When the Race Is Lost: The Clinical Impact of Prosthetic Joint Infections

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Abstract Joint arthroplasty, a procedure that can relieve patients of life-altering and debilitating pain, has proven to be so successful that over 1,000,000 procedures are performed annually in the USA alone. However, a prosthetic joint infection represents a devastating complication for patients which can lead to not only revision surgery but possible permanent loss of function, amputation, and even death. Infection can present not only in the immediate postoperative period but at any point for the duration of the implant's life.

The challenges confronting providers are numerous. Diagnostic testing has varying sensitivities and specificities depending on duration of infection meaning there is no true "gold standard" for testing. Additionally, once the diagnosis of infection is made, treatment options are limited and have high rates of morbidity and mortality.

Given the impending rise in total joint arthroplasty case volume and subsequent revision case volume due to PJI, an urgent need exists for continued work in the development of preventive, diagnostic, and therapeutic tools.

Keywords Joint arthroplasty · Infection · Biofilm · PJI · TJA · Diagnosis · Treatment

Epidemiology/Incidence

The goal of total joint arthroplasty (TJA) is to relieve a patient of debilitating joint pain by replacing the biological joint surface with prosthetic implants. This surgery is most often performed in the setting of severe osteoarthritis although rheumatoid arthritis and osteonecrosis of the hip are other common indications. A patient becomes an appropriate surgical candidate only after conservative measures such as

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B. Li et al. (eds.), *Racing for the Surface*,
https://doi.org/10.1007/978-3-030-34475-7_1

anti-inflammatory medications, physical therapy, and various injections have been exhausted and failed. TJA has proved to be one of the most successful surgeries performed, with consistently high patient satisfaction scores [1, 2]. The success of the procedure has led to more than 370,000 primary total hip arthroplasties (THA) and 680,000 primary total knee arthroplasties (TKA) performed in 2014 in the USA alone [3].

Periprosthetic joint infection (PJI) is one of the most feared and devastating complications of TJA due to clinical challenges in diagnosis and treatment and the extreme financial, physical, and emotional costs to the patient [4]. Despite evolving preoperative and intraoperative regimens to reduce infection risk, estimates of PJI incidence rates for both primary hip and knee arthroplasties range from approximately 0.5–2.0%, with a slightly higher rate of PJI in TKA compared to THA [5–8]. More troubling is that failure rates after the first line of treatment for PJI often exceed 25% with an increasing failure rate with repeated subsequent revision procedures. With an average cost of $116,383 for an infected total hip arthroplasty and $88,623 for an infected total knee arthroplasty, a substantial burden is placed on the healthcare system [9, 10]. Additional costs are assumed by the patient in extended rehabilitation, prolonged hospital stays, and emotional costs [11, 12]. Ultimately, PJI can lead to not only revision surgery but also possible is permanent loss of function, amputation (Fig. 1), and even death, with the 1-year mortality of PJI in THA at 7% between stages of a two-stage revision and 33% within 5 years of completion of revision [13, 14].

Among the many challenges facing clinicians are shifting definitions of PJI, myriad diagnostic tests that, while helpful in aggregate, lack 100% accuracy, treatment regimens that have unacceptably high failure rates, and a spectrum of disease representing a moving and evolving target. With a projected 1.9 million combined primary total hip and knee arthroplasties expected to be performed annually by 2030 in the USA alone [3], there is an expected proportional increase in the infection burden. Moreover, some research has indicated this projection may prove too conservative and a more dramatically exponential increase in the TJA caseload may be borne out [15]. Therefore, it is imperative that clinicians and basic scientists continue research into preventing, diagnosing, and treating this devastating complication.

Overview of Challenges

The diagnosis and treatment of PJI depends largely on two factors: the time since index surgery and the duration of a patient's signs and symptoms. While in reality the infectious process occurs on a continuum and does not adhere to discrete intervals, the sensitivity and specificity of various diagnostic tests as well as treatment algorithms have historically been categorized by these two crucial factors. Because successful eradication of infection depends in part on the identification of where a patient falls on this spectrum, several categorizations have been proposed [16–19].

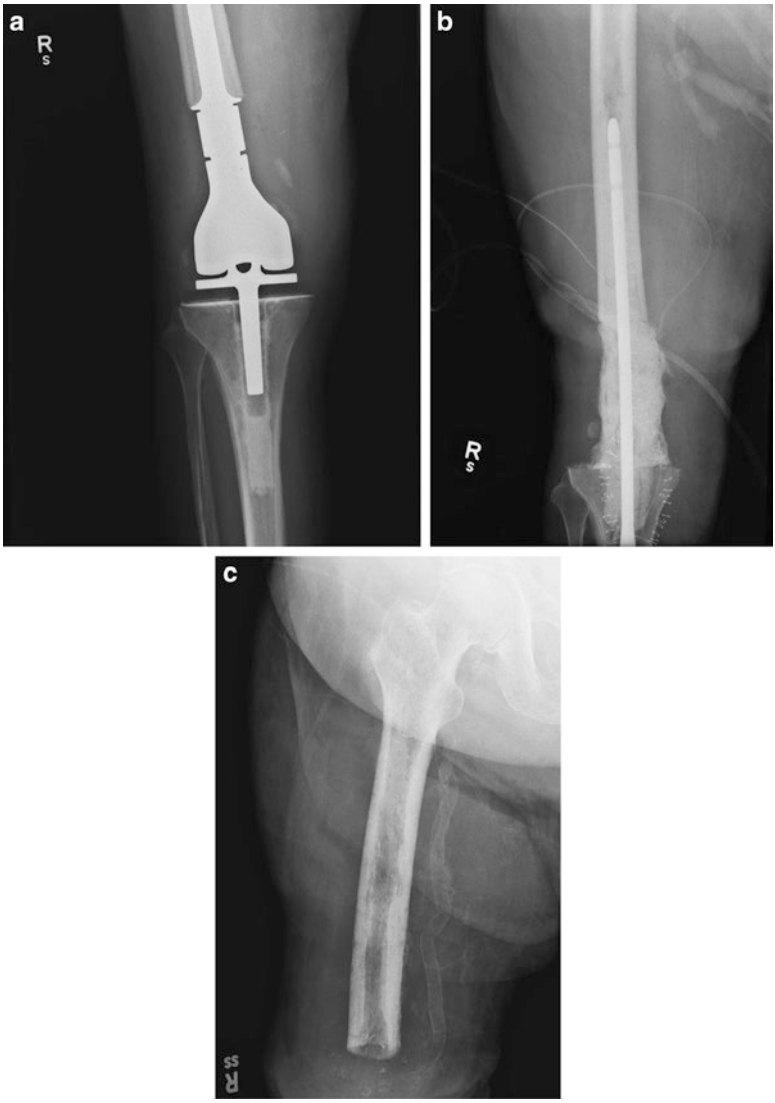


Fig. 1 (**a**–**c**) Progression in a single patient from infected revision total knee arthroplasty to knee fusion and ultimately to amputation due to recurrent infections. This patient eventually suffered multiorgan system failure and succumbed to his infection

For diagnostic and therapeutic purposes, PJI has been delineated into three broad categories [20]:

- Early postoperative infection: within 4 weeks of index surgery.
- Acute hematogenous infection (AHI): less than 3 weeks of symptoms. These infections typically cause an abrupt onset of symptoms that progress rapidly in severity.

