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Investigation and management of prosthetic joint infection in knee replacement: A BASK Surgical Practice Guideline

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ABSTRACT

Background: The burden of knee replacement prosthetic joint infection (KR PJI) is increasing. KR PJI is difficult to treat, outcomes can be poor and it is financially expensive and limited evidence is available to guide treatment decisions.

Aim: To provide guidelines for surgeons and units treating KR PJI.

Methods: Guideline formation by consensus process undertaken by BASK's Revision Knee Working Group, supported by outputs from UK-PJI meetings.

Results: Improved outcomes should be achieved through provision of care by revision centres in a network model. Treatment of KR PJI should only be undertaken at specialist units with the required infrastructure and a regular infection MDT.
This document outlines practice guidelines for units providing a KR PJI service and sets out:

- The necessary infrastructure required to provide a high-quality KR PJI service
- The MDT composition — who and when
- The KR PJI care pathway
- Medical and surgical treatment strategies
- The indications for referral to tertiary units (Major Revision Centres)
- Outcome metrics and auditable standards

Conclusions: KR PJI patients treated within the NHS should be provided the best care possible. This report sets out guidance and support for surgeons and units to achieve this.

1. Introduction

1.1. Background

Prosthetic joint infection (PJI) is potentially devastating complication following knee replacement (KR) surgery, affecting ~0.5 to one percent of primary KR patients [1–3]. The number of KRs performed is rising steadily due to population demographic

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changes (age, body mass index (BMI), gender) and although the incidence of PJI is relatively static [4] the overall PJI burden will increase [5,6].

PJI in the setting of KR is challenging to treat, with widely varied practice and reported outcomes [7]. PJI is best-treated by a multi-disciplinary team, with expertise across not just orthopaedic surgery, but including, for example, experts in infectious disease, microbiology, rehabilitation, pathology and imaging [8,9]. In cancer treatment improved outcomes for patients have been achieved through the introduction of multidisciplinary team (MDT)-based management [10]. The parallels between PJI and cancer are easily drawn; both require coordination of complex care, involving experts from several different fields. Furthermore, five-year mortality from PJI (~13%) is actually higher than three of the most common solid cancers (breast, prostate and melanoma) [11].

1.2. Rationale for this guideline

In 2015 the Getting it Right First Time (GIRFT) report recommended rationalisation of orthopaedic service delivery to improve both cost effectiveness and efficiency [12]. In recognition of these challenges British Association for Surgery of the Knee (BASK) developed a Revision Knee Working Group (RKWG). This guideline has been developed and approved by BASK through this working group, supported by GIRFT and NHS England and Improvement (NHSE+I), to deliver recommendations on service organisation, infrastructure and auditable outcome metrics for units treating KR PJI in the NHS.

1.3. Evidence checking and research priorities in revision knee surgery

As described in the parallel SPG Revision Knee Replacement Surgery in the NHS (under peer review at The Knee) a PRISMA compliant evidence checking process was undertaken to identify studies relating to investigation and treatment of infection [13]. The majority of published data are small retrospective case series and cohort studies. Additionally, a James Lind Alliance Priority Setting Partnership (JLA-PSP) identified 'What is the best way to diagnose and treat infection in a knee replacement?' as a Top 10 research priority in revision KR. Given the importance of the clinical problem and lack of high quality evidence to guide practice the UK-PJI undertook a national consensus meeting [14] and the BASK-RKWG undertook a Delphi process to develop consensus-based recommendations on KR-PJI.

1.4. UK-PJI consensus meeting

An open invitation was circulated nationally, inviting healthcare workers involved in the treatment of PJI to the first UK-PJI meeting; 63 clinicians from >30 centres in England, Wales, Scotland and Northern Ireland attended. A Delphi process was followed to determine consensus. Following presentation of a topic and pre-drafted statements, delegates voted (agree, disagree, modify). A threshold of 80% agree was required for statement acceptance and the final, accepted statements were reported [14].

