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Acute osteomyelitis due to *Staphylococcus aureus* in children: What is the status of treatment today?

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ABSTRACT

Osteomyelitis is an inflammatory process caused by microorganisms and usually accompanied by bone destruction. The process may be limited to one portion of the bone or spread to several areas such as the bone marrow, periosteum or cortex.¹ It is an infection that can occur at all ages. In children, the average age of onset is 6 years. Today, many of these risks factors are poorly understood or inadequately addressed in healthcare. If improperly treated, the infection can progress to chronicity, with possible recurrence several years after the acute episode. *Staphylococcus aureus* is the most frequently isolated pathogen. The treatment of acute osteomyelitis should be started at the earliest stage and initiated in hospital with intravenous antibiotics. The antibiotic molecules used must have good penetration in the bone and be bactericidal. The choice of the molecule for empirical treatment must take into account the local epidemiological features and results of bacteriological cultures. According to epidemiological data, the prevalence of Methicillin-resistant *Staphylococcus aureus* (MRSA) varies greatly from one country to another and from one continent to another. Overcrowding and low social-economic background are factors favouring the spread of MRSA in the community. Apart from ensuring early referral, the medical community also needs to do research on the main challenges facing us in the control of acute osteomyelitis, a disease that is especially serious in children, such as improved diagnosis, detection of drug resistance, shortened treatment regimens and clinical trials of new drugs.

Keywords:
Osteomyelitis
Children
Infection
Bone
Monitoring

1. Objective

Osteomyelitis is an inflammatory process caused by microorganisms and usually accompanied by bone destruction. The process may be limited to one portion of the bone or spread to several areas such as the bone marrow, periosteum or cortex.¹

It is an infection that can occur at all ages. In children, the average age of onset is 6 years. Today, many of these risks factors are poorly understood or inadequately addressed in healthcare. If improperly treated, the infection can progress to chronicity, with possible recurrence several years after the acute episode. *Staphylococcus aureus* (*S. aureus*) is the most

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frequently isolated pathogen. In practice, some cases are secondary to *S. aureus* bloodstream infections (bacteraemia) including those due to right-sided *S. aureus* native valve infective endocarditis caused by methicillin-susceptible and methicillin-resistant strains. Vancomycin is the antibiotic used as first choice in Methicillin-resistant *S. aureus* (MRSA) infections, despite the recent emergence of some strains resistant to this molecule. We propose in this article to take describe the state of practice in treating this infection.

Staphylococcus aureus (*S. aureus*) is the most pathogenic species of the genus *Staphylococcus*. It is a human commensal and opportunistic germ that becomes a pathogen in certain circumstances. *S. aureus* is found in healthy individuals in the nasal passages, throat, the gastrointestinal tract and on the perineum. From the nasopharynx, the bacterium is spread onto the skin of the face and hands by aerosols. *S. aureus* has pathogenicity, including potential invasiveness and toxicity. This depends on its invasive powers (the ability to spread in living tissue and establish one or several seats of infection), on its toxicogenic powers (i.e. its capacity to produce toxins) and its capacity to overcome the host's defence mechanisms. Toxins secreted by the bacterium have both toxic and antigenic properties. Its pathogenicity results from several specific secretions²:

- Deoxyribonuclease (DNase), protease;
- Toxins: enterotoxin (in some strains), staphylolysins and leucocidins;
- Enzymes: coagulase, fibrinolysin, phosphatase, hyaluronidase.

2. Materials and methods

S. aureus (SA) has a great ability to give rise to antibiotic-resistant mutants. MRSA is usually acquired in a hospital. However in recent years we are witnessing the emergence of MRSA in the community (CA-MRSA).³ SA strains were invariably sensitive to penicillin G at the beginning of its use. Then over the years there has been a gradual emergence of strains resistant to penicillin and then to methicillin, through the secretion of a specific enzyme. The advent of glycopeptides produced but a brief respite in the fight against methicillin-resistant SA because the 1990s saw the appearance of MRSA strains resistant to glycopeptides. While the problem of methicillin resistance was confined in hospitals, in the early 2000s MRSA clones were identified in the community. Today the problem of nosocomial MRSA as well as community MRSA has become a pandemic. According to Networks AZAY, SUCCEED, Ile de France, the percentage of MRSA bacteraemia in France amounted to 25.8% in 2007. The percentage of Community MRSA (CA-MRSA) and those secreting Panton-Valentine leukocidin (PVL) is less than 1% in a retrospective study from 2000 to 2003. CA-MRSA causes purulent, localized surface infections, such as boils, abscesses and infected lacérations occurring in patients without any risk factor for hospital acquired strains. In the United States, the problem of PVL-MRSA is higher reaching 57% of skin infections, 97% of which is accounted for by USA clone. Consequently, there is a difference between patients with nosocomial strain and

patients with a community strain (which may be more virulent).

