

Update on osteo-articular infections and severe skin and soft tissue infections

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The present article is an update on bone, joint, skin and soft-tissue infections. A panel of Spanish clinicians including orthopedic surgeons, infectious diseases specialists and microbiologists with extensive experience in these fields have commented on the most relevant medical articles published during the last two years. In the next section, we review and discuss 10 articles on pathogenesis (1), diagnostic methods (1), epidemiology (1) and general management of prosthetic joint infections (8) and three on severe and necrotizing soft tissue infections. Although the rate of joint arthroplasty infection is about 1-3%, the infection of an orthopedic implant is particularly devastating since it requires several interventions, prolonged hospitalization and antibiotic treatment for weeks or months. Taking into account the increasing number of arthroplasties performed each year, a parallel increase is expected in the number of prosthetic joint infections. In the absence of well-designed prospective, randomized, controlled studies, the diagnosis and treatment of prosthetic joint infections is based mainly on personal experience. For these reasons, the authors consider particularly interesting a critical review of the most important references in this field. Recently, emergent pathogens such as community-acquired methicillin-resistant *Staphylococcus aureus* have been involved in necrotizing fasciitis. In addition, new tools for the diagnosis and treatment of these infections have been described and are now reviewed in the present article.

Key words: Osteomyelitis. Prosthetic joint infection. Necrotizing fasciitis. Community-acquired infections. *Staphylococcus aureus*.

Actualización de las infecciones osteoarticulares y las infecciones graves cutáneas y de los tejidos blandos

El artículo presente recoge una actualización de las infecciones óseas, articulares, cutáneas y de los tejidos blandos. Un grupo de clínicos españoles constituido por traumatólogos, especialistas en enfermedades infecciosas y microbiólogos con amplia experiencia en estos campos ha comentado los artículos de mayor relevancia a este respecto publicados durante los 2 últimos años. En la sección siguiente se revisan y comentan 10 artículos sobre patogenia (1), métodos diagnósticos (1), epidemiología (1) y abordaje terapéutico general de las infecciones en las prótesis articulares (8); además, se exponen los resultados obtenidos en tres publicaciones sobre infecciones necrosantes graves de los tejidos blandos. A pesar de que la incidencia de infección de las artroplastias es de aproximadamente el 1-3%, la infección de un implante ortopédico es un cuadro especialmente grave debido a que obliga a la realización de varias intervenciones quirúrgicas, a una hospitalización prolongada y a la administración de tratamiento antibiótico durante semanas o meses. Considerando en conjunto el número creciente de intervenciones de artroplastias que se realizan anualmente, se espera un incremento paralelo en el número de infecciones de las prótesis articulares. En ausencia de estudios prospectivos y realizados con asignación aleatoria y control, el diagnóstico y el tratamiento de las infecciones de las prótesis articulares están fundamentados principalmente en la experiencia personal. Por estas razones, los autores consideran especialmente interesante una revisión crítica de las publicaciones más importantes que se han efectuado en este campo. Recientemente se han observado cuadros de fascitis necrosante de origen extrahospitalario causados por *Staphylococcus aureus* resistente a metilina. Además, en el artículo presente se revisan las nuevas herramientas introducidas para el diagnóstico y el tratamiento de estas infecciones.

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Palabras clave: Osteomielitis. Infección de prótesis articulares. Fascitis necrosante. Infecciones extrahospitalarias. *Staphylococcus aureus*.

State of the art

Osteomyelitis

Osteomyelitis continues to be difficult to treat. Rates of cure on antimicrobial therapy are inferior to those of most infectious diseases owing to the physiological and anatomical characteristics of bone¹.

Staphylococcus aureus is the most common causative agent due to its ability to adhere to the proteins present on bone surface and biomaterials, mediated by the expression of several receptors for them. *Enterobacteriaceae* and *Pseudomonas aeruginosa* are frequently isolated in nosocomial infections.

The key to successful management of osteomyelitis is early diagnosis. Conventional radiography is insensitive, because the first signs of abnormality are usually seen only 10 to 14 days after the onset of the infection. Nuclear imaging is highly sensitive for the early detection of acute osteomyelitis, but its specificity is limited. Both magnetic resonance imaging (MRI) and computed tomography (CT) are the preferred methods due to their excellent power of resolution, sensitivity and specificity, and ability to reveal alterations even when radiography is unrevealing. Surgical sampling or needle biopsy of infected bone for microbiology and histopathology examination is essential for the identification of the causative microorganisms and for tailoring treatment.

The goal of treatment is to eradicate the infection and to restore the function, and the strategy depends on the type of infection. In chronic cases with necrotic bone and formation of sequestrum, a combination of antibiotics and surgical debridement are required. By contrast, acute osteomyelitis can resolve with antibiotics alone.

The optimal duration of antimicrobial therapy in osteomyelitis has not been established. No prospective randomized clinical trials assess the length of antimicrobial therapy and the heterogeneous nature of the disease, although many experts consider as a general principle a minimal duration of 4 to 6 weeks, preferably by the intravenous route.

