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Multidrug-resistant and extensively drug-resistant Gram-negative prosthetic joint infections: Role of surgery and impact of colistin administration

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A B S T R A C T

Factors influencing treatment outcome of patients with Gram-negative bacterial (GNB) multidrug-resistant (MDR) and extensively drug-resistant (XDR) prosthetic joint infection (PJIs) were analysed. Data were collected (2000–2015) by 18 centres. Treatment success was analysed by surgery type for PJI, resistance (MDR/XDR) and antimicrobials (colistin/non-colistin) using logistic regression and survival analyses. A total of 131 patients (mean age 73.0 years, 35.9% male, 58.8% with co-morbidities) with MDR ($n = 108$) or XDR ($n = 23$) GNB PJI were assessed. The most common pathogens were *Escherichia coli* (33.6%), *Pseudomonas aeruginosa* (25.2%), *Klebsiella pneumoniae* (21.4%) and *Enterobacter cloacae* (17.6%). *Pseudomonas aeruginosa* predominated in XDR cases. Isolates were carbapenem-resistant ($n = 12$), fluoroquinolone-resistant ($n = 63$) and ESBL-producers ($n = 94$). Treatment outcome was worse in XDR versus MDR cases ($P = 0.018$). Success rates did not differ for colistin versus non-colistin in XDR cases ($P = 0.657$), but colistin was less successful in MDR cases ($P = 0.018$). Debridement, antibiotics and implant retention (DAIR) ($n = 67$) was associated with higher failure rates versus non-DAIR ($n = 64$) (OR = 3.57, 95% CI 1.68–7.58; $P < 0.001$). Superiority of non-DAIR was confirmed by Kaplan–Meir analysis (HR = 0.36, 95% CI 0.20–0.67) and remained unchangeable by time of infection (early/late), antimicrobial resistance (MDR/XDR) and antimicrobials (colistin/non-colistin) (Breslow–Day, $P = 0.737$). DAIR is associated with higher failure rates even in early MDR/XDR GNB PJIs versus implant removal. Colistin should be preserved for XDR cases as it is detrimental in MDR infections.

1. Introduction

An increasing number of prosthetic joints (arthroplasties) are being performed globally, almost doubling within the last decade [1]. Prosthetic joint infection (PJI) is one of the most devastating complications, with rates ranging between 1–2%, and is associated with substantial patient morbidity and treatment costs [2–4]. Treatment of PJIs is highly challenging as more than one surgical intervention as well as long-term antibiotic treatment are often required [4,5]. Although Gram-positive bacteria (mostly staphylococci) account for 60–80% of the causative agents, Gram-negative bacteria (GNB) are also detected in the context of monomicrobial or polymicrobial infections [6,7]. Recently, an increase in PJIs due to GNB (23–44%) has been reported [8–11]. Moreover, emerging antimicrobial resistance further reduces the therapeutic options for these difficult-to-treat infections [12,13]. Little is known about the epidemiology, clinical presentation, therapeutic strategies and outcomes of patients diagnosed with multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB PJIs. Few cases of PJI by MDR strains are reported even in large epidemiological studies or case series [6,14–17].

To investigate the factors associated with treatment outcome in PJI caused by MDR/XDR GNB, a multicentre epidemiological study on a large cohort of patients was conducted.

2. Materials and methods

2.1. Study design

A retrospective analysis of prospectively collected data for 281 patients with osteoarticular infections caused by MDR/XDR GNB originating from 18 centres across 10 countries from 2000–2015 was performed. The study was endorsed by the ESCMID Study Group for Implant-Associated Infections (ESGIAI) (http://www.escmid.org/research_projects/study_groups/implant_infections/) and was approved upon Ethics Consideration and Committees of each participating centre.

The current study analysis included 131 patients with PJI who had undergone surgery along with antimicrobial treatment and who were subsequently followed for a period of 24 months. The primary endpoint was the outcome (success versus failure) of treatment according to type of surgery, defined as debridement, antibiotics and implant retention (DAIR) versus non-DAIR (any other procedure with implant removal). Secondary endpoints were the impact of the type of resistance (MDR versus XDR) and antimicrobial treatment (regimen with/without colistin) on the 24-month designated outcome period.

