into account the unavailability of several compounds in pediatrics (cefadroxil, josamycin...), as well as advances in knowledge and epidemiological trends. Some of the proposed compounds do not have marketing authorization in France for pediatric SSTI. However, they do have marketing authorization for these indications in adults, and for indications in pediatrics other than SSTI, with known dosages and tolerability. In addition, a number of clinical situations were not addressed in HAS guidelines and are included in this guide. Table 1. presents the clinical situation the prefered antibiotic treatments the alternative mainly in case of allergy and the main comments for the situation. Table 2. presents the antiontic choice in case of bites first lines or in case of allergy.

Due to their superficial nature, and even though they are bacterially caused, these infections, frequently do not require antibiotic treatment; washing with soap and, above all, careful rinsing, are highly effective in eliminating the bacteria involved. Washing with a detergent (soap) not only removes scales and crusts, but also destroys the lipids making up the bacterial wall. Similarly, in abscessed lesions, it is the drainage of pus, whether spontaneous or surgical, that will enable healing, rather than antibiotic therapy, which will diffuse very poorly within the pus. In impetigo, local antibiotic therapy should be preferred, as it is effective and has less ecological impact, and does not diffuse the digestive, nasal and oropharyngeal microbiota. Skin infections should not be overlooked, however, as they can develop into extremely serious conditions involving extensive necrotic lesions and/or toxic shock syndrome, with a dreadful prognosis. The skin can also be a gateway for deep-seated infections, particularly staphylococcal.

Despite the visibility of the lesions, the precise diagnosis of skin infections can be difficult, and is even the subject of frequent disagreement between doctors. In this guide, crusty or bullous infections of the epidermis without deep dermal involvement (i.e., erythema no more than 2–3 cm above the lesion) are referred to as impetigo. Simple dermo-hypodermatitis is characterized by variably extensive erythema, sensitive to touch and only slightly

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Table 1
Details the situations necessitates first-line treatment and possible alternatives in case of allergy.

Clinical situation	Preferred antibiotics	Alternatives	Comments
Impetigo Main antibiotic targets: *S. aureus* *S. pyogenes*			Cleaning and detersion are always useful, and often sufficient. Local antibiotic therapy should be preferred wherever possible. Management of underlying dermatoses (Eczema in particular).
- If **localized** impetigo (crusty or bullous) (skin surface < 2%) < 5 lesion sites)	Hygiene care with soap and water and Local Antibiotic with **Mupirocin** 2-3 times/d for 5 to 7 days	Hygiene care with soap and water and Local Antibiotic with **Fusidic acid** 3 times/day for 7 days	72-hour exclusion from school if lesions not covered.
- If impetigo **extensive or deep** (>5 lesion sites) or Extensive or Immunocompromised	**Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) for 7 days	**Cefalexin**[*] (oral) 50 mg/kg/d In 2 or 3 divided doses *(maximum 2 g/day)* for (5 to 7 days) or **Clarithromycin** (oral) 15 mg/kg/d In 2 divided doses (maximum 1 gr/d) for 7 days or **Clindamycin**[**] (oral) 30 mg/kg/d In 3 divided doses (max *2400 mg/d*) for 7 days or **Cotrimoxazole** [***] 30 mg/kg/d Sulfamethoxazole PO In 2 divided doses *(max 1600 mg/day)* *for 7 days*	
"Simple" boils and skin abscesses Main antibiotic targets: *S. aureus* Frequent LPV production (>90% if recurrent)	**No antibiotics** Wet dressings Incision and drainage if necessary	**No antibiotics** Wet dressings Incision and drainage if necessary	Generally, antibiotics are not useful if drainage is correct.

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
High-risk" boils • Size > 5 cm • Associated dermo-hypodermatitis • Systemic S. • Age < 1 year • Co morbidity • Difficult drainage • Face location • No response to initial drainage	Local care (see above) and **Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) for 7 days or **Cefalexin** (oral) 50 mg/kg/d in 2 or 3 divided doses *(maximum 2 g/day)* for 7 days	Local care (see above) and if age < 6 years **Cotrimoxazole**[***] (oral) 30 mg/kg/d PO sulfamethoxazole in 2 divided doses *(*max *1600 mg/day)* for 7 days if age > 6 years[**] **Clindamycin** (oral) 30 mg/kg/d in 3 divided doses (max *2400 mg/d*) for 7 days	Pediatric infectious disease advice for decontamination in recurrent forms. No adaptation if clinical recovery after drainage (even if MRSA).
Paronychia and Blistering Distal Dactylitis [5] Main antibiotic targets: *S. pyogenes* (GAS) *S.* aureus Rapid Antigen Diagnostic Test (RADT) is the cornerstone of treatment	if RADT + **Amoxicilli**n (oral) 50 mg/kg/d in 2 divided doses *(maximum 3 g/day)* for 7 days if RADT- **No antibiotics** Wet dressings +/- Incision + Drainage if necessary	if RADT + **Cefalexin** (oral) 50 mg/kg/d in 2 or 3 divided doses *(maximum 2 g/day)* for 7 days **or** **Clindamycin** (oral) 30 mg/kg/d in 3 divided doses for 7 days (max *2400 mg/d*)	More frequent form of paronychia in childhood. If GAS-RADT is positive, incision and drainage usually unnecessary.
Other Panaritium Bacterial target *S. aureus*	Wet dressings +/- Incision + Drainage if necessary **No antibiotics**		Herpes simplex virus can cause pseudo-paronychia

(*continued on next page*)

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
Dermo-hypodermatitis with no signs of toxins or necrosis Main antibiotic targets: *S. pyogenes* *S. aureus* No risk factors* and no clinical signs of **severity**	**Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) for 7 days	**Cefalexin** (oral) 50 mg/kg/d in 2 or 3 divided doses *(maximum 2 g/day)* for 7 days or If age < 6 years **Cotrimoxazole** 30 mg/kg/d Oral sulfamethoxazole in 2 divided doses *(*max *1600 mg/day)* for 7 days If age > 6 years* **Clindamycin** 30 mg/kg/d Oral in 3 divided doses for 7 days (max 2*400 mg/d*)If IV Route chosen	**Risk factors:** Impaired general condition Age (<1 year) Immunodeficiency Extensive or rapidly progressing lesion Failure of oral antibiotic therapy Presumption of a secondary location (arthritis, etc.) Poor therapeutic compliance
With risk factors or signs of severity	**Amox-clavulanate** (IV) 100 mg/kg/d in 3 IV/day for 2 to 3 days Then rapid oral relay (as soon as clinical improvement occurs)	**Cefazolin** 150 mg/kg/d in 3 IV/day or **Clindamycin** 40 mg/kg/d in 3 or 4 IV/day for 2 to 3 days Then rapid oral relay (as soon as clinical improvement occurs)	
Dermo-hypodermatitis with toxin syndrome Main antibiotic targets: *S. pyogenes* *S. aureus*	**Amox-clavulanate** (IV) 150 mg/kg/d in 3 IV/day **+** **Clindamycin**$ 40 mg/kg/d in 3 or 4 IV/day	**Cefazolin** (IV) 150 mg/kg/d in 3 IV/day + **Clindamycin**$ 40 mg/kg/d in 3 or 4 IV/day	If allergic to cephalosporins Or MRSA Infectiologist's opinion. In case of necrotizing infection: emergency surgical debridement. Specialist advice Adaptation to sampling requirements
Necrotizing fasciitis Main antibiotic targets: *Frequent co-infections with Pseudomonas and/or enterobacteria in necrotizing forms or immunocompromised patients*	**Piperacillin-tazobactam (IV)** 300 mg/kg/d In 4 IV/day + **Clindamycin**[W] 40 mg/kg/d in 3 or 4 IV/day		In case of toxin shock: discuss Polyvalent immunoglobulins Prophylaxis of contact subjects if there is a risk subject in the immediate environment. (https://www.sante.gouv.fr/avis-et-rapports-du-cshpf.html)

Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
Post-surgical dermo-hypodermatitis (abdomen, perineum) Main antibiotic targets: Polymicrobial - *S pyogenes* - *S. aureus* - *Enterobacteriaceae* - *Pseudomonas* - *Anaerobes…*	**Piperacillin-tazobactam** (IV) 300 mg/kg/d In 4 IV/day **+** **Amikacin** 20–30 mg/kg/d in 1 perfusion of 30′ 3 days for 10 to 20 days	**Cefepime** (IV) 150 mg/kg/d **+** **Amikacin** 20–30 mg/kg/d in 1 30′ VILI + **Metronidazole** 30 mg/kg/d in 3 or 4 IV/day for 10 to 20 days	Emergency surgical debridement.
Acute staphylococcal epidermolysis Localized delamination (<20%) Moderate or absent general signs Bacterial target *Staphylococcus aureus* (exfoliatin producer)	**Amox-clavulanate** (oral) 80 mg/kg/d in 2 or 3 divided doses (maximum 3 g/day) for 7 days	**Cefalexin** (oral) 50 mg/kg/d in 2 or 3 divided doses *(maximum 2 g/day)* for 7 days or **Cotrimoxazole**[***] 30 mg/kg/d in 2 divided doses (max *1600 mg/day)* for 7 days	No benefit from anti-toxin treatments No carriage screening No decontamination.
Erythema migrans Main antibiotic targets: *Borrelia burgdorferi*	If < 8 years: **Amoxicillin** (oral) 50 mg/kg/d in 2 or 3 divided doses *(maximum 3 g/day)* for 14 days If > 8 years: **Doxycycline** (oral) 4 mg/kg/d in 2 doses (max *200 mg/day)* for 14 to 21 days	If allergic to penicillin **Doxycycline** (oral) 4 mg/kg/d in 2 divided doses (max *200 mg/day)* **or** **Azithromycin** (oral) 20 mg/kg/d in 1 daily dose (max *500 mg/day)* for 10 days	No systematic treatment for tick bites. See "Bites" table
Perineal (or perianal infection) [6] Main antibiotic targets: *S. pyogenes*	**RADT-** **No antibiotics** **RADT +** **Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) Duration of treatment 10 days	**RADT -** **No Antibiotics** **RADT +** **Cefpodoxime** (oral) 8 mg/kg/d in 2 divided soses *(maximum 400 mg/day)* for 10 days	Systematic anal RADT. Antibiotic treatment only if RADT positive. Penicillin V and amoxicillin give poorer results in terms of recurrence than ß-lactamase-resistant antibiotics

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Table 1 (*continued*)

Clinical situation	Preferred antibiotics	Alternatives	Comments
Folliculitis Main antibiotic targets: *S. aureus*	**No antibiotics**	**No antibiotics**	

$Clindamycin if clinda S and Ery S strains, otherwise Linezolid.
Prescription of doxycycline is possible before 8 years of age for treatment duration < 3 weeks.
* Cross-allergy between penicillin and cefalexin is rare but possible. To be avoided in cases of severe allergy prior to allergological investigation.
** In France, oral clindamycin is available only in tablet form, so can only be administered after the age of 6 years.
*** Cotrimoxazole is likely to cause severe skin reactions (Lyell syndrome) and should therefore be reserved for severe allergies in the absence of therapeutic alternatives. Furthermore, it is not recommended before one month of age.

indurated, whereas necrotizing dermo-hypodermatitis is characterized by highly indurated erythema, with the painful induration often exceeding the size of the erythema, thereby indicating deep-seated extension. Involvement of the deeper layers usually leads to significantly altered vascularization, resulting in necrotic lesions. Signs of deep involvement and necrosis, which are often associated, are always signs of severity. General signs (fever, asthenia) are constant and marked. Finally, the term "cutaneous abscess" designates a well-limited lesion, initially hard and painful, and evolving towards fluctuation reflecting purulent transformation. Abscesses often fistulate spontaneously (untimely manipulation, a source of complications, is not recommended) with the discharge of pus; if the drainage is complete, it is a mode of healing.

The bacteria involved are rarely "true" commensal skin bacterial species (coagulase-negative staphylococci, corynebacteria, *Propionibacterium*) with low virulence. Skin infections are most often caused by two intermittent hosts of the skin, which themselves possess a wide range of virulence factors: *Staphylococcus aureus* (SA) and *Streptococcus pyogenes* or Group A Streptococcus (GAS). However, special care must be taken in immunocompromised children and in cases of particular localization, particularly in the perineal region, where other bacteria may be involved, such as *enterobacterales*, anaerobes or *Pseudomonas*. Aside from these very specific situations, antibiotic therapy should therefore target SA and SGA, which are frequently associated [2]. GAS is consistently susceptible to beta-lactam antibiotics (amoxicillin and cephalosporins) and, more often than not, to macrolides, clindamycin (CNR 2020 data: < 7% macrolide resistance) and cotrimoxazole. However, the tolerance profile of cotrimoxazole is less favorable, with risks of hematological damage (leukopenia) and toxic epidermal necrolysis. Although exceptional, these risks must be weighed against the usefulness of systemic antibiotic therapy, which is essential only in serious infections. Specialist advice is often useful. In France, while the majority (90%) of S. aureus strains are sensitive to methicillin (SASM), they produce a beta-lactamase (penicillinase) responsible for resistance to amoxicillin. These SASM strains are sensitive to M penicillin, first or second-generation cephalosporins, and to amoxicillin-clavulanate. Patients allergic to beta-lactam antibiotics and suffering from MRSA infections can be treated with clindamycin or cotrimoxazole, the latter with the same precautions as above (National Reference Center 2022 data: for MSSA: 15% resistance to clindamycin, 12% to sulfamethoxazole-trimethoprim; for MRSA: 24% resistance to clindamycin, 13% to sulfamethoxazole-trimethoprim). For oral use, amoxicillin-clavulanate, with its excellent pharmacokinetic properties in cutaneous tissue, is the preferred choice for infections necessitating general antibiotic therapy. Oral penicillin M does not meet the predictive pharmacokinetic-pharmacodynamic efficacy criteria, and the only oral cephalosporin available is cefalexin. The choice of a beta-lactam as first-line treatment differs from guidelines from other countries (North America…). This is due to the different bacterial resistance patterns in the US, Canada, and some Mediterranean countries which have dealt with epidemics of community-acquired infections due to methicillin-resistant *S. aureus* (MRSA). The very high incidence of community-acquired MRSA is nevertheless declining in most countries. Except in primary abscesses that heal by drainage, MRSA prevalence is much lower in France (<10%), and is declining, and does not justify first-line use of antibiotics active against MRSA [1–3]. The final point to consider in the treatment of skin infections is whether or not toxin signs and symptoms are present. In fact, both *S. pyogenes* and *S. aureus* are able to produce large quantities of exotoxins, which may have local necrotizing properties, one example being such as Panton and Valentine leukocidin (PVL), or superantigenic properties (responsible for massive cytokine production, with hemodynamic and visceral repercussions), and the two types of toxin may be combined [4]. The involvement of these toxins should be suspected when skin infection is associated with signs or

Table 2
Lists the antibiotic choices in case of bites.

