

G97: Is mortality increased in patients with orthopedic implant associated infections?

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Response/Recommendation: Yes. There is an increased mortality rate following orthopedic implant associated infections.

Level of Evidence: Strong

Delegate Vote:

Rationale:

Total joint arthroplasty, spine surgery, and treatment of hip fractures is associated with large improvements in quality-of-life, and patients have a reduced mortality compared to the general population during the first decade following surgery^{1-3,1}. However, periprosthetic joint infection (PJI) and surgical site infection (SSI), that can occur in one to two percent of patients,^{4,5} adversely impacts function and quality of life. Orthopaedic related infections are associated with prolonged hospitalization, multiple revision surgeries, and prolonged courses of antibiotics.

In order to answer the question posed above, we conducted a comprehensive review of PubMed and Embase databases to identify all eligible publications. The initial search resulted in 513 potential studies. The abstracts of the latter studies were reviewed to identify 37 studies for full-text review, of which 27 studies were included in the final analysis. This systematic review identified 27 studies that included 1,034,897 cases (148,875 infected) assessing the impact of orthopedic related infections on mortality.

The analysis of data revealed that patients suffering orthopedic related infections had increased in-hospital mortality (1.8% [2,327 / 127,972] versus 0.6% [4,597/727,874]; $p<0.001$). These differences persist with increased follow-up (Table 1). In the fields of arthroplasty (hip, knee, and shoulder), patients with prosthetic joint infection have elevated risk of mortality at all time points (inpatient to twenty-year follow-up) relative to patients undergoing aseptic revision arthroplasty even when controlling for confounding variables. Elevated mortality risk is also seen in patients with surgical site infection following spine or hip fracture surgery in comparison to similar patients that do not develop infections. In patients with orthopedic implant infections, increased age, severity of comorbidities, and infecting organism have been consistently associated with mortality. Efforts to mitigate early mortality following orthopedic implant associated infections have unknown efficacy and require further investigation.

HIP AND KNEE ARTHROPLASTY

Much of the available literature on mortality and orthopedic-related infections focuses on PJI in the hip and knee (99.3% of the included cases in our systematic review were for hip and knee arthroplasty and 21⁶⁻²⁶ of the 27 included studies). Taken together, patients suffering PJI had a mortality rate of 4.6% (6,867 / 148,251) at a weighted average follow-up of 0.97 years compared to 3.4% (29,897 / 879,723; $p<0.0001$) for patients without infections. At every time point in this analysis, patients suffering from PJI had greater rates of death than patients undergoing primary or aseptic revision total hip or knee arthroplasty. This includes differences in inpatient deaths^{22,25} and an increased rate of mortality at 20-year follow-up²¹. Furthermore, these findings persist across different study designs: cohort studies, case-control studies from a single-institution, and case-control studies from large registries or administrative databases.

Consistently, these studies identified increasing age^{4,8,15-17,22,27} and comorbidities^{4,8,12,15-17,22,23,25-27} as factors associated with early mortality in patients with PJI. Given that increased comorbidities are associated with the development of PJI, it can be difficult to determine if PJI is truly independent risk-factor for death. However, studies employing techniques to control for confounding variables (such as indexes of comorbidities) through matching or multivariate analysis consistently found PJI to be a factor independently associated with early mortality.^{4,8,17,23} Other factors associated with early mortality were polymicrobial infections¹⁷, Enterococci infections^{20,27}, male gender,^{4,27} and suboptimal weight (underweight or obese).^{4,26} Kurtz et al and Ng et al identified a small but statistically

significantly decreased risk of mortality following PJI as time has progressed.^{4,25} This may be a sign of improving patient care, and therefore decreased mortality, in lower extremity PJI.

