ORIGINAL ARTICLE

Fosfomycin for the initial treatment of acute haematogenous osteomyelitis

N Corti, F H Sennhauser, U G Stauffer, D Nadal

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See end of article for authors' affiliations

Correspondence to:
Dr D Nadal, Division of
Infectious Diseases,
University Children's
Hospital of Zurich,
Steinwiesstrasse 75,
CH-8032 Zurich,
Switzerland;
david.nadal@kispi.unizh.ch

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Acute haematogenous osteomyelitis (AHOM) is a bacterial infectious disease which mainly affects the paediatric age group. In children the yearly incidence ranges between 1:5000 and 1:10 000.^{1,2} These relatively low figures hamper prospective antimicrobial treatment studies enrolling sufficiently large numbers of patients. Although *Staphylococcus aureus* is the most common identified causative agent,² a further obstacle to establishment of best modalities of anti-infective treatment is the failure to detect the causative organism in more than 30–50% of cases of AHOM.³ Thus, since optimal antimicrobial treatment in terms of antibacterial compound, application route, and duration remains to be determined, treatment modalities for AHOM practised by different centres may vary considerably.

At our institution, since 1984 the surgical and the medical departments have used different antimicrobial treatment regimens for AHOM. The surgical department favoured initial intravenous treatment with fosfomycin, and the medical department initial intravenous treatment with a β lactam antibiotic. This dichotomous prescription behaviour within the same centre offered us the unique opportunity to compare the performance of regimens containing fosfomycin, which penetrates leucocytes and shows activity against a broad spectrum of bacteria, versus regimens containing β lactams.

PATIENTS AND METHODS

Patients older than 1 month treated for osteomyelitis at the University Children's Hospital of Zurich during the period January 1984 to January 1998 were identified by computer search for the in-house code of discharge diagnosis osteomyelitis. Only patients with community acquired AHOM and no primary surgical treatment were included in this analysis. AHOM was defined by a history shorter than two weeks and the presence of two or more of the following criteria: local signs of inflammation, radiological signs (deep soft tissue

Background and Aims: At our institution there has been a dichotomous antimicrobial treatment behaviour for acute haematogenous osteomyelitis (AHOM) since 1984. The surgical department favoured fosfomycin as initial choice and the medical department β lactams. We aimed to compare the performance of both strategies.

Methods: Data from patients discharged with the diagnosis of AHOM between January 1984 and January 1998 were gathered from the charts by means of a questionnaire. Patients receiving fosfomycin treatment (FT) were compared with those receiving fosfomycin plus other antimicrobials (FT+) and those receiving no fosfomycin treatment (NFT).

Results: A total of 103 patients aged 0.1–15.5 years (mean 6.5, median 6.9) with AHOM received no surgical treatment initially. In 23 (22.3%) FT was instilled initially, in 47 (45.6%) FT+, and in 33 (32.0%) NFT. The pathogen was established in 30%, 36%, and 42% of FT, FT+, and NFT patients, respectively, *Staphylococcus aureus* being the predominant isolate. Mean C reactive protein levels and erythrocyte sedimentation rates normalised in all treatment groups after two and four weeks, respectively. The mean duration of intravenous antimicrobial treatment in FT patients was 2.5 weeks, in FT+ patients 3.1 weeks, and in NFT patients 3.8 weeks ($p < 0.05$), whereas the mean duration of intravenous plus oral treatment was comparable (7.1 v 6.8 v 6.5 weeks).

Conclusions: The leucocyte penetrating fosfomycin performed similarly to extracellular β lactams in the treatment of AHOM. Intravenous treatment for longer than 2.5 weeks offered no advantage.

swelling, and/or periosteal reaction, and/or bone destruction), and/or isolation of a pathogen from tissue puncture or blood.^{4–6} Patients with concomitant arthritis, chronic osteomyelitis, or osteomyelitis following a penetrating injury or surgery were excluded. Patient data were gathered from their records, by means of a questionnaire containing items relating to demography, clinical signs, diagnostic investigations, treatment, clinical course, and outcome.

Patients receiving fosfomycin treatment (FT) were compared with patients receiving FT plus other antimicrobial agents (FT+) and with patients receiving antimicrobial agents other than fosfomycin (NFT).

For statistical comparison of the three treatment groups, the Mann-Whitney U test and the χ^2 test were used. A p value < 0.05 was considered statistically significant.

RESULTS

Study population

Between January 1984 and January 1998 a total of 340 patients were discharged with the diagnosis osteomyelitis; 103 were included in the analysis as they fulfilled the criteria for AHOM, were beyond the neonatal age at onset of the disease, and were initially treated conservatively. The age range was 0.1–15.5 years (mean 6.5, median 6.9). FT was installed in 23 (22%) patients, FT+ in 47 (46%), and NFT in 33 (32%).

