

Research Paper

Clinical and Microbiological Characteristics of *Bacteroides* Prosthetic Joint Infections

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Abstract

Clinical and microbiological characteristics of patients with *Bacteroides* prosthetic joint infection (PJI) have not been well described in the literature. The aim of this retrospective cohort study was to assess the outcome of patients with *Bacteroides* PJI and to review risk factors associated with failure of therapy. Between 1/1969 and 12/2012, 20 episodes of *Bacteroides* PJI in 17 patients were identified at our institution. The mean age of the patients in this cohort at the time of diagnosis was 55.6 years; 59% (n=10) had knee involvement. Twenty four percent (n=4) had diabetes mellitus, and 24% had a history of either gastrointestinal (GI) or genitourinary (GU) pathology prior to the diagnosis of PJI. Thirty five percent (n=6) were immunosuppressed. The initial medical/surgical strategy was resection arthroplasty (n=9, 50%) or debridement and implant retention (n=5, 28%). Thirty seven percent (n=7) were treated with metronidazole. Eighty percent (n=4) of patients that failed therapy had undergone debridement and retention of their prosthesis, as compared to none of those treated with resection arthroplasty. Seventy percent (n=14) of patient episodes were infection free at their last date of follow up. In conclusion, a significant proportion of patients with *Bacteroides* PJI are immunosuppressed and have an underlying GI or GU tract pathology. Retention and debridement of the prosthesis is associated with a higher risk of treatment failure.

Key words: *Bacteroides*, prosthetic joint infection

Introduction

Prosthetic joint infections (PJI) are the most common cause of failure of total joint arthroplasty, resulting in additional procedures, increased health care costs, and increased morbidity for the patient [1-3]. The number of cases of PJI is rising, commensurate with the increasing number of prosthetic joints being implanted in the United States [4-6]. The Infectious Disease Society of America published guidelines in 2012 to help guide clinicians in the diagnosis and management of PJI. These guidelines primarily focus on the management of common pathogens associated with PJI, namely staphylococci and streptococci, and do not comprehensively address less commonly encountered

organisms associated with PJI.

Anaerobes account for 4% of PJI cases [6, 7]. Similar to other, more common pathogens, these organisms have the potential to create significant morbidity among patients, resulting in increased health care costs and prolonged hospital stay. *Bacteroides* species are obligately anaerobic, Gram-negative bacilli that are commensal members of the human gastrointestinal microbiota. [8-10]. Risk factors associated with clinical infections with *Bacteroides* sp. include immunosuppression, rheumatoid arthritis and intra-abdominal pathology [10, 11]. Despite the ability to produce significant patient morbidity, there are few data available on the

medical and surgical management of *Bacteroides* PJI [11].

Given the paucity of data associated with *Bacteroides* PJI, we performed a retrospective cohort study to describe the demographics, clinical characteristics and outcomes of patients with *Bacteroides* PJI. Results of this study will help guide both clinicians and microbiologists to effectively assess and manage such infections

Materials and Methods

Study Population

The medical records of all episodes of *Bacteroides* sp. total hip or knee arthroplasty infection seen at the Mayo Clinic in Rochester, MN between January 1, 1969 and December 31, 2012 were reviewed. *Bacteroides* PJI was defined according to a strict case definition, outlined below. All episodes were followed from the date of PJI diagnosis until treatment failure, prosthesis removal, death or the end of the study period. This study was approved by our institutional review board, and all patients had previously consented to participating in future research studies.

Data Collection

Data were obtained from the electronic and written medical records and transferred onto a structured data sheet, using the RedCAP™ database. The data was then analyzed using the JMP® (version 10.0.0) statistical program software. Data on date of birth, gender, medical comorbidities, type of surgery, and antimicrobial therapy was abstracted.

Definitions of terms used

(i) *Bacteroides* PJI was said to be present if at least two separate cultures grew *Bacteroides* sp. isolated from intra-articular aspiration or surgical specimens, or a single positive culture of *Bacteroides* sp. was isolated, along with any of the following: (a) purulence surrounding the prosthesis observed at the time of periprosthetic aspiration or during surgery; (b) acute inflammation consistent with infection on histopathologic examination; or (c) the presence of a sinus tract, found on examination or during operative repair. This definition was adapted from the Infectious Disease Society of America's guidelines for the management of PJI [6].

