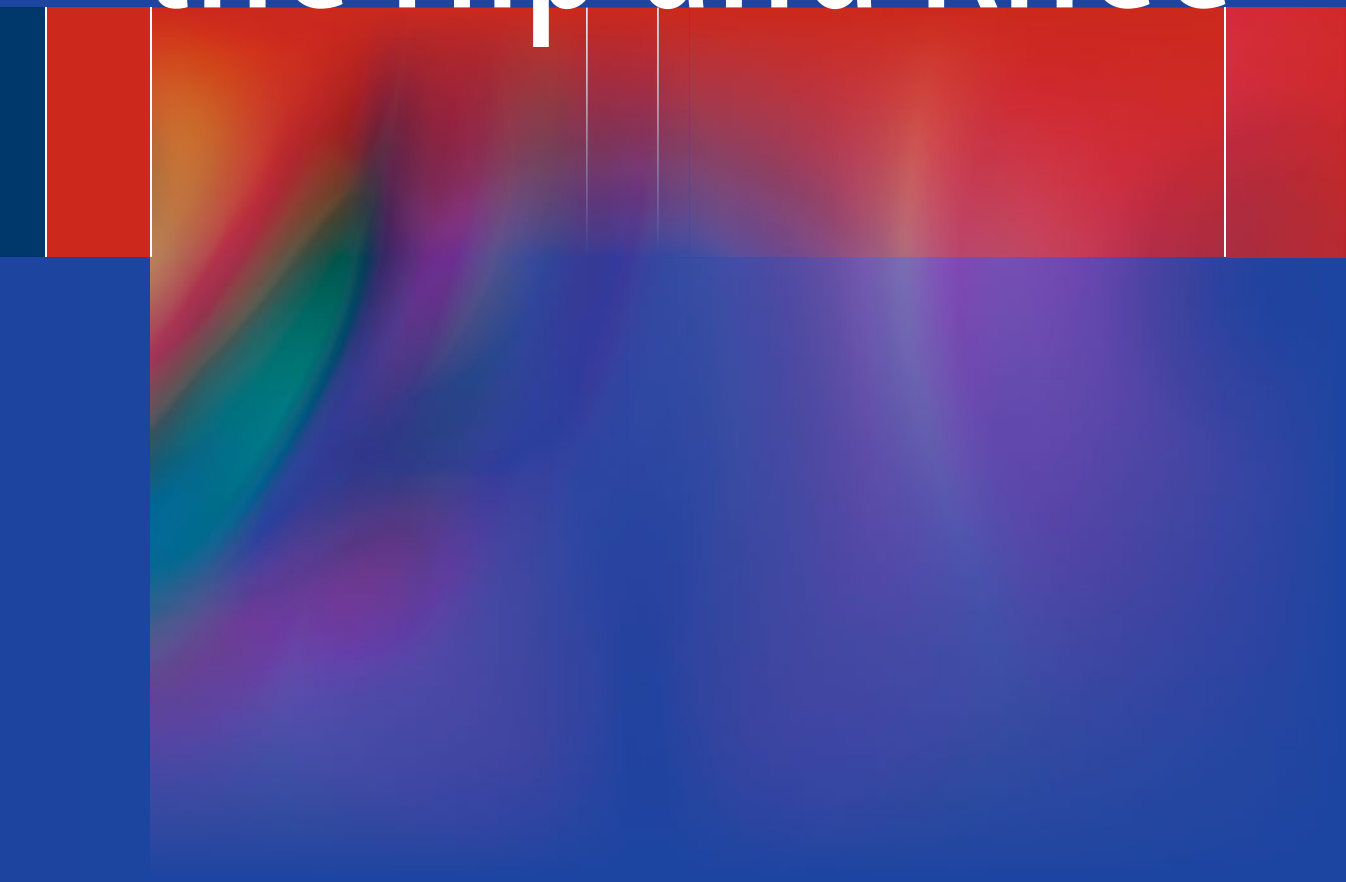
Bryan D. Springer · Javad Parvizi *Editors*

Periprosthetic Joint Infection of the Hip and Knee



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To those who have made my academic and personal life rewarding. To my wife, Fariba, who is the source of my inspiration. To my children Niosha and Cyrus who allow me to steal time from them for my selfish pursuits.

Javad Parvizi, M.D., F.R.C.S.

To my family, wife Summerson and children, Brycen, Finn, Bennett and Evie, whose true sacrifice allows me the time, energy, and effort to continue our work for the betterment of our patients.

Bryan D. Springer, M.D.

Foreword

The presence of periprosthetic total joint infection is frustrating for patient and surgeon alike. Patients who present for arthroplasty relying on a routine recovery are frequently devastated when on a rare occasion they incur a periprosthetic infection. These unexpected outcomes are costly and have significant socioeconomic implications. Therefore the clinician needs to be ever vigilant to correctly identify periprosthetic infection and treat such infections in an expeditious fashion.

While periprosthetic infection occurs infrequently, the number of arthroplasties performed continues to increase both nationally and internationally. Therefore the number of periprosthetic infections that occur even as a small percentage of the total number of implants in service results in a large infection burden. Therefore it behooves each and every arthroplasty surgeon to have an algorithmic approach to the recognition and treatment of such infections.

Dr. Springer and Dr. Parvizi have assimilated an international group of experts in periprosthetic infection to help guide the clinician through the diagnosis, treatment, and management of this difficult problem. The reader will find that if they apply the principles outlined in this book, satisfactory outcomes can be consistently obtained. While the diagnosis, management, and treatment of prosthetic infection will continue to evolve as more information becomes available, this book does an excellent job of synthesizing the current knowledge on this subject.

Charlotte, NC, USA — Thomas K. Fehring, M.D.

Preface

Very little in the care of total joint arthroplasty remains as devastating and vexing a problem as dealing with periprosthetic joint infection. There remain significant diagnostic and treatment hurdles in the prevention and cure of this entity. We are continually faced with more challenges, more resistant microbes, and less healthy host that require total joint arthroplasty. In addition, the economic impact of such treatment remains a tremendous burden to our healthcare system. All indicators point to an ever increasing burden of periprosthetic infection in our total joint arthroplasty population.

We are also at a time in the history of periprosthetic joint infection, where technology is offering us new insights into the prevention, diagnosis, and treatment of periprosthetic infection, where leading researchers and clinicians are working diligently to improve the outcomes of our patients faced with periprosthetic infection.

Despite these advances, there remains little consensus in many areas of periprosthetic infection. We hope that the work put forth in this book, by many of the thought leaders in periprosthetic infections, can serve as the reference for periprosthetic joint infection. The literature and data remain ever changing, but the foundation and principles of treatment remain the same.

Charlotte, NC, USA — Bryan D. Springer, M.D.
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Epidemiology of Total Hip and Knee Arthroplasty Infection

1

David J. Jaekel, Kevin L. Ong, Edmund C. Lau, Heather N. Watson, and Steven M. Kurtz

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are some of the most cost-successful surgical procedures and have allowed continued mobility and function for millions of patients with advanced degenerative joint disease. Continuous innovation and improvements of implants and surgical techniques have increased implant longevity and reduced implant wear and therefore negative patient outcomes [1–4]. However, the occurrence of infection has not reduced with advancement of implants and, in certain cases, has even increased [5–8]. Prosthetic joint infection (PJI) is a rare but devastating and sometimes life-threatening complication of total joint arthroplasty (TJA) that is associated with longer hospital stay, increased hospital cost, and higher morbidity. PJI is challenging to cure and is nonresponsive to systemic antibiotics because of how the infection develops on an implant surface. While short-term infection burden was originally reported as low as 0.2 % and 0.4 % for THA and TKA, respectively [9, 10], thousands of patients continue to present with painful complications and are an economic burden for hospitals because of inadequate reimbursement [11, 12]. To fully comprehend the societal burden of arthroplasty implant infection, the risk and incidence of this complication must be defined. Information on infection incidence in regard to THA and TKA from various sources ranging from single-center studies to large-scale multi-institution studies and national registries has been analyzed, but has not been synthesized for a broader view of the economic impact of PJI.

The later chapters of this book will discuss, in detail, the development and progression of PJI in THA and TKA, but the primary focus of this chapter is to catalogue the incidence of infection within populations across the globe and define what risk factors have the highest influence on infected revisions in the future. The first goal of this chapter is to collect and to compare infection

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rates from implant databases and national registries, which provide the largest sources for categorizing clinical utilization and device failure mechanisms. Next, this chapter identifies the influences of various risk factors such as age, sex, antibiotic cement use, and material type on the risk of PJI. Finally, the infection rates for revised components are discussed along with the overall economic impact of PJI in society.

Registries

International registries represent a vast and consistent source of data regarding the utilization of TJA in Australia and Europe. A registry is more than a data repository for basic clinical, patient, and implant data regarding the implantation and revision of TJAs. Where registries have been established, the information provides continuous feedback to clinicians in order to further the enhancement of surgical procedures. Sweden first established an orthopedic implant registry in the 1970s, with the rest of Europe and Australia following soon after.

National registries are significant in providing perspective on the current use and outcome of TJA across the globe; however, registries are not the only tool to measure the utilization of arthroplasty procedures. For example, neither the USA nor Germany currently has in place a national registry for joint replacements. These databases provide necessary information concerning the current use of TJA that is otherwise unavailable in these countries.

Public Data Sources

Administrative claims databases are an important source of data for TJA, even in countries with an established registry. These databases collect a sampling of electronic hospital discharge records, or as with the Medicare database in the USA, the complete insurance claim history for individual patients. Specific hip and knee replacement procedures are classified in these databases by hospitals in accordance with the codes from the International Classification of Diseases, Clinical Modification, 9th Revision (ICD-CM-9). Claims filed by surgeons and clinics often use current procedural terminology (CPT) codes. In the USA, three public sources of administration claims data are available and are summarized in the following subsections.

The National Hospital Discharge Survey (NHDS, http://www.cdc.gov/nchs/nhds/about_nhds.htm2009) is conducted annually by the National Center for Health Statistics (NCHS). The program was started in 1965 and has continuously recorded a statistically representative sample of hospitalizations from nonfederal and nonmilitary short-stay community hospitals across the USA. It is currently the oldest and most well-established inpatient discharge database available in the USA. The NHDS acquires inpatient records from 239 hospitals and samples ~300,000 discharge records each year. The NHDS database includes patient demographics (e.g., age and sex), disease diagnosis, procedures performed, resource utilization, and institutional characteristics.

The Nationwide Inpatient Sample (NIS, http://www.hcup-us.ahrq.gov/nisoverview.jsp) was established in 1988 by the Healthcare Cost and Utilization Project (HCUP) of the Agency of Healthcare Quality and Research (AHRQ). It has a far larger sample size than the NHDS in terms of both discharge records and number of hospitals. The NIS includes twice the number of hospitals and collects 25 times more records with an average of 5–8 million records per year. The NIS annually samples 20 % of US inpatient hospital stays. The NIS is able to capture patient, payer, and hospitalization factors, including charges, cost, and reimbursement information during hospitalization, which facilitates the evaluation of the economic impact of specific diagnoses and procedures.

Made available by the Center for Medicare and Medicaid Services (CMS), the 5 % Medicare Limited Data Set (LDS) consists of seven components: hospital inpatient, hospital outpatient, home health agency, skilled nursing facility, hospice care, physician carrier (Part B), and durable medical equipment. LDS also tracks the date of death or the rare withdrawal of a patient from the program with a denominator file. Medicare

beneficiaries in the LDS are identified with an encrypted identification number that is linked through all aspects of the database as well as time. For this reason, utilization of healthcare resources by a patient can be traced through different systems such as inpatient, outpatient, or home hospice care. Medicare data is also available in the 100 % format, i.e., for all Medicare beneficiaries. Of the seven file components, the inpatient, outpatient, home health agency, skilled nursing facility, and hospice care data are available in the 100 % format, but not the physician carrier and durable medical equipment data.

Infection and Reinfection Incidence in Primary and Revision TJA

In the modern history of arthroplasty surgery, the number of TKA procedures has been greater than the number of THA performed internationally; and therefore, in 2008, when one of the largest studies of a US medical database analyzed data collected by the NIS between 1990 and 2004, it was expected that the number of infections would follow similar trends. By 2004, approximately 5,838 knee arthroplasties were revised because of infection while only an estimated 3,352 hip arthroplasties were revised because of infection, yet both yielded similar infection rates of 1.04 % (Table 1.1) [13]. The data were collected using the ICD-9-CM procedure codes for primary or revision THA (81.51 and 81.53, 00.70–00.73, respectively) and TKA (81.54 and 81.55, 00.80–00.84, respectively). However, this method excluded infected arthroplasty devices that were removed as the first stage of a two-stage infection treatment protocol. Upon revisiting the NIS database in 2012, the analysis of the 2001–2010 datasets included ICD-9-CM procedural codes for arthrotomy or removal of a hip (80.05) or knee (80.06) prosthesis with PJI (ICD-9-CM 996.66), and the number of infected prostheses nearly doubled. In the updated analysis of the 2004 dataset, the number of infections increased for THA from 3,352 to 5,933 and for TKA from 5,838 to 10,677 (Tables 1.1 and 1.2).

The revision burden for infections as a proportion of the total number of primary and revision arthroplasties was additionally calculated; and in 2001, the infection burden rates for THA and TKA were 1.99 % and 2.05 %, respectively.

Table 1.1 Number of infections and infection rates from patients with both primary and revision hip or knee replacement surgery from the Kurtz et al. 2008 analysis of the NIS [13]

	Total hip arthroplasty				Total knee arthroplasty			
Year	Infected procedures	Percent surgery with infection (%)	Lower 95 % confidence interval (%)	Upper 95 % confidence interval (%)	Infected procedures	Percent surgery with infection	Lower 95 % confidence interval (%)	Upper 95 % confidence interval (%)
1990	1,104	0.66	0.51	0.80	1,090	0.63	0.52	0.74
1991	922	0.54	0.43	0.65	1,197	0.61	0.49	0.74
1992	1,192	0.66	0.56	0.77	1,629	0.71	0.59	0.84
1993	1,154	0.67	0.54	0.81	1,470	0.65	0.53	0.76
1994	1,207	0.66	0.51	0.82	1,577	0.63	0.54	0.73
1995	1,092	0.61	0.50	0.73	1,793	0.69	0.58	0.81
1996	1,350	0.71	0.60	0.83	2,105	0.74	0.63	0.85
1997	1,534	0.79	0.68	0.90	2,479	0.82	0.71	0.92
1998	1,797	0.92	0.75	1.10	2,771	0.98	0.85	1.11
1999	1,844	0.94	0.79	1.10	2,984	1.00	0.87	1.12
2000	1,989	0.96	0.82	1.11	3,051	0.97	0.86	1.08
2001	2,398	1.04	0.91	1.18	3,644	1.04	0.93	1.15
2002	2,879	1.17	1.01	1.32	4,273	1.09	0.96	1.22
2003	2,878	1.17	1.03	1.32	5,324	1.26	1.11	1.40
2004	3,352	1.23	1.07	1.40	5,838	1.21	1.07	1.36

Table 1.2 Number of infections, infection rates, and resource utilization from patients with both primary and revision hip or knee replacement surgery between 2001 and 2010

	Total hip arthroplasty in the USA				Total knee arthroplasty in the USA			
Year	Number of infected procedures [95 % CI]	Percentage of infected procedures [95 % CI]	Mean cost per case of infected (thousands 2011 US$) [95 % CI]	Mean length of stay per infected [95 % CI]	Number of infected procedures [95 % CI]	Percentage of infected procedures [95 % CI]	Mean cost per case of infected (thousands 2011 US$) [95 % CI]	Mean LOS per infected [95 % CI]
2001	4,545 [3,757–5,333]	1.99 % [1.78–2.21]	33.0 [29.8–36.2]	11.5 [10.3–12.7]	7,113 [6,038–8,187]	2.05 % [1.86–2.23]	26.7 [23.7–29.6]	9.3 [8.2–10.4]
2002	5,219 [4,346–6,092]	2.15 % [1.93–2.36]	33.4 [30.5–36.4]	12.1 [11.2–13.1]	8,532 [7,246–9,819]	2.20 % [1.99–2.41]	25.6 [23.7–27.4]	9.0 [8.4–9.7]
2003	5,271 [4,389–6,154]	2.20 % [1.97—2.43]	34.9 [31.2–38.5]	12.5 [11.4–13.5]	9,936 [8,377–11,495]	2.38 % [2.13-2.63]	27.9 [24.1–31.7]	9.0 [8.0–10.0]
2004	5,933 [4,965–6,901]	2.23 % [2.00–2.46]	31.2 [28.6–33.8]	10.5 [9.7–11.3]	10,677 [9,101–12,253]	2.26 % [2.06–2.47]	25.6 [23.7–27.5]	8.4 [7.8–8.9]
2005	5,634 [4,726-6,541]	2.03 % [1.83–2.22]	31.6 [28.8–34.5]	10.8 [10.0–11.6]	12,113 [10,341–13,884]	2.23 % [2.05–2.41]	25.6 [23.7–27.4]	7.9 [7.5–8.3]
2006	6,213 [5,167-7,268]	2.32 % [2.06–2.58]	31.9 [29.2–34.6]	11.1 [10.2–12.1]	12,488 [10,748–14,227]	2.30 % [2.12–2.49]	25.7 [24.6–26.8]	8.1 [7.8–8.5]
2007	6,926 [5,809-8,052]	2.36 % [2.16–2.56]	33.2 [30.3–36.1]	10.5 [9.7–11.4]	13,424 [11,551–15,298]	2.23 % [2.07—2.40]	25.7 [24.1–27.3]	7.8 [7.4–8.2]
2008	7,380 [6,195–8,564]	2.29 % [2.06-2.53]	31.5 [29.2–33.8]	9.5 [8.9–10.0]	15,983 [13,837–18,129]	2.37 % [2.17–2.56]	26.3 [24.9–27.7]	7.4 [7.1–7.7]
2009	7,162 [6,005–8,319]	2.18 % [1.97–2.39]	31.9 [29.1–34.7]	9.5 [8.8–10.2]	14,802 [12,681–16,924]	2.18 % [1.99–2.37]	25.5 [24.0–26.9]	7.2 [6.9–7.5]
2010	7,761 [6,518–9,005]	2.21 % [1.98–2.44]	31.7 [29.9–33.6]	9.3 [8.7–9.8]	16,798 [14,437–19,159]	2.32 % [2.14–2.50]	26.2 [24.6–27.8]	7.1 [6.8–7.4]

Source: Extracted from the Kurtz et al. 2012 NIS analysis [14]

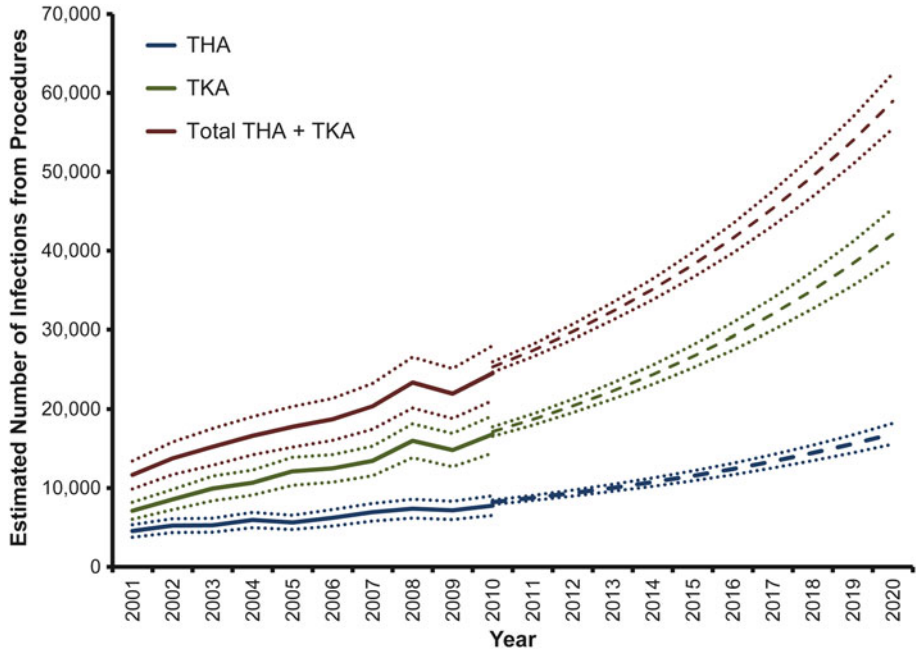

Fig. 1.1 Historical and projected number of infections with THA, TKA, and combined THA and TKA procedures within the USA between 2001 and 2020. *Dashed lines* represent the projected values per procedure, whereas the *dotted lines* represent the 95 % CIs of the NIS estimates from 2001 to 2010 and the statistical projections. The total cost was adjusted to 2012 using the Consumer Price Index [14]

These rates were also almost twice the previous calculations (1.04 % and 1.04 %, respectively). By 2010 (the most recent dataset available from NIS), the infection burden for both THA and TKA increased to 2.21 and 2.32 %; however, this increase was only significant for TKA. A more dramatic increase was observed in the raw numbers of infected arthroplasties, which grew from 4,545 and 7,113 in 2001 to 7,761 and 16,798 in 2010 for THA and TKA, respectively. The average infection burden across the sampled years remained similar at 2.20 % for THA and 2.25 % for TKA. Using a Poisson model coupled with population projections from the US Census Bureau, the NIS data were used to predict that the number of infected TKAs will increase from 16,798 in 2010 to 42,079 by 2020 (Fig. 1.1) [14]. The analysis of the NIS data also showed a steep decline in length of hospital stay for patients, which could influence the chance of discovering an early infection during the initial hospital stay and delay infection from a revision procedure [13].

