Efficacy of cotrimoxazole (Sulfamethoxazole-Trimethoprim) as a salvage therapy for the treatment of bone and joint infections (BJIs)

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Abstract

Introduction

Cotrimoxazole (Sulfamethoxazole-Trimethoprim, SXT) has interesting characteristics for the treatment of bone and joint infection (BJI): a broad spectrum of activity with adequate bone diffusion and oral and intravenous formulations. However, its efficacy and safety in BJIs are poorly documented and its use remains limited.

Methods

We conducted a retrospective study in 2 reference centers for BJIs from 2013 to 2018 among patients treated with SXT for a BJI. Data were collected from patient’s medical charts. Outcomes and adverse events were evaluated at day (D)7, D45 and D90.

Results

We analyzed 51 patients with a mean age of 60 ± 20 (SD) years of which 76% presented with an orthopedic device infection (ODI). Gram-negative bacilli (GNB) were involved in 47% of BJIs (n = 24). Moreover, they were often polymicrobial infections (41%). Doses of SXT ranged from 800/160mg bid (61%; n = 31) to 800/160mg tid (39%; n = 20). Median SXT treatment duration was 45 days (IQR 40–45). SXT was part of a dual therapy in 84% of patients (n = 43), associated mainly with fluoroquinolones (n = 17) or rifampicin (n = 14). Outcome was favorable at D7 in 98% (n = 50), at D45 in 88.2% (n = 45) and at D90 in 78.4% (n = 40). The second agent combined with SXT was not an independent factor of favorable outcome (p = 0.97). Adverse events were reported in 8% (n = 4) of patients, with a median of 21 days (IQR 20–30) from SXT initiation and led to discontinuation (n = 3).
Conclusion

SXT appears to be effective for treatment of BJIs as a salvage therapy, even in GNB or polymicrobial infection, including ODI. Further data are needed to confirm SXT efficacy as an alternative oral regimen in BJIs.

Introduction

Bone and joint infections (BJIs) are a real concern in the context of an increase of orthopedic device implantations in an aging population with comorbidities. In addition to surgery, adequate antimicrobial therapy is required to efficiently treat BJIs [1]. Rifampicin is deemed to be the best antibiotic active against Gram positive cocci (GPC) in case of BJI, especially due to *Staphyloccocus spp.*, in association with another antimicrobial agent [2,3]. One drawback with rifampicin is the frequent gastrointestinal side effects and the interaction with the p450 cytochromes, in particular in polymedicated elderly patients. Likewise, fluoroquinolones (FQ) are recommended in combination with rifampicin in staphylococcal BJI, or alone in infections due to Gram negative bacilli (GNB) [4–6]. This makes them particularly attractive due to a broad spectrum of activity with good bone diffusion and the possibility of oral administration [2]. Moreover, FQs have been shown to be as effective as intravenous beta-lactams for the treatment of osteomyelitis [7,8]. Thus, FQs took a central place in the treatment of BJIs with a high rate of success well-known since the 1990s [9]. However, in the last decades, resistance to FQs became increasingly prevalent [10]. In addition, a major drawback of prolonged FQ administration is the selection of Extended-Spectrum Beta-Lactamase (ESBL) producing *Enterobacteriaceae* [11] and their risk of induced-tendinitis but also neurotoxicity (around 2%) [12]. Another drawback of FQ therapy is the subsequent risk of *Clostridioides difficile* infection, in particular in the elderly. Therefore, alternative drugs to FQs are needed.

*Cotrimoxazole* (Sulfamethoxazole-Trimethoprim, SXT), is an inhibitor of folinic acid synthesis and has bacteriostatic activity against susceptible bacteria. SXT has some interesting characteristics for the treatment of BJIs. First, SXT is effective against both gram positive and gram negative bacteria, including MRSA [13–16]. Second, its bone diffusion is deemed to be adequate when high posologies are used, including when orally administered [17,18]. The efficacy of SXT in BJIs was first reported in the early 1970s [19]. Recent studies reported its efficacy especially in association with rifampicin in staphylococcal BJI [20,21], leading to the suggestion of SXT as an alternative to FQs in staphylococcal BJIs in the American, British and French guidelines [22–24]. Despite these encouraging data, SXT use remains limited, partly because of the related risk of adverse events, in particular cutaneous rash and haematotoxicity but also renal and hepatic impairment [25]. Therefore, new data to evaluate the efficacy and safety of SXT in BJIs are necessary, especially when other recommended oral agents cannot be prescribed.

The main objective of the study was to evaluate the effectiveness of SXT in BJIs after day 90. The secondary objective was to assess SXT-related adverse events.

