European Review for Medical and Pharmacological Sciences 2019; 23(2 Suppl.): 159-172

Trends in surgical management of the infected total ankle arthroplasty

A. MAZZOTTI, G. GERACI, A. PANCIERA, F. PERNA, N. STEFANINI, F. PILLA, A. RUFFILLI, C. FALDINI

1st Orthopaedic and Traumatologic Clinic, IRCSS Istituto Ortopedico Rizzoli, Bologna, Italy

Abstract. – OBJECTIVE: We performed a systematic review of surgical treatment of the infected total ankle arthroplasty. The purpose of this investigation was to describe the current trends and to perform a critical analysis of the evidence reported in the existing literature.

MATERIALS AND METHODS: A comprehensive search for all relevant articles published in English was conducted. Scientific databases were accessed to identify papers dealing with the management of the infected total ankle arthroplasty. We identified and collected every patient that underwent a surgical management of infected ankle arthroplasty. Data extracted were summarized and reported. A descriptive analysis was performed; when possible, a statistical analysis was accomplished.

RESULTS: Thirty-two papers (152 infected ankle arthroplasty) published in the last 20 years were identified. Twenty-seven patients (17.76%) were treated with irrigation and debridement, revision total ankle arthroplasty was performed in 72 cases (47.37%), arthrodesis was performed as a primary treatment in 30 patients (19.74%), 12 patients (7.89%) underwent a spacer arthroplasty while amputation was performed as a primary treatment in 9 patients (5.92%).

CONCLUSIONS: Our study reveals the improvement of the surgical management of the infected total ankle arthroplasty through the last 20 years. Irrigation and debridement and two-stage revision represent the most viable treatment in acute postoperative and late chronic infections respectively. We noted a trend towards maintaining articularity through a two-stage revision. The quality of evidence is weak with biases both in reporting and selection process. High quality randomized controlled trials are required to compare different treatments in order to introduce an evidence-based treatment protocol.

Key Words

Infection, Total ankle arthroplasty, Surgical management, Infected total ankle arthroplasty, PJI surgical management, Ankle replacement, Revision surgery.

Introduction

Approximately 1% of the adult population suffers from advanced painful ankle arthropathy[1]. Degenerative changes of the ankle are usually posttraumatic; secondary osteoarthritic forms may be caused by inflammatory diseases, haemophilia, hemochromatosis, gout, avascular necrosis, and post-infectious states. Arthrodesis has traditionally been the gold standard treatment for end-stage ankle osteoarthritis (OA). In the last 20 years, total ankle arthroplasty (TAA) has raised as a viable and effective treatment thanks to the advances in design, technology, and technique.

The increase in the number of primary procedures is unavoidably associated with the rise of complications[2].

Ankle-deeep periprosthetic joint infection (PJI) represents a high-grade complication, often requiring both medical and surgical treatment[3]. The frequency of ankle-deeep PJI reported by the literature ranges from 0% to 13%[4,5].

Different risk factors have been analyzed in literature: low BMI, inflammatory arthritis, peripheral vascular disease, and diabetes demonstrate to be independent risk factors[6]. Also, prior ankle surgery and wound healing problem more than 14 days postoperatively were assessed as relevant risk factor[7].

Deep PJI is classified in early postoperative, late and hematogenous. Usually, the onset within 4 weeks following surgery is consistent with a planktonic form of the bacterial burden. On the other hand, a late onset of the infection, 6 or more weeks postoperatively, is usually associated with the development of a bacterial biofilm. This mode of growth renders the infection both difficult to detect and diagnose using standard culture methods and especially difficult to treat, often requiring a more aggressive surgical treatment[8].

Corresponding Author: Giuseppe Geraci, MD; e-mail: giuseppe.geraci@ior.it

Surgical treatments goals are represented by infection eradication, pain relief, and ankle function preservation[9]. Several treatment protocols have been proposed, developed from PJI algorithm treatment in others joints[10], but no treatment algorithm for infected TAA has yet been validated in the current literature.

This review article analyses the current literature in order to summarize all the relevant available data regarding the surgical strategies in the treatment of the ankle-deeep PJI. The objective of the study is to evaluate the indications and results of the different surgical strategies.

Materials and Methods

Standard systematic review methods were used. The literature search was performed by two of the authors (GG and AM), independently of each other. The following medical databases were searched, from 1997 until December 2017: Medline, Cochrane, ProQuest, and PubMed. The search terms used were the following: "ankle replacement," "ankle arthroplasty," and "ankle prosthesis" in combination with "infection", "infected ", "septic".

Only articles written in the English language were included.

The literature references of identified papers were also searched in order to found further relevant articles.

All journals were considered. The research included: case reports, prospective and retrospective case series, cohort and case-control studies in order to obtain as many cases as possible.

We used the medical PRISMA flowchart to summarize the selection procedure of the reviewed papers.

Article titles and abstracts were reviewed and the articles of interested were selected for the full text. Articles that were unrelated to the topic of the study were excluded.

Exclusion criteria were: language different from English, expert opinion, reviews, paper not reporting any new case, not clear information about surgical treatments and outcomes. We also excluded all the papers reporting superficial infection and wound problem after ankle replacement without evidence of deep infection.

Our purpose was to identify and collect every single patient reported in the literature that underwent a surgical management of the ankle-deeep PJI.

The two reviewers (AM and GG) evaluated the full text of the selected articles to determine whether it was eligible for inclusion and collected data of interest. In case of doubt regarding the inclusion of an article, the senior author made the final decision. We ensured that every patient appeared only once.

Two reviewers assessed each paper for level of evidence and quality using the CMS (Coleman modified score) (Table II).

The data extracted from each study included: prosthesis infection rate in the series, onset of the infection (early postoperative, late or remote), acute or chronic infection, patient demographics (age of index surgery, gender, diagnosis for ankle replacement), information about the implant (primary or revision, model and manufacturing company), isolated microorganism, months to presentation of clinical relevant infection, first-line treatment, possible primary healing, re-infection rate, further treatment due to infection persistence, further treatments in case of problem different from infection, length of follow up, outcome, recommendations from the authors. When necessary relevant data were retrieved directly from the Authors of the study.

Given the poor quality of the studies identified and the lack of standardized methodology, we were forced to make some assumptions:

- We assumed that the treatment described is intended to be definitive, if no further treatments (following persistent infection or re-infection) are reported in the text or in the summarizing tables;
- We assumed that reinfection had not occurred during the follow-up period if not specified;
- When follow up for the single patients was not specified, we reported the mean follow-up of the series.
- When different conditions were pooled together with infected TAA, in the absence of detailed data regarding each patient, relevant data were reported as mean or percentage weighed on the number of the infected TAA.
- In the statistical analysis of the trend in surgical practices of the last 20 years, we performed the analysis in relation to the year of publication to simplify the process.

If any clinical outcome was reported, we presented it in the descriptive analysis.