- Chronic (late) hematogenous infection (CHI): seeded from a remote source and can be present at any point in the life of the patient after TJA, from months to years [21, 22]. Symptoms develop more gradually.

Part of the rationale for temporal categorization is directly related to one of the unique challenges inherent in PJIs: the ability of infective bacteria to form a "biofilm"—a metabolically cooperative colony surrounded by an extracellular glycocalyx (Fig. 2). Unfortunately, the same synthetic joint surface of the prosthesis which so successfully relieves pain in a patient makes the formation of this biofilm easier. Bacteria can adhere to prosthetic surfaces and resist mechanical disturbance making biofilm eradication especially challenging and often necessitates complete implant removal. Further, the glycocalyx protects bacteria not only from antibiotics and host antibodies but also detection from diagnostic testing. Biofilms have been found in samples from confirmed PJI cases in which preoperative cultures were negative [23]. It has been postulated that PJIs exhibit alternating periods of quiescent growth and acute exacerbations caused by the release of bacteria [24]. In the quiescent phases, few if any symptoms may be present, while during acute phases, symptoms may be limited locally to the affected joint or systemically manifesting as a fever, malaise, or frank septicemia. It is imperative that when a clinician suspects PJI, the patient is treated as soon as possible as a mature biofilm may be less likely to develop into acute PJI and implants may possibly be retained.

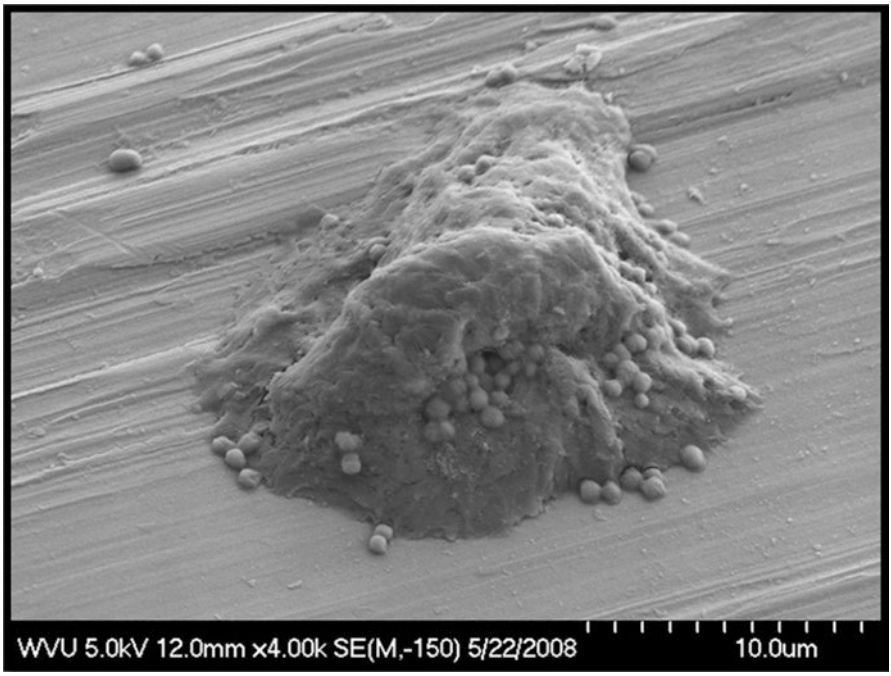


Fig. 2 Scanning electron microscopy image of *Staphylococcus aureus* biofilm adherent to a stainless steel disc

It should be noted that this categorization is more to help in the development of treatment algorithms and research purposes than based on a demonstrated bacterial threshold as studies have shown biofilm formation within mere hours of joint inoculation [25]. Therefore, the consideration of infection as a spectrum rather than a distinct acute/chronic dichotomy is likely more accurate.

Host Risk Factors

Prevention remains the best step in getting a head start in the race to the surface and several risk factors have been identified which aid clinicians in identifying patients predisposed towards PJI (Table 1). These include characteristics considered both modifiable, such as elevated body mass index, poorly controlled diabetes, tobacco

Table 1 Host risk factors for PJI/SSI in TJA [122]

Host risk factors for PJI/SSI in TJA	
Modifiable	Nonmodifiable
Active infection	Age
Alcoholism	ASA score > 2
Cardiovascular disease	Bariatric surgery
• Congestive heart failure	
• Cardiac arrhythmia	
Chronic kidney disease	Chronic anticoagulation
Chronic obstructive pulmonary disease	Hemiplegia/paraplegia
Clotting disorders	HBV
Depression	Osteonecrosis
Diabetes mellitus	Previous joint infection
• HbA1c	
• Serum glucose	
Drug abuse	Previous joint surgery
Frailty	Previous infection
HIV/AIDS	Sex
Immunosuppression	Transplant
Intra-articular steroid/viscosupplement injection	
Malnutrition	
MRSA colonization	
Obesity	
Peripheral vascular disease	
Psychosis	
Renal disease	
Rheumatoid arthritis	

Outlines the modifiable and nonmodifiable risk factors known to impact the risk for prosthetic joint infection as described by Cizmic et al.
HbA1c hemoglobin A1c, *HIV* human immunodeficiency virus, *AIDS* acquired immunodeficiency syndrome, *MRSA* Methicillin-resistant *Staphylococcus aureus*, *ASA* American Society of Anesthesiologists, *HBV* hepatitis B

use, alcohol consumption, and immunosuppression, as well as nonmodifiable, such as previous joint surgery and previous PJI [26, 27].

Body Mass Index (BMI)

BMI is recognized as a major risk factor with postoperative infection rates 6.7 times higher after TKA and 4.2 times higher after THA in patients with BMI $\geq$ 35 kg/m^2 compared to nonobese patients [28]. This risk elevates incrementally with each point increase in BMI > 25 kg/m^2 (hazard ratio of 1.09 per unit) [29, 30].

Diabetes

For diabetic patients, a hemoglobin A1c level of 7.5 has been shown to almost triple the risk of PJI in TKA when compared to those below this threshold [31]. Studies have demonstrated PJI rates in both TKA and THA rising from 0.8 to 5.4% with an A1c of 7.7 or higher compared to an A1c $\leq$ 7.6 [32].

Lifestyle Factors

Several other lifestyle factors have demonstrated an elevated risk of PJI. For instance, current tobacco users have more than double the risk of PJI than nonsmokers (OR 2.16 [1.57–2.97]) and this risk persists even after smoking cessation (OR 1.52 [1.16–1.99]) [33]. Alcohol consumption in the perioperative period has been shown to increase the risk of PJI and alcohol cessation is recommended at least 4 weeks prior to surgery to reduce postoperative morbidity [34–36]. Several of these lifestyle factors are related to effects on wound healing and coagulation.

