



Risks and complications of prolonged parenteral antibiotic treatment in children with acute osteoarticular infections

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This study aimed at assessing the prevalence of complications encountered during prolonged intravenous antibiotic (AB) therapy when treating acute osteoarticular (OA) infections in children. We reviewed retrospectively 60 paediatric patients treated in our department between 1988 and 1998 for acute osteoarticular infections (27 with acute haematogenous osteomyelitis, 25 with septic arthritis and 8 with septic osteoarthritis). C-reactive protein, erythrocyte sedimentation rate (ESR), and full blood count were monitored during the entire treatment. Body temperature was recorded three times per day until the fever subsided, and then daily during the remaining hospitalisation. Finally, we listed complications related to the antibiotic therapy and those linked to the presence of a venous catheter. Seventeen allergic reactions to drugs were recorded during the intravenous AB therapy. This complication occurred on average after 24.4 +/- 4.4 days of treatment. The clinical manifestations most often encountered were a delayed rise in temperature and cutaneous symptoms. Blood tests showed an isolated increase in the ESR and eosinophilia (> 1000 eosinophils/ml). Four venous catheters had to be removed, in two cases owing to their obstruction and in two cases owing to an infection. Prolonged intravenous AB therapy is not without complications due to its duration and its mode of administration. Drug allergies to AB constitute a major complication of the treatment. They may render the treatment of subsequent infections problematic and expose these patients to major allergic reactions if they accidentally encounter the molecule incriminated. Moreover, the anaesthetics required to insert a central venous catheter and the need to leave it in place for a prolonged duration constitute another source of potential complications. The duration of iv AB therapy could therefore be shorte-

ned if the clinical and biological evolution is favourable and the pathogen is identified.

INTRODUCTION

Osteoarticular infections in children are true emergencies requiring prompt institution of antibiotic therapy immediately after obtaining bacteriological specimens, without waiting for precise identification of the responsible pathogen (1, 6). Initial antibiotic therapy must be administered intravenously and the choice of the agent determined by Gram stain of the joint or bone fluid obtained (6). However, there is no precise rule for defining the duration and route of administration for the treatment of paediatric osteoarticular infections. While several studies have demonstrated the efficiency of subsequent oral administration of antibiotics (2, 5, 7, 10, 12, 14, 16, 19, 21), there is no

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agreement as to when the parenteral/oral switch should occur, nor as to optimal duration of total treatment. In view of the severe implications of incomplete treatment, most authors remain extremely prudent and recommend long intravenous regimens as the only safe option (4, 8, 13, 18). However, treatment failure is usually not due to insufficient antibiotic treatment, but to late diagnosis, inadequate surgery, or extremely aggressive microorganisms (15, 19). Very few studies have been devoted to the complications due to prolonged parenteral antibiotic treatment in children with acute osteoarticular infections. The aim of this study was to assess the prevalence of complications encountered during prolonged intravenous antibiotic therapy when treating 60 acute paediatric osteoarticular infections.

MATERIAL AND METHODS

We retrospectively reviewed 60 children (27 girls, 33 boys) treated in our hospital between 1988 and 1998 for acute osteoarticular infection. The diagnosis was based clinically on the characteristic signs and symptoms of bone and joint infection, and microbiologically on a positive blood, tissue or joint aspirate culture. The mean age of the patients was 5 years and 10 months, with a range from 10 days to 15 years and 2 months. Twenty-seven patients were diagnosed with acute osteomyelitis, 25 with septic arthritis and 8 with osteoarthritis. Bacteriological diagnosis was based on identification of the organism from haemoculture and from samples obtained at the site of infection. Haemoculture was performed in 55 patients and Gram stain and culture of joint aspirate samples or bone biopsy was performed in 53 patients. Laboratory studies included haematological evaluation, ESR and CRP. These parameters were measured at the time of admission and every 48 hours and continued to be measured weekly throughout the entire treatment period. Clinically, response to the treatment was followed by measuring body temperature, and a temperature greater than 37.5° was considered to be fever. Antibiotic therapy was instituted immediately after obtaining bacteriological specimens, without waiting for precise identification of the responsible organism. The Gram stain of the pus obtained from bone or joint aspirate determined the choice of the initial parenteral antibiotic. If no bacteria was noted, a wide-spectrum antibiotic was chosen based upon the most

likely organism responsible. When bacterial identification and sensitivity studies were available, the therapeutic regimen was subsequently changed accordingly.

We have recorded for every patient the duration of parenteral and total antibiotic treatment, the antibiotic(s) used, and the antibiotics changes. In addition, we have listed complications related to the antibiotic therapy and those linked to the presence of a venous catheter. Finally, we have identified the antibiotics responsible for drug allergies.