Single-institution studies in the USA indicated similar incidence of infection in their patient groups. Pulido et al. monitored 9,245 patients and measured an overall incidence of 0.7 % with joint-specific incidence of 1.1 % for TKA and 0.3 % for THA (Tables 1.3 and 1.4) [15]. Malinzak et al. reported infection rates of 0.52 % and 0.47 % for TKA and THA, respectively, after monitoring 8,494 cases from 1991 to 2004 [16]. When concentrating on the Medicare LDS, which thus limited the population to ages over 65, infection occurred in 2.01 % of TKA [17] and 2.22 % for THA [18]. This study followed similar trends that were observed nationally in the USA.

Internationally, hospitals and clinics also experienced an infection incidence of nearly 1 % (Tables 1.3 and 1.4) [19–22]. For TKA procedures, infection occurred in 0.8–0.9 % of cases in Finland when observed from single-institution studies or analysis of data from the Finnish Arthroplasty Register from 1997 to 2006 [20, 21]. Similarly, a single-institution study in Japan

Table 1.3 Infection rates for total hip arthroplasty (THA)

Country	Infection rate (%)	Time period analyzed	Literature source	Data source
USA	1.99–2.20	2001–2010	Kurtz et al. [14]	NIS
USA	0.3	2001–2006	Pulido et al. [15]	Single institution
USA	0.47	1991–2004	Malinzak et al. [16]	Single institution
USA	2.22	1997–2006	Ong et al. [18]	Medicare 5 %
Norway	0.7	2005–2006	Dale at al. [19]	Norwegian Registry

Table 1.4 Infection rates for total knee arthroplasty (TKA)

Country	Infection rate (%)	Time period analyzed	Literature source	Data source
USA	1.21	2001–2010	Kurtz et al. [13]	NIS
USA	1.1	2001–2006	Pulido et al. [15]	Single institution
USA	0.52	1991–2004	Malinzak et al. [16]	Single institution
USA	2.01	1997–2006	Kurtz et al. 2010 [17]	Medicare 5 %
Finland	0.8	2002–2006	Jamsen et al. [21]	Single institution
Finland	0.9	1997–2006	Jamsen et al. [20]	Finnish Arthroplasty Register
Japan	0.8	1995–2006	Susuki et al. [22]	Single institution

observed that infections occurred in 0.8 % of TKA procedures performed between 1995 and 2006 [22]. For THA, an analysis of the Norwegian Arthroplasty Register data from 2005 and 2006 revealed an infection incidence of 0.7 % [19]. Studies in the USA and abroad suggest that infection rates for the general population are similar and are estimated to range from approximately 0.7 to 2.25 % [13–16, 18–23]. It is unknown how many of these studies adjusted the numbers to include patients treated with a two-stage revision procedure. Generally, periprosthetic infections occur rarely but have a significant impact on morbidity and resource utilization. As the number of revisions continues to meet or exceed projected increases, infections will have an increased impact on the population of arthroplasty patients [13].

Infection can develop at various moments over the course of the lifetime of primary joint replacement implants and is not confined to the short period after surgery. Typically, time to infection diagnosis can range from 2 weeks postoperatively to over 3 years [15, 18, 19, 22, 24]. Nevertheless, understanding which periods most infections occur in is crucial to accurately enhancing future preventative measures. In a study of 9,245 patients in the USA, Pulido et al. reported that 27 % of infected TJA occurred within the first 30 days postoperatively while 65 % developed an infection within the first year postoperatively. The average time to diagnosis of infection was approximately 1.2 years [15]. In a retrospective analysis by Malinzak, 83.7 % of infections were diagnosed within 2 years with an average time to infection of 9.6 months [16]. For patients over 65 years of age in the US Medicare population, 73–77 % of all THA and TKA were diagnosed with infection within 2 years of primary surgery [17, 18]. Specifically for TKA, the incidence of infection was 1.55 % within 2 years, but dropped to 0.46 % between 2 and 10 years postoperatively [17]. In congruence with US data on TKA, the Finnish Arthroplasty Register reported that 68 % of patients operated on between 1997 and 2004 were diagnosed with PJI within the first year postoperatively [20, 21]. Suzuki et al. found that infection developed within 3 months in 65 % of primary TKA cases at a single institution in Japan [22]. The Norwegian Arthroplasty Register noted a median time to revision for infection with primary THA of 47 days (range 4–1,782 days) [19]. The incidence of revision due to infection increased rapidly in the first year after surgery but declined beyond 1 year in the patient population captured by the Australian Joint Replacement Registry [25]. Even though the sources of the data range in region and scope, the consensus shows that greater than 60 % of infections are detected within 1 year

Table 1.5 Incidence of infection within revisions

Country	Hip/knee	% of revisions	Time period	Source	Data source
USA	Hip	8.4	1990–2004	Kurtz et al. 2007 [53]	NIS
USA	Hip	14.8	2005–2006	Bozic et al. [27]	NIS
Australia	Hip	8.2	2010	National Arthroplasty Registry [25]	Registry
Norway	Hip	15–20	2009	National Arthroplasty Registry [28]	Registry
Sweden	Hip	10.8	2008	National Arthroplasty Registry [30]	Registry
USA	Knee	16.7	1990–2004	Kurtz et al. 2007 [53]	NIS
USA	Knee	25.2	2005–2006	Bozic et al. [26]	NIS
Australia	Knee	15.4	2010	National Arthroplasty Registry [25]	Registry
Sweden	Knee	~20	2011	National Arthroplasty Registry [30]	Registry

of surgery and an overwhelming majority is diagnosed by 2 years post-primary THA or TKA.

A recent analysis of NIS data from 2005 and 2006 revealed that infection is the third most frequent reason for revision of THA, accounting for 14.8 % of revisions and the most frequent for TKA with 25.2 % of revisions (Table 1.5) [26, 27]. Infection was also the most common indication for arthrotomy and removal of prosthesis for either THA (74.3 %) or TKA (79.1 %). Following similar trends, the Australian National Joint Replacement Registry 2010 annual report indicated infection as the third most prevalent reason for revision of THA (15.4 %) and the second most for TKA (17.1 %) [25]. Similarly, 15–20 % of THA revisions in Norway from 2007 to 2010 were due to infection [28] and 17 % of THA in Sweden in 2008 were due to infection [29]. An estimated 20 % of TKA revisions were caused by infection in the Swedish population in 2001 [30]. However, compared to other reasons for revision in Sweden, the frequency of infection reduced from 25.9 % during the first 2 years postoperatively to 2.9 % within10 years.

When the focus of the analysis is narrowed to revised ultra-high molecular weight polyethylene hip cup liners, similar trends are observed. In a study of 212 revised acetabular liners, the most frequent reason for revision was loosening (35 %), followed by instability (28 %) and infection (21 %) [24]. Infection was preceded by aseptic loosening as a more frequent cause of revision in almost all studies and data sources sampled. The one exception in the literature was a study by Bozic et al. which reported infection as an overwhelmingly more frequent reason for revision of TKA (25.2 %) than loosening (16.1 %) [26]. Recently, many experts suggest that the infection rates are masked by various clinical circumstances and in some cases of aseptic loosening and poor fixation, subclinical infections are the real cause [31–33]. Septic loosening was suspected when bacteria were recovered from aseptically loose implants by more vigorous methods for detecting surface bacteria, such as polymerase chain reaction assays and implant sonication [31–33]. If antibiotics are administered before the retrieval of diagnostic samples, there is also an increased probability of missing the infection [34]. With improved diagnostic techniques for detecting infected arthroplasty components, infection could become the primary cause of revision surgery. However, even without new diagnostic methods, PJI has the potential to become the most prevalent implant failure mode for TJA procedures in the USA and abroad within the next 2 decades.

Infection following a primary arthroplasty procedure is already a taxing ordeal because of pain, increased hospital stay, and the two-stage exchange process. Nevertheless, infection is additionally associated with higher reinfection rates [20, 35–37]. Revised TKA, regardless of revision reasons, is linked to lower infection-free survival rates than primary procedures and has an infection rate of approximately 8.25 % [20]. TKA devices specifically revised for infection have increased infection rates ranging from 10 to 33 % [35–37]. Many studies on reinfection suffer from small cohort sizes, which may explain the variability in infection rates. The largest study thus far was conducted at the Mayo clinic and focused on 368 patients who had TKA revised for infection between 1998 and 2006 [35]. 15.8 % of

the patients developed reinfection and 86 % of cases were categorized as late chronic infections. The median time to reinfection was 3.6 years (range: 0.01–7.82 years) and the only significant risk factor associated with reinfection was chronic lymphedema [35]. The findings fall in the ranges previously reported for reinfection and highlight the long-term effects of developing device-related infections.

Risk Factors Associated with PJI

In the literature, numerous patient, social, and surgery-related risk factors have been associated with PJI, ranging from sex to allogenic blood transfusion (Table 1.6) [9, 11, 15–22, 38–40]. Earlier in this chapter TKA was shown to be associated with minor but significantly higher infection rates than THA [13, 15, 16]; and for both procedures, the most commonly reported risk factor was gender. In eight studies reviewing risk factors for infection in multiple international registries and individual institutions, males were at higher risk than their female counterparts [9, 17–22, 29, 30, 41]. A 2010 report from the Australian Hip and Knee Registry found that at 9 years postoperatively, the cumulative incidence of infection was 1.3 % for males and only 0.6 % for females [25]. After a retrospective review of 2,022 primary TKAs, Suzuki et al. suggested the difference in infection rates could be due to differences between sexes in the pH level of the skin, sebum induction, and skin thickness [22]. In contrast, Dale et al. proposed that the disparities between sexes could be caused by differences in referral thresholds or bacterial flora [19]. However, definitive reasons for the differing infection rates remain unknown.

Elevated body mass index (BMI) is frequently reported as a risk factor for PJI [15, 16, 18, 22, 38, 39]. In a retrospective study of 6,108 THA and TKA patients by Malinzak et al., BMI greater than 50 was associated with an infection rate of 7.0 %, BMI greater than 40 but less than 50 was 1.1 %, and less than 40 was 0.47 %. When limited to TKA patients, BMI over 40 was 3.3 times more likely to lead to an infection when compared to BMI less than 40. In a similar analysis, Jämsen et al. reviewed 8,775 primary THA and TKA procedures recorded in the Finnish Joint Register that were performed between 2002 and 2008 [40]. Overall infection rates increased from 0.37 % in patients with normal BMI to 4.66 % in the morbidly obese. Obesity, however, was not a predictor of PJI if the BMI of the patient was below 40 kg/m^2 [40]. The underlying mechanisms for the increased infection rate may be linked to greater technical difficulty, longer duration of the procedure, poorly vascularized fatty tissue, and associated comorbidities in this elevated-BMI population [40].

Increased BMI could be compounded by diabetes, which has long been known as another risk factor for PJI [16, 18, 42, 43]. Diabetes has been shown to have a high correlation with PJI, in addition to elevating glucose levels postoperatively [16]. Jämsen et al. discovered that infection occurred in 1.59 % of THA and 2.19 % of TKA patients previously diagnosed with diabetes, while infection rates in nondiabetic patients were 0.66 % and 0.48 %, respectively [40]. Jamsen et al. found a correlation between elevated preoperative glucose levels and increased infection rate in obese patients. Patients with uncontrolled diabetes are potentially the population of arthroplasty patients with the poorest glycemic control, which directly influences their risk of infection [42]. However, a review of 751,340 primary and revision THA and TKA by Bolognesi et al. revealed no increase in the rate of infections in

Table 1.6 Risk factors commonly associated with PJI summarized from the literature [15, 16, 18, 22, 38, 39]

Patient-related risk factors	Social and surgery-related risk factors
Male gender	Larger, urban nonteaching hospitals
Higher BMI/obesity	Patients receive public assistance
Age	Longer-duration procedures
Preexisting comorbidities	Increased blood loss
Urinary tract infection	Allogenic blood transfusion
Rheumatoid arthritis	Lack of antibiotic cement
Diabetes	Revision TKA
Preoperative nutritional status	Emergency vs. planned surgery
ASA risk score > 2	Previous open reduction/ internal fixation
	Postoperative complications

the diabetic patient population [16, 18, 42, 43]. Patient management of the disease may also explain the discrepancy between the findings of these studies. Marchant et al. retrospectively compared hospitalizations from 1998 to 2005 from the NIS database with controlled and uncontrolled diabetes mellitus and found that there is a much higher chance of developing a wound infection when diabetes is inadequately controlled (odds ratio: 2.28) [42].

Other comorbidities amplify a patient's risk for PJI after TJA. The American Society of Anesthesiologists (ASA) physical status classification system assesses the physical state of a patient prior to surgery. In the literature, ASA scores greater than two have been identified as a risk factor for PJI, which signifies that the incidence of infection increases with even minor comorbidities [15, 19, 21]. Preexisting comorbidities have been previously connected to poor functional outcomes and other complications postoperatively. Ong et al. and Kurtz et al. identified several comorbidities as one of the primary risk factors for increased incidence of PJI as measured by the modified Charlson Index [17, 18]. Additionally, postoperative complications, previously linked to patient comorbidities prior to surgery, were also a risk factor for PJI [11, 20].

Rheumatoid arthritis (RA), as compared to osteoarthritis (OA), was also found to be a significant risk factor for infection by both the Norwegian and the Finnish Arthroplasty Registers [20, 21, 28]. A study of 2,647 patients reported an incidence of infection of 2.45 % for RA and 0.82 % for OA from 2002 to 2006 [21]. Other noted, but less prominent, risk factors for PJI mentioned in the literature were increased blood loss [11], elderly patients [19], emergency vs. planned surgery [19], revision TKA [20], race [9], previous open reduction or fixation surgery [22], nutritional status [44], urinary tract infection [15], and allogenic blood transfusion (Table 1.6) [15].

Multiple studies utilized the Charlson Comorbidity Index (CCI) to identify the presence of patient comorbidities in various databases and institutions, including the Medicare administrative claims database [9, 11, 15–22, 38, 39]. Studies by Kurtz et al. and Ong et al. identified preexisting comorbidities, longer-duration procedure, receiving public assistance for premiums, and male sex as risk factors for PJI in the Medicare population [17, 18]. The CCI evaluated preexisting conditions based on one composite score for 19 comorbid conditions; thus, patients with different combinations of preexisting conditions may still have the same CCI score.

Bozic et al. proposed that the CCI does not have the specificity to define the impact of individual diseases on patient outcomes, especially in elderly populations [45, 46]. Bozic et al. used the 5 % national sample of the Medicare database to detect associations between infection and specific preexisting medical comorbid conditions for either THA or TKA patients. A multivariate Cox regression was used to evaluate the link between infection and 29 distinct comorbidities. After adjusting for the effects of all 29 comorbidities, 13 conditions showed a significant effect on risk of infection following TKA. In order of significance for their impact on the outcome of TKA, the conditions with the highest risk of PJI were congestive heart failure, chronic pulmonary disease, preoperative anemia, and diabetes (Table 1.7) [45]. For THA, the highest attributable risk was associated with rheumatologic disease, obesity, coagulopathy, preoperative anemia, congestive heart failure, and diabetes (Table 1.7) [46]. The 5 % Medicare sample, compared to other databases, allowed for the identification of specific disorders as risk factors for infection. The focus of this research was to provide a basis for superior clinical decision-making in populations of patients aged 65 and above [45].

There are also several social and surgical risk factors for PJI. Public assistance is also associated with higher risk of infection [13, 17, 18, 47]. Ong et al. suggest that public assistance is an indication of socioeconomic status, which could indicate nutritional level, obesity, and existence of comorbidities that would predispose patients for higher risk of PJI [18]. Revision infection rates of primary TKA were also higher at large nonteaching urban hospitals as opposed to rural and teaching institutions [13, 26]. It is more likely a reflection of treatment patterns for revision surgery where urban nonteaching hospitals are often referral centers for revision (including

Table 1.7 Risk factors in elderly Medicare patients with TKA and THA compiled from Bozic et al. [45, 46]

Total knee arthroplasty		Total hip arthroplasty	
Risk factor	Adjusted hazard ratio	Risk factor	Adjusted hazard ratio
Congestive heart failure	1.28	Rheumatologic disease	1.71
Chronic pulmonary disease	1.22	Obesity	1.73
Preoperative anemia	1.26	Coagulopathy	1.58
Diabetes	1.19	Preoperative anemia	1.36
Depression	1.28	Diabetes	1.31
Renal disease	1.38	Cardiac arrhythmia	1.30
Pulmonary circulation disorders	1.42	Peripheral vascular disease	1.29
Obesity	1.22	Depression	1.38
Rheumatologic disease	1.18	Psychosis	1.48
Psychosis	1.26	Congestive heart failure	1.22
Metastatic tumor	1.59	Alcohol abuse	1.72
Peripheral vascular disease	1.13	Hypertension	1.14
Valvular disease	1.15	Malignancy	1.13

infection) when primary surgery was performed elsewhere [13]. Longer-duration procedures have also increased the risk of PJI in arthroplasty patients and could potentially be caused by increased wound exposure to foreign bacteria (*Staphylococci*, *E. coli*, etc.) and other virulent organisms that are causative agents for PJI [15, 17, 18, 48].

The use of bone cement can similarly impact the occurrence of infection in both hip and knee arthroplasties [19–21, 49]. The exclusion of antibiotic bone cement is one of the primary determinates for revision of either primary or revision TKA procedures [20]. Analysis of the Finnish Arthroplasty Register observed fewer infections when antibiotics were delivered in combination with bone cement and IV, although lack of bone cement alone elicited a more dramatic effect [20]. Multiple reviews of clinical results for THA have also shown up to a 50 % higher chance of infection when antibiotic bone cement was excluded [19, 49]. Antibiotics administered intravenously may not penetrate low vascular areas in high enough concentrations to adequately reduce infection, while bone cement facilitates the direct delivery of antibiotics locally to the surface of the implant and surrounding tissue [50].

PJI results when bacteria or other microbes attach to an implant surface; therefore, biomaterial selection could influence bacterial adherence and proliferation. Typically, bearing surfaces for replacement hips are either metal on polyethylene (M-PE), metal on metal (M-M), or ceramic on ceramic (C-C). By using the 100 % Medicare inpatient claims database from 2005 to 2007, Bozic et al. were able to compare infection rates between material couplings used for bearing surfaces [38]. After adjusting for patient and hospital factors, M-M bearings were found to be at a higher risk for infection (0.59 %) when compared with C-C bearings (0.32 %). However, the infection burden between M-M and M-P bearings and between C-C and M-P bearings was not found to be significantly different. Although the findings between certain bearing cohorts were significant, the clinical impact remains uncertain and needs to be studied in more detail [38].

Economic Impact of Infections

Challenging treatment options and the growing prominence among reasons for revision have led to a greater economic burden for infected revisions. The expansion of the Kurtz et al. analysis of the NIS data examined the growing economic impact of PJI treatment within the USA [16]. The estimated total hospital cost incurred for PJI treatment grew from $320 million in 2001 to $672 million in 2010. Based on the current NIS data,

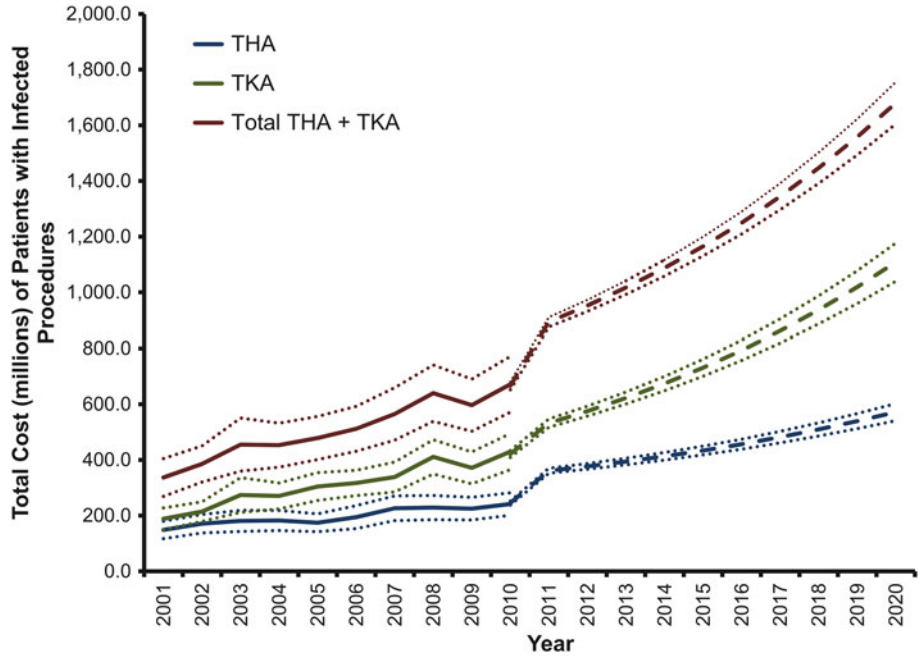

Fig. 1.2 Historical and projected total inpatient cost of infected THA, TKA, and combined THA and TKA procedures within the USA between 2001 and 2020. *Dashed lines* represent the projected values per procedure, whereas the *dotted lines* represent the 95 % CIs of the NIS estimates from 2001 to 2010 and the statistical projections. The total cost was adjusted to 2012 using the Consumer Price Index [14]

PJI treatment is expected to cost US hospitals more than $1 billion in 2013 and $1.68 billion by 2020 (Fig. 1.2). When comparing PJI to other reasons for revision, Bozic and Ries found in a retrospective study of arthroplasty patients from March 2001 to December 2002 that, compared to primary arthroplasty or revision for aseptic loosening, infected THA was associated with significantly increased total length of hospitalization, total hospital costs, and total outpatient charges [11]. Specifically, the direct medical costs for revision of THA because of infection were 2.8 times higher than revision for aseptic loosening and 4.8 times higher than for primary THA [11]. Analogous findings were observed in France, where Klouche et al. reported that revision of septic THA was 2.6 times more costly than aseptic revision and 3.6 times more than primary THA [51]. Kurtz et al. analyzed NIS records from 1990 to 2004 for both TKA and THA and found that the ratio of hospital charges for infected arthroplasty was 1.52 and 1.76 times higher than uninfected arthroplasty, respectively; and was associated with 1.87 and 2.21 times longer length of hospitalization, respectively [13].

