Describe management of
Osteo-Articular bacterial Infections
in orthopedic surgery : IOA

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Résumé

Objectifs : Cette étude évalue le taux de guérison sous antibiotiques des infections ostéo-articulaires en Algérie à 6 mois et 6 semaines. Elle identifie aussi les facteurs associés à la réussite du traitement et la guérison.

Patients et Méthodes : Cette étude nationale, multicentrique, observationnelle et longitudinale a été conduite dans 10 services de chirurgie orthopédique. Les patients éligibles étaient âgés de ≥15 ans, ayant subi une chirurgie orthopédique avec implantation de matériel d'ostéosynthèse et développé une infection ostéo-articulaire dans l'année suivant la chirurgie. Ils étaient suivis pendant 6 mois. Des prélèvements bactériologiques profonds ont permis l'établissement du diagnostic des infections ostéo-articulaires.

Résultats : 101 patients ont été inclus : âge moyen 51,2 ± 21,4 ans, 58,4% hommes.
88 (94,6%) des prélèvements bactériologiques étaient positifs: 38 bactéries Gram positives (Staphylococcus aureus et staphylococci coagulase-négatifs) et 68 Gram négatives (Enterobacteriaceae et Pseudomonas aeruginosa) étaient identifiées. Le taux de guérison était de 81,5% à 6 mois et 58,8% à 6 semaines. Les abcès (OR=8,24; IC 95% : 1,45-46,73) et au moins une nouvelle chirurgie durant les 6 semaines après le début de la prise en charge de l'infection ostéo-articulaire (OR=1,60; IC 95% : 2,98-103,78) étaient significativement associés au succès du traitement et à la guérison.

Conclusions : Les infections ostéo-articulaires aux entérobactéries Gram négatives étaient fréquentes avec un taux de guérison élevé à 6 mois. Les facteurs de réussite du traitement nous interpellent sur le rôle primordial de la prévention des infections ostéo-articulaires.

>>> ***Mots-clés :***
Antibiothérapie, facteurs de risque, infection ostéo-articulaire, résistance bactérienne.

Abstract

Objectives : This study aims to evaluate the cure rate of osteo-articular infections on material in orthopedic surgery treated with antibiotics within 6 months and 6 weeks in Algeria. It also identifies the factors associated to the treatment success.

Patients and methods : This is a national, multicenter, observational longitudinal study conducted in 10 orthopedic surgery departments. Eligible patients were ≥15 years old, underwent orthopedic surgery with implantation of osteosynthesis material, and developed osteo-articular infection within the year following the surgery. They were followed up for 6 months. Deep bacterial samples were considered for the diagnosis of osteo-articular infections.

Results : 101 patients were recruited: mean age 51.2 ± 21.5 years, 58.4% men. 88 (94.6%) of the 93 bacteriological samples performed were positive: 38 gram-positive (Staphylococcus aureus and coagulase-negative staphylococci) and 68 gram-negative (Enterobacteriaceae and Pseudomonas aeruginosa) bacteria were identified. The cure rate was 81.5% in 81 patients at 6 months and 58.8% at 6 weeks. Abscess (OR=8.24; 95%CI: 1.45 to 46.73) and at least one new surgery during the first 6 weeks following osteo-articular infection management (OR=1.60; 95%CI: 2.98 to 103.78) were significantly associated with treatment success and better cure.

Conclusions : Osteo-articular infections with gram-negative Enterobacteriaceae were frequent with a high 6-months cure rate. The identified factors for the treatment success echo the importance of continuously preventing and healing osteo-articular infections.

>>> ***Keywords :***
Antibiotherapy, bacterial resistance, osteo-articular infection, risk factors.