Table 1 gives a synopsis of the patients' characteristics with respect to demography, history, clinical signs and laboratory data on admission, and localisation of AHOM. Patients receiving FT were comparable with patients receiving FT+ or NFT,

Abbreviations: AHOM, acute haematogenous osteomyelitis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FT, fosfomycin treatment; FT+, fosfomycin plus other antimicrobials; NFT, no fosfomycin treatment

Table 1 Baseline characteristics of 103 patients with acute haematogenous osteomyelitis and no primary surgical treatment, segregated based on the initial intravenous antimicrobial treatment

Characteristics	FT (n=23)					FT+ (n=47)					NFT (n=33)				
	Mean	Median	Range	n	%	Mean	Median	Range	n	%	Mean	Median	Range	n	%
Demographics															
Age (years)	7.0	7.5	0.08–15			6.0	6.4	0.08–15.5			7.0	7.4	0.08–14.9		
<2 years				5	22%				11	23%				7	21%
≥2 years				18	78%				36	77%				26	79%
Gender															
Male				15	65%				29	62%				19	58%
Female				8	35%				18	43%				14	42%
History															
Duration of symptoms (days)	5	5	1–14			6	5	1–14			5	4	1–10		
Closed trauma				4	17%				15	11%				5	15%
Infection				8	35%				18	38%				16	48%
Trauma and infection				1	4%				2	4%				1	3%
Affected bones															
Lower limbs				10	43%				43*	91%				19	58%
Clavicle, sternum, spine, pelvis				3	13%				5	11%				8	24%
Upper limbs				5	22%				7	15%				7	21%
Multiple				5	22%				6	13%				3	9%
Clinical signs and symptoms on admission															
Body temperature (°C)	37.5†	37.5	36.5–39.5	23		37.9	37.7	36.5–40.1	44		38.1†	38.1	36.5–40.1	31	
Erythema				4	17%				13	28%				10	30%
Swelling				13	57%				26	55%				18	55%
Tenderness				12	52%				29	62%				20	61%
Warmth				12	52%				22	47%				13	39%
Sparing				3	13%				7	15%				8	24%
Limping				5	22%				11	23%				11	33%
Refusal to walk				3	13%				8	17%				2	6%
Decreased joint motility				8	35%				16	34%				16	48%
Laboratory parameters															
C reactive protein (mg/l)	44.0	37.0	1–117	18		59.0	25.0	1–360	41		62.0	33.0	1–270	27	
Erythrocyte sedimentation rate (mm/h)	55.0	56.5	12–116	22		49.0	46.5	3–190	40		46.0	40.5	7–138		
White cell blood count (G/l)	10.0	9.7	6.5–19.7	20		11.0	10.0	4.2–31	43		12.0	11.2	4–37	31	

*FT+ v FT or NFT, p<0.001.

†FT v NFT, p=0.048.

Table 2 Microbiological work up and rate of positive bacterial cultures

Performed cultures	Treatment group		
	FT (n=23)	FT+ (n=47)	NFT (n=33)
From total patients	22 (96%)	43 (92%)	31 (94%)
Blood	14 (61%)†‡	40 (85%)†	31 (94%)‡
Positive	2 (14%)*	13 (33%)*	13 (42%)*
Bone aspirate	10 (44%)	16 (34%)	10 (30%)
Positive	5 (50%)*	6 (38%)*	4 (40%)*
Blood plus bone aspirate	6 (26%)	13 (28%)	1 (3%)
Positive	0*	3 (23%)*	0*

*The percentage relates to the total number of cultures of the same material.

†p=0.03; ‡p=0.003.

except that the lower limbs were involved more often in FT+ patients than in FT or NFT patients (91% v 43% or 58%; $p < 0.001$), and the mean body temperature on admission was higher in NFT patients than in FT patients (38.1°C v 37.5°C; $p < 0.048$) (table 1).

Plain radiographs were performed in all patients. Pathological findings on admission were noted in 26% of FT patients, in 32% of FT+ patients, and in 12% of NFT patients. During the course no pathological radiological findings were recorded in 48% of FT patients, in 30% of FT+ patients, and in 30% of NFT patients. A bone scan was performed in 95% of FT patients, 96% of FT+ patients, and 94% of NFT patients. Increased uptake of ^{99m}Tc was found in 100%, 95%, and 90% of the patients, respectively. One FT+ patient and one NFT patient were subjected to computed tomography. Changes typical for osteomyelitis were seen in both. All FT patients (n = 2), FT+ patients (n = 2), and NFT patients (n = 4) undergoing magnetic resonance imaging showed signs consistent with osteomyelitis.

