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Original article

The outcomes of surgical management of failed two-stage revision knee arthroplasty

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Abstract. *Background:* Joint infection following total knee arthroplasty has significant consequences on both the patient and healthcare system. Two stage revision arthroplasty is viewed as the gold standard in management. However, recurrence of infection following this procedure is a growing clinical problem for a multitude of reasons. Despite a variety of surgical options for management of failure of two-stage revision arthroplasty, the potential for complications and functional limitation remains high, and the optimal strategy is yet to be determined. *Methods:* We performed a systematic review of all papers reporting on the outcomes of the surgical management of failure of two-stage revision arthroplasty published up to and including January 2020. Data was extracted on patient demographics, study design, methodological quality, indication for surgery, surgical technique, clinical and functional outcomes, and complications. *Results:* Nine papers with a total of 273 patients were found and analysed. All surgical techniques had mixed results in term of clinical and functional outcomes, and the rate of complications was high in all studies. Knee arthrodesis had the lower risk of failure than repeat 2 stage revision. Poor patient immunological status and limb status were weakly associated with increased risk of failure. *Conclusion:* Despite failure of two-stage revision arthroplasty being a growing clinical issue, we were not able to identify any consistently superior surgical technique for the management of this scenario. Knee arthrodesis appears to provide the best results for improving quality of life and reducing infection recurrence, although the complication rate is high, and the functional outcomes appear to be worse. Further larger and prospective studies are needed to elucidate optimal surgical management in different patient subsets.

Key words: Two stage knee arthroplasty, knee arthroplasty, joint infection, recurrence

Introduction

Infection of the joint after total knee arthroplasty is a life and limb threatening complication, with the potential to cause functional and economic sequelae (1,2). Management options available include prosthesis resection, debridement, and long term antibiotic therapy, two-stage revision arthroplasty using an antibiotic-containing cement spacer remains the most commonly used option (3)a staging system was evaluated as a possible prognostic tool for patients undergoing two-stage reimplantation of infected total knee arthroplasty (TKA(4). At the first revision surgery, the original components and associated cement are removed and an antibiotic-containing spacer inserted (5).

The 10-year infection free survival rate for two stage revision is consistently reported to be around 80% (6) suggesting that while the process is successful in majority of patients, failed two stage revision presents significant challenge for arthroplasty surgeons. Furthermore, success rates appear to be decreasing with time. Reasons postulated include a rise in multi drug resistant organisms and increasing complexity of patients cohorts (7).

The outcomes of management after a failed two-stage arthroplasty are not widely reported, and published studies are limited by small sample sizes (8–10). The measure of success must be a combination of eradication of infection, pain control, utility of the joint, as well as other surrogate markers such as gainful employment and return to hobbies. Options available to the surgeon include further two-stage revision arthroplasty, knee arthrodesis, irrigation and debridement with implant retention, amputation, and long-term antibiotic suppression. The outcome of continued surgical management in these cases remains poor, with the potential for a range of new complications (11–13)a two-stage exchange arthroplasty remains the preferred surgical treatment for chronic periprosthetic joint infection (PJI. Some patients may have to undergo multiple revision surgeries, with increasingly poor outcomes and a financial burden associated with the use of surgical instruments, prostheses, prolonged hospital admissions, and medications (14).

The purpose of our review is to investigate the optimal management of an infected knee replacement following a two-stage revision arthroplasty.

Materials and Methods

Eligibility criteria

Studies were considered eligible if (1) the authors described management of failed two-stage revision knee arthroplasty (2) patient's clinical and/or functional outcomes were reported (3) complications, intra-operatively or post-operatively were reported (4) ≥5 patients were included (5) the articles were written in English, German, Spanish or Italian. All articles that did not meet the above criteria were excluded. Case reports, literature reviews, letters to editors, and cadaveric studies were therefore all excluded.

