Is There an Association Between an Increased Number of Positive Cultures and an Increased Host Response? A Study of Bacterial Species and Virulence in Revision Shoulder Arthroplasty

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Introduction:
Patients found to have positive cultures taken at the time of revision shoulder arthroplasty often have variable presentations in terms of preoperative and intraoperative signs and symptoms of infection ranging from no apparent signs of infection to obvious signs of infection. The most common bacteria that is cultured at the time of revision is *Cutibacterium acnes*, but its presence is controversial in terms of whether treatment is necessary. Some regard *Cutibacterium* as a contaminant regardless of number of positive cultures, while others will treat dependent on a threshold of either ≥2 or ≥3 positive cultures. However, there is no available data to indicate whether an increased host response is seen with an increased number of positive cultures. Given our lack of understanding of bacterial virulence of *Cutibacterium* and coagulase negative *Staphylococcus* (CoNS) cultured at the time of revision shoulder arthroplasty, we attempted to answer two clinically-relevant questions:

1) Is an increased number of positive cultures associated with an increased host response?
2) How does the host response compare across different bacterial species?

Answering these questions will further our understanding of the relative virulence of certain bacterial species and how we may potentialy manage them.

Methods: Data was prospectively collected on 770 consecutive revision shoulder arthroplasty cases in the American Shoulder and Elbow Surgeons (ASES) Revision Shoulder Arthroplasty and PJI Multicenter Research Group. Intraoperative testing was standardized among participating surgeons prior to data collection including synovial fluid aspiration prior to arthrotomy, tissue sent for frozen section, and 5 deep tissue cultures sent for microbiological testing. Bacterial types were split into three categories: *Cutibacterium*, CoNS, and other species (including methicillin-sensitive *Staphylococcus aureus* [MSSA], methicillin-resistant *Staphylococcus aureus* [MRSA], etc). For each bacterial species, groups were created based on the number of positive cultures (no positive, 1 positive, 2 positive, 3 positive). Clinical signs and symptoms, radiographic findings, and serum and synovial labs were assessed across tiers of culture positivity. Two separate types of analyses were performed to answer each of the clinical questions. To address the question of whether there is an association of number of positive cultures and an increased host response, an analysis of variance (ANOVA) test was used to compare "within-species" to see if there was an increased proportion or value of the variable of interest as the number of positive cultures increased. To address the question of whether the host response is more mild or more severe with certain bacterial species, an ANOVA test was used to compare the host response "between-species."

Results: Of the 770 revision shoulder arthroplasties, 243 (32%) had at least one positive *Cutibacterium* culture, 70 (9%) had at least one positive CoNS culture, and 106 (14%) had at least one positive culture of other bacteria.

Clinical signs of host response: The presence of sinus tract or pus, unexpected wound drainage, and erythema all increased with more positive cultures of other bacteria ($p<0.001$) (Table 1). A similar trend was seen with sinus tract and pus with *Cutibacterium* ($p<0.001$), but not drainage or erythema. This trend was not seen with any of these clinical signs with CoNS ($p>0.066$). There was a significantly higher proportion of clinical signs of a host response (sinus tract, pus, drainage, erythema) with other bacteria compared to *Cutibacterium* and CoNS ($p<0.004$).

Component loosening and osteolysis: There was a trend of increased radiographic humeral osteolysis with all bacterial types ($p<0.029$) (Table 1).

Laboratory values indicative of host response: ESR and CRP values increased significantly with increased positive cultures with other bacteria ($p<0.001$), a trend not seen with *Cutibacterium* or CoNS. The proportion of patients with positive frozen sections increased with more positive cultures for all bacterial types ($p<0.014$) and was not different between bacterial species.

Conclusion: This study demonstrates that there are certain elements of the host response (sinus tract, pus, humeral osteolysis, frozen section) that are elevated with an increase in number of positive cultures with *Cutibacterium* and others that are not (serum ESR/CRP). Compared to *Cutibacterium*, the host response, on average, is more severe with other bacteria (eg, MSSA, MRSA) and more mild with CoNS. This data suggests that *Cutibacterium* should not always considered to be a contaminant. Further study on on the host response to different strains of *Cutibacterium* and optimal thresholds requiring treatment (≥2 or ≥3 positive cultures) are warranted.

Table I. Clinical and radiographic signs of host response across various bacterial species and increasing number of positive cultures.