2.2. Data collection and definitions

This retrospective analysis of prospectively collected data referred to all patients aged >18 years with a definite diagnosis of MDR or XDR GNB PJI from 2000–2015 in all collaborative centres. The following data were recorded: demographics; co-morbidities (i.e. diabetes mellitus, malignancy, rheumatoid arthritis, chronic renal failure); history of trauma or orthopaedic surgery; history of previous PJI and administration of antimicrobials; type, location, presenting clinical signs and microbiological documentation of MDR/XDR GNB PJI; time frame from arthroplasty implantation to infection onset; type of surgical intervention; antimicrobial treatment (regimen, duration); and patients' final outcome. Each case was reviewed by two authors (AP and EG). All queries were checked and answered by the investigators in all collaborating centres.

PJI was defined according to the Infectious Diseases Society of America (IDSA) guidelines as the presence of: (i) a sinus tract communicating with the prosthesis; (ii) purulence surrounding the prosthesis; (iii) acute inflammation of periprosthetic tissue on histopathological examination; and (iv) at least two intraoperative cultures or the combination of intraoperative cultures and preoperative aspiration cultures yielding the same micro-organism(s) [12]. Early PJI was defined as arthroplasty infections occurring within the first 4 weeks post-implantation, whilst late PJI was defined as arthroplasty infections occurring beyond this time interval [9].

GNB were identified by routine automated conventional biochemical and metabolic tests or by matrix-assisted laser desorption/ionisation–time-of-flight (MALDI-TOF). Antimicrobial susceptibility was assessed in each participating centre according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations (http://www.eucast.org/clinical_breakpoints/).

MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories (aminoglycosides, or antipseudomonal cephalosporins, or carbapenems, or fluoroquinolones, or penicillins plus β-lactamase inhibitors, or monobactams, or phosphonic acids, or polymyxins). XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) [18].

Treatment was evaluated by taking into account: (i) surgical treatment, which comprised DAIR and non-DAIR (removal of the infected implant, with or without re-implantation as one or two-stage revision); and (ii) type and duration of antimicrobial treatment, including the use of carbapenems, fluoroquinolones and colistin. Administration of antibiotics and type of surgical intervention relied upon each physician's decision based on current treatment guidelines for PJI and susceptibility testing results of the causative pathogen(s).

Outcome was considered successful if no clinical or microbiological signs of infection were assessed following surgical and antimicrobial therapy within the observation time frame of 24 months. Any other condition was considered as treatment failure.

2.3. Statistical analysis

The primary dependent variable was outcome (success versus failure) of curative surgery within the designated 24-month period. The primary independent variable was the type of surgery performed, grouped as DAIR and non-DAIR. The time to failure was also recorded. Fisher's exact test together with the odds ratio (OR) and 95% confidence interval (CI) were applied. Taking into consideration the time to failure, Kaplan–Meier survival analysis was performed reporting the log-rank (Mantel–Cox) statistic and the related hazard ratio (HR) with 95% CI. Probable confounding factors were also tested with the Fisher's exact test and the independent samples *t*-test. The variable reporting the time elapsed from arthroplasty to infection onset was recorded as 'Early' if $\leq$4 weeks and 'Late' if $>$4 weeks. Univariate statistics were replaced by multivariate stepwise logistic regression and Cox regression analysis. The homogeneity of the ORs of nested effects was tested with the Breslow–Day statistic. The level of significance was set at 0.05.

3. Results

Demographic and clinical characteristics of the study population ($n = 131$) by type of surgery (DAIR versus non-DAIR) are presented in Table 1. Patients were elderly (mean age 73.0 years) and female patients predominated ($n = 84$; 64.1%). Diabetes mellitus accounted for more than one-half of all described co-morbidities (42/77; 54.5%). Approximately one-third of patients (30.8%) had a history of trauma, whilst 43.8% had already undergone at least one surgical intervention for PJI along with antimicrobial treatment.