Methods

Setting

A retrospective study was conducted in 2 reference centers for BJIs treatment located in the Greater Paris area, France (Ambroise Paré Hospital, Boulogne-Billancourt, and Raymond
Poincaré Hospital, Garches). Those 2 teaching hospitals share common staff with weekly pluridisciplinary meetings with an infectious disease specialist, an orthopedic surgeon, a microbiologist and a pharmacist. In our local guidelines, patients undergoing surgery for a BJI were administered empiric broad spectrum intravenous antimicrobial therapy post-operatively combining daptomycin and piperacillin-tazobactam in case of orthopedic device infection (ODI), or vancomycin and piperacillin-tazobactam in case of a native BJI, as appropriate. All adult patients admitted for a BJI in orthopedics and treated with SXT from January 2013 to April 2018 were enrolled in the study. Those centers managed 1568 BJIs during this period. Exclusion criteria were: age under 18 years, being infected by a microorganism non-susceptible to SXT, duration of SXT prescription of less than 10 days prescribed for the drainage of an abscess and a suppressive antimicrobial therapy (more than a year of therapy) or declining to participate in the study.

Definitions

- Criteria for the diagnosis of acute bone and joint infection were based on clinical signs and symptoms of bone and joint infection associated with a positive bacteriological examination of blood, bone or joint fluid samples.

- Success was defined as the absence of local or systemic signs of infection, including delayed wound healing recorded in the medical chart, and a statistical diminution of the CRP value between admission and last follow-up consultation associated with absence of relapse. Cases who did not meet above-mentioned criteria were classified as “failure”.

- Salvage therapy was defined by the inability to use a recommended regimen for the treatment of BJIs, notably a combination therapy with fluoroquinolones and rifampin for staphylococcal infection, due to a resistance mechanism or intolerance. In case of polymicrobial infection or potentially resistant organism (such as ESBL or cephalosporinase producing organisms), SXT was prescribed in combination therapy mainly to prevent the emergence of fluoroquinolones resistant mutants or broaden the antibiotic spectrum.

- Multidrug-resistant organisms included ESBL-producing Enterobacteriaceae and/or methicillin-resistant Staphylococcus aureus strains.

Data collection

The following data were collected from patient’s medical charts:

- Patient characteristics: age, sex, diabetes, smoking habits, peripheral vascular disease, allergy to antibiotic, Charlson score at admission, number of previous surgeries,

- Infection characteristics: orthopedic device (OD) (prosthetic joint, osteosynthesis, vertebral OD), site of infection, mono or polymicrobial infection, microorganism and mechanism of resistance, concomitant bacteremia, C-reactive protein (CRP) at diagnosis,

- Treatment characteristics: surgery (device retention, removal or replacement), empiric antimicrobial therapy, duration of intravenous antibiotic therapy, SXT use, route of administration, dosing and duration of treatment, mono or combination therapy with associated drugs.

- Outcomes were evaluated at day (D) 7 after the surgery, D45 and D90. The occurrence of death, adverse event, length of stay (LOS) and CRP at the last follow-up was collected. Later events were documented by telephone interviews.
Statistical analysis

Descriptive results were expressed using median and interquartile range (IQR) for the continuous variables when appropriate, and in number with percentage for the categorical variables. Analyses were performed using Excel 2010 (Microsoft Corporation, Redmond, WA). Student’s t-test was performed to analyze continuous data using GraphPad Prism v.7.0 (GraphPad Software Inc., La Jolla, CA). Statistical significance was defined as $p<0.05$.

Compliance with ethical standards and approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The local Ethics Committee was contacted and there was a waiver of any need for consent, linked to the retrospective nature of this study, since data have already been collected and thereafter data analyzed anonymously.

Results

Study population and infection characteristics

Overall, 124 patients were screened and are presented in the flow-chart (Fig 1). Fifty-one patients were included in the study which represents 3.2% of all the admission for BJI during this period. The median LOS was 10 days (IQR 8–17). Population and infection characteristics

Fig 1. Flow chart of patients included in the study.

https://doi.org/10.1371/journal.pone.0224106.g001
are detailed in Table 1. The sex ratio was 1 and the mean (± standard deviation (SD)) age was 60 ± 20 years. Twenty-one (41%) infections were polymicrobial, involving 2 to 4 bacterial species. BJIs were caused by Gram positive (GP) bacteria only (53%; n = 27), Gram negative (GN) bacteria (18%; n = 9) and 29% both GP and GN bacteria (n = 15). GPC included 39% coagulase-negative Staphylococci (CoNS) (n = 20), 27% methicillin-susceptible Staphylococcus aureus (MSSA) (n = 14) and 12% methicillin-resistant S. aureus (MRSA) (n = 6). GNB included 43% Enterobacteriaceae (n = 22) and 10% non-fermenter GNB (n = 5). Enterobacteriaceae were cephalosporinases producing species in 27% (n = 14) of cases and one case of ESBL-producing E. coli. Microorganisms are detailed in Table 2.

