ORIGINAL ARTICLE

Adverse Events in Long-Course Intravenous Antibiotic Therapy for Pediatric Osteoarticular Infections

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Abstract

Introduction: Osteoarticular infections are commonly treated with long-course intravenous antibiotic therapy, leading to prolonged hospital stays. The aim of our study was to describe adverse events, namely adverse drug reactions, catheter associated complications and nosocomial infections, in pediatric patients treated for osteoarticular infections.

Methods: Retrospective observational and analytical study of pediatric osteoarticular infections from 1994 to 2014 in a tertiary hospital. Patients were divided in two groups based on the presence of adverse events.

Results: There were 134 patients treated with intravenous antibiotic therapy, with a median length of 19.5 (interquartile range 14.0-27.3) days. Adverse events occurred in 73.1% of patients (n = 98). Adverse drug reactions (n = 67) occurred in 50.0% of the patients and were associated with longer duration of parenteral treatment and vancomycin prescription. Catheter associated complications (29.1%; n = 39) included catheter-infiltration (13.4%), thrombophlebitis (9.7%) and cellulitis (6.0%). Thirty-three patients had nosocomial infections, mainly gastrointestinal (11.2%) and respiratory (8.2%). Comparing the groups with and without adverse events, there were no significant clinical or analytical differences, at admission and after starting antibiotic therapy, except for the duration of intravenous treatment and total length of hospital stay, which were significantly higher in patients with adverse events.

Discussion: Long-course intravenous antibiotic therapy for osteoarticular infections is frequently associated with adverse events. In patients with clinical and analytical improvement, early transition from intravenous to oral treatment should be considered in order to reduce the incidence and morbidity of these complications.

Keywords: Administration, Intravenous/adverse effects; Anti-Bacterial Agents/adverse effects; Arthritis, Infectious/drug therapy; Child; Osteoarthritis/drug therapy Osteomyelitis/drug therapy; Treatment Outcome

Introduction

Osteoarticular infections in children require early institution of antibiotic (AB) therapy as soon as bacteriological specimens are obtained. Initial AB must be administered intravenously to ensure adequate serum levels.[1] Successful treatment depends on the administration of appropriate antibiotic at sufficiently high dose, in order to achieve bactericidal levels in the bone and joint. Although early transition to oral antibiotic therapy is increasingly advocated nowadays, controversy remains, regarding timing of optimal parenteral / oral switch or total AB duration,[2-6] and occasional centers remain extremely prudent, recommending long intravenous regimens.[5,7]

Intravenous antibiotic (ivAB) therapy is often perceived as a relatively benign treatment. However, in the pediatric population adverse events rates can be high, ranging from 29% to 41%.[8,9] There is scarce literature on the adverse events related to prolonged ivAB in pediatric osteoarticular infections. Therefore, the aim of this study is to describe the adverse events, in particular the adverse drug-reactions, catheter-associated complications and nosocomial infections, in patients hospitalized and treated for osteoarticular infections in a tertiary hospital.

Methods

The records of patients who received ivAB for osteoarticular infections in our institution, between January 1st, 1994 and June 30th, 2014, were retrospectively reviewed with focus on demographic, clinical, analytical, microbiological and radiological data.

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Definitive diagnosis of osteoarticular infections was considered when there were characteristic signs and symptoms of bone and/or joint infection, compatible laboratory and imaging features, and a positive blood, tissue or joint aspirate culture. Probable osteoarticular infections diagnosis was considered when cultures were negative, despite other present features. Acute osteoarticular infections corresponded to a period of symptoms of less than 14 days, after which, subacute was assumed. Chronic infection was considered in the presence of radiologic evidence of devitalized bone. Patients were included if they were younger than 18 years old and treated with initial ivAB. Exclusion criteria included osteoarticular infections unlikely diagnosis (not fulfilling criteria for definite or probable diagnosis) and exclusively oral treatment.

Concerning patient's management, septic arthritis cases were managed with arthrotomy / arthrocentesis prior to ivAB, whereas osteomyelitis without abscess cases underwent AB alone. Empirical AB was started after obtaining bacteriological samples, before identification of the responsible organism. Antibiotic dosing was standardized in consonance with the clinical diagnosis, age of the child and probable pathogen. For every patient, data recorded included the type of prescribed antibiotic, duration of parenteral and total treatment, and need for antibiotic change. In addition, adverse events were listed for each patient and divided in adverse drug reactions, catheter associated complications and nosocomial infections. Long-course ivAB regimen was considered after 14 days of intravenous treatment.