The most prominent clinical features of the 131 PJIs caused by MDR/XDR GNB were fever (n =42), local pain ($n = 67$), soft tissue infection ($n = 87$) and sinus tract ($n = 39$), whilst ulcers were rare ($n = 3$). Infection was located at the hip ($n = 86$; 65.6%), knee ($n = 41$; 31.3%), shoulder ($n = 3$; 2.3%) and ankle ($n = 1$; 0.8%). Early PJIs accounted for 61.9% of cases ($n = 73$).

GNB strains (MDR/XDR) were distributed as follows: *Escherichia coli* ($n = 43/1$), *Pseudomonas aeruginosa* ($n = 18/15$), *Klebsiella pneumoniae* ($n = 24/4$), *Enterobacter cloacae* ($n = 22/1$), *Acinetobacter baumannii* ($n = 3/3$), *Proteus mirabilis* ($n = 2/2$), *Morganella morganii* ($n = 4/0$) and *Proteus* stuartii ($n = 2/0$). In 13 cases a second MDR/XDR GNB isolate was detected (polymicrobial infection).

Study pathogens were identified as extended-spectrum β-lactamase (ESBL)-producers ($n = 94$), fluoroquinolone-resistant ($n = 63$) and carbapenem-resistant ($n = 12$), whilst acquired resistance to colistin was reported only in one *K. pneumoniae* strain.

Age, co-morbidities, history of trauma and prior surgery for infection did not significantly affect the outcome of treatment (Supplementary Table S1). Moreover, outcome did not differ between hip and knee infections (success rate 58.1% vs. 61.0%; $P = 0.8$).

The mean $\pm$ standard deviation overall duration of antimicrobial therapy was 74.3 $\pm$ 67.6 days, whilst the mean duration of intravenous administration was 51.7 $\pm$ 37.3 days. The length of treatment as well as the number of administered antibiotics (monotherapy versus combined therapy) did not affect treatment outcomes (Supplementary Table S1).

Surgical treatment was assessed as DAIR ($n = 67$) versus non-DAIR procedures ($n = 64$), with the latter including implant explantation without re-implantation of device ($n = 39$), two-stage revision ($n = 16$) and one-stage revision ($n = 9$). Patients who underwent DAIR surgery demonstrated higher failure rates compared with non-DAIR implant removal procedures [35/67 (52.2%) vs. 15/64 (23.4%); OR = 3.57, 95% CI 1.68–7.58; $P < 0.001$] (Fig. 1A). If the results are nested by early and late PJI, the OR of success/failure in non-DAIR versus DAIR procedures did not differ between early and late interventions ($P = 0.268$). Specifically, both in early and late PJI the non-DAIR procedure achieved the highest success rates (88.5% and 75.0%, respectively), whilst the DAIR procedure achieves the lowest rates (44.7% and 47.1%, respectively) (Fig. 1B). The superiority of non-DAIR procedures is better illustrated in Fig. 2. The log-rank value indicates a statistically significant difference between the two surgery types, with non-DAIR procedures evidently being superior. The calculated HR was equal to 0.36 (95% CI 0.20–0.67).

Overall, treatment was more successful in MDR (72/108; 66.7%) than XDR (9/23; 39.1%) cases ($P = 0.018$) (Supplementary Table S1). However, the type of resistance did not significantly influence the impact of surgery on outcome. As shown in Fig. 3, non-DAIR procedures were significantly more successful in 79.6% of MDR and 60% of XDR cases. In contrast, DAIR demonstrated a respectively lower success rate in MDR (53.7%) and XDR (23.1%) infections. Therefore, success rates were higher in patients who underwent non-DAIR surgery, irrespective of the type of resistance. The homogeneity of the OR of success/failure in non-DAIR versus DAIR procedures was preserved (Breslow–Day, $P = 0.698$) amongst MDR and XDR infections.