Modifiable Medical Risk Factors

While some TJA patients suffer from chronic conditions such as rheumatoid arthritis (RA) which elevate the risk of PJI, these patients should be medically optimized prior to surgery [37]. For instance, those on biologic disease-modifying antirheumatic drugs (DMARDs) should discontinue these medications in the perioperative period (approximately 2 weeks before and after surgery, based on drug half-life) as numerous studies have shown an increased risk of surgical site infections (SSIs)/PJIs with perioperative use of these medications [38–40]. This elevated risk is borne out in patients using glucocorticoids within 90 days of surgery as well due to immu-

nosuppressive effects [37]. However, those on nonbiologic DMARDs (e.g., methotrexate, leflunomide) can continue these medications throughout the perioperative period. Finally, anemia has consistently been found to be a factor in both the incidence and failure of treatment of PJI and is another example of a modifiable medical risk factor [34, 35, 41, 42].

Nonmodifiable Risk Factors

Several significant nonmodifiable risk factors such as prior PJI and prior joint surgery have been identified. A history of prior joint infection increases the risk of PJI 5.0–21.0 times [43–45]. Patients with a history of previous joint surgery have almost tripled the risk of PJI [46]. While risk factors such as these cannot be modified, an awareness of these patient factors and heightened surveillance enables clinicians to detect PJI in its early stages thereby increasing the likelihood of treatment success. Further, it should be noted that, while many host factors exist, they should all be taken in the context of the patient to determine the overall risk of PJI with no single factor providing a definitive risk assessment.

To synthesize several of these risk factors, calculators are available online enabling clinicians to compute the overall risk of PJI. Risk factors utilized include BMI, sex, race, insurance status, smoking, drug abuse, prior surgeries, and various comorbidities [47]. While these calculators do not yield an absolute risk assessment, they can be a useful aid in guiding diagnostic testing.

Diagnosis

The diagnosis of PJI remains challenging due to the lack of a single test with 100% accuracy. Instead, a clinician must rely on a combination of clinical history, physical examination, imaging, laboratory testing including serological and synovial markers, microbiological culture, and intraoperative findings.

Clinical Presentation

Most often, PJI is suspected initially due to patient symptomatology rather than incidental findings on imaging or laboratory testing in an asymptomatic patient. Because a patient can become infected even years after surgery, any patient with a history of a TJA presenting with a painful joint should raise a clinician's suspicion. Unlike an acute infection typically associated with an abrupt onset of rapidly progressing symptoms, chronic PJI represents an indolent infection with gradual progression of less severe symptoms. In the settings of both acute and chronic PJIs, patients most

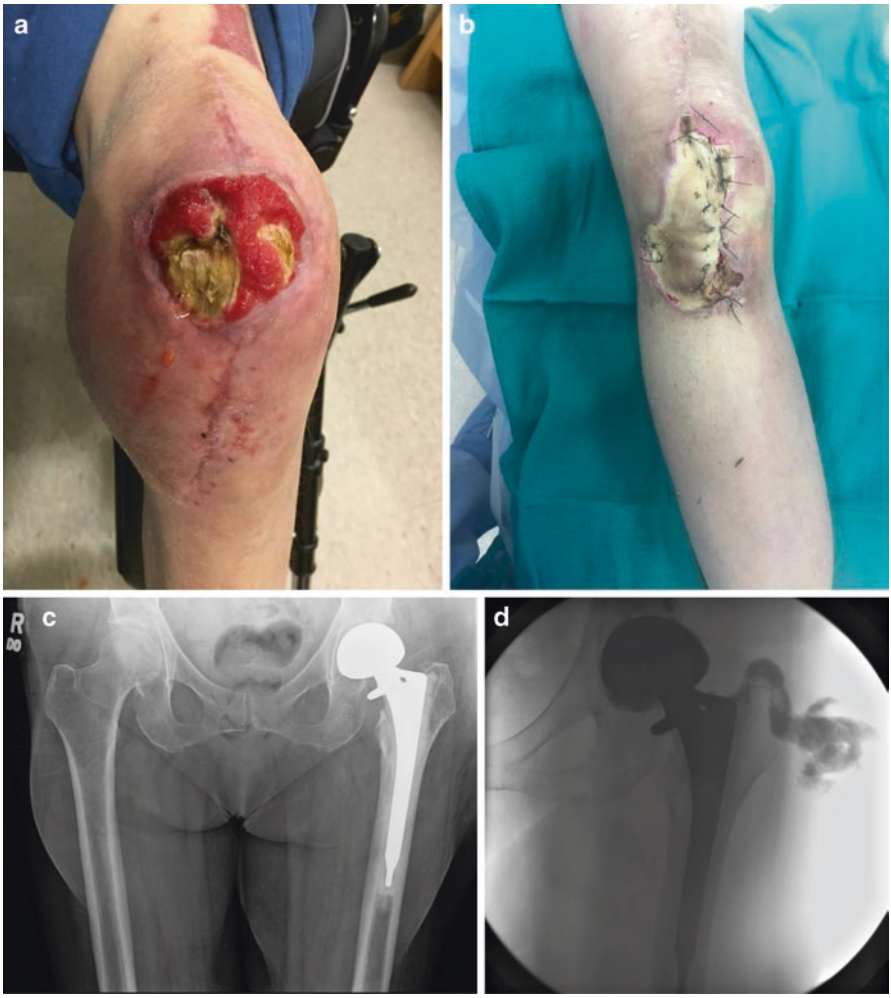


Fig. 3 (**a**, **b**) Clinical pictures of a suspected sinus tract and wound complication in the setting of a presumed PJI in a TKA. (**c**) Radiograph of a suspected infected THA. (**d**) Joint arthrogram confirming a sinus tract communicating from the joint directly to the skin surface. The presence of a sinus tract is diagnostic of a PJI

often present with a progressively painful joint [48]. Fever, while specific for PJI, is inconsistently present and has been found in 32.5% of early postoperative infections, 75.5% of AHI, and 14.0% of CHI [48]. Fever is also frequently present in the immediate postoperative period as a normal physiological response to surgery [49]. Local signs of inflammation such as warmth or diffuse swelling are more easily visible at the knee due to the more superficial nature of the joint. The presence of warmth in TKA and THA was found in 50% and 14% cases of PJI, respectively, while effusions were found in 75% and 29%, respectively [50]. Local warmth or hyperemia can be

Table 2 International Consensus Meeting (ICM) on Musculoskeletal Infection criteria [70]

Major criteria (at least one of the following)				Decision
Two positive growths of the same organism using standard culture methods				Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis				
Minor criteria	**Threshold**		**Score**	**Decision**
	Acute	Chronic		
Serum CRP (mg/L)	100	10	2	Combined preoperative and postoperative score:
or				≥6 infected
D-Dimer (μg/L)	Unknown	860		3–5 inconclusive[a]
Elevated serum ESR (mm/h)	No role	30	1	<3 not infected
Elevated synovial WBC (cells/μL)	10,000	3000	3	
or				
Leukocyte esterase	++	++		
or				
Positive alpha-defensin (signal/cutoff)	1.0	1.0		
Elevated synovial PMN (%)	90	70	2	
Single positive culture			2	
Positive histology intraoperative (whites/HPF)			3	
Positive intraoperative purulence			3	

International Consensus Meeting criteria for diagnosing a PJI. Acute infections defined as occurring less than 3 months from index arthroplasty, and acute hematogenous PJI, defined as symptoms occurring for less than 6 weeks but more than 3 months from index surgery

CRP C-reactive protein; *ESR* erythrocyte sedimentation rate; *WBC* white blood cell; *PMN* polymorphonuclear; *HPF* high-power field

Reprinted from The Journal of Arthroplasty, 34(2s), Shohat et al., Hip and Knee Section, What is the Definition of a Periprosthetic Joint Infection (PJI) of the Knee and the Hip? Can the Same Criteria be Used for Both Joints?: Proceedings of International Consensus on Orthopedic Infections, S325-s327, Copyright (2019), with permission from Elsevier

[a]Consider further molecular diagnosis

confusing in the acute postoperative period as this can often be related to increased blood flow in the area due to the normal healing response after surgery.