Emerging methicillin-resistant *S. aureus* (MRSA) is a current problem for the treatment of osteomyelitis. To date, vancomycin and teicoplanin are the drugs of choice for this microorganism, but their efficacy is inferior to that of β -lactams^{2,3}. Moreover, long-term treatment with glycopeptides is associated with adverse events due to the use of intravenous catheters and prolonged hospital stay. New antibiotics such as linezolid and daptomycin are a welcome addition to the field, although more clinical information is required before their definitive incorporation³. Linezolid has excellent activity against MRSA and oral bioavailability, therefore, it can be administered orally, thus helping to reduce hospital stay. It has been used when β -lactams or vancomycin cannot be administered, although prolonged use has been associated with a risk of pancytopenia and peripheral neuropathy.

Osteomyelitis associated with infected prostheses

Prosthetic joint infections are an uncommon complication (1 to 5%) of joint replacement surgery, but they lead to high morbidity and medical costs.

Staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci) are the most common infecting agents associated with prosthetic joint infections, and constitute about 50% of all isolates, although there are an unlimited number of causal pathogens. Staphylococci can form biofilms, which are difficult to penetrate for many antibiotics. Within these biofilms, bacteria live and multiply in different phases of growth in organized, complex communities with structural and functional heterogeneity, and resemble multicellular organisms, protected from antibiotics and leukocytes⁴. Besides, *S. aureus* is able to survive intracellularly, which could also contribute to the persistence of infection.

The diagnostic criteria of prosthetic joint infection have not been well established. Clinical diagnosis is only reliable when sinus tracts reach the prosthesis or purulent secretion is obtained from joint aspiration or during open surgery. Complementary information such as the increase in the erythrocyte sedimentation rate and C-reactive protein level, changes in plain radiographs and radionuclide scans and other tests are helpful, but are not specific enough to establish a diagnosis⁵.

Recovery of bacteria by aspiration of joint fluid or by tissue obtained during surgery remains the gold standard for the diagnosis of arthroplasty infections. Multiple specimens (at least three) should be obtained and rapidly cultured in appropriate media. Studies using molecular techniques (e.g. PCR) are still in the experimental phase, but they have shown good sensitivity⁶. Histopathological examination of periprosthetic frozen tissue has a very high sensitivity and specificity⁵.

Exchanging arthroplasty in one or two stages and aggressive resection of all infected tissue remains the standard approach to management of the infected prosthesis. Retention of the prosthesis with prolonged systemic antibiotic therapy for at least three months can be an option in the following circumstances: sepsis is not present, the prosthesis is not loose, symptoms last less than one month, soft tissue is in good condition, etiology is staphylococcal or streptococcal, and an oral antibiotic with good bioavailability and activity against biofilm microorganisms is available^{7,8}. Rifampin plus fluoroquinolones is a good combination and the most widely used. Other alternatives are a combination of rifampin and fusidic acid, and high-dose oral co-trimoxazole. More recently, favorable experience has been reported with linezolid⁹.

Skin and soft tissue infections

Skin and soft-tissue infections (SSTI) are among the most frequent human infections with a severity that ranges from mild to life-threatening¹⁰. They may be caused by a wide variety of microorganisms, including bacteria, fungi, viruses, protozoa, mycobacteria, and rickettsiae. However, the majority of SSTI are caused by aerobic Gram-positive cocci, specifically *Staphylococcus aureus* and streptococci. In specific clinical or epidemiological circumstances, a number of other infectious agents may also cause SSTI. Treatment of SSTI is often conditioned by the lack of scientific evidence available from randomized clin-

ical trials, and many decisions are based on the clinical experience of the physician. Initial management must be based on extent and depth of the infection, presence or suspicion of necrosis, systemic manifestations, and likelihood of disease progression due to comorbidities (vascular insufficiency, disrupted venous or lymphatic drainage, diabetes mellitus, etc)¹¹. In general, initial antibiotic therapy is empirical, and is usually modified after checking the results of stains and cultures of wound specimens. Surgery is crucial to the diagnosis and therapy of necrotizing fasciitis and myonecroses.

Emerging antibiotic resistance among *S. aureus* is problematic because it is a common microorganism in several SSTI and because empirical choice of antibiotics must frequently include agents with activity against these resistant strains¹². Recently, modern antibiotics such as linezolid, daptomycin, telavancin, dalbavancin and tigecycline have shown excellent efficacy in SSTI caused by MRSA¹³⁻¹⁷.

A panel of Spanish clinicians, orthopedic surgeons and microbiologists with interest and expertise in bone and joint infections, and SSIT has commented on the most relevant medical articles in these disciplines published in the last two years.

Pathogenesis

Fux CA, Costerton JW, Stewart PS, Stoodley P. Survival strategies of infectious biofilms. Trends in Microbiology. 2005;13:34-40.