Failure was intended in the inability both to eradicate infection and to restore ankle functionality.

In order to highlight for the changes in medical and surgical practices that occurred during the last 20 years, we performed a subset analysis in which we stratified patients according to 7 different time periods (1997 to 1999, 2000 to2002, 2003 to 2005, 2006 to 2008, 2009 to 2011, 2012 to 2014, 2015 to 2017).

Statistical Analysis

Data retrieved from the cases reported were described with use of descriptive statistics. Due to the little number of cases and to the weak level of evidence statistical analyses was performed only where appropriate.

Continuous variables were reported as mean (± standard deviation) and range. Categorical variables were summarized as frequencies and percentages.

Differences were assessed with the use of the Fisher's exact test, chi-squared test for categorical variables and the Student's *t*-test for continuous variables (Fisher's exact test or chi-squared test were applied where appropriate.). A two-tailed *p*-value < 0.05 was considered statiatically significant.

Data collection was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) for Windows 10. Data analysis was accomplished with SPSS Statistics version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. IBM Corp. Armonk, NY, USA).

Results

The initial search yielded 336 papers (99 from PubMed, 103 from Medline, 131 from ProQuest, 3 from Cochrane). After duplicates removal, 130 articles remained.

The titles and abstracts of 130 studies were screened, and 75 papers were excluded for not being relevant to the topic, leaving 55 that were studied in detail. Of these, 23 met the exclusion criteria, leaving 32 studies with 152 infected TAA met all eligibility criteria for inclusion into the database.

The selection procedure of the reviewed papers is summarized in Diagram I.

Information about the selected papers is provided in Table I.

Most of the selected studies were level IV (n= 24, 75%), level III studies were 3 (9.4%), and 5 (15.6%) level V were identified.

Considering the study design, 22 (68.75%) were retrospective case series, 5 (15.63%) were case report, 2 (6.25%) were case-control studies, 2 (6.25%) were prospective case series, and 1 (3.13%) was a prospective multicentre study. No randomized controlled trials were identified. The studies were published mainly in the last 5 years with only 11 papers published between 1997 and 2010.

The infection rate in the series was reported in 17 papers. Papers reporting only inflammatory joint diseases (IJD) or haemophilic patients were not considered due to the high percentage of infection. The percentage of infection ranged from 0.8% to 6.9% (mean 2.97%±1.76)

Only 7 studies gave a breakdown of information about the onset of the infection for each patient (n=94): 46 (48.9%) were acute postoperative infections, 37 (39.3%) were late chronic infections, 11 (11.7%) were remote hematogenous infections.

A total of 14 papers (comprising 104 patients) gave the distribution of gender: 55 (52.8%) were male and 49 (47.1%) female. The age at index surgery was reported in 23 papers: the mean age was 61(±9.3) years (range 34-80).

The indication for surgery was given in 21 papers (120 patients). The most common preoperative diagnosis was post-traumatic OA (45%, n= 55 patients), followed by primary OA (24.6%, n = 30), rheumatoid arthritis (17.2%, n = 21), unspecified IJD (6.5%, n = 8) and others diagnosis (6.5%, n = 8) (Haemophilia, Hemochromatosis, avascular necrosis (AVN), ankle fusion non-union, paralytic OA) (Figure 1). It was not possible to calculate RR for infection for each different diagnosis.

The type of prosthesis implanted was specified in 28 papers (106 pz); Agility implant (Agility LP Total Ankle System, Depuy, Warsaw, IN, USA) was used in 54 patients (50.94%); Salto (Salto Total Ankle prosthesis Tornier SA, Saint Ismier, France/Tornier, Inc, Bloomington, MN) in 13 patients (12.26%), Hintegra (HINTEGRA; Newdeal, Lyon, France/Integra, Plainsboro, NJ, USA) in 10 (9.43%), InBone (INBONE TAA Wright Medical Technology, Inc, Memphis, TN, USA) in 6 (5.66%), STAA (STAA ankle replacement (Waldemar Link, Hamburg, Germany) in 5 (4.72%), AES (Ankle Evolutive System1) prosthesis (Biomet, Nimes, France) in 4 (3.77%), others prosthesis were implanted in the remaining 14 patients (13.21%). These percentages are not intended to be representative because of a high risk of publication bias.