SHOULDER ARTHROPLASTY

A systematic review for this analysis provided three papers^{28–30} (1,588 patients [348 infections]) that analyzed the association between shoulder PJI and early mortality. Combined, these papers found a mortality rate of 14.6% (51/348) in infected patients compared to 9.2% (114/1240; $p=0.003$) in aseptic patients at a median study follow-up of 4.7 years. The largest of these papers, Austin et al,²⁸ found that patients with shoulder PJI had increased rates of mortality if they were older, had increased Charlson Comorbidity Index (sicker), and Methicillin Resistant *Staphylococcus aureus* (MRSA) infections. Specifically, *Cutibacterium acnes* infections were associated with decreased mortality rates in the shoulder PJI group.^{28,30}

HIP FRACTURE

Two studies^{31,32} were identified that assessed the impact of surgical site infection on mortality following treatment for hip fracture with arthroplasty or operative fixation. At one-year median follow-up, patients suffering from surgical site infection after treatment for hip fracture had significantly greater likelihood of death (43.2%; 35/81) than those without surgical site infection (26.5%; 1,184 / 4,474; $p=0.0007$). Duckworth et al³² identified dementia and *S. aureus* infections as factors associated with early mortality.

SPINE

To our knowledge, there is only a single study directly evaluating the impact of spine surgical site infections on early mortality. Casper et al³³ assessed identified 195 patients undergoing reoperation for SSI and matched these patients 1:3 for age, gender, body mass index, year of surgery, Charlson comorbidity index, spine region, and approach. At all time points, patients with SSI had greater rate of death culminating in a 5-year mortality rate of 7.7% compared to 2.25% ($p=0.001$). Mortality in the infected cohort was associated with increased age and Charlson Comorbidity Index.

In conclusion, our review of the literature revealed that patients with PJI of hip, knee and shoulder have elevated risk of mortality at all time points (inpatient to twenty-year follow-up) relative to patients undergoing aseptic revision arthroplasty even when controlling for confounding variables. Elevated mortality risk is also seen in patients with SSI following spine or hip fracture surgery in comparison to similar patients who do not develop infections. In patients with orthopedic implant infections, increased age, severity of comorbidities, and infecting organism have been consistently associated with mortality. Efforts to mitigate early mortality following orthopedic implant associated infections have unknown efficacy and requires further investigation.

Reference:

1. Harris, IA, Hatton, A, Pratt, N, Lorimer, M, Naylor, JM, de Steiger, R, Lewis, P, Graves, SE: How Does Mortality Risk Change Over Time After Hip and Knee Arthroplasty? *Clinical Orthopaedics and Related Research*® 2019;477:1414.
2. Maradit Kremers, H, Larson, DR, Nouredin, M, Schleck, CD, Jiranek, WA, Berry, DJ: Long-Term Mortality Trends After Total Hip and Knee Arthroplasties: A Population-Based Study. *The Journal of Arthroplasty* 2016;31:1163–1169.
3. Cnudde, P, Rolfson, O, Timperley, AJ, Garland, A, Kärrholm, J, Garellick, G, Nemes, S: Do Patients Live Longer After THA and Is the Relative... : *Clinical Orthopaedics and Related Research*®. at <https://journals.lww.com/clinorthop/fulltext/2018/06000/do_patients_live_longer_after_tha_and_is_the.10.aspx>.
4. Kurtz, SM, Lau, EC, Son, M-S, Chang, ET, Zimmerli, W, Parvizi, J: Are We Winning or Losing the Battle With Periprosthetic Joint Infection: Trends in Periprosthetic Joint Infection and Mortality Risk for the Medicare Population. *The Journal of Arthroplasty* 2018;33:3238–3245.
5. Padegimas, EM, Maltenfort, M, Ramsey, ML, Williams, GR, Parvizi, J, Namdari, S: Periprosthetic shoulder infection in the United States: incidence and economic burden. *J Shoulder Elbow Surg* 2015;24:741–746.