RESULTS

Culture of the joint aspirate sample or the bone biopsy was performed in 53 patients and permitted identification of the infecting organism in 46 cases (86.8%). Direct examination of the Gram stain of the bone or joint aspirate was of value in selecting the initial antimicrobial drug in 49% of cases (26 patients). Haemocultures were performed 55 times and were diagnostic in only 27 cases (49%). Definitive microbial diagnosis was obtained in 53 patients (88.3%). In four patients, the absence of bacteriological diagnosis was due to incomplete investigation and in three patients there was no diagnosis in spite of a standard bacteriological workup. In these latter patients, clinical presentation and the blood and radiographic examinations were sufficient to make the diagnosis of an acute osteoarticular infection obvious. *Staphylococcus aureus* was the most frequent infecting organism, accounting for 56.5% (30 cases) of the infections. In two cases, the infection was due to two different organisms. The other bacteria are listed in table I.

Antibiotic therapy was instituted immediately after obtaining bacteriological specimens, without waiting for precise identification of the responsible organism. Forty-eight children were treated with a single antimicrobial drug and two with two drugs simultaneously. The remaining 10 patients were initially treated with two drugs until a definitive bacteriological diagnosis permitted change to a single drug. The initial antibiotic was sufficiently active to be maintained throughout the entire treatment in one half of the cases (30 patients). Mean parenteral antibiotic duration was 35.9 days. In 9 patients the intravenous treatment was maintained for a mean of

Table I

Organisms identified	Number of cases
<i>Staphylococcus aureus</i>	30
<i>Staphylococcus capitis</i>	1
<i>Streptococcus pyogenes type A</i>	6
<i>Streptococcus agalactiae type B</i>	2
<i>Streptococcus pneumoniae</i>	2
<i>Streptococcus parasanguis type H</i>	1
<i>Haemophilus influenzae</i>	6
<i>Kingella kingae</i>	2
<i>Brucella melitensis</i>	1
<i>Borrelia burgdorferi</i>	1
<i>Salmonella type B</i>	1
<i>Salmonella pomona</i>	1
<i>Veillonella parvula</i>	1

Organisms involved in the osteoarticular infections: *Staphylococcus aureus* was the most frequent infecting organism and accounted for 56.5% (30 cases) of the infections.

29 days and switched to the oral route (mean duration 19.4 days, range 14-35 days), usually to consolidate the response to a previous intravenous treatment. In these cases, the peak antimicrobial serum inhibitory titer was not measured. Overall, the mean duration of medication was 38.8 days. Thirty antibiotic changes were required owing to allergic reactions (15 patients), adaptation to the infective organism (11 patients) and parenteral to oral switch (4 patients). Antibiotic therapy was curative in 59 cases, with only one patient presenting with recurrent septic arthritis after cessation of treatment. A surgical procedure was performed in the initial workup in 53 patients.

Seventeen allergic reactions to antibiotics were noted. The clinical manifestations were diverse, presenting either as fever, cutaneous symptoms, an isolated increase in the ESR (mean value 58 +/- 9.2 mm/h) or eosinophilia (> 1000 eosinos/ml). This complication appeared after a mean 24.4 +/- 4.4 days of treatment. Allergic complications were encountered with penicillins in 11 cases, with second-generation cephalosporins in 5 cases, and in one patient it was due to a glycopeptidic antibiotic (table II). Ninety-four per cent of these reactions (16 patients) occurred in children with no history of allergies or atopic diseases. All cases required interruption or modification of the antimicrobial regimen.

Table II

Allergic reactions noted with antibiotics	Number of patients
PENICILLINS	11
<i>Flucloxacillin</i>	7
<i>Methicillin</i>	1
<i>Amoxycillin</i>	1
<i>Penicillin G</i>	1
<i>Piperacillin</i>	1
CEPHALOSPORINS	5
<i>Cefuroxim</i>	5
AMINOGLYCOSIDES	1
<i>Vancomycin</i>	1

Legend : Antibiotics related with allergic complications.

Thirty-nine children received simultaneous placement of long-term central venous catheters (Hickmann type) and surgical procedures for diagnosis or treatment of the acute osteoarticular infection. In 21 patients, anaesthesia was performed only to install the central venous catheter. Four catheters were removed, two because the lumen became plugged, one because of line sepsis and one because of exit-site infection. All these catheters had to be reimplemented with another general anaesthesia. In 46 patients, removal of the central venous catheter required a general anaesthesia. In summary, seventy-one of the 133 general anaesthetics required in our study group were only for the implantation or removal of a central venous line. However, we did not note any complications related with the anaesthetic procedures.