Introduction :

No surgery is completely «aseptic» despite all precautions taken. The surgical site infections are considered nosocomial when they occur within 30 days following surgery or if this requires the implementation of prosthesis or an implant, in the year following the surgery [1].
In elderly patients, the osteo-articular infection in orthopedic and trauma surgery constitutes often a severe complication (source of morbidity), functional sequels and sometimes a risk of mortality in acute disease (sepsis). Moreover, the management of an infected patient is heavy, and represents a major therapeutic cost due to repeated surgical interventions, repeated hospitalizations, long-term antibiotic therapy, sick leaves and severe consequences for the young population [2,3].
Osteo-articular infections on material are conventionally attributed to Staphylococcus aureus, which represents two-thirds of identified germs [4,5]. However, the predominance of gram-negative bacteria (GNB) has been reported by authors in Algeria [6]. Also, the infection rate depends on the type of surgery performed and its classification. Two classifications are currently used: namely the National Research Council (NRC) and Altemeier classifications. The former is the oldest classification with 5 types of interventions, depending on the extent of contamination at the surgical site (hyper clean, clean, clean-contaminated, contaminated and dirty) [7]. As for Altemeier classification, it is used internationally for all the types of surgery with 4 classes of interventions (clean, clean-contaminated, contaminated and dirty), but seems less suitable for orthopedic surgery [7].
Currently, few multicenter studies in Algeria address this subject and no consensus or recommendations on prescribing curative antibiotics are available [6]. Therefore, the current study aim is to evaluate the rate of cure within the 6 months following antibiotherapy for osteo-articular infections on material in orthopedic surgery. The secondary objectives are to evaluate the rate of cure within the 6 weeks of treatment by antibiotic(s) and to identify risk factors for treatment failure (age [8], concomitant diseases such as neoplasia and diabetes [9], surgery history, concomitant treatment, the classifications of NRC and the American Society of Anesthesiology (ASA) of physical health, and clinical signs of infection at enrollment such as pain, fever and fistula [10]).

2. Materials and Methods

2.1. Study population and settings

This was a national, multicenter, observational and longitudinal study. It was conducted in 10 sites covering the main 3 regions of Algeria (center, east and west) from 13 January 2013 through 14 May 2014. Eligible patients were followed up at baseline (visit 1), then after 6 weeks (visit 2), and at 6 months (visit 3).
Were included patients aged over 15 years old, who underwent orthopedic surgery with implantation of osteosynthesis material regardless of the type, and who developed osteo-articular infection within the year following the surgery and prior to the inclusion in the study. Patients having fungal or mycobacterial infections, as well as acute and chronic blood-bore osteomyelitis were excluded.

2.2. Diagnosis of osteo-articular infections and data collection

Only deep bacterial samples were considered, and osteo-articular infections were diagnosed by the orthopedic department surgeon. Using the definition published by the Center for Disease Control (CDC) of Atlanta [7], the infections were defined according to the presence of at least one of the following conditions: clinical diagnosis by the surgeon, purulent discharge, isolated germ and obvious signs of infection at the surgery site [11].
While demographic data were collected during visit 1,

the clinical, biological and bacteriological characteristics, as well as the medical and surgical management were recorded at the 3 study visits.

2.3. Statistical analysis

Cure rate within 6 months following the treatment of osteo-articular infection in orthopedic surgery was not available. Therefore, to have 10% precision to detect a cure rate of 50% at the 5% significance level, a minimum of 100 patients were required for the study.
Statistical analysis plan was finalized before database lock. Sample characteristics were summarized using mean, standard deviation, median, quartiles and extreme values for quantitative variables, and frequency distributions along with confidence intervals determined at 95% (95%CIs) for qualitative variables. Frequency distributions were compared between qualitative independent variables using the chi-squared test. For continuous data, comparisons between 2 variables were made using Student t-test or Wilcoxon non-parametric test, whereas comparisons between more than 2 means were performed using one-way ANOVA or Kruskal-Wallis test for non-parametric data. The alpha risk was two-sided and set at 5%. The risk of treatment failure (or odds of cure) associated with each factor was quantified by the odds ratio (OR) along with their 95%CIs, the point being made at 6 months. In a second time, all significant factors or borderline significance ($p<0.10$) were introduced into a multivariate logistic model backward selection to assess the risk of each factor. Data were analyzed using SPSS software® version 18 for windows release (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

2.4. Ethical considerations

The study was approved by the ethics committees of the participating sites. It was performed in compliance with the guidelines for Good Epidemiology Practice. All patients were included in the study after reading and signing their informed consent. All data were collected and analyzed respecting the patients' anonymity and confidentiality.

