Multidrug resistant bacteria: An independent prognostic variable for failure in lower limb joint arthroplasty?

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1. Introduction

Arthroplasty procedures, particularly of the hip and knee, have demonstrated high levels of patient satisfaction and have been proven to be cost effective in relieving the disability of severe arthritis.¹ Despite improvements in peri operative care, periprosthetic joint infection (PJI) remains a serious although thankfully rare complication.² The significance of PJI has ramifications for the patient, with a significant reduction in patient reported outcomes³ and the need for revision of the prosthesis with a concurrent reduction in function. For society as a whole, PJI has a significant impact on health care provision. The evolution of bacteria in response to the widespread use of antibiotics has resulted in an increase in PJI secondary to multidrug resistant organisms.⁴ This has had significant socio-economic and health impacts. An evaluation by the World Health Organisation (WHO) suggests the economic impact of resistant bacteria equates up to 1.6% of gross domestic product.⁵

A recent international consensus⁶ defined the presence of resistance to at least one agent in three different families of antibiotics as constituting a multi-drug resistant (MDR) microbe. This international consensus also classified resistant microbes as extensively drug resistant (XDR), defined as microbes showing sensitivity to two or less agents, and pan-drug resistant microbes (PDR) resistant to all categories of

antibiotics.⁶

To date, there has been relatively little reported on the impact of PJI secondary to MDR microbes.^{7,8} What limited evidence that exists highlights the need for prolonged antimicrobial treatment and aggressive, often multiple revision procedures if eradication of infection is to be achieved. The aim, therefore, of this study was to compare the outcomes, defined by eradication of infection, following treatment for a PJI due to a MDR bacterium with those of a PJI secondary to a non-MDR (NMDR) organism. Where variation existed between these outcomes, we aimed to identify the presence of an MDR organism as an independent predictor for failure to eradicate the infection.

2. Method

The study comprised a retrospective analysis of a prospectively maintained database in a single institution, which collects all details relating to patients diagnosed and treated for a PJI in a tertiary referral orthopaedic centre. All adult patients diagnosed and treated for a PJI of either hip or knee arthroplasty between January 2011 and December 2014 with a minimum 1 year follow up having completed treatment, were included in the study. All patients were managed through a specialist bone and joint infection multidisciplinary team.

All patients were diagnosed with a PJI according to the criteria of

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Table 1
Demographic data for patients identified as eligible.

	Number	Male	Female	Site of infection	
				Hip	Knee
Total BIU population	240 (100%)	137 (57%)	103 (43%)	123 (51%)	117 (49%)
MDR group	74	39 (53%)	35 (47%)	33 (45%)	41 (55%)
N-MDR group	166	98 (59%)	68 (41%)	90 (54%)	76 (46%)

the Musculoskeletal Infection Society.⁹ Patients underwent one of three possible surgical strategies, defined by the International Consensus Meeting on Periprosthetic Joint Infection.¹⁰ Patients underwent either a staged revision comprising implant removal, debridement and insertion of an antibiotic loaded cement spacer, with additional antibiotics based on the preoperative culture, where known, or empirically, where the organism was not known, or a single stage revision consisting of removal of existing metalwork, debridement and re-implantation. The decision to undergo either single-stage or two-stage revision was governed by patient criteria, microbiology criteria, the soft tissue condition and the degree of bone loss. Patients presenting with acute symptoms of a PJI with symptom duration less than 4 weeks, without a sinus or evidence of implant loosening or bone loss, underwent debridement and implant retention (DAIR), as described by Byren et al.¹¹

All patients were treated with broad spectrum IV antibiotics until definitive microbiology culture of specimens taken at the time of surgery were known. At this stage, patients were converted to an antimicrobial regimen based on the infecting organism and its sensitivity. Where inflammatory markers did not normalise, or persistent discharge continued from the wound following the first stage, this procedure was repeated revising the antibiotic cement spacer. The time to re-implantation for two-stage revisions was governed by the clinical and biochemical response and was considered when inflammatory markers had normalised. Following reimplantation, antibiotics were continued until microbiology cultures of specimens taken at the time of the second stage confirmed no growth. For those where organisms were identified at the time of reimplantation, antibiotics were continued for a minimum period of 3 months but were only discontinued once inflammatory markers had normalised. In the case of one-stage revisions and those treated by DAIR, antibiotics were discontinued once inflammatory markers had normalised after a minimum period of 3 months.