These signs may be accompanied by skin changes such as erythema, puckering, or obvious drainage of fluid. Drainage must be examined with particular scrutiny as it may be the result of a sinus tract or fistula communicating directly with the joint (Fig. 3a–d). The presence of a sinus tract or abscess represents deep involvement and, due to its high sensitivity and specificity, represents one of the major criteria for diagnosis of PJI (Table 2).

On physical examination, a number of signs may be present with manipulation of the joint such as crepitus or bogginess. The patient may feel pain with either palpation or range of motion especially at extremes of motion. The reported presence of stiffness or restricted range of motion varies widely but has been reported as high as 74% in TKA and 85% in THA [50]. Conversely, laxity may be appreciated

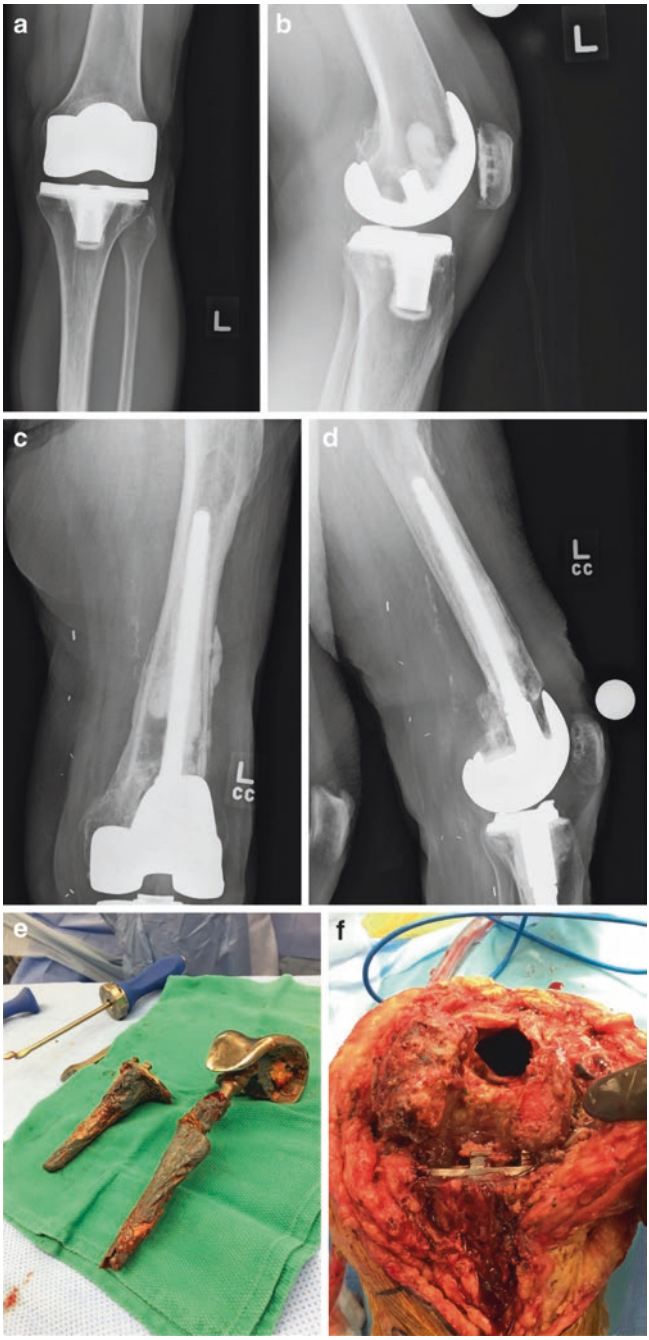


Fig. 4 (**a**, **b**) Normal postoperative radiographs showing a well-fixed prosthesis in a TKA with normal cement fixation. (**c**, **d**) Radiographs of a prior revision total knee arthroplasty in the setting of a PJI; classic signs of infection are visible including osteolysis, bone remodeling, loss of cement fixation, heterotopic bone formation, and migration of the prosthesis within the intramedullary canal. (**e**, **f**) Intraoperative findings demonstrating infection and loose femoral and tibial components

as a function of component subsidence or loosening. Unfortunately, all of these findings are fairly nonspecific.

Imaging

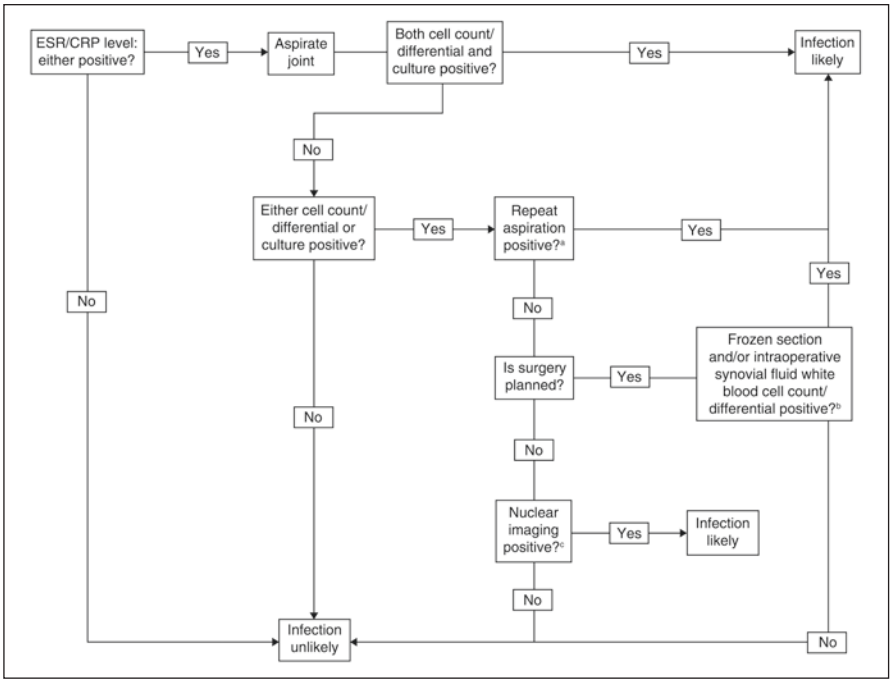
Initial imaging consists of anterior–posterior (AP) and lateral radiographs (X-rays) and should be compared to previous X-rays if available (Fig. 4a, b). Additional specialized views are not routinely acquired. Several signs are possible on X-ray imaging to support a diagnosis of PJI. Osteolysis, as represented by radiolucency, may be visible and may be indirectly seen as manifested by component loosening or subsidence, as the foundation upon which it rests has been compromised. Sinus tracts may be inferred by the appearance of a distinct interruption of the cortex. Finally, a generalized periosteal reaction may be seen (Fig. 4c–f). Unfortunately, X-rays are fraught with limitations due to their low sensitivity as a significant amount of cortical disruption must be present in order to be visible on an X-ray, diminishing their utility especially in early infections. Further, distinguishing loosening as a result of PJI vs. aseptic etiology is challenging [51]. Despite these limitations, the low cost and ease of acquisition make radiographs an ideal component of initial workup of a painful joint.

