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Review article

Is there a difference in treatment outcome for monomicrobial and polymicrobial periprosthetic joint infections? Systematic review and study quality analysis

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ABSTRACT

Purpose: To perform a systematic review comparing the functional and objective outcomes for periprosthetic joint infection (PJI) caused by a single organism versus polymicrobial PJI.
Methods: A systematic review of the treatments, as well as functional and objective outcomes of clinical studies comparing single organism and polymicrobial PJI was performed, with a mean follow up of at least 24 months and minimum level of evidence of III. Following review of the literature, a quantitative comparison between success/failure rates after the treatment of monomicrobial vs polymicrobial PJI was performed. The methodological quality of each study was assessed using a modified version of the Coleman methodology score (mCMS).
Results: The systematic search identified 6 studies, including 1075 patients (829 in the single organism group and 246 in the polymicrobial group). All the studies were case control studies. Definitions for success and treatment failure were heterogeneous. The mean success rate for any treatment of monomicrobial infection was 70.4% (range, 64.7–87.5%) and 58.4% (range, 27.8–85.7%) for polymicrobial infections, respectively ($p = 0.29$). The mean survivorship for treated monomicrobial and polymicrobial PJI were 69.4% (range, 66–72.8%) and 58% (52–63.8%).
Conclusions: Quantitative analysis demonstrated that although polymicrobial infections have been identified as a risk factor for failure after a PJI, they did not result in significantly worse outcomes after treatment. Though not statistically significant, polymicrobial PJI with gram negative organisms typically resulted in poorer outcomes as compared to PJI with gram positive organisms. Antibiotic coverage should be evaluated to ensure proper coverage of such gram-negative organisms.
Level of evidence: Systematic Review of Level III Studies.
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1. Introduction

Infection has been reported to be the most common etiology for revision after a total knee arthroplasty (TKA) and total hip arthroplasty (THA). According to the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database, periprosthetic infection accounts for 20.4%[1] and 14.8%[2] of complication following TKA and THA, respectively. Patients with a periprosthetic joint infection (PJI) have been reported to have significantly longer hospitalizations (5.3 vs. 3.0 days), higher rates of readmission (3.6 vs. 0.1 readmissions), and more clinic visits (6.5 vs. 1.3 visits) when compared to the matched group.[3] This represents an important economic burden to the healthcare system, with a calculated case cost of USD 390,806 per 65-year-old patient with an infected THA.[4]

Berbari et al.[5] reported that the four most important risk factors

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predictive of PJI were postoperative surgical site infection, national nosocomial infection surveillance score greater than 2, concurrent malignancy, and prior joint arthroplasty. Polymicrobial periprosthetic joint infections are relatively infrequent with a reported rate between 6% and 37%.[6–9] Despite this relative infrequency, polymicrobial PJI are believed to have higher failure rates as compared to single organism PJI. Potential explanations for the divergence in failure rates between poly- and monomicrobial PJI include older average age, greater comorbidities,[10,11] and more virulent organisms such as enterococcus and gram negatives,[9,11–13] among patients with polymicrobial PJI.[14,15]

Due to such aforementioned reasons, there is a critical need to determine differences in outcomes and failures rates between single and polymicrobial periprosthetic joint infections. Therefore, the purpose of this paper was to perform a systematic review on the outcomes for PJI caused by a single organism and multiple organisms. It was hypothesized that standard treatment would result in hardware retention in both single organism and polymicrobial PJI and there would be no significant differences in outcomes between the single organism polymicrobial PJI following treatment.

2. Materials and methods

2.1. Article identification and selection

This study was conducted in accordance with the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[16] A systematic review of the literature regarding functional and objective outcomes for PJI caused by a single organism and polymicrobial PJI was performed using the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (1990–2017) and Medline (1990–2017). The queries were performed in December 2017.

The literature search strategy inclusion criteria were as follows: functional and objective outcomes of clinical studies comparing single organism and polymicrobial PJI treatment, mean follow-up of at least 24 months, and a level I, II or III of evidence within the English literature.

The following 2 searches were performed.