2.1. Outcomes

Patient demographics, comprising age, gender and comorbidities were recorded. The site of infection, the number of surgical procedures and the previous surgical interventions were also recorded. All details relating to the infecting organism, including its resistance and sensitivities were also recorded. Patients were divided into two groups according to the resistance profile of the infecting organism:

- MDR group (defined by resistance to more than 2 classes of antibiotics¹²)
- N-MDR group

Recurrence of infection was defined by deterioration of symptoms, rising inflammatory markers and the presence of intra-articular microbes on aspiration. Failure to control the infection leading to implant removal and subsequent excision arthroplasty, arthrodesis or amputation was defined end points.

2.2. Statistical analysis

Simple summary statistics were collated using SPSS v 18.0 software (IBM Corp., Armonk, New York). Categorical data was compared using

Fishers Exact test, with an alpha value of 0.05 considered statistically significant. Continuous data was compared using a student's T-Test with an alpha value of 0.05 to be considered statistically significant.

3. Results

The study population comprised 240 patients who fulfilled the inclusion criteria. 74 (31%) patients were included in the MDR group and were compared to 166 (69%) in the N-MDR group. There was no significant difference in site of infection i. e hip or knee ($p = 0.208$) and gender ($p = 0.398$) between the MDR and N-MDR groups (Table 1).

3.1. Demographics

The median age for the study population was 70 years (range 19–92 years). The N-MDR group median age was 69 years (range 19–90 years). In comparison, the MDR-group median age was 72 years (range 39–92 years). The demographic features between groups were comparable (see Table 1).

3.2. Microbiology

77 of 240 (32%) patients underwent a pre-operative aspirate of which, 59 (77%) yielded a positive bacterial culture. Within the MDR group, 26 patients (35%) underwent a pre-operative aspirate of which 2 (8%) cultured the same MDR organism from deep tissue samples. This compares to the N-MDR group whereby 51 patients (31%) underwent a pre-operative aspirate. However the mean number of samples positive for bacteria was 2.5. This is divided into 2.5 for the N-MDR group and 2.64 for the MDR group showing no significant difference in the detection rate ($p = 0.634$).

94 patients (39%) were classed as polymicrobial (isolation of greater than one organism), leaving 146 patients (61%) were single organism isolates.

When stratifying this, in the MDR group there were 48 (65% of total MDR) polymicrobial isolates and 26 (35%) single organism isolates. The N-MDR group had 46 (32% of total NMDR) polymicrobial patients versus 120 (68%) single organism isolates. This is significantly different at $P < 0.0001$.

3.3. Primary outcomes

• MDR vs N-MDR failure

The total number of patients treated that resulted in a failure was 39 (16%). In terms of the number of failures by site of infection, 15 (12%) hip cases were classed as a fail and 24 (21%) knee cases.

The number of failures in the MDR group was 24 out of 74 (32%), which was significantly higher than that of the N-MDR group with 15 failures out of 166 (9%) ($p < 0.0001$).

The mean time to failure for the MDR group was 11.7 months and 8.9 months for the N-MDR group. This was not statistically significant ($p = 0.524$).

The mean number of surgical procedures for patients in both the N-MDR and MDR group was significantly higher in the cases that ultimately led to failure to salvage the joint. When comparing the mean

Table 2
Mean numbers of procedures stratified by group and by success/failure.