Table 1. Population and infection characteristics.

| Population characteristics | Total (N = 51) | Success (N = 40) | Failure (N = 11) | P |
|----------------------------|---------------|-----------------|-----------------|---|
| Male, n(%)                 | 25 (49)       | 20 (50)         | 5 (45)          | NS |
| Age (years), median (IQR)  | 60 (44–77)    | 60 (44–76)      | 70 (42–76)      | NS |
| Comorbidities, n(%)        | 29 (57)       | 24 (60)         | 5 (45)          | NS |
| Diabetes, n(%)             | 11 (22)       | 9 (23)          | 2 (18)          | NS |
| Smoking habits, n(%)       | 21 (41)       | 18 (45)         | 3 (27)          | NS |
| Peripheral artery disease, n(%) | 8 (16)     | 6 (15)          | 2 (18)          | NS |
| Charlson score, median (min-max) | 3 (0–8)     | 3 (0–8)         | 4 (0–8)         | NS |
| Previous surgery, median (min-max) | 1 (0–4)   | 1 (0–4)         | 1 (0–4)         | NS |
| Allergy, n(%)              | 5 (10)        | 3 (8)           | 2 (18)          | NS |
| Beta-lactam, n(%)          | 3 (6)         |                 |                 |    |
| Fluoroquinolone, n(%)      | 2 (4)         |                 |                 |    |

Infection characteristics

| CRP at diagnosis (mg/l), median (IQR) | Success (N = 40) | Failure (N = 11) | P   |
|--------------------------------------|------------------|-----------------|-----|
| 77 (26–111)                          | 67 (21–108)      | 78 (59–133)     | NS  |

| Type of infection | Total (N = 28) | Success (N = 20) | Failure (N = 8) | P   |
|-------------------|---------------|------------------|-----------------|-----|
| ODI, n(%)         | 39 (76)       | 29 (73)          | 10 (91)         | NS  |
| PJI, n(%)         | 28 (55)       | 20 (50)          | 8 (73)          | NS  |
| Osteosynthesis infection, n(%) | 10 (20)     | 9 (23)           | 1 (9)           | NS  |
| Vertebral ODI, n(%) | 1 (2)         | 0 (0)            | 1 (9)           | NS  |
| Osteomyelitis, n(%) | 6 (12)        | 5 (13)           | 1 (9)           | NS  |
| Arthritis, n(%)   | 5 (10)        | 5 (13)           | 0 (0)           | NS  |
| Spondylodiscitis, n(%) | 1 (2)     | 1 (3)            | 0 (0)           | NS  |
| Site of infection |                |                  |                 |     |
| Lower limb, n(%)  | 42 (82)       | 32 (80)          | 10 (91)         | NS  |
| Knee, n(%)        | 13 (25)       |                 |                 |     |
| Hip, n(%)         | 12 (24)       |                 |                 |     |
| Leg, n(%)         | 8 (16)        |                 |                 |     |
| Ankle/foot, n(%)  | 7 (14)        |                 |                 |     |
| Femur, n(%)       | 2 (4)         |                 |                 |     |
| Upper limb, n(%)  | 7 (14)        | 7 (18)           | 0 (0)           | NS  |
| Elbow, n(%)       | 5 (10)        |                 |                 |     |
| Shoulder, n(%)    | 2 (4)         |                 |                 |     |
| Vertebral, n(%)   | 2 (4)         | 1 (3)            | 1 (9)           | NS  |

CRP, C-reactive protein; ODI, orthopedic device infection; PJI, prosthetic joint infection.

https://doi.org/10.1371/journal.pone.0224106.t001
Overall, 25 patients had organisms which were resistant to fluoroquinolones and 5 patients were considered intolerant to the oral agents, notably among elderly patients related to confusional states.

### Surgical management

All patients underwent surgery during the course of therapy. The procedure consisted of debridement on native joint in 12 cases (24%) debridement and implant retention in 11 cases (22%) and debridement with OD removal in 28 cases (55%) (Table 3). Eight ODIs presented acutely versus 31 chronic ODIs. Debridement and implant retention was performed in 26% (n = 8) of cases vs debridement with OD removal in 74% (n = 23).

### Antimicrobial regimens

Median duration of first-line IV treatment was 7 days (ranging from 5 to 10 days).

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**Table 2. Microbiological characteristics.**

|                      | Total (N = 51) | Success (N = 40) | Failure (N = 11) | P  |
|----------------------|----------------|------------------|------------------|----|
| Polymicrobial, n(%)  | 21 (41)        | 16 (40)          | 5 (45)           | NS |
| GP and GN bacterial infection, n(%) | 15 (29)        | 12 (30)          | 3 (27)           | NS |
| CGP, n(%)            | 41 (80)        | 33 (83)          | 8 (73)           | NS |
| CoNS, n(%)           | 20 (39)        |                  |                  |    |
| MSSA, n(%)           | 14 (27)        |                  |                  |    |
| MRSA, n(%)           | 6 (12)         |                  |                  |    |
| Streptococcus, n(%)  | 4 (8)          |                  |                  |    |
| Enterococcus, n(%)   | 4 (8)          |                  |                  |    |
| GNB, n(%)            | 24 (47)        | 18 (45)          | 6 (55)           | NS |
| Enterobacteriaceae, n(%) | 22 (43)    |                  |                  |    |
| Enterobacter sp, n(%)| 10 (20)        |                  |                  |    |
| Escherichia coli, n(%)| 5 (10)        |                  |                  |    |
| Klebsiella sp, n(%)  | 3 (6)          |                  |                  |    |
| Morganella morganii, n(%) | 3 (6)  |                  |                  |    |
| Serratia sp, n(%)    | 3 (6)          |                  |                  |    |
| Proteus mirabilis, n(%) | 2 (4)       |                  |                  |    |
| Group 3 Enterobacteriaceae, n(%) | 14 (27) | 9 (23)          | 5 (45)           | NS |
| Non fermental BGN, n(%) | 5 (10)        | 4 (10)           | 1 (9)            | NS |
| Pseudomonas aeruginosa, n(%) | 2 (4)       |                  |                  |    |
| Stenotrophomonas maltophilia, n(%) | 2 (4)     |                  |                  |    |
| Acinetobacter sp, n(%) | 1 (2)          |                  |                  |    |
| Other, n(%)          | 4 (8)          | 3 (8)            | 1 (9)            | NS |
| Propionibacterium acnes, n(%) | 2 (4)       |                  |                  |    |
| Corynebacterium sp, n(%) | 2 (4)         |                  |                  |    |
| MDR bacteria, n(%)   | 7 (14)         | 5 (13)           | 2 (18)           | NS |
| MRSA, n(%)           | 6 (12)         |                  |                  |    |
| ESBL, n(%)           | 1 (2)          |                  |                  |    |
| Bacteraemia, n(%)    | 1 (2)          | 1 (3)            | 0 (0)            | NS |