Search 1 (Knee): periprosthetic[All Fields] AND (“joints"[MeSH Terms] OR ″joints"[All Fields] OR ″joint"[All Fields]) AND (“infection"[MeSH Terms] OR ″infection"[All Fields]) AND (“knee"[MeSH Terms] OR ″knee"[All Fields] OR ″knee joint"[MeSH Terms] OR (“knee"[All Fields] AND ″joint"[All Fields]) OR ″knee joint"[All Fields])

Search 2 (Hip): periprosthetic[All Fields] AND (“joints"[MeSH Terms] OR ″joints"[All Fields] OR ″joint"[All Fields]) AND (“infection"[MeSH Terms] OR ″infection"[All Fields]) AND (“hip"[MeSH Terms] OR ″hip"[All Fields])

Cadaveric studies, animal studies, basic science articles, editorial articles and surveys were excluded. Two investigators (initials blinded for review) independently reviewed the abstracts from all identified articles. Full-text articles were obtained for review if necessary to allow further assessment of inclusion and exclusion criteria. Additionally, all references from the included studies were reviewed and reconciled to verify that no relevant articles were missing from the systematic review.

2.2. Data collection and analysis

The level of evidence of the studies was assigned according to the classification as specified by Wright et al.[17] Patient demographics, follow-up, surgical techniques and objective and subjective outcomes were extracted and recorded. For continuous variables (e.g., age, timing, follow-up, outcome scores), the means, standard deviations, and interquartile ranges were collected (if reported). Data was recorded into a custom spreadsheet using a modified information extraction table.[18]

Means and standard deviations were required to calculate weighted mean differences of continuous outcomes between PJI caused by a single organism and polymicrobial PJI. For studies that only reported on ranges, the SD was imputed as range divided by 4 or interquartile range divided by 1.35.[19] Studies that only reported median subjective scores[20,21] were not included in the synthesis calculations as these outcome scales are known to have ceiling effects postoperatively, and thus the median is not considerate a good estimate of the mean.[22] For comparing survivorship, the paired samples *t*-test was utilized for normally distributed data. For non-parametric data, the Wilcoxon-Signed Rank test was used. Comparisons of two categorical data were performed by use of Chi-square tests and Fisher Exact tests. All p-values were two-tailed and p-values of <0.05 were considered significant.

2.3. Literature quality evaluation

Two reviewers (*initials blinded for review*) used a modified version of the Coleman methodology score (mCMS) [to better fit the included studies] to assess the methodological quality of each study.[23] The two-part mCMS grades cartilage-related studies based on ten criteria. The maximum score of the mCMS is 100, which indicates a study largely avoids chance, biases and confounding factors.

3. Results

3.1. Study selection

The process for study selection is presented in Fig. 1. Searches identified 1670 individual titles and abstracts. After removal of duplicates, 1520 studies were eliminated based on inclusion/exclusion criteria, leaving 134 articles for full-text review. After a thorough review of these articles and their citations, a total of 6 level III studies were identified that explicitly reported demographics and characteristics of mono and polymicrobial PJI.

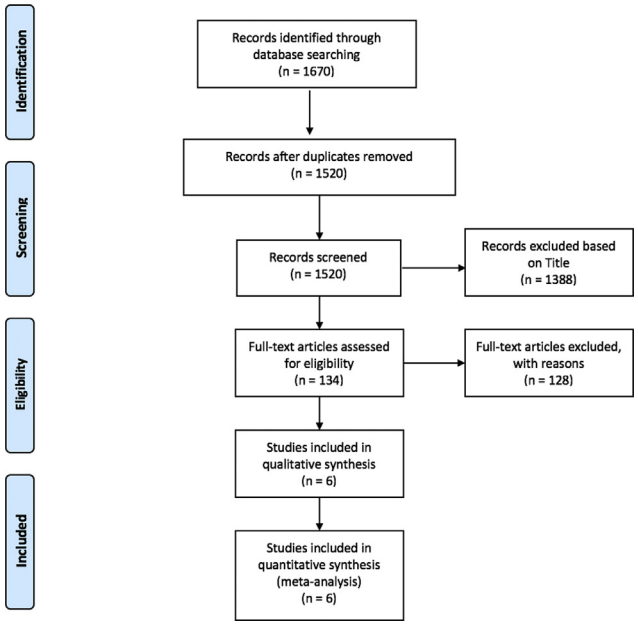

Fig. 1. PRISMA flowchart for the selection of the studies.

