Shoulder Periprosthetic Joint Infection and All-Cause Mortality: A Worrisome Association

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**Background:** Periprosthetic joint infection (PJI) can be a devastating complication following shoulder arthroplasty. PJI following hip and knee arthroplasties has been found to increase mortality. However, anatomical and bacteriologic differences could potentially result in a different trend after shoulder arthroplasties. Thus, the purpose of the present study was to determine whether there is an association between shoulder PJI and all-cause mortality.

**Methods:** Our institutional Total Joint Registry Database was queried to identify patients who underwent revision shoulder arthroplasty procedures between 2000 and 2018. A total of 1,160 procedures were then classified as either septic (21.8%) or aseptic (78.2%). Septic revisions were further subdivided into (1) debridement, antibiotics, irrigation, and implant retention (9.1%); (2) 2-stage reimplantation for deep infection (61.3%); (3) implant resection without reimplantation (3.6%); and (4) unexpected positive cultures at revision surgery (26.1%). The most common bacterium isolated was *Cutibacterium acnes* (64.4%). All-cause patient mortality was determined with use of our registry and confirmed with use of a nationwide mortality database. All-cause crude and adjusted mortality rates were then compared between groups.

**Results:** The 1-year crude mortality rate was 1.8% (95% confidence interval [CI], 0.9% to 2.6%) for the aseptic group and 2.8% (95% CI, 0.7% to 4.8%) for the septic group (p = 0.31). Multivariate Cox regression analysis demonstrated an elevated but statistically similar adjusted hazard ratio for 1-year all-cause mortality of 1.9 (95% CI, 0.8 to 4.6) when comparing the septic to the aseptic group (p = 0.17). The risk of 2-year all-cause mortality was significantly higher in the septic group, with a hazard ratio of 2.2 (95% CI, 1.1 to 4.5; p = 0.029). In univariate analyses, increased 5-year mortality in the septic revision group was associated with age, Charlson Comorbidity Index, and methicillin-resistant *Staphylococcus aureus* infection, whereas *C. acnes* infection was associated with lower mortality.

**Conclusions:** Shoulder PJI is associated with an adjusted 2-year all-cause mortality rate that is double that of aseptic patients. The results of the present study should be utilized to appropriately counsel patients who are considered to be at risk for infection following shoulder arthroplasty.

**Level of Evidence:** Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

The utilization of primary shoulder arthroplasty in the United States has increased dramatically over the last 2 decades and is projected to continue rising. The incidence of shoulder periprosthetic joint infection (PJI) can be anticipated to rise accordingly, as this complication is observed in approximately 1% of patients. Shoulder PJI has been associated with a number of factors including male sex, younger age, and reverse total shoulder arthroplasty, although the impact of medical comorbidities remains controversial. The economic costs associated with 2-stage reimplantation for shoulder PJI are substantial, not to mention the considerable impact on the quality of life of patients. The typical 2-stage reimplantation treatment algorithm for shoulder PJI requires 2 revision arthroplasty procedures and long-term intravenous antibiotics. Although the short-term mortality rate following primary total shoulder arthroplasty has been reported to range between 0.16% and 1.5% at 90 days and up to 3.8% at 1 year, rates as high as 3% have been reported at 90 days following revision shoulder arthroplasty in older patients. Factors associated with mortality have included male sex and increased age, but the direct impact of shoulder PJI on mortality is unknown. The lower-extremity arthroplasty literature provides strong evidence that hip and knee PJI are associated with a

Disclosure: The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A357).

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1.8 to 5-fold increase in the odds of 1-year mortality\textsuperscript{16,17}. However, this relationship has not been studied for shoulder PJI, in which anatomic and bacteriologic\textsuperscript{5,7,16} differences may translate into different mortality rates. The purpose of the present study was to compare all-cause mortality rates between patients who underwent a surgical procedure for shoulder PJI and those who underwent a revision for aseptic failure. Further, for patients with a shoulder PJI, we sought to determine patient and infection characteristics associated with mortality. We hypothesized that PJI would increase mortality in patients undergoing revision shoulder arthroplasty.