6. Matar, HE, Bloch, BV, Snape, SE, James, PJ: Septic Revision Total Knee Arthroplasty Is Associated With Significantly Higher Mortality Than Aseptic Revisions: Long-Term Single-Center Study (1254 Patients). *The Journal of Arthroplasty* 2021;36:2131–2136.
7. Webb, JE, Schleck, CD, Larson, DR, Lewallen, DG, Trousdale, RT: Mortality of Elderly Patients After Two-Stage Reimplantation for Total Joint Infection: A Case–Control Study. *The Journal of Arthroplasty* 2014;29:2206–2210.
8. Choi, H-R, Beecher, B, Bedair, H: Mortality after septic versus aseptic revision total hip arthroplasty: a matched-cohort study. *J Arthroplasty* 2013;28:56–58.
9. Lenguerrand, E, Whitehouse, MR, Beswick, AD, Kunutsor, SK, Webb, JCJ, Mehendale, S, Porter, M, Blom, AW: Mortality and re-revision following single-stage and two-stage revision surgery for the management of infected primary hip arthroplasty in England and Wales: data from the National Joint Registry. *Bone & Joint Research* 2023;12:321–330.
10. Wildeman, P, Rolfson, O, Söderquist, B, Wretenberg, P, Lindgren, V: What Are the Long-term Outcomes of Mortality, Quality of... : Clinical Orthopaedics and Related Research®. at <https://journals.lww.com/clinorthop/fulltext/2021/10000/what_are_the_long_term_outcomes_of_mortality.16.aspx>.
11. Sabah, SA, Knight, R, Alvand, A, Palmer, AJR, Middleton, R, Abram, SGF, Hopewell, S, Petrou, S, Beard, DJ, Price, AJ: Patient-Relevant Outcomes Following First Revision Total... : JBJS. at <https://journals.lww.com/jbjsjournal/fulltext/2023/10180/patient_relevant_outcomes_following_first_revision.6.aspx>.
12. Drain, NP, Bertolini, DM, Anthony, AW, Feroze, MW, Chao, R, Onyekweli, T, Longo, SE, Hersh, BL, Smith, CN, Rothenberger, SD, *et al.*: High Mortality After Total Knee Arthroplasty Periprosthetic Joint Infection is Related to Preoperative Morbidity and the Disease Process but Not Treatment. *The Journal of Arthroplasty* 2022;37:1383–1389.
13. de Araujo, LCT, Westerholt, A, Sandiford, AN, Gursche, A, Kendoff, D: Periprosthetic joint infections in patients with rheumatoid arthritis are associated with higher complication and mortality rates. *Arch Orthop Trauma Surg* 2024;144:5101–5109.
14. Yao, JJ, Hevesi, M, O’Byrne, MM, Berry, DJ, Lewallen, DG, Maradit Kremers, H: Long-Term Mortality Trends After Revision Total Knee Arthroplasty. *The Journal of Arthroplasty* 2019;34:542–548.
15. Villa, JM, Rajschmir, K, Lin, S, Higuera-Rueda, CA: What Is the True Impact of Periprosthetic Joint Infection Diagnosis on Mortality? *The Journal of Arthroplasty* 2024;39:S410–S414.
16. PERSSON, A, SKÖLDENBERG, O, MOHADDES, M, EISLER, T, GORDON, M: Increased mortality after total hip prosthetic joint infection is mainly caused by the comorbidities rather than the infection itself. *Acta Orthop* 2023;94:484–489.
17. Zmistowski, B, Karam, JA, Durinka, JB, Casper, DS, Parvizi, J: Periprosthetic joint infection increases the risk of one-year mortality. *J Bone Joint Surg Am* 2013;95:2177–2184.
18. Thompson, O, W-Dahl, A, Stefánsdóttir, A: Increased short- and long-term mortality amongst patients with early periprosthetic knee joint infection. *BMC Musculoskelet Disord* 2022;23:1–7.
19. Mundi, R, Pincus, D, Schemitsch, E, Ekhtiari, S, Paterson, JM, Chaudhry, H, Leis, JA, Redelmeier, DA, Ravi, B: Association Between Periprosthetic Joint Infection and... : JBJS. at <https://journals.lww.com/jbjsjournal/fulltext/2024/09040/association_between_periprosthetic_joint_infection.3.aspx>.
20. Gundtoft, PH, Pedersen, AB, Varnum, C, Overgaard, S: Increased Mortality After Prosthetic Joint Infection in Primary THA. *Clin Orthop Relat Res* 2017;475:2623–2631.
21. Yao, JJ, Maradit Kremers, H, Abdel, MP, Larson, DR, Ransom, JE, Berry, DJ, Lewallen, DG: Long-term Mortality After Revision THA. *Clin Orthop Relat Res* 2018;476:420–426.
22. Shahi, A, Tan, TL, Chen, AF, Maltenfort, MG, Parvizi, J: In-Hospital Mortality in Patients With Periprosthetic Joint Infection. *The Journal of Arthroplasty* 2017;32:948–952.e1.
23. Choi, H-R, Bedair, H: Mortality Following Revision Total Knee Arthroplasty: A Matched Cohort Study of Septic versus Aseptic Revisions. *The Journal of Arthroplasty* 2014;29:1216–1218.