3.2. Patient demographics

The 6 studies included 1075 patients (829 in the single organism group and 246 in the polymicrobial group), and reported on 323 TK A and 497 THA, as summarized in Table 1 (Table 1). Mean patient age was 65.8 (range, 28–93).

3.3. Treatment approaches

The overall mean time from primary surgery to primary debridement was 7.7 months (range, 0.47–337 months). Thirty-one percent of monomicrobial PJI were treated within three months of index joint replacement (mean: 8.1 months, range: 0.47–337 months). Forty-three percent of polymicrobial PJI were treated within 3 months of index joint replacement (mean: 7.2 months, range: 2.6–307 months). There was significantly greater number of monomicrobial PJI treated in the delayed phase compared to polymicrobial PJI ($p = 0.001$). Treatment modalities are reported in Table 2 (Table 2).

3.4. Outcomes of treatment

The mean success rate for any treatment of monomicrobial infection was 70.4% (range, 64.7–87.5%) and 58.4% (range, 27.8–85.7%) for polymicrobial infections ($p = 0.29$). Two studies reported two-year survivorship for both mono and polymicrobial PJI.[10,11] The mean survivorship for treated monomicrobial and polymicrobial PJI was 69.4% (range, 66–72.8%) and 58% (52–63.8%). One study reported 5 and 10-year survivorship following PJI. For mono and polymicrobial PJI the reported 5-year survivor ship was 64% and 49.3%, respectively. The reported 10-year survivorship for mono and polymicrobial PJI was 62% and 46.8%, respectively. Definitions of failure and outcomes of treatment are summarized in Table 3 (Table 3).

3.5. Literature quality evaluation

A detailed analysis of the quality is demonstrated in Table 4 (Table 4).

4. Discussion

The most important finding of this study was that, following treatment, the functional and objective outcomes of polymicrobial PJI are consistently poorer than single organism infections. However, no significant difference was found between survival rates of both groups. Patients with polymicrobial infections were older and usually included infections by enterococcus and gram negatives. Only one study reported on long term outcomes: for mono and polymicrobial PJI the reported 5-year survivorship was 64% and 49.3%, respectively. The reported 10-year survivorship for mono and polymicrobial PJI was 62% and 46.8%.[11] Methodologic quality of the included studies ranged from 48 to 69 points (out of 100 possible points) deeming the available literature as acceptable.

Although the risk of infection after primary joint replacement is relatively low (ranges from 1.7% to 2.1%),[24] the consequences of its occurrence are potentially devastating. PJIs have been reported to impact several aspects of patients' lives including ability to work, as well as straining relationships with family members who become care-givers during patient's relatively immobile periods .[25] Moreover, prolonged time of treatment was directly related with patient dissatisfaction.[25] Patients experienced a poorer sense of well-being following a 2-stage versus a 1-stage revision, due to greater immobility between stages, and higher rates of psychological distress.[25] Participants interviewed in this study, expressed a need for more psychological and rehabilitative support during treatment and long-term recovery.[25]

Staphylococcus aureus and coagulase negative staphylococci were the main pathogens reported for single organism PJI, whereas Enterococcus and gram negatives were more frequently reported for polymicrobial infections. Bozhkova et al.[13] reported that in the monomicrobial group, the proportion of methicillin-resistant strains in patients with unsuccessful and successful outcomes was 8.7 and 17.3%, respectively. Similar findings were found in the polymicrobial group with 23.6 and 35.3% of all staphylococci, respectively. Of note, Gram-negative pathogens caused polymicrobial PJI in 61.5% of cases with infection recurrence (OR 4.4; 95% CI 1.18–16.37; $p = 0.03$).[13] The authors suggested that cases with microbial associations were more likely to result in infection recurrence (OR 7.7; CI 95%,3.79–15.73).

Table 1
Characteristics of the selected studies. L.O.E: level of evidence, M: male, F: female.