Clinical situation	Preferred antibiotics	Alternatives	Comments
Dog and cat bites Main antibiotic targets: *Pasteurella* *Anaerobes* *S. aureus* *Capnocytophaga sp* (dog)	Treat only if risk factors* are present **Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) Duration of treatment depending on the evolution 3 to 7 days,	Treat only if risk factors* are present **Doxycycline** (oral) 4 mg/kg/d in 2 divided doses *(*max *200 mg/day)* Duration of treatment depending on the evolution 3 to 7 days	***Risk** factors: - cat bite - location of bite: face, near a tendon or joint, genitals - deep bite, - underlying condition: immunocompromised, asplenic (*Capnocytophaga*). Tetanus and rabies prophylaxis depending on the context (advice from rabies centers).
Human bites' Bacterial targets *Anaerobes* *S. aureus*	**Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) for 5 days	**Doxycycline** (oral) 4 mg/kg/d in 2 divided doses *(*max *200 mg/day)* for 5 days	Hepatitis B prophylaxis depending on the context.
Viper bites Potentially necrotic lesions	**Amox-clavulanate** (oral) 80 mg/kg/d In 2 or 3 divided doses (maximum 3 g/day) - for 7 days only if envenomated - discontinue treatment if no sign of envenomation		Discuss Viperfav® if envenomated.
Tick bites Bacterial target *B. burgdorferi*	antibiotic prophylaxis not recommended		* Antibiotic prophylaxis may be discussed in endemic areas, in subjects with a high risk of contamination (multiple bites and presumed duration of attachment greater than 48–72 hours).

symptoms of extensive necrosis and/or scarlatiniform generalized erythroderma, and/or hemodynamic instability leading to shock with possibly multiple organ failure [4]. In the event of toxin-like signs, addition to the initial treatment of an antibiotic with anti-toxin activity, such as clindamycin, is recommended [1–3]. The persistence of anti-toxin activity in clindamycin-resistant strains, or strains at risk of inducible resistance (clinda S but erythromycin-resistant strains), is much debated. In S. aureus infections resistant to clindamycin and/or erythromycin, the most logical anti-toxin alternative is linezolid, including in young children (off-label in this case, but justified by the severity of these infections). Despite its excellent pharmacokinetic properties and definite anti-toxin effect, rifampicin is not chosen as a first-line treatment, due to its sensitivity to strong inocula and the risk of rapid acquisition of resistance. In these serious infections, antibiotic therapy alone is insufficient, and should always be supplemented by symptomatic resuscitation measures, surgical debridement if possible, if not supplementary IV immunoglobulin therapy.

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YG and RC wrote the first draft of the article and all of the authors revised and approved the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Antibiotic therapy for osteoarticular infections in 2023: Proposals from the Pediatric Infectious Pathology Group (GPIP)

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ABSTRACT

Most osteoarticular infections (OAI) occur via the hematogenous route, affect children under 5 years of age old, and include osteomyelitis, septic arthritis, osteoarthritis and spondylodiscitis. Early diagnosis and prompt treatment are needed to avoid complications. Children with suspected OAI should be hospitalized at the start of therapy. Surgical drainage is indicated in patients with septic arthritis or periosteal abscess. *Staphylococcus aureus* is implicated in OAI in children at all ages; *Kingella kingae* is a very common causative pathogen in children from 6 months to 4 years old. The French Pediatric Infectious Disease Group recommends empirical antibiotic therapy with appropriate coverage against methicillin-sensitive *S. aureus* (MSSA) with high doses (150 mg/kg/d) of intravenous cefazolin. In most children presenting uncomplicated OAI with favorable outcome (disappearance of fever and pain), short intravenous antibiotic therapy during 3 days can be followed by oral therapy. In the absence of bacteriological identification, oral relay is carried out with the amoxicillin/clavulanate combination (80 mg/kg/d of amoxicillin) or cefalexin (150 mg/kg/d). If the bacterial species is identified, antibiotic therapy will be adapted to antibiotic susceptibility. The minimum total duration of antibiotic therapy should be 14 days for septic arthritis, 3 weeks for osteomyelitis and 4–6 weeks for OAI of the pelvis, spondylodiscitis and more severe OAI, and those evolving slowly under treatment or with an underlying medical condition (neonate, infant under 3 months of old, immunocompromised patients). Treatment of spondylodiscitis and severe OAI requires systematic orthopedic advice.

Most osteoarticular infections (OAI) in children occur via the hematogenous route, with 2 predominant germs: *Staphylococcus aureus*, at any age, and *Kingella kingae*, from the ages of 6 months to 4 years. They can also be caused by Group A Streptococcus (GAS or *Streptococcus pyogenes)* and, more rarely, by pneumococcus or meningococcus. Group B Streptococcus (*Streptococcus agalactiae)* and *Escherichia coli* are responsible for OAI in infants under 3 months of age, and *Salmonella sp.* for OAI in sickle-cell patients. Infections may affect the metaphysis of long bones, close to the growth plate (osteomyelitis), the joint cavity (septic arthritis), the vertebral body or the posterior arch of the vertebra (spondylodiscitis). Osteoarthritis combines osteomyelitis and arthritis, occurring most frequently in infants under 18 months

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Table 1
Probabilistic antibiotic therapy for community-acquired osteoarticular infections in children.

Clinical situations and ***Bacteriological target***	**Recommended regimens**	**Alternatives (contraindications of preferred treatment)**	**Comments**
Osteomyelitis, Spondylodiscitis, Arthritis **Children > 3 months** *Methicillin-sensitive S. aureus (MSSA)* *K. kingae (KK) majority between 6 months and 4 years of age*	**Cefazolin** (IV) 150 mg/kg/d in 4 divided doses **Duration of IV antibiotic therapy:** 3 days with oral relay of antibiotic therapy on D4 if favorable evolution **Antibiotic therapy to be adapted if bacteria identified** **Oral relay antibiotic therapy in the absence of documentation:** **Amox/Clav** 80 mg/kg/d amoxicillin In 3 divided doses o**r** **Cefalexin** 150 mg/kg/d in 3 divided doses **Minimum total duration of antibiotic therapy (IV + PO):** 14 days for arthritis 3 weeks for osteomyelitis 4–6 weeks for spondylodiscitis	**In case of allergy to beta-lactam:** **Children** **6 months- 4 years** (KK, SASM)**:** **Cotrimoxazole** (IV) 60 mg/kg/d **SMZ** in 2 divided doses **Children > 4 years** (mostly SASM)**:** or **Clindamycin** (IV) 40 mg/kg/d in 3 divided doses or **Cotrimoxazole** (IV) 60 mg/kg/d **SMZ** in 2 divided doses or **Vancomycin** (IV)* 60 mg/kg/d Divided in 4 IV (1-hour infusion) or continuous IV after loading dose of 15 mg/kg in a 1-hour infusion, followed by a maintenance dose of 60 mg/kg/d	Before starting antibiotics (even if the child is not febrile): **-2 aerobic blood cultures** (volume sampled adapted to the weight) **-pus removal** (abscess, joint fluid) **Direct inoculation of pus and joint fluid into a blood culture bottle** improves bacteriological diagnosis. In children > 4 years, **oxacillin and cloxacillin (***effective only on SASM***)** 200 mg/kg/d in 4 IV divided doses According to the data of the French Staphylococcal National Reference Center 5% of *S. aureus* strains are MRSA (higher prevalence in Mayotte, Mediterranean rim including North Africa) If all S. aureus Meti-S are susceptible to vancomycin, Pharmacokinetic-pharmacodynamic parameters are poor and the rate of clinical recovery is not optimal. However, resistance to cotrimoxazole and clindamycin for SASM is not negligeable: -R clindamycin in 15% of cases (24% if MRSA) -R to SMZ + TMP in 12% of cases (13% if MRSA) *Kingella kingae* is sensitive to beta-lactams and cotrimoxazole but naturally resistant to clindamycin and vancomycin.
Sickle cell disease Salmonella sp. *S. pneumoniae* *S. aureus*	**Cefotaxime** (IV) 300 mg/kg/d in 4 divided doses Oral relay and duration*:* Specialist advice **Oral relay:** If *Salmonella. sp* sensitive to ciprofloxacin **Ciprofloxacin** 45 mg/kg/d in 2–3 divided doses	**Specialist advice**	Choice of cefotaxime over ceftriaxone due to: - better PK/PD parameters for SASM - no biliary toxicity or risk of hemolytic anemia. **Avoid ciprofloxacin as initial probabilistic treatment.**
Patient < 3 months *S. agalatiae* (Group B Streptococcus) SASM *E. coli*	**Cefotaxime** (IV) 200 mg/kg/d in 4 divided doses **+** **Gentamicin** (IV) 6 mg/kg/d as 1 SIV/d (30′) for 48 h Duration IV (7 to 14 days) and oral relay: Specialist advice		**Specialist advice**
Patient with severe sepsis suggestive of toxigenic AOI (severe sepsis, skin rash, multifocal infection, venous thrombosis, myositis) *S. aureus* LPV *S. pyogenes*	**Cefazolin** (IV) 150 mg/kg/d in 4 divided doses **+** **Clindamycin (IV** 40 mg/kg/d in 3 divided doses **+** **Vancomycin** (IV) 60 mg/kg/d Divided in 4 injections, (1-hour infusion) or continuous IV after loading dose of 15 mg/kg in a 1-hour infusion, followed by a maintenance dose of 60 mg/kg/d ***IV duration and PO relay:***	**Specialist advice**	Adapt antibiotic therapy to the bacteria isolated. Discontinuation of vancomycin if no MRSA.

Table 2
Adaptation of antibiotic therapy for community-acquired osteoarticular infections in children, depending on the bacterium identified and its antibiogram.

Antibiotic treatment after bacteriological identification	Recommended regimens	Alternatives if allergic to beta-lactams	Comments
***S. aureus* Meti S**	**IV** **Cefazolin** 150 mg/kg/d in 4 divided doses Or **Cloxacillin** 200 mg/kg/d in 4 divided doses **Oral relay:** **Children < 6 years (drinkable suspension):** **Amox/Clav** 80 mg/kg/d amoxicillin In 3 divided doses Or **Cefalexin** 150 mg/kg/d In 3 divided doses **Children > 6 years** **Clindamycin*** 40 mg/kg/d In 3 divided doses Or **Cefalexin** 150 mg/kg/d In 3 divided doses	**IV:** **Clindamycin** 40 mg/kg/d In 3 divided doses **Oral relay:** **Children** **6 months-4 years:** **Cotrimoxazole** 60 mg/kg/d **SMZ** In 2 divided doses **In** **children > 6 years** **Clindamycin** 40 mg/kg/d In 3 divided doses	**Clindamycin** has good oral bioavailability and good tissue diffusion in bones and joints. = antibiotic of choice in children > 6 years of age if S. aureus without inducible MLSb phenotype (S clinda and S erythro) **Amox/clav** suspension 100 mg/12.5 mg/ml: one dose by weight supplied by the dosing device, divided into 3 divided doses per day, corresponds to 80 mg/kg/d of amoxicillin. For children > 40 kg: use more suitable tablets or sachets (max. dose: 1000 mg 3 times a day).
K. kingae	**IV:** **Amoxicillin (IV)** 100 mg/kg/d In 4 divided doses **Oral relay:** **Amoxicillin** 80–100 mg/kg/d In 3 divided doses	**IV:** **Cefotaxime** (IV) 200 mg/kg/d In 4 divided doses or **Ceftriaxone** (IV or IM) 75 mg/kg/d In one daily dose **Oral relay:** **Cotrimoxazole** 60 mg/kg/d **SMZ** In 2 divided doses Or **Ciprofloxacin** 40 mg/kg/d In 2 divided doses	
S. pyogenes ***S. pneumoniae*** **(CMI imperative)** ***S. agalactiae***	**IV:** **Amoxicillin** 150 mg/kg/d In 4 divided doses **Oral relay:** **Amoxicillin** 80–100 mg/kg/d In 3 divided doses	**IV:** **Cefotaxime** (IV) 200 mg/kg/d In 4 divided doses or **Ceftriaxone** (IV or IM) 75 mg/kg/d In one daily dose	
***S. aureus* Meti R** *After results of rapid tests for methicillin resistance and before complete antibiotic susceptibility testing*	**Vancomycin** (IV) 60 mg/kg/d Divided in 4 divided doses, 1-hour infusions or continuous IV after loading dose of 15 mg/kg in a 1-hour infusion, followed by a maintenance dose of 60 mg/kg/d + **Clindamycin** 40 mg/kg/d in 3 IV doses	**If renal failure:** **Linezolid** 30 mg/kg/d in 3 IVL in < 12 years 20 mg/kg/d in 2 IVL in > 12 years	**Infectiologist's opinion for adaptation** **Linezolid:** Max dose: 600 mg/12 h No MA in children < 18 years old Maximum treatment duration: 28 days.
***S. aureus* Meti R** *After complete antibiogram*	**If *S. aureus* S clinda and S erythro:** **Clindamycin (IV)** 40 mg/kg/d in 3 divided doses **If *S. aureus* R erythro:** **Linezolid** 30 mg/kg/d as 3 SIV in < 12 years old 20 mg/kg/d as 2 SIV in > 12 years old		**Infectiologist's opinion for adaptation and oral relay:** **Ceftaroline** (5th-generation broad-spectrum cephalosporin, active against MRSA) may be an alternative to vancomycin (infectious disease advice required). **Cotrimoxazole** Max dose IV or oral: 1600 mg SMX/12 h **Levofloxacin:** Max dose: 500 mg X2/d

(*continued on next page*)

Table 2 (*continued*)

Antibiotic treatment after bacteriological identification	Recommended regimens	Alternatives if allergic to beta-lactams	Comments
	Oral relay: **Children < 6 years:** **Cotrimoxazole** 60 mg/kg/d **SMZ** in 2 divided doses **In children > 6 years:** **Clindamycin** (oral) 40 mg/kg/d In 3 divided doses **Oral alternatives:** **Cotrimoxazole** 60 mg/kg/d **SMZ** in 2 divided doses **Or** **Rifampicin** 20 mg/kg/d in 2 divided doses **+** **Fusidic acid** 60 mg/kg/d in 3 divided doses **Or** **Rifampicin** 20 mg/kg/d in 2 divided doses **Or** **Levofloxacin** 20 mg/kg/d < 5 years 10 mg/kg/d > 5 years in 2 divided doses		Oral suspension 25 mg/ml (ATU) and scored tablet 500 mg
Neisseria meningitidis	**Ceftriaxone** 75 mg/kg/d IVL (2 IVL/d if > 4 g/d) Duration 7 days	**Ciprofloxacin** 30 mg/kg/d in 2–3 IV	

[*] Clindamycin (150 and 300 mg capsules) can be used in children > 6 years old who are able to swallow capsules if SA without inducible MLSb phenotype (sensitive to clindamycin and erythromycin).

of age, as the infection spreads via a common vascular network from the metaphysis to the epiphysis, and then into the joint. In older children, the epiphyseal and metaphyseal vascular networks are separate, but infection of the intra-articular part of the metaphysis can fistulate into the joint and generate osteoarthritis.

