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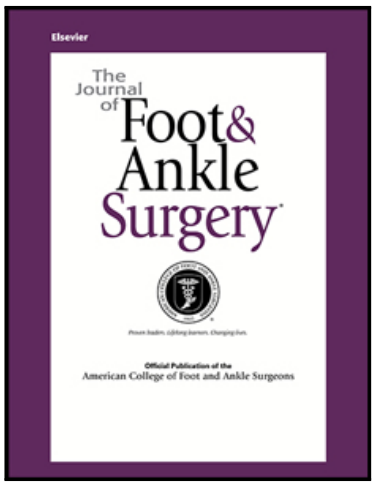

Time to Revision After Periprosthetic Joint Infection in Total Ankle Arthroplasty: A Systematic Review

Samantha A. Miner DPM, AACFAS ,
John A. Martucci DPM, AACFAS ,
Stephen A. Brigido DPM, FACFAS ,
Lawrence DiDomenico DPM FACFAS

PII: S1067-2516(22)00265-4
DOI: https://doi.org/10.1053/j.jfas.2022.09.001
Reference: YJFAS 53845

To appear in: *The Journal of Foot and Ankle Surgery*

Please cite this article as: Samantha A. Miner DPM, AACFAS , John A. Martucci DPM, AACFAS , Stephen A. Brigido DPM, FACFAS , Lawrence DiDomenico DPM FACFAS , Time to Revision After Periprosthetic Joint Infection in Total Ankle Arthroplasty: A Systematic Review, *The Journal of Foot and Ankle Surgery* (2022), doi: https://doi.org/10.1053/j.jfas.2022.09.001

Title
Time to Revision After Periprosthetic Joint Infection in Total Ankle Arthroplasty: A Systematic Review

Authors
Samantha A. Miner, DPM, AACFAS[1,*], John A. Martucci, DPM, AACFAS[2], Stephen A. Brigido, DPM, FACFAS[3], Lawrence DiDomenico, DPM FACFAS[4]

1 - Fellow, Reconstructive Foot & Ankle Surgery Fellowship, Coordinated Health-Lehigh Valley Health Network, Bethlehem, PA, USA
2 - Fellow, Reconstructive Rearfoot and Ankle Surgical Fellowship, NOMS Ankle & Foot Care Centers, Youngstown, OH, USA
3 - Director, Reconstructive Foot & Ankle Surgery Fellowship, Coordinated Health-Lehigh Valley Health Network, Bethlehem, PA, USA
4 - Director, Reconstructive Rearfoot and Ankle Surgical Fellowship, NOMS Ankle & Foot Care Centers, Youngstown, OH, USA
* Primary and Corresponding author. 240-344-5956, dr.sam.miner@gmail.com, 2775 Schoenersville Road, Bethlehem, PA 18017

Financial Disclosure: The authors received no financial support for this research.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Informed Consent: Institutional Review Board approval was not obtained for this study. This was a systematic review, and no patient information was collected. As a result, no informed consent was necessary to conduct this study.

Abstract

While not a common complication after total ankle arthroplasty (TAA), periprosthetic joint infection (PJI) presents a significant risk of implant failure. The primary aim of this systematic review was to evaluate time to revision after PJI in patients who had undergone TAA. An extensive search strategy via electronic databases initially captured 11,608 citations that were evaluated for relevance. Ultimately, 12 unique articles studying 3,040 implants met inclusion criteria. The time to revision surgery due to PJI was recorded for each study and a weighted average obtained. The prevalence of PJI

was 1.12% (n=34). We found that the average time to revision due to PJI was 30.7 months, or approximately 2.6 years after the index TAA procedure. By literature definitions, the majority of cases (91.2%, n=31) were beyond the “acute” PJI phase. The population was divided into two groups for further analysis of chronic infections. PJIs before the median were classified as “early” and those after as “late” chronic. The majority of cases (61.8%) were late chronic with an average time to revision of 44.3 months. A smaller number were early chronic (29.4%) with revision within 10.8 months. After summarizing the rates of infection and times to revision reported in the literature, we suggest modifying the current PJI classification to include early chronic and late chronic subgroups so that the total ankle surgeon is better prepared to prudently diagnose and treat PJIs.