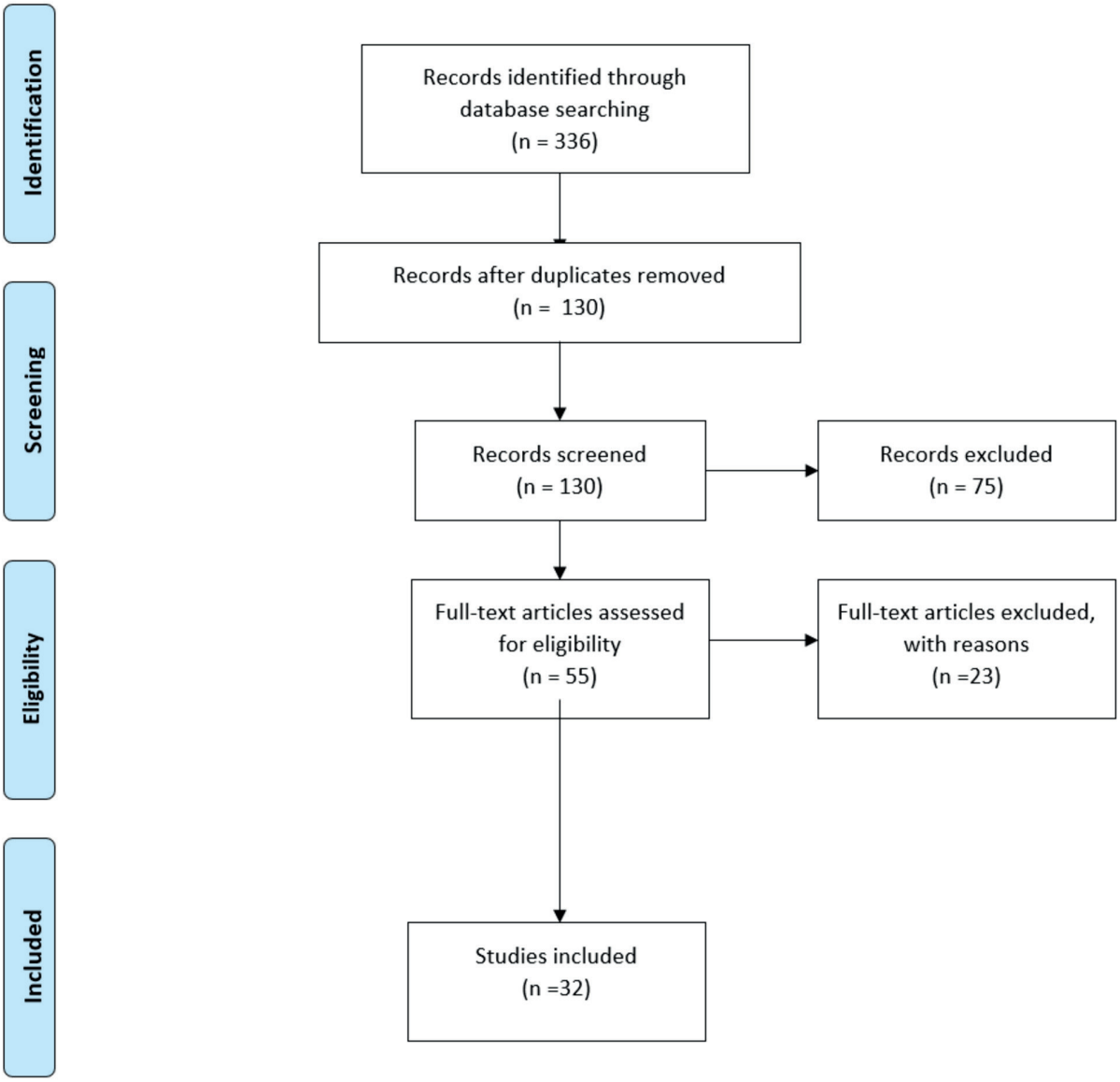

Diagram 1.

In 44 patients (31.4%) infection affected a revision implant.

Little information was given about wound healing complication immediately after surgery.

The average time between the index surgery and infection was 22.2 months (±26.5). Data were reported in 22 studies.

Details of microbiological findings were reported in 10 studies (92 patients) (Figure 2). In 35 (36.08%) patients *Staphylococcus aureus* was isolated, strictly followed by *CNS* (*Staph. Coagulase negative*) in 33 patients (34.03%). *Streptococcus and Enterococcus spp* (1 *VRE*) were found respectively in 7 (7.22%) and 6 (6.19%) patients. Other bacteria (1 *Citrobacter Koseri*, 1 *Klebsiella pneumonia*, 1 *Peptostreptococcus*, 2 *Proprionbacter*, 1 *Diphtheroids*, 1 *E. coli*, 3 *Pseudomonas*, 2 un-specified Gram-positive cocci and 1 *Corynebacterium*) were isolated in 13 patients (13.4%). Polymicrobial infection was diagnosed in 10 patients (10.8%). Gram-positive represented the majority of causative bacteria (n=88, 90.7%).

We divided the cases based on infection onset looking for a statistically significant difference in frequencies of isolated bacteria. Differences were found but still not significant ($p>0.5$).

Table I. Selected articles for review.

	Level of evidence	Study design	Title	Year	Journal	n. cases
Carlsson et al[29]	4	Retrospective case series	Arthrodesis of the ankle secondary to replacement	1998	Foot & Ankle International	4
Kofoed et al[30]	4	Retrospective case series	Ankle arthroplasty for rheumatoid arthritis and osteo-arthritis: Prospective long-term study of cemented Replacements	1998	The Journal of bone and joint surgery British volume	1
Spirt et al[31]	4	Retrospective case series	Complications and failure after total ankle arthroplasty	2004	The Journal of bone and joint surgery. American volume	5
Kotnis et al[22]	4	Retrospective case series	The management of failed ankle replacement	2006	Bone & Joint Journal	2
Doets et al[13]	4	Prospective case series	Total ankle arthroplasty in inflammatory joint disease with use of two mobile-bearing designs	2006	The Journal of bone and joint surgery. American volume	5
Lee et al32	4	Retrospective case series	Perioperative complications of HINTEGRA total ankle replacement: our initial 50 cases	2008	Foot & ankle international	1
Schutte et al[33]	4	Retrospective case series	Short-term results of our first 49 Scandinavian total ankle replacements (STAR)	2008	Foot & Ankle International	2
Van der Heide et al[34]	4	Retrospective case case	Total ankle prostheses in rheumatoid arthropathy	2009	Acta Orthopaedica	2
Young et al[35]	5	Case report	Infected total ankle arthroplasty following routine dental procedure	2009	Foot & Ankle International	1
Henricson et al[36]	4	Retrospective case case	The AES total ankle replacement: A mid-term analysis of 93 cases	2010	Foot and Ankle Surgery	4
Reuver et al[37]	4	Retrospective case case	Total ankle replacement outcome in low volume centers: short-term follow-up	2010	Foot & Ankle International	3
Stoodley et al[8]	5	Research article/case report	Characterization of a mixed MRSA/MRSE biofilm in an explanted total ankle arthroplasty	2011	FEMS Immunology & Medical Microbiology	1
Devries et al[38]	4	Retrospective case report	Revision total ankle replacement: an early look at agility to INBONE	2011	Foot & ankle specialist	2
Ferrao et al[26]	4	Retrospective case report	Cement spacer as definitive management for postoperative ankle infection.	2012	Foot & ankle international	6
McCoy et al[23]	4	Retrospective case	Circular external fixator-assisted ankle arthrodesis following failed total ankle arthroplasty	2012	Foot & ankle international	3
Rodrigues-Pinto et al[39]	4	Prospective multicentric study	Functional results and complication analysis after total ankle replacement: early to medium-term results from a Portuguese and Spanish prospective multicentric study	2013	Foot and Ankle Surgery	2
Borkosky[14]	5	Case report	Polyarticular sepsis originating from a prior total ankle replacement	2013	Clinics in Podiatric Medicine and Surgery	1

Continued

Table I (Continued). Selected articles for review.

	Level of evidence	Study design	Title	Year	Journal	n. cases
De Orio et al[40]	5	Expert opinion/ case report	Revision INBONE total ankle replacement	2013	Clinics in Podiatric Medicine and Surgery	1
Hintermann et al[19]	4	Retrospective case	HINTEGRA revision arthroplasty for failed total ankle prostheses.	2013	The Journal of bone and joint surgery. American volume	9
Sproule et al[41]	4	Retrospective case report	Clinical and radiographic outcomes of the mobility total ankle arthroplasty system: early results from a prospective multicenter study.	2013	Foot & ankle international	1
Pedersen et al[42]	3	Case-control studies	Outcome of total ankle arthroplasty in patients with rheumatoid arthritis and noninflammatory arthritis. A multicenter cohort study comparing clinical outcome and safety.	2014	The Journal of bone and joint surgery. American volume	1
Strauss et al[43]	4	Retrospective case series	Total ankle replacement in patients with haemophilia and virus infections–a safe alternative to ankle arthrodesis?	2014	Haemophilia : the official journal of the World Federation of Hemophilia	2
Brigido et al[44]	4	Prospective case series	Modular stem fixed-bearing total ankle replacement: prospective results of 23 consecutive cases with 3-year follow-up	2014	The Journal of Foot and Ankle Surgery	1
Myerson et al[12]	3	Retrospective case series	The management of infection following total ankle replacement: demographics and treatment.	2014	Foot & ankle international	19
Nodzo et al[45]	4	Retrospective case series	Short to midterm clinical and radiographic outcomes of the Salto total ankle prosthesis.	2014	Foot & Ankle International	1
Kessler et al[16]	4	Retrospective case series	The treatment and outcome of peri-prosthetic infection of the ankle: a single cohort-centre experience of 34 cases	2014	Bone Joint J	34
Roukis et al[46]	4	Retrospective case	Incidence of complications during initial experience with revision of the agility and agility lp total ankle replacement systems A Single Surgeon's Learning Curve Experience	2015	Clinics in Podiatric Medicine and Surgery	2
Patton et al[7]	3	Case-control studies	Infected total ankle arthroplasty: risk factors and treatment options	2015	Foot & ankle international	29
Mulhern et al[23]	5	Case Report	Salvage of failed total ankle replacement using a custom titanium truss	2016	The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons	1
Oliver et al[47]	4	Retrospective case series	Early patient satisfaction results on a modern generation fixed-bearing total ankle arthroplasty	2016	Foot & Ankle International	4
Tan et al[48]	4	Retrospective case series	Early Complications and Secondary Procedures in Transfibular Total Ankle Replacement	2016	Foot & ankle international	1
Wagener et al[49]	4	Retrospective Case series	Custom-made total ankle arthroplasty for the salvage of major talar bone loss	2017	Bone Joint J	1