Adverse drug reactions were considered as any reaction related to the prescribed antibiotic not otherwise explained. Recorded data included clinical adverse drug reactions such as rash, diarrhea, nausea, hives and fever; and analytical adverse drug reactions, including anemia, neutropenia, eosinophilia or elevated liver enzymes. Neutropenia was defined as an absolute neutrophil count (ANC) below 1.5 x 10^9 cells/L in children older than 12 months, 1.0 x 10^9 cells/L between 2 weeks and 1 year, and 1.5 x 10^9 cells/L under 2 weeks of age. Eosinophilia was defined as an eosinophil count over 600 cells/µL. Serum alanine aminotransferase (ALT) and aspartate aminotransferase values were considered increased two times over the upper limit of the age reference range, in the existence of a normal first control. Complete blood and differential cell count, as well as blood urea nitrogen, creatinine and hepatic enzymes serum levels were used to monitor for bone marrow, renal and hepatic toxicity. Age-specific normal values for children were considered. Missing values were coded when patients did not have at least two blood tests to monitor analytical adverse drug reactions (between 72 hours and 14 days of treatment and after completing 14 days).

Catheter-associated complications were defined as any mechanical or infectious complication associated with the catheter used for ivAB administration. We defined catheter infiltration as fluid or medications leak into surrounding tissues, caused by improper placement or catheter dislodgment. Nosocomial infection were identified according to the Centers for Disease Control criteria[10] as any localized or systemic infectious condition presenting more than 48 hours after hospitalization, with no sign of incubation or illness by the time of admission.

Complicated outcome was defined by the authors as need for repeated surgical intervention after initial approach; need to change antibiotic therapy due to lack of clinical and/or analytical improvement; development of musculoskeletal abscess and/or pyomyositis; chronic/recurrent osteomyelitis and/or clinical sequelae (limb-length discrepancy, limb deformity, pathologic fracture and bone avascular necrosis).

Patients were divided in two groups based on the development of any adverse event (drug reaction, catheter associated complication and/or nosocomial infection) and univariate analysis was made to find possible associated factors.

Statistical analysis was performed using Statistical Package for the Social Sciences® (SPSS IBM®, Statistics Inc., Chicago), 21st version. Values were expressed as percentages for discrete variables, or as mean and standard deviation for continuous variables. Median and interquartile ranges (IQR) were used for nonparametric variables. The statistical significance ($p < 0.05$) and the model fit of each independent variable were assessed with de Mann-Whitney test, Fischer exact test and chi-square analysis.

Results

One hundred and forty-one patients treated for osteoarticular infections were found, seven of which were excluded (one did exclusively oral treatment and in the other six cases, the diagnosis of osteoarticular infections was excluded during follow-up). One hundred and thirty-four children with osteoarticular infections treated with ivAB, were included. Median age was 5.6 (IQR 1.2-9.7) years, with male predominance (67.2%). Symptoms started on a median of 3 (IQR 2-8) days before admission, with fever present in 67.4% of patients, pain and functional impairment in 87.2% and 72.2%, respectively. Most cases were osteomyelitis (n = 61, 45.5%), followed by septic arthritis (n = 46, 34.3%)

and combined osteomyelitis and septic arthritis (n = 27, 20.1%). Acute presentation was the most frequent (n = 114, 85.1%). Femur (27.3%) and the knee (27.4%) were the most common involved bone and joint, respectively. Regarding microbiologic etiology, 58 cases (43.3%) were culture-confirmed. Information on blood culture was available for 122 patients (91.0%) and was diagnostic in 39 (32.0%). Culture of the joint aspirate sample or the bone biopsy was performed in 64 patients (47.8%) and allowed the identification of the infecting microorganisms in 29 cases (45.3%). *Staphylococcus aureus* was the most frequent infecting organism (51.7%), followed by *Streptococcus pyogenes* and *Streptococcus agalactiae* (Fig. 1). Two cases of *Kingella kingae* were diagnosed by molecular biology techniques.