In the initial phase of OAI, the main risks are severe sepsis (with *S. aureus* or *S. pyogenes*) and/or suppurative complications (arthritis, subperiosteal or soft-tissue abscesses); at a later stage, sequalae (necrosis of the femoral head, articular cartilage damage, growth impairment of a long bone through sterilization of the growth plate) may occur.

Functional impotence, ranging from partial to complete with pseudoparalysis, is the main clinical warning sign; fever is usually but not always present. The clinical pictures of these infections are varied, ranging from acute OAI associating fever, complete functional impotence, severe pain and local inflammatory signs, at times involving sepsis, to sub-acute, pauci-symptomatic OAI with little or no fever.

Treatment of OAI involves antibiotic therapy, always started intravenously in hospital after 2 blood cultures have been systematically taken, even in the absence of fever. Immediately severe OAI, complicated by sepsis or collections (joint effusion, subperiosteal abscess…) necessitates urgent advice from a pediatric orthopedist. Surgical puncture and/or drainage procedures are performed in children under general anesthesia [1–9].

Management of OAI in children varies according to severity. For some severe OAI (very febrile, with septic or toxin shock), antibiotic treatment must be started immediately, whereas surgical procedures may be delayed by the need to stabilize the child and perform complementary imaging (ultrasound, MRI). In less severe OAI, antibiotic therapy is started deep bacteriological samples have been collected during surgery. Some children, particularly those aged between 1 and 4, present with pictures suggestive of subacute osteomyelitis, with incomplete functional impotence, little or no fever, a normal physical examination, normal X-rays and normal or low CRP. In such cases, antibiotic therapy may be deferred for up to 48–72 h, allowing prior confirmation of osteomyelitis by imaging (bone scan or MRI) [2,9].

In recent years, studies have shown that depending on the patient's clinical and biological progress, it may be possible to shorten the antibiotic treatment of community-acquired OAI in children [10]. On the other hand, in the event of complex or unfavorable evolution, a longer course of antibiotics may be necessary. In 2008, the *Groupe de Pathologie Infectieuse Pédiatrique (GPIP) of the Société Française de Pédiatrie* (SFP) published therapeutic proposals aimed at simplifying and shortening antibiotic therapy [10,11]. These proposals are now applied in most centers in France [12–15]. Monotherapy is favored, targeting the most frequently found germs: *S. aureus* (>90% sensitive to methicillin in France) and *K. kingae* (sensitive to amoxicillin and cephalosporins), and treatment (IV and PO) is shortened. Severe OAI (initial septic shock, multi-focal IOA, associated with fasciitis, myositis, septic venous thrombosis or pneumonia) should suggest Panton Valentine leucocidin (PVL)-producing *S. aureus*, and require the addition of an antitoxin antibiotic (clindamycin…) to the initial antibiotic therapy [16,17].

With appropriate treatment, the majority of these infections evolve rapidly and favorably, allowing oral relay of antibiotic ther-

apy and continuation of treatment on an outpatient basis. In the event of unfavorable evolution after 48–72 h of treatment (persistence of fever and pain), it is necessary to ascertain that the antibiotic therapy administered is optimal (molecules, dosage, number of doses per 24 h), to continue antibiotic treatment by the venous route and to search by imaging (MRI, CT, ultrasound) for a complication (abscess, arthritis, septic thrombophlebitis) [2,9].

In the case of spondylodiscitis, in the absence of clinical studies recommending reduced duration of treatment, prolonged antibiotic therapy should be maintained for 4 to 6 weeks. Standard spinal X-rays and imaging (spinal MRI) are routinely performed, and an orthopedic opinion is sought to assess possible needs for immobilization (corset for pain relief) or surgical management (rarely) [2].

The GPIP has contributed to the recent recommendations of the *Société Française de Pathologie Infectieuse de Langue Française* (SPILF) on antibiotic treatment of bacterial arthritis in adults and children [18].

Table 1 presents the different clinical situations, the pathogens most often involved (targets of antibiotic treatment), preferred therapeutic choices and alternatives in the event of allergy.

Table 2 presents the adaptation of antibiotics according to bacterial species isolated and to antibiotic susceptibilities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Antibiotic treatment of neuro-meningeal infections

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ABSTRACT

In France, conjugated pneumococcal vaccination has considerably modified the profile of pneumococcal meningitis by eliminating the most virulent strains resistant to beta-lactams. Over recent years, the nationwide pediatric meningitis network of the Pediatric Infectious Disease Group (GPIP) and the National Reference Centre of Pneumococci have not recorded any cases of meningitis due to pneumococcus resistant to third-generation cephalosporins (C3G), even though in 2021, strains with a less favorable profile appeared to emerge. These recent data justify renewal of the 2016 recommendations and limitation of vancomycin to the secondary phase of treatment of pneumococcal meningitis when the MIC of the isolated strain against injectable C3Gs is >0.5 mg/L. The only major change proposed by the GPIP in this 2023 update of its recommendations is discontinuation of the recommendation of a combination of ciprofloxacin and cefotaxime in *Escherichia coli* meningitis in newborns and young infants.

The nationwide observatory of meningitis in children is a valuable tool because of its completeness and its continuity over the past 15 years. The maintenance of epidemiological surveillance will allow us to adapt new therapeutic regimens to the evolution of pneumococcal susceptibility profiles and to future serotype-specific changes. Community-acquired cerebral abscesses are rare diseases, of which the management requires a rigorous approach: high-quality imaging, bacteriological sampling prior to antibiotic therapy whenever possible, and antibiotic treatment including metronidazole in addition to cefotaxime. Multidisciplinary collaboration, including infectious disease and neurosurgical advice, is always called for.

1. Bacterial meningitis

Bacterial meningitis is a life-threatening infection of the central nervous system. The prognosis can be significantly improved if an antibiotic treatment adapted to the antibiotic susceptibility of the implicated strains is started immediately after the onset of infection. Any delay in treatment could be detrimental to the patient. The choice of initial treatment is empirical and probabilistic; even though identification of the bacterial strains from cerebrospinal fluid (CSF) is often very rapid (at times 1 or 2 h, due to real-time PCR techniques), determination of the susceptibility of the strains implicated to the usual antibiotics (beta-lactam antibiotics) usually requires at least 12–24 h of culture. Moreover, antibiotic diffusion across the blood–brain barrier is limited (10%), and influences the choice of molecules with pharmacokinetic and pharmacodynamic (PK-PD) parameters most apt to predict efficacy. Treatment recommendations for bacterial meningitis in infants and children are based on microbiological data from the *Centre National de Référence des Pneumocoques*, and on clinical and epidemiological surveillance data from the *Observatoire National des Meningites de l'Enfant*, which over the past 15 years has become a valuable tool due to its completeness and durability. Recommendations must be regularly updated to take into account possible changes in the antibiotic susceptibility profiles (ASP) of the main bacterial species, particularly pneumococcus. Due to over-prescription of antibiotics in France during the 1990 s, the ASPs of pneumococcus changed dramatically [1]. As a result, in cases of suspected pneumococcal meningitis, high doses of injectable 3rd-generation cephalosporins (3GC) in combination with vancomycin were recommended pending ASP results [2]. While the majority of intermediate or

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penicillin-resistant strains were susceptible to 3GC, in a significant percentage of cases these strains were intermediate or even resistant. Due to serotype replacement and non-vaccine serotypes, the introduction in 2006 in France of 7-valent pneumococcal conjugate vaccination led to only a modest drop in the number of cases of pneumococcal meningitis. That said, a significant reduction in pneumococcal resistance to antibiotics was observed, with the reduction of ß-lactam-resistant vaccine serotypes. However, and in opposition to the SPILF recommendations, due to the emergence of a particularly antibiotic-resistant non-vaccine serotype, serotype 19A, the GPIP maintained its recommendation unchanged [3–5]. It was only after the switch in 2010 to the second-generation 13-valent vaccine (Prevenar-13®, including serotype 19A) that the GPIP meningitis observatory and the *Centre National de Référence des Pneumocoques* were able to demonstrate the disappearance of meningitis caused by 3GC-resistant pneumococci [6]. These new data led the GPIP to recommend that vancomycin no longer be prescribed during the initial phase of pneumococcal meningitis (confirmed or only suspected), even though high doses of 3GC (300 mg/kg/d) were to be maintained pending ASP results. Depending on the susceptibility of the pneumococcus isolated in culture, a switch to the usual meningeal dose (200 mg/kg/d) could be considered if the MIC to 3GCs was <0.5 mg/L, whereas association with vancomycin while maintaining high doses of 3GCs was recommended only when the MIC of the isolated strain to 3GCs was >0.5 mg/L [7]. These recommendations were renewed in 2019 during the revision of the 17ème SPILF consensus conference on the management of acute community-acquired bacterial meningitis (excluding neonates), in which the GPIP participated [8]. In 2022, epidemiological surveillance by the *Centre National de Référence des Pneumocoques* showed slightly increased isolations of intermediate-susceptible and beta-lactam-resistant strains. While these results constitute a warning, they do not, for the moment, justify any modification of current recommendations for the initial management of pneumococcal meningitis. Continued epidemiological monitoring will enable new treatment regimens to be adapted, if necessary, to evolving pneumococcal susceptibility profiles and future serotype-specific changes. The only substantial change proposed by the GPIP in the 2023 update of its recommendations concerns deletion of ciprofloxacin-cefotaxime in *Escherichia coli* meningitis of newborns and young infants. A retrospective study by the GPIP, based on data from the meningitis observatory, demonstrated the irrelevance of this compound [9].

Where available, these new GPIP recommendations are based on published studies, and have taken into account those of the recent review of the consensus conference organized by the SPILF with other learned societies, including the *Société Française de Pédiatrie* (GPIP) [8].

Table 1 lists the pathogens most frequently implicated (targets of antibiotic treatment) in meningitis, the preferred initial therapeutic choice, and the alternatives in cases of severe allergy to beta-lactam antibiotics.

Table 2 presents the conditions for secondary adaptation of antibiotic therapy, based on the results of antibiotic susceptibility tests.

Table 3 sets out the recommended duration of treatment, with a suggested range for extending the duration in cases of severe or complicated disease.

2. Brain abscesses [10–13]

The European Society of Clinical Microbiology and Infectious Disease (ESCMID) [10] has recently published recommendations for the management of cerebral abscesses, but there is very little work specific to pediatrics [11]. Moreover, in the literature, there is often a confusion between post-operative abscesses complicating neurosurgical interventions, empyema complicating bacterial meningitis, "primary" community abscesses and empyema, which often complicates a locoregional infection. However, the epidemiology, favoring factors and bacterial etiologies are different. Schematically, postoperative abscesses frequently occur in the presence of equipment, in debilitated and/or immunosuppressed patients, and are caused by bacteria of the cutaneous flora, or, at times, nosocomial bacteria. Conversely, abscesses and empyema, whether primary or complicating meningitis, tend to occur in previously healthy children, and the responsible bacteria are derived from nasal or oropharyngeal microbiota.

Here, we will deal only with community-acquired abscesses and empyema, which occur outside any neurosurgical context. In complicated purulent meningitis, the bacteria responsible are those of childhood meningitis. The frequency of these complications varies according to the bacterial species. Meningococcus, for example, is not a major cause of empyema, whereas pneumococcus and, especially, *Haemophilus influenzae* are more often implicated [2]. In neonates, meningitis caused by enterobacterales, particularly *Proteus mirabilis*, is frequently associated with intracranial collections (3). In addition to meningitis, cerebral abscesses and empyema can complicate a loco-regional infection, with bacteriological causes differing according to age. In young children, the starting point is often complicated otitis: pneumococcus, *Haemophilus influenzae, S. pyogenes* and, more rarely, *S. aureus*. When the entry point is a more protracted, recurrent infection, the proportion of anaerobic bacteria (particularly *Fusobacterium necroforum*) increases, as does the frequency of multi-microbial infections. In older children and adolescents, brain abscesses and empyema most often complicate nasal-sinus infections (4), with a predominance of streptococci and, more rarely, *S. aureus* and Gram-negative bacteria. Among streptococci, the milleri group, i.e. *S. constellatus, S. intermedius* and *S. anginosus*, play an important role. The common characteristic of these three species is that they are frequently associated with other bacteria in the oral flora, especially anaerobic bacteria, and generate abscesses with very thick walls that hinder the diffusion of antibiotics. In addition, these anaerobic bacteria frequently produce beta-lactamases, which *in situ* can inhibit the action of amoxicillin, to which streptococci are usually highly sensitive. Cerebral abscesses in children may complicate endocarditis of the left heart (or occur in the context of a right-to-left shunt), or be secondary to venous thrombosis complicating cervical infections, causing septic emboli, first pulmonary and then systemic, resulting in Lemierre syndrome. In these cases, *Fusobacterium necroforum* is the main agent.

Regardless of the context, brain imaging is essential. MRI including DWI/ADC and T1-weighted images with and without gadolinium is recommended. If this is not possible, contrast-enhanced CT is an alternative, but can be misused, especially for small lesions.

Bacteriological documentation is extremely useful and, in many cases, a direct surgical approach to the abscess is necessary, with the exception of complicated but previously documented meningitis. While sampling of the initial infection may also be useful, deep, protected samples should be preferred (sinus or mastoid puncture, paracentesis), as superficial samples are difficult to interpret (commensal bacterial species). It is important to bear in mind the often multi-microbial nature of these lesions, with certain bacteria able to "mask" others during culture; the possibility of associated anaerobic bacteria should always be considered.

The antibiotics chosen must have sufficient cerebral diffusion, especially insofar as the thickness of the wall considerably impedes antibiotic action. The intravenous route and the use of high doses are essential. Given the poor distribution of beta-lactamase inhibitors (clavulanic acid, tazobactam...), beta-lactam + inhibitor com-

Table 1
Initial treatment of bacterial meningitis in infants and children.

