TABLE E-1 Outcomes of the Treatment of Periprosthetic Shoulder Infections* ➤

Study	No.	Presentation	Prosthesis	Most Common Pathogens
Braman et al.[68]	7	1 acute, 2 subacute, and 4 late	2 HA and 5 TSA	Staphylococcus epidermidis (3)
Muh et al.[75]	26	ND	7 HA, 6 TSA, and 13 RTSA	ND
Rispoli et al.[76]	18	ND	ND	ND
Themistocleous et al.[80]	11	ND	1 HA, 3 TSA, and 7 other	Staphylococcus aureus (10)
Ince et al.[69]	16	1 acute, 6 subacute, and 9 late	14 HA and 2 TSA	Staphylococcus epidermidis (5), P. acnes (4), and Staphylococcus species (3)
Mileti et al.[74]	4	ND	2 HA and 2 TSA	Staphylococcus epidermidis (3)
Coffey et al.[77]	16	ND	6 HA, 5 TSA, and 5 other	MRSA (3) and Staphylococcus epidermidis (3)
Seitz and Damacen[86]	8	ND	5 TSA and 3 other	Staphylococcus aureus (6) and Staphylococcus epidermidis (2)
Strickland et al.[71]	19	Acute (3), subacute (7) and late (9)	ND	P. acnes or coagulase-negative Staphylococcus (10)
Sabesan et al.[70]	17	2 acute, 8 subacute, and 7 chronic	10 HA, 4 TSA, and 2 RTSA	Coagulase-negative Staphylococcus (4), P. acnes (4), and Staphylococcus epidermidis (3)
Coste et al.[65]	42	12 acute, 6 subacute, and 24 late	ND	Staphylococcus epidermidis (9) and P. acnes (7)
Cuff et al.[89]	22	ND	17 HA and 5 other	Staphylococcus aureus (4) and coagulase-negative Staphylococcus (4)
Dines et al.[85]	5	ND	TSA	ND
Sperling et al.[25]	32	4 acute, 5 subacute, and 23 late	9 HA and 23 TSA	Staphylococcus aureus (13), coagulase-negative Staphylococcus (9), and P. acnes (5)
Verhelst et al.[72]	21	4 subacute and 17 late	4 TSA, 7 RTSA, and 10 other	Staphylococcus aureus (9), coagulase-negative Staphylococcus (12), and Propionibacterium species (4)
Weber et al.[73]	10	Mean, 19 mos (range, 7-37 mos)	3 TSA, 4 HA, 2 RTSA, and 1 IP	Staphylococcus epidermidis (4), P. acnes (2), and Staphylococcus aureus (2)

*ND = not documented, HA = hemiarthroplasty, TSA = total shoulder arthroplasty, IP = isoelastic prosthesis, VAS = visual analog scale, ASES = American Shoulder and Elbow Surgeons, UCLA = University of California at Los Angeles, DASH = Disabilities of the Arm, Shoulder and Hand, RTSA = reverse total shoulder arthroplasty, MRSA = methicillin-resistant Staphylococcus aureus.

TABLE E-1 (continued)