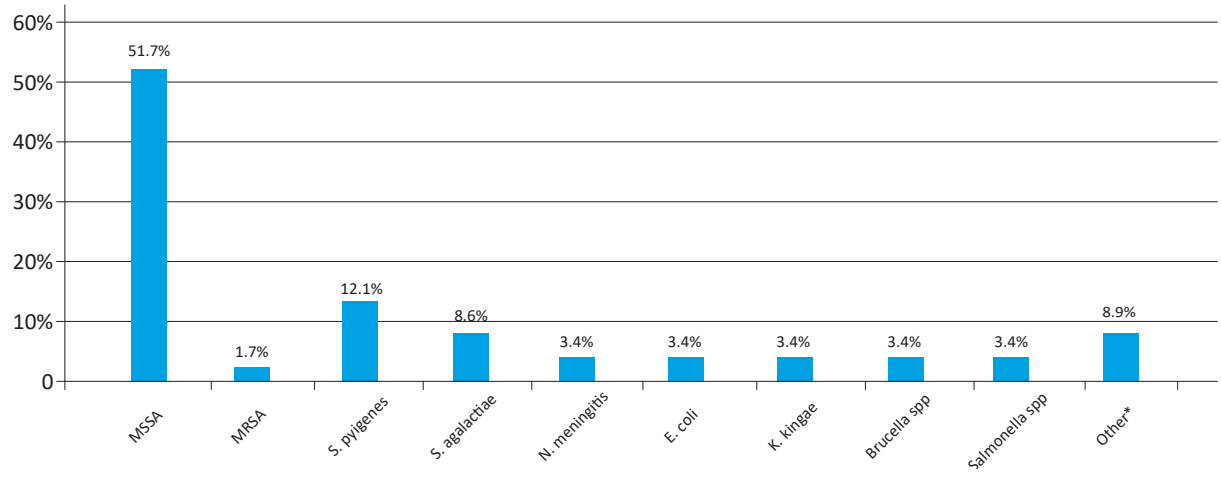
Intravenous AB therapy was started on a median of 7.0 (IQR 4.0-12.8) hours after admission and kept for a median of 19.5 (IQR 14.0-27.3) days. Antibiotics most frequently prescribed were flucloxacillin (58.2%), cefuroxime (38.1%) and ceftriaxone (15.7%). Two or more antimicrobials were used in 48.5% of the patients treated. The initial AB was changed after antimicrobial susceptibility in 22 patients (16.4%). Median total antibiotic therapy duration was 6.0 (IQR 4.8-8.0) weeks. Regarding clinical evolution, median time until apyrexy and clinical improvement was 2 (IQR 1-3) days and 4 (IQR 2-7) days, respectively. Also, median time until 50% decrease in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) was 4 (IQR 3-7) and 14 (IQR 10-21) days, respectively. Inflammatory markers median day of normalization was 10 (IQR 7-16) for C-reactive protein and 25 (14-38) for erythrocyte sedimentation rate. Complicated outcome occurred in 31.8% and included mostly musculoskeletal abscess and pyomyositis (29.3%) and need for surgical intervention (26.8%).

Adverse events of ivAB

Adverse events were found in 98 patients (73.1%), with record of 67 adverse drug reactions (50.0%), 39 catheter associated complications (29.1%) and 33 nosocomial infections (24.6%). Patients with or without adverse events did not differ in terms of demographics, clinical and analytical presentation, improvement or complicated outcome, as shown in Table 1. The duration of ivAB (median 21 *vs* 15 days, $p < 0.001$) and total length of hospital stay (median 23 *vs* 15 days, $p < 0.001$), was significantly higher in patients with adverse events.

Adverse drug reactions

In our sample, 67 patients presented adverse drug reactions (50.0%). The most frequent analytical observed side effects were eosinophilia (36.0%), followed by neutropenia, anemia and elevated liver enzymes (Fig. 2). Patients with adverse drug reactions completed longer courses of ivAB (median 23 *vs* 16 days, $p < 0.001$) (Fig. 3) and had longer total length of AB (median 45 *vs* 42 days, $p = 0.003$). Nevertheless, these patients did not differ in terms of clinical and analytical evolution (at admission or after treatment) from those without adverse drug reactions. Of those patients presenting adverse drug reactions, 88.1% (n = 59) completed more than 14 days of ivAB therapy ($p = 0.018$). Furthermore, analyzing the median day of onset of each side effect, we found that all occurred after a median of at least 18 days of treatment (Table 2). Vancomycin prescription was significantly more frequent in patients with adverse drug reactions (87.5% *vs* 12.5%, $p = 0.031$). In four patients (3.0%), adverse drug reactions lead to AB change. All four developed skin rash, associated with neutropenia in three cases (minimum neutrophil count 290-990 cells/



MRSA - methicillin-resistant *Staphylococcus aureus*; MSSA - methicillin-susceptible *Staphylococcus aureus*.