A variety of antimicrobial regimens was administered by the attending physicians to the patients with MDR/XDR GNB PJIs. The diversity of antibiotics in terms of combinations and length of administration as well as the sample size did not allow further stratification analysis. Therefore, the impact of individual classes of antibiotics on outcome was examined. Treatment by fluoroquinolones or carbapenems did not significantly influence the outcome of infection (data not shown). A colistin regimen was administered mostly in patients with XDR PJI (69.5%) compared with MDR PJI (11.1%) at a daily dose that ranged from 2×10^6 IU to 9×10^6 IU adjusted to renal function. As shown in Fig. 4, patients with MDR infections who received colistin presented significant lower success rates compared with patients treated by any other agent [4/12 (33.3%) vs. 67/94 (71.3%); $P = 0.018$). Colistin administration did not significantly influence the success rates in patients with XDR isolates (7/16 vs. 2/7; $P = 0.657$) (Fig. 4).

After adjustment for type of infection (MDR or XDR GNP PJI) and colistin administration, non-DAIR procedures demonstrated an independent favourable impact on successful outcome (OR = 0.23, 95% CI 0.10–0.53; $P = 0.001$). The superiority of non-DAIR surgical procedures remained unchangeable by time of infection onset (early/late), type of resistance (MDR/XDR) and antimicrobial treatment (colistin versus non-colistin) (Breslow–Day, $P = 0.737$). The stepwise analysis is presented in Supplementary Table S2.

4. Discussion

To our knowledge, this is the largest cohort study on MDR GNB PJIs. Data on MDR, and especially XDR, PJIs are scarce. Only three cases of PJI by carbapenemase-producing *Klebsiella* spp. were

Table 1
Descriptive characteristics of patients with prosthetic joint infection caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria, and comparisons between patients undergoing DAIR versus non-DAIR surgery[a]

Characteristic	DAIR ($n = 67$; 51.1%)	Non-DAIR ($n = 64$; (48.9%)	Total ($n = 131$)	P-value
Age (years) (mean ± S.D.)	74.6 ± 11.4	71.4 ± 13.9	73.0 ± 12.7	0.149
Sex				0.281
Male	21 (31.3)	26 (40.6)	47 (35.9)	
Female	46 (68.7)	38 (59.4)	84 (64.1)	
Co-morbidities				0.723
No	29 (43.3)	25 (39.1)	54 (41.2)	
Yes	38 (56.7)	39 (60.9)	77 (58.8)	
Diabetes mellitus				0.261
No	49 (73.1)	40 (62.5)	89 (67.9)	
Yes	18 (26.9)	24 (37.5)	42 (32.1)	
Rheumatoid arthritis				0.399
No	58 (86.6)	59 (92.2)	117 (89.3)	
Yes	9 (13.4)	5 (7.8)	14 (10.7)	
Malignancy				0.525
No	63 (94.0)	58 (90.6)	121 (92.4)	
Yes	4 (6.0)	6 (9.4)	10 (7.6)	
Chronic renal failure				0.586
No	58 (86.6)	58 (90.6)	116 (88.5)	
Yes	9 (13.4)	6 (9.4)	15 (11.5)	
History of trauma				0.173
No	50 (74.6)	35 (62.5)	85 (69.1)	
Yes	17 (25.4)	21 (37.5)	38 (30.9)	
Prior surgery for infection				0.467
No	35 (53.0)	33 (60.0)	68 (56.2)	
Yes	31 (47.0)	22 (40.0)	53 (43.8)	
Prior antimicrobials				0.588
No	32 (47.8)	30 (53.6)	62 (50.4)	
Yes	35 (52.2)	26 (46.4)	61 (49.6)	
Gram-negative bacterial resistance				0.649
MDR	54 (80.6)	54 (84.4)	108 (82.4)	
XDR	13 (19.4)	10 (15.6)	23 (17.6)	
Administration of colistin				1.000
No	52 (77.6)	49 (79.0)	101 (78.3)	
Yes	15 (22.4)	13 (21.0)	28 (21.7)	
Type of antimicrobial therapy				0.131
Monotherapy	17 (25.4)	24 (38.7)	41 (31.8)	
Combination therapy	50 (74.6)	38 (61.3)	88 (68.2)	
Duration of intravenous antibiotics (days) (mean ± S.D.)	55.6 ± 34.7	46.2 ± 40.4	51.7 ± 37.3	0.215
Total duration of antibiotics (days) (mean ± S.D.)	77.7 ± 63.4	70.1 ± 72.9	74.3 ± 67.6	0.545
Time from arthroplasty to infection onset				0.007*
Early (≤4 weeks)	47 (73.4)	26 (48.1)	73 (61.9)	
Late (>4 weeks)	17 (26.6)	28 (51.9)	45 (38.1)	
Outcome				0.001*
Success	32 (47.8)	49 (76.6)	81 (61.8)	
Failure	35 (52.2)	15 (23.4)	50 (38.2)	