GP, gram positive; GN, gram negative; CGP, cocci gram positive; GNB, gram negative bacilli; CoNS, coagulase-negative *Staphylococci*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MDR, multi-drug resistant; ESBL, extended-spectrum beta lactamase. Of note, the total number of microorganisms exceeds 100% as there are polymicrobial infections.

https://doi.org/10.1371/journal.pone.0224106.t002

Overall, 25 patients had organisms which were resistant to fluoroquinolones and 5 patients were considered intolerant to the oral agents, notably among elderly patients related to confusional states.
All patients received an oral regimen with SXT as part of a combination therapy, with 43 (84%) dual therapy and 8 (16%) tritherapy or more (detailed in Table 3). Of the eight patients treated with three or more antimicrobial agents, 88% were polymicrobial (n = 7) involving both GPC and GNB in 38% (n = 3).

The associated drugs used in dual therapy were mainly FQ or rifampicin (72%, n = 31). Among patients treated with a dual therapy including a FQ (n = 17), 11 (65%) were due to a cephalosporinase producing Enterobacteriaceae. Conversely, 12 (28%) cases received neither rifampicin nor FQ in bitherapy with SXT. The regimen included beta-lactams (n = 4) (amoxicillin-clavulanic acid (n = 3) and cefepime (n = 1)), clindamycin (n = 4), daptomycin (n = 2), vancomycin (n = 1) or linezolid (n = 1).

### Table 3. Surgical management and antimicrobial regimen.

|                  | Total (N = 51) | Success (N = 40) | Failure (N = 11) | P     |
|------------------|----------------|------------------|------------------|-------|
| **Surgical management** |                |                  |                  |       |
| Surgery, n(%)    | 51 (100)       | 40 (100)         | 11 (100)         | NS    |
| Debridement on native joint, n(%) | 12 (24) | 11 (28) | 1 (9) | NS    |
| Debridement and implant retention, n(%) | 11 (22) | 9 (23) | 2 (18) | NS    |
| Debridement with OD removal, n(%) | 28 (55) | 20 (50) | 8 (73) | NS    |
| 1 stage change, n(%) | 19 (38) | 14 (35) | 5 (45) | NS    |
| 2 stages change, n(%) | 1 (2) | 1 (3) | 0 (0) | NS    |
| No implantation, n(%) | 8 (16) | 5 (13) | 3 (27) | NS    |
| **Medical management** |                |                  |                  |       |
| Empiric antimicrobial therapy, n(%) | 50 (98) | 39 (98) | 11 (100) | NS    |
| Beta-lactam, n(%) | 49 (96) | 38 (95) | 11 (100) | NS    |
| Piperacillin-tazobactam, n(%) | 43 (84) | | | |
| Other, n(%) | 6 (12) | | | |
| Anti-MRSA ATB, n(%) | 46 (90) | 36 (90) | 10 (91) | NS    |
| Vancomycin, n(%) | 23 (45) | | | |
| Daptomycin, n(%) | 23 (45) | | | |
| Other, n(%) | 4 (8) | 3 (8) | 1 (9) | NS    |
| Intra-venous ATB duration (days), median (IQR) | 6 (5–7) | 6 (5–7) | 6 (5–8) | NS    |
| **SXT prescription modalities** |                |                  |                  |       |
| Daily dose, n(%) |                |                  |                  |       |
| 800/160mg bid, n(%) | 31 (61) | 25 (63) | 6 (55) | NS    |
| 800/160mg tid, n(%) | 20 (39) | 15 (38) | 5 (45) | NS    |
| Oral intake, n(%) | 51 (100) | 40 (100) | 11 (100) | NS    |
| Number of associated ATB, n(%) |                |                  |                  |       |
| 1, n(%) | 43 (84) | 36 (90) | 7 (64) | NS    |
| ≥2, n(%) | 8 (16) | 4 (10) | 4 (36) | NS    |
| Associated ATB in dual therapy, n(%) |                |                  |                  |       |
| FQ, n(%) | 17 (40) | 14 (35) | 3 (27) | NS    |
| RMP, n(%) | 14 (33) | 12 (30) | 2 (18) | NS    |
| Other, n(%) | 12 (28) | 10 (25) | 2 (18) | NS    |
| Oral ATB duration (days), median (IQR) | 45 (40–45) | 45 (40–45) | 37 (34–44) | NS    |
| Total ATB duration (days), median (IQR) | 47 (45–51) | 48 (45–51) | 42 (41–50) | NS    |