Bacteriological targets	Preferred antibiotics	Alternatives in cases of severe beta-lactam allergy	Comments
No bacteria on Gram stain	**Cefotaxime** 200 mg/kg/d in 4 SIV	**Ciprofloxacin** 30 mg/kg/d in 3 SIV + **Vancomycin** 60 mg/kg/d • in 4 SIV (60′) or • continuous infusion over 24 h with a loading dose of 15 mg/kg SIV (60′) administered as soon as continuous infusion begins	The absence of a germ on direct examination is an argument for meningococcus and against pneumococcus. Allergy to cefotaxime is exceptional: seek advice from an infectiologist to continue treatment.
Streptococcus pneumoniae (Gram-positive diplococcus on Gram stain exam)	**Cefotaxime** 300 mg/kg/d in 4 SIV	**Vancomycin** 60 mg/kg/d • in 4 SIV (60′) or • continuous infusion over 24 h with a loading dose of 15 mg/kg SIV (60′) administered as soon as continuous infusion begins + **Rifampicin** 20 to 30 mg/kg/d in 2 SIV (60′)	If cefotaxime MIC > 0.5 and < 2 mg/L: add vancomycin If cefotaxime MIC $\geq$ 2 mg/L: the recommended treatment is Vancomycin + Rifampicin
Neisseria meningitidis (Gram-negative cocci on Gram stain exam)	**Cefotaxime** 200 mg/kg/d in 4 SIV or **Ceftriaxone** 75 mg/kg/d as 1 or 2 SIV	**Ciprofloxacin** 30 mg/kg/d in 3 SIV (60′)	If severe beta-lactam allergy suspected, infectious disease specialist advice recommended)
Hemophilus influenzae (Gram-negative small bacilli on Gram stain exam, infant, toddlers)	**Cefotaxime** 200 mg/kg/d in 4 SIV	**Ciprofloxacin** 30 mg/kg/d in 3 SIV (60′)	Increasing incidence has been reported over recent years. If severe beta-lactam allergy suspected, infectious disease specialist advice recommended)
L. monocytogenes (Gram-positive bacilli on Gram stain exam)	**Amoxicillin** 200 mg/kg/d in 4 SIV + **Gentamicin** 8 mg/kg in 1 SIV (30′)	**Vancomycin** 60 mg/kg/d • in 4 SIV (60′) **or** • continuous infusion over 24 h with a loading dose of 15 mg/kg SIV (60′) administered as soon as continuous infusion begins **or** **Cotrimoxazole** 80 mg/kg/d (of sulfamethoxazole) in 4 SIVs + **Gentamicin** 8 mg/kg in 1 SIV (30′)	If severe beta-lactam allergy suspected, (infectious disease specialist advice recommended)
Escherichia coli (Gram-negative bacilli on Gram stain exam)	**Cefotaxime** (IV) 200 mg/kg/d in 4 divided doses	**Meropenem** (IV) 120 mg/kg/d In 3 divided doses	Combination with Ciprofloxacin is no longer recommended. In meningitis caused by extended-spectrum ß-lactamase-producing *E. coli*, Cefotaxime should be replaced by **Meropenem** (infectious disease specialist advice recommended)
S. agalactiae (Group B Streptococcus) *(Gram-positive cocci on Gram stain exam in newborn or young infant)*	**Amoxicillin** 200 mg/kg/d in 4 SIV + **Gentamicin** 8 mg/kg in 1 SIV (30′)	**Cefotaxime** 200 mg/kg/d in 4/d SIV **+** **Gentamicin** 8 mg/kg in 1 SIV (30′)	Increasing incidence of late and very late onset meningitis has been reported over recent years.

Note:
- SIV: slow intravenous.
- Some pediatric teams now prefer 24-hour continuous administration of Vancomycin, provided that the treatment is started with a loading dose of 15 mg/kg SIV (60′) to be administered concomitantly with the continuous infusion, and that the treatment is monitored by vancomycin assay after 24 h of continuous treatment and by monitoring renal function.
- Cefotaxime and Amoxicillin can also be administered as continuous infusion over 24 h, but with an initial loading dose of 50 mg/kg SIV (60′) to be administered at the start of continuous infusion.
- MIC: minimum inhibitory concentration.
- C3G: injectable 3rd-generation cephalosporins (Cefotaxime and Ceftriaxone).
- AMX: Amoxicillin.
- Maximum daily doses (in adults) not to be exceeded in older children:
Cefotaxime = 24 g.
Ceftriaxone = 4 g.
Amoxicillin = 16 g.
Ciprofloxacin: 800 to 1200 mg.
Rifampicin: 600 mg.

Table 2
Secondary adaptation of treatment for bacterial meningitis in infants and children (excluding neonates).

Bacteriological targets	Criteria for adapting treatment	Switching treatment	Comments
S. pneumoniæ	MIC C3G $\leq$ 0.5 mg/L and CMI AMX $\leq$ 0.5 mg/L	**Amoxicillin** 200 mg/kg/d in 4 SIV	To be continued until the end of treatment
S. pneumoniæ	MIC C3G $\leq$ 0.5 mg/L and AMX MIC > 0.5 mg/L	**Cefotaxime** 300 mg/kg/d in 4 SIV	Initial antibiotic therapy maintained to completion
S. pneumoniæ	MIC C3G > 0.5 mg/L and < 2 mg/L	**Cefotaxime** 300 mg/kg/d in 4 SIV **+** **Vancomycin** 60 mg/kg/day • in 4 SIV (60′) or • continuous infusion over 24 h with a loading dose of 15 mg/kg SIV (60′) administered as soon as continuous infusion begins	Add Vancomycin to Cefotaxime (infectious diseases specialist advice recommended)
S. pneumoniæ	MIC C3G$\geq$2 mg/L	**Vancomycin** 60 mg/kg/d • in 4 SIV (60′) or • continuous infusion over 24 h with a loading dose of 15 mg/kg SIV (60′) administered as soon as continuous infusion begins + **Rifampicin** 20 to 30 mg/kg/d in 2 SIV (60′)	Change to Vancomycin + Rifampicin (infectious disease specialist advice recommended)
N. meningitidis	CMI AMX $\leq$ 0.125 mg/L	**Amoxicillin** 200 mg/kg/d in 4 SIV	To be continued until the end of treatment
N. meningitidis	MIC AMX > 0.125 mg/L	**Cefotaxime** 200 mg/kg/d in 4 SIV or **Ceftriaxone** 75 mg/kg/d as 1 or 2 SIV	Initial antibiotic therapy maintained to completion
L. monocytogenes		**Amoxicillin** 200 mg/kg/d in 4 SIV	Gentamicin discontinuation after the 5th treatment day
S. agalactiae (Group B Streptococcus)		**Amoxicillin** 200 mg/kg/d in 4 SIV	Gentamicin discontinuation after 48 h of treatment
S. pyogenes (Group A Streptococcus)		**Amoxicillin** 200 mg/kg/d in 4 SIV	Add anti-toxin drug in case of severe sepsis and/or toxinic rash

Table 3
Duration of treatment for bacterial meningitis in infants and children (excluding newborns).

Bacteriological targets	Duration
S. pneumoniæ	10–14 days
H. influenzae b	7 days
N. meningitidis	5–7 days
L. monocytogenes	14–21 days
E. coli	21 days
S. agalactiae	14–21 days

Note. Processing times are presented as ranges.
The minimum value corresponds to the recommended duration in uncomplicated meningitis with a favorable course.
Longer durations may be considered in meningitis deemed more severe (infectious disease specialist advice recommended).
In the event of an empyema-type complication, consult an infectious disease specialist.

binations should be avoided. Probabilistic antibiotic therapy must target the bacteria at the entry point and be adapted according to the bacteriological results. Given the difficulty of interpreting samples, it is advisable to use a molecule that is active against anaerobes, at least in the initial phase of treatment. Specialist pediatric infectious disease advice is strongly recommended. Table 4 presents the antibiotic treatments proposed for brain abscess and empyema.

Aside from diagnostic procedures, drainage of abscesses is often useful, but can be technically difficult. Aspiration of the contents is often "easier" than excision of the abscess shell and would appear for some teams to be enough (3). In any case, the advice of an experienced neurosurgical team is essential. It is also important to consider surgical treatment of the entry point, which is often more accessible. On the other hand, empyema as a complication of meningitis does not appear to benefit from surgical treatment, except in cases of uncontrolled intracranial hypertension.

In the absence of specific studies, treatment duration is poorly codified, but if the clinical course is satisfactory, 4–6 weeks may be sufficient. Anti-anaerobic treatment appears to be shorter and can be discontinued after 10–15 days. As in complicated meningitis, the persistent fluid collection on imaging does not necessarily indicate that treatment should be prolonged. Multidisciplinary consultation is strongly recommended.

Occurrence of empyema during bacterial meningitis does not alter the initial treatment, which will remain the same, in terms of molecule and dosage, as that recommended for uncomplicated meningitis. Coverage of anaerobic bacteria is not indicated, as they are rarely implicated in this context. Only the duration of treatment will be longer, but in the absence of studies, it is not possible

Table 4
Brain abscess and e/mpyema.

Clinical situations and *Bacteriological targets*	Recommended regimens	Alternatives (contraindications of preferred treatment)	Comments
Brain abscesses complicating bacterial meningitis Subdural and extradural empyema - Pneumococcus - *H. influenzae* - *S. agalactiae* - *E. coli* - *Proteus* - *N. meningitidis*	Cefotaxime (IV) 200 to 300 mg/kg/d In 4 divided doses		Empyema occurrence does not alter the initial treatment, with molecule and dosage similar to those recommended for meningitis.
Primary brain abscesses (no known immunodepression) - *Streptococcus* species: *constellatus intermedius*, *anginosus*, - *Fusobacterium* sp - *Aggregatibacter* sp *Staphylococcus aureus,* Gram-negative bacilli	Cefotaxime (IV) 200 mg/kg/d in 4 divided doses + Metronidazole (IV) 30 mg/kg/d in 3 divided doses		**Imaging** - MRI highly recommended - If MRI not possible: CT scan with contrast medium Antibiotic treatment Not urgent if: - no clinical severity - surgery (puncture or excision) possible within 24 h **Duration of treatment** - If aspiration and no excision: 6 to 8 weeks IV - 4 weeks if excision surgery
Primary brain abscesses (immunodepression) organ transplantation, active chemotherapy, biotherapy, hematological malignancy - *Streptococcus* species notably *constellatus intermedius*, *anginosus*, - *Fusobacterium* sp - *Aggregatibacter* sp *Staphylococcus aureus,* Gram-negative bacilli *Nocardia* spp., *M. tuberculosis*, Fungi Parasites	Cefotaxime (IV) 200 mg/kg/d In 4 divided doses + Metronidazole (IV) 30 mg/kg/d in 3 divided doses + Cotrimoxazole 80 mg/kg/d (of sulfamethoxazole) in 4 divided doses + Voriconazole	**Meropenem** (IV) 120 mg/kg/d In 3 divided doses + **Cotrimoxazole** 80 mg/kg/d (of sulfamethoxazole) in 4 divided doses + Voriconazole	**No oral relay** **Corticosteroids** in perifocal edema or threat of herniation **No indication for anti-epileptic prophylaxis** (unless inaugural convulsion)

to define optimal duration. If the clinical course is favorable, it seems reasonable to treat for 3–4 weeks intravenously. Even if collections persist on imaging, prolongation of treatment is not justified, as recurrences after treatment cessation are exceptional. Given the difficulties of diffusion, the oral route, even as a relay, is not recommended.

For abscesses complicating ENT infections, probabilistic treatment must be sufficiently broad-spectrum. A combination of a high-dose 3rd-generation cephalosporin and an anti-anaerobic molecule such as metronidazole seems appropriate. Broader-spectrum beta-lactam antibiotics do not appear to be useful, except in complicated chronic otitis in which Pseudomonas aeruginosa may be involved. In such cases, C3G should be replaced by Ceftazidime until bacteriological results have been received. On the other hand, coverage for methicillin-resistant S. aureus (MRSA) is unnecessary, given their very low frequency in community ENT infections. Aminoglycosides are unnecessary and should be avoided.

3. Contributorship

YG and RC wrote the first draft of the article and all of the authors revised and approved the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Neonatal bacterial infections: Diagnosis, bacterial epidemiology and antibiotic treatment

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ABSTRACT

Severe bacterial infections have a higher incidence in the neonatal period than at any other pediatric age. Incidence is even higher in premature babies than in term newborns, and severity is increased in the absence of early diagnosis and treatment. By contrast, clinical signs are nonspecific and sometimes trivial, and biomarkers perform poorly during the first 24 hours of infection. For decades, this has led to having too many children treated for extended periods with broad-spectrum antibiotics. Today, the challenge is to prescribe antibiotics in a targeted way, by identifying truly infected newborns. Over the last ten years, major paradigm shifts have occurred and should be taken into account, as a result of growing awareness of the ecological impact of early antibiotic therapy, notably antibiotic resistance, by choosing the narrowest spectrum antibiotic and stopping antibiotic therapy as soon as the diagnosis of infection has been reasonably ruled out. Among the biological tests, the most important are blood cultures. At least one blood culture, taken under aseptic conditions, of sufficient volume (1 to 2 mL), and using pediatric bottles must be taken as soon as the decision to treat has been made, before starting any antibiotic therapy. The bacteria responsible for early-onset bacterial neonatal infections (EBNI) have not changed significantly over recent years and remain dominated by Group B *Streptococcus* and *Escherichia coli*, which are the main targets of treatment. GBS is largely predominant in full-term infants, but the proportion of infections due to *E. coli* increases with prematurity.

1. Introduction

Due to immune immaturity concerning both innate immunity (primarily polynuclear) and adaptive immunity (cellular and humoral), bacterial infections have a higher incidence in the neonatal period than at any other pediatric age. Newborn infections include early-onset or late-onset Bacterial Neonatal Infections (BNI), healthcare-associated infections, and community-acquired infections during the first 28 days of life. Incidence is even higher in premature babies than in term newborns, and severity is increased in the absence of early diagnosis and treatment.

In contrast to this high incidence and severity, clinical signs are nonspecific and any times trivial, and biomarkers perform poorly during the first 24 hours of infection. For decades, this has led to having too many children treated with very broad-spectrum antibiotics for extended periods of time. Today, the challenge is to prescribe antibiotics in a reasoned and targeted way, by identifying truly infected newborns, choosing the narrowest spectrum antibiotics and stopping antibiotic therapy as soon as the diagnosis of infection has been reasonably ruled out. Although the incidence of bacterial infections is higher in the neonatal period than at other stages of life, it has fallen considerably since the widespread introduction of screening and per partum prophylaxis in high-income countries, and now concerns 0.25/1000 births for Streptococcus B, the bacterium most often implicated (i.e. 1 newborn per year in a maternity hospital with 4,000 annual births).

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2. Early neonatal bacterial infections (EBNIs)

The diagnosis is based on clinical signs, history and additional tests [1]. Symptoms of EBNI almost always appear within 48 hours of birth, but very rarely afterwards. Formalized clinical monitoring (criteria and frequency) in the maternity unit is essential for the early detection of infected newborns. Thus, an asymptomatic child after 48 hours of surveillance has a very low probability of EONI.

The clinical signs are a variable combination of:

- Respiratory signs: respiratory distress (whining, nasal flaring, signs of retraction), tachypnea (RR > 60/min), and apnea, which may be associated with other pathologies common in the first days of life,
- Digestive signs: refusal to drink, vomiting, very common in the first days of life,
- General signs: fever (temperature $\geq$ 38.0 °C) or hypothermia (temperature < 36.0 °C) often absent, jaundice,
- Hemodynamic signs: gray or waxy complexion (often one of the first signs), tachycardia (>160 bpm) or bradycardia (<80 bpm), signs of shock (increased capillary refill time, pallor, hypotension, oliguria),
- Neurological signs: drowsiness, irritability, hypotonia, seizures.