DAIR, debridement, antibiotics and implant retention; S.D., standard deviation.
[a] Data are n (%) unless otherwise stated.
* Statistically significant ($P < 0.05$).

reported in a USA nationwide epidemiological study of nosocomial infections [19]. Only a few case reports and case series highlight the difficulty in diagnosis and treatment of these infections. PJIs by MDR GNB have included ESBL-producing Enterobacteriaceae, ESBL- or AmpC β-lactamase-producing *E. cloacae*, fluoroquinolone-resistant and MDR *P. aeruginosa*, and occasionally *Salmonella* spp., *Serratia marcescens, A. baumannii* and *Stenotrophomonas maltophilia* [3,13,20–26]. Amongst these studies, only 11 cases of carbapenem-resistant GNB (8 *P. aeruginosa* and 3 *K. pneumoniae*) were reported, whereas only a few strains could be considered as XDR [19,20,27,28].

The data reported here have a major strength: they strongly suggest that type of surgery is independently associated with outcome in patients with PJI by MDR/XDR GNB. DAIR had failed even in early infections. However, we must take into account that curative surgery is often scheduled before awareness of MDR/XDR GNB infections, as most cultures are taken intra-operatively. DAIR is a recommended procedure for surgical treatment of PJI under certain conditions. According to current data and guidelines, the prosthesis can be retained with debridement and exchange of modular components if the infection occurs within the first 4 weeks, the prosthesis is stable and the pathogen is susceptible to antibiotics [1,12]. The success of DAIR fluctuates from <50% to >80% as reported in different cohort studies [29]. In one series, application of DAIR in early PJI was associated with comparable cure rates both for *Staphylococcus aureus* infections and infections caused by other pathogens, including many fermentative GNB and *P. aeruginosa* (58% and 57%, respectively) [30]. However, treatment of PJI caused by methicillin-resistant *S. aureus* (MRSA) failed in 72% of cases, suggesting that resistance rather than microbial species is related to treatment failure, a finding compatible with other reports [29,31]. In another series, implant retention was not associated with failure in *S. aureus* hip and knee PJIs [32]. These results cannot be extrapolated in GNB PJIs. Hsieh et al. have reported a 27% 2-year survival free of treatment failure for DAIR compared with 87% for two-stage exchange and 69% for resection arthroplasty in patients with GNB PJIs [7]. Similar results were reported in a series of 102 PJIs caused by essentially non-resistant strains of *P. aeruginosa*. In that series, DAIR was associated with a 2-year cumulative survival free from failure of 21% compared with 83%