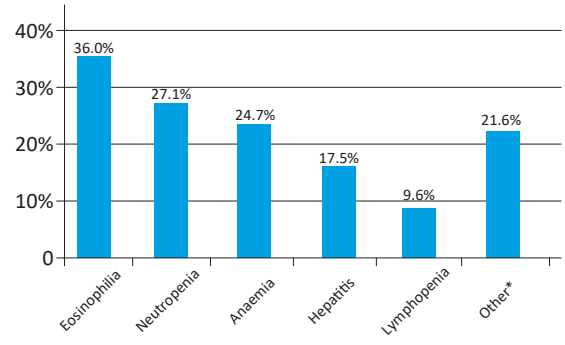
* *Haemophilus influenzae* (n = 1), *Streptococcus pneumoniae* (n = 1), *Staphylococcus epidermidis* (n = 1), *Staphylococcus warneri* (n = 1), *Prevotella bucae* (n = 1).

Figure 1. Causative microorganism in pediatric osteoarticular infections.

Table 1. Comparison of patients with and without adverse effects

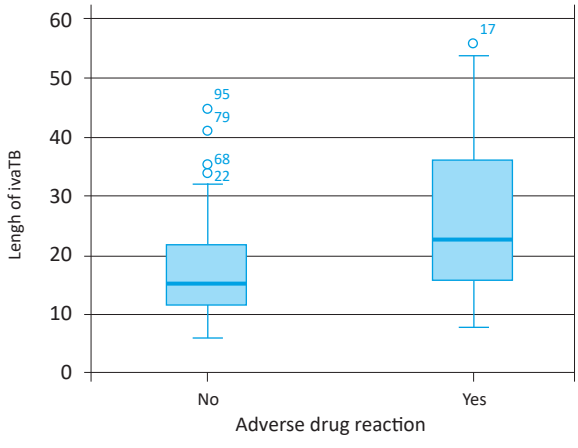
Variable	Total	With adverse event	Without adverse event	*p*
Age (months), median (IQR)	66.5 (13.8-116.3)	66,5 (12.8-120.8)	67.0 (16.0-110.8)	NS
Days of illness, median (IQR)	3 (1-8)	3 (1-7)	4 (1-8)	NS
ANC (cells/µL) at admission, median (IQR)	6320 (4465-9420)	6300 (4390-9325)	6700 (4930-11 170)	NS
CRP (mg/dL) at admission, median (IQR)	6.03 (1.79-11.93)	6.27 (2.43-12.22)	5.02 (1.20-10.19)	NS
ESR (mm/h) at admission, median (IQR)	46 (25-65)	45 (25-78)	47 (22-59)	NS
Multifocal involvement (%)	9.0	11.2	2.8	NS
Multiple ivAB therapy (%)	48.5	52.0	38.9	NS
Time to apyrexia*, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	NS
OA improvement*, median (IQR)	5 (3-7)	5 (3-7)	5 (2-6)	NS
50% CRP decrease*, median (IQR)	4 (3-7)	5 (3-7)	3 (2-4)	NS
CRP normalization*, median (IQR)	11 (8-17)	12 (8-17)	10 (7-15)	NS
20% ESR decrease*, median (IQR)	7 (6-12)	8 (7-12)	7 (4-13)	NS
50% ESR decrease*, median (IQR)	14 (10-21)	14 (10-21)	13 (9-16)	NS
Length ivAB therapy (days), median (IQR)	19.5 (14.0-27.3)	21 (15-30)	15 (10-21)	< 0.001
Length oral AB therapy (days), median (IQR)	21.0 (33.3-32.8)	21 (14-32)	21 (15-34)	NS
Total length of AB therapy (days), median (IQR)	42.0 (33.3-56.0)	42 (35-56)	42 (30-44)	NS
Length of hospital stay (days), median (IQR)	19 (14-28)	23 (15-30)	15 (12-21)	< 0.001
Complicated outcome (%)	31.8%	35.1%	21.9%	NS

ANC - acute neutrophil count; AB - antibiotic; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; IQR - interquartile range; ivAB - intravenous antibiotic; NS - not significant; OA - osteoarticular.
* days on antibiotic therapy.



* Rash (n = 12), fever (n = 6), gastrointestinal symptoms (n = 6) and thrombocytopenia (n = 3).

Figure 2. Frequency and type of adverse drug reactions observed.



ivAB - intravenous antibiotic.

Figure 3. Relationship of intravenous antibiotic therapy length with adverse drug reactions ($p < 0.001$).