Search strategy

A medical librarian-assisted electronic systematic literature search was performed by two authors (C.M. and A.V) via a computer-based search within the PubMed, EMBASE, Cochrane, Google Scholar, and Web of Science online databases for articles published up to and including January 2020. In each database an advanced search was conducted using the following key words alone or in combinations to identify relevant papers: knee, infection, arthroplasty, prosthesis, knee replacement, prosthetic joint infection, two-stage. The reference lists within identified articles were searched to identify any further eligible papers.

Identification of eligible studies

The systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with a PRISMA checklist and algorithm. Potential studies for inclusion were screened based on title or abstract by two authors (C.M. and A.V.), and then subsequently included based on the full text. Duplicates and articles that did not meet the inclusion criteria were excluded. Any disagreements about the eligibility of articles were solved by consensus.

Initial inclusion was initially based upon the study's title and abstract, but the latter stages of the review process excluded papers based on the full-text articles. Figure 1 illustrates the systematic exclusion of papers in this review.

Quality assessment

Two investigators (A.V. and C.M.) evaluated blindly each study using the Modified Coleman Methodology Score (15). The Modified Coleman Methodology score is a quality scoring system validated in orthopaedic literature; a perfect score of 100 signifies a study that minimises the chance of bias and confounding (16) functional outcomes, and complications after open and minimally invasive surgery for Achilles tendon ruptures.