1.5. Revision Knee Working Group and consensus process

Refinement of these statements with particular reference to revision KR was undertaken by the BASK-RKWG. The RKWG was selected based on National Joint Registry data and comprised high-volume revision units and surgeons. A Delphi consensus process was performed as previously described [15,16]. The consensus process and the composition of the RKWG are fully reported in the parallel SPG 'Revision Knee Replacement Surgery in the NHS: A BASK Surgical Practice Guideline' (under peer review at The Knee). Recommendations were circulated using an online survey tool (https://www.soscisurvey.de/) and a pre-determined mean score of ≥7/10 was required for acceptance. Revision and re-voting was undertaken until consensus was reached. All the recommendations included in this guideline have been through the Delphi consensus process and met these pre-defined criteria for acceptance.

1.6. The current landscape of KR PJI in the UK

Although the commonest indications for revision surgery are loosening and instability [17], in more specialist tertiary referral units infection is often the leading reason for revision surgery [18], and infection is the primary cause of re-revision surgery [19]. Revision surgery for infection is complex, often requiring advanced surgical techniques to deal with bone loss, debride infected tissue and restore extensor mechanism function [20]. It is also expensive [21], with high implant and equipment costs, patients regularly requiring multiple procedures, prolonged hospital stays and higher-level care (e.g. HDU). The cost for treatment of an infected TKR is ~£30,000 compared with ~£9000 for non-infected cases [21].

Currently revision KR in England and Wales is undertaken by a large number of surgeons performing a small number of procedures (data in press and [22]). The relationship between improved outcomes and higher surgeon and higher unit volume has been established in many areas of medicine, surgery and orthopaedics [23–25], and recent data has confirmed this relationship in revision hip and knee replacement [26–28].

1.7. Outcomes for KR PJI

Investigation of outcomes for treatment of KR PJI is challenging, with varied metrics being used, although broadly successful treatment is defined as no further surgical intervention required, and no imaging or clinical findings suggesting infection [29]. Infection eradication rates for surgical treatment are reported from ~10 to 100%, reflecting the heterogeneity of the clinical situation, different definitions of successful treatments and the different treatment approaches that are available. This heterogeneity of treatment is widely recognised, and there is significant need for controlled investigative trials [30,31].

1.8. The 'Infection MDT' and centralised care

Because of the relationship between higher volume and improved outcomes, in addition to the complex, multidisciplinary care required, the treatment of KR PJI patients should be undertaken in specialist units, organised into a network system, as described in the document 'Revision Knee Replacement Surgery in the NHS: A Surgical Practice Guideline' (in press).

All PJI treatment should be planned and coordinated by a specialist infection MDT. The MDT should comprise orthopaedic surgeons, infectious disease physicians or microbiologists, plastic surgeons, specialist nurses, pharmacists, a MDT coordinator and rehabilitation teams, as well as having administrative support. If emergency treatment is required in patients that are systemically unwell and this is undertaken before discussion in an MDT is possible, then post-event discussion of the case should be undertaken and the MDT should coordinate further treatment plans.

2. The care pathway

2.1. Aim of treatment

Individual patients should make treatment decisions in a shared decision-making process. Decision-making is challenging and complex and an infection MDT should support patients, with information tailored to specific patients' requirements. For most patients with KR PJI the aim of treatment is to optimise joint function and reduce pain; depending on patient and surgical factors surgery may or may not be indicated. All cases of suspected and confirmed PJI should be discussed in an infection MDT.

2.2. Definition of cure

PJI 'cure' is variably defined in the literature. Cure should be defined as freedom from clinical signs and symptoms of infection, normalised biochemical parameters (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) and no further requirement for surgical intervention or antibiotic therapy at two years post-treatment.