| ** Materials and Methods** |
|---------------------------|

**Patient Cohort**

All revision shoulder arthroplasty procedures completed between 2000 and 2018 within a multi-hospital single academic health system were retrospectively identified from our prospectively collected Total Joint Registry Database, yielding a total of 1,177 procedures. Patients were excluded if their arthroplasty was part of an oncologic reconstruction (11 patients), they had an antibiotic spacer for >1 year prior to reimplantation (5 patients), or records from referring hospitals were not available to classify them (1 patient). During this time period, 6,716 primary shoulder arthroplasty procedures were

| **TABLE I Comparison of Baseline Characteristics Between Cohorts** |
|---------------------------------------------------------------|
| **Characteristics** | **Septic (N = 253)** | **Aseptic (N = 907)** | **Total (N = 1,160)** | **P Value** |
| Age at surgery (yr) | | | | |
| Mean (std. dev.) | 62.4 (11.4) | 66.8 (11.2) | 65.8 (11.4) | <0.001\textsuperscript{†} |
| Median | 63 | 68 | 67 |
| Interquartile range | 56, 71 | 60, 75 | 59, 74 |
| Range | 28-85 | 29-92 | 28-92 |
| Sex* | | | | |
| Female | 82 (32.4%) | 514 (56.7%) | 596 (51.4%) | <0.001\textsuperscript{‡} |
| Male | 171 (67.6%) | 393 (43.3%) | 564 (48.6%) |
| Body mass index (kg/m\textsuperscript{2}) | | | | |
| Mean (std. dev.) | 30.4 (6.2) | 31.0 (7.3) | 30.9 (7.1) | 0.287\textsuperscript{§} |
| Median | 29.9 | 29.7 | 29.7 |
| Interquartile range | 26.1, 33.7 | 26.2, 34.8 | 26.2, 34.6 |
| Range | 16.9-54.6 | 14.7-65.8 | 14.7-65.8 |
| Smoking status* | | | | |
| Ever | 106 (41.9%) | 371 (40.9%) | 477 (41.1%) | 0.942\textsuperscript{†} |
| Never | 79 (31.2%) | 293 (32.3%) | 372 (32.1%) |
| Unknown | 68 (26.9%) | 243 (26.8%) | 311 (26.8%) |
| Charlson Comorbidity Index (severity- and age-weighted sum) | | | | |
| Mean (std. dev.) | 3.4 (2.7) | 4.0 (2.9) | 3.9 (2.8) | <0.001\textsuperscript{#} |
| Median | 3 | 3 | 3 |
| Interquartile range | 2, 4 | 2, 5 | 2, 5 |
| Range | 0-16 | 0-19 | 0-19 |
| ASA score | | | | |
| Mean (std. dev.) | 2.4 (0.6) | 2.4 (0.5) | 2.4 (0.5) | 0.200\textsuperscript{‡} |
| Median | 2 | 2 | 2 |
| Interquartile range | 2, 3 | 2, 3 | 2, 3 |
| Range | 1-4 | 1-4 | 1-4 |
| Surgical treatment* | | | | |
| 2-stage exchange | 155 (61.3%) | — | 155 (61.3%) | — |
| DAIR | 23 (9.1%) | — | 23 (9.1%) |
| Unexpected positive | 66 (26.1%) | — | 66 (26.1%) |
| Resection | 9 (3.6%) | — | 9 (3.6%) |

*Values are given as the count with the percentage in parentheses. †Two-sample t test assuming equal variances. ‡Chi-square test. §Two-sample t test assuming equal variances conducted on log transformation. #Wilcoxon rank-sum test.
completed at our institution, highlighting that revision arthroplasty accounts for 17% of procedures within our system. All living patients had at least 2 years of postoperative follow-up, with follow-up periods of <2 years representing deaths (average follow-up, 4.4 years; range, 3 days to 5 years). Aseptic revision procedures included all surgeries that involved exchange or replacement of any prosthetic component, without suspicion or postoperative treatment for infection.

A procedure was classified as septic if the patient was presumed to have a PJI on the basis of preoperative or intraoperative findings and was treated with antibiotics for a PJI postoperatively by the orthopaedic surgeon and consulting infectious disease specialist. Septic procedures were further grouped as (1) debridement, antibiotics, irrigation, and implant retention (DAIR); (2) 2-stage explant and delayed reimplantation with a temporary antibiotic spacer; (3) implant resection without reimplantation; or (4) unexpected positive cultures at revision surgery. Patients initially treated with DAIR but then treated with a 2-stage explantation procedure within the following year were classified as having a 2-stage revision. Additionally, patients in the unexpected positive cultures group were only included in the septic cohort if they were treated postoperatively for suspected deep infection with long-term antibiotics by our infectious disease physicians. Patients who underwent multiple revisions within the 19-year collection window were grouped into either the aseptic or septic cohort according to the classification of their first revision within the period.