	Mean number of procedures (MDR group)	Mean number of procedures (N-MDR group)	P-value
Successful salvage	2.9	2.3	0.057
Failed to salvage	6.7	4.0	0.034
P-Value	< 0.0001	0.002	

number of procedures in the groups that failed the MDR group was significantly higher ($p = 0.034$) than the N-MDR group-see Table 2.

- Demographic relationship with failure

In the N-MDR group, an age greater than or equal to 65 years was a significant factor for failure ($p < 0.0001$), however this was not the same for the MDR group ($p = 0.293$).

Gender showed no difference in outcome for the N-MDR group ($p = 1.000$) or the MDR group ($p = 0.7732$).

The Charlson Comorbidity Index¹³ was used to stratify patients into low, medium and high risk based on their co-morbidities at time of treatment for infection.

Within the N-MDR group there was no significant difference in outcomes between the low and medium groups i. e 0 vs 1–5 score ($p = 0.352$), the low and high risk groups i. e 0 vs > 5 score ($p = 1.000$) and the high and medium risk groups i.e. 1–5 vs > 5 score ($p = 1.000$).

Furthermore, there was also no statistically significant association discerned within the MDR group based on co-morbidity also. (p values = 0.1702, 0.665 and 0.1096 respectively). Refer to Table 3.

- Treatment relationship with failure

The highest frequency intervention was the staged revision at 130 (54% of all treatments) followed by DAIR (Debridement And Implant Retention) at 55 (23%) and single stage revision at 46 (19%). Nine (4%) patients, on referral to our unit, progressed directly to excision arthroplasty/amputation/arthrodesis (i.e failure outcome) either because the patient expressed a wish to do so, or because the MDT deemed the patient's infection/condition would not permit implantation of another joint arthroplasty.

There was a greater rate of failure of all treatments in the MDR group versus the N-MDR group. This was significant in the staged revision group ($P = 0.001$) and not the DAIR ($P = 0.1997$) or single stage group ($P = 0.137$), where larger numbers would be needed for more robust statistical analysis. See Table 4.

- Acute vs chronic infection (via treatment group)

The total number of patients undergoing treatment for an acute infection (i.e. those suitable for DAIR) was 55 (23%). The number of patients that underwent staged revision for chronic infection was 176 (73%). When comparing DAIR with staged revision there was an increase in the rate of failure for chronic patients (15% chronic vs 5% acute), however this difference was not found to be statistically significant ($p = 0.0664$).

Table 3
Association between demographic details and failure.

	Total Fail	Age		Sex		Charlson Co-morbidity index		
		< 65 years	> = 65 years	Male	Female	0 m (low)	1-5 (medium)	> 5 (high)
Total BIU population	39	12 (31%)	27 (69%)	18 (46%)	21 (54%)	25 (64%)	12 (31%)	2 (5%)
MDR group	24	10 (42%)	14 (58%)	11 (46%)	13 (54%)	13 (54%)	10 (42%)	1 (4%)
N-MDR group	15	2 (13%)	13 (87%)	7 (47%)	8 (53%)	12 (80%)	2 (13%)	1 (7%)

Table 4
Comparing treatment type with failure rate.

	Treatment Type					
	Staged		Single Stage		DAIR	
	Success	Fail	Success	Fail	Success	Fail
Total BIU	106 (82%)	24 (18%)	43 (93%)	3 (7%)	52 (95%)	3 (5%)
MDR	27 (61%)	17 (39%)	9 (82%)	2 (18%)	14 (88%)	2 (12%)
N-MDR	79 (92%)	7 (8%)	34 (97%)	1 (3%)	38 (97%)	1 (3%)

Failure rates are higher in all MDR infections versus N-MDR infections regardless of whether they were acute or chronic. This was shown to be statistically significant in those with chronic infection (i.e. comparing chronic MDR fails versus chronic N-MDR fails ($p < 0.0001$)). More data case numbers are needed for further analysis in the acute setting. See Table 5.