OD, orthopedic device; ATB, antibiotic; MRSA, methicillin-resistant Staphylococcus aureus; SXT, Sulfamethoxazole-trimethoprim; RMP, rifampicin; FQ, fluoroquinolone.

https://doi.org/10.1371/journal.pone.0224106.t003
Outcomes

The median duration of follow-up was 126 days (IQR 99–185); 5 (9.8%) patients were lost to follow-up at D90, including 2 cases before D45.

The median CRP level at the last follow-up was 10 mg/L (IQR 2–24) and lower than at the admission (see Table 1) (p < 0.0001). In our center, the CRP value was considered normal at a value of ≤5 mg/L and was found in 21 (41.2%) patients at the last follow-up consultation.

Considering those who were lost to follow-up as failures, outcomes were favorable at D7 in 98% (n = 50), at D45 in 88.2% (n = 45) and at D90 in 78.4% (n = 40). If we exclude those who were lost to follow-up from the final analyses (best-case scenario), outcomes were favorable at D7 in 98% (n = 50/51), at D45 in 91.8% (n = 45/49) and at D90 in 87.0% (n = 40/46). Outcomes at D90 depending on the drug used in combination therapy with SXT were comparable between groups (p = 0.97) and are detailed in Fig 2.

In univariate analyses, infection with a cephalosporin producing Enterobacteriaceae (n = 14) was not significantly associated with a worse outcome at D90 with a 64.3% (n = 9) cure rate vs other groups 83.8% (n = 31) (p = 0.15). Of note, 78.6% (n = 11) were treated with a dual therapy containing SXT/FQ.

No patient died nor was admitted to intensive care unit in the course of treatment. Twenty-one patients (41%) had a limitation in their function at the end of follow-up.

Adverse events

Adverse events were reported in 4 (8%) patients, with a median time of 21 days (IQR 20–30) from SXT introduction. Adverse events consisted of a mild hepatitis (values up to 3 times above the normal), a short duration watery diarrhea, a cutaneous maculopapular skin rash and an isolated fever in 1 case each. No renal failure was diagnosed during follow-up. SXT was interrupted in 6% (n = 3): 1 patient had replacement with a switch to another antimicrobial therapy (n = 1) and 2 antibiotic discontinuations were noted. Three of them were lost to follow-up at D90.

Discussion

This retrospective study documents numerous patients treated with a combination therapy based on SXT for the treatment of a polymicrobial BJI (41%). We observed a favorable outcome at D90 in 78.4%; nevertheless adverse events led to SXT discontinuation in 6% of patients. It is noteworthy that when used in dual therapy, the second agent combined with SXT did not impact the overall success rate.

A success rate of less than 80% can appear disappointing but it rises up to 87% in the best case scenario. This rate is gratifying if we consider the higher proportion than usual of these particular prosthetic joint infections due to polymicrobial and Gram-negative bacteria [10,26]. Moreover it concerns elderly and fragile patients with frequent comorbidities who underwent previous surgeries which failed initial therapy (as illustrated in Table 1) and therefore required the expertise of a reference center.

This rate of favorable outcome is slightly higher than previously reported in the literature in GPC and GNB BJIs treated with SXT. Indeed, Fica et al. reported a success rate of 61% (n = 23) with 9 failures requiring surgery [27]. In another study regarding early ODI due to GCP and GNB, Torenero et al. support the fact that SXT is inappropriate due to a high rate of failure but in a small sample size of 7 patients (including 5 due to GPC and 2 to GNB) [28].

Our results are similar to those more recently reported in GPC BJIs. Euba et al. showed that SXT in combination with rifampicin was as effective as intravenous cloxacillin in the treatment of 28 chronic staphylococcal osteomyelitis, with 88.9% success in intention to treat and 91.7%
Moreover, Nguyen et al. reported a success rate of 78.6% at the end of the treatment and 76.9% at 2 years. This study was conducted among 26 patients with a BJI treated with SXT in association with rifampicin. This latter study showed similar outcomes using this regimen based on SXT versus a combination of rifampicin plus linezolid [30]. Likewise, Harbarth et al. described an 85.7% success rate (n = 75) using SXT in association with rifampicin for the treatment of MRSA BJI in comparison with 55.6% when using linezolid.
alone [31]. Finally, in pediatrics, Messina et al. reported a success rate of 100% (n = 20) using a monotherapy of SXT for the treatment of acute *Staphylococcus aureus* osteomyelitis [32].

Of note, one major point pleading for the use of SXT over FQ is that MRSA strains seem to remain susceptible to SXT even after a SXT exposure [33]. However, physicians should be wary that there is a possible risk of emergence of resistance against rifampicin when prescribed in dual therapy with SXT, despite a combination therapy [34]. Nevertheless, it should be noted that those concerns are based on *in vitro* data and must be discussed in the light of clinical findings.