(ii) *Treatment failure* was defined as the occurrence of PJI, as outlined above, caused by *Bacteroides* or any other organism at any time after the original therapy episode.

(iii) The *original therapy episode* was defined as treatment that was undertaken during the initial hospitalization after diagnosis of PJI was established.

Statistical Methods

The number and percentage of episodes in each of the medical and surgical groups were calculated. Differences in demographic factors, clinical variables, and microbiology between the groups were compared using the chi-square test for categorical variables, and Wilcoxon rank sum analysis for continuous variables. Comparisons of the overall efficacy between the medical and surgical treatment strategies were performed by the use of the Petot-Petot Wilcoxon test.

Results

Study population

Between January 1, 1969 and December 31, 2012, 20 episodes of *Bacteroides* PJI in 17 patients were identified at the Mayo Clinic in Rochester, MN. Three of the patients had more than one episode, due to treatment failure. The overall mean age at the time of diagnosis was 55.6 years (range, 17 to 74 years). Ten (59%) patients had an infected knee arthroplasty infection, while seven (41%) had a hip arthroplasty infection. Twelve (71%) were females. All of the patients in this cohort were Caucasian. Nine patients (53%) had prosthesis placement at sites other than their primary site of infection, and 3 (18%) were associated with prior arthroplasty placement at the same site as the current PJI. Seven patients (41%) had prior PJI at the same site. One of these episodes was associated with a prior staphylococcal PJI, one with *Pseudomonas*, one with *Serratia marcescens*, and one was culture negative. There were 4 episodes associated with a prior *Bacteroides* PJI (one patient had 2 recurrences). Table 3 outlines the frequency of selected comorbidities in our study population. Of note, of the two patients (12%) that had an active malignancy at the time of diagnosis, one had osteosarcoma and one had multiple myeloma. Four patients (24%) had a history of gastrointestinal/genitourinary (GI/GU) pathology at the time of PJI diagnosis. This included a history of recurrent urinary tract infections, prior bowel resection, gastrointestinal perforation, cholecystectomy, and hysterectomy. Six patients (35%) were immunosuppressed at the time of PJI diagnosis; of note, four of these patients were taking prednisone at doses of less than 20 mg daily. Two of these patients were receiving methotrexate, and one was on prednisone doses of greater than 20 mg daily. One patient was on more than one immunosuppressive agent at the time of their PJI diagnosis. All patients were taking these medications due to underlying connective tissue disease or malignancy; the most common primary connective tissue disease associated with immunosuppressive use was rheumatoid arthritis.

Diagnostic methods

The diagnosis of *Bacteroides* PJI was based on the presence of at least two positive *Bacteroides* cultures obtained either from periprosthetic tissue or joint fluid in 12 of the 20 total episodes. Of those that did not fulfill this criteria (8 episodes), the diagnosis was made based on the presence of a single positive culture and the presence of a sinus tract (2 of the 8 episodes) or the presence of purulence around the joint space (6 of the 8 episodes). Ten patient episodes (50%) had elevated sedimentation rate and C-reactive protein; in the remaining episodes, markers were either normal or were not performed. Table 1 outlines some of the key clinical features associated with the *Bacteroides* PJI encountered at our institution, including treatment and history of prior *Bacteroides* PJI. There were 4 episodes associated with prior

Bacteroides infections, and eleven of the 20 total episodes of PJI (55%) were associated with coinfection with an organism other than *Bacteroides*. Companion organisms included coagulase negative staphylococci (most common), *Staphylococcus aureus*, *Providencia stuartii*, *Escherichia coli*, Group D and Group B streptococci, viridans group streptococci, and multiple anaerobes including *Actinomyces* species, *Clostridium* species, *Peptococcus* species and *Peptostreptococcus* species.