µL) and eosinophilia in two (maximal eosinophil count 1050 and 1320 cells/µL), none fulfilling criteria for drug induced eosinophilia and systemic symptoms (DRESS) syndrome. Only one presented with fever. No cases of anaphylaxis, pseudomembranous colitis or *Clostridium difficile* associated diarrhea were recorded.

Catheter associated complications

The overall rate of catheter associated complications was 29.1% (n = 39), including 18 infiltrations (13.4%), 13 thrombophlebitis (9.7%) and eight cellulitis (6.0%). Central venous catheters (CVC) represented 10.4% of the used devices during the reviewed period (n = 14), placed for a median time of 23 (IQR 23-42) days. Four patients (28.6%) with central venous catheter developed complications, namely two thrombophlebitis and two cellulitis. No cases of central venous catheter related bloodstream infections were recorded.

Nosocomial infections

Thirty-three patients presented with nosocomial infections (24.6%), mainly gastrointestinal (n = 15, 11.2%) and respiratory: lower respiratory tract in seven cases (5.2%) and upper respiratory tract in four (3.0%). Other documented nosocomial infections included conjunctivitis (n = 2), genitourinary infection (n = 1), chickenpox (n = 1), parvovirus infection (n = 1) and other

Table 2. Adverse drug reactions by median day of onset and median maximum and minimum values.

Adverse drug reaction	Days on ivAB at onset*	Value†
Max. eosinophil count (cells/µL)	18 (7-28)	1050 (800-1510)
Min. neutrophil count (cells/µL)	29 (20-41)	970 (650-1270)
Min. hemoglobin value (mg/dL)	18 (7-28)	9.90 (8.85-10.95)
Max. ALT level (UI/L)	26 (21-40)	77 (52-119)
Min. lymphocytes count (cells/µL)	21 (15-21)	1240 (925-1445)
Min. platelets count (cells/µL)	25 (15-25)	88 000 (88 000-102 000)

ALT - alanine aminotransferase; ivAB - intravenous antibiotic; Max. - maximum; Min. - minimum.
* Median days on intravenous antibiotic (interquartile range).
† Median (interquartile range).

unidentified viral infections (n = 2). Nosocomial infections were more common in younger patients (median 16 *vs* 77 months, $p < 0.004$) and with longer total hospital stay (median 24 *vs* 18 days, $p = 0.042$).

Discussion

In the present study, we describe a high rate of ivAB related-adverse events (73.1%). Adverse drug reactions were the most common, accounting to half of the cases (50.0%) and varied with the antibiotic prescribed. *A* similar proportion of adverse drug reactions in pediatric osteoarticular infections (51.0%) was reported,[11] with higher rates associated with vancomycin (85.7%). Additionally, reported allergic reactions to AB in 32.1% of children treated for osteoarticular infections were reported.[12] These complications, mainly appearing with penicillins and second-generation cephalosporins, occurred after a mean of 24.4 ± 4.4 days of treatment, all requiring interruption or modification of AB. Their frequency was lower than ours and of other authors,[10] possibly due to the unprecise definition of adverse drug reactions and the omission of analytical adverse reactions. The most frequent described adverse drug reactions were eosinophilia, which was similarly described in our study. In another study, complications of outpatient parenteral antibiotic therapy in children treated for various types of infection, were retrospectively review in a 5.5 year period.[13] Adverse drug reactions were detected in 29% of all outpatient parenteral antibiotic therapy courses, with average time until occurrence of 19 days. When comparing with the rate of neutropenia reported to that of other authors (13%),[13] we detected a rather higher rate (27.1%). However, no serious neutropenia related infectious were reported in our cohort, despite the need for isolation, involving more costs and stress to the families, and extending hospitalization. These comparisons are limited and not straightforward. However, they still highlight the high frequency of adverse events and the need to monitor them, as well as its late onset in the course of treatment. Some other clinical studies briefly mention adverse drug reactions and catheter associated complications, but information is scarce and usually neglected.[4,14,15]

Regarding catheter associated complications, rates in children range from 3% to 15% in epidemiologic studies,[4,15] contrasting with our sample, which presented these complications in nearly one third of the patients. A nonchalant approach to the care of these prolonged admitted patients, coupled with children´s careless and impatience behavior, may partially explain this high rate. A similar incidence of catheter associated complications was reported, ranging from 19.0% to 29.0%.[15,16] Central venous catheters are convenient to avoid frequent catheter changes.[13] These devices must be considered when courses with a predicted duration of more than 14 days are expected. We found similar results, both in central venous catheters and peripheral catheters, although we exhibit a small sample of patients with the first ones. Another advantage of central venous catheters is the avoidance of the multiple punctures, a significant cause of pain and discomfort in small children that should not be neglected. Nonetheless, the use of central venous catheters has also been associated with high rates of complications (41%) later in the course of outpatient parenteral antibiotic therapy, particularly in young children.[16]