Hospitals are also directly affected by the cost of infected arthroplasty devices. Hebert et al. revealed that infected TKAs utilized 2 times more hospital resources than their revision counterparts and were coupled with inadequate reimbursements that resulted in a net loss to the hospital of $30,000 per Medicare patient and $15,000 per standard patient [52]. Furthermore, the costs discussed are direct medical costs and only one aspect of the economic impact of infection. Infection was also associated with longer inpatient hospitalization and increased outpatient visits, which requires increased leave of absence from work and impacts daily activities and patient quality of life [13]. Elevated costs further elucidate the severity and wide-reaching impact of infection when compared to other arthroplasty complications.

Summary

Periprosthetic joint infection is a rare but devastating complication of TJA. Infection occurs after 1–2 % of TKA and THA procedures domestically and abroad and is projected to grow significantly by 2020 with the increase of the patient population and expansion of the use of arthroplasty for younger patients. Infection is currently one of the most frequent reasons for TJA revision and is projected to become the most prominent reason for revision within the next 2 decades. Within the past few decades, the use of infection registries and other public databases throughout the world has allowed clinicians to accurately track the use, incidence, outcomes, and trends in TJA.

The most prominent risk factors uncovered through multiple literature sources and databases were male sex, BMI > 50, increased procedure time, lack of antibiotic-loaded bone cement, and multiple comorbidities with diabetes being the most prevalent. As the number of infections continues to grow, the economic burden will be felt throughout the healthcare system due to inadequate reimbursement procedures, longer patient hospital stays, and subsequent increased consumption of hospital resources. The hope is that new techniques and innovative implants will curtail the impact of infection on arthroplasty patients and society, and therefore it is vital to understand the primary factors that influence development of PJI in order to design technology that will address these problems. With the current information available, physicians can begin to target preexisting patient conditions and create effective strategies to reduce infection in higher-risk groups.

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Risk Factors for Periprosthetic Joint Infection

2

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Introduction

Periprosthetic joint infection (PJI) is a potential complication in any prosthetic joint, even in the absence of known risk factors. However, effective minimization of the risk for PJI requires elimination of known factors that increase the opportunity for exposure of the joint to pathogens or limit the body's ability to eliminate intra-articular pathogens. Known risk factors for PJI can be categorized into patient-related, surgery-related, inpatient postoperative, and long-term factors. While overlap of factors can occur between these groups, it is important to appreciate that the presence of these risks at any point increases the opportunity for the development of PJI. This chapter discusses the mechanism and impact of the factors that compose these groups.

Much of the information regarding risk factors for the development of infection after total joint arthroplasty comes from uncontrolled case series or small case–control studies. Since PJI is an uncommon complication, most of the studies of adequate power represent those patients that were operated in large referral institutions. Unfortunately, these institutions represent only a minority of total joint replacement procedures that are performed [1]. Therefore, these studies may not be a precise representation of reality [1, 2]. Furthermore, disparity in the definition of periprosthetic infection in the literature is an important barrier to a clear understanding of the relationship between potential risk factors and PJI [3, 4]. When referencing this chapter and other sources, these shortcomings of the evidence should be considered.

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Patient-Related Risk Factors

Demographic Factors

Age

Kurtz et al., in a national study, observed that age was a risk factor for PJI following both total knee (TKA) and total hip arthroplasty (THA) [5]. They reported a bimodal distribution, with the lowest PJI incidence in 55–74 year olds. Interestingly, Soohoo et al. observed the same bimodal distribution in another large population-based study [6]. They studied readmission for PJI within 90 days of THA and found that patients older than 75 or younger than 55 years old had significantly higher probability of infection compared with patients between 55 and 74 years old, with an odds ratio of 1.28 and 1.34, respectively. Prior to

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this, Soohoo et al. published a similar investigation among TKA patients, finding those younger than 65 years of age at increased risk for 90 day readmission for infection [7].

Using surgical site infection (SSI) surveillance service database in England, Ridgeway et al. studied the link between various risk factors and SSI [8]. They found that an age over 80 years was a significant risk factor for SSI in primary THA. The same age group demonstrated an association with SSI following primary hemiarthroplasty. However, after adjusting for covariates, age was not a significant predictor of SSI in this cohort. Similarly, some Nordic registry-based studies did not find any link between age and PJI following TKA [9–11]. Dale et al. compared three Norwegian health registries for THA and found that advanced age was a risk factor for both SSI and revision due to infection [12]. Interestingly, for hip hemiarthroplasty secondary to fracture, age less than 60 years was found to increase the probability of revision due to infection, which was explained by the fact that young patients requiring hemiarthroplasty are likely to have severe comorbidities with a shortened life expectancy [12].

Patients in the senior age group usually undergo primary arthroplasty when they are in an optimal health condition. Various studies have reported a lower mortality rate in patients undergoing THA or TKA compared to general population, possibly related to a selection bias [8, 13]. However, the selection method for young patients may be different. Many young patients who undergo total joint replacement are likely to have comorbidities that can increase their susceptibility to PJI. This is indirectly supported by the evidence provided by Lie et al [8]. They observed that 8-year mortality rates in younger THA patients (under 60 years old) were higher than the corresponding general population with the same age and gender. The opposite was seen in patients over 60 years of age. It appears that advanced age may be a risk factor for PJI. However, the link between advanced age and PJI can be confounded to a certain extent by some other risk factors such as comorbidities, lower threshold for blood transfusion or longer hospital stay. Moreover, some studies have found a susceptibility of PJI in the youngest age group undergoing primary arthroplasty but the reason for this is yet to be exactly defined.

Gender

The prevalence of many musculoskeletal disease and infections is not similar between females and males. Sex hormones and sexual chromosome genetic content modulate both innate and adaptive immune system [14]. Therefore, the immune system of males and females may respond differently to pathogenic bacteria, possibly explaining why the prevalence of some infections is not similar between women and men. Most studies investigating whether both sexes are equally susceptible to PJI, have found that males are at greater risk compared to females [2, 5, 6, 9–12, 15–19]. Interestingly, Lubbeke et al. observed that although PJI was more common in men than in women among the non-obese population, obesity strikingly increased the incidence of PJI in women (16.1 times more compared to non-obese women). However, obese and non-obese male patients were not significantly different in terms of incidence of PJI following THA [18].

Nonetheless, some other studies have found higher rates of PJI in females and others did not observe any link between PJI and sex in total joint arthroplasty or in hip hemiarthroplasty [7, 8, 12, 20–22]. Due to these conflictive findings, some authors have not considered gender as an independent risk factor for PJI, suggesting that the difference seen between sexes is probably a proxy for some other risk factors that were not studied [23, 24].

Supporters of the link between PJI and gender have attributed this association to factors such as difference in skin and subcutaneous conditions like pH, sebum induction, skin thickness, fat distribution, and metabolism rate [25–27]. Moreover, it has been suggested that the microbial flora between males and females are different, and males have a higher likelihood for being persistent *Staphyloccoccus aureus* carriers [28]. Some investigators have reasoned that surgeons probably have lower thresholds for males when considering intervention or males

may have a greater chance of being referred to an orthopedic specialist by the primary physician [11, 12, 29–31].

Race

Existing evidence shows that the 90-day incidence of infectious and noninfectious complications following total joint arthroplasty (particularly knee replacement) along with mortality are generally higher among non-white racial groups in comparison with white patients [2, 6, 7, 17, 32]. All of these studies include a low proportion of non-white groups, rendering them underpowered for uncommon complications such as PJI. This may explain why they could not find any difference for PJI specifically, or why the same difference for overall infectious complications did not exist for THA [17, 32].

However, the demonstrated dissimilarity among racial groups merits several considerations. Disparity exists between races in utilization of total joint replacement that is not explained by a difference in prevalence of osteoarthritis, insurance status, or access to health care [33]. Osteoarthritis is more prevalent in African-American and Hispanic populations older than 70 years old compared with non-Hispanic Caucasians [34]. However, elderly African-Americans with osteoarthritis present later and are less likely to undergo total knee replacement than their white counterparts, even when there is no economic impediment [35, 36]. African-Americans have also been shown to have higher body mass index (BMI) at the time of TKA [36]. Non-white patients who undergo total joint arthroplasty have significantly longer length of postoperative stay than white patients, even when adjusted for comorbidities [37, 38]. Therefore, patients from different racial groups do not represent uniform perioperative conditions, and there are some potential risk factors for PJI that have been reported to be different among these groups in previous studies. However, the current evidence for association of PJI and minority groups should be interpreted cautiously since unrecognized and uncontrolled confounding factors may have contributed to this relationship.

Socioeconomic Status

Socioeconomic status is a complex factor that can potentially effect a patient's risk of PJI [6, 7, 15, 16, 39]. Theoretically, lower socioeconomic status can lead to less favorable overall health status due to poor nutritional status and suboptimal care of preexisting comorbidities—both of which are discussed elsewhere as potential risk factors for PJI. However, it can also be influenced by other confounding factors such as race. Unfortunately, the available evidence fails to address these complex associations.

Obesity

Obesity substantially increases the morbidity from osteoarthritis, and is prevalent in the arthroplasty population [40]. Associated comorbid conditions in obese patients, such as ischemic heart disease, hypertension, hypercholesterolemia, poor nutritional status, and type two diabetes mellitus or a constellation of these in the form of metabolic syndrome, delay postoperative recovery and increase the risk of perioperative complications [41–43].

A retrospective analysis has estimated a BMI over 35 kg per meter-squared (kg/m^2) increases the risk of SSI following TKA and THA by 6.7 and 4.2 times, respectively [44]. With a BMI of more than 40 or 50 kg/m^2 the odds of PJI increased 3.3 and 21 times, respectively [45]. Various factors can potentially predispose obese patients to PJI. These patients are at increased risk of postoperative surgical wound complications [46, 47]. The risk of wound dehiscence is higher due to increased surface tension at the incision site. Furthermore, extensive dissection during surgery may be required which may increase the risk of hematoma formation, seroma collection, or prolonged wound drainage [48]. On the other hand, poorly vascularized bulky subcutaneous fat tissue leads to lower oxygen tension in the peri-incisional zone, which is not favorable for wound healing [49]. Some studies have reported obesity as a risk factor for nasal carriage of *S. aureus* [28]. Also, innate immune response in the surgical field may be diminished in these patients, particularly in those with hyperglycemia [50, 51]. Prolonged surgical time due to intraoperative technical

challenges may increase the risk of PJI. Lastly, inadequate adjustment of prophylactic antibiotic dosing has also been mentioned as a potential cause for increased risk of PJI in obese patients [52]. These considerations provide ample explanation for the overwhelming evidence linking PJI and obesity [18, 53–56].

Smoking

Many smokers suffer from chronic obstructive pulmonary disease, atherosclerosis, and other systematic comorbidities that can confound the relationship between smoking and PJI. However, it has been demonstrated that smoking impedes the process of collagen synthesis and maturation in subcutaneous tissue surrounding surgical wounds [57].

It has also been demonstrated that smoking has a detrimental effect on bone healing following spinal fusion surgery [58]. Adequate oxygen supply is essential for tissue repair [59]. As well, wound hypoxia negatively affects neutrophil defense mechanisms against microorganisms and is a predisposing factor for infection [49]. Smoking can induce such hypoxia through different mechanisms. Nicotine releases catecholamines that lead to microvascular vasospasm and subcutaneous hypoperfusion. Nicotine also promotes platelet aggregation and formation of microthrombi. As well, inhaled carbon monoxide avidly binds hemoglobin to form carboxyhemoglobin, shifting the oxyhemoglobin dissociation curve to the left and significantly decreasing oxygen delivery to the peripheral tissues. Smoking cessation programs 6–8 weeks before elective hip or knee surgery have been effective in decreasing postoperative wound-related complications, especially infection [60, 61]. While detrimental effects of smoking on early postoperative complications seems to be evident, long-term studies on smokers who have undergone total hip or knee replacement have not found any significant association between smoking and PJI [54, 62].

Comorbidities

Patients undergoing joint arthroplasty commonly suffer from associated medical conditions [63, 64]. These conditions generally increase the risk of postoperative complications and negatively affect the final outcome of total joint arthroplasty [65–67]. They have also been related to higher mortality following total joint arthroplasty [8, 68].

Indices of Comorbidities

The number of comorbid conditions seems to have an independent cumulative effect on the risk of developing PJI [55]. Lai et al. demonstrated that the risk of PJI increased by 0.35 % for each additional patient comorbidity [69].

A number of methods to measure comorbidities have been described in the literature. The Charlson Index, initially created to predict 1-year mortality, has been validated for many different outcomes in various clinical conditions [70]. The Charlson Index is calculated utilizing a weighted set of comorbidities (Table 2.1) and age of the patient. Calculation is performed by summing the weighted comorbidities present and adding a point for each decade of life greater 40 years of age. Based on retrospective studies, it appears that progressive increase in Charlson Index

Table 2.1 Comorbidities included in the Charlson Comorbidity Index with their weighted scores

Weight	Disease
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Table 2.2 The three components of the NNIS System Surgical Patient Risk Index

American Society of Anesthesiologists Classification ≥ 3
Contaminated or dirty-infected wound
Surgery duration > 75th percentile of normal duration for surgery

greater than or equal to three significantly adds to the risk of infection [7, 71].

American Society of Anesthesiologists (ASA) physical status classification system is a nonspecific scoring to describe general health status before surgery, mainly by focusing on severity of comorbid conditions. It is utilized as an assessment tool for intra- and postoperative nonorthopedic complications. Although some studies have demonstrated a relationship between incidence of PJI and higher ASA scores [8, 56], others have found that the reliability and validity of the ASA score is questionable [72–74]. Moreover, ASA is principally based on severity rather than the type of comorbid conditions. Therefore, it is likely that the type of comorbidities might influence its predictive ability, rendering it less rewarding than other indices.

National Nosocomial Infections Surveillance (NNIS) System surgical patient risk index consists of three components (Table 2.2) [75]. The score ranges from zero to four, with one point assigned for each category. The 75th percentile for duration of arthroplasty has been listed as 2 h in previous reports, with some modifications suggesting a threshold of 1.5 h being appropriate [12, 76]. Some studies have indicated that NNIS index is a better predictor of SSI than its individual components and Berbari et al. observed a relationship between NNIS index and PJI [12, 75, 77, 78].

Specific Comorbidities

Rheumatoid Arthritis

Approximately 5 % of patients undergoing total joint arthroplasty have rheumatoid arthritis (RA) [78]. In multiple studies, the risk of PJI in patients with RA has been shown to be higher than patients without [52, 79, 80].

The mechanism, however, that increases the PJI risk in RA patients remains unclear. A combination of the disease itself, their immunosuppressive therapeutic regimens, or other factors may be the cause [78]. These patients are inherently more susceptible to all infectious disorders, particularly those affecting bone, joint and soft tissues [81]. Also, patients with RA are at increased risk of early surgical wound complications such as superficial infection or dehiscence [82]. This can be explained to some extent by corticosteroid medications or other immune system modulators used in RA therapy [52, 83]. The medications that are employed to control RA have suppressive effect on immune system and affect negatively patients' defense against pathogenic bacteria. These medications include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic agents (DMARD) such as methotrexate, and recently developed biological agents such as tumor necrosis factor (TNF) antagonists or interleukin-1 (IL-1) antagonists.

S. aureus has been accounted as the most common pathogenic bacteria causing PJI in RA patients [84]. Interestingly, it has been shown that RA patients may be more likely to be colonized by *S. aureus* in their oropharynx and skin—possibly related to the combination of anti-TNF and methotrexate therapy [85, 86].

Methotrexate, a folate analogue, is the most common DMARD and has been considered the standard against which newer agents in the class are evaluated [87]. It inhibits neovascularization and decreases cytokine production. Although some studies had previously reported fewer complications with perioperative cessation of methotrexate in the RA population [88], prospective randomized studies in patients with methotrexate therapy who underwent elective orthopedic surgery (predominantly joint replacement surgeries) have not shown any increase in the risk of infection with continuation of methotrexate treatment within 1 year of surgery [89].

Cytokines are implicated in many aspects of pathogenesis of RA and modulation of their action alters the outcome of RA. Therefore, targeting these inflammatory mediators, especially

TNF, has been converted into a standard part of treatment in these patients [90]. It has been observed that anti-TNF therapy in RA patients who undergo total joint replacement increases the risk of PJI [91, 92]. A recent systematic review confirms that use of anti-TNF antibodies in the treatment of rheumatoid arthritis increases the risk of infections that require antimicrobial therapy and/or hospitalization [93].

Whether long-term methotrexate or anti-TNF therapy can be blamed for increased risk for PJI remains to be clarified, although recent reviews point out that higher doses of these medications did not impose a higher risk on these patients for severe infectious complications [94].

Lastly, being subjected to multiple joint replacements makes these patients more susceptible to hematogenous PJI during any episode of bacteremia. Furthermore, infection of one implant can predispose other implants to PJI although the risk of reinfection of the same implant is greater than a distant infection [79, 80, 95].

Hyperglycemia and Diabetes Mellitus

Based on the Nationwide Inpatient Sample (NIS) database, during the years 1988–2003, 8.5 % of patients who underwent primary or revision total joint replacement in the United States were diabetic [96]. Hyperglycemia with or without diabetes is a risk factor for suboptimal perioperative outcomes in patients undergoing orthopedic and non-orthopedic procedures. Clinical studies indicate that improvement in glycemic control lowers the rate of perioperative complications [97, 98].

Although little doubt exists regarding the role of diabetes and hyperglycemia as a risk factor for postoperative infectious and noninfectious complications in both diabetic and nondiabetic patients, it is less clear what parameter best delineates the riskiest situation for PJI among diabetics [51]. Some studies have reported patients with insulin-dependent diabetes are at greater risk of infection than non-insulin-dependent diabetics [99, 100]. Marchant et al. found that the odds of urinary tract infection (UTI) and cerebrovascular accidents were significantly higher in patients diagnosed with uncontrolled diabetes compared to controlled diabetics [101]. Soohoo et al. considered complicated diabetics as those patients with any end-organ damage due to diabetes and found that both uncomplicated and complicated diabetes increased the risk of acute onset PJI after THA (1.7 and 3.7 times, respectively) [6].

The state of glycemic control appears to be another important aspect of infection prevention [23, 101, 102]. The link between hyperglycemia and the susceptibility to infection has been well-established [50]. The degree of consistent hyperglycemia correlates with impairment in various aspects of defense against bacteria, including vascular permeability, oxygen delivery and redox reactions, neutrophil adherence, chemotaxis, phagocytosis, efficacy of antibodies, function of complement components, and intracellular bactericidal activity. Furthermore, glucose can act as a pro-inflammatory mediator, stimulating cytokine production and inhibiting endothelial nitric oxide levels [51]. The preoperative serum glucose level at admission has been shown to be independent predictor of both morbidity and mortality in acute medical and surgical emergency settings [101]. Jämsen et al. demonstrated the link between preoperative outpatient hyperglycemia and PJI in TKA that remained significant even after adjustment for BMI [23]. Mraovic et al. reported that patients with PJI had significantly higher perioperative blood glucose values, including nonfasting preoperative and postoperative day one blood glucose levels [102]. They also observed that postoperative morning hyperglycemia greater than 200 mg per deciliter (mg/dL) doubled the risk of PJI. Moreover, nondiabetic patients were 3 times more likely to develop PJI, if their first postoperative morning blood glucose level was more than 140 mg/dL. Glycosylated hemoglobin or Hemoglobin A1c (HbA1c) level represents an average serum glucose concentration over the past 3-month period. Tight control of HbA1c has significantly decreased the occurrence and severity of many long-term complications of diabetes [103–105]. However, Iorio et al. did not observe any significant association between HbA1c levels and incidence of superficial or deep infections and concluded HbA1c is not a predictive marker for infection after TJA in diabetic patients [100].

Uncontrolled diabetes and hyperglycemia have been shown to be associated with an increased incidence of postoperative morbidity and mortality as well as increased length of hospital stay following lower extremity total joint arthroplasty [101, 102, 106–112]. The presence of diabetes raised the odds of developing PJI in both TKA and THA settings [55, 69, 99, 109, 110, 113]. In two retrospective investigations performed by Lai et al. and Iorio et al., diabetic patients had a fourfold increased risk for infection following total joint arthroplasty [69, 100]. The risks were stratified by Iorio et al. based on the procedure and were found to be much higher among hip procedures than among knee procedures [100]. This finding has not been confirmed by other studies [78].

Prolonged uncontrolled diabetes imposes a challenge to the surgeon, anesthesiologist, and other members of care-providing team [114]. Concomitant comorbidities such as obesity, metabolic syndrome, atherosclerosis, and hypertension along with already present multi-organ damage influence perioperative outcome of total joint replacement [115]. Furthermore, surgical wound healing is a concern among diabetic patients as hyperglycemia delays collagen synthesis. Wound-related complication rates following TKA have been reported between 1.2 % and 12 % in diabetic patients [108, 109, 111, 112].