Treatment Method	Mean Follow-up (range) (mo)	Results	Level of Evidence
Resection arthroplasty	20 (12-41)	0/7 recurrent infections; Neer subjective outcomes: 7 unsatisfactory	IV
Resection arthroplasty	41 (12-130)	Resection arthroplasty performed for RTSA results in worse outcomes than for HA and TSA. Mean VAS score decreased from 6 to 3. (Infection was the indication for surgery in 85% of patients in this study.)	IV
Resection arthroplasty	100 (30-197)	0/13 recurrent infections; Neer subjective outcomes: 2 satisfactory, 16 unsatisfactory. (Infection was the indication for surgery in 72% [13] of 18 patients in this study.)	IV
Permanent antibiotic-eluting cement spacer	22 (15-26)	0/11 recurrent infections; only 2 underwent revision arthroplasty. Mean QuickDASH of 37.5. All patients were satisfied. (All patients in the study were treated with a permanent-eluting cement spacer shoulder arthroplasty.)	IV
One-stage revision	69 (13-159)	0/9 recurrent infections; for 9 with available data, mean UCLA score was 18.3 and mean VAS score was 5.8; 6 were satisfied, and 3 were worse	IV
Resection arthroplasty to reimplantation	88 (24-180)	0/4 recurrent infections; Neer subjective outcomes: 2 satisfactory and 2 unsatisfactory	IV
Two-stage revision	20 (12-30)	0/16 recurrent infections; mean ASES increased from 16 to 74, mean VAS score decreased from 8.4 to 0.5, and mean UCLA score increased from 7 to 26	IV
Two-stage revision	57 (36-96)	0/8 recurrent infections; mean Penn shoulder score of 63	IV
Two-stage revision	27 (7-80)	7/19 recurrent infections; Neer subjective outcomes: 2 excellent, 4 satisfactory, and 13 unsatisfactory	IV
Two-stage revision to RTSA	46 (22-80)	1/17 recurrent infections; mean Penn shoulder score improved from 24.9 to 66.4; 35% complication rate (5 had instability and 1 had infection)	IV
Group 1: antibiotics alone (5); Group 2: resection arthroplasty (10); Group 3: irrigation and debridement (8); Group 4: one-stage revision (3); Group 5: two-stage revision (10); and Group 6: other (6)	32 (12-96)	Recurrent infection by group: 60% in Group 1; 30% in Group 2; 12% in Group 3; 0% in Group 4; 0% in Group 5; and 17% in Group 6. Subjective scores not documented	IV
Group 1: one-stage revision to RTSA (10) and Group 2: two-stage revision to RTSA (12)	43 (25-66)	0/22 recurrent infections; 11 complications and 1 dislocation; mean ASES increased from 32 to 57, and mean VAS score decreased from 6.3 to 3.5	IV
Group 1: two-stage revision (3) and Group 2: resection arthroplasty (2)	76 (24-128)	1/5 recurrent infection (resection arthroplasty); mean UCLA score of 8.0, and mean L'Insalata score of 26.3. All patients had worse functional outcome than prior to the infection	II
Group 1: resection arthroplasty (21); Group 2: irrigation and debridement (6); Group 3: one-stage revision (2); and Group 4: two-stage revision (3)	78 (33-157)	Recurrent infection was 28% in Group 1, 50% in Group2, 50% in Group 3, and 0% in Group 4	III
Group 1: resection arthroplasty with spacer, and Group 2: resection arthroplasty without spacer	46 (17-101)	Recurrent infection was 2/11 in Group 1 and 0/10 in Group 2 (p = 0.48); mean DASH score was 52.7, and mean VAS decreased from 6.5 to 2.6; no difference in functional outcome between groups	III
Group 1: resection arthroplasty (5), Group 2: two-stage revision (4), and Group 3: irrigation and debridement (1)	48 (14-120)	0/10 recurrent infections; mean Constant score of 33 in Group 1, 40 in Group 2, and 61 in Group 3	IV

TABLE E-2 Most Common Microbes Responsible for Periprosthetic Infections of the Hip and Knee*	
Microbe	Percentage of Infections
Coagulase-negative staphylococci	30-43
Staphylococcus aureus	12-23
Polymicrobial	10-12
Streptococci species	9-10
Enterococci species	3-7
Gram-negative bacilli	3-6
Anaerobes	2-4

*According to the studies by Zimmerli et al.[30], Loehr[95], and Trampuz and Zimmerli[96].

TABLE E-3 MSIS Definition of Periprosthetic Joint Infection*
1   Presence of a sinus tract communicating with the prosthesis; or
2   A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
3   Three of the following minor criteria exist†   a. Elevated ESR and CRP level   b. Elevated synovial leukocyte count or ++ change on leukocyte esterase test strip   c. Elevated synovial neutrophil percentage   d. Isolation of a microorganism in one culture of periprosthetic tissue or fluid   e. Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification

*Based on the report by Della Valle et al.[98]. MSIS = MusculoSkeletal Infection Society. †Periprosthetic joint infection may also be present if fewer than four of these criteria are met. ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, and ++ = reading from test strips that has been found to correlate with the presence of an infection.

TABLE E-4 The Effect of Infection Prevalence on the Predictive Value of a Diagnostic Test*

	Occult Infection	Aseptic Failure	Row Total
Example 1			
Positive culture	95	45	140
Negative culture	5	855	860
Column total	100	900	1000
Example 2			
Positive culture	475	25	500
Negative culture	25	475	500
Column total	500	500	1000

*Positive predictive value (PPV) in example 1 = (occult infections with positive culture results) / (all positive cultures) = 95/140 = 0.68. The PPV in example 2 = 475/500 = 0.95. The PPV is dependent on the prevalence of a condition in a given population. A sample size of 1000 and prevalence of 0.1 and 0.5 are demonstrated in examples 1 and 2, respectively. The sensitivity and specificity of the diagnostic test (bacterial cultures) are 95% in both examples.