Author (Year)	Journal	L.O.E	Type of Study	Group	Microorganisms (majority)	# of Patients	Sex Distribution	Age (range)
Marculescu (2008)	Clin Orthop Relat Res	III	Retrospective	Monomicrobial	Gram Positive	140	M: 60 F: 80	63 (28–89)
				Polymicrobial	Gram Positive	34	M: 15 F: 19	69.5 (32–93)
Zmistowski (2011)	J Arthroplasty	III	Retrospective	Monomicrobial	Gram Positive/Neg	270	NR	66.4 (33–89)
				Polymicrobial	Gram Positive	12	NR	73.7 (67–80)
Wimmer (2015)	International Orthopaedics (SICOT)	III	Retrospective	Monomicrobial	Gram Positive	40	M: 26 F: 14	68.8 (NR)
				Polymicrobial	Gram Positive	37	M: 16 F: 21	67.9 (NR)
Tan (2016)	J Bone Joint Surg	III	Retrospective	Monomicrobial	Gram Positive	200	M:102 F: 98	65.4 (41.4–85.4)
				Polymicrobial	Gram Positive	95	M: 50 F: 45	65 (43.8–86.2)
Bozhkova (2016)	J Orthopaed Traumatol	III	Retrospective	Monomicrobial	Gram Positive	135	M: 92 F: 97	57 (49–67)
				Polymicrobial	Gram Positive	54	NR	57 (44–69)
Figa (2017)	Anaerobe	III	Retrospective	Monomicrobial	Gram Positive	24	M: 9 F: 15	73 (66.5–77.8)
				Polymicrobial	Gram Positive	14	M: 12 F: 2	63 (52.5–69.3)

Table 2
Treatment characteristics for both monomicrobial and polymicrobial infections. NR: not reported, abx: antibiotics. DAIR: debridement and implant retention.

Author (Year)	Group	Mean time primary surgery to primary debridement (Months)	Early (<3 months)	Delayed (>3 months)	Antibiotic Therapy	Single or Staged Surgery	Main Procedure
Marculescu (2008)	Monomicrobial	15.1 (0.47–337.7)	28.6	71.4	Depending on the specimen	Single: 65% Staged: 35%	Debridement and retention
	Polymicrobial	1.7 (3.3–307)	55.9	44.1	Depending on the specimen	Single: 73.6% Staged: 26.4%	Debridement and retention
Zmistowski (2011)	Monomicrobial	NR	16	84	NR	Single: 15% Staged: 85%	2 Stage- removal at first stage, abx spacer, replant
	Polymicrobial	NR	50	50	NR	Single: 33.3% Staged: 66.7%	2 Stage- removal at first stage, abx spacer, replant
Wimmer (2015)	Monomicrobial	2.6 (NR)	NR	NR	Depending on the specimen	Single: 48.1% Staged: 51.9&	
	Polymicrobial	4.3 (NR)	NR	NR	Depending on the specimen	Single: 51.9% Staged: 48.1%	
Tan (2016)	Monomicrobial	NR	NR	NR	Depending on the specimen	NR	NR
	Polymicrobial	NR	NR	NR	Depending on the specimen	NR	NR
Bozhkova (2016)	Monomicrobial	12 (3–50)	27.4	23.7	Vancomycin with beta-lactam or quinolones; alternatively, betalactam with quinolones or aminoglycosides	Staged	
	Polymicrobial	20 (10–52.5)	20.4	25.9			
Figa (2017)	Monomicrobial	2.8 (2.6–3)	54	46	Clindamicin	Single: 42% Staged: 58%	2-Stage, Non-DAIR 1 Stage
	Polymicrobial	2.8 (2.6–3)	43	57	Clindamicin + Rifampin	Single: 7% Staged: 93%	2 Stage; Non-DAIR

Table 3
Failure definitions by each of the studies and rates of success and failure. %: percentage; ys: years; NR: not reported.