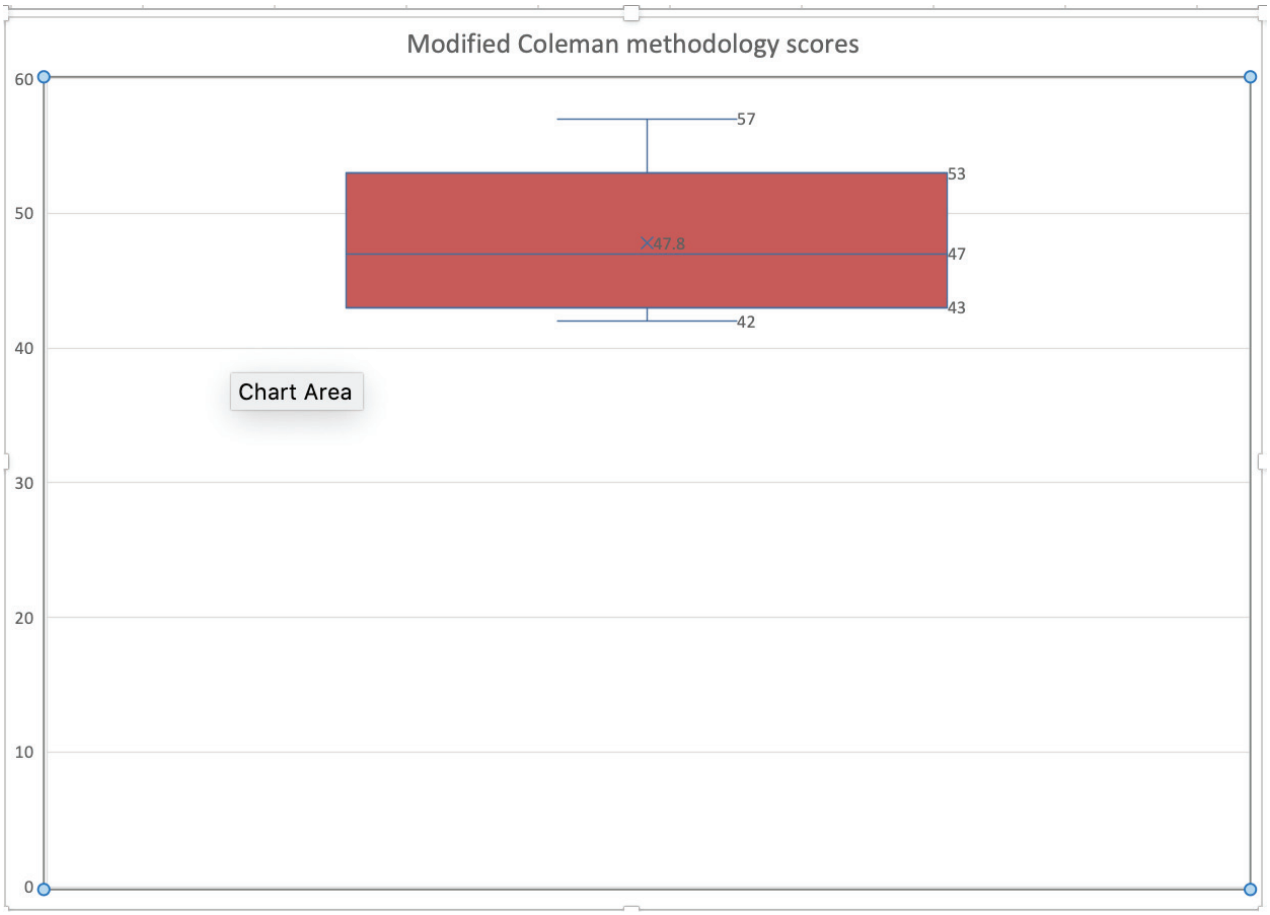

Figure 1. Coleman methodology scores

We systematically searched Medline (PubMED. Two authors scored the methodological quality of the studies twice, with a 10-day interval between assessments. If disagreements were encountered, the two investigators debated controversial scores until a consensus was reached. Papers were not excluded because of their score.

Data extraction

Two authors independently extracted and then reviewed the following data from each eligible paper: author, year published, geographical location of the study, study design or level of evidence, number of patients, mean age at surgery, comorbidities, indication for surgery, surgical technique, length of follow up, outcomes, and complications both intra-operatively and post-operatively.

Results

The literature searched identified 87 potentially relevant studies. 69 were excluded based on title and abstract as they did not meet the inclusion criteria. Of the remaining, 18 studies were selected for reading the full text, and of these 9 fulfilled the inclusion criteria and were eligible for analysis.

The median Modified Coleman methodological quality assessment score was 47 (range 42 to 57) (Figure1). Reasons for the low scores were predominantly due to low patient numbers, retrospective nature of the studies and lack of description of post-operative protocols. see figure 1. All 9 studies were retrospective studies (3,8,17–23). Of the 4 papers that reported it, the mean age was 66.6 years (8,19,20,22). The number of participants ranged from 16-58 (3,17) with

273 patients in total, and the mean follow up was 57 months/4.8 years (range 6 days to 11.5 years (3,22)). Of the 6 papers that reported it, the male:female ratio was 97:73.

Comorbidities

In several papers the patients had significant pre-existing comorbidities such as heart disease, diabetes mellitus, rheumatoid arthritis, chronic kidney disease, and cancer (3,8,22).

Kubista et al. found a positive correlation between diabetes mellitus and joint re-infection but it did not reach statistical significance (p = 0.099) (3). They also found that 86% of cases were late chronic infections (defined as infections of >4 weeks' duration) (3). In Fehring et al.'s retrospective study (18) found that all joint infections were 'late chronic'; of their 45 patients, the majority (60%) were medically compromised – type B – hosts, with 18% substantially compromised and rated 10% uncompromised; the status of the limb was compromised in the majority of their patients (69%), substantially compromised in 11%, and uncompromised in 20%. In their analysis they found that the relationship between deteriorating host status and reinfection following two stage revision does not reach statistical significance (p=0.084).

Kubista et al. found 45% of the re-infected patients to be immunocompromised, and 41% had compromise of the soft tissue around the joint (3). In contrast, the majority (61%) of the patients undergoing knee arthrodesis in the study by Robinson et al. (2018) fit into the 'mild comorbidity' group, with chronic, but stable conditions such as diabetes mellitus and hypertension (22).

Of the four papers that reported BMI, the mean was 31.4 (8,19,20,22).