3. Results

3.1. Patients disposition and characteristics

At inclusion, 101 patients were recruited, of whom 97 patients were followed up until the 6-week visit, and 81 patients until the 6-month visit. 80.2% of the patients completed the 3 visits. Sixteen (15.84%) patients were lost to follow-up and 4 (3.96%) died.
The patients' mean age at inclusion was 51.2 ± 21.5 years with a predominance of male (59 men/42 women, sex M/F ratio=1.40). Ten (9.9%) patients were older than 80 years old and 11 (10.9%) were obese.
Two (2%) patients had rheumatic arthritis, one (1%) patient had neoplasia, and 28 (27.7%) had diabetes. Also, 24 (23.8%) patient were previously operated on the same section. The NRC and the ASA classifications were reported for all participating patients. The patient distribution according to ASA showed that 35.6% (36 cases) of the patients were type 2 whereas 59.4% (60 cases) were ASA I. Five cases were ASA III (5.0%) and none was ASA IV (Table 1).

Risk Factor	**N (%)**
Age > 80 years	10 (9.9%)
Rheumatoid arthritis	2 (2.0%)
Corticosteroid therapy	2 (2.0%)
Neoplasia	1 (1.0%)
Immunosuppressive treatment	0 (0.0%)
Diabetes	28 (27.7%)
Immunodeficiency	1 (1.0%)
Obesity	11 (10.9%)
Surgery history on the same section	24 (23.8%)
Other infections	2 (2.0%)

ASA classification of physical health	
I : normal healthy patient	60 (59.4%)
II : patient with mild systemic disease well stabilized under treatment	36 (35.6%)
III : patient with one or several systemic disease not stabilized even under treatment	5 (5.0%)
IV : patient with severe systemic and disabling disease that is a constant threat to life	0 (0.0%)
NCR classification	
1 : hyper clean	20 (19.8%)
2 : clean (orthopedic, closed fracture)	61 (60.4%)
3 : clean-contaminated (open fracture type 1)	10 (9.9%)
4 : contaminated (open fracture type 2 and 3)	10 (9.9%)
5 : dirty (osteitis)	0 (0.0%)
Clinical signs of infection at enrollment	
Abscess	31 (30.7%)
Fistula	45 (44.6%)
Pain	6 (5.9%)
Inflammatory scar	62 (61.4%)
Fever	41 (40.6%)
Other signs	28 (27.7%)

Table 1 : Distribution of associated risk factors considered in the present study
Abbreviations : ASA : American Society of Anesthesiologists; NCR : National Research Council.

The main reason of initial hospitalization was osteosynthesis of fracture in 78 cases (77%) and the main type of surgery was bone plate in 28 cases (27.7%). Total hip replacement (9 patients, 8.9%) and knee replacement (3 patients, 3%) were observed in 11.9% of the patients.
The time between surgery and inclusion was reported for 100 patients, with an average of 5.0 ± 7.1 days (range 0–46 days).
Out of the 101 patients, 65 (64.4%) patients were cured at 6 months while 16 (15.9%) were not, data were missing for 20 (19.8%) patients.

3.2. Biological and bacteriological assessments

The biological assessment at baseline showed an increase in white blood cells in 55/88 patients (62.5%), an accelerated erythrocyte sedimentation rate in 59/65 patients (90.8%) and a C-reactive protein (CRP) increase in 60/70 patients (85.7%).