Level of Evidence: Level IV

Key words: Total ankle arthroplasty, total ankle replacement, periprosthetic joint infection, deep infection, revision

Introduction

Utilization of total ankle arthroplasty (TAA) for the treatment of end-stage ankle arthritis continues to increase over time. Therefore, surgeons should be prepared to manage associated postoperative complications. PJI, periprosthetic joint infection or deep infection, presents a significant risk to implant failure and patient morbidity after TAA.

Incidence of PJI after TAA ranges from less than 1% to 14.7% (1-3). While not common, it is considered a high-grade complication (4).

Risk factors for PJI after TAA include history of prior surgery at the infection site, wound healing problems, diabetes, peripheral vascular disease, longer procedure duration, increased body mass index, tobacco use, and lower preoperative functional scores (5-8). Traditionally, PJIs are classified as acute, chronic, or remote hematogenous. The definition of acute PJI varies in the literature, but is typically described as occurring within the first 90 days, or 3 months, after implantation (6, 9-10). This classification was first described in the total knee and hip arthroplasty literature, and has since been adopted for use in the TAA literature (11-12). The majority of deep infections after TAA are exogenous in origin, and are classified as chronic (5, 13).

Revision surgery is typically required after PJI. This may be a single or two-staged approach. For early and focal infections, debridement, antibiotics, irrigation, and retention of implant (DAIR) may be possible. A surgeon may also opt for a polyethylene liner exchange. Chronic PJIs may be best treated with removal of the implant, insertion of an antibiotic spacer, and eventual revision of TAA or conversion to ankle fusion. The treatment is often patient-specific and surgeon-dependent. Currently, there is no consensus regarding standard of care for treatment of PJI after TAA. (9, 14-16)

The purpose of this systematic review was to evaluate time to revision after PJI in patients who had previously undergone TAA. To our knowledge, this is the first study

investigating the temporal relationship between PJI and TAA revision. By reviewing the rates of infection and times to revision reported in the literature, the total ankle surgeon can be more prepared to recognize and treat potential PJIs in an effort to reduce patient morbidity and improve implant survivorship.

Materials and Methods

Eligibility Criteria

This systematic review was designed in accordance with PRISMA 2020 guidelines (17). Eligibility criteria were established prior to implementation. Level I, II, III, and IV studies written in the English language and published in 2010 or later were eligible for inclusion in our review. Studies were also required to report prevalence of deep infection or PJI, as well as time to infection or time to revision due to infection. Review articles, unpublished manuscripts, studies with less than one year of postoperative follow up, and studies of implants discontinued prior to 2010 were not considered for inclusion. We also excluded studies reporting on revision TAA or patients with history of prior infection. Inclusion and exclusion criteria for article selection are listed in Table 1.

Search Strategy

An extensive search strategy was performed from inception in August 2021 to May 2022 via available electronic databases. This included PubMed (https://pubmed.ncbi.nlm.nih.gov), Google Scholar (https://scholar.google.com), Science Direct (https://www.sciencedirect.com), Cochrane Library ((https://www.cochranelibrary.com), JSTOR (https://www.jstor.org), CINAHL

(https://www.ebsco.com/products/research-databases/cinahl-complete), and MEDLINE (https://www.nlm.nih.gov/medline/index.html). Databases were searched for relevant articles. The medical subject heading (MeSH) search terms utilized included: “ankle arthritis” OR “ankle arthroplasty” OR “ankle replacement” OR “ankle prosthesis” AND “infection”.

Data Extraction

Captured articles were read and evaluated by two independent reviewers (SM, JM), who are both fellowship-trained foot and ankle surgeons. Disagreements were resolved by a third independent reviewer (SB), if needed.