Table II. Two reviewers (A.M. and G.G.) assessed each paper for level of evidence and quality using the CMS (Coleman modified score).

	Part A							Part B			
	1	2	3	4	5	6	7	1	2	3	Total
Carlsson et al[29]	0	0	0	0	5	3	10	4	5	5	32
Kofoed et al[30]	7	10	10	0	5	3	10	5	8	5	63
Spirt et al[31]	10	7	10	0	5	3	10	5	8	5	63
Kotnis et al[22]	0	0	7	0	5	5	0	0	5	0	22
Doets et al[13]	7	7	10	10	5	5	10	7	8	5	74
Lee et al[32]	4	4	10	0	5	3	10	5	8	5	54
Schutte et al[33]	4	4	10	0	3	3	10	2	5	5	46
Van der Heide et al[34]	7	4	0	0	5	3	10	5	5	5	44
Young et al[35]	na										
Henricson et al[36]	7	4	10	0	5	3	10	2	3	0	44
Reuver et al[37]	7	4	10	0	5	3	10	5	8	5	57
Stoodley et al[8]	na										
Devries et al[38]	0	0	10	0	5	5	10	7	8	5	50
Ferrao et al[26]	0	0	7	0	5	3	10	2	8	5	40
McCoy et al[23]	0	4	10	0	5	5	10	5	5	5	49
Rodrigues-Pinto et al[39]	10	4	10	10	5	5	10	5	8	5	72
Borkosky et al[14]	na										
De Orio et al[40]	na										
Hintermann et al[19]	10	7	10	0	5	5	10	4	8	5	64
Sproule et al[41]	7	4	10	0	0	5	10	7	8	5	56
Pedersen et al[42]	10	7	0	0	5	3	10	7	8	5	55
Strauss et al[43]	0	4	10	0	5	3	10	5	8	5	50
Brigido et al[44]	0	4	10	10	5	3	10	7	8	5	62
Myerson et al[12]	0	4	7	0	5	5	10	7	5	5	48
Nodzo et al[45]	7	4	10	0	0	5	10	5	8	5	54
Kessler et al[16]	4	4	0	0	5	5	10	4	5	5	42
Roukis et al[46]	4	4	10	0	0	5	10	5	5	5	48
Patton et al[7]	0	4	0	0	5	5	10	5	5	5	39
Mulhern et al[23]	na										
Oliver et al[47]	10	4	10	0	0	3	10	7	8	5	57
Tan et al[48]	0	0	10	0	5	5	0	7	8	5	40
Wagener et al[49]	0	7	10	0	5	5	0	7	5	5	44

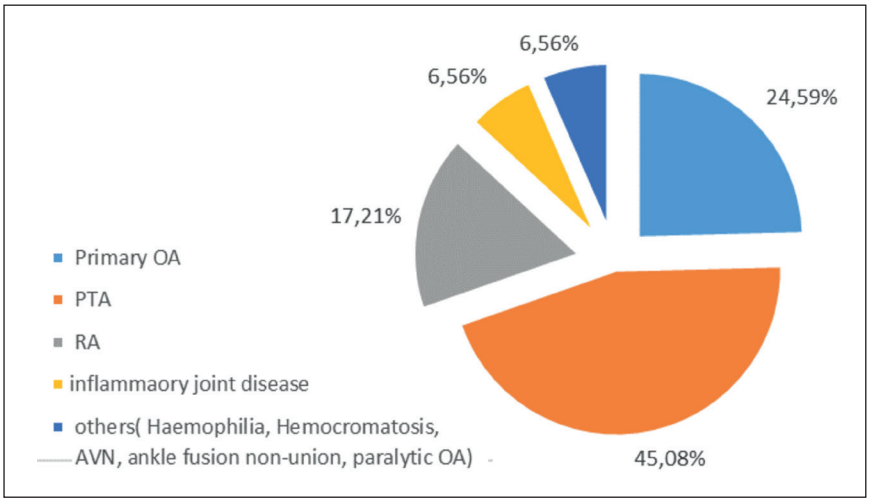

Figure 1.

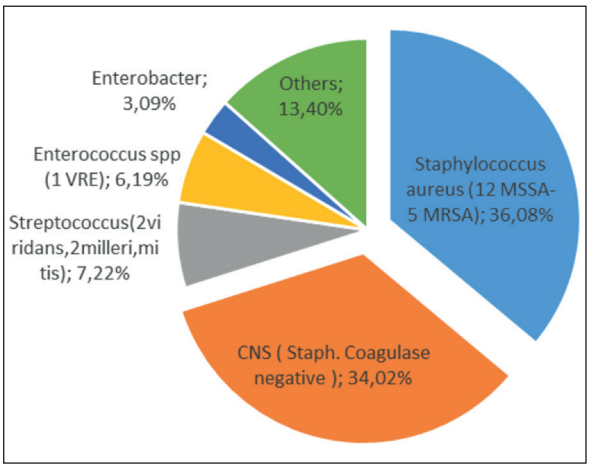

Figure 2.

Length of follow-up was specified in 25 studies, ranging from 7 to 58 months, mean 35.5 (± 13.8) months.