Nosocomial infectious are an avoidable burden, representing an important cause of morbidity and increased costs.[17] They usually occur latter during the hospital stay, with median onset of 15-19 days after admission.[18,19] Viruses account for 14%-22% of all nosocomial infections, and are major pathogens in gastrointestinal and respiratory tract nosocomial infections,[18] as reflected in our sample. Major risk factors for acquisition of nosocomial infections in pediatric patients comprise age less than 2 years, severity of underlying disease, comorbidities, presence of invasive procedures, long length of hospital stay, use of

antibiotics, and patient-nursing contacts.[18-20] Nosocomial infections are often underestimated in osteoarticular infection patients, because of antibiotic coverage and the misconception that they are rare. These patients are seldom in isolation, and due to their long hospitalization time, they tend to circulate longer in common areas such as hallways and the playroom, facilitating the acquisition of nosocomial infections. One quarter of our sample presented this complication, highlighting the importance of prompt identification of these high-risk patients, and institution of active surveillance and patient education, in order to reduce the burden of this problem.

With no clear guidelines on duration of treatment, there is a tendency to overtreat in many centers.[1,5] Our study reflects this trend, through the long median hospital stays and ivAB duration, contrasting with the rapid median clinical and analytical improvement. Shortened regimens of mainly oral AB appear to simplify the entire treatment process in terms of hospital stay, antibiotics used, and the risk of adverse events, also reducing treatment costs and bacterial resistance.[21] Early transition to oral treatment in osteoarticular infections is increasingly advocated nowadays, especially since the publication of some randomized clinical trials.[22,23] The majority of the studies support a short ivAB courses (3-7 days) as sufficient for the vast majority of patients with uncomplicated acute osteoarticular infections.[3,4,7,24-26] When appropriate treatment is initiated, the C-reactive protein level increases for one to two days, followed by a steady decline.[22] Therefore, improving clinical signs and symptoms coupled with quickly decline in serum C-reactive protein provide a basis for safely transitioning to oral therapy.[1,27] These recommendations can be applied in patients with uncomplicated osteoarticular infections (more than 3 months old, less than 14 days of symptoms, infection not associated with trauma and not requiring extensive surgical intervention), and do not include patients with comorbidities such as sickle-cell disease or immunodeficiency, in which, worse prognosis requires more interventive management.

This study has several limitations, starting with its retrospective nature, resulting in important missing data, mainly in the first reviewed years, due to the lack of an approach and treatment protocol by that time. Also, approach patterns were reformulated during the studied period. We have included approximately 20% of patients with subacute and chronic presentations, for whom, longer parental therapy is needed, which partially explains the long median total duration of AB therapy in our sample, although probably interfering with data analysis. Type of treatment and respective prognosis were beyond the objectives of this article. Overtreatment is certainly a problem that implicates a different analysis and auditory from the study. Another important limitation is the lack of microbiological identification in cases of nosocomial infections, making it only a presumptive diagnosis. Also, the low rate of *Kingella kingae* identification reflects the fact that molecular studies for this pathogen were started to be routinely performed only after 2013.

Despite these limitations, we describe a significant sample of patients, that allowed us to compare with similar available literature. Our analysis suggests that prolonged ivAB and longer hospital stays increases the chance of several different types of complications. We highlight the importance of analytical monitoring, catheter associated complications early recognition, optimal nursing management of venous catheterization and preventive measures of nosocomial infections, with particular importance to patient education. As most adverse events arise late in the course of ivAB, shorter intravenous courses can prevent these complications, adding lower costs and increased convenience, and without jeopardizing clinical improvement. Growing evidence that ivAB may be quickly and safely substituted for oral antibiotics in patients who show early clinical improvement and rapid C-reactive protein normalization, strengthens this approach. A more detailed analysis of complications, psychosocial impact and issues such as infection control needs to be conducted.