- Microbiological outcomes

- Polymicrobial relationship with failure

When comparing all cases, there was a significantly higher rate of failure in polymicrobial patients versus single organism patients ($P < 0.0001$).

When stratifying by the presence of an MDR organism versus an N-MDR organism, both polymicrobial sub groups showed a greater rate of failure than their single organism counterparts, however this was only significant in the MDR group and not the N-MDR group ($p = 0.0007$ vs $p = 0.123$).

Furthermore the polymicrobial MDR group showed a statistically significant higher rate of failure versus the polymicrobial N-MDR group ($p = 0.002$).

The mean number of organisms isolated from polymicrobial MDR patients was 2.67 and the mean number for polymicrobial N-MDR patients was 2.55. This was not statistically significant ($p = 0.6667$). Please refer to Table 6.

- Relationship to organism type

The most frequent type of organism encountered in the MDR group was Coagulase negative staphylococcus (CoNS) with 62 of 74 cases (84%). There were several other species that made up the remaining 12 cases (16%). These included six cases of Vancomycin Resistant Enterococcus (8% of MDR population) and three cases of Klebsiella ESBL (Extended spectrum Beta Lactamases) (4%), and one case each (1%) of corynebacterium, pseudomonas and E. Coli respectively.

Thus a significant comparison could only be made of patients with

Table 5
Comparing failure rate by chronicity (from treatment type).

	Acute infections (DAIR)		Chronic Infections (Stage)		P-value
	Success	Fail	Success	Fail	
Total BIU	52 (95%)	3 (5%)	149 (85%)	27 (15%)	0.0664
MDR	14 (88%)	2 (12%)	36 (65%)	19 (35%)	
N-MDR	38 (97%)	1 (3%)	113 (93%)	8 (7%)	
P-value	0.1997	< 0.0001			

Table 6
Association of multiple and mono organism with failure.

	Poly microbial		Mono microbial		P-Value
	Success	Fail	Success	Fail	
Total BIU	65 (69%)	29 (31%)	136 (93%)	10 (7%)	< 0.0001
MDR	26 (54%)	22 (46%)	24 (92%)	2 (8%)	0.0007
N-MDR	39 (85%)	7 (15%)	112 (93%)	8 (7%)	0.123

staphylococcus aureus MDR infection against those with a N-MDR staphylococcus aureus infection. There was 17 (27.4%) failures in the MDR staphylococcus aureus infections versus 5 failures (6.5%) in the N-MDR equivalent which is statistically significant ($p = 0.0007$).

When comparing the staphylococcal group of MDR organisms against the non-staphylococcal MDR group there was a significantly higher rate of failure in the non-staphylococcal MDR organisms ($p = 0.048$) but this was not significant when polymicrobial cases were excluded ($p = 0.740$). This relationship was not demonstrated in the N-MDR group. See [Table 7](#).

- Relationship to sensitivity (MDR group)

The mean number of classes of antibiotics tested per MDR group organism available to the treating clinician was 6 classes.

Using the International consensus¹⁰ definition (i.e. if a strain has up to 2 sensitive classes they are classed as extensively drug resistant bacteria), there was a significantly greater rate of failure in patients most closely associated with extensively drug resistant strains ($p = 0.0152$)- see [Table 8](#).

4. Conclusion

Our study has shown that Multi Drug Resistant Bacteria infection in lower limb arthroplasty results in a significantly worse outcome for patients. We have demonstrated that the presence of an MDR organism is an overwhelmingly strong and independent predictor for poor outcome after at least one year.

The mean number of surgical procedures with the MDR patients highlights the complex management these patients are subjected to, which is in keeping with the current literature.^{14,15} The data also indicates that the mean number of procedures is significantly higher in

Table 7
Relationship of MDR staphylococcus to failure.