All articles meeting the selection criteria had the following variables extracted: study name, primary author, year of publication, study design, type of implant (if available), number of implants, number of implants developing deep infection or PJI, and time to revision. “PJI” or “deep infection” had to be referred to specifically in the studies reviewed in order to be included. Revision surgery was defined as any unplanned procedure after index TAA due to deep infection.

Data Analysis

The primary outcome measure was time to revision after PJI. When possible, we used individual data points from each study for time to revision. However, in some studies with multiple PJIs, the average time to revision for all PJIs in their population was reported and used for analysis. With the data from all included studies, the total

prevalence of PJIs, the average time to revision, and the median time to revision were calculated.

Results

11,608 citations were initially captured from the seven available databases. Title review produced 81 articles for abstract screening. This, in turn, produced 47 articles to be read in entirety. Of these, 12 articles studying 3,040 implants met all prospective inclusion criteria for analysis (18-29). The PRISMA 2020 flow diagram is demonstrated in Figure 1.

PJI occurred in 1.12% (n=34) of cases. The studies reported on a wide variety of implants currently utilized in the United States (US) and abroad, but the most common were STAR and HINTEGRA. Regarding level of evidence, seven of the included studies were Level IV, three were Level III, and two were Level II. Further details regarding the studies included in our analysis can be found in Table 2.

The average time to revision due to PJI was 30.7 months (range, 2.0 to 97.2 months) from index TAA. The median time to revision due to PJI was 13.5 months. In our population, only three individuals (8.8%) presented with a PJI within the acute infection period, which has been defined in the literature as less than 3 months after a total joint procedure (6, 9-10). The average time to revision for the acute PJI group was 2.3 months. Further, none of our captured PJIs were defined as remote hematogenous.

The vast majority of PJIs in our population occurred greater than 3 months after index TAA (91.2%, n=31), and were therefore defined as chronic. The average time to revision for this population was 33.5 months (range, 6.0 to 97.2 months). Given the uneven distribution of time to revision within our chronic infection population as demonstrated in Table 2, we opted to perform a sub-analysis in which we formed two groups; early and late time to revision after PJI. Early chronic PJI was defined as less than or equal to our population's median, 13.5 months. Late chronic PJI was defined as greater than 13.5 months. An average of time to revision after early and late chronic PJI was obtained, respectively.

Those defined as early chronic PJIs went on to revision within 10.8 months (range, 6.0 to 13.2 months) of initial implantation. Those defined as late PJIs went on to revision within 44.3 months (range, 31.2 to 97.2) of index TAA. Of all 34 PJIs, 29.4% (n=10) were classified as early chronic, and 61.8% (n=21) were classified as late chronic. Table 3 demonstrates the time to revision and number of PJIs in each subgroup.

Discussion

The prevalence of PJI after TAA occurred in just over 1% of implants included in our study, which is consistent with those reported in prior studies (30-31). The average time to revision after PJI was just over 2.5 years after TAA implantation. While there are other potentially catastrophic postoperative complications of TAA, we chose to focus on PJI for several reasons. It is a high-grade complication of TAA per the Glazebrook classification (4). If a PJI is present based on clinical and diagnostic criteria, revision

surgery is required (4, 32). While an initial PJI alone is devastating, recurrent infection after inadequate treatment can lead to amputation, and therefore can greatly impact patient morbidity (33). Further, there is limited data on this topic due to the low incidence rates reported in the TAA literature. To our knowledge, we are the first systematic review to focus on time to revision in TAA patients after deep infection.