These clinical signs are not specific of infection, but their presence during the first 48 hours of life should raise the possibility of EBNI. Their presence (especially hemodynamic and neurological signs, which are signs of severity) determines the urgency of treatment.

The risk factors for EBNI are well-known:

- symptoms and signs evocating intra-uterine inflammation or infection (Box 1) [2]
- maternal Group B *Streptococcus* (GBS) colonization or history of neonatal GBS infection in a previous pregnancy,
- rupture of membranes lasting over 12 hours,
- maternal fever,
- maternal urinary tract infection, even if not febrile,
- spontaneous and unexplained prematurity.

These risk factors alone, with no associated clinical signs, do not require antibiotic therapy, but rather careful, standardized clinical monitoring [1].

For late-onset bacterial neonatal infections (LBNI), while they may share the same clinical and biological signs, risk factors for EBNI are generally lacking. GBS prophylaxis during labor has not proven efficacy in their prevention, and GBS-LBNI incidence has increased in several countries, and the proportion of GBS meningitis is higher than that observed for EBNI. Lastly, urinary tract infections due to enterobacterales (notably *E. coli)* are a significant cause of severe infections during the first month.

3. Biological tests

The most important are blood cultures. At least one blood culture, taken under rigorous aseptic conditions, of sufficient volume (1 to 2 mL) and using pediatric vials, must be taken as soon as the decision to treat has been made, on the basis of clinical signs and before starting any antibiotic therapy. We suggest that, whenever possible (especially in the absence of emergency clinical signs), two blood cultures be taken under the same conditions. Bacterial urine examination is not necessary according to the fact that urinary tract infections are uncommon during the first day of life. The presence GBS in the vaginal swab is a risk factor for EONI, but not documentation of infection in the newborn. The development of per-natal screening for Streptococcus B should enable better identification of women colonized at the time of birth, and optimize the indications for antibiotic prophylaxis.

Available biomarkers are represented by C-reactive protein (CRP) and procalcitonin (PCT). The main disadvantage of measuring C reactive protein (CRP), once the decision to start antibiotic therapy has been taken, is that its peak concentration is not reached for 48 hours. Performed at an early stage, CRP is not very sensitive, and its main interest is kinetic, when making the decision to stop antibiotic treatment. The use of micromethod CRP could help to monitor the kinetic.

The main disadvantage of procalcitonin (PCT) levels is that they increase physiologically in the first few days of life. However, curves are available for premature and full-term infants in the first few hours of life [3]. Here again, the kinetics are the main factor of diagnostic value. Furthermore, the interpretation of biomarkers must take into account, the signs and symptoms recorded, gestational age, the results of further tests and the kinetics of dosage.

4. Bacterial epidemiology and empirical antibiotic treatment of EBNI

The bacteria responsible for EBNI have not changed significantly over recent years and remain dominated by Group B Streptococcus (GBS or *Streptococcus agalactiae*) and *Escherichia coli*, which are the main targets of treatment. GBS is largely predominant in full-term infants, but the proportion of infections due to *E. coli* increases with prematurity. [4]. Amikacin is bactericidal against GBS and *E. coli*. Bacterial epidemiology is not the only parameter to be taken into account when choosing a course of treatment: maternal colonization, gestational age at birth and severity of the clinical picture must also be considered.

Over the last ten years, major paradigm shifts have occurred and should be taken into account, as a result of growing awareness of the ecological impact of early antibiotic therapy (antibiotic resistance, deleterious long-term consequences of disrupting the establishment of microbiota) and the evolution of antibiotic resistance, particularly in *E. coli.* The emergence of *E. coli*- producing extended-spectrum ß-lactamases (ESBL) has changed the situation. These strains are resistant to all third-generation cephalosporins (3GC) and are less frequently sensitive to the piperacillin-tazobactam combination and to gentamicin. However, the vast majority remain susceptible to amikacin and (obviously) to penems. Because penems promotes the emergence of Gram-negative bacilli resistant to all antibiotics, their use must be limited. These findings point in three directions:

- The first is the imperative need to drastically reduce the use of unnecessary antibiotics.
- The second is to limit the use of antibiotics with a high ecological impact on the intestinal microbiota (3GC, piperacillin-tazobactam and penem).
- The third is to give preference (if the risk of ESBL is of concern) to amikacin among aminoglycosides. In area where the rates of ESBL- *E. coli* are low for neonatal infections or from the mother's urinary tract infections or vaginal samples, gentamicin remains an acceptable choice. Aminoglycosides have little ecological impact on this ecosystem, but when used alone or in combination with an inactive antibiotic, they may not be sufficient to treat a true invasive bacterial infection due to Gram-negative bacteria. In general, they should be prescribed only for one dose or for very short periods and, if the infection is confirmed, be replaced by ß-lactams active on the isolated strain.

Table 1 shows the initial treatment proposals for EBNI. Empirical antibiotic treatment in EBNIs relies on previously

Table 1
Initial treatment of bacterial neonatal infection (EBNI).

Clinical situation	Recommended antibiotics	Comments
- Suspected EBNI - AND no contributory sample from the mother - > 34 weeks - AND No signs of severity* • *Group B Streptococcus* • *E. coli*	Amoxicillin 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 injection over 30'.	The main target is GBS (hence the use of penicillin G instead of amoxicillin in many countries), but *E. coli* cannot be ruled out, hence the interest in Amikacin (bactericidal on *E.coli).* In areas where the incidence of ESBL-E. coli is low, gentamicin (6 to 7 mg/kg/d in 1 injection over 30') can be prescribed). Antibiotics discontinued after 36-48 hours if clinical improvement, blood culture(s) negative. Staphylococcus coagulase negative is never implicated in EONI, but must be considered as contaminant.
- Suspected EBNI - And no contributory sample from the mother - < 34 weeks or - Signs of severity* • *Group B Streptococcus* • *E. coli* • *Listeria monocytogenes*$	Cefotaxime 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 injection over 30'.	The proportion of *E. coli* increases in premature babies. However, if the clinical presentation is not severe, amoxicillin can replace cefotaxime, even in premature babies. In areas where the incidence of ESBL-*E. coli* is low, gentamicin (7 mg/kg/d in 1 injection over 30' can be prescribed). Amoxicilin + gentamicin is the recommended treatment of L. monocytogenes infections.
- Suspected EBNI - and mother's blood culture, urinary culture or vaginal swab positive for GBS	Amoxicillin 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'.	Oral relay is possible only for GBS infections in the absence of meningitis and after clinical improvement. In area where the incidence of ESBL-E. coli is low, gentamicin can be prescribed.
- Suspected EBNI - and mother's blood culture, urinary culture or vaginal swab positive for *E. coli* (even AMPI S, Cefotaxime S)	Cefotaxime 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'.	Even if the *E. coli* is susceptible to amoxicillin, PK/PD parameters favor the use of 3GC In areas where the incidence of ESBL-E. coli is low gentamicin can be prescribed.
- Suspected EBNI - and mother's blood culture, urinary culture or vaginal swab positive for *E. coli* (cefotaxime R, AMPc producer strains)	Cefepime 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'.	
- Suspected EBNI - and mother's blood culture, urinary culture or vaginal swab positive for *E. coli* (cefotaxime R, by ESBL)	Meropenem 40 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'.	
- Suspected EBNI - and mother's blood culture, urinary culture or vaginal swab positive for *P. aeruginosa* (very premature babies only)	Ceftazidime 80 mg/kg/d in 2 divided injections + Tobramycin ≅ 6 mg/kg/d in 1 IV over 30'. or Meropenem 40 mg/kg/d in 2 divided injections	

(*continued on next page*)

Table 1 (*continued*)

Clinical situation	Recommended antibiotics	Comments
	+ Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'.	
Late onset Bacterial Neonatal infection (LBNI) Main bacterial species - GBS - *E. coli*	Cefotaxime 100 mg/kg/d in 2 divided injections + Amikacin€ ≅ 20 mg/kg/d in 1 IV over 30'. If meningitis or urinary tract infections are excluded Cefotaxime could be replaced by Amoxicillin 100 mg/kg/d in 2 divided injections	GBS prophylaxis during labor has not proven efficacy on LBNI occurrence. In several countries, the incidence of LBNI due to GBS is increasing. The proportion of GBS meningitis is higher than that observed for GBS EBNI. Urinary tract infections due to enterobacterales (notably *E. coli)* are a significant cause of severe infections during the first month. In case of meningitis, dosage of cefotaxime or amoxicillin should be increased.

EBNI, early onset bacterial neonatal infection; IV, intravenous; GBS, Group B *Streptococcus*; 3GC, third-generation cephalosporin.
* Hemodynamic disorders requiring vascular filling or the administration of vasoactive drugs, or neurological clinical signs (disturbed consciousness or convulsions).
$ If **listeriosis** is suspected, add amoxicillin 50 mg/kg/12h in 2 injections + gentamicin.
€ For precise Amikacin dosages according to gestational age and post-natal age, see Table 2.

detailed principles: keep a spectrum that covers GBS and Gram-negative bacilli, using a combination of 2 antibiotics, while avoiding the use of 3GC and penems (in patients without microbiological orientation and without signs of severity).

Table 2 presents the aminoglycoside dosages proposed by the French drug agency [5].

Box 2 presents the general rules for continuing or stopping antibiotics in EBNIs.

5. Healthcare-associated infections and necrotizing enterocolitis (NEC)

Nosocomial (healthcare-associated) neonatal bacterial infections (HNBI) are defined as the occurrence of an infection in a newborn after 72 hours of life (as opposed to early onset BNI) and hospitalized in neonatology for more than 48 hours. These infections are frequent due to the vulnerability and immaturity of newborns, as well as the duration of use of central venous catheters (CVCs) or during rare prolonged intubations, leading to Ventilation-Associated Pneumonia (VAP)**.** They lead to short- and long-term morbidity and increase the risk of death.

5.1. Risk factors

Risk factors associated with these infections include low gestational age and/or birth weight, intrauterine growth retardation, presence of a CVC, delayed enteral feeding, and prior antibiotic administration (notably 3GC). In half of cases, the CVC is the source of the infection.

5.2. Bacterial epidemiology and empirical antibiotic treatment

Not surprisingly, the bacteria involved in these infections are, in around 75% of cases, coagulase-negative staphylococci (CoNS), often resistant to methicillin, notably *S. epidermidis, S. capitis and S. haemolyticus* [6]. Other microorganisms include enterobacterales and *S. aureus,* more rarely *Candida*, *Bacillus cereus* or *E. faecalis*.

The diagnosis of late-onset sepsis must include the association of clinical signs with the presence of at least one blood culture positive for an identified bacterium known to be potentially responsible for sepsis [6,7]. However,

- The clinical signs selected are not specific. Cardiorespiratory instability (brady-apneic syndrome, desaturation and hypotension) may be part of the clinical picture of direct complications of prematurity, and thermoregulation problems may be influenced by the use of an incubator.
- CoNS are both classic agents of neonatal sepsis and commensal microorganisms of the skin, and they frequently contaminate blood cultures (Box. 3) [7]. As a result, two or more blood cultures collected on separate occasions and growing the same common commensal organism are needed to confirm bloodstream infection with these agents [8].
- Finally, delay in initiating effective antibiotic therapy constitutes a poor prognostic factor.

To counteract these difficulties, several attitudes should be adopted:

- The first and most important is to perform at least one high-quality blood culture: take a sterile sample of at least 1 ml, and place it in a pediatric bottle.
- In the absence of signs of severity, whenever technically possible, try to take a second blood culture rapidly under the same conditions.

Table 2
Dosage of aminoglycosides [5]. 30-minute IV.

Post-conceptional age (weeks)	≥37	34–36	30–33	<30
- Gentamicin	6 mg/kg	6 mg/kg	7 mg/kg	7 mg/kg
Interval between 2 injections (4 × $T_{1/2}\beta$ *)	24 h	36 h	36 h	48 h
- Tobramycin	6 mg/kg	6 mg/kg	7 mg/kg	7 mg/kg
Interval between 2 injections (4 × $T1_{/2}\beta$ *)	36 h	48 h	60 h	72 h
- Amikacin	30 mg/kg	30 mg/kg	35 mg/kg	35 mg/kg
Interval between 2 injections (4 × $T_{1/2}\beta$ *)	24 h	36 h	48 h	60 h

$T1_{/2}\beta$, half life

Table 3
Initial treatment of healthcare-associated neonatal bacterial infections (HNBI) and NEC [6,9,10–13].

Clinical situation	Recommended antibiotics	Comments
Suspicion of HNBI, in the presence of CVC with no other origin and no signs of severity, - CoNS meti R	Vancomycin 20 to 40 mg/kg/d (administration as continuous IV or IV over one hour) + Amikacin€ 20 mg/kg/d in 1 IVL over 30'.	Empirical antibiotic therapy must cover meti-R CoNS. Vancomycin dosage is highly variable: serum concentrations depend above all on renal function (term, age…) and on other potentially nephrotoxic treatments. Vancomycin levels are necessary if treatment exceeds 48 hours. To be effective, they must be > 8-10 times the MIC or AUC/MIC>400 mg.h/L [8]. The addition of an aminoglycoside (amikacin or gentamycin) provides transient coverage of enterobacterales
Suspicion of HNBI, in the presence of CVC with signs of severity - CoNS meti R - Enterobacterales - *S. aureus*	Vancomycin 20 to 40 mg/kg/d (administration as continuous IV or IV over one hour) + Amikacin€ ≅ 20 mg/kg/d in one IV over 30' + Cefotaxime 100 mg/kg/day in two injections	Vancomycin levels are necessary if treatment exceeds 48 hours. To be effective, they must be > 8-10 times the MIC or AUC/MIC>400 mg.h/L. In all situations where cefotaxime is used empirically, it must be replaced by: - Cefepime if the child is colonized by cephalosporinase-producing enterobacteriaceae. - Meropenem, if colonized by an ESBL strain
Necrotizing Enterocolitis (NEC) • Enterobacterales including *E. coli* • Anaerobes (including Bacteroides fragilis) *Coagulase-Negative Staphylococcus (CoNS)*	Cefotaxime 100 mg/kg/d in 2 injections + Amikacin€ ≅ 20 mg/kg/d in 1 IVL over 30'. + Metronidazole ———————————— or Piperacillin-tazobactam + Amikacin€ ≅ 20 mg/kg/d in 1 IVL over 30'. ———————————— +/- Vancomycin 20 to 40 mg/kg/d (administration as continuous IV or IV over one hour)	NEC is not an infectious disease. Bacteremia (secondary to pullulation, itself secondary to digestive stasis) is detected only in 1/3 of cases. The initial empirical antibiotic treatment is of interest only to prevent bacterial translocation and should be reassessed at H 36 - H 48, or adapted if blood culture is positive. -In case of ESBL enterobacterale colonization: Meropenem (20 mg/Kg/12h ≤D 7 or 20 mg/kg/8h >D7, for 10 days + 1 single dose of Amikacin. - In case of colonization by *E. cloacae,* even if 3GC susceptible: Cefepime (50 mg/Kg/12h ≤D 7 - 50 mg/kg/8h >D7; 10 days) + 1 single dose of Amikacin. Depending on local bacterial epidemiology, the addition of vancomycin as an empirical agent may be considered. CoNS are more frequent in isolated perforations than in NEC [12,13]. A peritoneal fluid culture should be obtained in all neonates with intestinal perforation, regardless of cause, because it may help to direct the choice of the most effective antimicrobial [12,13].

