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Safety of antibiotics combinations against *Staphylococcal* bone and joint infections

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1. Introduction

Nowadays, there is an increasing incidence of bone and joint infections (BJI). [1]. *Staphylococci* are the predominant etiologic agent [2]. Our aim was to examine the rate of antibiotic adverse events (AE) concerning different antibiotics associations (ATB-A) in *Staphylococcal* BJI.

2. Methods

Patients were selected through the dashboard of our department (Nice, France), based on a specific software (Statview® version 4.5) [3]. Comorbidities, length of hospitalization, precise diagnosis, microbiological results, antibiotics prescribed and AE were recorded prospectively during hospitalization. All the monobacterial *Staphylococcal* BJI from July 2005 to December 2012, defined by microbiologic harvesting or positive blood cultures, were selected. Isolated monoarthritis were excluded (because antibiotic management was different). During ambulatory care, occurrence of any antibiotic-related AE, modification of ATB-A prescribed, evolution and duration of follow-up were retrospectively recorded. In our department, rifampin dosage was 10 mg/kg twice a day. Aerobic and anaerobic cultures were performed, with blood cultures, and in few cases 16s rRNA gene sequencing was used. Only AE requiring ATB discontinuations were considered here. Evolution was classified as recovery in the absence of clinical and/or microbiological relapse over the period of care.

Relationship between variables was evaluated using the χ^2 statistic (categorical variables), Student's *t*-test (normally distributed continuous variables), and the Mann–Whitney *U* test (non-parametric comparisons). Univariate correlates and clinically significant variables ($P < 0.1$) were then entered into stepwise logistic regression analyses.

Table 1
Characteristics and comorbidities of the 238 patients presenting with staphylococcal bone and joint infections.

Characteristics	
Age (years mean ± SD)	62 ± 17
Sex ratio (male/female)	2.01 (159/79)
Cardiovascular disease	100 (42%)
Diabetes mellitus	44 (18%)
Hepatic disorder	32 (13%)
Nervous system disorder	30 (13%)
Renal disorder	28 (12%)
Neoplasm	14 (6%)
HIV infection	4 (1.7%)
Bone and joint infections	
Prosthesis or device-related infection	108 (45%)
Spondylodiscitis	47 (20%)
Other BJI	83 (35%)

BJI: bone and joint infections.

3. Results

Finally, 238 patients with *Staphylococcus* BJI were treated, with 186 (78%) *Staphylococcus aureus* (17% methicillin-resistant), and 52 (22%) coagulase negative *Staphylococcus* (40% methicillin-resistant). The main clinical characteristics and repartition of BJI are presented in Table 1. The 3 main ATB-A prescribed were fluoroquinolones and rifampin (FQ + RF), rifampin and clindamycin (RF + CD) and clindamycin and fluoroquinolones (CD + FQ). All other ATB-As were classified as "other associations". The mean duration of total antibiotic treatment was 6 weeks.

Among the 61 AE leading to ATB discontinuation, 41 (67%) concerned hospitalization's period and 20 (33%) concerned ambulatory care.

Classification of the AE is presented in Table 2. RF + FQ was the leading ATB-A source of AE followed by RF + CD and FQ + CD. Gastrointestinal disorders represented 13/33 (39%) of the AE. There was no *Clostridium difficile*-associated diarrhea. The mean time of follow-up (± SD) was 11 ± 12 months. At the end of the study, 160 patients recovered, while 40 patients relapsed (17%), 31 patients (13%) were lost to follow-up and 7 patients died.

In univariate and then multivariable analysis, AE related to ATB-A were associated with female gender (OR [95% CI]) 1.99 [1.07–3.69], $P = 0.028$, but not with comorbidities, presence of material, duration of hospital stay and outcomes.

4. Discussion

The best-tolerated ATB-A in monobacterial *Staphylococcal* BJI was FQ + CD. Rifampicin [4–7], clindamycin [8] and fluoroquinolones [9,10] have already been studied in *Staphylococcal* BJI, but our study is the first to compare 3 ATB-As in this indication. One third of the AE were recorded during ambulatory care, underlying the importance of a regular follow-up by specialists.

Prospective studies are required to determine the real place of clindamycin for *Staphylococcal* BJI, in terms of cure rate and AE. Clindamycin could be the first drug to consider as an alternative companion for FQ when RF is not tolerated or contraindicated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Table 2
Adverse event (AE) rate of the different antibiotic associations used for staphylococcal bone and joint infections.

	RF + FQ[a]	RF + CD[b]	FQ + CD[c]	Others[d]
Hospitalization	89 (37%)	33 (14%)	23 (10%)	93 (39%)
Prescriptions *n* (%)	20	3	1	17
AE (*n*)	22%	9%	4%	18%
Rate	89 (37%)	33 (14%)	23 (10%)	93 (39%)
Ambulatory care				
Prescriptions *n* (%)	68 (29%)	32 (13%)	27 (11%)	111 (47%)
AE (*n*)	4	3	2	12
Rate	6%	9%	7%	11%
Overall rate	15%	9%	6%	14%
System organ class affected by the AE				
Gastrointestinal disorders	9	4	0	12
Hepatobiliary disorders	5	0	0	6
Skin disorders	3	0	2	3
Musculoskeletal disorders	3	0	0	2
Renal disorders	1	1	1	1
Hematological	0	0	0	4
Nervous system disorders	1	0	0	0
General disorder[e]	1	0	0	0
Others	1	1	0	1

[a] Rifampin and fluoroquinolones.
[b] Rifampin and clindamycin.
[c] Fluoroquinolones and clindamycin.
[d] Others antibiotics association.
[e] General disorder refers to fever. Classification of adverse events was the Common Terminology Criteria for Adverse Events version 4.0.

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Acute crystal-induced arthritis and rheumatoid factor seropositivity

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The seronegativity of acute gout has been contested historically by several authors who documented the presence of rheumatoid factor (RF) activity in the sera and joint fluid in gout [1]. We revisited this debate by studying patients with acute gout or pseudogout confirmed by the presence of intra-articular monosodium urate monohydrate (MSUM) or calcium pyrophosphate dihydrate (CPPD) crystals, who had serological testing for rheumatoid arthritis (RA) at the time of admission, by measuring RF. Patients fulfilling American College of Rheumatology RA criteria were excluded. Twelve patients with serological data for the diagnosis of RA at the time of the acute attack who had prior ($n = 3$) or subsequent ($n = 12$) determinations of serum RF were included. Ten of these had acute gout and 2 were admitted with pseudogout. All patients were negative