TABLE E-5 Antibiotic Treatment Recommendations for Common Microorganisms Identified in Periprosthetic Shoulder Infections*

Microorganism	Antibiotic of Choice	Alternative(s)
Staphylococcus aureus or coagulase-negative staphylococci		
Methicillin susceptible	Nafcillin or cefazolin ± rifampin	(1) Clindamycin, (2) trimethoprim-sulfamethoxazole, and (3) vancomycin
Methicillin resistant	Vancomycin ± rifampin	(1) Linezolid, (2) daptomycin, and (3) rifampin and ciprofloxacin, or levofloxacin, or trimethoprim-sulfamethoxazole, or minocycline
Propionibacterium acnes and corynebacterium species	Penicillin G	(1) Third-generation cephalosporin, (2) vancomycin, and (3) clindamycin
Streptococcus species	Penicillin G	(1) Third-generation cephalosporin and (2) vancomycin
Enterococcus species (penicillin susceptible)	Penicillin G	(1) Ampicillin or amoxicillin and aminoglycoside and (2) vancomycin
Enterococcus species (penicillin resistant)	Vancomycin	Linezolid
Enterobacter species	Meropenem, ertapenem, or imipenem	(1) Ciprofloxacin and (2) cefepime
Pseudomonas aeruginosa	Cefepime or ceftazidime	(1) Meropenem or imipenem, (2) aminoglycoside, and (3) ciprofloxacin

*The recommendations are based on the reviews provided by Zimmerli et al.[30], Kowalski et al.[49], Sankar and Esterhai[123], and Peel et al.[124]. The antibiotics listed should be used as general guidelines. Antibiotic type, route, dose, and duration should be discussed with a medical infectious disease consultant, and final determination should be guided by the final culture sensitivities of the pathogen(s) isolated in culture.

Appendix E-1 Microbiology

Until recently, the relative frequencies of the microorganisms identified in periprosthetic shoulder infection were thought to mirror the most common agents responsible for periprosthetic infections of the hip and knee (Table E-2)[30,95,96]. While reported distributions have remained constant in the lower extremities, several investigations have revealed *Propionibacterium acnes* to be the most common causative microorganism of periprosthetic shoulder infection[24,41,44,45,97]. The true prevalence of its presence at other sites of the body may be underestimated on the basis of what has been learned in the experience of the shoulder over time. Singh et al. noted that, prior to 2001, Staphylococcus species predominated[22,23]. However, since then, periprosthetic shoulder infections with *P. acnes* have been equally frequent. The reason for this increased frequency is not clear, although contributing factors may include changes in laboratory culture techniques, extension of incubation times, increased surveillance, discrepancies in the definition of a periprosthetic joint infection, and changes in perioperative antibiotic protocols. Despite the alarming frequency with which *P. acnes* has been implicated in periprosthetic shoulder infections, the establishment of *P. acnes* as a pathogen has evolved slowly because of the diagnostic challenges it has presented.

Defining a Periprosthetic Shoulder Infection

A universally accepted definition of *periprosthetic shoulder infection* is crucial to creating evidence-based diagnostic and treatment algorithms. The MusculoSkeletal Infection Society (MSIS) convened an international workgroup to systematically evaluate the available literature on periprosthetic joint infection[98]. It was agreed that certain indolent infections (i.e., *P. acnes*) may not meet the consensus definition of periprosthetic joint infection (Table E-3)[98]. This brings into question how to characterize microbes with low virulence that are identified at the time of revision shoulder reconstruction.

The shoulder region has unique microflora compared with other regions of the body. Specifically, there are higher rates of colonization[99] and infection[97] of the shoulder with *P. acnes* compared with the hip and knee. *P. acnes* has only recently been implicated as a pathogen following shoulder surgery[42,45,100-102] because, under most circumstances, it is considered a commensal organism due to its low level of virulence[103]. Unfortunately, for patients who have gone on to poor outcomes following shoulder arthroplasty, no preoperative sign, symptom, or screening test has been found to reliably predict the presence of an indolent infection caused by this fastidious microorganism[24]. Additionally, identification of *P. acnes* at the time of revision surgery via culture analysis does not necessarily indicate a causal relationship. Some patients with delayed positive cultures indicate the pathogenic presence of *P. acnes,* some are indicative of a false-positive culture result, and some may theoretically indicate the coincident presence of commensal colonization[41,44,45,97]. Since positive cultures remain the only reliable test, it is, de facto, the gold standard. Unfortunately, the lack of a confirmatory test means that the false-positive rate of these cultures has not been well defined. A large prospective study is currently under way to help answer this question.