Overall, bacteriological samples were performed in 93 out of 101 patients: puncture bacteriological sampling was obtained in 27 (29%) patients versus 52 (55.9%) per surgical sample. Among the 93 bacteriological samples, 88 (94.6%) samples were positive. The results were negative in 3 (3.2%) cases and the information had not been specified in 2 (2.2%) cases. No significant link was detected between the type of sampling and identification of the bacteria type (p=0.783). The number of germs per patient varied from 0 to 3, where one microbial agent was detected in 72 (81.8%) patients, 2 bacteria in 14 (15.9%) patients and 3 in 2 cases (2.3%).
A total of 106 bacteria (38 gram-positive bacteria [GPB] and 68 GNB) were identified. The GNB were more common in the lower limb (68%) and the spine (62.5%) (Table 2). There was a significant predominance of GNB (64.2%) composed of 58.8% of *Enterobacteriaceae (Escherichia coli, Proteus, Enterobacter, Klebsiella). Pseudomonas aeruginosa* was identified for 28% of gram-negative germs. Staphylococcus aureus was the most common GPB (47.36%) followed by coagulase-negative staphylococci (Table 3).
Antibiograms were available for 83 pathogens. For Staphylococcus aureus, resistance to methicillin was 56%, resistance to rifampicin was 28.5%, 25% for fusidic acid and 20% for lincomycin. The resistance rates of coagulase-negative staphylococci were also 50% for methicillin and 25% for rifampicin. We noted a relevant resistance to fusidic acid (66.6%).The sensitivity was 100% for glycopeptide (vancomycin and teicoplanin) for both

types of staphylococci. Regarding GNB, Pseudomonas aeruginosa resistance was 7.7% to quinolones, 50% to ceftazidime and 11.8% to imipenem. All pseudomonas strains were sensitive to colistin. The study of susceptibility and resistance for the most frequent enterobacteria (*Proteus, Enterobacter and Klebsiella*) showed a significant resistance to amoxicillin-clavulanic acid (87%) and to cefotaxim (66.6%). Resistance rate of enterobacteria to colistin was 36.8%. It was 28.9% for quinolones and 11.7% for imipenem. All enterobacteria tested were sensitive to ticarcillin and piperacillin.

Table 3 : Distribution of bacteria according to Gram classification

Location	**At least one gram-positive bacterium**	**At least one gram-negative bacterium**	**At least one bacterium**
Upper limb	5 (62.5%)	3 (37.5%)	8
Lower limb	28 (32.0%)	49 (68.0%)	72
Spine	3 (37.5%)	5 (62.5%)	8

Table 2 : Type of bacteria per infection's location

Type of Bacteria	Bacteria	N
Gram-positive bacteria	Staphylococcus aureus	18
	Staphylococci coagulase -	8
	Streptococci	2
	Enterococci	1
	Corynebacterium	1
	Other	8
	Total identified GPB	38 (35.8%)
Gram-negative bacteria	Escherichia coli	6
	Proteus	7
	Pseudomonas aeruginosa	19
	Enterobacter cloacae	13
	Klebsiella	14
	Other	9
	Total identified GNB	68 (64.2%)

Table 3 : Distribution of bacteria according to Gram classification

[English legend]
Abbreviations : GNB : gram-negative bacteria; GPB: gram-positive bacteria.
[French legend]
Abréviations : GNB (BGN): bactérie à gram négatif; GPB (BGP): bactérie à gram positif.

3.3. Curative antibiotherapy

The curative treatment was probabilistic in 29 patients and based on the antibiograms results in 72 patients. In the 3 remaining cases, initial treatment was probabilistic then modified according to antibiograms results. Overall, 67 (66.3%) patients received at least 2 antibiotics.

The overall duration of antibiotic treatment, observed in 98 subjects varied from 6 to 90 days, with an average of 30.8 ± 18.3 days. The number of antibiotics given to the patients varied from 1 to 4 antibiotics : one antibiotic was dispensed in 34 (33.7%) cases; 52 (51.4%) patients received 2 antibiotics, 14 (13.8%) patients received 3 antibiotics and one (1%) patient was administered 4 antibiotics.

Out of the 97 patients who performed the 6-week visit, 87 patients had a positive response to the treatment (presumption of cure or improvement of the general health status) 89.7% (95% CI: 80.6% to 93.6%). In parallel, 57 (58.8%) of the 97 patients were at a presumption of cure. The results of the primary endpoint show that the infection cure rate at 6 months based on the investigator's judgment on visit 3 was 81.5% (95% CI: 72.0% to 89.0%) in 81 patients.