Group	Staphylococcus aureus		Non staphylococcal		P-Value
	Successful	Fail	Successful	Fail	
All MDR	45 (73%)	17 (27%)	5 (42%)	7 (58%)	0.048
Monomicrobial only (MDR)	21 (95%)	1 (5%)	2 (67%)	1 (33%)	0.740
All N-MDR	77 (94%)	5 (6%)	74 (88%)	10 (12%)	0.279
Monomicrobial only (N-MDR)	46 (96%)	2 (4%)	69 (96%)	3 (4%)	1.000

Table 8
Relationship of sensitivity of bacterium to failure rate.

MDR group sensitivities	Success	Fail	P-Value
< / = 2 class sensitivities	35 (60%)	23 (40%)	–
> 2 class sensitivities	14 (93%)	1 (7%)	0.0152

the MDR failure group versus the N-MDR failure group (7 vs 4 procedures respectively), which suggests that a number of 4 surgical attempts at salvage during a single infected episode should be the threshold level set when failure is becoming increasingly inevitable.

Historically, poor outcomes in infected arthroplasty have been linked to co-morbidities and have further been used as a factor when considering amputation.^{16,17,18} The demographic stratified data from our study has shown that neither age, sex nor co-morbidity had any bearing on the rates of failure for an MDR organism. Furthermore, only increased age was shown to be a significant factor for the N-MDR group in relation to failure rates.

The internationally recognised management strategies for periprosthetic infection are followed by our institution. Despite this uniformity, the MDR group has shown a higher rate of failure versus the NMDR across all treatment groups. Although this was shown to be significant in the staged revision group, the other groups are showing a trend towards statistical significance and greater patient numbers may be required to prove this. By examining the most acutely infected group, i.e. those suitable for DAIR, against the staged revision treatment group, we attempted to account for chronicity as a confounding factor. Although there was a higher rate of failure amongst all chronic patients, again in keeping with current evidence,^{16,17} this was not found to be statistically significant and thus cannot be an independent factor for failure nor account for the significant difference in failure between both groups.

Existing literature has also established the polymicrobial element in patient infection to be a bad prognostic factor.¹⁸ Some studies have even noted a higher rate of MRSA and other resistant bacteria with polymicrobial infections.¹⁹ Our study confirms this finding, but the difference did not remain when analyzing the NMDR group. Therefore, we propose an interesting alternative to the widely held belief that the presence of more than one bacteria leads to a poor outcome. Our study suggests the presence of more than one organism, where one organism is an MDR, is the explanation behind existing and, indeed, our own findings. Despite this observation, more research is perhaps needed to examine the pathophysiological nature of MDR organisms with polymicrobial infections.

Due to the large number of MDR staphylococcal infections documented a direct comparison could only realistically be made to the staphylococcal infections in the N-MDR group. The significantly higher rate of failure when stratifying for the organism type (for staphylococcus aureus at least) again underlines the message that the multi drug resistance is the main driving factor behind the poor outcomes. This may be due, in part, to the polymicrobial relationship with other organisms but again this requires further research.

Within the MDR group we discovered the presence of XDR organisms and so called PDR organisms. We used the class sensitivity data available to the clinician from the database as these are what the clinician will utilize in their management protocol. We discovered that there was a significant rate of failure within the organisms with 2 or less class sensitivities. This has never been demonstrated in the orthopaedic literature and suggests that our current management strategy of surgical intervention and antibiotics may be ineffective. With fewer antibacterial agents in the clinician's arsenal this can explain a poorer outcome. However, further work is required to develop antibiotic and possibly surgical regimes to combat more resistant organisms.

In conclusion, this study has demonstrated that the presence of an MDR organism in infected hip and knee arthroplasty will lead to a long

and protracted journey for the majority of patients. The worse outcomes, irrespective of demographics, treatment, chronicity or multiple organisms strongly suggest that the MDR organism itself is a significant factor for the failure of joint arthroplasty. Clinicians faced with this must risk stratify when determining their treatment and individually factor this threat into their assessments and counselling of the patient.

Statement

No conflict of interests declared.

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