In addition, data are scarce concerning GNB prosthetic joint infections, which represents 15% of BJIs and are known to be difficult to treat [35]. Nevertheless, our data did not show any statistical differences in terms of outcomes between cephalosporinase producing *Enterobacteriaceae* and the other cases, likely because of an underpowered dataset (n = 51). A combination therapy of SXT with a FQ in these patients was associated with a favorable outcome in 82.3%. Although the systemic use of a combination therapy against GNB including cephalosporinase producers might have been overcautious, it may have helped to preserve FQs acquiring resistance.

In addition, median duration of treatment was 6 weeks which is generally compliant according to the French guidelines [22] and promoting the appropriate use of antibiotic duration. In such prolonged therapy, an efficient oral regimen can be helpful to reduce LOS. Indeed, our reported LOS was quite short with a median of 10 days. Previously published studies have also reported a diminution of the LOS for BJI while using SXT [27,30]. Likewise, although costs have not been studied, some literature has already reported a diminution of costs when prescription included SXT [26,30,36].

Even if the reason to prescribe SXT over other molecules was not clearly stated in the medical records, most of the prescriptions were supported by the resistance to either FQ or rifampicin. Indeed, allergy was not the main reason for prescribing SXT since only a few patients presented allergy to FQ and none to rifampicin.

Overall, SXT’s broad spectrum activity could be of interest in various populations, including elderly patients with polymicrobial infections, previously exposed to usual classes of antibiotics (i.e. FQ and rifampicin).

Interestingly, the doses of SXT we used were frequently lower than recommended by the French (3200/640mg) and US guidelines (8 mg/kg of trimethoprim) [22,23], but also lower than the ones reported in previous cohorts of BJIs treated with SXT [27,29–31]. This can be explained by the fact that physicians did not want to use high doses considering the elderly population with an increased risk of side effects. Although it can be argued that lower doses can be responsible for antibiotic selective pressure, our prescriptions were performed as combination therapy, thereby reducing the potential risk of the appearance of mutants.

SXT is responsible for various adverse events such as cutaneous rash, gastrointestinal disorders, hepatitis, cytopenia [25] or acute renal failure [37,38]. In our study, adverse events were reported in only 8% of patients, leading to SXT interruption in 6%. A similar rate was reported in previous studies concerning staphylococcal BJI with 12% adverse events and 7% SXT discontinuation due to adverse events [29,31]. Likewise, Valour et al. reported a comparable rate of 15% of adverse events in patients treated with various other antibiotics for methicillin-sensitive *Staphylococcus aureus* BJI [39]. However, Nguyen et al. reported a higher rate of 46% of adverse events using SXT [30]. These results can partly be explained by the long mean duration of therapy of 17.8 weeks. Likewise, Fica et al. reported 43% of SXT discontinuation mainly due to hyperkalemia in patients treated with drugs active against the renin-angiotensin system [27]. Those adverse events must be balanced with the new alert of aortic aneurysm and
dissection due to the prolonged used of fluoroquinolones (>14 days) [40], that is a serious threat to consider in such population of elderly and comorbid patients suffering from BJIs.

Finally, our study presents some limitations. First, it is a retrospective study with a relatively limited sample size; thereby its results might not be extrapolated to other healthcare facilities. Second, the infections included are heterogeneous with OD and native BJI caused by GPC and GNB infections. However, it reinforces the usefulness of SXT when clinicians are dealing with polymicrobial infections. Third, we faced a substantial number of patients lost to follow-up despite a relatively short median duration of follow-up for a BJI, considering that infection cure is usually defined after a one-year follow-up. However, individuals who were lost to follow-up were interpreted as failures to avoid an over-estimation of the success rate in final analyses and this is what we observed in real-life.

Conclusion
Cotrimoxazole appears to be effective for the treatment of BJIs. Its broad spectrum activity makes it particularly interesting in polymicrobial infections with GPC and GNB as illustrated in our work. It can prove helpful as a salvage therapy when the preferred combination therapy with FQ or rifampicin is unusable, but also in case of deadlock situations requiring intravenous and prolonged therapy. Although the described rate of reported adverse events was acceptable, physicians should be wary that most patients who experienced adverse events required discontinuation of their therapy. We believe our work will encourage reference centers taking into consideration the use of SXT. Further prospective data are needed to confirm SXT efficacy as an alternative regimen in common BJIs.

Acknowledgments
Authors would like to thank their colleagues, particularly Pr Anne-Claude Cremieux and Dr Pierre de Truchis for their unfailing support.