- Take into account the time to positivity of blood culture: the majority of true bacteremia cases grow in less than 18 hours. Beyond 24 hours, especially if a commensal is involved, contamination is most likely.
- Finally, integrate biomarker results. Although their value is limited to the initial phase of infection, and even if none of them can be used on their own to confirm or rule out infection, an increase in CRP, PCT, white blood cell count or, conversely, leuko-neutropenia can join the set of arguments used to refine the diagnosis.

Table 3 presents the initial therapeutic proposals for HNBI and NEC. In the case of a newborn with suspected nosocomial infection, empirical antibiotic therapy will take into account the local clinical and epidemiological context.

Box 4 sets out the rules for monitoring antibiotic treatments of HNBI.

Box 1
Symptoms and signs suggesting intra-uterine infection (professional agreement).

Fever defined by maternal temperature greater than or equal to 38 °C confirmed at 30-minute interval without identified extra- gynecological cause, associated with at least two of the following criteria:
- persistent fetal tachycardia > 160 bpm,
- uterine pain or painful uterine contraction,
- spontaneous onset of labor,
- purulent amniotic fluid.

Box. 2
General rules for continuing or stopping antibiotics in EBNIs.

1) **Uninfected newborn:**
Favorable clinical course, negative blood culture(s), inflammatory parameters not indicative of bacterial infection: discontinue treatment at H36-48
2) **Confirmed EBNI:**
Adapt antibiotic treatment to the bacteria found:
- Blood culture positive: Continue beta-lactam monotherapy and systematically perform lumbar puncture
o Blood culture positive for GBS: amoxicillin 50 mg/kg/12h for 7 days.
o Blood culture positive for 3GC-sensitive *E. coli* (even if ampicillin S): cefotaxime 50 mg/kg/12h for 7 days.
o Blood culture positive for ESBL Gram negative bacilli: Meropenem (3-hour IV); 20 mg/kg/12h.
o Blood culture positive for another organism: seek specialist advice.
- **Meningitis: continue treatment with beta-lactam antibiotics**:
o *GBS:* amoxicillin 200 mg/kg/d in *4 injections for 14 days.*
o 3GC-sensitive *E. coli:* 200 mg/kg/d in 4 injections, *21-day treatment.*
o *Enterobacterales ESBL:* Meropenem 120 mg/kg/d in 3 *injections.*
o In case of meningitis caused by another organism: seek pediatric infectious disease advice.

EBNI, early onset Bacterial Neonatal Infection; 3GC, third-generation cephalosporin; GBS, Group B streptococcus; ESBL, extended spectrum ß-lactamases.

Box. 3
Coagulase-negative staphylococci.

Comprising several species, the most common are *S. epidermidis, S. capitis and S. haemolyticus*. Coagulase-negative staphylococci (CoNS) are most often resistant to methicillin, and therefore to all ß-lactam antibiotics.
They are commensals of the skin and the primary cause of blood culture contamination. When a central venous catheter is in place, they can be responsible for true septicemia. CoNS infections are often characterized by mild clinical pictures and modest changes in biomarkers. Infections with *S. capitis and S. haemolyticus are* probably more severe than those caused by other CoNS.

Box. 4
General rules for continuing or stopping antibiotics in HNBI

Empirical antibiotic therapy must be re-evaluated no later than after H36-H48 of blood culture:
-Favorable clinical course, negative blood culture(s), inflammatory parameters not indicative of bacterial infection: discontinue treatment at H36-48

- If the blood culture is positive, antibiotic therapy must be adapted to the species and then to the antibiogram, aiming for the narrowest possible spectrum.
- In the case of meticillin-resistant CoNS (including *S. capitis* and *S. haemolyticus*), first-line treatment with vancomycin is recommended (most CoNS are resistant to aminoglycosides, so there is no point in maintaining them in combination). Linezolid has no place as a first-line treatment, due to its solely bacteriostatic activity (by inhibiting protein synthesis) and the risk of resistance emergence. It may be considered as a 2nd-line treatment when well-administered vancomycin fails, in the case of vancomycin-resistant bacteria, or in the event of a difficult route of administration (oral form with good bioavailability). Daptomycin has not been extensively studied in neonates, and is not approved for use before the age of 1 year, due to its potential side effects on the muscular and/or nervous systems. It is therefore not recommended for treatment of neonatal CoNS infections.
- In the case of *S. aureus*, treatment with oxacillin or cefazolin is recommended if the strain is suceptible to meticillin. If exceptionally *S. aureus* méti R, vancomycin must be continued. A rapid susceptibility test (PLP2a test) can be carried out in the laboratory as soon as the species has been identified, enabling antibiotic therapy to be adapted before the full antibiogram is available.
- If Gram-negative bacilli: adapt antibiotic therapy to the antibiogram, keeping the spectrum as narrow as possible; maintain aminoglycoside treatment for 2 doses.
In the event of positive blood culture, it is recommended to sample a control blood culture at 48 hours after start of antibiotic treatment.
In the case of infections involving bacteria with a meningeal tropism (particularly Gram-negative bacilli), lumbar puncture should be performed as soon as the patient's condition allows it.
If vancomycin treatment is continued beyond 48 hours, vancomycin levels should be monitored. To be effective, they must be > 10 times the MIC or AUC/MIC>400 mg.h/L [10].
If aCVC is present, its removal is recommended in cases of severe sepsis, suppurative thrombophlebitis, endocarditis, or isolation of a pathogen with biofilm-producing potential (particularly S. aureus, Candida, Gram-negative bacilli) as soon as the first positive blood culture is obtained. For infections involving CoNS, catheter removal is recommended if bacteremia persists (two successive positive blood cultures). In all patients, the CVC should be removed as soon as the patient no longer needs it.
The duration of antibiotic therapy is usually between 7 and 10 days (15 days in the case of S. aureus). It may be increased or shortened depending on the clinical situation, the length of time the catheter has to be kept in place, the control blood culture and the bacteria identified [11]

6. Conclusion

For either early-onset, community-acquired or healthcare-associated neonatal bacterial infections, clinical and biological diagnosis remain challenging with unspecific signs and poor biomarkers. Bacterial documentation with quality blood cultures should be a priority at initiation of treatment. The choice of empirical antibiotic treatment for these infections should be determined by the patient's clinical state, bacterial epidemiology and specific local ecology, while keeping in mind the need to limit antibiotics with a high ecological impact, and to re-assess treatment within the first 48 hours.

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Review

Treatment of Resistant Gram-negative bacilli in children

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Child

ABSTRACT

Resistance of Gram-negative bacteria to the most widely used antibiotics, particularly β-lactams, is now considered as major public health problem. The main resistance mechanisms to β-lactams in Enterobacterales are the production of extended spectrum β-lactamases (ESBL) or carbapenemases, which hydrolyze virtually all β-lactams. However, a substantial proportion of carbapenem-resistant Gram-negative bacilli do not produce carbapenemase but combine overproduction of a cephalosporinase and/or ESBL with very low penem hydrolysis and reduced outer membrane permeability. The arrival of new antibacterial agents active on some of these multidrug-resistant strains, such as new β-lactam inhibitors, has marked a turning point in treatment and represents real progress. In-depth knowledge of resistance mechanisms is crucial to the choice of the most effective molecule, and their prescription requires close collaboration between microbiologists, infectious disease specialists and intensive care physicians. While these compounds are significantly more active against resistant strains than those previously available, their spectrum of activity does not cover all resistance mechanisms in Gram-negatives, nor in other bacterial species potentially involved in polymicrobial infections. The use of these new compounds does not alter antibiotic regimens in terms of duration and indication of combined antibiotic therapy, which remain very limited.

1. Introduction

The resistance of Gram-negative bacteria to commonly used antibiotics, particularly β-lactams, is now considered as major public health problem for humanity. While some "non-fermenting" Gram-negative bacterial species such as *Acinetobacter* spp., *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* have long been known to be resistant to almost all antibiotics, the rapid worldwide emergence since the early 2000s of Enterobacterales resistant to all antibiotics [1,2] has worsened the situation. Enterobacterales include bacterial species that belong to the intestinal microbiota of many mammals, and are far more transmissible from one individual to another, compared to the "non-fermenting" Gram-negative bacteria, which are more likely to be detected in the environment and mainly affect patients with severe underlying conditions [3].

In Enterobacterales, the most worrisome resistance mechanisms to β-lactams are the production of β-lactamases that hydrolyze virtually all β-lactams, including carbapenems, hence the name carbapenemases. However, a non-negligible proportion of carbapenem-resistant Gram-negative bacilli do not produce any carbapenemase. These carbapenem-resistant Enterobacterales (CRE) without carbapenemase production (non-CPE CRE) combine decreased outer membrane permeability with

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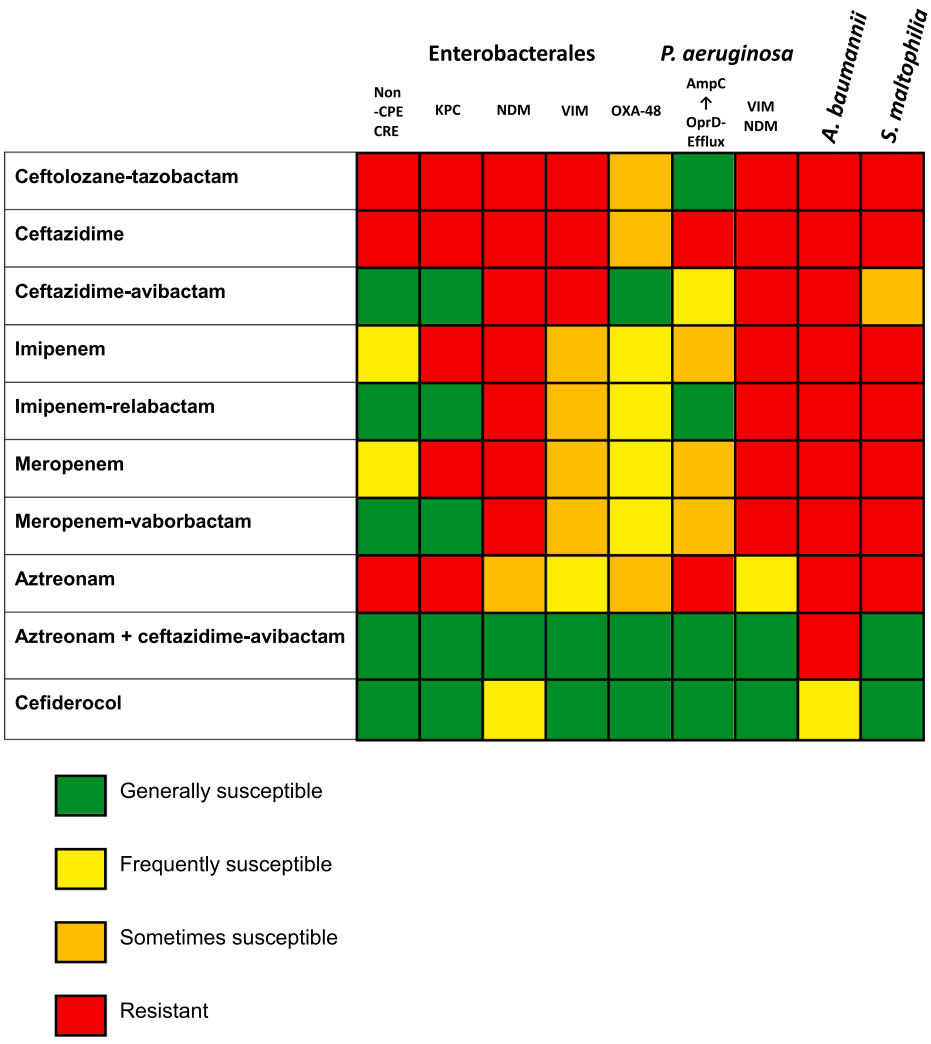

Fig. 1. Activity of new compounds according to bacterial species and resistance mechanisms.

overproduction of a cephalosporinase and/or an extended spectrum β-lactamase (ESBL), both having very low carbapenem hydrolytic activity.

The emergence of antibiotic-resistant bacteria is not a new phenomenon. For example, when infection-causing enterobacteria become resistant to aminopenicillins, other antibiotics can be administered, without any real loss of chance for the patient (e.g. β-lactamase inhibitors such as clavulanic acid, or 3rd-generation cephalosporins). When the first isolate of ESBL-producing Enterobacterales appeared in the early 1980's, carbapenems were already available and could be prescribed to adequately treat severely infected patients. However, the recent emergence of carbapenem-resistant strains has made the situation more complex, preventing the use of not only the main β-lactams, but also other molecules such as cotrimoxazole, aminoglycosides and fluoroquinolones. In addition, this kind of co-resistance to several antimicrobial families is related to the carriage of transmissible mobile genetic elements (e.g. plasmids) that accelerate the dissemination of multidrug resistance. Finally, the only antibiotics currently active "*in vitro*", such as colimycin, tigecycline or fosfomycin, have very modest pharmacokinetic / pharmacodynamic performances, resulting in limited real impact on the standard of care for patients. Since 2015, the licensing of new compounds from the β-lactam family, particularly those associating new inhibitors active on some of these multidrug-resistant strains, has marked a turning point in the treatment of these infections and represents real progress. Their use is complex and requires thorough understanding of resistance mechanisms so as to prescribe the most effective molecule. Unfortunately, acquired resistances to several of these new antibiotics have appeared very rapidly. Therefore, prescription of these new therapeutic alternatives requires close collaboration between microbiologists, infectious diseases specialists and intensive care physicians. While these compounds are clearly more active against resistant strains than those previously available, they do not cover all resistance mechanisms. Furthermore, the molecules need to be prescribed according to their PK/PD parameters.

The use of these new compounds does not alter antibiotic regimens in terms of duration and indication of combined antibiotic therapy, which remain very limited.

1) Classification of different β-lactamases [4–7]

The most widely used a classification of β-lactamase is the Ambler's. It groups β-lactamases into 4 classes:

- Class A: serine β-lactamases including ESBLs and KPC-type carbapenemases. These enzymes can be inhibited by clavulanate, tazobactam, avibactam, relebactam and vaborbactam.
- Class B: metallo β-lactamases including carbapenemases of NDM, VIM and IMP types. These enzymes cannot be inhibited by any currently available β-lactamase inhibitors.
- Class C: cephalosporinases (also named AmpC). It includes chromosome-encoded AmpCs and acquired AmpCs (mostly plasmid-

Table 1
Antibiotics recommended according to the mechanisms of resistance and the type of infections.