Microbiological Data

Table 2 summarizes the microbiological characteristics of the *Bacteroides* isolates isolated at the time of diagnosis. Of note, we did not find any significant difference in overall outcome when comparing monomicrobial vs. polymicrobial *Bacteroides* PJI (p=0.892),

Table 1. 17 Patients with *Bacteroides* PJI, classified by species isolated, medical and surgical therapy and prior exposure

Patient Number	Episodes Per Patient	<i>Bacteroides</i> sp.	Primary Medical Therapy	Surgical Therapy	Prior Infection with <i>Bacteroides</i> sp.	Outcome per episode
1	1	<i>B. fragilis</i>	Imipenem	Retention	No	Treatment Success
2	1	<i>B. fragilis</i>	Tetracycline	Resection	Yes	Treatment Success
3	1	<i>B. melaninogenicus</i>	Penicillin G	2- stage	No	Treatment Success
4	1	<i>B. fragilis</i>	Metronidazole	Chronic suppression	No	Treatment Success
5	2	<i>B. fragilis (both episodes)</i>	Clindamycin/Metronidazole	Retention/Resection	Yes/Yes	Treatment Failure/Treatment Success
6	1	<i>B. melaninogenicus</i>	Lincomycin	Retention	No	Treatment Failure
7	2	<i>B. vulgatus (both episodes)</i>	Cefadroxil/ Amoxicillin-Clavulanate	Retention/Chronic suppression	No/No	Treatment Failure/Treatment Failure
8	2	<i>B. fragilis (both episodes)</i>	Imipenem/Imipenem	Retention/Resection	No	Treatment Failure/Treatment Success
9	1	<i>B. fragilis</i>	Clindamycin	2-stage	No	Treatment Success
10	1	<i>B. ovatus</i>	None	Amputation	No	Treatment Success
11	1	<i>B. melaninogenicus</i>	Penicillin G	Resection	No	Treatment Success
12	1	<i>B. fragilis</i>	Metronidazole	Resection	Yes	Treatment Success
13	1	<i>B. bivius</i>	Metronidazole	Resection	No	Treatment Success
14	1	<i>B. ovatus</i>	Moxalactam	Resection	No	Treatment Success
15	1	<i>Bacteroides (species not identified)</i>	Metronidazole	Resection	No	Treatment Success
16	1	<i>B. fragilis</i>	Metronidazole	Resection	No	Treatment Success
17	1	<i>B. ovatus</i>	Metronidazole	2-stage	No	Treatment Failure

Table 2. Various *Bacteroides* species isolates and susceptibility data based on antibiotics tested

Antimicrobial Agent	<i>B. fragilis</i> MIC (mg/L)	<i>B. melaninogenicus</i> MIC	<i>B. vulgatus</i> MIC	<i>B. ovatus</i> MIC	<i>B. bivius</i> MIC
Penicillin	64, 50, >4, 6.25, 64, 64, 100		0.5	>64	64
Clindamycin	1, 1, 25, 3.1, 12.5, 1, 1, <0.78		0.5, <0.5	<0.5	<0.5
Cefoxitin	4, 12.5, 4, 4		4	32	<0.5
Metronidazole	4, 1, 0.8, 1.5, 4, 4		2, 2	<0.5	
Imipenem	0.5, 0.5, 0.5, 0.5		0.5, <0.5		
Ampicillin	12.5				
Ampicillin/Sulbactam	8/4				
Ceftizoxime	32				
Erythromycin	>100				
Mezlocillin				32	32
Moxalactam				32	<0.5
B-lactamase	2 strains positive	2 strains negative			

Table 3. Clinical Factors observed with *Bacteroides* PJI

Clinical Factor	# of Patients (% total)
Rheumatoid Arthritis	6 (35%)
Immunosuppression	6 (35%)
Diabetes mellitus	4 (24%)
GI/GU tract pathology	4 (24%)
Active smoking	3 (18%)
Renal disease	2 (12%)
Active malignancy	2 (12%)
Aseptic necrosis of bone	1 (6%)

Surgical Intervention

Of the 18 total episodes that underwent a surgical intervention, nine (50%) were managed with resection arthroplasty. Three (17%) episodes were treated with two-stage exchange procedure, with the mean duration between staged procedures of 409 days (range 202-572 days). Five episodes (28%) were managed with irrigation, debridement and retention of the prosthesis. One episode (6%) was managed with amputation and two episodes were managed with chronic antimicrobial suppressive therapy alone, without any surgical interventions.