Author (Year)	Definition of Failure	Group	Failure (%)	Success Rate (%)	Survivorship (2ys)	Survivorship (5ys)	Survivorship (10ys)
Marculescu 2008	Relapse, Reinfection, presence of acute infection/purulence in the joint space, development of a sinus tract communicating with the prosthesis, superinfection or indeterminate clinical failure	Monomicrobial	32.8	67.2	72.8	NR	NR
		Polymicrobial	35.3	64.7	63.8	NR	NR
Zmistowski 2011	Need for infection related component removal after first surgical treatment	Monomicrobial	33.3	66.7		NR	NR
		Polymicrobial	66.7	33.3		NR	NR
Wimmer 2015	Persistence or recurrence of PJI with the same or an unknown pathogen during or after the completion of antimicrobial therapy	Monomicrobial	12.5	87.5		NR	NR
		Polymicrobial	33.4	67.6		NR	NR
Tan 2016	(1) Failure to eradicate infection (indicated by presence of wounds with fistula, drainage, pain, infection by same organism strain), (2) need for surgical intervention for infection after reimplantation surgery, (3) occurrence of PJI-related mortality.	Monomicrobial	31.5	68.5	66	64	62
		Polymicrobial	50.5	49.5	52.2	49.3	46.8
Bozhkova 2016	Inflammatory signs remained or reappeared during the period between first step and reimplantation presence of acute inflammation with high levels of serum CRP, development of a sinus tract and relapse or reinfection.	Monomicrobial	25.2	74.8	NR	NR	NR
		Polymicrobial	72.2	27.8	NR	NR	NR
Figa 2017	Recurrence of PJI with any pathogen despite either 1 or 2 stage procedure + Abx	Monomicrobial	20.8	79.2	NR	NR	NR
		Polymicrobial	14.3	85.7	NR	NR	NR

Traditionally, polymicrobial infection is associated with higher failure rates and was considered a contraindication for one stage re-implantation in the management of PJIs. Previous studies demonstrated persistent infection in 6%–28% of patients after first-stage debridement, thus requiring repeated debridements.[13] Zmitowski et al.[26] reported that a single debridement and retention of prosthesis was successful in 70% of isolated gram negative cases, compared with 33.3% of methicillin-sensitive gram positive, 48.9% of methicillin-resistant gram positive, and 57.1% of polymicrobial cases. Of those patients undergoing a planned 2-stage exchange, a successful re-implantation was performed in 52% of gram-negative, 51% of methicillin-resistant gram-positive, 69% of methicillin-sensitive gram-positive, and 0% of polymicrobial PJI cases. The authors suggested that PJIs due to gram-negative (E Coli, Proteus, Serratia) pathogens, although less common, have poorer outcomes due to their limited treatment success.[26] Similarly, Yoon et al.,[27] reported an increased debridement frequency correlated significantly with high comorbidity ($P < 0.001$), a lower preoperative Harris hip score (HHS; $P < 0.001$), antimicrobial resistance, and gram-negative and polymicrobial infection ($P = 0.002$) at 5.4 years follow-up. Marculescu and Cantey[10] identified patients 65 years of age and older, presenting with a soft tissue defect or wound dehiscence and drainage, and those who had prior local irradiation and less bacteremia as potential risk factors predicting polymicrobial infections in a univariate regression. The presence of a sinus tract was reported as an additional risk factor for polymicrobial PJI, according to Tan et al., likely due to the lack of soft tissue integrity which allows for entry of organisms into the joint. Obesity and elevated CRP have also been found to increase risk of polymicrobial PJI.[13]

Tan et al. also evaluated the survivorship of the polymicrobial periprosthetic joint infection group and reported a 52.2%, a 49.3%,

Table 4
Modified version of the Coleman methodology score (mCMS).