DISCUSSION

Osteoarticular infections in children are true emergencies requiring prompt institution of antibiotic therapy immediately after obtaining material for bacterial identification. Most reports in the literature series propose three to six weeks of antibiotic therapy for the treatment of acute osteoarticular infections. Initial antibiotic therapy must be administered intravenously and the choice of agent determined by Gram stain of the joint or bone fluid obtained. Although there is no debate as to the necessity of initial parenteral antibiotics, there is no

consensus as to the duration of this initial therapy and the mode of administration once the acute phase is over. While several studies have demonstrated the efficiency of subsequent oral administration of antibiotics (2, 5, 7, 10, 12, 14, 16, 19, 21), there is no agreement as to when the parenteral/oral switch should be instituted nor as to the optimum total treatment duration. In many reports, the duration of intravenous therapy is at least 4 weeks for an acute osteomyelitis (8, 13, 18). Dich *et al* showed treatment failure rates of 19% when the duration was reduced to three weeks, whereas a 2% failure rate was achieved with four weeks of therapy (4). More recently, Spindler *et al* proposed that initial antibiotic treatment should be carried out parenterally for at least 3 weeks (18). Finally, Krogstad *et al* still advise to use a prolonged parenteral antibiotherapy (4-6 weeks) although they report the possibility to use the oral administration of antibiotics after a initial parenteral treatment (8).

However, there has been very little recent information on the complications of long-term parenteral antibiotic therapy. Cefatoxime treatment was evaluated by Lefrock *et al* in 41 patients with severe bone and joint infection (9). In their series, 13 patients suffered side effects, which were attributed to intravenous antibiotic therapy. Six patients had a direct positive Coomb's test, two were noted to be neutropenic, two developed a macular rash, two presented with phlebitis, and there was one child who developed eosinophilia (total eosinophil count $> 500/\text{mm}^3$). The direct Coomb's test became positive in these six patients after an average of 24.5 days. Sonnen *et al* (17) advise performing additional laboratory tests to monitor antimicrobial side effects, such as monitoring hepatic transaminases which can become elevated with cephalosporin or oxacillin use, and possible bone marrow suppression with cephalosporin usage. However, there are no statistics in his report about the incidence of such complications. In our series, seventeen allergic reactions to antibiotics were noted. Their clinical manifestations were diverse, presenting either as a resumption of fever or cutaneous symptoms (erythematous rash). For an unexplained reason, we always noted an isolated increase in ESR (mean value $58 \pm 9.2 \text{ mm/h}$)

while the CRP value remained normal. Eosinophilia was consistently present and reached levels greater than 1.000 eosinos/ml. This allergic complication appeared after a mean of 24.4 ± 4.4 days of parenteral antibiotic therapy. Ninety-four per cent of these (16 patients) occurred in patients with no prior history of allergy or atopic diseases. All cases required interruption or modification of the antimicrobial regimen. We note that the delay between the start of the antimicrobial therapy and the presence of the allergic complication (24.4 days) is very similar to those before positive Coombs test (24.5 days) in the Lefrock *et al* series (9). This similar interval suggests that there is a probable causal relationship between duration of the therapy and the development of a positive direct Coomb's test or other signs of an allergic reaction. We feel that this complication must be kept in mind, particularly when the intravenous antibiotic therapy continues for more than 20 days. Another important factor with prolonged intravenous antibiotic therapy is that it usually requires an implanted central venous line to deliver the drugs. The central venous catheter may itself be a source of complication. Benak *et al* (3) reported that four of 105 catheters required removal because of infectious complications. Upadhyay *et al* (20) reported that two of the 20 inserted central venous lines had to be removed, one because of line sepsis and one because of exit-site infection. Of the 38 catheters reported in a series by Parker *et al* (11), five were removed, three because of mechanical failure and two because the lumen became plugged. Our patients had no serious complications related to the insertion and use of the central venous catheter, but four catheters were removed; two because the lumen became plugged, one because of line sepsis and one because of exit-site infection. Although these complications were not severe, they were sufficiently significant to require another anaesthesia. But perhaps, these complications are actually avoidable since we have pointed out that oral antibiotics may be quickly substituted for intravenous antibiotics in patients who show early clinical improvement and rapid normalisation of C-reactive protein. However, transition to oral treatment requires that certain parameters be known (6).

The infective organism must be identified, so that an adequate antibiotic may be employed. Host characteristics are also important, as infections of neonates or immunosuppressed children have a less favourable outcome. The infected site can also influence the outcome since local conditions can impair antibiotic access and/or action (local pH, anaerobiosis, abscess, bone sequestrum).

CONCLUSION

Emergent treatment of an osteoarticular infection is necessary in view of the major functional sequelae that may result from delayed or incomplete treatment. However, treatment failure is usually not due to insufficient antibiotic treatment, but to late diagnosis, inadequate surgery, or extremely aggressive microorganisms. Long-term intravenous antibiotic therapy does not itself guarantee a cure, and the necessary indwelling central catheters and the general anaesthetics required to install and to remove them, are not without their own complications. Allergic sensitisation of young patients to antibiotics also exposes them to potentially severe reactions in the event of subsequent exposure. A timely transition to oral antibiotics can markedly decrease the number of complications without exerting a negative influence on the treatment results. This transition should occur after 10 to 14 days of intravenous antibiotic therapy, if the CRP and temperature have reverted to normal. Finally, such a treatment protocol can contribute to overall cost-efficiency by decreasing the duration of in-patient treatment, the number of operative procedures, and the number of possible complications.

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