Systemic Malignancy

Berbari et al. reported systemic malignancy not involving the index joint as a risk factor for PJI. They speculated that it was due to immunosuppressive effect of treatment for malignancy or unknown factors associated with the malignancy itself [78]. Bozic et al., however, observed that malignancy and metastatic tumor were not associated with an increased incidence of acute postoperative PJI [116]. Several case reports of hip and knee PJI due to uncommon pathogenic bacteria in the context of an underlying malignancy have been published [117–121]. These include PJI due to uncommon species of group D Streptococcus or Clostridium genera, *Klebsiella pneumoniae*, *Lysteria monocytogenes*, and Mycobacteria and other microbes mainly associated with colon, breast, ovarian and bladder cancers, as well as hematologic dyscrasia. While these associations suggest a sentinel role for uncommon microbes causing PJI (and a paraneoplastic role for PJI), they also demonstrate the exceptional vulnerability of the prosthetic host with baseline systemic cancer. Little evidence is available regarding the biologic mechanism. However, cancer and immune system dysfunction are in close relationship [122]. As many of these pathogens are traditionally intestinal, it is possible that weakened systemic and local defenses at the mucosal level, due to the cancer itself or anticancer therapy, were responsible for altered bacterial flora. Klein et al. demonstrated that patients with colon cancer had positive stool cultures for uncommon group D streptococci, significantly more commonly than matched controls [123]. These bacteria likely overcome the debilitated mucosal immune barriers and infect prosthetic material via hematogenous spread. As well, cases of PJI caused by *Mycobacterium bovis* have been described in patients who had previously been treated with intra-vesicular instillation of BCG vaccine (composed of *Mycobacterium bovis*) as immunotherapy for superficial bladder cancer [124].

Human Immunodeficiency Virus (HIV) Infection

The introduction of new antiretroviral regimens has led to a considerable improvement in both quality and life-expectancy of HIV-infected patients. As a consequence, an increase in the number of HIV patients presenting for total joint arthroplasty has been noted [52, 125]. An important subgroup of HIV-positive patients undergoing arthroplasty are hemophilic patients infected by contaminated factor concentrates in the past [126]. The main indications for arthroplasty in HIV/AIDS patients are osteonecrosis and hemophilic arthropathy, while simple osteoarthritis is not a common indication in this younger patient population [125, 127]. Hicks et al. found that the infection rate in HIV-positive hemophiliacs is greater than the general arthroplasty population—up to 18.7 % for primary surgery and 36.3 % in revision surgery during an average

follow up of 5.7 years [128]. Moreover, they observed that the risk of infection increased with time, and PJI-free survival at 1, 5, and 15 years was 95, 85, and 55 %, respectively.

HIV affects the immune system through depletion of CD 4+ lymphocytes. These leukocytes are mainly involved in cell-mediated immunity. However, other arms of the immune system are also indirectly affected [129]. During the course of the disease, disturbances in humoral immunity, monocyte-macrophage lineage, cytokine production, and polymorphonuclear function occur. These alterations, together with associated comorbidities such as malnutrition and intravenous drug abuse, predispose HIV-positive patients to common, as well as opportunistic, infectious complications [125, 129]. Moreover, due to the same mechanism of immune system malfunction, wound healing can also be influenced [129]. Furthermore, asymptomatic HIV-positive patients are twice as likely to be carriers of *S. aureus* [130]. Nevertheless, total joint replacement does not have any adverse effect on the rate of CD4+ reduction and progression to AIDS [131–133].

Common shortcomings of the studies regarding PJI in the context of HIV/AIDS seem to be small sample size, methodology issues, and confounding influence of hemophilia [52, 129]. While some authors believe the risk of late hematogenous infection increases with the deterioration in the immune system [129, 134], others are unable to confirm a link between lower CD4+ counts and the occurrence of surgical wound complications [125, 135, 136]. Others have proposed a viral load of over 10,000 copies per milliliter and symptomatic HIV-positive status as risk factors for SSI [52, 129]. The influence of HIV-positivity on the risk of late periprosthetic infection has been obscured by concomitant hemophilia in previous studies. There is no evidence to demonstrate whether HIV-positivity per se (and in the absence of other confounding risk factors such as intravenous drug use or hemophilia with frequent self-injections) increase the risk of late hematogenous PJI [129, 137, 138]. Unger et al. presented midterm follow up of 26 TKA in 15 HIV-positive hemophiliacs (mean follow-up: 6.4 years; range: 1–9) without any case of PJI [132]. Some authors have suggested the risk of early and late PJI in HIV-positive non-hemophilic patients is probably higher than general population but lower than HIV-negative hemophilic patients, but this hypothesis is yet to be supported by evidence [126].

Sickle Cell Hemoglobinopathies

Advances in medical management of the patients with sickle cell hemoglobinopathies (SCH) have dramatically increased their life expectancy [139, 140]. This population undergoes total joint replacement usually at young age because of activity limitation and pain caused by osteonecrosis, most often in the hip and less commonly in the knee. Unfortunately, SCH patients present a unique set of challenges in terms of perioperative management and surgical technique [141, 142]. THA has been reported to have the highest rate of perioperative complications among orthopedic procedures performed for these patients [142]. Moreover, SCH patients are at greater risk for short-term and mid-term postoperative aseptic and septic complications [143]. Although earlier small case series reported an infection rate of up to 20 % following THA [144, 145], a recent report has demonstrated a much lower rate of 3 % that is still higher than general population [143]. Salmonella has classically been associated with bone infections in SCH. Yet, this microbe has not been reported as a cause of PJI in SCH, with *S. aureus* and gram-negative microbes being the most common pathogens [140, 142, 143]. Circumstances that can act as potential contributors to increased risk of PJI in SCH patients are coexistence of latent infection, osteonecrosis of the femoral head, increased intra- and postoperative blood loss due to bleeder hyperplastic bone marrow, increased surgical time due to surgical technical difficulties, and prolonged perioperative length of stay [141–143, 146]. Immunosuppressive effect of long-term treatment with hydroxyurea, the presence of stasis leg ulcers that exist in up to 20 % of SCH

patients, and hematogenous seeding following bacteremia that recurrently in this population can increase the risk of late hematogenous PJI [139–141]. The choice of cemented or cementless arthroplasty has been a matter of debate in SCH patients. Regarding PJI, some older studies suggested higher rate of infection with cemented THA [144, 145]. As well, a more recent case-series found only one case of PJI in 18 cementless THA [147]. Unfortunately, strong evidence directly comparing cemented versus uncemented arthroplasty in these patients is still lacking.

Hemophilia

Hemophilic patients may require arthroplasty at young age, due to debilitating end-stage chronic hemophilic arthropathy [148–150]. The prevalence of PJI in hemophilic patients has been reported from 1.4 to 16 % in recent studies [149–155]. Concerning for hemophiliac arthroplasty patients, Galat et al. reported that patients with surgical site hematoma requiring early evacuation within 1 month of arthroplasty are more likely to suffer bleeding disorders and are at increased risk of PJI and major revision surgery [156]. Nevertheless, improvement of perioperative care has considerably decreased the occurrence of PJI [149]. Late PJI is now the main concern following TKA in hemophilic patients [151, 155]. Goddard et al. reported a 20-year survival rate of 97 % with infection as the endpoint, which is superior to the 10-year survival rate of 90 % and 77 % reported by Silva et al. and Zingg et al., respectively [149, 155, 157].

Complexity of TKA in these patients, due to anatomical challenges (severe arthrofibrosis, deformity, and bone stock deficiency), as well as high risk of surgical site hematoma and/or hemarthrosis may contribute to immediate postoperative risk of PJI [153, 155]. Immunosuppression associated with HIV/AIDS and Hepatitis C infection, and remote infections have been suggested as other predisposing factors for PJI in these patients [155].

Norian et al. reported *Staphylococcus epidermidis* to be the most common cause of PJI in these patients and concluded that hematogenous spread during frequent intravenous self-administration of clotting factor concentrate is an important route of PJI in hemophilic patients [148].

Malnutrition

Optimal nutritional status is crucial for favorable surgical outcome. Malnutrition impedes collagen and proteoglycan synthesis and negatively affects wound remodeling. It also interferes with immune system function.

Several indices have been utilized for definition of malnutrition, the most common of which are serum albumin less than 3.5 g/dL, serum transferrin less than 200 mg/dL, and total lymphocyte count less than 1,500 per millimeter cubed [158, 159]. Other less common indicators of nutritional status are arm circumference and skin antigen-testing [158]. While these indices in general are good indicators of protein deficiency, they do not represent other aspects of malnutrition such as calorie and vitamin deficiency that can potentially be present in patients preparing to undergo total joint arthroplasty [160]. An increased rate of surgical wound complications has been observed in patients with perioperative nutritional depletion [159].A post-surgical catabolic state follows any major surgery and is accompanied by loss of appetite and increased nutritional demand. Adequate nutritional reserve can lessen adverse effects of this physiologic response [161]. Malnutrition has been associated with increased surgical and anesthesia time, delayed wound healing, prolonged rehabilitation recovery, longer postoperative in-hospital stay, and increased hospital consults [159, 161–164]. Interestingly, malnutrition has been associated with failure of irrigation and debridement in the setting of persistent wound drainage following total joint replacement [165]. Various underlying conditions including aging can contribute to suboptimal nutritional status in malnourished patients. Whether malnutrition is an independent factor or it just represents patients' comorbid conditions has not been clearly addressed yet. Studies investigating long-term risk of PJI in nutritionally deficient patients are lacking.

History of Depression

In two separate analyses performed recently, Bozic et al. identified risk factors for PJI in the United States Medicare population [116, 166]. Notably, their analysis in TKA cases found that depression was an independent predictor of subsequent PJI [166]. The pathophysiology of this relationship is unknown and unconfirmed by other studies. However, Bozic et al. did hypothesize that the physiologic depression may be associated with malnutrition leading to the increased risk of PJI. Interestingly, Bozic et al. also identified psychoses as independent predictor of PJI following both THA and TKA [116, 166].

Posttraumatic Arthritis

Patients who undergo total hip replacement because of posttraumatic osteoarthritis have been demonstrated to be at higher risk for PJI in comparison with those with arthroplasty due to primary osteoarthritis [20]. Potential explanations for this include the complexity of the procedure, prolonged surgical time, and less favorable status of soft tissue.

Moreover, secondary total hip replacement due to hip fracture has also been shown to be an independent risk factor for PJI [8, 20]. The reason for this finding is unknown, but systemic reactions to trauma as well as local tissue injury at the site of arthroplasty may predispose these patients to infection. Other possible factors are unfavorable underlying health status of the patient suffering hip fracture and lack of adequate preoperative conditioning (such as optimal control of comorbid conditions or associated infections).

Similar to hips, previous knee trauma requiring open reduction and osteosynthesis, particularly with the remnants of internal fixation material at the time of arthroplasty has been reported as a risk factor for PJI [9, 167]. However, arthroscopy and high tibia osteotomy did not increase the risk of PJI [167]. The vulnerability of patients who undergo TKA for posttraumatic osteoarthritis is particularly important since these patients are often younger than the typical population requiring arthroplasty.

Medications

Non-steroidal Anti-inflammatory Drugs

NSAIDs exert their analgesic and anti-inflammatory effect through two different mechanisms: inhibition of prostaglandin (especially prostacyclin) and thromboxane synthesis by cyclooxygenase enzymes (COX-1 and COX-2) and also by interference with protein–protein signals that lead to white blood cell activation [168]. These agents play a crucial role in the multimodal perioperative pain management for total joint arthroplasty [136]. Some concerns have been expressed for the use of NSAIDs in this setting, mainly because of their adverse effect on platelet aggregation and subsequently increased risk of bleeding [52]. These drugs have a variable effect on hemostasis as far as bleeding risk is concerned [170]. While Robinson et al. demonstrated increased risk of excessive blood loss with the use of NSAIDs [171], analysis of more recent data does not show a significant increase for bleeding risk or transfusion requirement with NSAIDs or selective COX-2 inhibitors [169]. Regardless, direct evidence linking the use of NSAIDs with increased risk of PJI does not exist. In the study reported by Pederson et al. based on Danish arthroplasty registry, incidence of PJI among patients who received postoperative NSAIDs as prophylaxis for heterotopic ossification was the same as those who did not receive it [11].

Platelet Function Inhibitors

Clopidogrel inhibits platelet aggregation by binding to adenosine deaminase G-protein-coupled receptor on the platelet surface. Due to its irreversible binding, the effect of Clopidogrel will persist for the remainder of the platelet's existence, approximately 1 week. Similarly, low-dose aspirin permanently inhibits platelet activation by blocking thromboxane-dependent pathways [172].

Unfortunately, little evidence exists regarding the impact of antiplatelet medications in patients undergoing arthroplasty and most of the studies have been performed in the field of coronary artery bypass surgery.

Platelet function inhibition can cause excessive bleeding, leading to considerable blood loss and requirement for blood transfusion and surgical site complications such as prolonged drainage, hematoma formation, or infection [173, 174]. Furthermore, the risk of infection at the surgical site appears to be greater if the patients are under dual antiplatelet therapy (aspirin plus Clopidogrel) preoperatively [173].

Basic science studies also suggest a role for platelets in the innate and adaptive immune system. Platelets contribute to recruitment of leukocytes to the site of vascular injury, release cytokines that augment the immune response, liberate some antibacterial proteins, and expand antibody production through their interaction with lymphocytes [175, 176]. However, the clinical consequence of platelet function blockade on the immune system has not been precisely investigated. In a retrospective study, Nandi et al. found that discontinuation of Clopidogrel 5 days before elective hip and knee arthroplasty was associated with a lower rate of reoperation and antibiotic use for infection, wound cellulitis, and wound drainage [177]. They also observed that the timing of Clopidogrel resumption following arthroplasty did not affect the rate of postoperative events. Another finding of this study was the unexpectedly higher rate of infection (6 %) among patients taking Clopidogrel, which could be due to multiple other factors, but underscores consideration of these patients as high risk for PJI.

Anticoagulants

Anticoagulation is a routine component of perioperative management of arthroplasty patients in order to reduce the risk of postoperative thromboembolic complications [178, 179]. A wise balance should exist between efforts to prevent thromboembolism and the potential risk of bleeding complications [180]. However, evidence shows that hemorrhagic complications are not the sole concern with prophylactic anticoagulation therapy. Blood collections (hematomas) usually resorb without any associated adverse event, but when large enough, they can lead to surgical wound problems such as skin necrosis and persistent wound drainage [181, 182]. Galat et al. observed hematomas that required evacuation within 1 month of TKA were associated with significantly increased risk of PJI with 2-year cumulative probability of 10.8 % in comparison with 0.8 % in patients without hematomas [156].

Higher rates of clinically important hemorrhagic complications have been reported among patients taking injectable forms of low molecular weight heparin compared to oral warfarin [182, 183]. One study comparing patients who received warfarin as preoperative thromboprophylaxis for total joint arthroplasty with those who did not receive any form of thromboprophylaxis, reported that prophylactic warfarin was associated with greater likelihood of both superficial and deep surgical wound infections [184]. Furthermore, Minnema et al. and Parvizi and et al. found that international normalized ratio (INR) greater than three is significantly associated with wound-related complications (such as bleeding, hematoma formation, persistent drainage) as well as deep PJI [180, 185]. These findings suggest a relationship between the degree of anticoagulation and the risk of PJI that may negate the beneficial effects of anticoagulation.

Previous Operation in the Same Joint

Several retrospective studies have indicated previous operation at the site of arthroplasty is a risk factor for PJI for both hip and knee joints [55, 78, 186, 187]. It has been hypothesized that scar tissue formation due to prior surgical procedures can result in longer surgical time [55]. Moreover, poorly planned skin incisions, and devitalized peri-incisional tissues can also contribute to surgical wound complications [186].

Staphylococcus Aureus Colonizers

Nasal carriage of *S. aureus* was identified as a risk factor for SSI several decades ago. External nares are the most consistent area in the body from which *S. aureus* can be isolated [188]. Colonization occurs through interaction of staphylococcal surface proteins and mucin carbohydrates on the

surface of the epithelial cells [189]. Recent technology has made it possible to detect nasal *S. aureus* carriage within hours [190]. Elimination of nasal carriage by topical nasal antibiotic has led to disappearance of *S. aureus* from other parts of the body. Moreover, correlation between the colonization density of *S. aureus* at the carriage site and the risk of infection reinforced the theory of this causal relationship [188]. In a prospective study, Kalmeijer et al. demonstrated that nasal carriage was the single independent risk factor for the development of *S. aureus* SSI [24]. The general population can be divided into three groups according to the pattern of carriage: persistent carriers (20 %), intermittent carriers (60 %), and noncarriers (20 %). Current carriage of *S. aureus* in the general population has been reported to be 37.2 % [188]. A diverse set of factors including demographic, genetic, immunologic, hormonal, and healthcare-related, along with bacterial antigenic factors have shown to influence the staphylococcal nasal carriage state. In patients with staphylococcal SSI, indistinguishable strains of *S. aureus* have been isolated from the surgical site and nares of 80 % of patients [191]. Moreover, colonizing strains may spread to other patients.

The most recent Cochrane analysis of surgical trials studying the effect of preoperative nasal mupirocin application in *S. aureus* carriers to decolonize the patient demonstrated a significant reduction in the rate of nosocomial *S. aureus* infection rate. However, when SSI was analyzed as the primary outcome, no statistically significant difference was found [192]. Interestingly, analysis of the infection rate caused by microorganisms other than *S. aureus* demonstrated slightly higher (Relative Risk = 1.38) but statistically significant risk of infectious complications in mupirocin group. This may indicate a risk of *S. aureus* being replaced by other microbes in patients who receive nasal mupirocin. Other studies, however, have shown that eradication of *S. aureus* before surgery appears to lower SSI rates due to *S. aureus* [193, 194]. While a clear link appears between nasal carriage of *S. aureus* and SSI, its association with deep infection and the effect of decolonization require further research for clarification.

Surgical-Related Risk Factors

Surgeon and Hospital Volume

The incidence of postoperative complications, including PJI, following joint arthroplasty has been shown to be related to both the surgeon's and hospital's arthroplasty volume [1, 195–198]. These findings hold after adjusting for potential confounders that may have been associated with volume, such as patient age, gender, and overall health. This association may be explained by the link between increased surgeon volume and decreased operative time, an indication of improved operative technique, decreasing the risk of contamination [16, 55, 56, 199, 200]. As well, Bozic et al. described a relationship between increased surgeon volume and decreased hospital length-of-stay [195], likely resulting in decreased exposure to nosocomial organisms [56]. Similarly, increased hospital arthroplasty volume has been associated with decreased length-of-stay [56, 201]. It could be expected that the healthcare team at a high-volume institution is more familiar with the early signs and risks of developing infection and therefore is more able and quick in implementing preventative care to mitigate PJI. Katz et al. studied the relationship between decreasing rates of PJI with increasing arthroplasty volume for both knees and hips [1, 196]. In these analyses the risk of PJI decreased by approximately half for surgeons and hospitals performing greater than 50 and 100 arthroplasties per year, respectively. While this trend ($p < 0.1$) did not achieve statistical significance, it is a concerning finding that highlights the importance of experience in minimizing postoperative complications, especially PJI.

Joint

Prosthetic hips and knees may not be in equal jeopardy of infection. Kurtz using National Inpatient Sample database between years 1990 and 2004 observed that the incidence of PJI in both knees and hips were similarly progressively increasing, with the incidence doubling

for both joints at the end of the same time period. However, the burden of PJI following TKA was consistently greater than following THA [5]. Pulido et al. also indicated TKA as a risk factor for PJI (hazard ratio of 2.85) [56]. Other studies have reported more infections occur after tricompartmental than unicondylar knee replacement, rising to a threefold difference in PJI incidence after 10 years of follow-up [10, 19, 202, 203].

Revision Arthroplasty

Revision arthroplasty has consistently been reported to be at higher risk of infection in comparison to primary arthroplasty [2, 9, 78, 113]. Poss et al. reported that revision arthroplasty was 8 times more likely to be infected [204]. Jämsen et al. reported mean hazard ratios of 3.4 and 4.7 for partial and total knee revision, respectively, based on registry analysis with a median follow up of 3 years [9]. Blom et al. observed that introduction of strategies such as strict use of prophylactic antibiotic regimens, antiseptic solutions, occlusive clothing, and vertical laminar flow in operating rooms considerably reduced the incidence of PJI following primary and revision TKA from 4.4 % and 15 % to 1 % and 5.8 %, respectively [205]. However, they found revision procedures to be at significantly higher risk of PJI. Moreover, Ahnfelt et al. confirmed that higher numbers of previous revision procedures have been associated with greater risk of PJI [206]. Prolonged operating time, comorbidities, increased need for blood transfusion, and higher incidence of postoperative wound complications could confound the association between revision surgeries and PJI, but even after accounting for these variables, the link between revision arthroplasty and PJI remained [78].

Operative Time

Operative time—the duration from skin incision to completion of closure—has been linked to PJI as an independent parameter and also as a component of NNIS index [8, 78, 200, 207, 208]. Berbari et al. defined a long arthroplasty procedure as one taking greater than 3 h [78]. When incorporating this definition into the NNIS surgical patient risk index score (a composite of surgical and patient factors), they found a significant independent association between this index and subsequent PJI. Similarly, Leong et al. defined an prolonged THA or TKA as greater than 2 h [208]. In their analysis, the incidence of SSI was significantly higher for prolonged procedures [208].

Ridgeway et al. studied primary and revision THA separately and found a significant increase in the incidence of SSI for interventions that lasted more than 2 h in comparison with those lasting between 60 and 89 min [8]. However, they did not observe any significant association between the procedure time and PJI in hip hemiarthroplasty. The same observation was reported by Leong et al [208]. Since the incidence of PJI in hip hemiarthroplasty was nearly twice of THA in both studies, this may indicate that the presence of other risk factors in patients undergoing hip hemiarthroplasty (particularly patient-related factors such as age, comorbidities, and baseline level of activity) may have obscured the effect of procedure duration on incidence of PJI.