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References
1. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004; 351: 1645–1654. https://doi.org/10.1056/NEJMoa040161 PMID: 15463283
2. Darley ESR. Antibiotic treatment of Gram-positive bone and joint infections. J Antimicrob Chemother. 2004; 53: 928–935. https://doi.org/10.1093/jac/dkh191 PMID: 15117932

3. Ferry T, Uçkay I, Vaudaux P, François P, Schrenzel J, Harbarth S, et al. Risk factors for treatment failure in orthopedic device-related methicillin-resistant *Staphylococcus aureus* infection. Eur J Clin Microbiol Infect Dis. 2010; 29: 171–180. https://doi.org/10.1007/s10096-009-0837-y PMID: 19946789

4. Sennerville E, Joulié D, Legout L, Valette M, Dezeque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis. 2011; 53: 334–340. https://doi.org/10.1093/cid/cir402 PMID: 21810745

5. Stengel D, Bauwens K, Sehoulí J, Ekkernkamp A, Porzsoff F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis. 2001; 1: 175–188. https://doi.org/10.1016/S1473-3099(01)00094-9 PMID: 11871494

6. Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis. 2005; 9: 127–138. https://doi.org/10.1016/j.ijid.2004.09.009 PMID: 15840453

7. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother. 1991; 35: 538–541. https://doi.org/10.1128/aac.35.3.538 PMID: 2039205

8. Karamanis EM, Matthaiou DK, Moraitis L, Falagas ME. Fluoroquinolones versus beta-lactam based regimens for the treatment of osteomyelitis: a meta-analysis of randomized controlled trials. Spine (Phila Pa 1976). 2008; 33: E297–304. https://doi.org/10.1097/BR.0b013e3181f6c22 PMID: 18449029

9. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012; 54: 393–407. https://doi.org/10.1093/cid/cir322 PMID: 22157324

10. Titec M, Sennerville E, Wallet F, Dezèque H, Migaud H, Courcol R-J, et al. Bacterial epidemiology of osteoarticular infections in a referent center: 10-year study. Orthop Traumatol Surg Res OTSR. 2013; 99: 653–658. https://doi.org/10.1016/j.otsr.2013.02.011 PMID: 23988422

11. Colodner R, Rock W, Chazan B, Keller N, Sakran W, et al. Risk factors for the development of Extended-Spectrum Beta-Lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis. 2004; 23: 163–167. https://doi.org/10.1007/s10096-003-1084-2 PMID: 14986159

12. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011; 34: 465–488. https://doi.org/10.2165/11587280-000000000-00000 PMID: 21585220

13. Elwell LP, Wilson HR, Knick VB, Keith BR. In vitro and in vivo efficacy of the combination trimethoprim-sulfamethoxazole against clinical isolates of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 1986; 29: 1092–1094. https://doi.org/10.1128/aac.29.6.1092 PMID: 3488022

14. Kaka AS. Bactericial activity of orally available agents against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother. 2006; 58: 680–683. https://doi.org/10.1093/jac/dkl283 PMID: 16840428

15. Yeldandi V, Strodtman R, Lentino JR. In-vitro and in-vivo studies of trimethoprim-sulphamethoxazole against multiple resistant *Staphylococcus aureus*. J Antimicrob Chemother. 1988; 22: 873–880. https://doi.org/10.1093/jac/dkt267 PMID: 3266621

16. Burman LG. The antimicrobial activities of trimethoprim and sulfonamides. Scand J Infect Dis. 1986; 18: 3–13. https://doi.org/10.3109/00365548609032299 PMID: 3515508

17. Saux MC, Le Rebelle A, Leng B, Mintosse J. [Bone diffusion of trimethoprim and sulfamethoxazole high pressure liquid chromatography (HPLC) (author’s transl)]. Pathol Biol (Paris). 1982; 30: 385–388.

18. Stein GE, Throckmorton JK, Scharmen AE, Weiss WJ, Prokai L, Smith CL, et al. Tissue penetration and antimicrobial activity of standard- and high-dose trimethoprim/sulfamethoxazole and linezolid in patients with diabetic foot infection. J Antimicrob Chemother. 2013; 68: 2852–2858. https://doi.org/10.1093/jac/dkt283 PMID: 23873647

19. Craven JL, Pugsley DJ, Blowers R. Trimethoprim-sulphamethoxazole in acute osteomyelitis due to penicillin-resistant *staphylococci* in Uganda. Br Med J. 1970; 3: 201–203. https://doi.org/10.1136/bmj.3.5716.201 PMID: 5448781

20. Stein A, Bataille JF, Drancourt M, Curvale G, Argenson JN, Groulier P, et al. Ambulatory treatment of multidrug-resistant *Staphylococcus* infected orthopedic implants with high-dose oral co-trimoxazole (trimethoprim-sulfamethoxazole). Antimicrob Agents Chemother. 1999; 42: 3086–3091. PMID: 9835495

21. Seng P, Amran S, Million M, Stein A. Old antimicrobials and Gram-positive cocci through the example of infective endocarditis and bone and joint infections. Int J Antimicrob Agents. 2017; 49: 558–564. https://doi.org/10.1016/j.ijantimicag.2017.03.004 PMID: 28365430

22. Société de Pathologie Infectieuse de Langue Française (SPILF). Recommandations de pratique clinique, infections ostéo-articulaires sur matériel (prothèse, implant, ostéosynthèse) [Internet]. 2009.
Available: http://www.infectiologie.com/UserFiles/File/medias_documents/consensus/inf-osseuse-court.pdf

23. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011; 52: e18–e55. https://doi.org/10.1093/cid/ciq146 PMID: 21208910