We identified 5 different type of surgical treatment groups (Figure 3):

1. Irrigation and debridement (I&D) were performed in 27 cases (17.76%) (11 poly exchange were mentioned). Healing from infection has occurred in 14 (51.8%) cases, while 13 (48.2%) patients needed another treatment for persistent infection or re-infection: In 4 patients I&D was repeated (2 positive outcomes, 1 persistent infection leading to below-the-knee amputation (BKA)), in 4 cases arthrodesis was performed (2 positive outcomes), in 2 cases management resulted in BKA (2 positive outcomes), 1 case was treated with revision TAA, and in 2 cases prosthesis was explanted and definitive spacer arthroplasty was made. In 9 cases (30%), a good functional outcome was specified.
2. Revision TAA was performed in 72 cases (47.37%) (32 two-stage revision, 2 one-stage revision, 15 non-specified one or two-stage procedure). In 21 patients one or both components were retained. Further surgical treatment for persistent infection, re-infection or infection from a different microorganism was necessary in 15 cases (20.8%): infection after revision surgery was treated with repeated revision in one case with positive results, in 4 patients tissue loss lead to amputation, in 7 patients arthrodesis was performed. In 3 cases we were not able to retrieve information about further specific surgical treatment. During the follow-up period, subsequent surgeries were required in four patients. Two arthrodeses and two revision TAA were performed because of the failure of the revision implant (problem different from infection). In 39 patients (54.16%) a good outcome was specified.
3. Arthrodesis was performed in 30 patients (19.74%) (6 with an external fixator, 3 using intramedullary ankle nail for tibio-talo-calcaneal (TCC) fusion, 1 using screws, 20 arthrodesis technique was not specified). Failure intended as persistent infection resulted in 1 case leading to amputation. A well-documented fusion was achieved in 24 patients, in 3 cases a revision arthrodesis was necessary, 1 nail removal due to pain, and 1 delayed fusion were described. Leg length discrepancy was

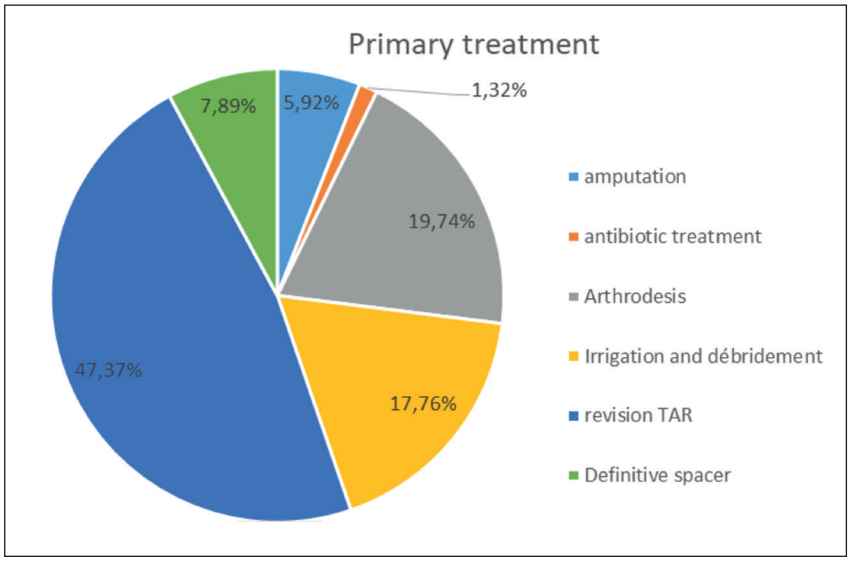

Figure 3.

resolved with the use of regenerate bone technique (ad modus Ilizarov, 173 to 216 days of treatment), using bone graft during surgery or with the use of a shoe lift. In 12 cases (40%), a good outcome was specified obtaining a stable plantigrade foot with minimal limp.

4. In 12 patients (7.89%), a spacer arthroplasty was implanted as a definitive treatment because of tissue loss, persistent infection, systemic condition that prevented further surgical treatments, or because patients refuse any further procedures. Complications reported were subluxation (n=3) and loosening (n=1).
5. Amputation was performed as a primary treatment in 9 patients (5.92%) (8 BKA, 1 above the knee amputation (AKA)) due to soft tissue loss, chronic pain, systemic conditions, ipsilateral PJI of the knee. Amputation was also performed as salvage procedures in 7 patients previously subjected to arthrodesis, I&D and revision procedures because of chronic pain, spacer complication or most commonly for persistent infection. Amputation showed a 100% rate of infection resolution.

Limb salvage was accomplished in the 89.5% of cases.

We noted that treatment was different in relation to the patient's age. A significant statistical difference in average age was noted between groups of treatment ($p<0.05$). I&D was performed in a significantly younger age-group ($p=0.02$). Patients treated with definitive spacer arthroplasty were older, but this difference was not significant ($p=0.43$).

Treatment was different in relation to the infection onset. Differences were found to be significant ($p=0.019$) between acute onset and late chronic infection: I&D was most likely performed in acute onset while a revision surgery was performed in case of chronic onset.

Significant differences ($p=0.006$) were found also comparing treatment in specific diagnosis group: IJD were more likely to be treated with arthrodesis compared to post-traumatic and primary OA that were likely to be treated through revision arthroplasty.

Revision implants were treated differently compared to primary arthroplasty: revision implants were most likely treated with another revision arthroplasty procedures (59%), while this percentage decrease in primary implants (31.4%). Differences were found to be statistically significant ($p=0.047$).

To evaluate changes in surgical practices during the last 20 years, we performed a subset analysis in which we stratified patients according to 7 different time periods (1997 to 1999, 2000 to2002, 2003 to 2005, 2006 to 2008, 2009 to 2011, 2012 to 2014, 2015 to 2017). Statistically significant differences ($p<0.05$) were delineated between treatment groups (Figure 4).

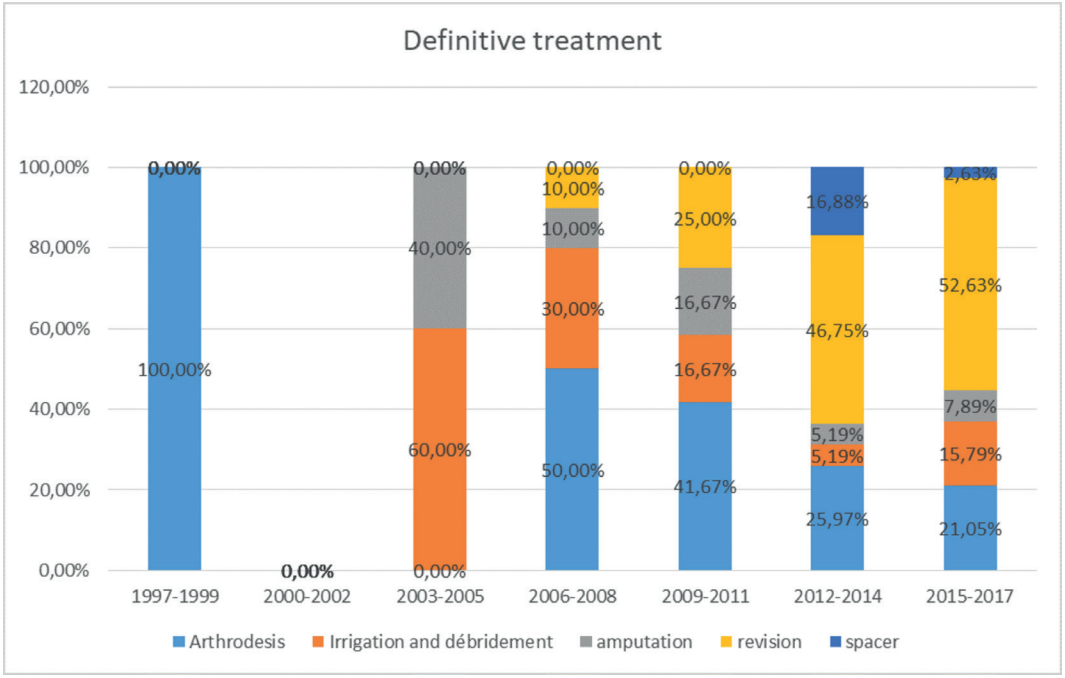

Figure 4.