2.3. Initial assessment in primary care

Awareness of a potential diagnosis of PJI is critical to avoid delays in treatment and referral to secondary and tertiary care. Specialist infection units should raise awareness of PJI through communication with primary care centres and put referral pathways in place to co-ordinate timely investigation and management of suspected PJI. It is imperative that primary care givers are aware of and have access to these pathways. Key information required on initial assessment includes:

- duration of symptoms
- date and location of primary implantation
- change in range of motion and joint pain, particularly on weight bearing
- other potential sources of infection or systemic illness
- co-morbidities making infection more likely (e.g. immunocompromised/suppression, diabetes, high BMI, smoking status)

2.4. Red flags for urgent referral

Any features suggesting acute infection require urgent referral and same-day clinical review. These features include:

- new or worse pain, swelling or redness in a recently performed or a previously well-functioning KR
- systemic illness with increasing or worsening pain in a recently performed or previously well-functioning KR

2.5. Referral of patients with suspected chronic PJI

Recently unchanged, chronic symptoms such as pain and poor function without an acute deterioration in symptoms or development of systemic symptoms may be caused by chronic PJI. Patients with suspected chronic PJI ideally require outpatient review within four weeks and timely investigations. If PJI has been confirmed, the patient needs referral to the MDT coordinator for discussion at the next meeting.

2.6. Indications for regional referral

Tertiary referral to a Major Revision Centre (MRC) is indicated in complex cases, including all previous failed revisions for PJI. A complexity grading tool, such as the Revision Knee Complexity Classification (RKCC) system, may be used to help determine which cases to refer directly. It is recommended that all RKCC 3 (the most complex revisions) are transferred to Major Revision Centres [32].

2.7. Diagnosis of KR PJI

Diagnosis should be made using standardised criteria defined in the 2013 International Consensus Meeting (ICM) on PJI [33–35] (Table 1). Laboratories in centres treating PJI should have the facility to undertake these investigations, in particular synovial fluid white cell count and leukocyte esterase. All patients with suspected PJI require CRP serological analysis (±ESR or PV). Abnormal results should prompt aspiration ± biopsy to confirm the diagnosis and identify the sensitivities of any organism cultured. Normal blood tests do not rule out infection and patients where a suspicion of PJI remains should have further investigations discussed in a MDT. Aspiration or biopsy should be performed in a clean environment such as an operating theatre, or interventional radiology suite using an aseptic technique. When safe, antibiotics should be stopped for at least two weeks prior to the procedure. Aspirated fluid should be placed in sterile pots, and when possible, also inoculated into blood culture bottles to improve culture yield. There should be a locally agreed protocol to obtain a synovial fluid leucocyte count and neutrophil differential. Additional synovial markers of infection such as leucocyte esterase may be useful in some cases. Plain imaging (X-rays) are required in all cases. A bone scan is not routinely recommended, however newer nuclear imaging techniques with a strong negative predictive value (e.g. SPECT–CT) may be useful in cases of diagnostic uncertainty.

During surgery, five separate surgical specimens are required to be taken, each with clean, separate instruments. Samples should be sent for microbiology and histology. Microbiology samples should be processed in accordance with UK Standards for Microbiology Investigations. Peri-prosthetic histopathology samples should have a quantitative assessment of neutrophil infiltrate. In cases highly suspicious for PJI where cultures are negative, the MDT may consider additional fungal or mycobacterial cultures and/or molecular testing.

3. Treatment in secondary care

3.1. Principles of management

Successful PJI treatment requires surgical intervention and medical therapy in the majority of cases. The goals of treatment are to eradicate infection, minimise joint pain, restore joint function and minimise PJI-related morbidity and mortality. Not all these goals will be achievable in all patients; each patient requires an individualised treatment plan, which is only achievable with multi-disciplinary input.