Although prolonged operative time can be considered a measure of duration of exposure to potential contaminants, it can also reflect complexity and technical aspects of the procedure as well as the degree of tissue damage during the surgery [8, 208]. While procedure duration is an intuitive and well-proven indicator of PJI risk, the evolution of surgical techniques for arthroplasty has likely led to shorter procedure times with different techniques and therefore these arbitrary thresholds of duration may have varying efficacy in predicting PJI.

Previous Procedure in Operating Room

A common sense practice in orthopedic surgery, and especially in arthroplasty, is organizing the operating room (OR) such that confirmed or suspicious cases of infection are performed at the end of the OR session minimizing the risk to

uninfected procedures. Whether the practice of performing the so-called clean arthroplasty procedure following an infected case increases the probability of infection has not been adequately studied. The only evidence is a retrospective study in which 39 "clean" total joint replacement procedures were performed after a confirmed infection-related intervention. Of these, only one case developed PJI within 9 weeks of surgery with the same pathogenic bacteria as encountered in the preceding infectious case [209]. Despite lacking definitive evidence of cross-contamination, the theoretical risk exists and should be considered.

Anesthetic Management

Although the influential role of anesthesia processes during the surgical intervention for immediate perioperative outcomes is well-known, up until recent years less attention has been devoted toward long-term consequences of intraoperative anesthetic management [210]. Modern anesthetic process utilizes short acting medications and the operative time and consequently anesthesia time are shortening. Nonetheless, some aspects of anesthetic management can improve host defense against contamination during surgery and therefore are considerable prophylactic measures against SSI [211]. These practices are: maintaining physiologic normothermia, providing supplemental oxygen, retaining euvolemic state, adequate peripheral tissue perfusion, optimal management of hyperglycemia, timely administration of antibiotics, and judicious use of blood transfusion in the perioperative period [210, 211]. Intraoperative hypothermia is thought to increase the risk of SSI through vasoconstriction and reduction of oxygen supply in the subcutaneous tissue. Adequate perfusion and oxygen tension at the surgical site are mandatory for optimal function of different arms of the immune system, as well as wound healing process [212]. Short-term hyperglycemia has detrimental influence on body defense against microbes in the surgical field [213]. Nonenzymatic glycosylation deactivates antibodies and blocks C3 complement component. Hyperglycemia also impairs chemotactic, bactericidal, and phagocytic performance of the neutrophils [211, 213].

Although some retrospective studies, designed for investigation of risk factors for adverse outcomes of total joint replacement were unable to find any statistically significant difference between types of anesthesia and PJI [11, 214], one retrospective population-based study focusing specifically on the relationship between type of anesthesia and SSI in arthroplasty found that total hip and knee arthroplasty under general anesthesia are associated with higher risk of SSI compared with neuraxial (epidural or spinal) anesthesia. The odds ratio of SSI after adjusting for type of surgery, age, sex, comorbidities, year of surgery, surgeon's age, and teaching status of the hospital was found to be 2.21 for general anesthesia compared to neuraxial [215]. This finding has been explained by different mechanisms. First, the peripheral vasoconstriction induced by surgical stress is probably more pronounced in general anesthesia, since this type of anesthesia unlike neuraxial anesthesia does not block the sympathetic autonomic system. This can lead to lower perfusion and oxygen tension at the site of surgical wound. Second, volatile anesthetics and opioids can negatively affect various types of cells involved in the immune response. Lastly, neuraxial anesthesia provides postoperative analgesia that prevents pain-induced generalized vasoconstriction and diminished peripheral perfusion [215, 216].

Postoperative Risk Factors

Prior to Discharge

Persistent Postoperative Wound Drainage

Persistent postoperative wound drainage has been shown to be associated with deep infection after total joint arthroplasty [180, 217]. A clear definition for persistent postoperative wound drainage does not exist. Generally it is accepted that wounds that continue to drain more than 48 h postoperatively should be cautiously monitored [165]. It has been proposed that if the surgical

wound continues to drain more than 5–7 days, it is 12.5 times more likely to develop infection and often the drainage is prolonged [217, 218]. Evidence shows with every additional day of prolonged drainage, the probability for infection is substantially increased by 42 % in hips and 29 % in knees [48]. Moreover, prolonged drainage extends the hospital stay [48].

Risk factors associated with prolonged wound drainage are numerous. Higher volume of drain output is an independent factor [48]. Conditions that intervene with wound healing (i.e., diabetes mellitus, rheumatoid arthritis, malnutrition, immune modifying medications, smoking, advanced age, and obesity) can potentially predispose the patients to worrisome wound drainage [219]. Postoperative antithrombotic prophylaxis with low molecular weight heparin has been associated with longer drainage in comparison with aspirin and warfarin [48]. Persistent postoperative wound drainage clearly increases the risk of PJI. However, a clear delineation between prolonged drainage and the inevitable development of PJI has yet to be determined, complicating management.

Surgical Wound-Related Complications

Although surgical wound-related complications such as dehiscence, skin-edge necrosis, superficial infection, and delayed healing rarely require surgical intervention, it has been shown that they are associated with deep wound infection and increase the risk of PJI up to 4 times within 5 years after total knee replacement [81]. Therefore, patients with successful treatment of SSI should be closely monitored for any possibility of deep PJI in the future [217]. As discussed below, any tactic that decreases the incidence of SSI confers significant benefit for the prevention of PJI.

Distant Infection

The presence of infection distant to the prosthetic joint can be an initiating event in the development of PJI. Through hematogenous spread, organisms incubating at a distant site can be introduced to the prosthetic joint, which can provide an optimal site for growth. Common infections in the hospital setting that have been shown to predispose to PJI include UTI, pneumonia, bacteremia, and SSI [9, 56, 78, 185, 220–222]. Pulido et al., in a case–control series, found that postoperative UTI independently increased the risk of PJI by over fivefold [56]. This relationship has been supported by other investigations [78, 113, 185]. In an analysis of Gram-negative PJI, Zmistowski et al. found PJI had developed secondary to UTI in 13 % of those patients with Gram-negative PJI compared to 0.4 % in Gram-positive PJI [222]. Use of an indwelling urinary catheterization is a known risk factor for UTI [223, 224]. Indwelling catheter use, however, has been promoted in anesthetized patients during joint arthroplasty due to concern regarding urinary retention [225, 226]. Interestingly, Iorio et al. found a significant relationship between the development of UTI and the use of indwelling catheterization versus straight catheterization [223]. This is contrasted with Hozack et al., who found no benefit of straight catheterization over indwelling catheterization in the perioperative setting [227]. In patients receiving indwelling catheters, the risk of UTI development, and hypothetically the risk of PJI, is proportional to the duration of catheterization [224]. The management of urinary retention and patients presenting with asymptomatic UTI in the perioperative arthroplasty setting remains controversial. Regardless, the theoretical risk of seeding a prosthetic joint leading to PJI from the urinary tract has been observed on numerous occasions justifying concern for joint integrity when presented with UTI.

The development of nosocomial pneumonia during a hospital stay is not an uncommon event [228–230]. However, pneumonia complicating the postoperative course of joint arthroplasty is a much less common event. In two separate analyses, Parvizi et al. and Pulido et al. found a 0.1–0.15 % incidence of in-hospital pneumonia following total joint arthroplasty [231, 232]. As well, Mahomed et al. found that 1.4 % of patients developed pneumonia within 90 days of knee arthtroplasty [2]. The development of pneumonia provides another opportunity for pathogen (notably *Streptococcus pneumoniae*) exposure to the prosthetic joint. In their case–control analysis,

Berbari et al. found that patients suffering PJI were over twice as likely to have a history of nosocomial infection, including pneumonia, compared to the uninfected controls [78]. This finding was not statistically significant ($p<0.1$) and did not survive multivariate analysis; however, this could be argued to be a type-two error due to the low incidence of nosocomial infections in post-arthroplasty patients. Puldio et al. also investigated the possibility of a relationship between postoperative pneumonia and PJI, with no significant findings [56]. Interestingly, Katz et al. found that both surgeons and hospitals with high annual knee arthroplasty volumes had significantly lower rates of postoperative pneumonia development [1].

The development of bacteremia in the hospital can occur secondary to many diseases, some of these already discussed. However, another route of entry is via venous catheters, which provide pathogens a direct route of entry into the blood stream [233]. Following joint arthroplasty, the development of documented bacteremia is uncommon [232]. Yet, bacteremia, specifically *Staphylococcus aureus* bactermia (SAB), has been associated with the development of PJI [220, 221, 234]. Murdoch et al. found an incidence of PJI development through hematologic seeding of the joint in 34 % of patients who presented with concomitant prosthetic joint and SAB [220]. Similarly, Sendi et al. found that 39 % of patients presenting with SAB and in situ prosthetic joint developed PJI [221]. It is worth noting, however, that in attempts to isolate only cases with PJI secondary to bacteremia (not cases of bacteremia secondary to PJI), Sendi et al. and Murdoch et al. limited their definition of hematogenous spreading to those cases that occurred at a minimum of 1-year postimplantation. Therefore, the relationship between bacteremia in the acute postoperative hospital setting and PJI remains unknown. However, it has been found that hospital-acquired SAB carries a lower risk of subsequent PJI than community-acquired SAB [221, 234].

Postoperative pathogen introduction into the joint during the hospital stay that does not require the traditional hematogenous seeding is superficial SSI. The association between SSI and the development of deep infection is well established [78, 113, 217]. In the acute setting there exists minimal barrier between the superficial compartments and the joint space. Of course this ease of passage provides ambiguity in the temporal relationship between deep PJI and SSI. In their case–control study Berbari et al. observed an adjusted odds ratio of nearly 36 for an association between SSI and PJI [78]. These findings exhibit the strong relationship between SSI and PJI. Factors leading to poor wound closure or introduction of pathogens into the superficial space predisposes to SSI and therefore PJI. One such factor is postoperative hematoma formation. It is evident and expected that infectious events occurring regional to the joint strongly predispose to PJI.

Cardiovascular Complications

As a primary transporter in immunologic response, required nutrients for timely wound closure, and potential pathogens, the cardiovascular system plays an important role in the development of PJI. Specific diseases that have been known to facilitate PJI are postoperative atrial fibrillation and myocardial infarction. Pulido et al. reported that atrial fibrillation and myocardial infarction had odds ratios of 6.2 and 20.4, respectively, as independent predictors of PJI [56]. The authors hypothesized that these findings were associated with subsequent anticoagulation and association with overall poor health and therefore led to the development of PJI. Subsequently, Bozic et al. utilized a large national database to isolate congestive heart failure, peripheral vascular disease, and valvular disease as cardiovascular diseases predisposing to PJI [116, 166]. The pathophysiology leading from cardiovascular disease to PJI remains unknown, yet the relationship is established and many potential mechanisms can be described. These include increased use of anticoagulation, deprivation of essential nutrients and hypoxia, and effects from thromboembolic events.

Allogenic Blood Transfusion

The use of blood products in the postoperative setting is an essential management tool for

postoperative anemia, and in many ways aids in the prevention of PJI [56, 116]. However, when autologous blood products are not available or depleted, the use of allogeneic blood becomes necessary. Such use has been associated with PJI [56, 78, 180, 235]. Transfusion of allogeneic blood has a known immunomodulating response, which may be the cause for increased risk of PJI [236]. However, Parvizi et al. hypothesized that allogeneic transfusions are simply a proxy for increased blood loss, hematoma formation, and wound drainage—the true causes of PJI [180].

Length of Stay

As has been previously discussed, increased duration of hospital stay provides increased risk for establishment of PJI. Exposure to nosocomial pathogens, including those already mentioned, suggests caution in increasing hospital length of stay. Such nosocomial infections include the development of pneumonia, UTI, and bacteremia. An increased length-of-stay may also indicate a poor postoperative course with noninfectious complications increasing the risk of joint contamination. Cardiac, pulmonary, or wound complications would create such a scenario. Appropriate length-of-stay remains a contentious issue in the arthroplasty community with conflicting reports. On the one hand, it is argued that the shift to shorter hospital stay has led to increased rates of preventable readmissions [64]. While on the other hand, evidence has been provided that earlier discharge of a stable patient has no effect on rates of readmission [237, 238]. From the perspective of PJI, it is logical that removal from the hospital setting would lessen the risk of contamination. This logic is supported by the association between high-volume arthroplasty centers and decreased length-of-stay with concordant decreased rate of PJI [1, 195, 196]. The appropriate length-of-hospital-stay remains unproven, yet it is accepted that importance exists in minimizing the risk of PJI by decreasing the duration to the shortest length without compromising the health of the individual. This appropriate duration is likely dependent upon the individual, surgeon, and hospital and not constant throughout the joint replacement community.

Post-discharge

Dental Work

Another potential nidus for infection is dental compromise. In this case, normal dental flora can cause transient bacteremia. The normal flora is most often not pathogenic. However, the theoretical risk for the development of PJI in the setting of poor dental hygiene or following dental procedures has led many surgeons and organizations to adopt prophylactic guidelines including the use of pre-arthroplasty dental clearance and post-arthroplasty antimicrobial prophylaxisis prior to dental procedures. The necessity of these guidelines is controversial due to the lack of strong evidence supporting them [239–243]. Berbari et al. performed a case–control study investigating an association between post-arthroplasty dental work and PJI with no association identified [244]. However, anecdotal evidence provided by case reports and series do suggest that bacteremia with a dental source can lead to PJI [245–248]. While the theoretical risk of hematogenous prosthetic seeding does exist, it has been argued that the volume of bacteria introduced into the bloodstream is insufficient for creation of PJI [239]. Furthermore, with the relatively low incidence of PJI, it has not yet been possible to accurately determine the risk of subsequent dental procedures for the development of PJI, or more importantly the protective effect of antibiotic prophylaxis prior to such procedures.

Subsequent Surgery

As often discussed in this chapter, anything providing a risk of bacteremia provides a risk of PJI. Invasive surgery, including subsequent arthroplasty on another joint or revision surgery provides such a risk. As well, the risk of PJI developing in prosthetic joints when distant to an infected joint has been investigated [95]. Jafari et al. studied 55 cases in which a patient suffering PJI had another prosthetic joint, finding that 11 cases (20 %) developed PJI in the distant joint. However, it is unknown if this increased risk exists due to seeding from the infected joint or because these patients are predisposed to infection secondary to other risk factors. The later theory is supported by the

finding that only four cases (7.2 %) were infected by the same pathogen in both joints.

Similarly, when providing patients relief from multiple degenerated joints, arthroplasty as staged or simultaneous procedures must be considered. When patients require bilateral arthroplasty, simultaneous arthroplasty appears to be protective against PJI over staged bilateral arthroplasty [249–251]. However, other complications—thrombolytic, cardiac, and overall mortality—have been shown to be increased in simultaneous compared to staged bilateral procedures [252]. Regardless of the timing, multiple surgical procedures around or following arthroplasty, does provide an increased risk for PJI and the influence of any other present factors will influence the outcome.

Long-Term Stay in Healthcare Facility

Length of hospital stay has been shown to be a risk factor for PJI likely both as a marker of decreased health status and increased exposure to nosocomial pathogens. The same logic could be applied to the discharge to long-term healthcare facilities and increased length of stay at such facilities rather than a discharge home. The evidence to support this logic, however, is lacking. Discharge disposition following arthroplasty has been contentious recently for its potential effect on hospital readmission rates. Due to the aforementioned reasons, it is likely to be found predictive of subsequent PJI as well. Eliminating the events leading to prolonged hospitalization and discharge to a long-term care facility is likely to lower the risk of PJI.

Conclusion

Many factors are associated with the development of PJI. They include patient, institutional, surgical, and postoperative care factors. Patient selection, or rather optimization, prior to elective arthroplasty is imperative in lowering the risk of a devastating complication that can lead to systemic injury. Unfortunately, the evidence on correction of host disease and the effect on risk of PJI is limited. However, it is well established that patients with significant comorbidities are at great risk for PJI and should be counseled as such. Institutional and surgical teams should also be well-informed of practices—such as early treatment of wound discharge, decreased operative times, and improved anesthesia—that can limit the risk of PJI. No arthroplasty patient is ever PJI risk-free; however, knowledge of these established risk factors and appropriate patient care may help to mitigate such risks.

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Prevention of Periprosthetic Joint Infection

3

G. David Potter, Nalini Rao, and Tad M. Mabry

Introduction

Prosthetic joint infection (PJI) is a relatively rare but devastating complication following total joint replacement. While PJI may occur at any time following joint replacement surgery, the majority are diagnosed within the first 2 years of the index procedure [1, 2]. The diagnosis of a PJI has significant effects beyond the morbidity associated with infection treatment. PJI has been associated with a mortality rate from 2.7 to 18 %, which is far in excess of the mortality rates associated with primary joint replacement and aseptic revision surgery. [3–8]. Furthermore, the subsequent cost of treating PJI incurred by both the patient and the health care system is approximately 4 times the cost of a primary total joint arthroplasty (TJA) [4, 5, 7].

Given the impending changes in population demographics, the burden of treating these difficult infections will only increase over time. Projections by Kurtz et al. suggest a 673 % increase in primary total knee arthroplasties and a 174 % increase in primary total hip arthroplasties performed annually in the United States by the year 2030. Dramatic increases are also expected in the number of revision arthroplasties performed annually. [9]. Given the expanding size of the population at risk, every effort must be made to implement effective infection prevention strategies.

There are multiple factors associated with the development of PJI, including patient-related factors, surgical factors, environmental factors, and the emergence of drug-resistant microorganisms. Effective prevention strategies must address these factors in the preoperative, intraoperative, and postoperative settings. The purpose of this chapter will be to review known PJI prevention strategies, with a special emphasis on *Staphylococcus aureus* screening and decolonization.

Risk Factors

Identifying at-risk patients is the first step in medical optimization and targeted risk reduction. Preoperative patient risk factors for infection are outlined in Table 3.1. [1–3, 10–12]:

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Table 3.1 Patient risk factors

Non-modifiable risks
• Low income patients (Medicaid)
• Age over 75 years
• Males
• Systemic malignancy
• ASA score >2
• Prior joint surgery (i.e., revisions, prior fracture surgery)
• National Nosocomial Infections Surveillance risk index >1
• Lower volume hospitals/surgeons
Potentially modifiable risks
• Morbid obesity
• Longer duration of surgery (>210 min)
• Simultaneous bilateral procedures
• Preoperative stay >2 days
• Longer hospital stay (>5 days)
• Blood transfusion
• Postoperative wound complications

Preoperative Infection Prevention Strategies

Medical optimization prior to the operation is crucial to the success of the procedure. Basics of optimization include reducing the insult of other comorbidities, improving nutrition, smoking cessation, weight management, blood sugar management, and *S. aureus* screening and decolonization [13, 14].

The authors recommend that all patients have a preoperative medical evaluation for general health optimization. Chronic medical conditions, especially cardiopulmonary issues, should be identified and optimized preoperatively. Remote site infections (e.g., poor dentition and urinary tract infection) should be investigated and treated prior to the procedure.

Nutritional status is often neglected during the preoperative evaluation; however, ensuring proper nutrition is quite important. Malnourished patients have demonstrated a five- to sevenfold increased risk in developing major wound complications [15]. Preoperative screening for malnutrition should be employed in patients felt to be at risk based on the history and physical examination. Several laboratory tests have been proven to predict postoperative complications[16, 17]. Indicators of possible malnutrition include: body mass index (BMI) <20, total cholesterol <160 mg/dL, total lymphocyte count <1,500 cells/mm^3, transferrin <200 mg/dL, and albumin <3.5 mg/dL. These tests may be collected at the same time as other routine preoperative labs. When diagnosed preoperatively, malnutrition should be treated under the guidance of the appropriate medical specialist until corrected. In the postoperative period, proper nutrition should be encouraged. Every attempt should be made to minimize the period of restricted oral intake. Enteral supplements, protein supplements, and multivitamins should be considered during the postoperative period for at-risk patients.

Smoking cessation should be highly encouraged as another means to optimize patients prior to joint replacement surgery. Carbon monoxide and other components of tobacco smoke result in decreased blood flow to the surgical site, decreased aerobic metabolism and oxygenation, and increased local platelet aggregation. Furthermore, restricted circulation decreases the local delivery of the humoral and cellular mechanisms of immunity to the surgical site [18]. In addition to the risks of PJI, smoking has been shown to cause accelerated bone density loss, increased risk of hip fracture, lumbar disk disease, increased incidence of low back pain, increased risk of wrist fracture, and delayed fracture healing [17, 19]. Smoking cessation at least 6 months prior to the orthopedic procedure is recommended [17]. Proven techniques that promote prolonged cessation include counseling, self-help groups, nicotine replacement therapy, and physician counseling. Pharmacologic agents, such as bupropion and varencicline, are effective methods of increasing the likelihood of smoking cessation, especially when combined with the above-mentioned modalities [18].

Obese patients have a significant increase in periprosthetic joint infection risk compared to those with a normal BMI [20]. Obesity is defined as a BMI >30 kg/m^2. Postoperative complication rates increase with larger BMI. Obese patients incur significant perioperative risks involving the cardiac and pulmonary systems as a result

of increased cardiac work, decreased lung compliance, and decreased functional residual capacity. Obesity is felt to increase the risk for PJI in a multifaceted manner. First, obesity may significantly distort the local anatomy and add greatly to the difficulty, and therefore the duration, of the operative procedure. Next, poorly vascularized subcutaneous fat and the resultant postoperative dead space from the added surgical dissection contribute to both hematoma and seroma formation, which are known risks for infection. One representative study demonstrated a significantly elevated complication rate in patients with a BMI ≥40 when compared to patients with BMI <40 [21]. Although no absolute "cutoff" value with respect to BMI is utilized, the authors feel that every attempt should be made to reduce the BMI to <40 preoperatively, while maintaining appropriate overall nutritional status.