Advanced imaging modalities include bone scintigraphy, or "bone scan," which may be utilized when infection is strongly suspected but serological markers or synovial fluid analysis are equivocal. Leukocyte, antigranulocyte, and combined leukocyte and bone marrow scintigraphy are also available. All scintigraphy modalities are fairly sensitive (80–99%); however, the specificities among the tests vary widely due to false positives from conditions such as a fracture or bone remodeling. This trend is especially true in the first 12 months following surgery as periprosthetic bone remodeling continues. Therefore, these studies are typically reserved for the setting of chronic or low-grade infection and can be a useful adjunct in diagnosis. Positron emission tomography can be employed and has a sensitivity of 70% and specificity of 84%. However, due to its high cost, it is rarely used [52].

Computerized tomography (CT), magnetic resonance (MR), and ultrasound imaging are not routinely employed in the diagnosis of PJI due to their significant limitations. CT and MR both suffer from beam hardening and projection data noise resulting in image artifacts, making it difficult to distinguish bony architecture surrounding the prosthesis. Ultrasound is most useful in evaluating small areas of soft tissue architecture or the presence of fluid collections or sinus tracts [53], but does not provide useful information about bone morphology or implant position.

Criteria

Once a thorough history and clinical examination raise suspicion for a PJI, the algorithm endorsed by the American Academy of Orthopaedic Surgeons (AAOS) begins with the noninvasive serum biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [54] (Fig. 5). Due to their high sensitivities, they have been used as reliable predictors of the absence of infection [55]. Recent meta-analysis, however, suggests sensitivities of 88% and 75% and specificities of 74% and 70%, respectively and debate continues as to their utility [56]. It should be noted that CRP increases postoperatively from a baseline, peaking on postoperative day 2–3 and normalizing by day 21 [57]. Therefore, the thresholds used are >100 mg/L in the acute phase and >10 mg/L in the chronic phase. Similarly, ESR



Algorithm for patients with a higher probability of hip or knee periprosthetic joint infection.
[a] Perform repeat aspiration when a discrepancy exists between the probability of infection and the result of the initial aspiration culture
[b] Perform frozen section when the diagnosis has not been established at the time of surgery; synovial fluid white blood cell count and differential may also be obtained intraoperatively
[c] Nuclear imaging modalities: labeled-leukocyte imaging combined with bone or bone marrow imaging, F-18 fluorodeoxyglucose–positron emission tomography, gallium imaging, or label-leukocyte imaging
CRP = C-reactive protein, ESR = erythrocyte sedimentation rate

Fig. 5 An algorithm endorsed by the American Academy of Orthopaedic Surgeons used in the diagnosis of a PJI. (Reprinted with permission from Della Valle et al., Diagnosis of Periprosthetic Joint Infections of the Hip and Knee, Journal of the American Academy of Orthopaedic Surgeons, 18(12), 762, https://journals.lww.com/jaaos/Fulltext/2010/12000/Diagnosis_of_Periprosthetic_Joint_Infections_of.6.aspx#pdf-link)

increases immediately postoperatively, though it demonstrates a slow and irregular decline for several months after surgery and thus has more diagnostic utility in a chronic PJI with a threshold of >30 m/h [57, 58]. Ultimately CRP and ESR, as with other serum and synovial markers, must be interpreted with respect to time from index surgery.

Research is underway examining the utility of D-Dimer, a fibrinolytic by-product. One study found that using a threshold of 850 ng/mL resulted in a sensitivity of 89% and a specificity of 93% compared to a combined CRP/ESR sensitivity and specificity of 84% and 47%, respectively [59]. Further studies are underway to validate its utility but, due to its success, it is included in the current International Consensus Meeting on Musculoskeletal Infection (ICM) criteria (Table 2).

Joint Aspiration

If either ESR or CRP is elevated, the clinician should consider aspiration of the concerned joint for synovial fluid analysis which provides the most direct non operative assessment. If no serological markers are elevated, PJI is unlikely though continued clinical suspicion warrants aspiration. Analysis of synovial fluid yields a variety of diagnostic tests including cell count, culture, and inflammatory biomarkers. Synovial fluid cell count with differential and leukocyte esterase is most commonly obtained. Leukocyte count (WBC), leukocyte esterase, and polymorphonuclear cell percentage (PMN%) have demonstrated sensitivities of 89%, 77%, and 89%, respectively, and specificities of 86%, 95%, and 86%, respectively. Alpha-defensin is a marker which has grown in popularity due to its reported 97% sensitivity and 96% specificity, though recently its sensitivity of point of care testing and sensitivity after prior treatment for PJI have both been called into question [60–62]. Regardless, initial promising studies have warranted its inclusion in the current ICM criteria. As with serological markers, synovial markers are affected by proximity to surgery. For example, the threshold for WBC in the acute period is 10,000 cell/μL and 3000 cells/μL in the chronic period. Several other synovial markers, such as interleukin-6 (IL-6), IL-8, and CRP, demonstrate high sensitivities and specificities but are not routinely available at all institutions and therefore are not included in the standard workup for PJI.

Culture

Joint aspiration also allows for bacterial and fungal culture of synovial fluid which has been found to be 94% specific and subsequently is part of the criteria for PJI, though two positive cultures are required as part of the major criteria. However, while culture may seem a likely candidate for a "gold standard" diagnostic test, it has also been found to have only 62% sensitivity [62]. Further, a review of the most

recent literature indicates a culture-negative PJI rate from 7.0% to as high as 42.1% [63, 64]. The most common risk factors identified for culture-negative results were antecedent antibiotic use and presence of postoperative wound drainage. A culture-negative sample may be due to the presence of a biofilm in a quiescent state with a relative lack of planktonic bacteria to sample. Though the outcome of culture-negative PJIs is similar to that caused by known organisms, a negative culture hinders diagnosis and presents challenges in postoperative treatment as antibiotics cannot be tailored to specific sensitivities [65].