WHAT THIS STUDY ADDS

- Prolonged intravenous antibiotic therapy and longer hospital stays increases the chance of several different types of complications in pediatric osteoarticular infections.
- Analytical monitoring, optimal nursing management of venous catheterization and preventive measures of nosocomial infections, are fundamental to minimize adverse events in the course of intravenous antibiotic therapy.
- Intravenous antibiotic therapy may be quickly and safely substituted for oral antibiotics in patients who show early clinical and analytical improvement, adding lower costs and increased convenience.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Poster presentation in the 15º Congresso Nacional de Pediatria, held in Portugal, October 2014.

Winner of the award Prémio Melhor Trabalho na Área da Infecciologia Pfizer Vacinas - Sociedade Portuguesa de Pediatria.

References

1. Howard-Jones AR, Isaacs D. Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children. J Paediatr Child Health 2013;49:760-8. doi: 10.1111/jpc.12251.

2. Calvo C, Núñez E, Camacho M, Clemente D, Fernández-Cooke E, Alcobendas R, et al. Epidemiology and management of acute, uncomplicated septic arthritis and osteomyelitis: Spanish multicenter study. Pediatr Infect Dis J 2016;35:1288-93. doi: 10.1097/INF.0000000000001309

3. Ballock RT, Newton PO, Evans SJ, Estabrook M, Farnsworth CL, Bradley JS. A comparison of early versus late conversion from intravenous to oral therapy in the treatment of septic arthritis. J Pediatr Orthop 2009;29:636-42. doi: 10.1097/BPO.0b013e3181b2b860.

4. Keren R, Shah SS, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, et al. Comparative effectiveness of intravenous vs oral antibiotics for post discharge treatment of acute osteomyelitis in children. JAMA Pediatr 2015;169:120-8. doi: 10.1001/jamapediatrics.2014.2822.

5. Spyridis N, Syridou G, Goossens H, Versporten A, Kopsidas J, Kourlaba G, et al. Variation in paediatric hospital antibiotic guidelines in Europe. Arch Dis Child 2016;101:72-6. doi: 10.1136/archdischild-2015-308255.

6. Castellazzi L, Mantero M, Esposito S. Update on the management of pediatric acute osteomyelitis and septic arthritis. Int J Mol Sci 2016;17:pii:E855. doi: 10.3390/ijms17060855.

7. Pääkkönen M, Peltola H. Antibiotic treatment for acute haematogenous osteomyelitis of childhood: Moving towards shorter courses and oral administration. Int J Antimicrob Agents 2011;38:273-80. doi: 10.1016/j.ijantimicag.2011.04.007.

8. Dodwell ER. Osteomyelitis and septic arthritis in children: Current concepts. Curr Opin Pediatr 2013;25:58-63. doi: 10.1097/MOP.0b013e32835c2b42.

9. Liu RW, Abaza H, Mehta P, Bauer J, Cooperman DR, Gilmore A. Intravenous versus oral outpatient antibiotic therapy for pediatric acute osteomyelitis. Iowa Orthop J 2013;33:208-12.

10. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC-definitionen fur nosokomiale infektionen 1988. Z Arztl Fortbild 1991;85:818-27.

11. Faden D, Faden HS. The high rate of adverse drug events in children receiving prolonged outpatient parenteral antibiotic therapy for osteomyelitis. Pediatr Infect Dis J 2009;28:539-41. doi: 10.1097/INF.0b013e318193ef38.

12. Ceroni D, Regusci M, Pazos JM, Saunders CT, Kaelin A. Risks and complications of prolonged parenteral antibiotic treatment in children with acute osteoarticular infections. Acta Orthop Belg 2003;69:400-4.

13. Gomez M, Maraqa N, Alvarez A, Rathore M. Complications of outpatient parenteral antibiotic therapy in childhood. Pediatr Infect Dis J 2001;20:541-3.

14. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: A systematic review of the literature. J Bone Joint Surg Br 2012;94:584-95. doi: 10.1302/0301-620X.94B5.28523.

15. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics 2009;123:636-42. doi: 10.1542/peds.2008-0596.

16. Ruebner R, Keren R, Coffin S, Chu J, Horn D, Zaoutis TE. Complications of central venous catheters used for the treatment of acute hematogenous osteomyelitis. Pediatrics 2006;117:1210-5. doi: 10.1542/peds.2005-1465.

17. Oskouie SA RM, Ghabili K, Firoozi F. An epidemiological study of nosocomial infections in Tabriz children's hospital based on national nosocomial infection surveillance system (NNIS). Life Sci J 2013;10:277-9.