Indication for surgery

Re-infection was the most common indication for surgery reported in three papers (17–19). In one paper, 71% of the patients who were receiving a 2nd two-stage arthroplasty had a prior failed attempt to suppress the infection with antibiotics (3). The failure rates of the two-stage revision arthroplasty were reported in three papers at 11.6% (19), 14.8% (17), and 15.8% (3). Signs of re-infection included joint swelling/redness, chronic pain, or radiographic markers of implant loosening (8). Kubista et al. defined prosthetic infection by the presence of ≥1 of: 2 positive pre-operative aspiration cultures, purulence around the prosthesis, histopathological evidence of periprosthetic acute inflammatory processes in tissue samples, 2 positive intraoperative cultures with identical organisms, or a cutaneous sinus tract communicating with the prosthesis (3). In Azzam et al.'s study, the authors confirmed re-infection with positive cultures in 17/19 patients, and raised ESR >30mm/hr or CRP >1mL/dL, raised joint leucocyte aspiration count, or evidence of purulence during surgery in the others (8). The group obtained tissue specimens during the first stage resection, which showed acute inflammation in 76% of cases. The average ESR and CRP of 6.4 prior to the repeat resection were 61.1mm/hr and 22.9 respectively (20,22). Seven papers isolated the organisms that led to failure of the initial two-stage arthroplasty. Azzam et al. found the causative organism to be the same as the initial infection in 16/17 patients (8). Coagulase-negative *Staphylococcus* was the most common microorganism found (18,20,21,23), followed by *Staphylococcus aureus* (3,22).

Prediction of failure after initial two-stage revision arthroplasty

The mean time between first and second two-stage arthroplasties was reported in four papers, by Ma et al. as 22 months (17), Vadiee et al. as 32 months (20), and Kubista et al. as 3.6 years (3). Ma et al. found the four factors most strongly associated with failure after an initial two-stage revision arthroplasty were BMI ≥30, operating time >4 hours, the presence of gout, and *Enterococcus* species during resection arthroplasty (17); in their study the failure rate associated with *Enterococcus* infection was 50% after the initial two-stage, and a further repeat surgery was necessary in 2 patients to control the infection.

Surgical technique

The surgical technique for the management of failure of the initial two-stage arthroplasty varied

between studies. The most frequently reported was a second two-stage arthroplasty (3,8,17,18,20,21,23); other techniques reported included knee arthrodesis (3,17,22), irrigation and debridement (I&D) (3,17,19), and above knee amputation (3,17).

Repeat two-stage arthroplasty: The technique used for the repeat two-stage arthroplasty varied between the five papers that described it (3,8,17,18,20). During the first stage, Azzam et al. used the prior incisions and a medical parapatellar arthrotomy to expose the new joint (8). All hardware and cement fragments were removed from the femoral and tibial intramedullary canals and the tissues extensively debrided (8,20). Fehring et al. inserted a static spacer in all patients between the two stages, and re-implanted the prosthesis only once the patient had completed at least a six month course of intravenous antibiotics, and biochemical and clinical markers of infection were trending towards resolution (18). Azzam et al. opted to use a static spacer with 3.6g Tobramycin and 3g Vancomycin in fifteen patients, and a dynamic spacer in four patients (8). By contrast, Kubista et al. (3) and Azzam et al. (8) put patients on intravenous antibiotics for 4-6 weeks after the resection and Ma et al. (17) for 4 weeks followed by a two week course of oral antibiotics, but also performed the reimplantation only when clinical and biochemical findings suggested resolution of infection and only after having stopped all antibiotics for 2 weeks to allow intraoperative cultures to be taken (8,17). The repeat reimplantation was done at an average of 24 weeks after the resection (8). At the repeat reimplantation, cemented stems were used in 91% of cases; the technique consisted of a rotating hinge TKA in 47%, varus-valgus constrained total knee arthroplasty in 51%, and a posterior-stabilised TKA in 2% (18). When antibiotics were used at reimplantation, the choice was 1g of vancomycin and 1.2g of gentamicin (18) or 2-4g of vancomycin and 2-4g of piperacillin/ceftazidime per 40g of bone cement (17). The average time between the resection and prosthesis reimplantation was 15 weeks (18). Of the papers that reported it, the mean ESR was 23.5mm/hr (reference range 0-22) and the mean CRP was 6mg/L (reference range 3-17.5) before the reimplantation (8,18).