Bacterial species	Antibiotic choices	
Enterobacter cloacae, ***Klebsiella aerogenes,*** ***Citrobacter freundii,*** ***Serratia marcecens,*** ***Morganella morganii,*** ***Providencia* spp.,** ***Hafnia alvei*** **Susceptible to cefotaxime-ceftriaxone**	-The recommended treatment for severe infections is **cefepime** -when possible, oral switch for TMP-SMX or fluoroquinolones may be proposed if the strain is susceptible, depending on the clinical situation -TMP-SMX, fosfomycin trometamol, nitrofurantoin or cefixime may be considered for the treatment of cystitis	This choice is driven by the risk of emergence of resistant strains during treatment (derepressed cephalosporinase) and to a lesser extent *Serratia marcescens, Morganella morganii, Providencia* spp., *Hafnia alvei) (Ambers class D)*.
Enterobacter cloacae, ***Klebsiella aerogenes,*** ***Citrobacter freundii,*** ***Serratia marcecens,*** ***Morganella morganii,*** ***Providencia* spp.,** ***Hafnia alvei*** **Resistant to cefotaxime-ceftriaxone by cephalosporinase de-repression (Ambler class C).**	-The recommended treatment for severe infections are **cefepime or meropenem** according to the strain susceptibility - when possible, oral switch for TMP-SMX or fluoroquinolones (if the strain is acid nalidixic susceptible) may be proposed, depending on the clinical situation -TMP-SMX, Fosfomycin-trometamol, nitrofurantoin (except *Morganella*, *Serratia* and *Providencia*) may be considered for the treatment of cystitis	
C3G-resistant and carpenem-susceptible Enterobacterales due to extended spectrum β-lactamase ***Severe infections*** (shock, sepsis regardless of location) **or locations other than urinary tract or biliary tract infections**	**Meropenem** Imipenem can be used when polymicrobial infection that also involves enterococci.	When possible, oral switch with cotrimoxazole or the combination cefixime+amoxi/clav (only for *E. coli, K. pneumoniae or* ESBL-producing *Proteus* if *"in vitro"* susceptible to piperacillin-tazobactam and/or MIC of cefixime in synergy with Amox/clav $\leq$ 1mg/l), or ciprofloxacin.
Febrile urinary tract infections **Initial treatment**	**Amikacin** Temocillin Cefoxitin (*E. coli* only)	
Oral relay according to sensitivity profile	TMP-SMX or Cefixime + amox/clav [8,9] or Ciprofloxacin	
If no oral alternative is available according to the susceptibility profile	Amikacin (5 days maximum) or Temocillin or Cefoxitin	
Non-febrile urinary tract infections (- no risk factors)	Amox/clav or TMP-SMX	
Carbapenem-resistant Enterobacteriaceae (CRE) **OXA 48 & OXA 48-like:**	**ceftazidime-avibactam**	High doses meropenem is recommended if MIC < 8 mg/l in some guidelines.
KPC	**ceftazidime-avibactam** meropenem-vaborbactam imipenem-relebactam	The recommendations the Société Française de Microbiologie require the microbiologist to comment "used carbapenem in high dosage and in combination if carbapenemase is produced". Combination with an antibiotic from another class is not recommended for new compounds.
Metallo-ß-lactamases and resistant to all other ß-lactams	**ceftazidime-avibactam +** **aztreonam** or cefiderocol	
Severe infections susceptible *in vitro* only to polymyxins, aminoglycosides, tigecycline or fosfomycin, or in case of unavailability of new BL/IBLs	Colimycin combined with: Meropenem (if MIC to Mero < 8) or Tigecycline or Fosfomycin	

(*continued on next page*)

Table 1 (*continued*)

Bacterial species	Antibiotic choices	
***Pseudomonas* aeruginosa** *Piperacillin-susceptible*	**Piperacillin** (or piperacillin-tazobactam)	Before the results of antibiotics susceptibility testing, association with aminoglycoside (Tobramycin or Amikacin) is the rule. For some authors, monotherapy could be prescribed only for ceftazidime or when the bacterial inoculum seems controlled.
Piperacillin-resistant ceftazidime-susceptible	**Ceftazidime**	
Resistant to the two previous antibiotics and sensitive to meropenem	**Meropenem**	
Also resistant to carbapenems	**Ceftolozane-tazobactam** Ceftazidime-avibactam Imipenem-relebactam Cefiderocol	
In the absence of other alternatives,	Combination therapy with colimycin, aminoglycosides or fosfomycin	
Carbapenem-resistant *Acinetobacter baumanii*	A combination of 2 *in vitro*-active antibiotics is recommended, with preference given to Ampicillin-sulbactam + one of the following antibiotics: colimycin, aminoglycosides, tigecycline. Cefiderocol (combined therapy) considered in last resort	
Stenotrophomonas maltophilia	TMP-SMX or Levofloxacin or aztreonam + ceftazidime-avibactam or Minocycline or Tigecycline or Cefiderocol	Association of 2 antibiotics is suggested for severe infections until clinical improvement is observed

Table 2
Doses proposed for new compounds in children [13,14]. The doses proposed for the new antibiotics have to be validated before prescriptions taking into account the latest data.

Trade name	Compounds	Dosages	Remarks
Azactam®	Aztreonam	40 to 60 mg/kg/8 hours (not to exceed 2g/8h)	
Zerbaxa®	Ceftolozane + Tazobactam	20 mg/kg/8 hours (not to exceed 3g/8h)	For cystic fibrosis patients and nosocomial pneumonia, higher doses should be considered (up to 120mg/kg/d). To extend the time above the MIC, IV infusion can be prolonged for up to 3 hours.
Zavicefta®	Ceftazidime + Avibactam*	< 6 months :40 mg/kg/8 hours of ceftazidime > 6 months: 50 mg/kg/8 hours (not to exceed 2g/8h)	2-hour infusion 4-hour infusion if MIC > 8 mg/L
Vaborem®	Meropenem + Vaborbactam*	40 mg meropenem /kg/8 hours (not to exceed 2 g /8h)	
Recarbio®	Imipenem + Relebactam*	15 mg imipenem /kg/6 hours (not to exceed 500 mg/6h)	
Fetcroja®	Cefiderocol* Not licensed in children	60 mg/kg/8 hours (not to exceed 2g/8h)	For cystic fibrosis patients, higher doses should be considered

encoded). These enzymes can be inhibited by avibactam, relebactam and vaborbactam.
– Class D: oxacillinases. This group is very diverse, including OXA-48 carbapenemases. The OXA-48-like enzymes can be inhibited only by avibactam.

The activity of new compounds and/or inhibitors essentially depends on the carbapenemase produced.

2) **New compounds** [8,9]

They represent real progress, with clinical results on carbapenem-resistant strains better than those obtained with colimycin, tigecycline or fosfomycin. Despite their recent and relatively limited use, resistance has already been described, and sometimes emerged even during treatment. Except for imipenem-relebactam, all of these new molecules are inactive against enterococci and anaerobes. Currently only **ceftazidime-avibactam and ceftolozane-tazobactam** have marketing authorization in pediatric infections. These antibiotics should only be used for curative treatment of microbiologically documented infections, and not for probabilistic antibiotic therapy. These molecules should only be prescribed for the treatment of infections due to Gram-negative bacteria resistant to cephalosporins and carbapenems, in the absence, of alternatives and after identification of the resistance mechanisms involved and confirmation of susceptibility to the chosen molecule (minimum inhibitory concentration (MIC) determination if possible). They do not constitute a carbapenem-sparing strategy. Their prescription must be strictly controlled (collaboration between microbiologists, pediatric infectiologists and intensivists).

- **Ceftolozane-tazobactam**

Its main target is *P. aeruginosa*: over 80% of ceftazidime-resistant strains are susceptible, as are over 50% of strains resistant to all other anti-*Pseudomonas* β-lactams.

- **Ceftazidime-avibactam**

Metallo-β-lactamase producers (Ambler class B), mostly NDM and VIM producers, are intrinsically resistant to ceftazidime-avibactam. In France, this association remains active on almost 100% of KPC and OXA-48-like producing Enterobacterales. Of note, ceftazidime-avibactam-resistant variants of KPC have emerged recently (mostly in the USA, Italy, Portugal and Spain). Since avibactam is an efficient inhibitor of ESBLs and AmpCs, it remains an alternative treatment of infections caused by non-CPE CRE. Ceftazidime-avibactam is ineffective towards *Enterococci* and anaerobes.

- **Meropenem-vaborbactam**

Metallo-β-lactamase producers (Ambler class B), mostly NDM and VIM producers, are intrinsically resistant to meropenem-vaborbactam. Vaborbactam is a very efficient inhibitor of KPC enzymes, often leading to very low MICs of the meropenem-vaborbactam association. Usually, KPC variants resistant to ceftazidime-avibactam remain susceptible to meropenem-vaborbactam. OXA-48 enzymes are not significantly inhibited by vaborbactam. Since vaborbactam is an efficient inhibitor of ESBLs and AmpCs, it remains an alternative treatment of infections caused by non-CPE CRE. Meropenem-vaborbactam is ineffective towards *Enterococci* and anaerobes. The meropenem-vaborbactam association does not have any advantage compared to meropenem alone for *P. aeruginosa*.

- **Imipenem-relebactam**

This association has not yet been approved for pediatric use. Metallo-β-lactamase producers (Ambler class B), mostly NDM and VIM producers, are intrinsically resistant to imipenem-relebactam. It possesses a spectrum close to meropenem-vaborbactam except for its activity towards *Enterococcus faecalis* and anaerobes. Contrary to vaborbactam, relebactam is an inhibitor of *P. aeruginosa* AmpC. Accordingly, imipenem-relebactam might be a therapeutic option for the treatment of infections caused by imipenem-resistant (+/- ceftolozane-tazobactam-resistant) *P. aeruginosa*. Since relebactam is an efficient inhibitor of ESBLs and AmpCs, it also remains an alternative treatment of infections caused by non-CPE CRE.

- **Cefiderocol**

It is a cephalosporin with a novel mechanism of action, as it uses iron channels (it chelates iron and is perceived as a siderophore) enabling bypass of Gram-negative bacteria's outer membrane porins. It appears to be highly stable to hydrolysis by virtually all β-lactamases, which theoretically allows it to act against all Gram-negative bacterial species resistance mechanisms (including metallo-β-lactamase-producing Enterobacterales, with imipenem-resistant *A. baumannii* (ABRI), *P. aeruginosa* pan-resistant-R and *S. maltophilia*). Of note, among metallo-β-lactamases producers, NDM producers possess increased MICs to cefiderocol compared to VIM producers. Cefiderocol is ineffective towards *Enterococci* and anaerobes.

- **Aztreonam + ceftazidime/avibactam**

Aztreonam (a long-established molecule) is not hydrolyzed by class B metallo-β-lactamases. The addition of an inhibitor (avibactam) enables it to act on several other resistance mechanisms (ESBL, cephalosporinase, other carbapenemases). Accordingly, most multidrug- resistant Enterobacterales appear susceptible to aztreonam-avibactam, including metallo-β-lactamase producers. However, while this combination is also effective against *S. maltophilia,* it offers little benefit against *P. aeruginosa* and is not active against *A. baumannii*.

Fig. 1 presents the activities of new compounds according to bacterial species and resistance mechanisms.

3) Antibiotics proposed according to bacterial species, resistance mechanisms and site and severity of infection [4–12]

Choices should be prioritized according to the following clinical criteria:

- Severity (defined as the presence of sepsis or septic shock).
- Infection location: urinary/biliary infection or not (excluding bone, neurological and foreign material infections).

Table 1 presents the choices proposed according to mechanisms of resistance and type of infections.

Table 2 presents the doses of the new compounds proposed for pediatric patients.

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RC and JT wrote the first draft of the article and all of the authors revised and approved the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review

Antimicrobial treatment of infrequent bacterial species

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ABSTRACT

This section summarizes empirical antimicrobial treatment for the less frequent bacterial species less frequently causing infection, whether it be community-acquired or healthcare-associated. It specifies their role in different diseases and the recommended antibiotics, taking into account their natural and most common acquired resistance and the relevant pharmacokinetic-pharmacodynamic parameters. The advice of an infectious disease specialist or microbiologist is frequently needed.

The choice of antibiotics is generally empiric, made before the results of bacteriological sample cultures and antibiotic susceptibility testing have been obtained. While mass spectrometry shortens time to identification of the bacterial species, as of now it is unable to determine susceptibility to antibiotics. Polymerase chain reaction assays (PCR) enable more rapid identification of bacterial species, being more sensitive to those for which culture is difficult. They may also be of use once antibiotic treatment has started, and can in certain cases help to identify mechanisms of resistance. That said, they do not fully indicate the antibiotic susceptibility of the stain.

Empiric antibiotic treatment attempts to target the bacteria most frequently responsible for community-acquired or nosocomial bacterial infections:

- *Neisseria meningitidis* or *S. pneumoniae* for childhood meningitis,
- *S. pneumoniae*, *Haemophilus influenzae* for respiratory tract infections,
- Group A *Streptococcus* for strep throat, complicated ENT (Ear, Nose and Throat) infections and skin infections,
- *Staphylococcus aureus* for skin, bone, and some serious respiratory infections,
- *Escherichia coli* for urinary tract infection
- *E. coli, Listeria monocytogenes* and *Group B Streptococcus* for neonatal infections;
- *Shigella*, *Salmonella*, and *Campylobacter* for digestive tract infections.

The preferred antibiotic treatments for each of these bacterial species are indicated in the chapters corresponding to the different diseases.

Some bacterial species are more rarely implicated in pediatric infectious diseases.

Table 1 lists these bacterial species in alphabetical order. It details their role in pathology as well as the recommended antibiotics, taking into account the natural or acquired resistance of the bacterial species and the pharmacokinetic and pharmacodynamic parameters of the antibiotics. Treatment of most of these bacteria requires specialized advice (consultation with an infectious disease specialist or microbiologist), particularly in high-risk diseases (immunodepression, presence of material, etc.). The differential diagnosis between infection and colonization can be difficult. All of the suggested antibiotic treatments are in accordance with the most recent edition (32st Edition 2021–2024) of Redbook (American Academy of Pediatrics) [1,2]

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Author contribution

RC and JR wrote the first draft of the article and all of the authors revised and approved the manuscript.

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Table 1
Recommended treatment of infrequent bacterial species isolated in children.