3.2. Specific organisms

The most common organisms responsible for KR PJI are *S. aureus* (~20%–60%) and coagulase negative staphylococcus (~20%) [36,37]. These organisms, along with gram-negative bacilli (e.g. *E. coli*, five percent) are particularly important in early infection caused by intra- or peri-operative inoculation (presenting approximately one to three months post-surgery), and in late infection caused by haematogenous spread (presenting >1 to two years post-surgery). Delayed onset infection (approximately three months to two years) is often caused by less virulent organisms, such as coagulase-negative staphylococci and enterococci. Approximately 10% of KR PJI is polymicrobial, ~10% is culture negative, and ~0.5% is caused by fungal species [37]; these three conditions present particular, specific challenges.

3.2.1. Polymicrobial infection

Polymicrobial infection occurs in ~35% of early-onset infection, compared to <20% of delayed or late infection, often with *enterococci*, *S. aureus* or *pseudomonas*. Patients that are immunocompromised, with rheumatoid arthritis or have multiple comorbidities are more likely to have polymicrobial infection [38].

Table 1
ICM diagnostic criteria (2013) for PJI Diagnosis is made on the basis of one major criterion or three minor [33].

Major	Two positive periprosthetic cultures with phenotypically identical organisms or a sinus tract communicating with the joint, or
Minor	Having three of the following minor criteria:
	• Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR) • Elevated synovial fluid white blood cell (WBC) count or + +change on leukocyte esterase test strip • Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) • Positive histological analysis of periprosthetic tissue • A single positive culture

3.2.2. Culture negative joint infection

Culture negative joint infection (CNJI) can occur in ~20% of patients with no microbiological evidence of infection, such as periprosthetic purulence, acute inflammation determined by histopathology, or a sinus tract communicating with the joint, in the absence of identified causative microorganisms. The primary risk factor for CNJI is previous antibiotic therapy [39], alongside immunosuppressive therapy and diabetes. Strict withholding of antimicrobials prior to surgery and improvements in microbiological techniques may decrease the number of culture-negative infections. Culture negative infection samples in cases highly suspicious for PJI should be sent to a second, specialist, regional laboratory for culture and further testing which may include fungal or tuberculosis (TB) culture and polymerase chain reaction (PCR).

3.2.3. Fungal infection

Fungal infection causes <1% of PJI, and candida species are found to be the cause in >80% of these cases [40]. Concomitant bacterial infection is found in ~20% of cases. Fungal PJI is more common following revision surgery [40]. Fungal infection is challenging to treat and should always be referred to the regional MRC MDT.

3.2.4. Oral versus intravenous therapy

On the presumption of higher bioavailability, conventional management of PJI uses intravenous (IV) antibiotic therapy, particularly in the approximately six week post-operative period following surgical intervention for infection. However, recent trial data has demonstrated non-inferiority of oral therapy in a trial of ~2000 patients with bone and joint infection (including >60% of patients with metal-work associated infection) compared with intravenous [41]. The oral versus intravenous decision should be made in a shared decision making process, involving the patient and the MDT, but IV therapy is not mandated post-surgery.

3.3. Surgical decision making

3.3.1. General considerations

The evidence-base for recommendations on surgical strategies is currently poor. However, the following core principles should be adhered to for any surgical intervention for PJI:

- *Sufficient tissue samples* must be obtained with great care to avoid contamination (ideally five to six samples from various regions of the joint).
- *Adequate debridement* to clear all infected, devitalised, inflamed or unhealthy tissue must be performed.
- *Thorough lavage* with at least six litres of saline or another suitable antiseptic agent such as chlorhexidine must be performed.
- *Antibiotic therapy* is always required, and should be guided where practicable by pre-operatively obtained samples. This should be prescribed in parallel with the operative induction antibiotics and the antibiotic used in the cement.

If adequate clearance may compromise soft tissue coverage, plastic surgery input is mandatory and should be anticipated and planned. The indications for each surgical strategy are summarised in Table 2. Surgical decision-making is presented in Figure 1.