Antibiotics are sometimes given empirically against MRSA which obviously do not work and additionally have the risk of accentuation of the multidrug-resistant strains. Hence, timely collection of sample material for laboratory testing and analysis is advised prior to treatment activity.

There are different sources of material for culture to identify *S. aureus* strains, such as the nasal membrane, pus, blood, and skin. In vitro diagnostic tests are based on the analysis of a biological sample taken from body parts and organs (e.g. mouth, nose and hands) using sterile swabs. A variety of MRSA strains may be isolated from different clinical infection sites: calf wound, thigh wound, abdominal pus, lungs, vagina, eye, nose, inguinal region, axilla, umbilicus, and nails, tongue and wound pus.⁴ Generally, MRSA strains are collected from various clinical specimens from different university hospitals or from immediate environment (e.g. airways) of the patients and their relatives or visitors in diverse hospital settings (e.g. neonatal, surgical and intensive care units).

MRSA strains are isolated and stored at appropriate temperature in suitable culture media and invigorated using basic microbiological procedures. For instance, nasal samples can be analysed for *S. aureus* by typical quantitative culture means using a selective and differential medium. The isolation and identification of MRSA can also be done by means of agar diffusion methods in solid medium or through liquid medium procedures. In particular, chromogenic agar media test enables visual characterization of MRSA colonies in a presumptive patient sample.⁵ Such an approach generally fits into the group of screening methods that are frequently based on microbiological growth inhibition, anti-microbial resistance risk assessment or chromogenic responses allowing identification of a suspected element of MRSA.⁶

Subsequently, the culture media is made using sterilized bacterial screens for cultivation of pathogenic bacterial isolates, according to guidelines of the media supplier. In practice, several techniques can be used for the identification and detection of MRSA using a variety of laboratory diagnosis and susceptibility testing approaches⁷: The laboratory diagnosis techniques for bacterial isolation and biochemical identification of MRSA include Tube coagulase test, Slide coagulase test, Latex agglutination tests, DNase and heat-stable nuclease tests, Commercial biochemical tests and Molecular tests.

In addition, different methods have been established for antibiotic susceptibility testing of MRSA. These methods comprise Dilution methods, E-test method, Breakpoint methods, Agar screening method, Disc diffusion, Latex agglutination, Automated methods, Quenching fluorescence method and Molecular methods. Particularly, Molecular methods may be used for direct identification of MRSA in blood cultures or identification of MRSA in endotracheal aspirates and other clinical samples.

Furthermore, detection of MRSA in screening samples is made either with conventional methods (solid agar media and enrichment) or with molecular methods. Lastly, confirmation and quantitative analysis of MRSA is determined by the minimum inhibitory concentration values and the bacterial

growth is characterized by the absence of the target colouration to indicate drug resistance.

3. Results

In the authors' experience, MRSA is identified using conventional laboratory methods (e.g. Disc diffusion test by Kirby–Bauer method, Oxacillin MIC, Oxacillin screen agar test, etc.). These laboratory methods provide relevant information for identifying bacteria (especially presence of MRSA)⁸ and testing their susceptibility to antibiotics: this is called antibiogram analysis.⁹ Antibiograms are intended to help clinicians choose the appropriate antibiotic.

In Africa we are seeing the emergence of MRSA as illustrated by data from a study conducted by the Pasteur Institute in five African countries (Cameroon, Senegal, Morocco, Niger and Madagascar) wherein 87% of strains were resistant to methicillin, including three major clones: ST 239/241, ST 88 and ST5. In the city of Yaoundé, Cameroon, the dominant ST 88 -SCCmec produces Hlb toxin. It is a new clone of MRSA specific to Africa and sensitive to other antibiotics. There is a high prevalence of PVL + MRSA in Africa: (57%), with a higher prevalence in Cameroon: 74%. It is a routine practice to involve a large number of family members in the care of patients in hospitals in Africa. This practice is responsible for the distribution of hospital MRSA strains with high prevalence in the community.

The treatment of acute osteomyelitis should be started at the earliest stage, and initiated in hospital with intravenous antibiotics. The antibiotic molecules used must have good penetration into bone and be bactericidal. The choice of the antibiotic molecule for empirical treatment must take into account the local epidemiological features and the results of bacteriological cultures. Germs that should be priority targets are Methicillin Sensitive Staph. Aureus (MSSA), *Kingella kingae*, Group A Streptococcus and Pneumococcus. Intravenous therapy may be continued for 4–7 days if the response is favourable. Intravenous antibiotic therapy is then replaced by oral treatment for a period of 2–4 weeks.¹⁰ In general, an initial monotherapy is sufficient, except in cases of prosthetic infection or sepsis or shock associated toxin, where combination therapy is necessary. The molecules that may be used are described in Table 1.