Altogether, a total of 1,160 revision shoulder arthroplasty procedures were included within the analysis, with 907 (78.2%) of those being classified as aseptic and 253 (21.8%) as septic (Table I). Of those in the septic group, 155 (61.3%) underwent a 2-stage exchange, 66 (26.1%) had unexpected positive cultures, 23 (9.1%) were treated with DAIR, and 9 (3.6%) had an implant resection. In the septic cohort, 85.4% of patients were found to have at least 1 positive culture. *C. acnes* was the most common bacterium and was observed in 64.4% of infected shoulders, whereas coagulase-negative staphylococci were the second most common bacteria and were cultured in 23.6% of infections (Table II). Polymicrobial infections constituting more than 1 bacterium other than *C. acnes* were rare (n = 12, 5.6%).

### Mortality

Patient survival and all-cause mortality events were captured through routine contacts by the registry, and confirmed when needed with use of a nationwide mortality database (Accurint by LexisNexis). When utilizing the nationwide database, a 6-month lag period was included in order to ensure that all deaths were given an appropriate interlude to be recorded accurately, similar to the methodology in previous studies. Time-to-death calculations were performed according to the first revision surgery for patients in the aseptic, DAIR, resection, and unexpected culture groups. For patients in the 2-stage septic group, the date of reimplantation was utilized as the start of their timeline, as this was the point at which they were routinely captured by our Total Joint Registry Database. Utilization of the explantation date as the start of the mortality timeline in 2-stage patients was avoided because it could lead to an immortal time bias whereby patients were inaccurately attributed extra survival time prior to enrollment, since by definition all subjects must have survived that time period in order to be captured by the registry. Baseline patient demographics, severity- and age-weighted Charlson Comorbidity Index, and infection characteristics were extracted from our registry and by chart review.

### Statistical Analysis

Kaplan-Meier analyses were utilized to compare overall survival between groups of interest with up to 5 years of follow-up and to report mortality rates at 90 days, 1 year, 2 years, and 5

TABLE II Culture Data from the Septic Cohort*

| Category                          | Value   |
|----------------------------------|---------|
| Any bacteria (n = 253)           |         |
| Any recorded                     | 216 (85.4%) |
| None recorded                    | 37 (14.6%)  |
| *C. acnes* (n = 216)             |         |
| Yes                              | 139 (64.4%) |
| No                               | 77 (35.6%)  |
| Coagulase-negative Staphylococcus (n = 216) |         |
| Yes                              | 51 (23.6%)  |
| No                               | 165 (76.4%) |
| MSSA (n = 216)                   |         |
| Yes                              | 13 (6.0%)   |
| No                               | 203 (94.0%) |
| MRSA (n = 216)                   |         |
| Yes                              | 11 (5.1%)    |
| No                               | 205 (94.9%) |
| Gram-negative bacteria (n = 216) |         |
| Yes                              | 12 (5.6%)    |
| No                               | 204 (94.4%) |
| Streptococcus (n = 216)          |         |
| Yes                              | 7 (3.2%)     |
| No                               | 209 (96.8%) |
| Other bacteria (n = 216)         |         |
| Yes                              | 19 (8.8%)    |
| No                               | 197 (91.2%)  |
| *C. acnes* only (n = 216)        |         |
| Yes                              | 114 (52.8%)  |
| No                               | 102 (47.2%)  |
| Polymicrobial (n = 216)          |         |
| Yes                              | 12 (5.6%)    |
| No                               | 204 (94.4%)  |

*Values are given as the count with or without the percentage in parentheses.
years post-revision. The log-rank test was utilized to determine if observed crude mortality rates were significantly different between cohorts within these analyses. In order to understand the independent association of shoulder PJI with mortality, Cox logistic regression was utilized in order to build multivariable models adjusted for age, sex, body mass index, smoking, American Society of Anesthesiologists (ASA) score, and severity- and age-weighted Charlson Comorbidity Index when possible, with the number of adjusters dependent on the number of mortality events within the period of interest. Finally, possible associations between patient and infection characteristics with mortality following shoulder PJI were assessed with use of univariate Cox regression with variables of interest. In all analyses, significance was set at 0.05. All statistical analyses were performed with use of SAS (version 9.4M6; SAS Institute) and R (version 3.6.2; R Foundation for Statistical Computing).

Source of Funding
No external funding was utilized for this project.

Results
The baseline patient demographics were significantly different between the cohorts (Table I). The septic cohort had a significantly lower mean age at the time of surgery (62 years) and a significantly greater proportion of male patients (68%) compared with the aseptic cohort (67 years and 43%; p < 0.001 for both comparisons). The severity- and age-weighted Charlson Comorbidity Index was significantly lower in the septic group. The ASA score, body mass index, and smoking status did not differ significantly between the cohorts.