3.3.2. Intra-operative sampling

During all surgical procedures five separate surgical specimens are required to be taken with clean instruments for each sample. Microbiology samples should be processed in accordance with UK Standards for Microbiology Investigations. A further separate sample must also be sent for histopathological analysis as per ICM 2013 criteria.

Table 2
Indications, contraindications, and cautions for the three main surgical strategies for treating KR PJI.

	Indications	Contra-indications	Cautions
DAIR	Well-fixed, well-functioning implant Acute onset early or late infection	Loose components Primary wound closure is not possible Infection by resistant organisms (fungal/multi-resistant/atypical).	Draining sinus Immunocompromised host Significant patient co-morbidities
Single stage revision	Positive pre-operative culture sensitive to antibiotic regimen Not caused by fungal or atypical organisms (polymicrobial infection is acceptable if sensitive antibiotic regime is achievable)	Systemic sepsis Previous failed revision for infection Inability to achieve soft tissue cover at time of surgery	Culture negative case Resistant organism — fungal/atypical/polymicrobial Immunosuppression or significant co-morbidities
Two stage revision	Negative pre-operative culture Fungal/atypical/polymicrobial/multi drug resistant organisms Staged soft tissue reconstruction required Significant immunocompromise Systemic sepsis	Inability to achieve adequate temporary stability of the joint	Patient inability to tolerate a two stage procedure