Discussion

Deep-ankle PJI is one of the most devastating and expensive complications following TAA.

The percentage of infected TAA is rising with the increasing number of TAA implanted every year[2]. No clear consensus on the treatment of infected TAA exists and no protocol has been validated.

The purpose of this paper was therefore to introduce an overview of the current literature about surgical treatment of infected TAA.

The review of selected articles showed an infection rate within 0.8% to 6.9% (mean 2.97%±1.76). This finding is consistent with others metanalysis[4].

Depending on several factors, different surgical treatments have been proposed: I&D with or without polyethylene component exchange, one stage or two-stage revision arthroplasty, two stage arthrodesis conversion, prosthesis removal and definitive cement spacer implantation and amputation (BKA or AKA).

Irrigation and debridement are usually performed in early postoperative PJI, more commonly associated to polyethylene exchange. No strong evidence exists regarding the effectiveness of this procedure and especially on indication and timing (cut-off) after joint replacement[11]. Myerson reported the results of 4 cases treated with irrigation and debridement; however, a 100% re-infection rate requiring a two-stage revision or arthrodesis was described[12]. Similarly, Spirt reported 80% rate of failure after I&D in 5 cases of infected TAA. Doets et al[13] described one failure in a cohort of 5 infected TAA treated with open lavage combined with culture-specific systemic intravenous antibiotics: this failure required arthrodesis as salvage procedures.

For some authors, the results of these procedures may be influenced by the difficulty in reaching the posterior aspects of the gutters, thus not allowing a complete debridement[12].

In our analysis, I&D presented the higher percentage of persistent infection or re-infection (48.2%) compared to other treatment. In case of persistent infection, I&D can be repeated but very little evidence about its effectiveness are available in the current literature[14].

One-stage or two-stage revision arthroplasty preserves ankle motion and theoretically decrease the risk of adjacent joint arthritis[15]. This procedure is usually performed in late infections due to the formation of bacterial biofilm. Biofilm represents a well-recognized problem in infected arthroplasties both at diagnostic and treatment level: bacteria growing in a biofilm are difficult to detect using standard culture methods and especially difficult to treat, often requiring the removal of the prosthetic component. In this setting I&D cannot be adequate to eradicate the infection.

Just two cases of one stage revision were described in the selected literature[7,16], while a two-stage procedure seems to be more feasible. A two-stage revision consists in a first procedure in which the prosthetic components are removed, followed by radical debridement of both bone and soft tissue. Afterward, an antibiotic-loaded cement spacer is placed. Antibiotic mixed in Polymethylmethacrylate (PMMA) should be heat stable and available in a lyophilized form to be effective against microorganism. Some authors describe the use of gentamicin-loaded cement while others vancomycin and tobramycin per batch of cement[12,17].

The explanted prosthetic component should be sonicated to increase bacteria detection thanks to the detachment of adherent biofilm[8,17,18].

A culture-specific antibiotic therapy is also required. Unfortunately, literature does not always specify the type of antibiotic, which is administered in relation to local infectious disease protocols.

A 6 to 8 weeks of antibiotic treatment seems mandatory[7,16]. After this period, in the presence of laboratory data normalization, negative functional imaging, and negative intra-operative cultures, the revision procedure can be performed[17].

Once the infection is eradicated, the use of dedicated revision components is suggested[9]. Despite that, some authors[19] prefer to use primary prosthetic components even for revision procedures.

A variety of different outcomes are reported by the literature after two-stage revision arthroplasty. Myerson[12] performed a revision arthroplasty in 7 patients out of a cohort of 19 infected TAA. The procedure was successful only in 3 patients: in 3 cases a recurrent infection and in 1 case aseptic loosening were reported. Kessler[16] reported a 100% rate of infection-free survival in 9 patients treated with a two-stage revision procedure, while in the same series 21 PJI were treated with retention of one or both component resulting in a 66.7% rate of infection-free survival. While Hintermann[19] reported that medium term results of revision arthroplasty after failed TAA were similar to those of after primary ankle replace-

ment, in other studies patients often complain persistent chronic pain after revision surgery, requiring amputation in some cases[7].

In the descriptive analysis of selected articles, revision surgery was the most frequently performed procedure in late infections. The literature review reported 72 patients treated with revision arthroplasty (47.37%). Further surgical treatments for persistent infection, re-infection or infection from different microorganism were necessary in 15 cases (20.8%).

Despite the infection or re-infection rate following a revision procedure appears still high, we noted an increasing percentage of revision arthroplasty over time. This may be related to the advances in surgical experience and techniques in complex ankle replacement and to the introduction of revision-dedicated implants.

The two-stage arthrodesis conversion represents a viable option when a TAA revision is not achievable. This procedure still represents one of the most common salvage procedure, in particular when facing a compromised general status of the patient, a vascular or a soft-tissue impairment, uncontrolled diabetes, and bone stock loss[9,12,19,20].

The current literature describes various surgical techniques and fixation methods for TAA arthrodesis conversion: fusion can be achieved through screws, intramedullary devices for TCC fusion or Ilizarov frame[16,21,22]. In case of severe bone loss after the prosthesis removal bone allografts, autografts, or replacement materials (porous metals such as Trabecular Metal™) can be used to bridge the defect[23]. Despite its common use, arthrodesis can be associated with leg length discrepancy, malunions, nonunions, gait abnormalities, and adjacent joint OA. In a systematic review, Gross et al[24] analyzed the outcome of arthrodesis after TAA failure showing an overall failure (nonunion) rate of 10.6%[24]. Other authors reported that the outcome after salvage arthrodesis seems to be less satisfactory compared to primary arthrodesis outcomes[25]. In the papers included in this review article, arthrodesis was performed in nearly 20% of the infected TAA: a documented fusion was reported in 24 patients, while a persistent infection was described in one case (3.33%). A revision arthrodesis was necessary in 3 patients (10%). In 12 cases, a good outcome was specified.

Prosthesis removal and definitive cement spacer implantation have been described as a treatment option for the infected TAA. Only a few studies described this procedure.