Microbiological findings

A microbiological investigation was undertaken in 96 (93%) patients. In 38 (40%) of the 96 investigated patients cultures from blood, bone aspirate, or both grew bacteria. Bacterial growth was found in 28 (33%) of 85 blood cultures, in 15 (42%) of 36 cultured bone aspirates, and in three (15%) of 20 pairs of blood cultures and cultures from bone aspirate. Table 2 gives the results segregated by treatment group. A microbiological work up was performed in 96% of FT patients, 92% of FT+ patients, and 94% of NFT patients. Blood cultures were drawn in 61% of FT patients, 85% of FT+ patients, and 94% of NFT patients (FT v FT+, $p = 0.03$; and FT v NFT, $p = 0.003$) and were positive in 14%, 33%, and 42%, respectively ($p > 0.05$). Bone aspirates for bacterial culture were carried out in 44% of FT patients, 34% of FT+ patients, and 30% of NFT patients; cultures grew bacteria in 50%, 38%, and 40%, respectively (table 2). *Staphylococcus aureus* was the most frequently isolated bacterium in all treatment groups: 57% in FT patients, 65% FT+ patients, and 57% in NFT patients. Coagulase negative staphylococci were isolated from FT patients and FT+ patients and accounted in FT patients for 43% and in FT+ patients for 18% of the bacterial isolates. Other isolated bacteria included *Streptococcus pyogenes*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Brucella melitensis* and *Salmonella panama* (table 3).

Antimicrobial treatment regimens

All 23 FT and 47 FT+ patients received intravenous fosfomycin at a mean daily dose of 200 mg/kg. In the 47 FT+ patients fosfomycin was combined in 38 with flucloxacillin, in two with amoxicillin, in four with amoxicillin/clavulanic acid, in two with clindamycin, and in one with gentamicin. The regimen was switched once to other combinations in 11 of these

Table 3 Bacteria isolated from blood cultures or cultures of bone aspirates

Isolated bacteria	Initial intravenous treatment		
	FT	FT+	NFT
Total	7	17	14
<i>Staphylococcus aureus</i>	4 (57%)	11 (65%)	8 (57%)
Coagulase negative staphylococci	3 (43%)	3 (18%)	0
<i>Streptococcus pyogenes</i>	0	2 (12%)	1 (7%)
<i>Streptococcus pneumoniae</i>	0	1 (6%)	1 (7%)
<i>Haemophilus influenzae</i>	0	0	2 (14%)
<i>Brucella melitensis</i>	0	0	1 (7%)
<i>Salmonella panama</i>	0	0	1 (7%)

patients and twice in two patients. The reasons were isolation of an organism resistant to fosfomycin (*S aureus* and coagulase negative staphylococci, once each), side effects (n = 5), poor clinical response (n = 3), and targeted treatment after identification of the causative organisms (n = 2). In one case the reason for switching could not be clarified. The intravenous antimicrobials prescribed to the 33 NFT patients were amoxicillin/clavulanic acid alone (n = 15) at a mean daily dose of 126 mg/kg or in combination with gentamicin (n = 2); flucloxacillin alone (n = 7) or combined with gentamicin (n = 5); amoxicillin plus gentamicin (n = 2); clindamycin (n = 1); or ceftriaxone plus gentamicin (n = 1). In eight of these patients antimicrobial therapy was switched: in six once, in one twice, and in one three times because of poor clinical response (n = 4), side effects (n = 3), susceptibility of the isolated bacteria (n = 2), or not stated (n = 3).

Oral antimicrobials subsequent to fosfomycin were prescribed to 20 (87%) FT patients; these were clindamycin (n = 10), amoxicillin/clavulanic acid (n = 6), cefaclor (n = 2), or flucloxacillin (n = 2). In one patient clindamycin was switched to another antimicrobial because of side effects. Oral antimicrobials following intravenous treatment were prescribed to 42 (89%) of the FT+ patients; these were clindamycin (n = 34), amoxicillin/clavulanic acid (n = 5), flucloxacillin (n = 2), and flucloxacillin plus clindamycin (n = 1). The 27 (82%) NFT patients prescribed oral antimicrobials following intravenous treatment received amoxicillin/clavulanic acid (n = 9), flucloxacillin (n = 5), clindamycin (n = 4), amoxicillin (n = 3), cefaclor (n = 3), co-trimoxazole (n = 1), or penicillin (n = 1). The patient with AHOM caused by *B melitensis* was treated with rifampicin and co-trimoxazole.