Knee arthrodesis: Robinson et al. performed knee arthrodesis as a salvage procedure after failed two-stage arthroplasty with intramedullary nailing, external fixation, or tibiofemoral screw-plate fixation after there were clinical and biochemical signs of the eradication of infection (22).

Irrigation and debridement: Faschingbauer et al. performed irrigation and debridement on patients after initial failed two-stage arthroplasty using pre-existing incisions (19). They removed the articular insert following synovectomy and irrigation of the knee joint. 10L of anti-infectious irrigation was performed, and the wound was closed in layers. A repeat procedure was performed 3-6 days later if there was evidence of persistent infection intraoperatively, post-operative sepsis or a raised CRP with clinical signs suggestive of infection.

Post-operative care: Three papers described the post-operative care. After reimplantation, Ma et al. treated all patients with prophylactic intravenous antibiotics for 4 or 5 days until intraoperative cultures came back with no growth (17). In contrast, Azzam et al. gave extended intravenous antibiotics to 2 patients whose intraoperative cultures came back positive, and suppressive oral antibiotics to 9 patients for 6-60 months who were considered higher risk for re-infection because of significant comorbidities, sepsis, or delayed wound healing (8). Following irrigation and debridement, patients took antibiotics for a maximum of two weeks, with no suppressive therapy used (19).

Outcomes

The results of a repeat two-stage arthroplasty are variable. A retrospective study of 45 patients found that at the average follow up of 74 months, 23/45 (51%) had not undergone another revision surgery for infection, and of these 14/23 were on long term suppressive antibiotics (18). Of the twenty-two patients who developed infection and underwent further surgery: 5 had a another two-stage revision arthroplasty, while 17 underwent I&D, resection arthroplasty, or amputation. Of the patients who remained free from infection, functional outcomes were poor, with 15/23 70% requiring gait aids, and 9/23 39% having an extension lag of at least 10°. The host immune status was a risk factor for failure of the repeat two-stage arthroplasty ($p = 0.084$ for uncompromised vs. substantially

compromised hosts) (18). Staats et al. concluded that if patients have a failed initial two-stage arthroplasty, they are very likely to undergo multiple revision surgeries thereafter, with a 47.7% chance of a resulting failed endoprosthetic reconstruction with amputation or arthrodesis at a mean follow up of 5 years (21). However, another study reported a higher success rate of 74%, defined by absence of infection at final follow up, after a repeat two-stage arthroplasty (20). A third study found a success rate of 62% after a 2nd two-stage arthroplasty at a minimum of 12 months follow up (23). Finally, a fourth study reported a 78% success rate in eradicating infection after a repeat two-stage revision, although 9 out of 14 patients were kept on chronic suppressive antibiotic therapy (8). At an average follow up of 40 months after the repeat surgery, radiographic evaluation showed good tibiofemoral alignment in all patients.

Faschingbauer studied I&D after failure of the initial two-stage arthroplasty in 19 patients (19) showing 63.2% of patients with symptoms <3 weeks' duration being infection free after a minimum 2 year follow up. In contrast, however, Kheir et al. report a success rate of 62% after 2nd two-stage arthroplasty, compared to 43% in those who initially received an I&D (23).

Robinson et al reported the highest success rate with the use of knee arthrodesis, which achieved a limb stability with evidence of radiographic union and eradication of infection in 87% of cases (20/23 knees), with 80% of patients ambulating with minimal levels of pain (22). The average time to radiographic bony fusion was 11.3 months. The most effective type of arthrodesis was with a long IM nail, with 94% of these patients achieving clinical fusion Their mean follow-up period was relatively short at 40.4 months, with all cases being followed for minimum 12 months.

Functional outcomes

Only two studies (8,22) used functional outcomes scores to evaluate the patients following the procedures.