More than 60% of bacterial infections involve bacterial biofilms. These infections include those related to foreign material (joint prosthesis, ventriculo-peritoneal shunts, catheters) and many other infections, which are not related to biomaterials such as dental infections, cystic fibrosis pneumonia, endocarditis, osteomyelitis, prostatitis, etc, are also caused by bacterial biofilms. A biofilm is defined as a bacterial community embedded in a polysaccharide matrix where the cells are protected from host defenses. The most important clinical consequence of the biofilm mode of growth is its high tolerance to all kinds of antibiotics. Several specific mechanisms may explain the tolerance of biofilms to some antibiotics: i) betalactamases, which are accumulated in the biofilm matrix, avoid the diffusion of betalactams, ii) a negatively-charged extracellular matrix binds to positively-charged antibiotics such as aminoglycosides, impeding their diffusion, and iii) biofilm matrix reduces the activity of glycopeptides through unknown mechanisms. However, the most important mechanism that explains the tolerance of biofilms is related to the low metabolic and duplicative rate of bacteria found in the deep strata. Mature biofilms contain different microenvironments in terms of osmolarity, nutritional supply and cell density, and in these conditions bacteria are able to turn on stress-response genes and switch to a low metabolic state more tolerant to antibiotics. Indeed, a top-to-bottom gradient of decreasing antimicrobial susceptibility has previously been described. Moreover, bacterial biofilms contain a few clones of bacteria, known as persisters, which exhibit growth rates below the threshold for antibiotic damage. These findings probably explain why antibiotics that perform well against sta-

tionary phase bacteria in vitro (i.e. rifampin) are more successful in clearing biofilm formation in vivo¹⁸.

Diagnostic methods

Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infections. Am J Med. 2004;117:556-62.

The diagnosis of prosthetic joint infection (PJI) is not always an easy task, especially in patients with late infections, which must be distinguished from those with aseptic loosening (AL). PJI is treated with a prolonged course of antibiotics and, in most cases, with a two-stage exchange arthroplasty, while AL is managed with a one-stage exchange arthroplasty and only 1-2 days of prophylactic antibiotics. Pre-operative studies usually include C-reactive protein (CRP), nuclear imaging studies and culture of synovial fluid. These three tests are not completely sensitive and specific, and sometimes give contradictory results. Since information about the characteristics of synovial fluid leukocyte count in PJI and AL is scarce, the authors studied the value of the synovial fluid leukocyte count to identify the etiology of arthroplasty failure.

This prospective study included 133 patients; 34 with PJI and 99 with AL. Patients with underlying inflammatory joint diseases, crystal-induced arthropathy, or connective tissue diseases were excluded. Synovial fluid was collected before surgery of revision arthroplasty. Patients were classified according to predefined accepted criteria of AL or PJI. Optimal cut-off values, neutrophil percentages, and the accuracy of different leukocyte counts were calculated. The cut-off value of the leukocyte count for optimal sensitivity and specificity to differentiate AL from PJI was 1700 leukocytes/ μ L (Se = 94%; Sp = 88%). This value is clearly lower than in septic non-prosthetic arthritis where the leukocyte count is over 50,000 per μ L. However, it is worthy of note that a leukocyte count lower than 50,000 per μ L was associated with low virulent microorganisms such as coagulase-negative staphylococci or *Corynebacterium* sp, while for *S. aureus* the value was always over 100,000 leukocytes/ μ L. The second parameter evaluated was the neutrophil percentage. A neutrophil percentage over 65% had a high sensitivity and specificity (Se = 97%; Sp = 98%), and only one PJI had a percentage below 65%. Therefore, a low leukocyte count in synovial fluid from a joint prosthesis does not rule out the diagnosis of infection. In these cases a neutrophil percentage over 65% is strongly associated with prosthetic joint infection due to low-virulence microorganisms.

Epidemiology

Mohanty SS, Kay PR. Infection in total joint replacements. Why we screen MRSA when MRSE is the problem? J Bone Joint Surg (Br). 2004;86:266-8.

Infection by methicillin-resistant *Staphylococcus aureus* (MRSA) is difficult to treat and standard antibiotic prophylaxis is insufficient. Since nasal colonization by MRSA

is an important risk factor for the development of surgical wound infection¹⁰, the authors decided to evaluate MRSA colonization among 8911 patients who underwent total joint arthroplasty, and the etiology of infections during the study period. They found only 83 patients colonized by MRSA (0.9%) and these patients received adequate prophylaxis. *S. aureus* was isolated in 13.6% of the 844 infected patients and only 1% were due to MRSA. In contrast, the authors highlight that the most frequent pathogen was coagulase-negative staphylococci (CNS) isolated in 43.4% of cases (366 out of 844) and in 55% of cases it was resistant to methicillin (MR-CNS). From these results, the authors considered that prophylaxis should focus on MR-CNS rather than MRSA. In addition, they include interesting information about the progress of 156 episodes of hip revision arthroplasties with positive intra-operative culture. MS-CNS was isolated in 106 cases and MR-CNS in 50. The mean time free of infection after arthroplasty was 82.8 months for those patients with MS-CNS and 52.9 for those with MR-CNS.