Surgical intervention may be necessary in case of purulent collections. Sometimes several interventions are needed to control the situation. In emergency, it is recommended to make a simple incision with drainage of the subperiosteal collection. Cortical trephination and intra metaphyseal curettage are contraindicated because they may cause the spread of infection to the metaphysis. The following clinical signs should lead us to suspect a *S. aureus* producing PVL: initial septic shock, with multifocal bone infection, necrotizing myositis and associated necrotizing pneumonia. Effective antibiotic treatment must be urgently instituted in order to limit the production of toxin. It should be noted that despite effective antibiotic therapy associated with early surgical drainage, the evolution of PVL-SA osteomyelitis may not improve rapidly. Complications are frequent such as subperiosteal abscess and muscle necrosis. Bone-related

Table 1 – Given current patterns of patient treatment.

Germs	Intravenous treatment (IV treatment)		Oral relay	
	First choice	Alternatives	First choice	Alternatives
SAMS	Cloxacillin 50 mg/kg/6 h	Amoxicillin/clavulanic acid 35 mg/kg/6 h or Clindamycin 10 mg/kg/6 h	Amoxicillin/clavulanic acid 80 mg/kg/24 h	Clindamycin 15 mg/kg/8 h or Cotrimoxazole 15–20 mg/kg/8 h
SARM	Vancomycin 15 mg/kg/6 h, or IV continuous + Rifampicin 10 mg/kg/12 h	Clindamycin 10 mg/kg/6 h	Clindamycin 15 mg/kg/8 h	Rifampicin 10 mg/kg/12 h + Cotrimoxazole 15 with 20 mg/kg/8 h or + Fusidic acid 15 with 20 mg/kg/8 h
SARM–PVL	Clindamycin 10 mg/kg/6 h + Gentamicin 5–7, 5 mg/kg/24 h	Rifampicin 10 mg/kg/12 h + Gentamicin 5–7, 5 mg/kg/24 h		

sequelae may ultimately require reconstructive surgeries at a later date.¹¹

4. Discussion

According to epidemiological data, the prevalence of MRSA varies greatly from one country to another and from one continent to another. Overcrowding and poor socio-economic status are factors favouring the spread of MRSA in the community.¹² Pathogenic strains also differ according to the environment. Correct identification of the strain is very important for deciding the choice of antibiotic treatment. The role of the laboratory is important here to determine the types of strains involved in infections, as well as to determine the resistance rate of MRSA to antibiotics or other anti-microbial agents.¹³ Delay in laboratory identification should not however delay the initiation of empirical antibiotic treatment. Vancomycin remains the first choice in the treatment of acute MRSA osteomyelitis in children. Its use as monotherapy is not recommended. The choice of antibiotics should also take into account the severity of the clinical picture and the epidemiological situation. If the clinical picture is suggestive of serious sepsis, fasciitis or necrotizing myositis and associated pneumonia, then one must suspect an MRSA-PVL. In this case it is recommended to use a molecule which can reduce toxin production such as clindamycin or rifamycin, and start with combination treatment rather than monotherapy. Elements used to monitor the response to treatment (which is important to decide the duration of treatment) in recent studies were the reduction of certain clinical signs, decreased CRP below 20 mg/l, and the decrease in ESR. The treatment consists of initial intravenous antibiotic for 4–7 days, followed by switch to oral if there is a favourable outcome, for a total duration of treatment from 2 to 4 weeks. This scheme has the advantage of reducing the length of hospitalization, and therefore the cost of treatment and the risk of nosocomial infections. It is necessary to perform randomized studies to codify the duration of treatment of MRSA-PVL osteomyelitis and improve medical practice.

5. Conclusion

Apart from ensuring early referral, the medical community also needs to do research on the main challenges facing us in the control of acute osteomyelitis,¹⁴ a disease that is especially serious in children, such as improved diagnosis, detection of drug resistance, shortened treatment regimens and clinical trials of new drugs. Principally, knowledge about MRSA propagating clones is essential to implement any policies to monitor the spread of MRSA either within hospitals or in community.¹⁵ Particular anti-staphylococcal antibiotics should be considered in experienced-based treatment of sepsis among them.¹⁶

Ecological approaches provide interesting information on alternative methods to prevent infections with a non-antibiotic strategy.¹⁷ An example of such alternative methods is the use of probiotics that are described as products which include viable non-pathogenic microorganisms capable to give health

advantages to the host.¹⁸ For instance, treatment with selects probiotic strains is promising since lactic acid bacteria strains (cultivated on natural media, such as milk or soya) express an anti-MRSA activity.¹⁹ Finally, applicable prevention and infection control practices (e.g. Intravenous immunoglobulin, anti-staphylococcal monoclonal antibodies, granulocyte/granulocyte-macrophage colony-stimulating factors and judicious use of antibiotics) are essential for advances in the treatment of paediatric infectious diseases.²⁰

Conflicts of interest

All authors have none to declare.

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