Various bacteria have been implicated in PJIs with a preponderance for gram-positive organisms with *Staphylococcus aureus* (*S. aureus*) the most prevalent followed by coagulase-negative *Staphylococcus* [64]. Finally, in rare cases, PJI may result from fungal or mycobacterium species. In the case of fungal PJIs, which account for <1% of all PJIs, cultures may require up to 4 weeks of incubation [66, 67].

Next-generation (next-gen) sequencing, capable of sequencing all DNA present in a sample concurrently, allows for a more complete assessment of the microbes present. Studies have shown its ability to outperform traditional microbial culture with an 89.3% sensitivity vs. 60.7%. Moreover, next-gen sequencing was able to detect bacteria in 81.8% of culture-negative samples from PJIs and 25.0% in presumed aseptic culture-negative revisions [68]. Finally, next-gen sequencing has demonstrated an ability in some cases to reveal a polymicrobial infection, which on culture initially grew only a single organism [69]. This finding may explain failure of some prior therapies and aid antibiotic selection in future cases. Further studies are underway but, due to the relatively high cost, next-gen sequencing is not a first-line test but may prove to be a useful adjunct.

Ultimately, these tests should be interpreted in the context of a patient's clinical history and presentation. To consolidate information and offer guidelines for clinicians, recommendations made by the Musculoskeletal Infection Society in 2011 and further amended at the International Consensus Meeting (ICM) in 2013, set forth guidelines to aid in the diagnosis of PJI. These guidelines were further amended and externally validated for chronic infections in 2018 and found to have a sensitivity of 97.7% and specificity of 99.5% [70] (Table 2). A robust debate continues within the orthopedic community as to the importance of each of the individual components; however, the establishment and revisiting of the Musculoskeletal Infection Society (MSIS) criteria provides a discussion and common roadmap for clinicians for the diagnosis of PJI.

Treatment

Once the diagnosis of PJI has been made, treatment is beset by its own challenges. There are a myriad of treatment regimens available with numerous surgical techniques, implant options, and antimicrobial therapies from which to choose. However, despite advancements and research over the last several decades, there remains a high recurrence rate. For instance, one study of 1.5 million infected TKA knees

found a 26% recurrence rate of infection after first-line treatment [71]. The selection of treatment and success of that regimen require a keen clinical acumen and continued surveillance.

Suppressive Antibiotic Therapy (SAT)

For some patients, medical treatment alone via long-term antibiotic suppression may be the only choice. The goal of therapy is to reduce or at least keep in check the bioburden and thus the incidence of systemic effects cause by the bacterial infection. The scope of patients for whom this treatment would be considered is narrow, as it is not a curative option, but typically includes those medically unsuitable to undergo surgery, those who refuse surgery, and those for whom surgery would not improve functional outcomes. Antibiotic therapy should be continued for the remainder of the patient's life; however, adverse reactions may limit the patient's ability to tolerate such therapy. Several small studies indicate moderate success with 68.5–86.2% of patients maintaining a functioning prosthesis [72–74]. However, complete resolution of a PJI requires surgical intervention; therefore, SAT should only be considered a palliative option.

Surgery

Because of the presence of biofilm which prevents antibiotics from fully permeating and completely eradicating an infection, the only definitive procedure for the elimination of a PJI is open surgery.

Debridement and Irrigation with Implant Retention (DAIR)

DAIR involves an open exposure of the joint to visualize and access the prosthetic implants. Most surgeons employ a surgical/mechanical debridement along with a chemical debridement. All surfaces are scrubbed with an antiseptic solution and irrigated with 6–9 L of sterile saline via low-pressure lavage while the easily exchanged components are removed and replaced, both to improve access to the joint and decrease the bioburden present. The indications for the procedure are narrow: early postoperative infections and acute hematogenous infections. Further, patients must be appropriate surgical candidates, have a microbial isolate of low virulence, and no sinus tract or wound complication present [75]. Several factors have been associated with treatment failure including presence of bacteremia and infection caused by *S. aureus* or *Enterococci* [76].

The advantage is a much faster, less expensive procedure with less morbidity and quicker recovery time. The operative time and blood loss are greatly increased when

components are removed which is avoided in this procedure. However, numerous studies have shown failure rates of 56–76% across multiple PJI chronicities caused by multiple organisms [77–79]. Outcomes appear to be improving, however, with time from surgery (<7 days) as a major factor in that success [80], and subsequent risk of failure rising with each additional day from the onset of symptoms [81]. For the right patient population, DAIR is a viable option that can be considered.

Exchange Arthroplasty

The current definitive treatment for PJI is an open procedure in which all components are removed and new components are implanted. There is an ongoing debate in the orthopedic community as to whether component exchange should be done in a single procedure or in two stages.

Single-Stage Exchange

In a single-stage exchange procedure, infected components and bone cement are removed, tissue is aggressively debrided, and definitive implants are placed in the same surgical setting. Local antibiotics are delivered during the procedure while postoperatively patients receive 4–6 weeks of intravenous antibiotics tailored to culture growth and sensitivities obtained from samples obtained during surgery. Indications include absence of bacteremia, positive isolation of causative organism with sensitivities, and minimal bone and soft tissue loss [82, 83]. Relative contraindications include bacteremia, culture-negative PJI, poor bone stock for fixation of new components, presence of a sinus tract, and soft tissue deficiencies which would preclude adequate closure of the wound [84–88].

The advantages of one-stage exchange compared to two-stage exchange are clear: decreased morbidity and mortality, reduced cost, and earlier functional return as only one surgery is required. However, research is conflicting with some data suggesting equivalence or superiority to two-stage exchange [89–91] while others suggest an elevated risk of reinfection [92]. However, research comparing the two treatment options suffer from heterogeneity of patient populations and are predominantly retrospective in nature. Therefore, several multicenter, prospective, randomized, controlled studies are underway to answer this important clinical question.

Two-Stage Exchange

In a two-stage exchange, the removal of infected components and reimplantation of new components occurs in two surgeries separated in time by the retention of an intra-articular polymethyl methacrylate (PMMA) spacer implanted during the first

procedure. The PMMA spacer, which may be retained for several months or even years, is impregnated with antibiotics which passively elute over time. The patient additionally receives 4–6 weeks of intravenous and/or oral antibiotics. While there is no definitive threshold as to when it is safe to reimplant, most surgeons will monitor serological and/or synovial markers. When they feel it is clinically appropriate, the spacer is removed and new components are implanted in a second procedure.

The PMMA spacer utilized during a two-stage exchange may be static, preventing motion through the implantation of a joint-spanning rod, or dynamic which allows partial to full range of motion (Fig. 6a, b). Due to the exothermic reaction (82–86 °C in femurs and 115 °C in tibias) that occurs during the curing of PMMA, the scope of antibiotics able to be incorporated is limited to those with heat stability, such as vancomycin or tobramycin [93]. Recent investigations suggest antibiotics once considered "heat-sensitive," such as ceftazadime, may be more resilient than previously thought but until more data are available, the antibiotic arsenal able to be incorporated into PMMA spacers remains limited [94, 95]. Further, the antibiotics in a PMMA spacer elute in a burst fashion, peaking in concentration on postoperative days two and three and quickly decreasing over several weeks. Finally, the spacer cannot be redosed with antibiotics once implanted. Research has demonstrated low-dose intraosseous or intra-articular vancomycin administration results in equal or better tissue and synovial fluid concentrations when compared to systemic administration and minimizes side effects [96, 97]. Methods to improve drug delivery options may provide improved treatment success allowing for minimization of both dosing concentrations and time needed for treatment.