Clinical and Radiographic Findings	0 Positive	1 Positive	2 Positive	3 Positive	4 Positive	Within-Species Comparison	Between-Species Comparison
Sinus Tract or Intra-articular Pus							
Cutibacterium	47 (8.9%)	7 (9.7%)	4 (7.1%)	4 (12.1%)	20 (24.4%)	**<0.001**	
CoNS	69 (9.9%)	5 (11.4%)	2 (14.3%)	4 (33.3%)		0.066	**0.001**
Other	50 (7.6%)	8 (13.1%)	7 (38.9%)	15 (55.6%)		**<0.001**	
Unexpected Wound Drainage							
Cutibacterium	26 (4.9%)	3 (4.2%)	2 (3.6%)	1 (3.0%)	9 (11.0%)	0.148	
CoNS	38 (5.5%)	1 (2.3%)	1 (7.1%)	0 (0.0%)		0.654	**0.002**
Other	22 (3.3%)	6 (9.8%)	3 (16.7%)	10 (37.0%)		**<0.001**	
Erythema							
Cutibacterium	33 (6.3%)	4 (5.6%)	5 (8.9%)	4 (12.1%)	12 (14.6%)	0.059	
CoNS	53 (7.6%)	2 (4.5%)	1 (7.1%)	1 (8.3%)		0.911	**0.004**
Other	36 (5.5%)	6 (9.8%)	4 (22.2%)	11 (40.7%)		**<0.001**	
Intraoperative Humeral Loosening							
Cutibacterium	91 (17.3%)	12 (16.7%)	13 (23.2%)	7 (21.2%)	15 (18.3%)	0.831	
CoNS	122 (17.5%)	9 (20.5%)	2 (14.3%)	5 (41.7%)		0.179	0.177
Other	112 (17.0%)	14 (23.0%)	5 (27.8%)	7 (25.9%)		0.370	
Radiographic Humeral Loosening							
Cutibacterium	81 (15.4%)	12 (16.7%)	9 (16.1%)	4 (12.1%)	10 (12.2%)	0.934	
CoNS	101 (14.5%)	8 (18.2%)	2 (14.3%)	5 (41.7%)		0.083	**0.032**
Other	96 (14.5%)	13 (21.3%)	3 (16.7%)	4 (14.8%)		0.746	
Radiographic Humeral Osteolysis							
Cutibacterium	104 (19.7%)	18 (25.0%)	22 (39.3%)	10 (30.3%)	26 (31.7%)	**0.002**	
CoNS	157 (22.6%)	11 (25.0%)	5 (35.7%)	7 (58.3%)		**0.029**	0.158
Other	141 (21.4%)	19 (31.1%)	7 (38.9%)	12 (44.4%)		**0.006**	

Table II. Laboratory values indicative of host response across various bacterial species and increasing number of positive cultures.

Laboratory Tests	0 Positive	1 Positive	2 Positive	3 Positive	4 Positive	Within-Species Comparison	Between-Species Comparison
Serum ESR Value							
Cutibacterium	24.8 ± 24.0	20.4 ± 20.1	16.6 ± 17.2	18.2 ± 19.6	25.2 ± 29.2	0.103	
CoNS	23.9 ± 24.4	20.1 ± 17.6	19.2 ± 17.7	23.0 ± 15.3		0.728	**<0.001**
Other	22.1 ± 22.7	25.9 ± 27.2	23.0 ± 12.8	51.6 ± 28.6		**<0.001**	
Serum CRP Value							
Cutibacterium	9.9 ± 23.4	15.5 ± 38.8	6.3 ± 10.7	10.5 ± 14.5	11.6 ± 22.3	0.428	
CoNS	10.5 ± 24.8	7.2 ± 11.1	18.4 ± 32.8	7.9 ± 8.0		0.588	**<0.001**
Other	8.8 ± 21.0	11.3 ± 19.2	11.4 ± 12.7	48.5 ± 60.8		**<0.001**	
Frozen Section (>5 per 5 HPF)							
Cutibacterium	31 (5.9%)	4 (5.6%)	5 (8.9%)	6 (18.2%)	20 (24.4%)	**<0.001**	
CoNS	57 (8.2%)	2 (4.5%)	1 (7.1%)	4 (33.3%)		**0.014**	0.599
Other	3 (0.5%)	3 (4.9%)	3 (16.7%)	6 (22.2%)		**0.004**	
WBC Count from OR aspirate							
Cutibacterium	5567 ± 40000	4883 ± 14163	2201 ± 6048	3857 ± 7255	18932 ± 35500	0.411	
CoNS	4335 ± 14921	40065 ± 138253	15166 ± 29580	3033 ± 3465		**<0.001**	0.609
Other	5980 ± 37320	4255 ± 10643	11052 ± 15115	20094 ± 37096		0.693	
Neutrophil % from OR aspirate							
Cutibacterium	41.6 ± 31.8	44.1 ± 33.6	40.7 ± 30.8	49.7 ± 35.0	62.3 ± 37.2	**0.039**	
CoNS	43.8 ± 32.4	41.5 ± 41.6	46.3 ± 38.0	56.8 ± 33.3		0.795	0.833
Other	42.8 ± 32.5	41.3 ± 34.5	65.2 ± 37.4	66.3 ± 26.7		**0.049**	