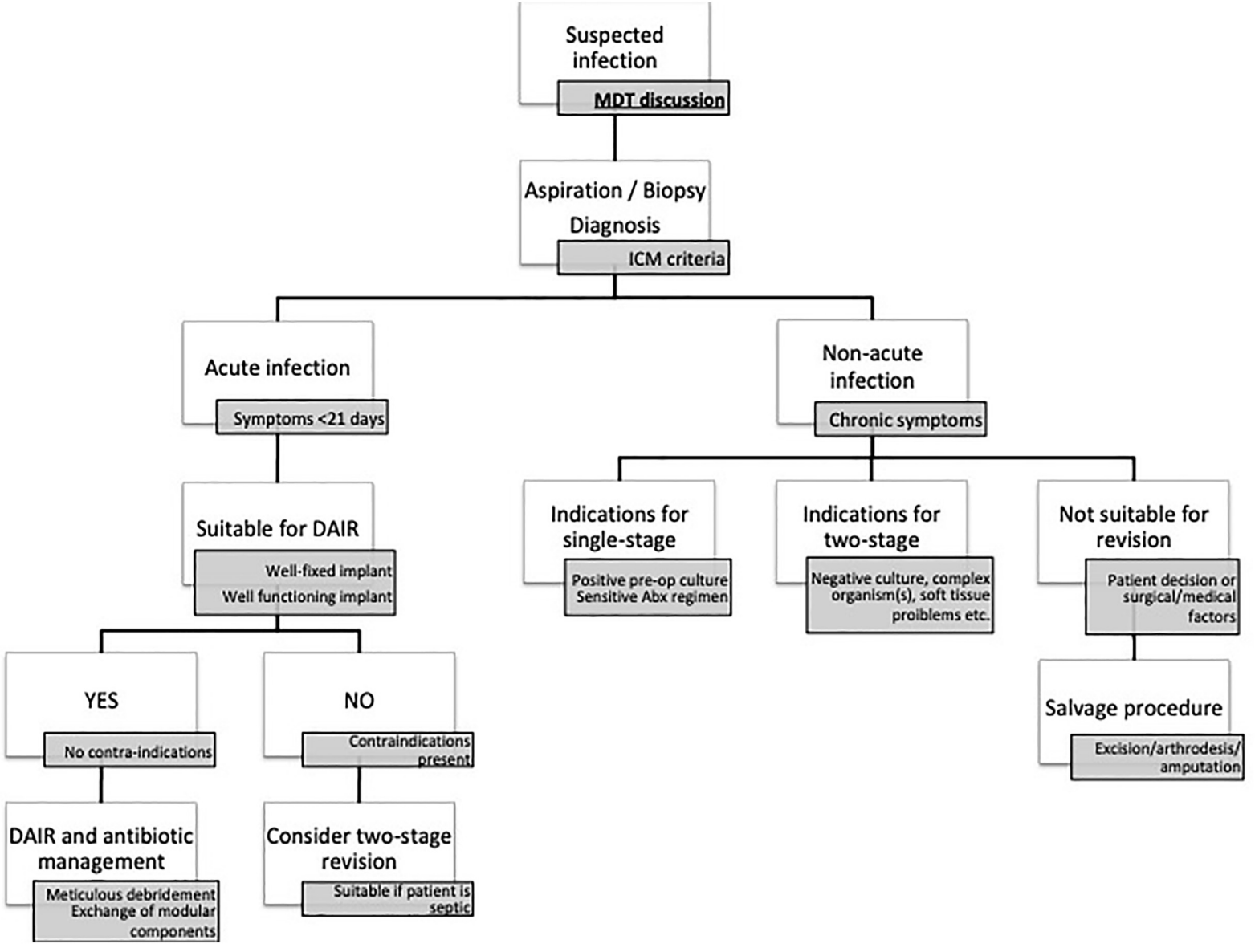

Figure 1. Basic surgical treatment algorithm for KR PJI. Note that MDT discussion should be undertaken as early as possible, although this may not be achieved in cases requiring urgent treatment for sepsis. At all points in the pathway re-discussion with the MDT is encouraged e.g. following acquisition of new surgical samples, which will affect subsequent management decisions.

3.3.3. Acute surgery

Arthroscopic washout has no role in the definitive management of PJI, and should only be performed as a life-saving measure to reduce the septic load and allow patient optimisation prior to a formal debridement, antibiotics and implant retention (DAIR) or revision procedure. Blood cultures must be obtained in septic patients before arthroscopic washout or acute surgical intervention.

3.3.4. Debridement, antibiotics and implant retention (DAIR)

DAIR procedures should be considered a formal revision procedure and should be undertaken by experienced arthroplasty surgeons with the support of an MDT. They require meticulous debridement and modular components must be exchanged where possible. DAIR is indicated principally in the setting of early infection and in late acute infection in the presence of a well-functioning joint replacement, with well-fixed components. The chronicity of infection is important, providing a window to intervene prior to the establishment of a biofilm. DAIR is absolutely contraindicated in the presence of loose components, when primary wound closure is not possible and in the setting of difficult-to-treat infection (fungal/multi-resistant/atypical infection). Polymicrobial infection is not an absolute contraindication, providing an effective antibiotic regimen is available. Worse outcomes have been recorded in the presence of a sinus, infections caused by difficult-to-treat bacteria or fungi, and caution is recommended in immunocompromised patients or those with multiple comorbidities.

It is not absolutely required to identify the pathogenic organism(s) prior to DAIR, although this is desirable to enable targeted post-operative antimicrobial therapy. Furthermore identification of responsible organism(s) may highlight cases in which DAIR is likely to fail (e.g. fungal PJI). Cure rates of 50–75% may be expected following a DAIR procedure [30].

3.3.5. Single stage revision

The benefits of single stage versus two-stage revision include earlier rehabilitation and lower morbidity and mortality. Although considerable cohort data exists on the effectiveness of single-stage revision for PJI, particularly from European centres, where it is the mainstay of surgical treatment [31], there are no high quality studies comparing one and two stage strategies and many surgeons remain in equipoise over this question.

We suggest that single-stage revision is indicated in patients with positively identified organisms from peri-operative samples and in patients that would not tolerate a two-stage procedure. Contraindications to single-stage revision are systemic sepsis, previous failed revision for infection and an inability to achieve soft-tissue coverage. Caution should be exercised in culture-negative infection, resistant organisms or in immunocompromised patients. It is recommended in the absence of contra-indications to discuss the option of a one or two stage revision strategy with the patient.