PJIs have traditionally been classified similarly throughout the total joint literature, and are primarily based on outcomes from hip and knee total joint replacements. The source of PJI is either exogenous or hematogenous. Exogenous PJIs are further classified into acute and chronic. The definition of acute PJI is where the literature diverges. The Musculoskeletal Infection Society (MSIS) defines acute PJI as occurring within 90 days of implantation, while the Infectious Disease Society of America (IDSA) defines an acute PJI as presence of symptoms for 3 weeks duration, or joint age less than 4 weeks (14, 34). In 2018, the International Consensus Group on Periprosthetic Joint Infections utilized the MSIS definition of acute and chronic PJI to develop their diagnostic criteria (12). While there is no consensus regarding PJI definition specific to TAA, the majority of the TAA literature also uses the MSIS definition for classifying PJI (6, 9-10). Similarly, we too chose to utilize the MSIS definitions of acute and chronic PJI in this review.

Acute infections after TAA are better understood and more easily recognized, as they are associated with early postoperative concerns like wound healing delay or incision dehiscence. As detailed in Table 4, there is often also associated cellulitis, drainage, or presence of a sinus tract (14). Systemic signs of infection are also common with acute

PJIs (35). The timeline for when an acute infection would present itself can make more sense for not only the surgeon, but also the patient experiencing the setback in their recovery. However, acute PJIs after TAA tend to be less common than chronic, with incidences ranging from 21-38% in the TAA literature (5-6, 13). We found that this was indeed the case in our study, with just three PJIs (8.8%) occurring within the acute period (≤ 3 months).

The remaining 91.2% of PJIs captured in our review were therefore deemed chronic PJIs based on the MSIS classification. Chronic infections occur greater than 3 months after implantation and present with a more vague set of symptoms (6, 9-10, 35). There may be a history of wound healing delay or superficial infection early after implantation, but the primary symptom is ongoing pain and the absence of other reasons for a painful implant. This can often be difficult to distinguish clinically from aseptic loosening, as there are often signs of prosthetic loosening seen on radiographs (35). The time range for the chronic cases identified in this study was 6 months to over 8 years from implantation. Given this variability, we did not find the current PJI classification useful in describing our population. Additionally, the presentation and timing of a chronic infection may not be as well understood by the surgeon, or expected by the patient.

We therefore propose classifying time to revision after PJI to include “early” or “late” chronic. We chose the median of 13.5 months as a division between our two populations of chronic infections. Using our modified classification, early chronic PJIs were revised within 11 months, while late chronic PJIs were revised more than 3.5

years after index TAA. Approximately one-third (32%) of the chronic PJIs were in the early group, while the remaining two-thirds (68%) were in the late group (Table 3). These results support encouraging yearly follow up with TAA patients.

Like all systematic reviews, this study had several limitations. Our initial search yielded over 11,000 results, yet our strict inclusion criteria provided only 12 studies for review of just 34 PJIs. We excluded studies that did not report deep infection or had zero infections, which could have created a selection bias. As a result, our reported prevalence of PJI could be higher than the actual prevalence. A variety of implants were utilized in our included studies, many of which are not approved for use in the US. Further, the Mobility Total Ankle System was utilized in two of our included studies. While this prosthesis was extremely popular, and one of the most used implants in Europe and elsewhere from 2005 to 2015, it was discontinued in 2016 (36). Unfortunately, none of the fourth-generation implants that are currently being heavily used in the US were included for analysis given lack of long-term studies reporting PJIs.

An inherent limitation of our systematic review is the quality of the studies available. We were reliant on details provided by the included studies, which were largely Level IV retrospective case series. While specific analyses were not performed, we realize that there is inherent heterogeneity and bias between the individual included studies which impacts our pooled averages. As a result, this limits the validity of our findings to some degree. While time to PJI and time to revision are associated, these were not equivalent in all cases.

The definition of revision was not clearly reported in all studies, and there was significant variability in the protocols used for revision surgery after PJI. Surgical revisions included incision and drainage, single-stage polyethylene liner exchange with retention of implant, and two-stage prosthesis explantation with conversion to fusion or revision arthroplasty. Of the outcomes reported, only one PJI ultimately resulted in a below-knee amputation.