Part A	Score	Figa	Bozhkova	Tan	Wimmer	Marculescu	Zmitowsky
Study size: Number of patients							
>60	10		10	10	10	10	10
41–60	7						
20–40	4	4					
>20, not stated	0						
Mean follow-up, month							
>60	10		10	10	10		
24–60	7	7				7	7
12–24	4						
<12, not stated	0						
No. of different treatment procedures included in each reported outcome. More than 1 method may be assessed, but separate outcomes should be reported							
1 procedure	10			10	10		
Surgical methods and/or nonoperative treatment methods More than 1 method but >90% of subjects undergoing the 1 procedure	7	7	7				7
Not stated, unclear, or <90% of subjects undergoing the 1 procedure	0					0	
Type of study							
Randomized control trial	15						
Prospective cohort study	10						
Retrospective cohort study	0	0	0	0	0	0	0
Description of surgical procedure given							
Adequate (technique stated and necessary details of that type of procedure given)	5	5	5				5
Fair, technique only stated without elaboration	3			3	3	3	
Inadequate, not stated or unclear	0						
Cohort comorbidities matching				0			
Cohorts matched	5		5	5	5	5	5
Unmatched or undefined	0	0					
Description of postoperative rehabilitation							
Well described	5						
Not adequately described	2						
Protocol not reported	0	0	0	0	0	0	0
Laboratory assessment							
Reported	10	10	10	10	10	10	10
Not reported	0						
Part B							
Outcome criteria							
Outcome measures clearly defined	3			3	3	3	3
Use of outcome criteria that has reported good reliability and sensitivity	2	2	2	2	2	2	2
Treatment success definition							
Well defined	5	5	5	5	5	5	5
Not defined	0						
Implant survivorship							
Reported	5			5		5	5
Not reported	0	0	0		0		
Procedure for assessing clinical outcomes							
Patients recruited (i.e., result not taken from surgeon' files)	3	3	3	3	3	3	3
Investigator independent of surgeon	4					4	
Completion of assessment by patients themselves with minimal investigator assistance	2						
	3			3	3	3	3
	5	5	5				
	3						
Total		**48**	**62**	**69**	**64**	**60**	**65**

and a 46.8% survival rate at the 2, 5 and 10-year follow-up respectively.[11] Patients with polymicrobial periprosthetic joint infection had higher rates of amputation (odds ratio [OR], 3.80 [95% confidence interval (CI), 1.34 to 10.80] p 0.012), arthrodesis (OR, 11.06 [95% CI, 1.27 to 96.00] p 0.029), and periprosthetic joint infection-related mortality (OR, 7.88 [95% CI, 1.60 to 38.67]p 0.0011) compared with patients with monomicrobial periprosthetic joint infection.[11] Similar findings were reported for Marculescu and Cantey,[10] who showed that the 2-year cumulative probability of success of polymicrobial PJIs was 63.8% (95% confidence interval [CI], 43.8%–80.5%) and that of monomicrobial PJIs was 72.8% (95% CI, 63%–80.9%). Conversely, Figa et al. reported no significant outcome differences between monomicrobial and polymicrobial PJIs cases; with success rates of 79.2% and 85.7% respectively ($P > 0.05$).[28]

Among the interventions commonly used to treat PJI, 2-stage revision resulted in consistently better outcomes, as compared to 1-stage revision or debridement and retention.[10,11] This may be due to the use of an antibiotic spacer in the 2-stage technique. Of note, however, Zmistowski et al.[26] noted that 2-stage revision is less successful in the treatment of polymicrobial PJI with gram negative organisms than it is with polymicrobial PJI with gram positive organisms. Gram negatives release lipopolysaccharide which initiates persistent inflammation and increases the ability of other organisms to implant, enhancing its virulence which may contribute to poorer treatment outcomes.[26]

The authors acknowledge limitations to the present study, including heterogeneity in the reporting of subjective outcomes, definitions of successful treatment and failure of the procedure. Furthermore, surgeon specific indications for performing specific antibiotic therapy and single or staged procedures may have affected the results in the included studies. Finally, some of the included studies included concomitant pathology and/or procedures, which may have altered outcomes. As with all systematic

reviews, it possible that relevant articles or patient populations were not identified with our search criteria.

5. Conclusion

Quantitative analysis demonstrated that although polymicrobial infections have been identified as a risk factor for failure after a PJI, they did not result in significantly worse outcomes after treatment. Though not statistically significant, polymicrobial PJI with gram negative organisms typically indicated poorer outcomes as compared to PJI with gram positive organisms. Antibiotic coverage should be evaluated to ensure proper coverage of such gram-negative organisms. As heterogeneous success/failure rates were reported in the literature, further research using standardized definitions, is indicated.

Disclosures

The authors have no disclosures to report.

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