3.3.6. Two stage

Two-stage revision involves implantation of a temporary joint spacer, commonly manufactured from antibiotic loaded cement. The timing of the second stage is variable but must only be performed once clinical, laboratory and radiological signs of infection have shown eradication. Routine aspiration or biopsy prior to second stage is only recommended in the presence of ongoing clinical concern or persistently raised markers. Antibiotic therapy must be continued following the second stage until culture samples are declared as negative.

Two-stage revision may be preferred in culture-negative infection, in infection caused by fungal, atypical, polymicrobial or multi drug resistant organisms, when staged soft tissue reconstruction is required, in patients with immunocompromise or those with sepsis. The only contra-indication to two-stage revision is an inability to achieve adequate temporary stability of the joint.

3.3.7. Salvage procedures

In patients that cannot tolerate or do not want to undergo revision surgery (and are not willing to consider amputation), a salvage procedure may be required. Knee arthrodesis is a salvage technique to provide the patient with a stable, pain-free joint with which they can mobilise, and may be achieved with an arthrodesis specific implant system, an intramedullary nail, external fixator, or internal plate fixation. Excision arthroplasty has a high success rate for PJI cure, but obviously results in an unstable limb, with associated disability, pain, and reduced quality of life [42].

4. Organisational structure and infrastructure required to treat KR PJI

4.1. Development of regional specialist revision KR networks

Regional care networks have successfully improved outcomes in diverse areas of healthcare in the UK from cancer care to major trauma [43,44]. A network recognises both the positive relationship between volume of patients treated by surgeons and centres and patient outcomes, and the requirement for multiple different specialists to care for complex patients. Revision KR units should be organised into clinical care networks comprised of MRC, Revision Units (RU) and Primary Arthroplasty Units (PAU). These guidelines are published separately ('*Revision Knee Replacement Surgery in the NHS: A BASK/BOA/GIRFT Surgical Practice Guideline*', in press). It is particularly important that KR PJI cases are managed by teams familiar with this complex group of patients and the devastating outcomes that can occur as a result both of infection and the complications of management.

4.2. Infrastructure required to treat KR PJI

The infrastructure and support required to treat KR PJI as a MRC or RU is outlined separately in the Surgical Practice Guideline. Points of particular note are:

- The make-up of the Infection MDT (outlined above)
- Standardisation of MDT discussion, accurate record keeping and regular audit
- Access to ring-fenced elective level 1.5 care, HDU or equivalent beds
- Availability of timely access for patients referred into the MDT

4.3. Outcome metrics and mandated standards

Units should record and monitor their practice according to the '*Revision Total Knee Replacement Surgical Practice Guidelines*', '*Investigation and Management of Prosthetic Joint Infection in Knee Replacement*' and '*Investigation and Management of Patients with Problematic Knee Replacements*'. Auditable standards and key outcome indicators are outlined in the Surgical Procedure Guideline.

4.4. Coding and tariff

Accurate coding of procedures is vital for appropriate financial reimbursement and data collection. The most common diagnostic and procedural codes for PJI are listed in the accompanying SPG Revision Knee Replacement Surgery in the NHS: A BASK Surgical Practice Guideline (under review at The Knee).

5. Summary

Treatment of KR PJI is challenging and routinely involves complex decision making processes, requiring both medical and surgical management of infection, alongside rehabilitation and imaging expertise. Best outcomes are achieved when this complex care is regularly and routinely coordinated by experts organised into an MDT.

This document provides a framework for the care of patients with KR PJI. Medical and surgical care is discussed, but equal importance is assigned to establishment of revision KR networks to coordinate care and provide robust patient pathways for referral of patients to specialist bone infection units with the expertise and infrastructure to treat them.

Ethics statement

Ethical approval was not required for this manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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