Strict perioperative glycemic control is becoming a better recognized means of reducing the risk for PJI. Controlled glycemic levels provide patients with significant risk reductions when compared to those with uncontrolled levels in areas beyond infection. These include length of stay, stroke, myocardial infarction, postoperative hemorrhage, urinary tract infection, and pneumonia. When properly controlled, patients with diabetes can lower their risk of infections to levels near those without diabetes [22].

S. aureus Screening and Decolonization

S. aureus is the leading cause of orthopedic surgical site infection (SSI), and the prevalence of methicillin-resistant S*taph aureus* (MRSA) SSI is increasing in community and healthcare settings [23–28]. The two strains of *S. aureus* responsible for these infections are methicillin-sensitive *Staph aureus* (MSSA) and MRSA. SSIs due to MRSA have been associated with increased morbidity, morality, and increased length of hospital stay [29].

S. aureus resides on the skin surfaces in one-third of the general population who remain asymptomatic [30]. Studies have demonstrated that MSSA/MRSA can be detected in moist areas of the body such as nares, throat, axilla, and perineum. Nasal screening identified 66 % of the carriers; while combining nasal and perineal swabs gave the best two-site combination (82 %). [31]. Since the anterior nares are the site of highest colonization, this is the traditional site for screening tests [32]. New developments such as real time PCR offer rapid, sensitive, and specific strain identification of *S. aureus* [33]. Nasal carriage of *S. aureus* is strongly associated with skin colonization and such patients are 2–9 times more likely to acquire SSI. *S. aureus* nasal carriage was the only independent risk factor for SSI following orthopedic implant surgery in several studies [34–37].

One of the strategies that has shown a great deal of promise is the use of staphylococcal decolonization to eradicate the nasal/skin colonization of *S. aureus* (MSSA, MRSA) to prevent SSI. Surveys administered in the United States and Europe show that decolonization is being attempted frequently in various settings. [38, 39]. Many agents and various approaches have been used to eradicate *S. aureus* colonization. Most strategies result in only short-term decolonization. Eradication of nasal and skin carriage at the time of surgery would seem to be a logical approach to reduce the risk for postoperative staphylococcal infection [40].

The most common and well-studied decolonization protocol used selectively in colonized patients is the use of topical intranasal mupirocin ointment twice daily and chlorhexidine body washes for 5 days immediately prior to surgery. In addition, patients who are colonized with MRSA receive perioperative intravenous vancomycin prophylaxis in place of, or in addition to, a first-generation cephalosporin antibiotic [41].

A systematic review inclusive of retrospective and prospective studies that evaluated the effect of *S. aureus* decolonization in orthopedic patients showed a significant reduction in SSI. The prospective data conducted at our institution (N.R.) performed two analyses and compared the intervention group with two different control groups. In the first analysis, none of the carriers in the intervention group developed SSI during a 2-year

follow-up period, whereas 19 patients in the concurrent control group developed SSI (0 % vs. 3.3 %). In the second analysis, screening and selective decolonization appeared to be associated with a decrease in the overall SSI rate compared to that during the pre-intervention period (1.2 % vs. 2.7 %)—again approximating previous findings (1.4 % vs. 2.7 %). Importantly, the protocol reduced *S. aureus* infection without increasing the rate of infections due to other pathogens [41]. The effect of screening and decolonization on SSI in orthopedic patients is outlined in Table 3.2.

Overall reduction in SSI was significant when the studies were aggregated, as implementation of decolonization was associated with lower infection rates [41–49]. At our institution (N.R.), the efficacy of the decolonization protocol in eradication of MSSA colonization was significant ($p<0.001$) while the eradication of MRSA colonization approached statistical difference (5/5, $p=0.063$) (unpublished data).

The cost-effectiveness using economic models demonstrates that screening and decolonization of *S. aureus* in orthopedic patients, specifically in TJA patients, would be an economically dominant strategy [41, 43, 47, 49–53]. Mupirocin and chlorhexidine are safe and cost-effective agents. The protocol is simple, practical to implement, and achieves a high rate of compliance. The authors believe that all patients scheduled for total joint replacement should be screened for the presence of *S. aureus*, and patients screened as positive for colonizations should be treated accordingly.

Intraoperative Infection Prevention Strategies

In the operating room, lowering the risk for PJI requires appropriate skin preparation for bacterial reduction at the surgical site. Preoperative hair removal does not have significant data to support its use and some surgeons advocate against it, citing a potentially increased risk of SSI. However, the use of clippers, in which the cutting edges do not touch the skin, demonstrates a reduction in postoperative infection rates and relative risk for infection when compared to skin shaving with a razor. It is important to note that hair reduction should be performed immediately prior to, rather than the night before, the planned surgical procedure [54–56]. The ideal skin preparation for sterility requires a scrub that will have both antimicrobial and anti-spore activities with residual activity well after the time of application. Common agents used for skin preparation include povidone-iodine (Betadine), alcohol, ChloraPrep® (CareFusion Corporation, San Diego, CA), and DuraPrep™ (3M Corporation, Saint Paul, MN).

Alcohol has the fastest microbial reduction and may increase the antiseptic activity of povidone-iodine solutions if used jointly. However, alcohol does not have residual activity and allows rebound microbial growth [57]. Betadine is effective as paint, but fails to provide adequate drape adherence in order to prevent lift-off. DuraPrep™ is as effective as Betadine in bacterial reduction and is far superior in terms of drape adherence than both Betadine and ChloraPrep [57, 58].

Draping is a multistep process that involves many different materials. Plastic adhesive tape drapes do not permit vertical migration of bacteria compared to the tenfold increase that cloth drapes allow. Additionally, use of iodine-impregnated drapes reduces the rate of recolonization when combined with plastic adhesive drapes. While literature supports the reduction in postoperative wound contamination in critical care and obstetrics, orthopedic specific literature does not show any decrease in wound infection rate [57].

The greatest source of airborne bacteria comes from operating room personnel, and therefore traffic should be reduced to a minimum [59, 60]. Surgical attire for the operating room can greatly reduce the airborne bacterial load by covering hair, ears, and fully covering beards. Wrap around gowns and personal exhaust systems are associated with reduced numbers of colony-forming units when compared to standard cotton gowns or surgical attire [61]. Proper surgeon preoperative hand scrubbing is another means of reducing the bacterial load within the surgical environment. While the traditional scrub brush with a povidone-iodine or

Table 3.2 Studies evaluating *Staphylococcus aureus* decolonization in TJA

Author (year)	Country/design	Patient population	Sample size	Controls	% Colonized	Patients decolonized	Protocol	% Reduction in SSI	*P* value
Rao et al. (2011) [19]	US/prospective	TJA	3,025	Concurrent Historic	MSSA 22 % MRSA 3 %	Positive nasal screens	2 % Mupirocin × 5 days Chlorhexidine × 5 days	76.9 % reduction in SSI	0.009
Kim et al. (2010) [20]	US/prospective	TJA/spine sports	7,019	Historic	MSSA 22.6 % MRSA 4.4 %	Positive nasal screens	2% Mupirocin × 5 days Chlorhexidine × 5 days	81.3 % reduction in SSI	0.009
Rao et al. (2008) [21]	US/prospective	TJA	1,966	Concurrent Historic	MSSA 23 % MRSA 3 %	Positive nasal screens	2 % Mupirocin × 5 days Chlorhexidine × 5 days	200 % reduction in SSI	0.016
Sankar et al. (2005) [22]	UK/prospective	TJA	395	Historic	N/A	Positive nasal, groin, axilla wound	Mupirocin/povidone-iodine/triclosan	200 % reduction SSI	0.05
Wilcox et al. (2003) [23]	UK/prospective	Orthopedic patients with metal prosthesis and/fixation	2,178	Historic	MSSA 27 % MRSA 38 %	All patients	Mupirocin × 5 days Triclosan × 1 day	149 % reduction MRSA SSI	0.001
Hadley et al. (2010) [24]	US retrospective	TJA	2,058	Concurrent	MSSA 21.4 % MRSA 3.5 %	Positive screens	2 % Mupirocin × 5 days Chlorhexidine × 1 day	12.5 % reduction of SSI	0.809
Hacek et al. (2008) [25]	US/retrospective	TJA	1,495	Historic	*S. aureus* 24.5 %	Positive nasal screens	2 % Mupirocin × 5 days Chlorhexidine × 1 day	75.3 % reduction of SSI	<0.1
Price et al. (2008) [26]	US/retrospective	Elective orthopedic patients	284	None	MSSA 28.5 % MRSA 1.8 %	Positive nasal screens	2 % Mupirocin × 5 days	200 % reduction of SSI	NA
Nixon et al. (2006) [27]	UK/retrospective	Elective and trauma orthopedic patients	5,594	Historic	MRSA elective 1.3 % Trauma 3.8 %	Positive nasal screens	2 % Mupirocin × 5 days	Trauma 56 % reduction of MRSA	0.035
							Triclosan × 5 days	SSI elective 70 % reduction of MRSA SSI	0.06

TJA total joint arthroplasty, *MRSA* methicillin-resistant *Staphylococcus aureus, MSSA* methicillin-sensitive *Staphylococcus aureus*, *SSI* surgical site infection, *NA* not available, *UK* United Kingdom, *US* United States of America

chlorhexidine is effective, proper procedure regarding the actual wash is not strictly followed. Newer, scrubless skin preparation options demonstrate better adherence to proper protocol, take less time, and have better antibacterial efficacy with prolonged use [62–64].

Double-gloving is recommended as it reduces the risk of perforation of the inner glove and subsequent surgical site contamination. Routine changing of the outer gloves during the procedure further reduces the risk of inner glove perforation and is an effective way to reduce bacterial contamination prior to handling of the implant [65, 66].

Laminar airflow, in which air filters remove particles >0.3 μm, demonstrates decreased bacterial wound contamination when compared to conventional air flow [67]. When controlled for antibiotic use, laminar airflow has been associated with lower prevalence of infection. Both Charnley and Ritter demonstrated successful infection reduction after implementation of laminar airflow when compared to operations without laminar airflow. The success is dependent upon patient positioning, personnel location, surgery type (hip or knee), and direction of flow. Knee surgery appears to benefit less than hip surgeries. The effect of the directed air decreases when personnel move in the way of the air flow. Further, cost may be prohibitive as retro-fitting and operating may cost a significant amount of money [68, 69]. The relative benefit of laminar airflow remains a controversial topic.

Ultraviolet (UV) light is another method of minimizing the risk of intraoperative wound contamination. Several studies evaluating the effectiveness of UV light have shown a decrease in the rate of infection compared to operating rooms without ultraviolet lights. UV lights are of low cost, low maintenance, and are relatively safe with proper protection equipment that can contribute to lower infection rates. However, there are concerns regarding UV lights, such as overexposure, severe conjunctivitis, blindness after prolonged exposure, and superficial erythema [68].

Prolonged operative time has been identified as a significant risk factor for the later development of PJI [57, 70, 71]. Although the exact time at which an operation becomes "prolonged" is impossible to determine, there is certainly never a benefit to a more lengthy procedure. In total knee replacement, an operative time greater than 120 min is a significant risk factor for infection. The association between operative time and infection risk is likely multifactorial, as it may be a proxy for other issues that predispose to complications, such as hypothermia, increased local tissue damage related to added dissection and/or prolonged retraction, and greater blood loss. Every effort should be made to maximize surgical efficiency.

The risk of PJI is increased for patients requiring allogeneic blood transfusion [72–74]. A comprehensive blood management plan is part of any PJI risk reduction strategy and involves treating preoperative anemia, minimizing intraoperative blood loss, and avoidance of postoperative transfusion unless truly indicated [74].

Prophylactic Antibiotics

The benefit of timely and appropriate prophylactic antibiotics prior to total joint replacement is unquestioned. Henley used a prospective randomized double-blinded study of general orthopedic procedures showing prophylactic antibiotics had a 1.6 % infection rate compared to the placebo group of 4.2 % [75]. Prophylactic antibiotics reduce the absolute risk and relative risk when compared to the same procedure without antibiotic prophylaxis [76, 77]. For the antibiotics to be effective, they must target the appropriate organism. Most sources of bacterial contamination arise from the patient's skin or airborne sources. In primary joint arthroplasties, *Staphylococcal* and *Streptococcal* species are the primary targets. A long half-life, excellent tissue penetration and effectiveness against *Staphylococcal* and *Streptococcal* organisms make first-generation cephalosporins the antibiotic of choice for the vast majority of orthopedic procedures, including total joint replacement [12, 78–81]. Vancomycin, either alone or in combination with a first-generation cephalosporin, should be used for MRSA-colonized patients [57]. Although many patients

self-report a history of "penicillin allergy," rates of true cross-reactivity with penicillin and cephalosporin and the risk for subsequent anaphylaxis vary from 0.0001 to 0.1 % [82]. Patients should be specifically tested for a true cephalosporin reaction in the preoperative period whenever possible in order to both avoid the overuse of vancomycin and realize the efficacy of the cephalosporin. Patients with confirmed beta-lactam allergy should receive vancomycin or clindamycin as the alternative method of antibiotic prophylaxis.

Cefazolin should be dosed based on the patient's body mass: 1 g for weight <80 kg, 2 g for weight >80–120 kg, and 3 g for weight >120 kg. It is redosed every 2–5 h. Vancomycin is given at a dose of 15 mg/kg and is redosed every 6–12 h. Clindamycin is standardized at 600 mg per dose and redosed every 3–6 h. The antibiotics should be administered and completed within 1 h of incision. Subsequent doses should be administered if the length of the procedure exceeds the half-life of the drug, or if greater than 70 % of circulating blood volume is lost [57, 59]. The postoperative duration of antibiotic administration should be confined to 24 h. There is no significant difference in infection prevention when comparing postoperative antibiotics for 24 h vs. 3–14 days. Further, minimizing the length of postoperative antibiotic duration reduces the cost of healthcare [83–87].

Antibiotic-impregnated bone cement is a means of local antibiotic delivery. Using cement as a delivery mechanism allows for local elution of the majority of the antibiotics in the first 9 weeks [88]. Local delivery allows for tissue antibiotic levels far superior to those seen after systemic administration alone [69]. The beneficial effect is therefore in the reduction of implant colonization from intraoperative contamination. Antibiotic cement used at the time of arthroplasty is unlikely to confer any risk reduction for the development of late hematogenous infection. When combined with systemic antibiotics, antibiotic-impregnated cement for cemented total hip arthroplasty has shown a reduction in revision rates for infection as well as all-cause revisions. [89, 90].

Additional Intraoperative Infection Prevention Strategies

Intraoperative irrigation removes debris, blood clots, and reduces bacterial contamination. There is no absolute consensus as to the use of pulsatile lavage rather than bulb lavage. While the higher pressure of pulse lavage does remove a larger bacterial load than bulb lavage, it also has an increased rate of deep bacterial seeding in bone. High pressure may also increase muscle damage and decrease particulate removal when compared to bulb irrigation [91, 92]. Normal saline and soap solutions remove significantly more bacteria from the surgical field when compared to antibiotic-mixed irrigation. Further, antibiotic solution has potential for tissue toxicity and has evidence of wound-healing problems [93, 94]. While there is strong evidence that soap irrigation is superior to antibiotic-impregnated or normal saline solution, there are no strong human studies to indicate the routine addition of antibiotics to irrigation solution. In routine orthopedic procedures, low-to-intermediate lavage is adequate and high pressure lavage should be reserved for severely contaminated and/or open fractures in which treatment is delayed [59].

While the use of drains may theoretically reduce the risk for postoperative hematoma formation, there is no current literature to support the use of drains in routine primary arthroplasties. Multiple studies demonstrate no difference in rates of infection, wound complications, thromboembolic complications, hospital stay, or hematoma formation with or without the use of a postoperative suction drain. However, if a drain is used, it should be removed within 24 h of the procedure in order to minimize the risk of PJI [95, 96].

No evidence is available to support a specific method of wound closure that reduces the rates of infection or wound complications in routine orthopedic procedures. Occlusive surgical dressings provide protection from bacteria, faster re-epithelialization, faster collagen synthesis, and create an environment in which fibroblast and angiogenesis occur [97, 98]. Current recommendations based on literature include a three-layer dressing.

The first layer is directly over the wound and is a non-adherent hydrophilic dressing followed by an absorptive layer of gauze. The third and outer later is the occlusive layer that adheres the dressing to the skin [96, 99].

Postoperative Infection Prevention Strategies

The elevated risk for venous thromboembolism (VTE) following total joint replacement requires the use of a multimodal VTE risk reduction strategy which often requires some type of chemoprophylaxis. Potent anticoagulants are a major contributor to hematoma formation in the postoperative period. Subsequent infection at the site of hematoma is a significant risk for PJI [100]. Parvizi et al. found that excessive anticoagulation (INR >1.5) and the development of a hematoma had a significant increase in periprosthetic infection rate [101]. In another study, operative evacuation of a postoperative hematoma significantly increases the risk for the development of a PJI and the need for further surgery [102].

The routine use of prophylactic antibiotics prior to invasive procedures remains controversial. While no definitive evidence is available to show the association between dental procedures and periprosthetic joint infection, the AAOS recommends antibiotic prophylaxis for patients who undergo dental procedures after having joint arthroplasties [103]. Current antibiotics for dental procedures are given 1 h prior to the procedure. Drug options include 2 g of amoxicillin, 2 g of cephalexin, or 600 mg of clindamycin. For any genitourinary or gastrointestinal procedures, 750 mg of ciprofloxacin is recommended 1 h before the procedure.

Conclusion

PJI is a devastating complication following total joint replacement that leads to excess morbidity, mortality, and cost. This chapter has outlined effective prevention strategies that may be utilized in all phases of perioperative care. A multifaceted approach to the patient undergoing total joint replacement will have the greatest positive effect. Further study will be needed to identify and share "best practice" models that might be emulated to lower the PJI risk for all patients.

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Medical Optimization of Patients Prior to Surgery

4

Gregary D. Marhefka and Geno J. Merli

Background

In 2007, Kurtz et al. projected that by the year 2030 the number of total hip arthroplasties (THA) will grow by 174 % to 570,000 and the number of total knee arthroplasties (TKA) by 673 % to 3.48 million. Concordantly, the number of total hip and total knee revisions is expected to grow by 137 % and 601 %, respectively. Prosthetic joint infections (PJI) have been reported to occur in 1.5–2.5 % of all THA and TKA. Mortality from a PJI may be as high as 2.5 %, up to 7 % in the older population above 80 years of age. With the increase in an aging population as a whole and a projected increased number of arthroplasties, the number of infections may also increase, necessitating an increase in revision surgeries to treat the PJI. There are no data pertaining to the optimal medical management specifically for PJI revision surgery. General perioperative management of the noncardiac surgery patient usually applies. In this chapter, we review the medical optimization of orthopedic patients prior to surgery and the management of cardiovascular complications following surgery.

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Preoperative Evaluation

For patients who already have a diagnosis of stable coronary artery disease (CAD) (prior myocardial infarction (MI)), coronary artery stents or bypass surgery (CABG), heart failure (HF), arrhythmias (including pacemakers and implantable cardioverter defibrillators), or significant valvular disease (including previous valve replacement), the family medicine physician, internist, or cardiologist should be consulted. It is recommended that patients with suspected cardiovascular disease (e.g., previously unevaluated angina or anginal equivalents, dyspnea, presyncope or syncope, patients older than 50 with reduced exercise tolerance, uncharacterized murmur, or abnormal electrocardiogram (ECG)) also be evaluated. The primary role of the medical consultant is to evaluate the patient's medical history, identify any new diagnoses, stratify the patient's risk for cardiovascular events, and ultimately optimize medical treatment to minimize complications. Communication between the medical consultant, orthopedic surgeon, and anesthesiology team members is paramount.

The first step is to determine the patient's current cardiovascular status. The four active cardiac

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conditions identified in the 2009 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines on Perioperative Cardiovascular Care of Noncardiac Surgical Patients that mandate consultative evaluation and treatment before proceeding with surgery are: (1) acute coronary syndrome (unstable angina, non-ST elevation, and ST elevation MI with acute MI defined as occurring within the past 7 days); (2) acute decompensated HF; (3) unstable arrhythmias (symptomatic bradycardia, high grade or third-degree atrioventricular block, ventricular tachycardia, uncontrolled atrial arrhythmias such as rapid atrial fibrillation); and (4) severe valvular disease (usually severe symptomatic aortic or mitral stenosis or regurgitation). In the absence of emergent surgery or one of these four contraindications, the medical consultant will next assess the patient's functional status (Table 4.1). If the patient is able to asymptomatically perform more than four METS (Metabolic Equivalents) of activity, typically the patient can proceed to surgery without further testing. If, however, the patient cannot perform four METS of activity, Revised Cardiac Risk Index factors are identified (Table 4.2). If none of these factors are present, patients may proceed to surgery without further testing. If one or more risk factor is identified, then the medical consultant may consider noninvasive stress testing if it will change management (Fig. 4.1). If significant CAD is revealed, ultimate decisions about revascularization with coronary artery stenting or CABG are made independent of the planned orthopedic surgery. Coronary artery revascularization outside of the standard indications has never been proven to protect patients from perioperative cardiovascular events. Standard indications for stable, elective coronary artery revascularization include: (1) significant left main CAD (defined as a stenosis >50 %), (2) patients with stable angina and 3-vessel disease or 2-vessel disease that includes proximal left anterior descending artery disease (particularly with a reduced left ventricular ejection fraction 50 %), and (3) angina symptoms that limit activity despite optimal medical therapy.