Bacteria	Diseases	Recommended regimens	Alternatives	Comments
Acinetobacter sp.	• Nosocomial infections • Septicemia • Urinary tract infections	Imipenem or Meropenem + Amikacin	According to the antibiotic susceptibility: Colimycin Tigecycline Rifampicin Sulbactam Cefiderocol	
Actinomyces sp	Localized or systemic infections: • Stomatological • Thoracic • Abdominal • Pelvic • Brain abscess Considered pathogenic only when isolated from a normally sterile site.	Penicillin G or Amoxicillin	Ceftriaxone or Macrolides or Doxycycline if > 8 years	Its pathogenic role should be recognized only after critical analysis of the situation (frequent contaminant). Considered pathogenic only when isolated from a normally sterile site or specific changes in histological examination. Prolonged treatment duration: 4–12 months is necessary. Surgical drainage often useful.
Aeromonas hydrophila	• Diarrhea • Wound infections • Septicemia • Meningitis	Antibiotic therapy not necessary for common diarrhea	Cotrimoxazole or Cefotaxime or Ceftriaxone or Aminoglycosides or Chloramphenicol	Antibiotics are indicated only for systemic and severe forms of diarrhea.
Aggregatibacter (formerly Haemophilus) aphrophilus	• Septicemia • Endocarditis +++ • Abscess (brain) • Osteitis	Amoxicillin/clavulanate or Cefotaxime if cerebral localization	Cefotaxime	Often associated with anaerobic bacteria
Bacillus anthracis	• Anthrax • Skin infections	Ciprofloxacin	Doxycycline after 8 years or Amoxicillin 30 mg/kg (if strains is sensitive)	*Zoonoses or Bioterrorism* Treatment duration: 60 days due to spores. The need for prolonged treatment (6 weeks) contraindicates Doxycycline in children under 8 years old.
***Bacillus* sp.**	• Frequent contaminant : retain only several positive samples from normally sterile media to draw a conclusion on liability • Septicemia	In most cases, no treatment is necessary. Bacillus sp. are most often sensitive to amoxicillin.		To be adapted according to antibiotic susceptibility and location of infection.
***Bacteroides* sp.**	• Peritonitis • Sepsis • Abscess • Pneumonia	Piperacillin-Tazobactam or Amoxicillin/clavulanate	Metronidazole or Cefoxitin or Clindamycin or Penems	Frequent association of different anaerobes at the same site of infection.
Bartonella henselae	• Lymphadenopathy • Endocarditis • Parinaud's syndrome • Spondylodiscitis • Disseminated diseases	Azithromycin	Doxycycline or Ciprofloxacin or Ceftriaxone or Gentamicin or Rifampicin	Zoonosis The majority of adenopathies due to *B. henselae* recover spontaneously within a few weeks and do not warrant treatment. Various treatments have been proposed but even though *B. henselae* is susceptible, none have proved effective. However, Doxycycline or Azithromycin are indicated for immunocompromised patients and in cases of neuroretinitis.
Bartonella quintana	• Trench fever • Bacillary angiomatosis	Azithromycin	Doxycycline	*Zoonosis*

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Table 1 (*continued*)

Bacteria	Diseases	Recommended regimens	Alternatives	Comments
Bordetella pertussis	• Whooping cough	Clarithromycin	Azithromycin Cotrimoxazole	
Borrelia Burgorferi Lyme disease	***Erythema migrans***	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum 200 mg/day) for 10 days OR Amoxicillin, 50 mg/kg per day, orally, divided into 3 doses (maximum 1.5 g/day) for 14 days OR Cefuroxime, 30 mg/kg per day, orally, in 2 divided doses (maximum 1 g/day) for 14 days		*Vector-borne disease* Treatment depends on the stage and clinical form of the disease. Doxycycline is the reference treatment for all clinical forms, but the duration of treatment varies: • 10 days to erythema migrans • 14 days for b atrioventricular lbloc, facial paralysis and meningitis 28 days for arthritis
	Isolated facial palsy	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum 200 mg/day), for 14 days		
	Arthritis	An oral agent as for early localized disease, for 28 days		
	Atrioventricular heart block or carditis	An oral agent as for early localized disease, for 14 days OR Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14 days (range 14–21)		
	Meningitis	Doxycycline, 4.4 mg/kg per day, orally, divided into 1 or 2 doses (maximum 200 mg/day) for 14 days OR Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14 days		
Borrelia recurrentis	• Recurrent fever	Doxycycline	Macrolides	*Vector-borne disease* Treatment duration: 5 to 10 days.
Brucella sp.	• Brucellosis	If > 8 years Doxycycline + Rifampicin	If < 8 years Cotrimoxazole + Rifampicin	*Zoonosis* The need for prolonged treatment (6 weeks) contraindicates Doxycycline in children under 8 years old.
***Burkholderia cepacia* complex**	• Cystic fibrosis superinfection • Chronic granulomatosis • Nosocomial infections	Meropenem + Cotrimoxazole	According to the antibiotic susceptibility: Ceftazidime Imipenem or Meropenem Chloramphenicol	
Burkholderia pseudomallei	• Melioidosis	Ceftazidime + Aminosides	Cotrimoxazole Penem Doxycycline	If severe Penem + Cotrimoxazole
Campylobacter jejuni and Campylobacter coli	• Diarrhea • Septicemia • Meningitis	Azithromycin	Ciprofloxacin (if susceptible) or Imipenem or Aminosides or Amoxicillin/clavulanate (if susceptible)	Other macrolides could be used. Azithromycin not adapted in case of exceptional septicemic forms

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Table 1 (*continued*)

Bacteria	Diseases	Recommended regimens	Alternatives	Comments
Chlamydophila pneumoniae	Pneumonia and other lower respiratory tract infections	Clarithromycin	Doxycycline	
Chlamydophila psittaci	Psittacosis	Macrolides	Doxycycline	
Chlamydophila trachomatis	• Neonatal conjunctivitis • Trachoma • Interstitial lung disease • Pneumonia • Urethritis, epididymitis • Vaginitis, Cervicitis, Salpingitis, Pelvic inflammatory diseases • Arthritis	Azithromycin	Doxycycline	
Clostridium sp.	• Tetanus • Gas gangrene • Septicemia • Botulism	Amoxicillin	Clindamycin Metronidazole Penicillin G	
Clostridium difficile	• Pseudomembranous colitis • *Post-antibiotic diarrhea*	Metronidazole	oral Vancomycin	- Recurrent or resistant forms: Fidaxomicin - carriage frequent, single diarrhea should not be treated in immunocompetent host.
Corynebacterium diphteriae	• Diphtheria	Amoxicillin	Azithromycin	Serotherapy is usually required.
Corynebacterium jeikeium	• Nosocomial sepsis • Urinary tract infections	Vancomycin	Teicoplanin	
Cutibacterium acnes	• Skin infections (acne) • Ocular infections • Septicemia • Bone infections	Amoxicillin	Clindamycin Doxycyclin	Several positive samples are necessary before incriminating this bacterial species in a deep infection. Macrolide resistance is common.
Eikenella corrodens	• Bite infections • Oral infections • Abscess (brain) • Meningitis • Endocarditis	Amoxicillin	Doxycycline	
Enterococcus faecalis	Urinary tract infections Endocarditis Septicemia Intra-abdominal infections	Amoxicillin + Gentamicin	Vancomycin or teicoplanin + Gentamicin	
Enterococcus faecium	Urinary tract infections Endocarditis Septicemia Intra-abdominal infections	Vancomycin or Teicoplanin + Gentamicin	Linezolid + Gentamicin	
Francisella tularensis	• Tularemia	Ciprofloxacin	Doxycycline Chloramphenicol	*Zoonosis*
Fusobacterium* sp. including *Fusobacterium necrophorum	• Oral cavity commensal bacteria • Oral-dental infections • Severe infections such as Lemierre syndrome	Amoxicillin/ clavulanate	Metronidazole Cefoxitin Clindamycin Piperacillin-Tazobactam	Fusobacterium sp. are highly sensitive to amoxicillin, but amoxicillin +clavulanate is suggested, due to the frequency of co-infections Fusobacterium sp are naturally resistant to aminoglycosides and quinolones.
Gardnerella vaginalis	• Genital infections	Metronidazole	Amoxicillin/ clavulanate or Clindamycin	
Hafnia alvei	• Urinary tract infections • Septicemia • Nosocomial infections	Cefotaxime or Ceftriaxone	Cotrimoxazole or Meropenem or Ciprofloxacin	
Kingella kingae	• Osteo-arthritis • Septicemia • Endocarditis	Amoxicillin	Amoxicillin/ clavulanate or Aminoglycosides or Cotrimoxazole Or Oral Cephalosporins	A few strains are β-lactamase- producing. Naturally resistant to clindamycin and vancomycin.

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Table 1 (*continued*)

Bacteria	Diseases	Recommended regimens	Alternatives	Comments
***Legionella* sp.**	• Pneumonia • or other lower respiratory tract infections	Macrolides IV	Levofloxacin Doxycycline Cotrimoxazole	Very rare in children Biological confirmation (antigenuria or PCR or culture) mandatory. Association with rifampicin for more serious cases.
***Leptospira* sp.**	• Leptospirosis	Penicillin G or Amoxicillin	Ceftriaxone Doxycycline	*Zoonosis*
Listeria	• Sepsis • Meningitis	Amoxicillin + Gentamicin	Cotrimoxazole + Gentamicin	Preferentially involves newborns, pregnant women and the immunocompromised.
***Moraxella* sp.**	• Eye infections • ENT infections	Amoxicillin/ clavulanate	Cefotaxime or Ceftriaxone or Carbapenem	
Mycobacterium tuberculosis	• Tuberculosis	Isoniazid + Rifampicin + Pyrazinamide ± Ethambutol		Adapt to antibiotic susceptibility results (National Reference center if Antibiotic-resistant strains)
Mycobacterium avium complex	• Lymphadenopathy • Pneumonia • Disseminated infections (immunocompromised)	Clarithromycin or Azithromycin + Rifabutin	Isoniazid + Rifampicin + Ethambutol or Fluoroquinolones	Most lymphadenopathy due to Mycobacterium avium complex recovers spontaneously within a few weeks and does not warrant treatment.
Mycobacterium fortuitum	• Soft tissue and wound infections • Adenolymphadenitis	According to antibiotic susceptibility	According to antibiotic susceptibility	
Mycobacterium kansasii	• Lung disease (immunosuppressed)	Isoniazid + Rifampicin + Ethambutol		High-dose isoniazid (low level of resistance).
Mycobacterium leprae	• Leprosy	Dapsone + Rifampicin	Clofazimine	
Mycobacterium marinum	• Cold abscess • Papules (M arinum)	Doxycycline	Clarithromycin Rifampicin Cotrimoxazole	Often no treatment.
Mycoplasma pneumoniae	• Upper and lower respiratory tract infections • Pneumonia • Rashes including polymorphous erythema • Several neurologic involvement (aseptic meningitis, encephalitis, ataxia…) • Myocarditis-Pericarditis • Arthritis • Hemolytic anemia, thrombocytopenia purpura, hemophagocytic disorders	Clarithromycin	Azithromycin Doxycycline Ciprofloxacin	Evidence of the benefit of antibiotic therapy for non-hospitalized children with lower respiratory tract disease is limited. Some data suggest that hospitalized children benefit from appropriate antibiotic therapy. However, despite the paucity of studies, it is reasonable to treat serious extra-pulmonary infections such as central nervous system disease or septic arthritis in an immunocompromised patient. The usual duration of treatment is 7 to 10 days.
Mycoplasma genitalium	• Non-gonococcal urethritis	Clarithromycin	Doxycycline Ciprofloxacin	
Mycoplasma hominis	• Genital infections • Neonatal infections • Intra-abdominal abscess, septic arthritis, endocarditis, • pneumonia, • meningoencephalitis, brain abscess • surgical wound infection	Clindamycin	Doxycycline Ciprofloxacin	M. hominis is resistant to macrolides
Nocardia sp.	• Nocardiosis • Pneumonia • Abscess (brain)	Cotrimoxazole	Ciprofloxacin Meropenem	Rapid and accurate identification of Nocardia isolates and antimicrobial susceptibility testing are essential tools. Nocardia species possess

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Table 1 (*continued*)

Bacteria	Diseases	Recommended regimens	Alternatives	Comments
				intrinsic resistance to multiple drugs. Combination drug therapy is recommended for patients with serious disease (pulmonary infection, disseminated disease, central nervous system involvement) and for infection in immunocompromised hosts. Initial combination treatment should include TMP/SMX, amikacin, and penem
Pasteurella multocida (zoonose)	• Animal bites • Abscess • Septicemia (immunosuppressed)	Amoxicillin/clavulanate	Doxycycline Cotrimoxazole	If bites, other bacteria could be implicated.
Peptostreptococcus	• Septicemia • Oral and dental infections • Swallowing pneumonia • Intra-abdominal infections	Amoxicillin/clavulanate	Piperacillin-Tazobactam Vancomycin Linezolid Meropenem	Frequently associated with other anaerobic bacteria.
Plesiomonas shigelloides	• Diarrhea • Meningitis	Cotrimoxazole	Ciprofloxacin Meropenem	
Rickettsia sp.	• Mediterranean spotted fever • Typhus G • Q fever • Rocky Mountain spotted fever	Doxycycline	Azithromycin Clarithromycin	
Salmonella typhi and paratyphi	• Typhoid fever	Ceftriaxone or Ciprofloxacin	Azithromycin Cotrimoxazole	Strains resistant to ciprofloxacin are increasing. Check antibiotic susceptibility.
Stenotrophomonas maltophilia	• Superinfections in cystic fibrosis • Nosocomial infections • Sepsis • Pneumonia	Cotrimoxazole + Ciprofloxacin, Ceftazidime, Tobramycin	Aminosides Rifampicin Colimycin Levofloxacin Aztreonam + ceftazidime-avibactam Cefiderocol	
Treponema pallidum	• Syphilis	Extencilline or Penicillin G	Azithromycin single dose Doxycycline Ceftriaxone	Amoxicillin is not active against Treponema sp in vivo.
Ureaplasma urealyticum	• Urogenital infections • Pneumonia (premature baby)	Azithromycin	Doxycycline (>8 years)	A positive sample from a non-sterile medium does not imply a pathogenic role for *Ureaplasma.* Treatment of asymptomatic forms is not justified.
Vibrio cholerae	• Cholera	Ciprofloxacin	Doxycycline or Azithromycin	
Vibrio parahaemolyticus	• Gastroenteritis	Doxycycline (>8 years)	Cotrimoxazole or Ciprofloxacin	
Yersinia enterocolitica and Yersinia pneudotuberculosis	• Pseudo-appendicular pictures • Gastroenteritis • Sepsis • Erythema nodosum • Reactive arthritis • Febrile syndromes	Cotrimoxazole	Doxycycline or Ciprofloxacin	
Yersinia pestis	• Plague • Sepsis • Pneumonia • Bioterrorism	Gentamicin + Doxycycline or Ciprofloxacin Dual therapy required	Gentamicin Ciprofloxacin Chloramphenicol	*(Zoonosis or bioterrorism)*

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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