18. Ford-Jones EL, Mindorff CM, Langley JM, Allen U, Nàvàs L, Patrick ML, et al. Epidemiologic study of 4684 hospital-acquired infections in pediatric patients. Pediatr Infect Dis J 1989;8:668-75.

19. Muhlemann K, Franzini C, Aebi C, Berger C, Nadal D, Stahelin J, et al. Prevalence of nosocomial infections in Swiss children's hospitals. Infect Control Hosp Epidemiol 2004;25:765-71. doi: 10.1086/502474.

20. Pourakbari B, Rezaizadeh G, Mahmoudi S, Mamishi S. Epidemiology of nosocomial infections in pediatric patients in an Iranian referral hospital. J Prev Med Hyg 2012;53:204-6.

21. Pääkkönen M, Peltola H. Acute osteomyelitis in children. N Engl J Med 2014;370:1365-6. doi: 10.1056/NEJMc1402234.

22. Peltola H, Pääkkönen M, Kallio P, Kallio MJ. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis 2009;48:1201-10. doi: 10.1086/597582.

23. Peltola H, Pääkkönen M, Kallio P, Kallio MJ. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J 2010;29:1123-8. doi: 10.1097/INF.0b013e3181f55a89.

24. Faust SN, Clark J, Pallett A, Clarke NM. Managing bone and joint infection in children. Arch Dis Child 2012;97:545-53. doi: 10.1136/archdischild-2011-301089.

25. Jagodzinski NA, Kanwar R, Graham K, Bache CE. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop 2009;29:518-25. doi: 10.1097/BPO.0b013e3181ab472d.

26. Saavedra-Lozano J, Calvo C, Huguet Carol R, Rodrigo C, Nunez E, Obando I, et al. Documento de consenso SEIP-SERPE-SEOP sobre el tratamiento de la osteomielitis aguda y artritis septica no complicadas. An Pediatr 2015;82:273.e1-10. doi: 10.1016/j.anpedi.2014.10.005.

27. Majewski J, Del Vecchio M, Aronoff S. Route and length of therapy of acute uncomplicated hematogenous osteomyelitis: Do we have the answers yet? Hosp Pediatr 2014;4:44-7. doi: 10.1542/hpeds.2013-0035.

Eventos Adversos da Antibioterapia Intravenosa de Longa Duração para Infeções Osteoarticulares Pediátricas

Resumo:

Introdução: As infeções osteoarticulares são comummente tratadas com longos cursos de antibioterapia endovenosa, conduzindo a tempos de hospitalização prolongados. O objetivo do nosso estudo foi descrever os eventos adversos, nomeadamente reações adversas medicamentosas, complicações associadas a cateter e infeções nosocomiais, em pacientes pediátricos tratados por infeções osteoarticulares.

Métodos: Estudo retrospetivo observacional e analítico das infeções osteoarticular pediátricas de 1994 a 2014 num hospital terciário. Os pacientes foram divididos em dois grupos de acordo com a presença de eventos adversos.

Resultados: Foram identificados 134 pacientes tratados com antibioterapia endovenosa, com uma duração mediana de 19.5 dias (amplitude interquartil 14.0-27.3). Eventos adversos ocorreram em 73.1% dos pacientes (n = 98). Reações adversas medicamentosas (n = 67) ocorreram em 50.0% dos pacientes e estiveram associadas com duração mais longa de tratamento parentérico e com a prescrição de vancomicina. Complicações associadas ao cateter (29.1%; n = 39) incluíram infiltrações de cateter (13.4%), tromboflebites (9.7%) e celulites (6.0%). Trinta e três pacientes apresentaram infeções nosocomiais, nomeadamente gastrointestinais (11.2%) e respiratórias (8.2%). Comparando os grupos com e sem eventos adversos, não foram detetadas diferenças clínicas ou analíticas significativas, na admissão e após iniciar antibioterapia, exceto para a duração da terapêutica endovenosa e duração total de internamento, a qual foi significativamente mais alta em doentes com eventos adversos.

Discussão: A antibioterapia endovenosa prolongada em infeções osteoarticulares está frequentemente associada a eventos adversos. Em pacientes com melhoria clínica e analítica, uma transição precoce de antibioterapia endovenosa para oral deve ser considerada de forma a reduzir a incidência e morbilidade destas complicações.

Palavras-Chave: Administração Intravenosa/efeitos adversos; Antibacterianos/efeitos adversos; Artrite Infecciosa/terapia; Criança; Osteoartrite/terapia; Osteomielite/terapia; Resultado do Tratamento