The authors concluded that it is necessary to screen for colonization by MR-CNS in those patients who undergo total joint arthroplasty. Obviously, this measure is difficult and very expensive to implement since CNS colonizes almost everybody and, therefore, an antibiogram would be necessary for each patient. The authors recommend screening in high-risk patients, such as those with prior hospitalization, chronic ulcers or prior antimicrobial therapy. However, the risk factors for MR-CNS are not well defined.

We agree with the authors that CNS is the main pathogen in prosthetic joint infection, which raises another question: Should antibiotic prophylaxis cover MR-CNS? Currently, the question is, should a glycopeptide be included in antibiotic prophylaxis? Centers for Disease Control and Prevention (CDC) guidelines for prevention of surgical site infection discourage the routine use of glycopeptides in antimicrobial prophylaxis and recommend restricting them to certain situations such as documented local increase in the frequency of postoperative MRSA infections, and only after consultation with an infectious diseases specialist¹⁹.

General management of prosthetic joint infections

Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351:1645-54.

This article is a review of the management of prosthetic joint infections by authors with extensive clinical experience and many important articles published in this field in recent years. The document clarifies the absence of uniform criteria for the diagnosis and treatment of these infections.

The most frequent causes of PJI are coagulase-negative staphylococci (CoNS) (30-43%) and *Staphylococcus aureus* (12-23%), but the authors remark that in more than 10% of cases with clear evidence of infection, no microorganism is detected. Molecular techniques, such as polymerase chain reaction (PCR), could help to identify etiological agents in these cases. On the other hand, a common

clinical situation is the isolation of low-virulence microorganisms that are typically part of normal skin flora (i.e. CoNS or *Propionibacterium acnes*) and their pathogenic role is difficult to establish. According to the authors, in these cases, the interpretation of the microbiology results is determined by the growth of the same microorganism in more than one sample, a short growth time, a positive Gram stain and the presence of acute inflammation in the histological study. However, there is little information on the clinical impact of intra-operative positive cultures in those patients with no other symptoms or signs of infection. In fact, some authors have considered this situation as a different form of prosthetic joint infection (PJI). The authors classified PJI as early (< 3 months after surgery), delayed (3 to 24 months), and late (> 24 months after surgery).

Ideally, the antimicrobial agent should have bactericidal activity against surface-adhering, slow-growing and biofilm-producing microorganisms. As rifampin fulfils these requirements, it should be used whenever possible, but should never be administered alone, since staphylococci rapidly develop antimicrobial resistance. Newer quinolones (levofloxacin and moxifloxacin) are excellent in combination with rifampin due to their pharmacokinetics (high bioavailability and once-a-day administration), safety profile, and antimicrobial activity. However, methicillin-resistant Gram-positive cocci are becoming more prevalent and clinical experience with cotrimoxazole, linezolid or daptomycin is scarce.

In chronic infections, prostheses can be replaced in one or two stages. The prerequisites for a one-stage exchange are satisfactory condition of soft tissue, and absence of severe coexisting illnesses and difficult-to-treat microorganisms. In these situations, the rate of success in patients with hip prosthesis is around 85%. The efficacy of antibiotic-loaded cement and the duration of systemic antimicrobial treatment after the replacement need further evaluation. When a one-stage exchange is not possible, a two-stage exchange is performed, with around 90% success. Finally, when surgery is contraindicated or refused by the patient, long-term suppressive antimicrobial therapy with tetracyclines or cotrimoxazole has been reported to have a high success rate (80%).

Stengel D, Bauwens K, Sehoul J, Ekkernkamp A, Porzolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis. 2001;1:175-88.

The objective of the study was to evaluate the clinical efficacy of individual antibiotic agents for bone and joint infections in adults. Published and unpublished controlled trials reported between 1966 and 2000 were identified with online medical databases, clinical trials registers, a manual search among various sources, and contact with experts and drug companies working in the field. The following medical subject headings (MeSH) were explored and connected by Boolean operators: antibiotics; arthritis; arthroplasty; bone diseases, infectious; fracture, open, comminuted, fixation (intramedullary); joint prosthesis; orthopedic fixation devices; osteitis; osteomyelitis; placebo; sepsis. A trial was considered valid for inclusion of po-

tentially eligible studies when the patients were randomized or quasi-randomized to treatment arms. The primary end points were quiescence of inflammation at the end of treatment and after at least 12 months of follow-up.

Twenty-two trials including 927 patients were eligible for final analysis. Methodological quality was poor in most studies and interpretation of results was further limited by small sample sizes, missing descriptions of patient populations and disease characteristics. Taking into account these limitations, the authors concluded that: i) A trend towards improved, long-lasting infection control was observed in favor of a rifampin-ciprofloxacin combination versus ciprofloxacin monotherapy for the treatment of staphylococcal infections related to orthopedic devices (absolute risk difference 28.9%; 95% confidence interval [CI] -0.7-54.4%)²⁰; ii) unbalanced comparative studies showed some benefit of ticarcillin for bone infections caused by *Pseudomonas* species; and iii) no significant differences in therapeutic efficacy were found in trials comparing oral fluoroquinolones with intravenous beta-lactam drugs for both end-of-treatment (odds ratio [OR] 0.8; 0.5-1.4) and long-term results (OR 1.3; 0.8-2.1). A variety of drugs were used as controls, thereby leading to inconsistent findings of drug-related side effects.