Of the 11 patients that participated in self-reported measures after arthrodesis, the average KSS score was 44, KSS Functional Score was 27.7, KOOS Symptom Score was 73.1, and KOOS Pain Score 85.4 (22), suggesting that while the patients were largely free from pain the procedure led to significant functional limitations. Another study which used functional scores, reporting on repeat two-stage arthroplasties, reported an average a KSS score of 73 and KSS Functional Score of 49 at the last follow up of a mean of 40 months (8). Two patients reported no pain, six reported mild pain and six reported moderate levels of pain.

Complications

Complication rates were high throughout the six studies that reported them (Table 1). Fehring et al. in their study of 45 patients undergoing a repeat two-stage arthroplasty, had 11 cases (24%) experiencing no complication or further operation for infection or intra-operative or post-operative complications and the overall reinfection rate was 49% (18). The most frequent complications seen occurred intra-operatively, including new disruption of the extensor mechanism or fracture, this was followed by post-operative complications such as aseptic loosening of the implant or knee instability. Most cases (62%) studied went on to have further revision surgery. In contrast, another study found a lower rate of complications, present in 28%, after a repeat two-stage, again including disruption of the extensor mechanism, operative fracture and MCL instability (20).

The reported complication rate was lower in those cases that underwent I&D, with 57.1% of knees being infection-free after the minimum follow-up of 2 years (19). Although the clinical outcomes after knee arthrodesis were deemed successful in the majority of cases, there were still a significant number of complications with only 35% having no negative outcomes (22). External fixation arthrodesis complications included distal pin loosening and skin impingement, while reported complications of IM nail arthrodesis included in foot drop, anterior thigh abscesses, and tibial osteomyelitis.

Discussion

We were unable to identify any consistent superiority of any different surgical technique included in this review.

Table 1. Complications of surgical management of failed two-stage revision knee arthroplasty.

Paper	Surgical technique	No of patients with complications	Type of complication	Further management
Fehring et al. 2017 (18)	Repeat two-stage arthroplasty	14 (31%)	New disruption of the extensor mechanism (3), intraoperative fracture at the time of resection/reimplantation (3), stem-condyle bolt failure in a varus-valgus constraining knee implant (3), postoperative fracture (2), aseptic loosening of the implant (2), instability (2)	62% of patients went on to have further revision surgery
Azzam et al. 2009 (8)	Repeat two-stage arthroplasty	5 (28%)	Recurrence of infection incl. VRE (4), loosening of the tibial component at 2 year follow up (1)	Suppressive antibiotics, 3rd two-stage arthroplasty (2)
Kheir et al. 2016 (23)	Repeat two-stage arthroplasty	24 (57%)	Failure to complete the 2nd two-stage arthroplasty (14), reinfection (9), death due to PJI (1)	Spacer exchange (4), amputation (5), arthrodesis (1)
Robinson et al. 2018 (22)	Knee arthrodesis	15 (65%)	Reinfection (2), non-union (1) External fixation: Distal pin loosening, pin-tract infection, skin impingement, wound dehiscence IM nailing: Painful screws, foot drop, anterior thigh abscess, tibial osteomyelitis, compartment syndrome, wound dehiscence	Chronic suppressive oral antibiotics (1), removal of screws (4), AKA (3), vacuum-assisted closures (3), three attempts at fusion (1), antibiotic bead placement (1), split thickness skin graft (1)
Vadiee et al. 2018 (20)	Repeat two-stage arthroplasty	5 (28%)	Disruption of the extensor mechanism (3), post-operative fracture (1), MCL rupture causing instability (1)	Not described
Faschingbauer et al. 2018 (19)	Irrigation and debridement	7 (37%)	Recurrent deep infection (6), death (1)	Not described

Based on the included studies, knee arthrodesis (22) appears to produce the most consistent outcomes in terms preventing recurrence of infection with a complete eradication in the 87% of cases and relieving pain in patients for whom a two-stage revision arthroplasty has failed. Although the complication rate in these patients is high at 65%, the clinical and functional outcomes compared well to repeat two-stage arthroplasty, irrigation and debridement, and above-knee amputation.