A total of 26 of 253 patients in the septic cohort and 92 of 907 patients in the aseptic cohort had died at the time of the latest follow-up. Kaplan-Meier curves produced an estimated 1-year mortality rate of 2.8% (95% confidence interval [CI], 0.7% to 4.8%) in the septic cohort and 1.8% (95% CI, 0.9% to 2.6%) in the aseptic cohort; these crude rates were not significantly different (p = 0.31) (Table III, Fig. 1). The log-rank test did not demonstrate any significant differences between the unadjusted crude mortality rates of the groups at any point.

Multivariate Cox regression analysis demonstrated an elevated but statistically similar adjusted hazard ratio (HR) for 1-year all-cause mortality of 1.89 (95% CI, 0.77 to 4.62) for the septic compared with the aseptic cohort (p = 0.17) (Table IV). The 2-year risk of all-cause mortality was significantly higher in the septic group, with an HR of 2.21 (95% CI, 1.09 to 4.47; p = 0.029). At 5 years, the risk of all-cause mortality remained higher in the septic group (HR, 1.47; 95% CI, 0.93 to 2.32), although this trend did not reach significance (p = 0.10). When eliminating patients with unexpected positive cultures from the analysis, the overall results were similar except that all-cause mortality remained significantly higher in the septic group at 5 years.

In the septic cohort, univariate Cox regression analysis did not find any associations between all-cause mortality at 1, 2, or 5 years and sex, body mass index, or Gram-negative infection (see Appendix 1). As expected, patient age was associated with mortality at 2 and 5 years, whereas the Charlson Comorbidity Index were associated with increased mortality at all time intervals. Notably, infections with *C. acnes* only were associated with a significantly lower risk of mortality at 2 years (HR, 0.11; 95% CI, 0.01 to 0.83; p = 0.033) and at 5 years (HR, 0.29; 95% CI, 0.11 to 0.77; p = 0.012) (Table V). A methicillin-resistant *Staphylococcus aureus* (MRSA) infection was associated with a significantly increased risk of mortality at all time points (HR, 9.62; 95% CI, 1.87 to 49.6; p = 0.007 at 1 year). There was a trend toward a higher 2-year mortality rate in patients with polymicrobial infection, although this did not reach significance (p = 0.076). Mortality rates differed between procedure types in the septic group and were highest among patients who underwent resection (Fig. 2).

Discussion
As the number of shoulder arthroplasty procedures continues to grow, it is important to understand the potential adverse effect of shoulder PJI because the prevalence

| TABLE III Estimated Crude Mortality Rates in Groups of Interest |
|-----------------|-----------------|-------------|-------------|-------------|-------------|
| N               | Events          | 90 Days     | 1 Year      | 2 Years     | 5 Years     |
| Total           | 253             | 26          | 0.8 (0.0-1.9) | 2.8 (0.7-4.8) | 4.7 (2.1-7.3) | 11.5 (7.2-15.6) |
| Two-stage/DAIR/resection | 187          | 23          | 1.1 (0.2-2.5) | 3.2 (0.6-5.7) | 5.3 (2.1-8.5) | 13.7 (8.3-18.9) |
| Two-stage       | 155             | 16          | 0.6 (0.1-1.9) | 1.9 (0.4-4.1) | 3.2 (0.4-6.0) | 11.8 (6.1-17.2) |
| DAIR            | 23              | 3           | 0.0 (0.0-0.0) | 4.3 (0.0-12.3) | 8.7 (0.0-19.5) | 14.1 (0.0-27.7) |
| Unexpected cultures | 66            | 3           | 0.0 (0.0-0.0) | 1.5 (0.0-4.4) | 3.0 (0.0-7.1) | 5.0 (0.0-10.4) |
| Resection       | 9               | 4           | 11.1 (0.0-29.4) | 22.2 (0.0-45.1) | 33.3 (0.0-58.0) | 44.4 (0.3-69.0) |
| *C. acnes* only | 114             | 5           | 0.0 (0.0-0.0) | 0.9 (0.0-2.6) | 0.9 (0.0-2.6) | 5.6 (0.6-10.3) |
| Aseptic         | 907             | 92          | 0.3 (0.0-0.7) | 1.8 (0.9-2.6) | 2.9 (1.8-3.9) | 11.4 (9.1-13.6) |

*Values are given as the estimated mortality rate with the 95% CI in parentheses.*
of this complication will certainly increase accordingly. The results of the present study indicate that, after adjusting for baseline differences between cohorts, patients undergoing revision arthroplasty for shoulder PJI are more than twice as likely to die within 2 years of surgery compared with those undergoing an aseptic revision. These findings confirm our hypothesis that shoulder PJI is associated with increased mortality risk. Further, not all shoulder PJIs have an equal impact on