Only one randomized trial suitably investigated the impact of polymethylmethacrylate gentamicin bead chains compared with parenteral antibiotics for skeletal infections, although patients receiving both combined local and systemic antibiotic therapy biased this study. Whereas intention-to-treat evaluation suggested a therapeutic advantage of systemic over local therapy, this trend diminished in the per-protocol analysis (1-year follow-up ARD -2.3; -17.5-10.8%).

In conclusion, there exists little high-quality evidence on antibiotic therapy for osteomyelitis and septic arthritis. The heterogeneity observed among patient populations and medical and surgical treatment concepts precludes reliable inferences from the available data.

Rao N, Crossett LS, Sinha RK, Le Frock JL. Long-Term Suppression of Infection in Total Joint Arthroplasty. Clin Orthop. 2003;414:55-60.

This article evaluates the efficacy of oral antibiotic therapy over a long period in prosthetic joint infections treated without removal of the implant.

The criteria for considering this therapeutic alternative were as follows: 1) patients eligible for high-risk surgery, or who refuse surgery, 2) no loosening of the prosthesis, 3) microbiologically documented infection, and 4) microorganisms sensitive to oral antibiotics.

The initial goal of the study was the disappearance of clinical symptoms and signs of infection and a return to normal inflammatory parameters.

The study included 36 consecutive patients with a prosthetic joint infection and a mean age of 77 years (62-96). The infection was located in 15 hip prostheses, 19 knee prostheses and 2 elbow prostheses. The onset of symptoms was acute in 17 (47%) cases (less than 30 days) and chronic in 19 (53%). Presentation of infection was early in 13 patients (36%) (less than one year) and late in 23 (64%) (more than one year). The microorganisms involved were

methicillin-susceptible *S. aureus* in 7 (19%), methicillin-resistant *S. aureus* (MRSA) in 6 (17%), coagulase-negative staphylococci (CNS) in 18 (50%), and others in 5 (14%) cases. All patients underwent initial open debridement and parenteral antibiotics for 4-6 weeks; afterwards, they took oral suppressive antibiotics for 52.6 months (6-128). The most frequent schedules were minocycline-rifampin (100-600 mg qd) in 11 cases, levofloxacin (500 mg qd) in 5 cases, dicloxacillin (500 mg bid) in 5 cases and cephalexin (500 mg bid) in 4 cases.

Outcome was favorable in 31 (86%) patients and in 9 out of 13 (69%) infections caused by *S. aureus*. Advanced age, joint location, duration of symptoms and time of onset of infection were not predictors of failure. The major concern in this article is the tolerance of chronic oral antimicrobial therapy in elderly patients. Only 8% of patients developed diarrhea and there were no other important adverse events. According to the authors, the main drawback of this study is that many of these patients could have stopped antibiotic therapy earlier, which highlights the need for studies designed to evaluate the optimal duration of antibiotic therapy. We consider that the main factor involved in the prognosis of prosthetic joint infection treated without removal of the implant is the duration of clinical symptoms (acute or chronic infections).

Pavoni GL, Giannella M, Falcone M, Scorzoloni L, Liberatore M, Carlesimo B et al. Conservative medical therapy of prosthetic joint infections: retrospective analysis of an 8-year experience. Clin Microbiol Infect. 2004;10:831-7.

This is a retrospective review of 34 elderly patients with prosthetic joint infections (24 hips and 10 knees), who received standardized antimicrobial therapy lasting 6 or 9 months for hip and knee prosthetic infections, respectively. Patients with unstable implants were excluded from the study. Twelve patients had early infections (less than 3 months), 16 had delayed infections (3 months-two years) and 6 had late infections (> 2 years). The etiology was *S. aureus* in 4, MRSA in 8, CNS in 9, others in 4 and unknown in 9 cases. An open debridement was performed in 14 cases. Overall, mean duration of antimicrobial therapy was 41.2 weeks (24-96), mainly with minocycline (200 mg/d) ± rifampicin (600 mg/d) or ciprofloxacin (1.5 g/d) ± rifampicin. Follow-up after finishing therapy was 22 months (9-57). The global success rate was 50%, although it is remarkable that the success rate of early infection was 75% (9 out of 12), while in late infections it was 36.6% (8 out of 22) ($p = 0.03$).