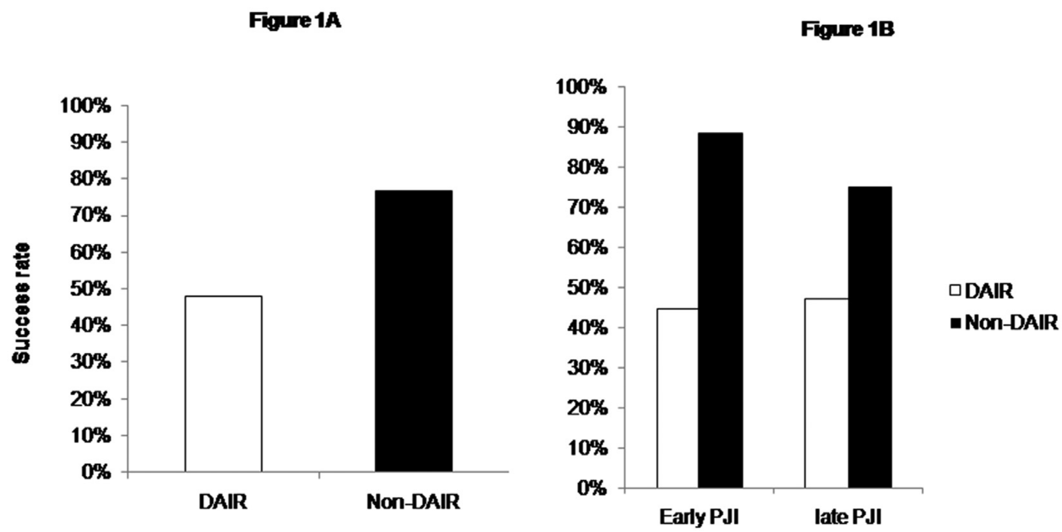

Fig. 1. Proportion of success depending on (A) type of surgery (DAIR versus non-DAIR) and (B) nested within early and late prosthetic joint infection (PJI). DAIR, debridement, antibiotics and implant retention.

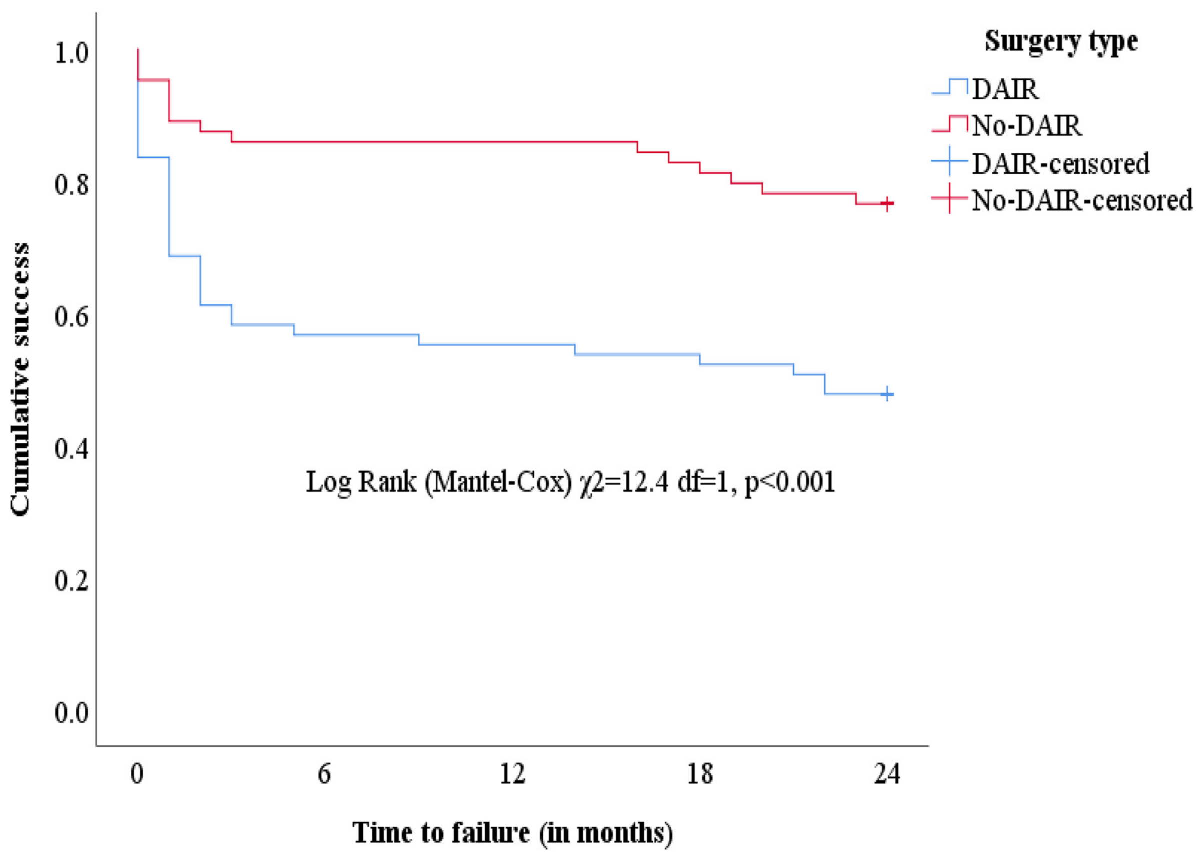

Fig. 2. Cumulative success of DAIR versus non-DAIR surgical treatment of prosthetic joint infections. DAIR, debridement, antibiotics and implant retention.