Medical Therapy

Of the 19 total episodes that were treated with antimicrobial therapy, seven (37%) received a course of metronidazole, 3 (16%) received either clindamycin or lincomycin, 1 (5%) received tetracycline, and 8 (42%) received a β -lactam (imipenem, penicillin, amoxicillin-clavulanate, moxalactam, oxacillin). The mean duration of primary therapy was 57.1 days (range, 14-360 days). Three of the seven episodes that were managed with metronidazole developed peripheral neuropathy. One of these patients developed diarrhea not associated with *Clostridium difficile* colitis. Eight patient episodes received oral antimicrobial suppressive therapy following the initial therapy course, of which three were placed on metronidazole, two were on clindamycin, and one patient episode each was on penicillin VK, doxycycline and amoxicillin-clavulanate. Antibiotic poly (methyl methacrylamide) spacers were placed in only 2 episodes, of which one had a vancomycin/gentamicin spacer placed, and the other had a vancomycin/tobramycin spacer placed.

Outcome data

Table 1 outlines the various medical and surgical interventions provided for each patient and episode, including outcomes of each episode.

Discussion

To our knowledge, this is the largest study of patients with *Bacteroides* prosthetic joint infections

published in the literature. Based on our data, a significant proportion (35%) of patients with *Bacteroides* PJI had underlying immunosuppression, with a significant number of patients in this study presenting either with diabetes mellitus (24%), and rheumatoid arthritis or the use of immunosuppressive therapy (35% for each). Eighteen percent of the patients in this study had a history of active smoking. In addition, two of the patients (12%) had an active malignancy during their PJI diagnosis. Previous findings by other authors align with this finding [10]. Eight of the seventeen patients (47%) in this study had prior infection of their prosthesis at the same site as their PJI, suggesting that this too is a possible risk factor associated with *Bacteroides* PJI; of note, 4 of the patients previously had a *Bacteroides* PJI (at an outside institution), suggesting that prior infection with this organism increases the risk of reinfection. Our study found a relatively high proportion of patients (24%) with a history of underlying GI/GU pathology. Intra-abdominal pathology has been associated with *Bacteroides* infections, due to the fact that this organism is a commensal of the human gastrointestinal tract [8-10]. Our findings seem to reinforce this as well.

Based on our findings, a significant proportion of patients had a polymicrobial infection (55% of the total episodes). However, we did not find any significant difference in overall outcome when comparing monomicrobial vs. polymicrobial *Bacteroides* PJI ($p=0.892$). We noticed a high failure rate associated with debridement with prosthesis retention and chronic suppressive therapy alone, with 80% of the treatment failure episodes are accounted for by one of these two management strategies. In addition, among the patients who were treated successfully in this study, the majority underwent either resection arthroplasty or 2-stage exchange (9 of 14 episodes, or 64%). Together, these findings suggest that removal of all hardware may improve outcomes associated with these infections; however our cohort did not contain enough patients to make a definitive conclusion with regards to this. From an antimicrobial standpoint, the majority of our patients were treated with metronidazole or imipenem. In general, both of these agents are well tolerated for short periods of time, with minimal associated side effects. Both have good bone penetration as well, based on prior PK/PD studies [13]. The rate of *Bacteroides* resistance to metronidazole is still <1%. *Bacteroides* sp. are highly susceptible to carbapenems; however the rate of resistance to these agents is also increasing [12]. In this study, all of the tested isolates were susceptible to imipenem, and the majority were susceptible to

metronidazole.

There are a number of limitations associated with our study inherent to its retrospective nature; there is the risk of recall bias, along with selection bias. Our study did not contain a sufficient number of patients to perform reliable outcome analyses, and therefore was restricted to being primarily descriptive in nature.

In conclusion, *Bacteroides* PJIs have distinctive clinical characteristics. The majority of isolates were susceptible to metronidazole, imipenem, tetracyclines and clindamycin. Episodes treated with prosthesis retention appeared to have worse outcomes than episodes treated with resection arthroplasty or 2-stage exchange. A high proportion of underlying immunosuppression and a history of GI/GU pathology were observed as significant risk factors in this cohort. Future cohort studies are warranted to confirm these findings.

Competing Interests

The authors have declared that no competing interest exists.

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