The mean duration of intravenous antimicrobial administration in FT patients, FT+ patients, and NFT patients was 2.5 weeks, 3.1 weeks, and 3.8 weeks, respectively ($p < 0.05$ for all groups), and the mean duration of hospitalisation 3.4 weeks, 3.7 weeks, and 4.8 weeks, respectively ($p < 0.05$). The total mean duration of antimicrobial therapy in FT patients, FT+ patients, and NFT patients was comparable (7.1 weeks v 6.8 weeks v 6.5 weeks).

Table 4 lists the side effects noted during antimicrobial therapy. Fosfomycin, flucloxacillin, and clindamycin were involved in the majority of cases.

Responses to antimicrobial treatment and outcome. The responses to antimicrobial treatment were assessed by analysis of the values for C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), respectively. Figure 1 presents the mean values for CRP and ESR. CRP values decreased from week 1 onwards and in a parallel fashion for the three treatment groups. By comparison, baseline mean ESR values in FT patients, FT+ patients, and NFT patients were comparable, increased by week 1 in NFT patients but remained at a similar level in FT patients and NFT+ patients, and thereafter

Table 4 Side effects noted during intravenous antimicrobial treatment

Antimicrobials	Side effects		
	Exanthema	Diarrhoea	Leucopenia*
Fosfomycin	0	1	0
Fosfomycin/flucloxacillin	10	1	1
Flucloxacillin	3	1	2
Amoxicillin	3	0	0
Flucloxacillin/clindamycin	1	0	0
Amoxicillin/clavulanic acid	0	3	1
Clindamycin	7	3	0

*Leucopenia was defined as leucocytes <1 G/l.

Figure 1 C reactive protein level (A) and erythrocyte sedimentation rate (B) in patients with acute haematogenous osteomyelitis. Values are given as mean $\pm$ SD. The numbers indicate the number of patients from each treatment group investigated at a given time.

showed a parallel decrease for the three treatment groups. Normal values for CRP and ESR were attained by all treatment groups after two and four weeks, respectively. One FT patient underwent secondary surgical treatment during hospitalisation to evacuate pus.

Within four weeks after discharge, one FT+ patient and one NFT patient manifested localised inflammatory signs, showed increased CRP and ESR, and were rehospitalised for additional antimicrobial treatment. Eventually, all hospitalised patients recovered without further sequelae.

DISCUSSION

A similar efficacy of antimicrobial treatment of AHOM was observed in paediatric patients beyond neonatal age initially receiving the leucocyte penetrating antimicrobial fosfomycin and in patients initially receiving leucocyte non-penetrating antimicrobials—that is, β lactams. Moreover, intravenous

antimicrobials for a mean of 2.5 weeks proved to be as safe as for longer periods.

Our cohort of 103 subjects is one of the largest in the literature devoted to AHOM in children. Higher numbers of patients were included in four other studies,^{3–6} but none compared different antimicrobial treatments. In agreement with these studies we noted that the lower limbs were the most commonly affected bones and that *S aureus* was the most frequently isolated pathogen. Coagulase negative staphylococci as the sole identified pathogen, in our study the second most frequently detected microorganism in FT patients and FT+ patients, has been reported by others.^{6–9} Nevertheless, its role as a pathogen or contaminant remains elusive, as neither we nor others could support positive blood cultures by positive bone aspirate cultures or vice versa. The 39.5% rate of bacteriological diagnosis in our study is within the range of 30–75% documented by others in children with AHOM.^{4,6,8–11}

The majority of patients reported here were initially treated with fosfomycin. This compound, originally a fermentation product of *Streptomyces fradei*, *S viridochromogenes*, and *S wedmorensis* and now produced synthetically, is an organic phosphonate which interferes with bacterial cell wall synthesis by inhibiting phosphoenolpyruvate transferase and exhibits activity against a broad range of pathogens including those usually isolated in AHOM.¹² The available formulation of the leucocyte penetrating compound¹³ is for intravenous application only and is licenced in Europe, Japan, Brazil, and South Africa, but not in the United States and Canada. There are only a few reports in the literature on the application of fosfomycin in AHOM.^{14,15} Our study provides for the first time data on the use of fosfomycin on a large scale.