for two-stage exchange and 80% for resection arthroplasty. All patients who underwent DAIR failed within 3 years [20]. In a few reports of PJI and other device-related infections caused by ESBL-producing GNB, DAIR was associated with failure in 47–57% and hardware removal was often necessary [16,21,22]. However, the results from these studies are not comparable owing to the diversity of pathogens and treatment strategies. Bacterial strains may have a severe impact on infection outcome. It has been postulated that patients with PJIs caused by carbapenemase-producing *K. pneumoniae* have limited antibiotic options and demand multiple surgeries, suffering frequent infection relapses, significant disabilities or even death [19]. Moreover, *P. aeruginosa* is a virulent pathogen with an adverse impact on outcome, therefore combination antimicrobial treatment is highly recommended [33]. It is probable that the combination of extensive microbial resistance and the presence of device-associated biofilms is deleterious and, in conjunction with limited antibiotic choices, leads to poor treatment outcomes [15]. The current data suggest that in MDR/XDR GNB infections, an early aggressive surgical approach with prosthesis removal in combination with all available options of antimicrobial

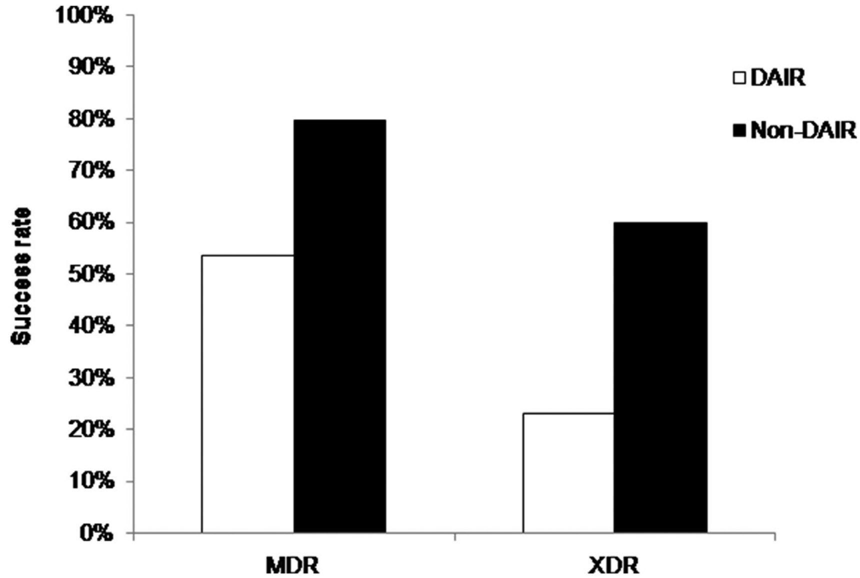

Fig. 3. Proportion of success depending on type of surgery nested within prosthetic joint infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria. DAIR, debridement, antibiotics and implant retention.