Though the two-stage exchange procedure is associated with high rates of infection control for those patients who complete both stages (83–89.8%), it has also been shown to have substantial mortality [13, 92]. Prior reports in the 90–95% success range likely did not account for the attrition due to death between stages [89, 98]. After just the first stage for TKA, the 30-day readmission rate is 11.1% and 90-day mortality rate is 2.6% [99]. The 1-year and 5-year mortalities for completed TKA two-stage revision have been reported as 4.33% and 21.64%, respectively [100]. While considered the "gold standard" in the USA, two-stage revision leaves room for improvement of outcomes and places a substantial burden on the patient.

Resection Arthroplasty

When the race is truly lost in the face of recalcitrant infections, several procedures are available as salvage options to maximize the function and health of the patient. The decision to employ one of these options is a result of host factors, namely, poor soft tissue envelope or bone stock, a patient's physical and emotional exhaustion, and a reluctance or inability to continue with therapy.

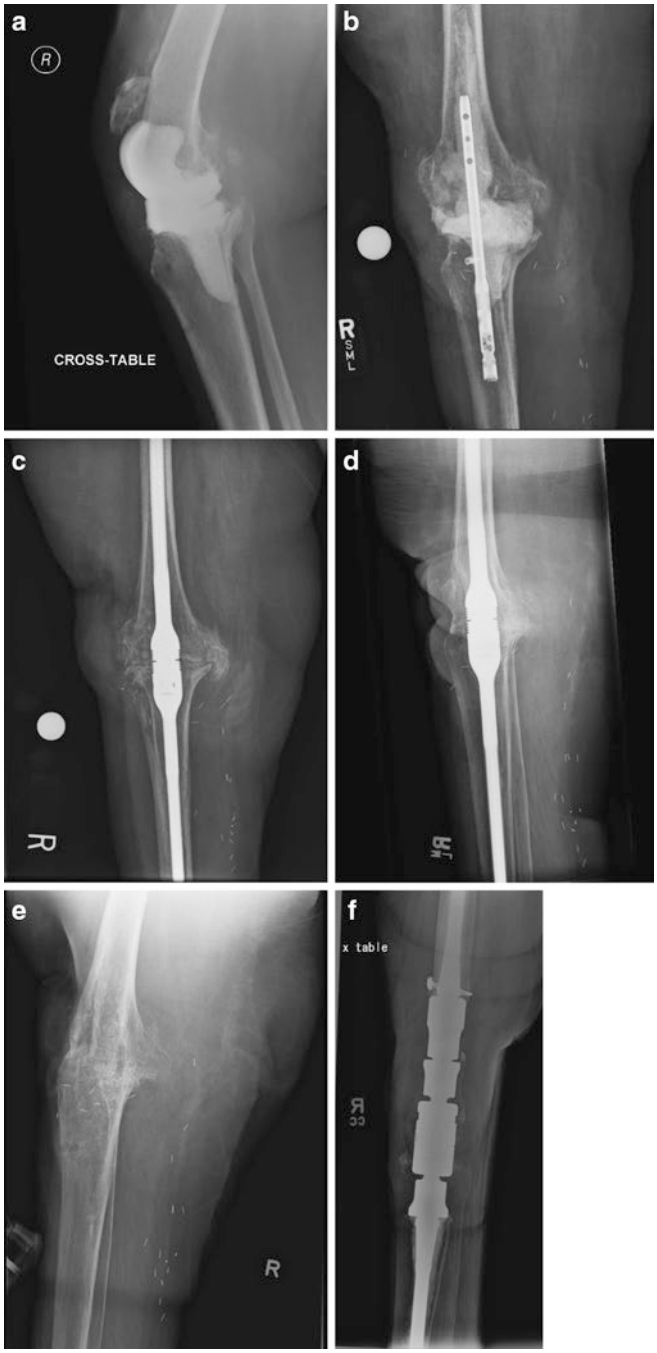


Fig. 6 (**a**) Lateral radiograph of an infected articulating spacer with an extensor mechanism disruption as demonstrated by the high-riding patella. (**b**) The same patient status post placement of a static spacer, in this case a humeral nail with high dose antibiotic cement. (**c**) Following explant of the static spacer, an intramedullary nail was placed for the knee fusion. (**d**) Due to the patient's poorly controlled diabetes and renal dysfunction requiring dialysis, 2 years later she presented with a reinfected implant though healed fusion. (**e**) The infected nail was removed and after debridement, the healed fusion was able to be retained. (**f**) If bony fusion is unobtainable, intercalary fusion presents another treatment option

Knee Arthrodesis and Above the Knee Amputation

In the setting of an infected TKA, knee arthrodesis (KA) may be employed to provide a stable, painless knee via intramedullary nail or compression plating which may be augmented temporarily by external fixation once all infected TKA components have been removed (Fig. 6c–f). The intramedullary nail may be coated with PMMA impregnated with antibiotics for further infection control. The knee is fused in full extension and therefore requires a rehabilitative period for gait training. Once fused, the patient can ambulate on their native leg and KA requires a lower energy expenditure (0.16 mL O_2/kg/min vs. 0.20 mL O_2/kg/min) when compared to an above the knee amputation (AKA) [101, 102]. The retention of the native knee, however, does retain a possible nidus for latent infection and reinfection rates of 5.4–10.6% have been reported [103]. Further, a significantly higher rate of postoperative complications has been associated with KA when compared to AKA [104]. Conversely, KA has been associated with improved functional outcomes and lower mortality when compared to AKA [105, 106]. Further, AKA has been associated with more systemic complications, longer hospital stays, and higher readmission rates [107]. Barring poor host factors such as severe comorbidities and poor soft tissue envelope or bone stock, KA is the preferred salvage procedure compared to its lower incidence of complications, lower mortality, and superior functional outcomes [104, 108].

Girdlestone and Hip Disarticulation

In the setting of recurrent THA infection, the Girdlestone procedure provides the surgeon with a salvage procedure in which prosthetic components are removed and infection is controlled at the expense of joint functionality (Fig. 7a–d). After implant removal, an osteotomy is performed just above the greater trochanter resecting the femoral neck and head. The hip capsule remains and fibrous tissue fills in creating a pseudarthrosis. No bony fusion occurs, allowing for a limited range of motion [109]. Patient satisfaction varies widely with the procedure (13–83%) with resolution of infection occurring in 80–100% of cases [110]. Conversely, a hip disarticulation, in which the entire lower extremity is amputated at the level of the hip joint, is considered a morbid procedure and reserved typically for life-threatening scenarios such as systemic sepsis or extreme soft tissue compromise [111]. In addition to limitations with weight bearing, special postoperative considerations exist such as wheelchair use requiring a special balance of weights to compensate for loss of the entire limb.