24. Laughlin, MS, Vidal, EA, Drtil, AA, Goytia, RN, Mathews, V, Patel, AR: Mortality After Revision Total Hip Arthroplasty. *J Arthroplasty* 2021;36:2353–2358.
25. Ng, MK, Kobryn, A, Emara, AK, Krebs, VE, Mont, MA, Piuizzi, NS: Decreasing trend of inpatient mortality rates of aseptic versus septic revision total hip arthroplasty: an analysis of 681,034 cases. *Hip Int* 2023;33:1063–1071.
26. Rullán, PJ, Orr, MN, Emara, AK, Klika, AK, Molloy, RM, Piuizzi, NS: Understanding the 30-day mortality burden after revision total hip arthroplasty. *Hip Int* 2023;33:727–735.
27. Fischbacher, A, Borens, O: Prosthetic-joint Infections: Mortality Over The Last 10 Years. *J Bone Jt Infect* 2019;4:198–202.
28. Austin, DC, Townsley, SH, Rogers, TH, Barlow, JD, Morrey, ME, Sperling, JW, Sanchez-Sotelo, J: Shoulder Periprosthetic Joint Infection and All-Cause Mortality: A Worrisome Association. *JB JS Open Access* 2022;7:e21.00118.
29. Rondon, AJ, Paziuk, T, Gutman, MJ, Williams, GR, Namdari, S: Spacers for life: high mortality rate associated with definitive treatment of shoulder periprosthetic infection with permanent antibiotic spacer. *Journal of Shoulder and Elbow Surgery* 2021;30:e732–e740.
30. Chen, RE, Vaughan, AK, Cox, RM, Alfonsi, S, Belden, KA, Namdari, S: Shoulder periprosthetic joint infection is associated with increased mortality. *Journal of Shoulder and Elbow Surgery* 2023;32:S1–S7.
31. Pollmann, CT, Dahl, FA, Røtterud, JHM, Gjertsen, J-E, Årøen, A: Surgical site infection after hip fracture – mortality and risk factors: an observational cohort study of 1,709 patients. *Acta Orthopaedica* 2020;91:347–352.
32. Duckworth, AD, Phillips, S-A, Stone, O, Moran, M, Breusch, SJ, Biant, LC: Deep infection after hip fracture surgery: Predictors of early mortality. *Injury* 2012;43:1182–1186.
33. Casper, DS, Zmistowski, B, Hollern, DA, Hilibrand, AS, Vaccaro, AR, Schroeder, GD, Kepler, CK: The Effect of Postoperative Spinal Infections on Patient Mortality. *Spine (Phila Pa 1976)* 2018;43:223–227.

Figures

Category		Minimum Follow-up					
		All Follow-up	60 days	1 year	5 year	10 year	20 year
Infected	Total	148,875	18,670	13,733	7,610	2,522	894
	Deceased at follow-up	6,983	4,633	4,543	2,413	1,113	724
	Mortality rate	4.7%	24.8%	33.1%	31.7%	44.1%	81.0%
Not Infected	Total	886,022	136,880	117,192	97,262	50,537	3,637
	Deceased at follow-up	31,215	26,480	26,395	20,570	16,032	2,728
	Mortality rate	3.5%	19.3%	22.5%	21.1%	31.7%	75.0%
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002

Table 1. Mortality rate for patients suffering from orthopedic-related infection versus those without.