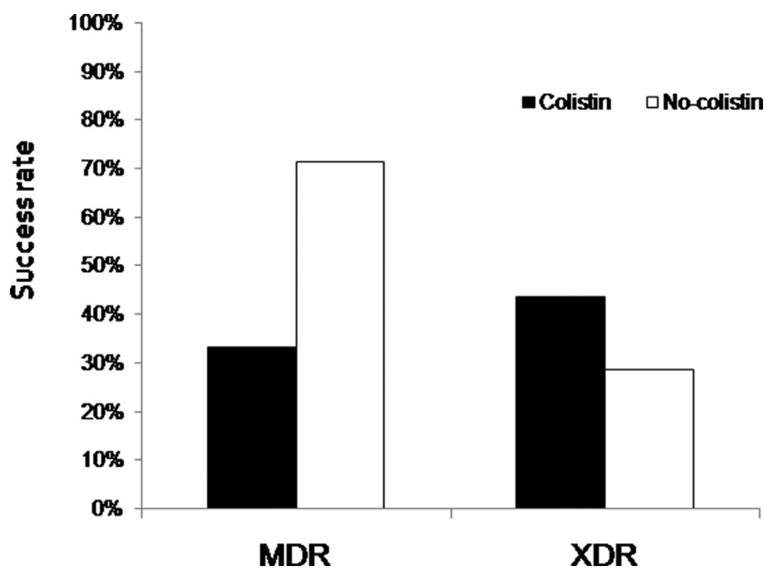

Fig. 4. Proportion of success depending on colistin administration nested within prosthetic joint infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram negative bacteria.

treatment is the preferable treatment option. However, we cannot neglect that in >40% of cases overall, DAIR was successful. These results further indicate the need for individualisation of therapy. In the cohort described in this study, antibiotics were administered for a mean of 74.3 days, however the optimal duration of treatment in PJI caused by MDR/XDR GNB is still unknown.

Previous experience with GNB PJIs underscored the use of fluoroquinolones as a predictor of successful outcome [6,10]. However, this effect was not observed in this study as <50% of the pathogens were susceptible to fluoroquinolones. The fact that in this study *P. aeruginosa* predominated in XDR infections may explain the unsuccessful outcome of XDR PJIs, as treatment options stagnated, limited to a colistin-based regimen. Few published data on colistin use exist from case reports on colistin administration combined with β-lactams or on colistin-impregnated bone cement [24,27,34]. Colistin has been tested in *in vitro* and *in vivo* experimental models in combination with rifampicin or fosfomycin, but clinical data are lacking [35,36]. The current cohort study provides important clinical data on colistin use for MDR/XDR PJIs. Administration of colistin in MDR cases significantly increases the odds of failure. These odds are somewhat reduced in XDR patients treated with colistin, suggesting that colistin administration in these cases may be beneficial. It is possible that the small number of cases may have failed to demonstrate a clear benefit of colistin-based treatment in XDR GNB PJI. However, the very low rate of success of DAIR in XDR GNB (23%) was not influenced by the use of colistin. This indicates that surgery type remains the most significant predictor of outcome and its effect is independent of resistance and/or type of antimicrobial treatment.

The study has some limitations. As a multicentre cohort, we cannot ensure a homogeneous surgical approach and similar strategy on antimicrobial treatment. Moreover, comparison between one- and two-stage revision is not feasible owing to the small number of patients. However, data are provided from referral academic centres with long-standing experience in the management of orthopaedic infections. Therefore, we can strongly suggest that high therapeutic standards are followed and the quality of data corroborates our results. Another limitation is that data on molecular mechanisms of resistance are not available and grouping of diverse antimicrobial regimens into comparable categories could not be performed owing to the retrospective nature of the analysis. However, data provided by this large cohort clearly suggest surgical and antimicrobial treatment options for MDR/XDR GNB PJIs.

5. Conclusions

Analysis of this large cohort of PJIs caused by MDR/XDR GNB clearly demonstrated that DAIR has a greater probability of failure compared with implant removal (non-DAIR) not only in late but also in early PJI by MDR/XDR GNB. This finding was independent from any other confounding factor, such as the level of GNB resistance and the antimicrobial treatment options. However, we cannot rule out DAIR options that might be successful in some cases. Moreover, the use of colistin should be preserved only for XDR infections as it was related to failure in MDR cases. The presence of XDR infections or the administration of colistin bear a detrimental effect on surgical outcome, a fact that underlines the difficulty in treatment and the adverse, even poor, outcomes of those infections for which there are limited treatment options in the therapeutic armamentarium.

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Competing interests

None declared.

Ethical approval

Approval by the Hospital Ethical Committee of 'ATTIKON' University General Hospital (Athens, Greece) was given for the epidemiological study of all bone and joint infections [ΔΠΠΚ 91/03-03-10].

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.018.

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