The information from this article suggests that only in those patients with an early acute infection (less than 3 months before arthroplasty) is it possible to stop antibiotic therapy with good results. In late infections, even if long courses of rifampin combinations are administered, the failure rate is high and forces antibiotics to be maintained as a chronic suppressive therapy (as described by Rao N et al). In the future, we must establish whether it is possible to reduce antimicrobial therapy to less than 6 months in acute infections and define the role of new antibiotics such as linezolid, daptomycin or tygecycline, which are highly active against Gram-positive cocci.

Trebse R, Pisot V, Trampuz A. Treatment of infected retained implants. J Bone Joint Surg (Br). 2005; 87-B:249-56.

The present article is similar to the studies by Rao et al. and Pavoni et al. The inclusion criteria were the same: 1) absence of prosthesis loosening and fistula, 2) microbiologically documented infection and 3) microorganisms sensitive to oral antibiotics. Twenty-four patients with an orthopedic implant infection (14 hip prostheses, 5 knee prostheses, 1 ankle prosthesis and 4 osteosynthesis devices) were prospectively studied. Open debridement was performed in 70% of cases. The most important difference with previously reviewed studies was that the duration of treatment was shortened to 3-6 months and the most frequent antimicrobial regimen was rifampin plus a fluoroquinolone. After 3.7 years of follow-up, the success rate was 83%. However, as in the Pavoni study, the success rate in acute infections was 90% and only 37.5% in chronic infections. These results suggest that early acute infections can be treated without removing the implant and by using an antimicrobial regimen including rifampin for 3 to 6 months^{20,21}. On the other hand, the present results confirm that, in chronic infections, any antibiotic combination obtains acceptable results.

Kutscha-Lissberg F, Hebler U, Muhr G, Köller M. Linezolid penetration into bone and joint tissues infected with methicillin-resistant staphylococci. Antimicrob Agents Chemother. 2003;47:3964-6.

One of the most important characteristics of linezolid is its extensive tissue penetration due to low polarity, small size and high liposolubility. As a result, high concentrations of linezolid are reached in several tissues where access is limited for other antibiotics, e.g. bone and joint. Prior experience analyzed the bone concentration of linezolid in bone samples from 12 healthy individuals who underwent an arthroplasty. After 600 mg intravenously, the linezolid bone, muscle, fat or post-surgical hematoma concentrations were over 50% of plasma levels²². In the analysis under review, the concentration of linezolid was measured in 13 patients with an orthopedic implant infection due to methicillin-resistant staphylococci. During surgical debridement of necrotic and infected tissues, samples were collected 35 to 124 min after linezolid intravenous infusion began. Simultaneously, 2 ml of peripheral venous EDTA-anticoagulated blood was drawn separately. The mean and standard deviation of linezolid concentrations were 13.1 ± 5.4 mg/L in fascia; 12.6 ± 2.9 mg/L in joint capsule; 3.9 ± 2 mg/L in bone; 10.5 ± 2.2 mg/L in bone marrow; 10.3 ± 1.4 mg/L in granulation tissue; 13.2 ± 1.1 mg/L in subcutis; 14.5 ± 3.5 mg/L in tendon and 17.1 ± 5.1 mg/L in plasma. The concentrations in all samples were over 60% of the serum concentration except for necrotic bone. In 2 patients who underwent further surgery 15 days after taking 600 mg/12 h of linezolid, bone tissue showed similar linezolid concentrations. This study demonstrated the high and rapid diffusion of linezolid to devitalized tissue (with the exception of bone samples), even after several doses. Therefore, it is suggested that an aggressive surgi-

cal approach to remove devitalized bone should be performed whenever possible.

Bassetti M, Vitale F, Melica G, Righi E, Di Biagio A, Molfetta L et al. Linezolid in the treatment of Gram-positive prosthetic joint infections. J Antimicrob Agents. 2005;55:387-90.

The authors described their experience with linezolid in 20 patients with a prosthetic joint infection. There were 14 cases of infection due to methicillin-resistant *S. aureus* (MRSA), 5 methicillin-resistant coagulase-negative staphylococci (MR-CNS), and one *Enterococcus* spp. The objective was to investigate the clinical efficacy and safety of prolonged treatment with oral or intravenous linezolid. This was a retrospective study carried out at the Department of Infectious Diseases of San Martino Hospital in Genoa. Primary end-points were the patient's clinical outcome at the end of treatment and after long-term follow-up (up to 12 months after the end of treatment). Nine out of 20 patients had an acute infection (45%) and 11 a chronic infection (55%). Patients were given intravenous therapy for 3-7 days as inpatients, and then oral therapy as outpatients accompanied by weekly laboratory testing. The overall mean (sd) duration of treatment was 7.2 (2) weeks (range 6-10 weeks). After 1 year of follow-up, they observed four cases of failure due to relapsing infections. The other 16 patients treated with linezolid did not need further surgical substitution of prosthesis or surgical joint check-up. However, the authors do not describe in detail initial surgical treatment, whether the implant was removed, or the success rate regarding the type of infection (acute or chronic). Linezolid was well tolerated, and no drug-related events leading to discontinuation of treatment were recorded.