![Survivorship free of all-cause death within 5 years](image)

Fig. 1
Kaplan-Meier 5-year survivorship curves for the septic and aseptic cohorts. These unadjusted rates demonstrate the trend toward increased all-cause mortality in the septic cohort, although the crude rates were statistically similar (p > 0.05).

| TABLE IV Multivariate Cox Regression Results Comparing Adjusted Mortality Rates Between the Septic and Aseptic Cohorts |
| --- |
| **Death Within 1 Year** | **Death Within 2 Years** | **Death Within 5 Years** |
| | Adjusted HR (95% CI)* | P Value | Events | Adjusted HR (95% CI)† | P Value | Events | Adjusted HR (95% CI)‡ | P Value |
| Septic versus aseptic | | | | | | | | |
| Septic (n = 353) | 7 | 1.89 (0.77-4.62) | 0.166 | 12 | 2.21 (1.09-4.47) | 0.029 | 26 | 1.47 (0.93-2.32) | 0.101 |
| Aseptic (n = 907) | 16 | — | — | 26 | — | — | 92 | — | — |
| Surgical treatment | | | | | | | | |
| Two-stage/DAIR/resection (n = 187) | 6 | 2.10 (0.82-5.39) | 0.123 | 10 | 2.34 (1.10-4.99) | 0.027 | 23 | 1.74 (1.08-2.81) | 0.023 |
| Aseptic (n = 907) | 16 | — | — | 26 | — | — | 92 | — | — |

*Adjusted for age, sex, body mass index, smoking, ASA score, and severity and age-weighted Charlson Comorbidity Index. †Adjusted for age, ASA score, and severity/age-weighted Charlson Comorbidity Index. ‡Adjusted for severity and age-weighted Charlson Comorbidity Index.
| TABLE V Univariate Cox-Regression Analyses Evaluating Associations with Mortality in the Septic Cohort |
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patients, as MRSA infections were associated with a mortality risk that was 9.6 times greater than that for other infections, and isolated *C. acnes* infections were associated with a mortality risk that was 0.1 times that for other organisms.

The lower-extremity arthroplasty literature has previously shown significantly higher mortality rates among patients with hip and knee PJI\(^1\)\(^6\),\(^7\). An institutional registry study observed an adjusted odds ratio for 1-year mortality of 5.9 in patients undergoing septic versus aseptic revision lower-extremity arthroplasty. Additionally, a study from the Danish Joint Registry observed an adjusted odds ratio for mortality of 1.87 in patients undergoing revision total hip arthroplasty for PJI\(^1\)\(^7\). We chose to utilize Cox regression and hazard ratios in our study in order to better evaluate the changes in mortality rate over time\(^2\)\(^9\), making it impossible to directly compare the magnitudes of effects between studies. However, the results of the present study agree with the overall trend that PJI is associated with increased all-cause mortality.

The previous 2 studies from the lower-extremity arthroplasty literature demonstrated significantly increased mortality rates in the septic cohorts within 1 year of revision surgery, whereas the present study showed no significant difference until 2 years postoperatively. It is impossible to know if this discrepancy represents a true underlying difference between lower and upper-extremity PJI because the discrepancy could be explained by the smaller sample sizes of the present cohorts and the overall scarcity of mortality events, and because there was a nonsignificant but elevated rate of 1-year all-cause mortality in the septic cohort (HR, 1.89; 95% CI, 0.77 to 4.62; \(p = 0.17\)). However, 1 prior study found that the elevated mortality rates in the septic cohort were limited to the first postoperative year and disappeared beyond that time frame\(^6\), whereas our observations became stronger between 1 and 2 years. These differences could be a result of the different analytic methods utilized in the present study or could highlight that shoulder PJI carries an increased risk of mortality that is smaller in magnitude but more extended in duration.

Interestingly, the previously observed 1-year mortality rates for aseptic revision total hip arthroplasty (5%; 95% CI, 4% to 6%) and septic revision total hip arthroplasty (8%; 95% CI, 6% to 11%)\(^1\)\(^7\) were substantially higher than those observed at 1 year in the present study (septic cohort: 2.8%; 95% CI, 0.7% to 4.8%; aseptic cohort: 1.8%; 95% CI, 0.9% to 2.6%). This difference highlights the greater toll associated with
Shoulder Periprosthetic Joint Infection and All-Cause Mortality: A Worrisome Association

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