We observed two distinct groups with regard to chronic infections. However, we are unable to determine if there is any clinical or prognostic significance to this observation, and it is therefore a limitation of this study. Additional studies are needed to identify differences in presentation and diagnostic criteria between the early and late chronic groups. There is currently no standard of care for treatment of PJI after TAA (10). Further differentiation of these proposed time periods for onset of PJI may inform treatment algorithms. For now, the approach to revision after PJI remains primarily surgeon-dependent and patient-specific.

While the prevalence of PJI remains low, it is potentially one of the most devastating complications of TAA. In this first systematic review of its kind, we found that revision due to PJI did not frequently occur within the acute period after TAA. Given our findings, we propose continuing to classify PJIs as either acute or chronic, with further division into early (≤13.5 months postoperatively) or late chronic (>13.5 months postoperatively). Over 60% of reported PJIs were late chronic, therefore the total ankle surgeon must

remain vigilant for complications beyond the first year after TAA implantation. While future studies are needed to better characterize PJIs after TAA, it is our hope that these findings assist the total ankle surgeon in understanding these difficult cases, and managing patient expectations before and long after implantation.

Acknowledgements

None.

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Tables

Table 1. Inclusion and exclusion criteria utilized for article attrition.

Inclusion Criteria	Exclusion Criteria
Level I-IV studies published in 2010 or later	Review articles
Studies written in the English language	Studies with less than 1 year follow up
Study reports “Deep Infection” or “Periprosthetic Joint Infection”	Studies on implants discontinued prior to 2010
Study reports “Time to Infection” and/or “Time to Revision Due to Infection”	Studies reporting on revision surgery or patients with history of prior ankle infection

Table 2. Summary of included studies with number of PJIs and the average time to revision by study.

	Study	Study Design	Implant Used	Implants (n=3040)	PJIs (n=34)	Time to Revision (months)
Acute	*Kerkhoff et al, 2015*	Level IV	Mobility	67	1	2.0
	Tan et al, 2016	Level IV	Zimmer	20	1	2.0
	Halai et al, 2020	Level III	HINTEGRA, Mobility, STAR	54	1	3.0
Early Chronic	*Bai et al, 2010*	Level III	HINTEGRA	67	1	6.0
	Rodrigues- Pinto et al, 2013	Level II	Salto Talaris	119	2	9.5
	Usuelli et al, 2017	Level III	HINTEGRA, Zimmer	150	4	10.5
	Mann et al, 2011	Level IV	STAR	84	3	13.2
Late Chronic	*Koo et al, 2018*	Level II	Salto Talaris	46	1	31.2
	Najefi et al, 2019	Level IV	BOX	34	2	32.0
	Barg et al, 2013	Level IV	HINTEGRA	722	3	43.2
	Lachman et al, 2018	Level IV	INBONE, STAR, Salto Talaris	1600	14	43.4
	Brunner et al, 2013	Level IV	STAR	77	1	97.2