Appendix E-2 Bayesian Analysis Demonstrating the Effect of Relative Prevalences on the Predictive Value of a Diagnostic Test[29,104] and Future Directions

The relative prevalence of periprosthetic infection in a given cohort of patients with failed arthroplasties affects the predictive value of culture results. This can be demonstrated with a theoretic Bayesian analysis using two different prevalences. For example, if the prevalence of a periprosthetic infection at the time of revision surgery is assumed to be 10%, the probability of failure from aseptic causes would then be 90%. Utilizing an imaginary intraoperative test with sensitivity and specificity of 95%, the chances of a patient without an infection having a positive culture (a false-positive result) is 5%. If a patient has an occult infection, the probability of a having a positive culture is 95% on the basis of the sensitivity. In this example with an infection prevalence of 10%, a patient with a positive culture has a 68% probability of having a true infection (or positive predictive value) and a 32% probability of not having an infection (Table E-4). If the prevalence of a periprosthetic infection in a given cohort could be increased to 50% using a preoperative screening test to exclude patients with a low probability of infection, the combined probability that a patient with a positive culture also has an infection rises dramatically to 95% (Table E-4). In the setting of a possible hip or knee periprosthetic infection, this is achieved by evaluating the levels of serum inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein level. Unfortunately, the predominant pathogen identified in subacute and late periprosthetic shoulder infections, *P. acnes,* does not predictably cause an abnormal increase in these serum inflammatory markers. No test, or combination of tests, has yet to be identified with reproducible sensitivity or specificity to help to deduce the likelihood of its presence. These examples underscore the importance of using intraoperative cultures as a confirmatory test rather than as a screening test. It also highlights why the rate of positive cultures in revision shoulder arthroplasty has varied substantially throughout the literature.

Future Directions

Several novel techniques that may have clinical utility in the evaluation of failed shoulder arthroplasties have been developed. The propensity of *P. acnes*[105-107] and other microorganisms[108-110] to form biofilms has been targeted with the use of implant sonication

techniques. Piper et al. found that sonication increased sensitivity of culture analyses from 55% to 67% (p = 0.046)[43]. They also found that *P. acnes* was the most common organism identified among culture-positive definite shoulder infections, with a prevalence of 41%. Sonicate fluid culture may be useful in the diagnosis of prosthetic shoulder infections, may lead to a diagnosis of infection prior to positive synovial fluid or tissue culture results, and warrants further investigation.

On the basis of the premise that tissue cultures are the most accurate diagnostic tool currently available, Morman et al.[62] suggested an alternative. They present the cases of two patients for whom the decision was made to perform an outpatient arthroscopy at least two weeks prior to scheduled revision shoulder surgery to obtain tissue cultures. The two-week time frame was chosen to allow for the growth of indolent organisms, specifically *P. acnes*. The clinical scenarios they present highlight how management decisions can vary greatly, depending on the results of the cultures. Although this diagnostic algorithm may allow for more informed management decisions at the time of revision, it is also associated with additional risks. This process has not been validated in larger series, but offers another diagnostic option that may be worthy of additional study.

Molecular techniques, such as polymerase chain reaction[111,112], messenger RNA microarray analyses[113], and both serum and synovial fluid inflammatory proteomic analyses[77,114-117], to determine the likelihood of infection-related implant failure, have been studied. While these techniques offer great potential as adjuncts to traditional tests, they are not widely available and are currently considered investigational.

It has also been hypothesized that bacteria from a distant site can translocate to the joints of patients with rheumatoid arthritis or osteoarthritis and promote arthritic degeneration without apparent purulence. Surgical intervention may not be required to introduce these organisms into the glenohumeral joint. There is a small body of evidence that previously assumed nonpathogenic microorganisms such as *P. acnes* could also play a role in the underlying pathogenesis of degenerative joint disease in addition to prosthetic joint failure[118-121]. Levy et al. demonstrated that >40% of patients undergoing primary shoulder arthroplasty without any clinical signs or symptoms of infection may have *P. acnes* in their glenohumeral joint synovial at the time of surgery[122]. Although preliminary in nature, these data supporting an infective etiology of degenerative joint disease also merit further investigation. ∎