3.4. Risk factors for treatment failure

The univariate analysis showed no significant relationship between the patient-related risk factors (such as age) and the treatment failure. As for factors related to the disease, the National Nosocomial Infections Surveillance (NNIS) index was significantly associated to the cure status (p=0.026) with index zero being predominant in cured patients. No significant relationship between the clinical signs of infections (fistula, pain and fever) and the cure status was observed, except for abscess (p=0.03) which showed better healing in the cured patients and inflammatory scar (p=0.057) which showed a lower cure rate in the cured patients. The association between the infection location and better healing was only significant for the lower limb (p=0.018). Moreover, the infection and surgery types were not significantly associated with the cure status. In parallel, no significant relationship at inclusion was established with biological assessment, except for CRP (p=0.018). Regarding factors related to treatment, no new surgery during the first 6 weeks (p=0.012) and no improvement at 6-weeks (p=0.058) following osteo-articular infection management were associated to treatment failure (Table 4).

As for the multivariate analysis, only abcess (OR=8.24 ; 95%CI: 1.45 to 46.73) and a new surgery during the first 6 weeks following osteo-articular infection management (OR=17.60 ; 95%CI : 2.98 to 103.78) were retained as significant factors associated to treatment success.

Variable	**Number (n)**	**Cured (n=65)**	**Not cured (n=16)**	**p-value* NNIS index**
0	34	31 (47.7%)	3 (18.8%)	0.026*
1	23	18 (27.7%)	5 (31.3%)	
2	1	0 (0.0%)	1 (6.3%)	
Clinical signs of infection				
Abscess	28	18 (27.7%)	9 (56.3%)	0.030*
Fistula	40	33 (50.7%)	7 (43.8%)	0.615
Pain	4	2 (3.07%)	2 (12.5%)	0.119
Inflammatory scar	52	45 (69.2%)	7 (43.8%)	0.057*
Fever	31	25 (38.5%)	6 (37.5%)	0.943
Location of infection				
Upper limb	12	11 (16.9%)	1 (6.3%)	0.443
Lower limb	64	48 (73.8%)	16 (100.0%)	0.018*
Spine	7	7 (10.8%)	0 (0.0%)	0.335
Biological assessment [a]				
Leukocytosis	69	57.9 ± 34.6	54.3 ± 25.8	0.859
ESR at 1 hour	53	17.0 ± 23.0	11.6 ± 5.9	0.811
CRP	50	30.5 ± 26.6	50.3 ± 30.8	0.018*
Factors related to treatment				
Therapeutic approach				
Probabilistic	23	18 (27.7%)	5 (31.3%)	0.777
Antibiogram	58	47 (72.3%)	11 (68.8%)	
Cure status at 6 weeks following antibiotherapy for osteo-articular infections				
No improvement	2	1 (1.5%)	1 (6.3%)	0.058*
Improvement	27	19 (29.2%)	8 (50.0%)	
Presumed cured	48	43 (66.2%)	5 (31.3%)	
New surgery performed before 6 weeks following antibiotherapy for osteo-articular infections				
Yes	21	12 (18.5%)	9 (56.3%)	0.012*

No	58	51 (78.5%)	7 (43.8%)	
New surgery performed between 6 weeks and 6 months following antibiotherapy for osteo-articular infections				
Yes	19	13 (20.0%)	6 (37.5%)	0.108
No	60	51 (78.5%)	9 (56.3%)	

Table 4 : Univariate analysis: risk factors for non-healing at 6 months

[English legend]
* Significance level set at 10%.
a : mean ± standard deviation at inclusion.
Abbreviations : CRP : C-reactive protein; ESR : erythrocyte sedimentation rate ; NNIS : National Nosocomial Infections Surveillance.
[French legend]
* Niveau de significativité statistique de 10%.
a : moyenne ± écart-type à l'inclusion.
Abréviations : CRP : protéine C réactive; ESR (VS) : vitesse de sédimentation ; NNIS : National Nosocomial Infections Surveillance.