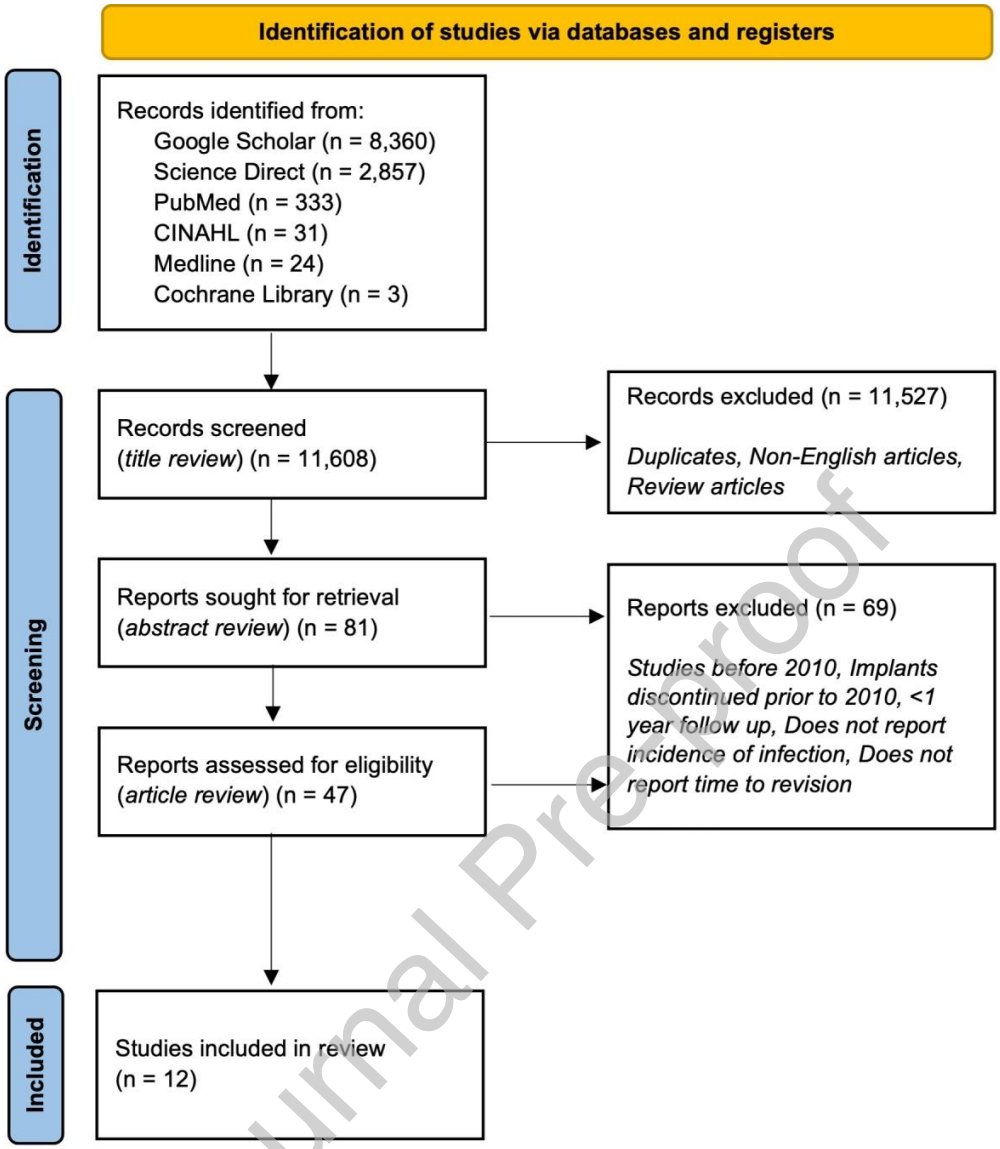
Table 3. Average time to revision sub-analysis based on PJI classification.

Classification		Time to revision (months)[a]	PJIs[b]
Acute		2.3	3 (8.8%)
Chronic		33.5	31 (91.2%)
	Early	10.8	10 (32.3%)
	Late	44.3	21 (67.7%)
Total		30.7	34 (100%)

[a]Values in average
[b]Values in no. (%)

Table 4. Modified classification system for PJI after TAA with early and late chronic subgroups.

Source	Classification	Time from TAA implantation	Presentation
Exogenous	Acute	≤3 months	Erythema, cellulitis, edema, pain, drainage, and delayed wound healing; may have systemic signs of infection
	Chronic		
	Early	>3 months, ≤13.5 months	Symptoms more vague – chronic pain, may have history of wound healing delay or superficial infection, no systemic signs, absence of obvious mechanical reason for painful prosthesis
	Late	>13.5 months	
Hematogenous		Anytime	Sudden onset of pain, recent infection elsewhere in the body



Figures

Figure 1. PRISMA flow diagram for systematic review search and study inclusion.