Indications are usually represented by asymptomatic patients after the cement spacer insertion, medically unfit patients who do not desire any further revision surgery or local tissue impairment[26,27]. In this literature review, only 12 patients treated with a spacer arthroplasty were found. Complication reported were subluxation and loosening[12,26]. Ferrao et al[26] reported a series of six infected TAA treated with retained antibiotic cement spacer as definitive treatment. Good clinical outcomes were described after a mean follow up of 20 months. Despite some good results reported by the literature this treatment has very limited indications and can be rarely considered as a definitive solution.

Amputation should be considered in cases of persistent and active infection that is not controlled both by medical or surgical treatment, vascular compromise, severe soft-tissue impairment, extensive bone loss, medical co-morbidities or chronic pain[7]. Also, immunosuppressive therapy for rheumatoid arthritis can be considered an indication for amputation[21]. In our systematic review amputation was performed as a primary treatment in 9 patients (8 BKA, 1AKA) and as salvage procedures in 7 patients previously subjected to arthrodesis, I&D, and revision procedures.

The choice of the most viable treatment depends on surgeon experience, on patient's characteristics and on infection onset. A culture-specific antibiotic therapy is always required to obtain infection eradication.

This review has highlighted how the type of treatment is often influenced from the patient age: patients treated with I&D were significantly younger (p=0.02). On the contrary spacer retention was more likely performed in older patients.

Regarding the infection onset, differences were found to be significant between acute and late chronic infection. I&D was mostly performed in acute onset while a revision surgery was performed in case of late chronic onset.

Significant differences (p=0.006) were found also comparing treatment in specific diagnosis group: IJD were more likely to be treated with arthrodesis compared to post-traumatic and primary OA that were likely to be treated through revision arthroplasty.

Differences were noted in treatment in the setting of primary implant versus revision implant. The latter was more likely treated with another revision arthroplasty procedures (59%), while this percentage decrease in primary implants (31.4%).

Microbiological finding extracted from this literature review are consistent with hip and knee PJI[10]: Staphylococcal species represents the most common cultured microorganism. Methicillin-resistant *S. aureus* was found in 5 patients. Polymicrobial infection was diagnosed in 10 patients (10.8%).

The risk factor cannot be assessed given the low quality of data available, medical comorbidities were cited in some studies, but a statistically significant conclusion could not be inferred.

Conclusions

This paper introduced an overview of the current treatments of the infected TAA. However, it was not able to provide a direct comparison between the different surgical procedures. Some limitations must, therefore, be acknowledged: the inherently poor quality of the evidence, the inclusion of English papers only may have excluded important literature, the heterogeneity in study design, the variability in patient's selection, the absence of standardized methodology and objective reported outcomes, the different length of follow-up among the studies. Moreover, the level of surgeon experience was not mentioned in most studies, and the low number of patients identified should be considered as an indicator of publication bias. Additionally, the lack of a standardized approach regarding terminology and diagnostic criteria hinders the accurate reporting and interpretation of data.

Considering all this limitation, we were not able to develop evidence-based guidelines for the treatment of the infected total ankle arthroplasty: I&D, revision arthroplasty, arthrodesis, cement arthroplasty, and amputation seems to be viable treatment options in patients with ankle-deeep PJI and should be considered each with its own advantages and disadvantages. Surgeons must identify patients at risk and consider all options to minimize the possibility of re-infection[28].

Future studies are warranted to confirm these findings: prospective comparative trials and standardized approaches are needed in order to make a direct comparison between different treatment options.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

References

1) Glazebrook M, Daniels T, Younger A, Foote CJ, Penner M, Wing K, Lau J, Leighton R, Dunbar M. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. J Bone Joint Surg Am 2008; 90: 499-505.
2) Zaidi R, Cro S, Gurusamy K, Sivanadarajah N, Macgregor A, Henricson A, Goldberg A. The outcome of total ankle replacement: a systematic review and meta-analysis. Bone Joint J 2013; 95: 1500-1507.
3) Glazebrook MA, Arsenault K, Dunbar M. Evidence-based classification of complications in total ankle arthroplasty. Foot Ankle Int 2009; 30: 945-949.
4) Gougoulias N, Khanna A, Maffulli N. How successful are current ankle replacements?: a systematic review of the literature. Clin Orthop 2010; 468: 199-208.
5) Zhou H, Yakavonis M, Shaw JJ, Patel A, Li X. In-patient trends and complications after total ankle arthroplasty in the United States. Orthopedics 2016; 39: e74-79.
6) Althoff A, Cancienne JM, Cooper MT, Werner BC. Patient-related risk factors for periprosthetic ankle joint infection: an analysis of 6977 total ankle arthroplasties. J Foot Ankle Surg 2018; 57: 269-272.
7) Patton D, Kiewiet N, Brage M. Infected total ankle arthroplasty: risk factors and treatment options. Foot Ankle Int 2015; 36: 626-634.
8) Stoodley P, Conti SF, DeMeo PJ, Nistico L, Melton-Kreft R, Johnson S, Darabi A, Ehrlich GD, Costerton JW, Kathju S. Characterization of a mixed MRSA/MRSE biofilm in an explanted total ankle arthroplasty. FEMS Immunol Med Microbiol 2011; 62: 66-74.
9) Alrashidi Y, Galhoum AE, Wiewiorski M, Herrera-Pérez M, Hsu RY, Barg A, Valderrabano V. How to diagnose and treat infection in total ankle arthroplasty. Foot Ankle Clin 2017; 22: 405-423.
10) Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013; 56: e1-25.
11) Bibbo C. Controversies in Total Ankle Replacement. Clin Podiatr Med Surg. 2013; 30: 21-34.
12) Myerson MS, Shariff R, Zonno AJ. The management of infection following total ankle replacement: demographics and treatment. Foot Ankle Int 2014; 35: 855-862.
13) Doets HC, Brand R, Nelissen RGHH. Total ankle arthroplasty in inflammatory joint disease with use of two mobile-bearing designs. J Bone Joint Surg Am 2006; 88: 1272-1284.
14) Borkosky SL, Mankovecky M, Prissel M, Roukis TS. Polyarticular sepsis originating from a prior total ankle replacement. Clin Podiatr Med Surg 2013; 30: 97-100.
15) Stavrakis AI, SooHoo NF. Trends in complication rates following ankle arthrodesis and total ankle replacement. J Bone Joint Surg Am 2016; 98: 1453-1458.