4. Discussion

The bone and joint infection in orthopedic surgery is a serious source of morbidity, functional impairment and sometimes a risk of mortality by septicemia in acute phase [2]. Its management is heavy, and represents a major therapeutic cost for society due to repeated surgical interventions, long-term antibiotic therapy and absenteeism. Only few multicentric studies in Algeria addressed the osteo-articular infections [6].
The main objective of this study was to estimate the cure frequency during the 6 months following osteo-articular infection management in orthopedic surgery. The secondary objectives were to determine the response rate at 6 weeks of antibiotherapy. This study also allowed us to better know the epidemiology of these infected patients, their clinical and microbiological profile and to identify the risk factors for no healing.
Early infection seemed to be common in our study. The delay between the surgical intervention and the infection occurrence ranges from 2 to 90 days, with an average of 14.9 ± 14.1 days. No late infections of more than 30 days were reported, mainly because of a contamination of the surgical site during surgery or immediately in postoperative [7].
According to literature, risk of infection in orthopedic surgery can be attributed to factors such as age greater than 65 years, the existence of another infectious site in the patient, prolonged preoperative stay, obesity, corticosteroid therapy, a rheumatoid arthritis, diabetes, recent local radiotherapy, an eschar proximity and the occurrence of postoperative hematoma [3,5]. In our study, the patients were mostly male (sex ratio equal to 1.40), with a mean age of 51.2 ± 21.5 years and the risk factors were dominated by diabetes (27.7%), intervention history on the same segment (23.8%), less frequently obesity (10.9%) and being aged more than 80 years (9.9%). The postoperative complications were frequent (72% of cases), and dominated by postoperative hematoma and flow drain beyond 48 hours after inclusion.
ASA score allows determining the preoperative patient health to assess the risk of postoperative infections and mortality. It also serves to determine the NNIS index [1,7]. The intervention was most often classified as type 1 or type 2 according to NRC [7]. The patients' ASA score was I in 59.4% of cases, nonetheless 4 (3.8%) patients deceased. The causes of death were a digestive hemorrhagic stroke, a cardio-respiratory complication, a postoperative complication in elderly patients and renal failure with septic shock.
The microbiological data of the main studies done on materials infections showed that *staphylococci* were the most frequently isolated bacteria and infections were most often monomicrobial [3,7]. In our study, BGN were significantly predominant (64%), and composed of a high proportion of enterobacteria (*Escherichia coli, Proteus, Enterobacter, Klebsiella*) representing 58.8% of the strains. Pseudomonas was found for 28% of gram-negative germs. *Staphylococcus aureus* was the most frequent gram-positive bacterium (36%) followed by coagulase-negative *Staphylococcus*. These very alarming findings confirm the few bacteriological studies conducted in Algeria [6], and reflect the character of nosocomial infection because of a poor hygiene. Consequently, the fight against these infections must be developed and mastered [6].
As for antibiogram results, bacterial resistance was equally important for gram-positive and GNB. In parallel, antibiotics were prescribed because of their availability, whereas the poor knowledge of antibiotic practices in some cases needs some recommendations. Indeed, the prescription of antibiotics in the bone and joint infections complies with certain obligations[3] : documented infection; probabilistic antibiotherapy initiated after microbiological sampling; association of antibiotics ;

high plasma levels to be reached by the antibiotics ; and use of molecules having a good bone diffusion, for a recommended duration of 6 weeks.
The rate of presumption of cure at 6 weeks was 58.8% whereas the rate of cure at 6 months was 81.5 %. These results cannot be compared to the cure results in literature because most of the studies were conducted in different settings and the healing criteria were difficult to be defined as infectious or functional [2,3]. Finally, we found 2 major risk factors significantly influencing the cure rate, namely the existence of an abscess and at least one surgical revision during the first 6 weeks.

5. Conclusions

This study provided data about the epidemiological and therapeutic aspects of osteo-articular infection on material in 10 orthopedic surgery departments in Algeria. The results showed a high proportion of infection with GNB (64%) where *Enterobacteriaceae* are the most frequent pathogens. The importance of multi-resistant bacteria is also highlighted for *Staphylococcus aureus* and coagulase-negative *staphylococci* and for *Enterobacteriaceae.* Ultimately, these observations shed the light on the importance of continuously preventing and healing osteo-articular infections.

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FZ designed the protocol, performed the statistical analysis and wrote the manuscript.

Disclosure of interest

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