In addition to the Revised Cardiac Risk Index, another preoperative risk assessment algorithm has been devised called the Gupta Perioperative Cardiac Risk Index. It is derived from a database of 211,410 surgical patients of which 9,272 (4.4 %) had orthopedic procedures. The five indicators shown to be predictive of perioperative MI or cardiac arrest are: (1) type of surgery, (2) dependent functional status, (3) abnormal creatinine, (4) American Society of Anesthesiologists' class,

Table 4.1 Metabolic equivalent (MET) of certain activities

1 MET	Eat, dress, use the toilet	4 METs	Climb a flight of stairs or walk up a hill
↓	Walk indoors around the house	↓	Walk on level ground quickly at 4 mph
	Walk a block or two on level ground		Run a short distance
4 METs	Do light work around the house like dusting or washing dishes		Do heavy work around the house, like scrubbing floors, or moving heavy furniture
			Play golf, bowling, dancing, doubles tennis, throwing a baseball or football
		More than 10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, skiing

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. Circulation 2009; 120: e 169–276

Table 4.2 Revised cardiac risk index factors: history of (1) ischemic heart disease, (2) compensated or prior heart failure, (3) cerebrovascular disease, (4) diabetes mellitus, (5) renal insufficiency (creatinine >2 mg/dL)

Number of factors	Major cardiac complication rate (%)
0	0.4
1	0.9
2	7
≥3	11

Major cardiac complications: myocardial infarction, pulmonary edema, ventricular fibrillation, primary cardiac arrest, and/or complete heart block

Adapted from Lee TH, Marcantonio ER, Mangione CM, et al. Circulation 1999; 100: 1043–49

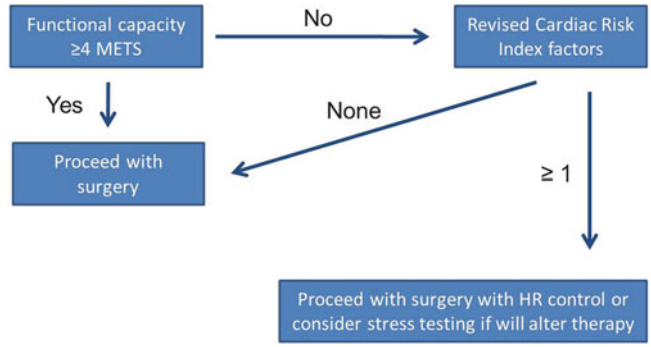

Fig. 4.1 Perioperative cardiac risk evaluation algorithm for intermediate-risk orthopedic surgery (in the absence of need for rare emergent surgery or in the absence of active cardiac conditions (such as acute coronary syndrome, decompensated heart failure, unstable arrhythmias, or severe valvular disease)). See Table 4.1 for metabolic equivalent (MET) definition. See Table 4.2 for revised cardiac risk factors (adapted from Fleisher LA, Beckman JA, Brown KA, et al. Circulation 2009;120:e169-276)

and (5) increasing age. Its predictive performance appeared to outperform that of the Revised Cardiac Risk Index. The Gupta Perioperative Cardiac Risk Index is available online where the variables can be inserted and a percentage risk will be displayed.

Coronary Artery Disease

Apart from acute venous thromboembolic disease, another potentially life-threatening postoperative complication is MI. The European Society of Cardiology (ESC), ACC, AHA, and the World Heart Federation (WHF) 2012 Third Definition of Myocardial Infarction defines MI as a rise and fall of troponin with at least one value above the 99th percentile of the upper reference limit and at least one of the following: ischemic symptoms, dynamic ECG ST-T wave changes, new left bundle branch block, new pathologic ECG Q waves, imaging evidence of new loss of viable myocardium, a new segmental wall motion abnormality, or findings of intracoronary thrombus by angiography. Most postoperative MIs are non-ST elevation and often lack angina. Monitoring for intra- and postoperative ST segment changes is generally recommended in patients with known significant CAD or multiple risk factors.

Antiplatelet Therapy

Patients with known CAD should be seen before surgery in consultation with a family medicine physician, internist, or cardiologist. Aspirin is uniformly the most commonly prescribed medication for this subset of patients. Aspirin, with its irreversible cyclooxygenase inhibitory effects and reduction of thromboxane A2 production, reduces platelet activation and aggregation, thereby increasing the risk of bleeding. In patients without coronary artery revascularization (coronary stents or CABG), the decision to stop aspirin should be made on an individual basis. However, in patients who have been revascularized (particularly with coronary artery stents), decisions regarding perioperative antiplatelet agent management are critically important. As much as 5 % of patients will undergo elective noncardiac surgery within 1 year of a coronary intervention. Aspirin is recommended indefinitely in patients after CABG or coronary artery stenting.

Following CABG, aspirin reduces the risk of saphenous vein graft closure. After coronary artery stenting, dual antiplatelet therapy with aspirin and either clopidogrel, prasugrel, or ticagrelor prevents acute stent thrombosis. In addition, clopidogrel or ticagrelor is indicated along with aspirin after an acute coronary

syndrome regardless of whether or not a coronary stent has been placed; prasugrel is only prescribed in those who receive a coronary stent. Clopidogrel and prasugrel irreversibly bind platelet P2Y12 adenosine diphosphate receptors, reducing platelet activation and aggregation. Prasugrel was proven to be slightly more effective than clopidogrel but is contraindicated in anyone who has a history of stroke or transient ischemic attack; it is also not recommended in those over the age of 75. Slightly more bleeding was demonstrated with prasugrel compared to clopiodgrel.

Ticagrelor is a direct-acting, reversibly binding P2Y12 receptor antagonist, found to be slightly better than clopidogrel following an acute coronary syndrome. Similar to prasugrel, ticagrelor appears to cause slightly more bleeding than clopidogrel. Of note, the maximum dose of aspirin allowed with concurrent ticagrelor is no more than 100 mg. The duration of dual antiplatelet therapy depends on the type of stent and every attempt should be made not to disrupt the dual antiplatelet therapy in this time frame. The nidus for stent thrombosis is exposed stent struts. Bare metal stents quickly endothelialize within weeks, and therefore the second antiplatelet agent may be stopped after 4 weeks (and in emergent situations after a minimum of 2 weeks), though ideally dual antiplatelet therapy should continue uninterrupted for a year if possible if the stent was placed for an acute coronary syndrome. On the other hand, drug-eluting stents have a delayed endothelialization due to drug eluting agents that are designed to prevent restenosis. Dual antiplatelet therapy is critical in the first year following a drug-eluting stent; and given that late and very late stent thromboses have been described with drug-eluting stents (thought to be in part due to the delayed endothelialization), aspirin should ideally never be stopped. Continuing the second agent beyond the first year may even be beneficial.

As stent thrombosis is associated with significant morbidity and mortality, elective surgery should be delayed while on dual antiplatelet therapy until at least 1 month following a bare metal stent and at least 1 year after a drug-eluting stent. Patients should proceed with emergent surgery as indicated despite antiplatelet therapy. Platelet transfusion may even be rarely required for major, life-threatening bleeding in the perioperative period. This needs to be balanced with the recognized risk of acute stent thrombosis if the recommended time period for dual antiplatelet therapy has not yet elapsed. Daily assessment for the safe timing of re-initiation of at least aspirin and eventually the second antiplatelet agent in the postoperative period is essential. When an urgent procedure cannot be postponed during the recommended dual antiplatelet period but an increased minor bleeding risk is acceptable, the procedure should be performed on dual antiplatelet therapy, with both the surgeon and patient being aware of the increased risk of minor bleeding. If the surgeon determines that increased bleeding will result in significant morbidity or mortality with dual antiplatelet therapy, they need to carefully discuss the risks and benefits with the consulting family medicine physician, internist, or cardiologist. If agreed upon, every attempt should be made to continue aspirin in this critical time period to offer some protection against stent thrombosis, which is seen more commonly with complete, premature cessation of dual antiplatelet therapy. In this situation, clopidogrel or ticagrelor may be stopped 5 days prior to the procedure and prasugrel 7 days prior. Again, daily postoperative assessment for re-initiation of dual antiplatelet therapy, when considered safe, is essential. Consideration should also be given to reloading with the second agent. Laboratory testing with available functional platelet assays to guide therapy remains clinically unproven. Preoperative bridging therapy with intravenous antiplatelet agents (e.g., eptifibitide or cangrelor) while the oral antiplatelet agent is wearing off may be a future option in high risk patients but warrants further study.

Beta-Blocker Therapy

In the last 2 decades, the evidence for the perioperative protective effects of beta-blocker therapy in reducing myocardial infarction and death

has varied. The landmark trial by Mangano et al. was a randomized, double-blind, placebo-controlled trial assessing atenolol administered intravenously preoperatively (12–15 % of patients underwent orthopedic surgery) and orally up to 1 week postoperatively. It revealed a major reduction in adverse cardiovascular events; however, there was no mortality benefit in the immediate perioperative period (only significantly reduced ischemia by Holter monitoring was observed (24 % vs. 39 %; $p=0.03$). Interestingly, the mortality benefit was delayed and seen only at 6 months (mortality 1 % vs. 10 %; $p<0.001$) and out to 2 years.

The largest clinical trial, the randomized, placebo-controlled POISE trial (Devereaux PJ, et al.) (21 % of which were orthopedic surgery patients), found a reduction in the risk of MI, cardiac revascularization, and atrial fibrillation, but at the cost of an increase in death, stroke, and clinically significant hypotension and bradycardia. In this trial extended-release metoprolol was started 2–4 h prior to surgery and given for 30 days after. It has been suggested that perhaps the aggressive dosing was what led to the untoward effects in these beta-blocker naïve patients. Another trial (DECREASE IV) (Dunkelgrun M, et al.), studied bisoprolol initiated and titrated a median of 34 days prior to the procedure (16 % of which were orthopedic surgery patients), and continued for 30 days after. This trial found a lower incidence of cardiac death and nonfatal MI (2 % vs. 6 %; $p=0.002$), with the same number of strokes (four in bisoprolol patients and three in placebo patients). Specifically for orthopedic surgical procedures, a Canadian retrospective review of 5,158 patients undergoing hip and knee arthroplasty in the 2000s (van Klei, et al.) found that 18 % were treated with beta-blockers on the day of surgery; and in 25 % of these, it was discontinued. The discontinuation of beta-blockers after surgery was significantly associated with MI and death. It was unknown, however, whether the patient was already on a beta-blocker or why the beta-blocker was discontinued in this retrospective analysis.

Given the mixed data, the 2009 ACC/AHA Guidelines on Perioperative Cardiovascular Care of Noncardiac Surgical Patients recommend continuing beta-blockers in those to whom they have already prescribed, given their potentially protective effects and the potential dangers of withdrawal. Initiating and titrating beta-blocker therapy is deemed reasonable only in patients identified to have CAD or more than one Revised Cardiac Risk Index factor (Table 4.2). In all other patients, the data are uncertain.

Statins

More than a decade ago, perioperative statin therapy was thought to be potentially risky with cases of rhabdomyolysis being reported in the anesthetized and immobile surgical patient. However, in a subsequent prospective, case-controlled observational study of patients undergoing elective arthroplasty, no increase in muscular adverse effects was found. Furthermore, the pleotrophic and anti-inflammatory properties of statins may reduce the risk of perioperative cardiac events and its withdrawal has been associated with worse outcomes in some types of surgery, such as vascular surgery. In the large, prospective, randomized DECREASE IV trial, fluvastatin was studied in intermediate-risk surgery patients (16 % orthopedic surgery) and showed a trend toward reduced 30 days cardiac death and MI, but did not reach statistical significance. Nonetheless, statin therapy appears to be safe and beneficial; therefore, in those already prescribed this type of therapy, every attempt should be made to continue it perioperatively.

Heart Failure

HF is a clinical syndrome of decreased exercise tolerance, and/or fluid retention with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and/or lower extremity edema. Alternatively, patients may be asymptomatic without a clinical syndrome but be at risk due to evidence of cardiac enlargement and/or diastolic or systolic dysfunction. In patients older than 65 years of age, the prevalence of HF is 2–3 %, and approaches 80 % in patients older than 80. HF carries a worrisome

prognosis, with a high readmission rate of 50 % at 6 months following the first hospitalization and a mortality rate as high as 25–35 % at 12 months. HF is split equally between diastolic (preserved left ventricular function) and systolic (reduced left ventricular function). There are several factors involved in developing or exacerbating perioperative HF, including a potentially infectious and/or inflammatory state, intravenous fluids, interstitial fluid shifts, hypertension, myocardial ischemia, atrial fibrillation, renal failure, and anemia. Acute volume overload with an S3 and/or S4 and pulmonary edema should be managed with intravenous diuretic therapy. If there is clinical evidence of poor perfusion, consideration of inotropic therapy may be required. One should be mindful with dobutamine if myocardial ischemia is considered to be the trigger, as this agent increases myocardial oxygen demand and may worsen the clinical status.

In addition, a form of hypertrophic cardiomyopathy exists in the elderly, with the potential for outflow obstruction due to a thickened sigmoid-shaped septum brought on by a small ventricle, hypovolemia; and tachycardia where inotropic therapy could actually worsen the clinical situation and possibly cause cardiovascular collapse. Careful cardiovascular examination and an echocardiogram are helpful in sorting out these particulars. In extreme situations, management with a pulmonary artery catheter may be considered in an experienced intensive care unit setting under the guidance of an experienced consulting cardiologist and/or intensivist. If acute hypertension is thought to be contributing to HF, management should include oral agents such as angiotensin-converting enzyme inhibitors, hydralazine, or nitrates when possible. If the patient is not able to take oral medication, or if they are critically ill, continuous intravenous agents such as nitroprusside or nitroglycerin for rapid afterload reduction may prove beneficial. Short-acting medications such as intravenous hydralazine or short-acting oral or sublingual dihydropyridine calcium channel blocker medications are not recommended as they can precipitate significant hypotension. Beta-blockers and non-dihydropyridine calcium channel blockers should not be initiated in acutely decompensated HF because the condition may worsen or these agents may precipitate a potentially low flow state. If a patient is already on a beta-blocker, this medicine should be continued cautiously or at a reduced dose in acutely decompensated HF.

Arrhythmias

Perioperative atrial and ventricular tachyarrhythmias, particularly in the older and more complicated patient, are common. Sinus tachycardia is usually caused by pain, hypovolemia, medication or substance withdrawal, anemia, or fever. Other serious causes include hypoxia, myocardial ischemia, or pulmonary embolus. Usually premature atrial complexes are benign but could be a precursor to atrial fibrillation or other forms of supraventricular tachycardia (SVT). An acute onset of a narrow complex, regular SVT can be treated with vagal maneuvers (such as Valsalva or careful carotid artery massage in the absence of a carotid bruit). Alternatively or if these maneuvers fail, adenosine 6 mg intravenously can be given rapidly, followed by a 20 cc sterile saline flush. AV nodal reentrant or atrioventricular reentrant tachycardia will often break with these maneuvers or medication. Other arrhythmias may slow enough to reveal the underlying atrial activity, allowing further directed treatment. Rapid atrial fibrillation and atrial flutter will often need intravenous beta-blocker therapy (e.g., metoprolol or esmolol) or non-dihydropyridine calcium channel blockers (e.g., diltiazem or verapamil) followed by oral administration (Fig. 4.2). Digitalis intravenously or orally may prove ineffective in the postoperative state where sympathetic tone is high, but may be one of the only medications available if blood pressure is low. Cardioversion is not recommended unless there is urgent hemodynamic instability, as the underlying trigger is often persistent. In addition, if atrial fibrillation or atrial flutter is present more than 48 h, cardioversion should not be performed electively in the absence of full anticoagulation given the potential risk for acute thromboembolism.

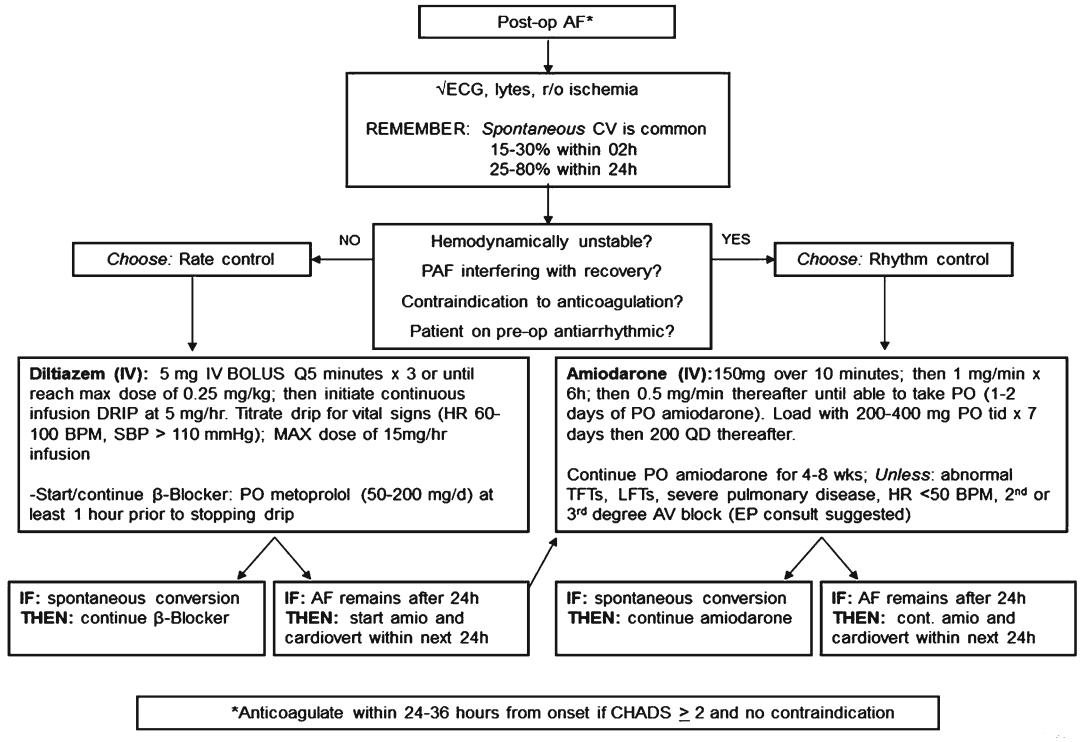

Fig. 4.2 Proposed management of postoperative atrial fibrillation in the surgical patient. *AF* atrial fibrillation, *ECG* electrocardiogram, *CV* cardioversion, *PAF* paroxysmal atrial fibrillation, *IV* intravenous, *HR* heart rate, *BPM* beats per minute, *SBP* systolic blood pressure, *PO* per os, *tid* three times per day, *TFTs* thyroid function tests, *LFTs* liver function tests, *EP* electrophysiology, *CHADS* atrial fibrillation stroke risk score (see Tables 4.3 and 4.4) (courtesy of Daniel Frisch, M.D.)

Cardiology consultation with consideration of intravenous amiodarone for a brief period (days) is reasonable if the atrial arrhythmia is particularly recurrent and very symptomatic with borderline hemodynamic instability. Ideally amiodarone should not be used after 48 h for atrial fibrillation or flutter in the absence of anticoagulation, due to potential cardioversion and associated acute thromboembolic risk. In the patient with borderline blood pressure, if digitalis proves ineffective or time does not allow, amiodarone can be used as it may not cause as much hypotension as the other agents. However, with its multiple antiarrhythmic properties, it still has the potential to cause hypotension, bradycardia, and a low output state. Ultimately, control and treatment of the underlying cause (e.g., pain or hypoxia) will often improve most tachyarrhythmias. Attention should also be placed on maintaining normal electrolytes, especially potassium and magnesium, in the cardiac patient.

In patients with premature ventricular complexes that become frequent, symptomatic and/or develop into long runs of nonsustained ventricular tachycardia, consultation with cardiology should be undertaken. Evaluation for ischemia or HF is indicated and ventricular arrhythmias can be carefully treated with beta-blockers, amiodarone, lidocaine, or procainamide. As in usual advanced cardiac life support, cardioversion is recommended for sustained or hemodynamically compromising ventricular tachyarrhythmias. Reviewing lists for medication combinations that may prolong the QT interval is also important (e.g., antiemetics, antipsychotics, and/or antibiotics). Long QT can

lead to iatrogenic ventricular tachyarrhythmias such as polymorphic ventricular tachycardia (torsades de pointes). Bradyarrhythmias may also be iatrogenic in etiology (e.g., medications) or due to electrolyte disturbances, ischemia, or less commonly sinus node dysfunction or heart block, which should mandate an urgent cardiology consult.

Management of Perioperative Anticoagulation Therapy in Atrial Fibrillation

Unrelated to surgery, decisions about anticoagulating patients with nonvalvular atrial fibrillation are made by assessing their risk using the $CHADS_2$ or CHA_2DS_2-VASc score (Tables 4.3 and 4.4). Current guidelines recommend full anticoagulation in those patients with 2 or more $CHADS_2$ or CHA_2DS_2-VASc risk factors. If there is only one risk factor, the 2011 ACCF/AHA/Heart Rhythm Society Focused Updates Incorporated into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation recommend either aspirin or full dose oral anticoagulation. Alternatively, the 2012 American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines, 9th Ed., recommend either full dose oral anticoagulation or aspirin plus clopidgrel for those with one risk factor.

In general, cessation of coagulation for up to 1 week before a procedure without bridging anticoagulation therapy is acceptable for most patients. However, in higher risk patients with prior stroke, transient ischemic attack, systemic embolization, or mechanical valves, therapeutic intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) should be administered in the perioperative period as bridging therapy. For 50 years, warfarin has been the only oral anticoagulent available, but there are now two newly approved oral anticoagulants for stroke prevention in high risk nonvalvular atrial fibrillation: dabigatran, which was approved in October 2010; and rivaroxaban, which was approved in November 2011. Warfarin inhibits factors II, VII, IX, X, and proteins C and S. It is typically discontinued 5 days before surgery. For more urgent or emergent surgery, therapeutic or supratherapeutic INRs may require treatment with either fresh frozen plasma or prothrombin complex concentrate, along with oral vitamin K as directed by the American College of Chest Physicians Antithrombotic Therapy guidelines. Warfarin can be restarted following the procedure when deemed safe. In higher risk patients described above, or if the period of being off anticoagulation exceeds a week, bridging therapy may be indicated.