This is an encouraging experience of the usefulness of linezolid in orthopedic implant infections. Case reports of chronic prosthetic joint infections cured with short courses of linezolid (about 2 months) have been described elsewhere²³⁻²⁵. In the present series of 20 cases, the authors showed that a short course of linezolid (6-10 weeks) obtains good results (80% success rate). The authors did not specify the cure rate by the type of infection, but, assuming that all 4 failures were chronic infections (4 out of 11), the cure rate would be 64%. This result is clearly better than that shown by Rao et al and Pavoni et al in chronic infections (37%). It is always difficult to compare studies of prosthetic joint infection, but the present results suggest that linezolid may be an effective alternative therapy for orthopedic infections caused by Gram-positive resistant pathogens, and that a prospective and comparative evaluation of linezolid in this setting is necessary.

Septic arthritis

Gavet F, Tournadre A, Soubrier M, Ristori JM, Dubost JJ. Septic Arthritis in Patients Aged 80 and Older: A Comparison with Younger Adults. J Am Geriatr Soc. 2005;53:1210-3.

The incidence of bacterial arthritis has not decreased but its distribution is changing, with elderly people be-

come increasingly affected. Age is a risk factor for septic arthritis and a factor in poor outcome²⁶. Prior reviews of septic arthritis define elderly people as over 60, but given the continuing increase in life expectancy, it is necessary to evaluate the characteristics of septic arthritis in the elderly. The objective of this study was to compare the frequency and characteristics of septic arthritis in patients younger than 80 and aged 80 and older. It was a retrospective study with 335 patients admitted to a French hospital for septic arthritis. Forty-two out of 335 (12.5%) patients were ≥ 80 years old, 164 (49%) were between 60 and 79 years old and 129 (38.5%) were < 60 years old.

The main differences in septic arthritis among people? 80 years old were 1) absence of fever in 23% of cases and normal leukocyte count in 50%. The consequence of this abnormal clinical presentation was frequently a failure in diagnosis and a mean delay of 3 weeks to establish the correct diagnosis. 2) Although the most frequent pathogen was *Staphylococcus aureus* (66%), a higher frequency of coagulase-negative staphylococci (34%), *Streptococcus agalactiae* (12%) and Gram-negative bacilli (14%) was observed. The reason for these variations could be related to the higher number of prosthetic joint infections and urinary tract infections in elderly people. 3) Mortality was 9% in patients older than 80, 4.8% in those between 60 and 79, and 0.7% in those younger than 60.

In conclusion, in elderly people (≥ 80 years old) with joint pain and/or synovial effusion, it is necessary to rule out septic arthritis in spite of the absence of typical symptoms and signs of infection. In these cases, it is recommended to culture the synovial fluid and to start empirical antibiotics against staphylococci, streptococci and Gram-negative bacilli until definite microbiological results are available.

Severe skin and soft tissue infections

Wong CH, Khin LW, Heng KS, Tan KCh, Low ChO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32:1535-41.

Necrotizing fasciitis (NF) is an infrequent infection characterized by rapid progression of tissue necrosis (fascia, subcutaneous tissue or muscle) and high morbidity and mortality. In many cases, mortality is associated with the development of "toxic shock syndrome", which is present in about 50% of cases of necrotizing fasciitis caused by *Streptococcus pyogenes*. The prognosis depends on early debridement of all necrotic tissue²⁷. In order to decrease mortality and the need for aggressive surgical debridements including amputation, it is necessary to establish an early diagnosis. Although there are clinical symptoms that help physicians to identify deep necrosis, such as crepitation, skin necrosis or anesthesia, these symptoms are not always present and appear later during the course of the infection, when they require aggressive surgery. The initial manifestations of NF are very similar to non-necrotic soft-tissue infections such as cellulitis. Computed tomography (CT) and magnetic resonance (MR) are use-

ful tools to differentiate between necrotic and non-necrotic infections, although these techniques are expensive and only a low percentage of cellulitis is true necrotizing fasciitis.

At this point, the article reviewed tries to identify whether routine biochemical parameters could be used as early markers of NF and help to distinguish it from other soft-tissue infections. This was a retrospective study of 89 patients with a definitive diagnosis of NF based on operative findings and 225 control patients with severe non-necrotizing cellulitis based on the need for intravenous antibiotics and more than 48 hours of hospitalization as controls. Thirteen biochemical parameters obtained on admission were evaluated but only 6 were independent factors associated with necrotizing fasciitis in the univariate and multivariate regression model (in parenthesis the cut-off point and its regression coefficient (RC): white cell count (15,000-25,000/mm³, RC: 0.5 and $> 25,000/\text{mm}^3$, RC: 2.1), C-reactive protein (≥ 15 mg/dL, RC: 3.5) and hemoglobin (11-13.5 g/dL, RC: 0.6 and < 11 mg/dL, RC: 1.8), sodium (≥ 135 mmol/L, RC: 1.8), glucose (> 180 mg/dL, RC: 1.2) and creatinine (> 1.6 mg/dL, RC: 1.6) serum concentrations. Adjusting regression coefficient to the nearest unit, the authors generated a score from 0 to 13 points. Those patients with ≤ 5 points had a probability of NF lower than 50% and those with ≥ 8 points a probability of NF higher than 75%. From this information the authors established 3 risk-groups of NF: a) ≥ 5 points, lower risk, b) 6-7 points, intermediate risk, and c) ≥ 8 points, high risk. They recommend urgent complementary studies (CT or MR) when the score is higher than 5.