As mentioned earlier failure of initial 2 stage revision presents a significant challenge to arthroplasty surgeons as all potential options achieve inconsistent functional outcomes with high complication rates. Furthermore, there is a lack of validated predictors of failure in these cases. The reasonably high rates of failure of the initial two-stage arthroplasty – around 15% - mean that a clearer treatment algorithm would be useful (17).

The lack of clarity is due to several reasons. The rarity of such cases being chief among them which explains the low patient numbers included in each individual study.

The potential improved functional outcome a successful 2 stage revision provides needs to be balanced against the benefits of an increased risk of clearing the infection and reduced pain that knee arthrodesis appears to provide. One also needs to consider the possibility that further debridement will reduce the soft tissue envelope thereby increasing future risk of complications if the patient were to require further surgery after the 2-stage revision. This could potentially increase the risk of an above knee amputation. Patient wishes will play a role, previously more active patients may find the functional outcomes of arthrodesis unacceptable and may express a wish to attempt a further 2 stage revision. Wu et al. (24) in their review reported utilities – a patient-centred score created from self-reported measures of well-being – of 0.47 (2 stage revision), 0.74 (knee arthrodesis), and 0.42 (above knee amputation) respectively, concluding that arthrodesis was therefore the optimal method for enhancing function and reducing further risk of infection (24). However, they do postulate that lower patient expectations may have contributed to the lower well-being score.

Complications are seen in all surgical techniques and include fracture, joint instability, disruption of the extensor mechanism, and re-infection. In all studies complication rates, intra-operative and post-operative, were significantly high ranging from 28% (8) to 65% (22) of the cases. Re-infection after further surgical management appears to be related to host immune status, with a study on healthier patients reporting lower rates (18). Even in the techniques that appear to result better infection-free outcomes such as arthrodesis, the rate of complications and functional limitations remains relatively high. The host immune status, functional status and limb status may therefore play a role in counselling patients towards repeat 2 stage

revision or arthrodesis. Fehring et al. emphasised the importance of individual patient factors on predicting the success of a repeat two-stage arthroplasty (18).

A number of studies demonstrated and association between infecting organism with Vadiee et al. noted a statistically significant risk of failure of 2nd two-stage revision with multi organism infection and MRSA (p value 0.04 and 0.019 respectively) (20).

Encountering difficult to treat species in the joint culture may direct the surgeon away from carrying out a further 2 stage revision.

It is therefore necessary consider individual patient differences when weighing the risks and benefits of further operations as well as to inform the patient that management of the failed initial two-stage surgery may begin a path of multiple revisions and further problems with the limb. Taking into account the disability introduced by arthrodesis, a 2nd two-stage arthroplasty may then be the overall best option for some (24).

Irrigation and debridement produced mixed results but may be favoured by surgeons and patients alike who wish to avoid – or are unable to undergo – another larger operation.

Of the surgical options available, above knee amputation provides the most reliable means of controlling infection. However, it arguably provides the most inconsistent functional outcomes which is highly dependent on the ability in to fit a functioning prothesis which reportedly occurs in less than 50% of cases (24).

This review paper has several limitations. Firstly, the studies which were included were single centre studies with significant variations in the length of follow up, small patient numbers, and studies not using consistent or traditional functional outcome measures, which hindered our ability to conduct a meta-analysis of the reported results. The pooling of data from such heterogenous studies means there is a high risk of selection and treatment bias. Secondly, not all papers reported complication rates meaning we may have underestimated the overall rate of complications for each procedure, making it more difficult to conclude firmly which technique may be optimal for each subcategory of patient. Thirdly, the studies were all retrospective in nature leaving them highly prone to recall bias.

Unfortunately, there is no clear surgical pathway for dealing with failed 2 stage revision. Our findings are largely open to interpretation depending on how the surgeon or patient define a successful outcome. This review can potentially guide the surgeon regarding the relative risk benefits or the options available. This review also highlights the need for prospective studies or randomised large multi-centre-controlled trials to directly compare the different surgical techniques in a consistent patient cohort and might provide an answer as to which is the best treatment management when dealing with failure of second stage revision knee arthroplasty.

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