The decrease of the mean values for CRP and ESR in FT patients, FT+ patients, and NFT patients following antimicrobial treatment evolved in a parallel fashion and without any statistically significant differences between the three treatment groups. The CRP values normalised at least two weeks prior to the ESR values (fig 1). These results are in line with studies showing CRP to be a more sensitive tool to monitor the effectiveness of treatment of AHOM than ESR¹⁶ and suggest a similar efficacy of FT and NFT. The time to normalisation of CRP values (<20 mg/l) of two weeks following antimicrobial treatment in our study was one week longer than the periods reported when using intravenous treatment with a first generation cephalosporin or clindamycin,⁵ or oxacillin or ampicillin.¹⁶ Since our FT+ and NFT patients received antimicrobials similar to those prescribed in the quoted studies, one likely reason for the difference could be that we did not segregate the patients according to the severity of their illness.^{16,17} Nevertheless, as normalisation of ESR in effectively treated AHOM has been shown to occur after a mean of four weeks,^{6,8} the interpretation that the treatments reported here resulted in responses similar to the ones reported in the literature is justified.

Patients receiving FT or FT+ were prescribed intravenous antimicrobials for a significantly shorter duration than patients receiving NFT. This was a result of the different treatment regimens entertained in the Department of Paediatric Surgery and the Department of Paediatrics, which was also the basis for a significantly shorter hospitalisation of FT patients and FT+ patients versus NFT patients (mean difference 1.4 weeks and 1.1 weeks, respectively). However, the mean duration of total antimicrobial therapy was similar in all three treatment groups and comparable with that reported by two of the other large studies.^{6,7} Antimicrobial treatment of AHOM used to be entirely intravenous administration for 4–8 weeks,^{9,10} but by the end of the 1970s sequential intravenous–oral treatment was starting to be advocated,^{11,18,19} and later became the accepted standard.⁶ The recommended duration of intravenous therapy ranges from 3 to 10 days and depends on whether surgical drainage was done and on the clinical response.^{11,18,20,21} More recently, a simplified treatment for staphylococcal osteomyelitis has been

proposed by Finnish colleagues who, in a non-controlled study, switched intravenous therapy with a first generation cephalosporin or clindamycin to oral clindamycin, mostly within four days, with satisfying results.²² Our data from a unique cohort enabling comparison of different regimens did not fully support this extremely short intravenous regimen. However, we can conclude that initial intravenous therapy for 2.5 weeks was as effective as intravenous therapy for longer periods. Furthermore, normalisation of mean CRP values by two weeks in our large cohort of patients suggests that a mean duration of intravenous treatment of two weeks, followed by an oral regimen, could be safe. The optimal length of total antimicrobial treatment remains to be determined.

Finally, administration of the leucocyte penetrating fosfomycin with a broad spectrum of activity resulted in no overt advantage over other antimicrobials, most of them leucocyte non-penetrating, except for a lower rate of side effects (table 4). This observation and the epidemiological findings of the present analysis and previous studies,^{1 2 4 6 22 23} that after the introduction of the conjugated vaccine against *H influenzae* type b in the early 1990s this pathogen is of no more concern as a potential cause of AHOM, and that *S aureus* is the main target in all paediatric age groups except in newborns, would support the general initial use of a narrow spectrum antimicrobial. Nevertheless, fine needle aspirates or biopsy specimens for Gram staining and cultures should be obtained before deciding on antimicrobial treatment as microbiological diagnosis remains a cornerstone for successful treatment. This is of particular importance for infants and toddlers with a negative history of *H influenzae* type b vaccination, for sickle cell anaemia patients who are prone to infections with Gram negative bacteria such as *Salmonella* spp., and for immunocompromised patients. In these patients a third generation cephalosporin, for example, ceftriaxone or cefotaxime should be administered if the results of Gram staining are inconclusive.²⁴ For the intravenous treatment phase in other patients or patients shown to be affected by Gram positive cocci, flucloxacillin would seem more apt than clindamycin, which has a broader spectrum of activity. By contrast, based on the pharmacokinetics and pharmacodynamics, clindamycin would seem more appropriate for the oral treatment phase. As the rate of methicillin resistant *S aureus* isolates from the community is increasing,^{25 26} the future detection of such strains as a cause of AHOM seems likely. Thus, in agreement with the notion of a judicious use of antimicrobials, it is appropriate to reserve fosfomycin for such cases where its efficacy has been documented.^{27 28} As a result of this study, both departments at our institution have implemented the above described prescription policy for the treatment of AHOM beyond the neonatal age—that is, start with intravenous flucloxacillin followed by oral clindamycin except for the above outlined special conditions.

Authors' affiliations

N Corti, D Nadal, Division of Infectious Diseases, University Children's Hospital of Zurich, Zurich, Switzerland
F H Sennhauser Department of Paediatrics, University Children's Hospital of Zurich
U G Stauffer, Department of Paediatric Surgery, University Children's Hospital of Zurich

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