Adjunctive Antibiotic Therapy

Postoperative antibiotics are required regardless of procedure selected by the surgeon. Ideally, a causative organism with sensitivities is identified prior to surgery. Multiple samples are taken at the time of implant removal, and patients are started

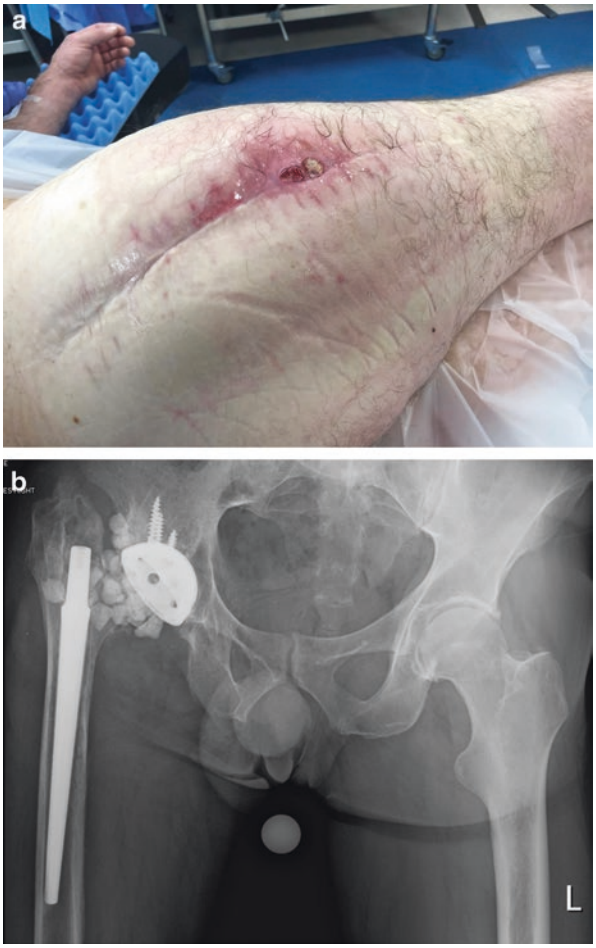


Fig. 7 (**a**) Clinical picture of a draining wound in a male with a history of multiple hip surgeries and eventual partial hip exchange for MRSA infection. Given his medical comorbidities, it was decided to proceed with a Girdlestone procedure, as any attempt for reimplantation would likely result in repeat infection. (**b**) Radiograph of the patient's prior partial hip resection. The femoral stem and acetabular cup were retained with placement of nonabsorbable antibiotic-impregnated PMMA beads. (**c**) Postoperative radiograph after debridement and removal of all components with placement of absorbable calcium sulfate high-dose vancomycin beads. (**d**) Radiograph 5 months after a Girdlestone procedure demonstrating the greater trochanter articulating with the pelvis. The patient now ambulates with a shoe lift and crutches

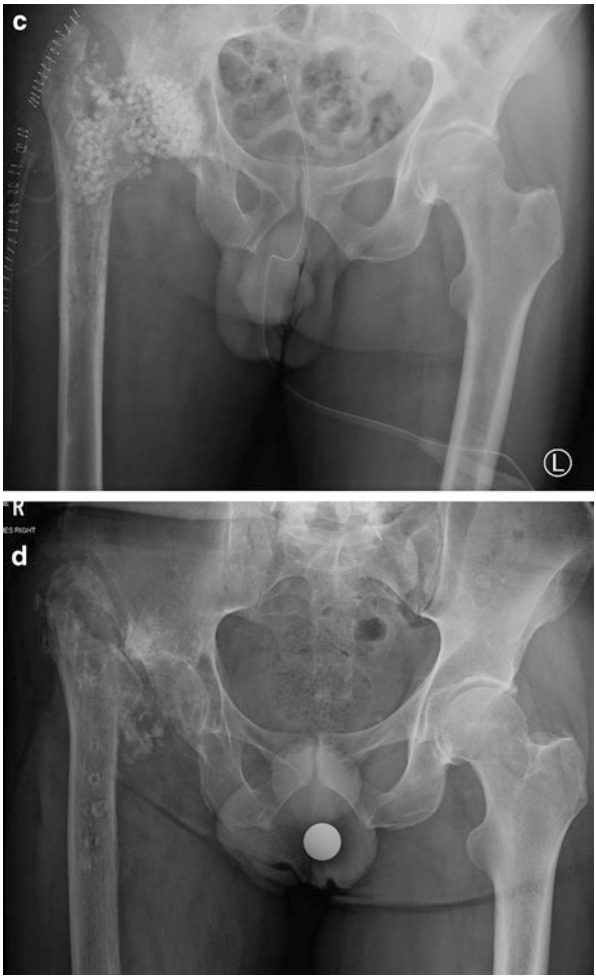


Fig. 7 (continued)

immediately postoperatively on empiric intravenous antimicrobials. Once sensitivities are obtained, drugs are then tailored to the specific organism(s). Multiple studies have demonstrated a success rate of 90–100% with the use of 6 weeks or less of intravenous antibiotics [112, 113] with one study directly examining a 1-week course vs. 6-week and finding no superiority [114]. Bernard et al. examined the outcomes of 144 patients treated with DAIR, one- and two-stage exchange, Girdlestone, or KA and found no advantage to antibiotic therapy longer than 6 weeks [115]. To date, no studies published have directly compared exclusively

oral vs. exclusively intravenous antibiotics. However, studies have demonstrated equivalent efficacy of beginning antibiotic therapy parenterally and then transitioning to oral [116–118]. The Infectious Disease Society of America currently endorses a 4–6-week course of intravenous or highly bioavailable oral antibiotics with a six-week course endorsed for more virulent organisms.

Negative Pressure Wound Therapy (NPWT)

NPWT or "wound vac" is often applied as an adjunct for wound closure and to contend with postoperative drainage in both primary and revision cases. Studies have demonstrated reduced wound exudate, fewer dressing changes required postoperatively, and a decreased rate of superficial wound infections [119, 120]. Given that the rate of infection increases 29% for TKA and 42% for THA for each additional day of postoperative drainage, many surgeons apply NPWT prophylactically [121].

Call to Action

Despite surgical, technological, and medical advances, the infection rate in total joint arthroplasty has remained largely unchanged for the last 30 years. Some have speculated infection can never truly be prevented and subsequently healthcare providers must remain ever vigilant in the face of this devastating complication. The race for the surface may not be a winning vs. losing proposition but rather is likely a continuous spectrum. The treatment for each patient should be as individualized as the clinical scenario and depends on host factors, microbial isolates, and treatment regimens available.

As bacteria adapt to our arsenal, so too must we continue our efforts against them. There is a critical knowledge gap and growing need for continued treatment evolution in the way of improved osteoinductive/antimicrobial materials at time of a reimplant, in addition to prevention technology. Given the impending rise in total joint arthroplasty case volume and subsequent revision case volume due to PJI, an urgent need exists for continued work in the development of preventive, diagnostic, and therapeutic tools.

Acknowledgements The authors would like to thank Suzanne Danley for her assistance and critical review of the manuscript.

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