The authors' work is excellent and the approach could help in the early diagnosis of NF; however, the article has some drawbacks. First, this is a retrospective analysis that needs further prospective studies to validate the efficacy of the score. Second, although only 2.2 and 0.9% of severe cellulitis had ≥ 6 and ≥ 8 points, respectively, 10% of NF had ≥ 5 points. This means that the specificity and negative predictive value are high, but sensitivity and positive predictive values are not so high. Therefore, it is important to clinically monitor the progress of patients with severe soft tissue infections and remember that disproportional pain, rapid progression or the presence of shock associated with any skin lesion, even if it is not severe, suggests necrotizing fasciitis.

Miller LG, Perdreau-Remington F, Sheherbano Mehdi GR, Perlroth J, Bayer AS, Tang AW et al. Necrotizing Fasciitis Caused by Community-Associated Methicillin-Resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med. 2005;352:1445-53.

Methicillin-resistant *S. aureus* is an emergent community-acquired pathogen (CA-MRSA) and its most common clinical presentation is as skin and soft tissue infections such as folliculitis or subcutaneous abscess²⁸. However, Miller et al from Los Angeles, U.S.A. have retrospectively described 14 cases of well-documented necrotizing fasciitis due to CA-MRSA as the only pathogen (n = 12) or as a part of polymicrobial flora (n = 2), over a 1-year period (2003-2004). It is worth noting that 43% were current or former intravenous drug users, 43% had been hospitalized the year before, 21% were diabetics, 14% had a previous ex-

posure to betalactam drugs and 29% had no risk factor for MRSA infection. Although all patients survived, they had serious complications, including the need for reconstructive plastic surgery in 3 patients (21%) and an ICU stay in 10 (71%). Eleven patients (79%) required surgical debridement that was described as either "wide" or "radical", often with incisions longer than 15 cm, and three required subsequent skin grafting. Strains from 5 patients were available and all showed the same pulse-field gel electrophoresis pattern and carried the SSCmec type IV cassette and Panton-Valentine Leukocidin gene.

CA-MRSA necrotizing fasciitis is an emerging disease in areas where this pathogen is endemic such as Los Angeles, where CA-MRSA represents 60% of all *S. aureus* isolated from the community. However, CA-MRSA is also emerging worldwide, and active surveillance is necessary to adapt empirical antibiotics for community-acquired skin and soft tissue infections.

Norrby-Teglund A, Muller MP, Mcgeer A, Gan BS, Guru V, Bohnen J et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis.* 2005;37:166-72.

The management of necrotizing fasciitis associated with toxic shock syndrome (TSS) includes an aggressive debridement of necrotic tissue, antibiotics and general measures to maintain the vital signs. However, in many cases the patient is unstable and the decision to perform aggressive surgery is delayed. The authors in the present study reviewed their experience in 7 cases of severe skin infection caused by group A streptococci (GAS) treated with antibiotics, general supportive measures, intravenous infusion of 2 g of polyspecific immunoglobulin G (IVIG)/ kg of body weight for 3 hours at the time of admission and no surgery or minimal debridement. In those cases without improvement, the same dosage of IVIG was repeated after 48-72 hours. All the patients survived without the need for further interventions. Immunostaining of tissue biopsies from 2 of the patients initially revealed high levels of Group A *Streptococcus*, superantigen and pro-inflammatory cytokines, which were dramatically reduced after 66 h of IVIG. GAS secrete several exotoxins with superantigenic activity that are thought to play a major role in the pathogenesis of these infections. The findings presented in this article support the hypothesis that polyspecific immunoglobulin G is able to block superantigen activity.

Taking into account that the reported mortality of this infection is around 70%, the results of Norrby-Teglund A et al. are surprising and support prior clinical experience. Kaul et al²⁹ described 21 patients with streptococcal TSS treated with a median dose of 2 g of IVIG /kg (cases) and were compared with 32 patients with streptococcal TSS who did not receive IVIG therapy (controls). The proportion of cases with a 30-day survival was higher than that of the controls with a 30-day survival (67% vs. 34%, respectively; $p = 0.02$). Multivariate analysis revealed that IVIG and a lower APACHE II score were associated with

survival; the odds ratio for survival associated with IVIG therapy was 8.1 (95% confidence interval, 1.6-45; $p = 0.009$).

In conclusion, IVIG may be an effective adjunctive therapy for streptococcal TSS, however, the opinion of the reviewers is that when TSS is associated with necrotizing fasciitis, early and aggressive surgical debridement is still mandatory to improve outcome.

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