16) Kessler B, Knupp M, Graber P, Zwicky L, Hintermann B, Zimmerli W, Sendi P. The treatment and outcome of peri-prosthetic infection of the ankle: a single cohort-centre experience of 34 cases. Bone Joint J 2014; 96: 772-777.
17) Bibbo C, Kovach SJ. Primary and revision total ankle replacement. Springer, 2016.
18) Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, Mandrekar JN, Cockerill FR, Steckelberg JM, Greenleaf JF, Patel R. Sonication of removed hip and knee prostheses for diagnosis of infection. N Engl J Med 2007; 357: 654-663.
19) Hintermann B, Zwicky L, Knupp M, Henninger HB, Barg A. HINTEGRA revision arthroplasty for failed total ankle prostheses. J Bone Joint Surg Am 2013; 95: 1166-1174.
20) Horisberger M, Henninger HB, Valderrabano V, Barg A. Bone augmentation for revision total ankle arthroplasty with large bone defects. Acta Orthop 2015; 86: 412-414.
21) Kotnis R, Pasapula C, Anwar F, Cooke PH, Sharp RJ. The management of failed ankle replacement. J Bone Joint Surg Br 2006; 88: 1039-1047.
22) McCoy TH, Goldman V, Fragomen AT, Rozbruch SR. Circular external fixator-assisted ankle arthrodesis following failed total ankle arthroplasty. Foot Ankle Int 2012; 33: 947-955.
23) Mulhern JL, Protzman NM, White AM, Brigido SA. Salvage of failed total ankle replacement using a custom titanium truss. J Foot Ankle Surg Off Publ Am Coll Foot Ankle Surg 2016; 55: 868-873.
24) Gross C, Erickson BJ, Adams SB, Parekh SG. Ankle arthrodesis after failed total ankle replacement: a systematic review of the literature. Foot Ankle Spec 2015; 8: 143-151.
25) Rahm S, Klammer G, Benninger E, Gerber F, Farshad M, Espinosa N. Inferior results of salvage arthrodesis after failed ankle replacement compared to primary arthrodesis. Foot Ankle Int 2015; 36: 349-359.
26) Ferrao P, Myerson MS, Schuberth JM, McCourt MJ. Cement spacer as definitive management for postoperative ankle infection. Foot Ankle Int 2012; 33: 173-178.
27) Lee H, Ahn J, Lee J, Lee J, Jeong J, Choi YR. Cement arthroplasty for ankle joint destruction. J Bone Joint Surg 2014; 96: 1468-1475.
28) Onesti MG, Carella S, Scuderi N. Effectiveness of antimicrobial-coated sutures for the prevention of surgical site infection: a review of the literature. Eur Rev Med Pharmacol Sci 2018; 22: 5729-5739.
29) Carlsson AS, Montgomery F, Besjakov J. Arthrodesis of the ankle secondary to replacement. Foot Ankle Int 1998; 19: 240-245.
30) Kofoed H, S. Sørensen T. Ankle arthroplasty for rheumatoid arthritis and osteoarthritis: Prospective long-term Study of Cemented Replacements. J Bone Joint Surg Br 1998; 80: 328-332.
31) Spirt AA, Assal M, Hansen ST. Complications and failure after total ankle arthroplasty. J Bone Joint Surg Am 2004; 86: 1172-1178.
32) Lee K-B, Cho S-G, Hur C-I, Yoon T-R. Perioperative complications of HINTEGRA total ankle replacement: our initial 50 cases. Foot Ankle Int 2008; 29: 978-984.
33) Schutte BG, Louwerens JWK. Short-term results of our first 49 Scandanavian total ankle replacements (STAR). Foot Ankle Int 2008; 29: 124-127.
34) van der Heide HJL, van der Linden HMJE, Huizinga TWJ, Visser LG. [Haematogenous infection of a prosthetic joint]. Ned Tijdschr Geneeskd 2013; 157: A5448.
35) Young JL, May MM, Haddad SL. Infected total ankle arthroplasty following routine dental procedure. Foot Ankle Int 2009; 30: 252-257.
36) Henricson A, Knutson K, Lindahl J, Rydholm U. The AES total ankle replacement: a mid-term analysis of 93 cases. Foot Ankle Surg Off J Eur Soc Foot Ankle Surg 2010; 16: 61-64.
37) Reuver JM, Dayerizadeh N, Burger B, Elmans L, Hoelen M, Tulp N. Total ankle replacement outcome in low volume centers: short-term followup. Foot Ankle Int 2010; 31: 1064-1068.
38) Devries JG, Berlet GC, Lee TH, Hyer CF, Deorio JK. Revision total ankle replacement: an early look at agility to INBONE. Foot Ankle Spec 2011; 4: 235-244.
39) Rodrigues-Pinto R, Muras J, Martín Oliva X, Amado P. Functional results and complication analysis after total ankle replacement: Early to medium-term results from a Portuguese and Spanish prospective multicentric study. Foot Ankle Surg 2013; 19: 222-228.
40) DeOrio JK. Revision INBONE total ankle replacement. Clin Podiatr Med Surg 2013; 30: 225-236.
41) Sproule JA, Chin T, Amin A, Daniels T, Younger AS, Boyd G, Glazebrook MA. Clinical and radiographic outcomes of the mobility total ankle arthroplasty system: early results from a prospective multicenter study. Foot Ankle Int 2013; 34: 491-497.
42) Pedersen E, Pinsker E, Younger ASE, Penner MJ, Wing KJ, Dryden PJ, Glazebrook M, Daniels TR. Outcome of total ankle arthroplasty in patients with rheumatoid arthritis and noninflammatory arthritis. A multicenter cohort study comparing clinical outcome and safety. J Bone Joint Surg Am 2014; 96: 1768-1775.
43) Strauss AC, Goldmann G, Wessling M, Gravius S, Müller MC, Wimmer MD, Wirtz DC, Oldenburg J, Pennekamp PH. Total ankle replacement in patients with haemophilia and virus infections--a safe alternative to ankle arthrodesis? Haemoph Off J World Fed Hemoph 2014; 20: 702-708.
44) Brigido SA, Galli MM, Bleazey ST, Protzman NM. Modular stem fixed-bearing total ankle replacement: prospective results of 23 consecutive cases with 3-year follow-up. J Foot Ankle Surg Off Publ Am Coll Foot Ankle Surg 2014; 53: 692-689.
45) Nodzo SR, Miladore MP, Kaplan NB, Ritter CA. Short to midterm clinical and radiographic outcomes of the Salto total ankle prosthesis. Foot Ankle Int 2014; 35: 22-29.
46) Roukis TS, Simonson DC. Incidence of complications during initial experience with revision of the agility and agility lp total ankle replacement systems: a single surgeon's learning curve experience. Clin Podiatr Med Surg 2015; 32: 569-593.

47) Oliver SM, Coetzee JC, Nilsson LJ, Samuelson KM, Stone RM, Fritz JE, Giveans MR. Early patient satisfaction results on a modern generation fixed-bearing total ankle arthroplasty. Foot Ankle Int 2016; 37: 938-943.
48) Tan EW, Maccario C, Talusan PG, Schon LC. Early complications and secondary procedures in transfibular total ankle replacement. Foot Ankle Int 2016; 37: 835-841.
49) Wagener J, Gross CE, Schweizer C, Lang TH, Hintermann B. Custom-made total ankle arthroplasty for the salvage of major talar bone loss. Bone Joint J 2017; 99: 231-236.