24. Gemmell CG, Edwards DI, Fraise AP, Gould FK, Ridgway GL, Warren RE. Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. J Antimicrob Chemother. 2006; 57: 589–608. https://doi.org/10.1093/jac/dkl017 PMID: 16507559

25. Ho JM-W, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. Can Med Assoc J. 2011; 183: 1851–1855. https://doi.org/10.1503/cmaj.111152 PMID: 21989472

26. Grammatico-Guillon L, Baron S, Gettnner S, Lecuyer A-I, Gaborit C, Rosset P, et al. Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. J Hosp Infect. 2012; 82: 40–48. https://doi.org/10.1016/j.jhin.2012.04.025 PMID: 22738613

27. Fica A, Lamas C, Olivares F, Ramírez D, Soto A, Porte L, et al. Cotrimoxazole in bone-related infections: toxicity and clinical and economic impact. Rev Chil Infectol Organ Of La Soc Chil Infectol. 2015; 32: 609–617. https://doi.org/10.4067/S0716-10182015000000017 PMID: 26928496

28. Tornero E, Morata L, Martínez-Pastor JC, Angulo S, Combalia A, Bori G, et al. Importance of selection and duration of antibiotic regimen in prosthetic joint infections treated with debridement and implant retention. J Antimicrob Chemother. 2016; 71: 1395–1401. https://doi.org/10.1093/jac/dkv481 PMID: 26929270

29. Euba G, Murillo O, Fernández-Sabé N, Mascaro J, Cabo J, Pérez A, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacin in treatment of chronic staphylococcal osteomyelitis. Antimicrob Agents Chemother. 2009; 53: 2672–2676. https://doi.org/10.1128/AAC.01504-08 PMID: 19307354

30. Nguyen S, Pasquet A, Legout L, Beltrand E, Dubreuil L, Migaud H, et al. Efficacy and tolerance of rifampicin-linezolid compared with rifampicin-cotrimoxazole combinations in prolonged oral therapy for bone and joint infections. Clin Microbiol Infect. 2009; 15: 1163–1169. https://doi.org/10.1111/j.1469-832X.2009.02692.x PMID: 19438638

31. Harbarth S, von Dach E, Pagani L, Macedo-Vinas M, Huttner B, Olearo F, et al. Randomized non-inferiority trial to compare trimethoprim-sulfamethoxazole plus rifampicin versus linezolid for the treatment of MRSA infections. J Antimicrob Chemother. 2015; 70: 264–272. https://doi.org/10.1093/jac/dku352 PMID: 26209610

32. Messina AF, Namtu K, Guild M, Dumois JA, Berman DM. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. Pediatr Infect Dis J. 2011; 30: 1019–1021. https://doi.org/10.1097/ INF.0b013e31822db658 PMID: 21817950

33. Munckhof WJ, Kleinschmidt SL, Turnidge JD. Resistance development in community-acquired strains of methicillin-resistant *Staphylococcus aureus*: an in vitro study. Int J Antimicrob Agents. 2004; 24: 605–608. https://doi.org/10.1016/j.ijantimicag.2004.08.009 PMID: 15555885

34. El Haj C, Murillo O, Ribera A, Lloberas N, Gómez-Junyent J, Tubau F, et al. Evaluation of linezolid or trimethoprim/sulfamethoxazole in combination with rifampicin as alternative oral treatments based on an in vitro pharmacodynamic model of staphylococcal biofilm. Int J Antimicrob Agents. 2018; 51: 854–861. https://doi.org/10.1016/j.ijantimicag.2018.01.014 PMID: 29374577

35. Hsieh P, Lee MS, Hsu K, Chang Y, Shih H, Ueng SW. Gram-Negative Prosthetic Joint Infections: Risk factors and outcome of treatment. Clin Infect Dis. 2009; 49: 1036–1043. https://doi.org/10.1086/605593 PMID: 19691430

36. Campbell ML, Marchaim D, Pogue JM, Sunkara B, Bheemreddy S, Bathina P, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with a minimal inhibitory concentration of 2 μg/mL to vancomycin: old (trimethoprim/sulfamethoxazole) versus new (daptomycin or linezolid) agents. Ann Pharmacother. 2012; 46: 1587–1597. https://doi.org/10.1345/aph.1R211 PMID: 23212935

37. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012; 67: 1271–1277. https://doi.org/10.1093/jac/dks030 PMID: 22351681

38. Gentry CA, Nguyen AT. An evaluation of hyperkalemia and serum creatinine elevation associated with different dosage levels of outpatient trimethoprim-sulfamethoxazole with and without concomitant medications. Ann Pharmacother. 2013; 47: 1618–1626. https://doi.org/10.1177/1060028013509973 PMID: 24259630

39. Valour F, Karsenty J, Bouaziz A, Ader F, Tod M, Lustig S, et al. Antimicrobial-related severe adverse events during treatment of bone and joint infection due to methicillin-susceptible *Staphylococcus aureus*
40. Lee C-C, Lee MG, Hsieh R, Porta L, Lee W-C, Lee S-H, et al. Oral fluoroquinolone and the risk of aortic dissection. J Am Coll Cardiol. Elsevier; 2018; 72: 1369–1378. https://doi.org/10.1016/j.jacc.2018.06.067 PMID: 30213330