Dabigatran is a reversible direct thrombin inhibitor and is found to be non-inferior to

Table 4.3 Risk Factors for CHA_2DS_2-VASc scoring system for risk of stroke in nonvalvular atrial fibrillation

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	9

Adapted from Camm AJ, Kirchhof P, Lip GY, et al. Eur. Heart J. 2010; 31: 2369–2429

Table 4.4 Adjusted stroke rate in nonvalvular atrial fibrillation based on CHA_2DS_2-VASc score from Table 4.3

CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Adapted from Camm AJ, Kirchhof P, Lip GY, et al. Eur. Heart J. 2010; 31: 2369–2429

warfarin in nonvalvular atrial fibrillation stroke reduction. Its advantages are fixed dosing and fewer drug–drug interactions. Its disadvantages are less familiarity and lack of a specific antidote. Perioperative management of dabigatran depends on the patient's creatinine clearance and the risk of perioperative bleeding and is best guided by the consultant. With normal renal function, dabigatran is typically discontinued 36 h, or up to 48 h before high bleeding risk procedures. With a creatinine clearance of 30–50 mL/min, dabigatran should be stopped for at least 3 days. If the creatinine clearance is <30 mL/min, dabigatran should be held for 5 days prior to the procedure. Resumption of dabigatran can usually occur 72 h postprocedure (with lower dose prophylactic heparin or LMWH). As there is no specific antidote for dabigatran, consultation with both a hematologist and nephrologist may be required for clinical bleeding or to evaluate questions of anticoagulant reversal in urgent or emergent surgery, as prothrombin complexes, activated factor VII, and/or dialysis may be indicated. Unlike prothrombin time and INR assessment for warfarin, a thrombin time or a dilute thrombin time (depending on the laboratory) may be helpful to assess residual anticoagulant effect with dabigatran before surgery.

Rivaroxaban is a direct factor Xa inhibitor found to be noninferior to warfarin therapy for stroke reduction in nonvalvular atrial fibrillation. Rivaroxaban is less cleared by the kidneys than dabigatran. In most cases, rivaroxaban can be stopped 2 days before the procedure. Anti-factor Xa chromogenic assays are being evaluated for assessing rivaroxaban. An increased rate of stroke was observed when discontinuing rivaroxaban in the clinical trial ROCKET-AF (Patel MR, et al.) and there is a black warning stating that in the absence of pathologic bleeding an alternate anticoagulant should be considered. Of note, other factor Xa inhibitors are currently pending US Food and Drug Administration (FDA) approval for nonvalvular atrial fibrillation (apixaban) and awaiting completion of a phase III trial for endoxaban for the same diagnosis.

Management of Perioperative Antithrombotic Therapy in Prosthetic Valves

Warfarin is also indicated long term for mechanical valves and in most cases in the 3 months following bioprosthetic valves (note that dabigatran and rivaroxaban have not been studied and are not approved for use in mechanical valves). In patients with a bileaflet mechanical aortic valve replacement in the absence of high risk features such as atrial fibrillation, previous thromboembolism, left ventricular dysfunction, a hypercoagulable condition, an older-generation thrombogenic valve, or more than one mechanical valve, therapeutic intravenous unfractionated heparin is usually not necessary and warfarin may be interrupted for 2–3 days before and preferably restarted within 24 h of the surgery. In other higher risk patients where potentially catastrophic acute valve thrombosis is more likely, warfarin should be discontinued 5 days before surgery and therapeutic dose, subcutaneous, LMWH, or full dose intravenous heparin started 3–4 days before surgery. Re-initiation of therapeutic bridging anticoagulation should be started postoperatively when safe and oral warfarin is restarted. High-dose vitamin K is not recommended to reverse anticoagulation in the setting of a mechanical valve as this will make re-anticoagulation with warfarin more prolonged to achieve therapeutic levels.

Hypertension

Uncontrolled hypertension is best managed preoperatively to avoid lability that often occurs during induction of anesthesia, which may lead to microvascular ischemia of any end organ. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, deferring elective surgery for blood pressure >180/110 mmHg is recommended, though no data exist to suggest that control modifies perioperative risk. However, hypertension identified in the preoperative period can sometimes be the first indicator of

this diagnosis for a patient, providing a unique opportunity to initiate general management of this cardiovascular risk factor. Controlled hypertensive patients should be maintained on their outpatient regimen, including on the day of surgery, particularly if they are on a beta-blocker or clonidine to avoid withdrawal. Postoperative hypertension is common, secondary to pain, increased intravascular volume, sympathetic tone, and vascular resistance. Resumption of outpatient medications as soon as possible postoperatively is essential.

Summary

As the baby boomer generation ages, the population over the age of 65 will continue to expand. Commensurately, so will the number of arthroplasties performed and, as a result of potential infection, likely the number of revisions. Therefore, appropriate and careful preoperative cardiovascular risk assessment and perioperative care of the patient with PJI who requires revision surgery are necessary and similar to that provided to patients for other types of noncardiac surgery. Orthopedic surgeons should consult family medicine physicians, internists, or cardiologists to assist in identifying and managing patients who have a history of cardiovascular procedures and are taking a growing list of complex medications.

Suggested Reading

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Diagnosis of Periprosthetic Joint Infection: An Algorithmic Approach to Patients

5

H. John Cooper and Craig J. Della Valle

Introduction

The diagnosis of periprosthetic joint infection (PJI) following total knee arthroplasty (TKA) or total hip arthroplasty (THA) can often be difficult, and many tests are available to the clinician. Identification of a periprosthetic infection is paramount, as the treatment between a septic and nonseptic failure is fundamentally different, and a missed diagnosis of PJI will lead to recurrent failure. With the increasing burden of infected arthroplasties anticipated in the future, the orthopedic community must approach the diagnosis of PJI in a systematic manner. The American Academy of Orthopaedic Surgeons (AAOS) has published a clinical guideline on the diagnosis of PJI that can assist the clinician in choosing among the various tests available for diagnosis [1].

Given the multitude of imperfect tests available to the treating clinician, there has not been a universally accepted definition of what constitutes the presence of active PJI [1]. There have been dozens of different reference standards applied to define PJI, which affects the performance of the various tests discussed throughout this chapter. For this reason, a work group convened by the Musculoskeletal Infection Society (MSIS) in 2011 analyzed the available evidence and proposed a new definition for PJI (Table 5.1) [60]. In the absence of a true gold standard, this definition can be helpful to the treating clinician both when treating patients and interpreting the existing literature. Furthermore, widespread adoption of this definition will allow results of future studies of various diagnostic tests to be truly comparative among different institutions.

The goal of this chapter is to review the literature regarding diagnosis of PJI and to offer an algorithmic approach to help orthopedic surgeons make the correct diagnosis of a condition where no true gold standard exists. When considering these various diagnostic tests, it is important to remember the possibility of harm that can result, patient pain or discomfort associated with these procedures, cost, and unnecessary treatment that can result from a false positive result. Mutual communication between the patient and clinician is necessary to discuss potential risks and benefits of available diagnostic procedures.

Prevalence

PJI unfortunately is not a rare complication after THA and TKA. Examination of the Medicare 5 % national sample administrative data demonstrates that the risk of infection within the first 2 years is 1.55 % following TKA and 1.63 %

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Table 5.1 Musculoskeletal Infection Society (MSIS) criteria defining periprosthetic joint infection (PJI)[a]

Based on the proposed criteria, definite PJI exists when
(1) There is a sinus tract communicating with the prosthesis; or
(2) A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
(3) Four of the following six criteria exist
(a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration
(b) Elevated synovial leukocyte count
(c) Elevated synovial neutrophil percentage (PMN%)
(d) Presence of purulence in the affected joint
(e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or
(f) Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 9,400 magnification

[a]Adapted from Parvizi et al. [60]

Table 5.2 Risk factors for PJI

Established risk factors	Potential risk factors
History of superficial SSI[a,b]	Hematoma formation
History of prior joint infection[b]	Delayed wound healing
Obesity[a,b]	Prolonged drainage
Immunosuppressive conditions[b]	Recent bacteremia
Operative time >2.5 h[a,b]	Skin disorders
	IV drug use
	Active infection at another site
	Smoking
	Prior open surgery
	Simultaneous bilateral surgery
	Prolonged hospitalization
	Allogeneic transfusion
	Medical comorbidities

[a]Established risk factor following THA
[b]Established risk factor following TKA

following THA, with an additional risk of infection between 2 and 10 years after surgery of 0.46 % for TKA and 0.59 % for THA [41, 57].

When looking at patients undergoing revision surgery, PJI is the most common reason for revision after TKA at 25.2 % [9], and it is the third-most common reason for revision surgery after THA at 14.8 % [10], behind instability and mechanical loosening. Furthermore, multiple recent epidemiologic studies have suggested both the incidence and prevalence of PJI may be increasing over time [40, 42], with the overall infection burden (i.e., the projected overall incidence of infections among all primary and revision arthroplasties) predicted to rise from 1.4 to 6.8 % for TKA and 1.4 to 6.5 % for THA [42].

History (Risk Factors)

When evaluating patients with the various tests discussed throughout in this chapter, it is worthwhile to consider the pretest probability of PJI, as this affects the value of any diagnostic test. Thus it may be helpful to identify patients as having an increased or decreased probability of infection prior to initiating a diagnostic evaluation. Patients deemed to be at higher risk for PJI warrant a more vigorous diagnostic evaluation, whereas those thought to be at a low risk may need an evaluation that is less extensive. Although high-level data regarding specific risk factors for PJI is limited in the orthopedic literature, there are factors in a patient's history that clinicians can use to identify those at higher risk for infection (Table 5.2).

History of a superficial surgical site infection (SSSI) is an independent risk factor for PJI in both the hip and the knee. In a matched case–control study of 924 patients who underwent THA or TKA at the Mayo Clinic, patients who developed a SSSI not involving the prosthesis had an odds ratio of 35.9 of developing a PJI compared to the control group [5]. Similar findings have been confirmed in other large studies [71, 86]. A history of prior joint infection has also been shown to predispose to repeat infection after TKA [30], but interestingly, a large study did not reveal a history of prior joint infection to be an independent risk factor for developing PJI after THA [5]. Lachiewicz et al. [43] demonstrated that the duration the implant had been in situ was a significant predictor of PJI, with an inverse association between time in situ and risk of infection.

Obesity (body mass index >30 kg/m^2) and morbid obesity (BMI >40 kg/m^2) have been associated with a substantially increased risk of developing PJI after total joint arthroplasty in multiple studies [19, 20, 47, 49, 62, 67]. Likewise, systemic immunosuppressive conditions such as rheumatoid arthritis [30, 86], diabetes [20, 49, 62], and chronic immunosuppressive therapy [62] have been demonstrated to increase the risk of patients developing PJI after TKA. However current available evidence is lacking in support of immunosuppression as a risk factor for development of PJI after THA. Extended operative times (>2.5 h) have also been associated with an increased risk of PJI after both hip [29, 76] and knee [29, 62] arthroplasty operations.

Hematoma formation [5, 24, 59, 67, 71], delayed wound healing [5, 67, 86], and prolonged postoperative wound drainage [5, 59, 61, 67, 71] have all been associated with PJI. Although each of these variables appears likely to increase the risk of PJI on univariate analysis, they were not confirmed as independent risk factors by a multivariate analysis [1]. The use of drains has been investigated extensively and has not been shown to increase the risk of infection after THA or TKA [12, 13, 22, 27, 31, 32, 37, 38, 56, 58, 70, 82].

Other potential risk factors have not been examined in high-quality studies, but should still be considered as potential risk factors for PJI. The following are supported as risk factors by consensus approval of the AAOS Guidelines committee on diagnosis of PJI: recent (<1 year) bacteremia or candidemia [53], metachronous prosthetic joint infection [47, 54], skin disorders (e.g., psoriasis, chronic cellulitis, lymphedema, chronic venous stasis, and skin ulcers), IV drug use, recent (<3 years) MRSA infection or colonization, and active infection at another site.

Other factors such as smoking [36, 62], prior open surgery [62], simultaneous bilateral surgery [67], prolonged hospital stay [67], allogeneic transfusions [67], and medical comorbidities [5, 41, 67] have been identified as potential risk factors for PJI, but have not yet been supported by enough high-quality evidence to be considered with the factors mentioned above.

Physical Exam Findings

Although the physical exam is an important part of the overall picture and therefore should not be ignored, the literature has demonstrated poor reliability of exam findings for prediction of active PJI. Several studies have examined findings such as warmth, swelling, or erythema around both hip and knee replacements [48, 79]. In these studies, although the specificity was good (0.90–1.0), the sensitivity of these findings was quite poor (0.12–0.24), making them inadequate screening tools to use for diagnosis of PJI.

The presence of an active draining sinus tract (Fig. 5.1) has been used to define PJI [60], and when present, the joint in question should be considered infected until proven otherwise. In a study by Magnuson et al., 7 of 7 patients with a sinus tract had a periprosthetic infection with the reference standard being intraoperative cultures or histology [48]. Of note, clinicians should not culture fluid from a draining sinus or draining wound, as these are often colonized by multiple bacteria and may not reflect the actual pathogen responsible for the PJI.

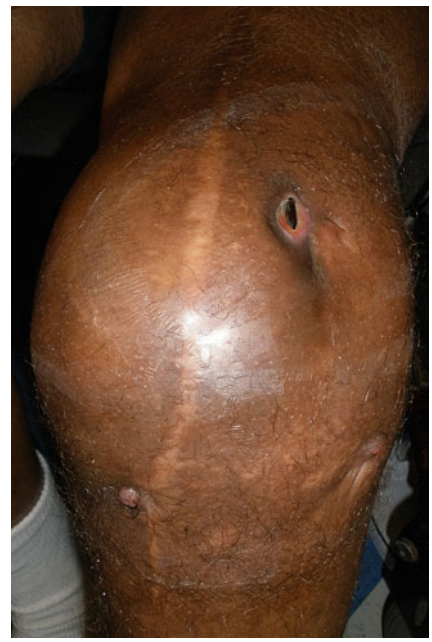

Fig. 5.1 Draining sinus tract with an exposed femoral component in a patient with an infected total knee arthroplasty (TKA)

Imaging

Plain radiographs should be obtained in all patients in whom PJI is suspected. These may be normal in a majority of patients, but early radiographic osteolysis or implant loosening (Fig. 5.2) clearly increases the pretest probability of joint infection [1]. In addition, these often provide alternative explanations for joint pain or dysfunction in the evaluation of the painful or failed hip or knee arthroplasty (which may not necessarily exclude concurrent PJI).

Various nuclear imaging studies have been investigated regarding their role for diagnosis of PJI (Table 5.3). Labeled leukocyte imaging studies, including both Technetium-99 (Tc-99) [26, 72, 75, 78] and Indium-111 (In-111) scans [26, 33, 48, 64, 68], have demonstrated value in diagnosis of infection; among these studies, In-111 demonstrated more effectiveness as a "rule out" test. Furthermore, several studies examined a combination of Tc-99 bone scans with either Tc-99 [65] or In-111 white blood cell (WBC) scans [33, 73, 79], which improved the overall diagnostic value. Likewise, labeled leukocyte imaging combined with bone marrow imaging demonstrated effectiveness in diagnosis of PJI [34, 46, 51, 75]. Gallium-67 imaging has shown excellent specificity, but relatively poor sensitivity [39, 69], while fluorodeoxyglucose positive emission tomography (FDG-PET) imaging has shown value in both ruling in and ruling out PJI [11, 15, 46]. Of note, triple-phase Tc-99m bone scintigraphy failed to show consistent evidence of diagnostic benefit in multiple studies [6, 45, 55]. Given the variability in results of these tests, along with their added time and expense, they are not recommended in patients whom a diagnosis of PJI has already been established or in patients who are already scheduled for revision surgery. However, given the importance of recognizing subclinical infection, they remain reasonable options in those patients where a diagnosis remains unclear. It is important to note that these imaging studies may require special expertise and consultation with an imaging provider in order to attain accurate results.

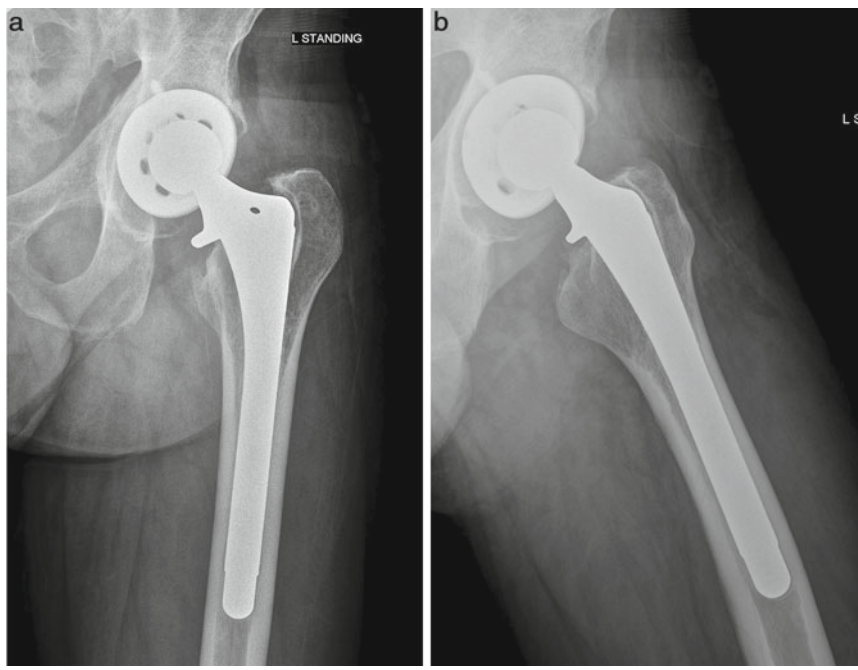

Fig. 5.2 (**a**) AP and (**b**) lateral radiographs of a patient with loosening of the acetabular component secondary to an chronic low-grade PJI

Table 5.3 Nuclear imaging studies in diagnosis of PJI[a]

Test	Number of studies	Positive likelihood ratio	Negative likelihood ratio	Sensitivity	Specificity
Tc-99 WBC imaging	4	1.39–22.0	0.06–0.52	0.5–1	0.31–1
IN-111 WBC imaging	5	1.9–14.0	0.03–0.63	0.38–1	0.5–1
Combined Tc-99 bone and labeled WBC imaging	4	5.8	0.32	0.72	0.88
Combined bone marrow and labeled WBC imaging	4	9.8–45.5	0.02–0.34	0.67–1	0.91–1
Gallium imaging	2	24.4–111	0.07–0.62	0.38–0.95	1
FDG-PET imaging	3	11.4–19.2	0.16–0.66	0.26–0.85	0.93–1
Triple-phase Tc-99m bone scan	3	2.33–8.53	0.13–0.78	0.33–0.88	0.76–0.90

[a]Adapted from AAOS Guidelines [1]

Table 5.4 ESR and CRP in diagnosis of PJI[a]

Test	Number of studies	Positive likelihood ratio	Negative likelihood ratio	Sensitivity	Specificity
ESR	6	2.9	0.15	0.90	0.69
CRP	6	2.4–27.1	0.05–0.8	0.30–0.95	0.71–0.96
ESR and CRP (if both positive)	2	4.34–12.1	0.14–0.21	0.80–0.89	0.79–0.93
ESR and CRP (if one positive)	2	1.74–4.22	0–0.06	0.96–1	0.43–0.77

[a]Adapted from AAOS Guidelines [1]

Other advanced imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) have little data to support their use in the diagnosis of PJI. In a study of 65 patients, CT was found to be accurate in the diagnosis of painful infection at the site of a hip prosthesis on the basis of soft-tissue findings (sensitivity, 1.0; specificity, 0.87), while periprosthetic bone abnormalities were not found to be useful [14]. MRI may be helpful in detecting extracapsular spread of infection and abscess formation [66, 84], and the appearance of the joint may also be helpful, as infected synovium typically demonstrates a hyperintense laminar appearance [66]. However, until further research is published regarding diagnosis of PJI with these modalities, their value is limited and their use should be restricted.

Laboratory Tests

Blood tests, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are an excellent screening tool for PJI. Because these tests are inexpensive, ubiquitous, pose a low risk for patients, and have such high sensitivity, they should be obtained prior to every revision and in all cases where a painful prosthesis is being evaluated for PJI.

Seven high-quality studies to date have examined the use of ESR and/or CRP in diagnosis of PJI (Table 5.4) [8, 17, 23, 28, 35, 72, 74]. Only two of these studies investigated the combined use of ESR and CRP [28, 74], while the rest investigated each test in isolation. A negative result on both tests was extremely good in ruling out active PJI. A positive result on both tests more reliably rules in PJI compared to a positive result on just a single test (positive likelihood ratio (LR): 4.34–12.1 vs. 1.74–4.22). The use of either test alone in isolation is less reliable than when both tests are combined.

Of note, when positive results are encountered, the clinician should also consider other conditions that can lead to elevation of these inflammatory markers such as inflammatory arthritis, cancer, temporal arteritis, polymyalgia rheumatic, coronary artery disease, lupus, gout, inflammatory bowel disease, or other infections elsewhere in the body.

Table 5.5 Selective aspiration after ESR and CRP for diagnosis of PJI[a]

Probability of infection	ESR and CRP results	Planned reoperation status	Recommendation
Knee			
n/a	+/+	n/a	Aspiration
n/a	+/–	n/a	Aspiration
n/a	–/–	n/a	No further testing
Hip			
Higher	+/+ or +/–	n/a	Aspiration
Lower	+/+ or +/–	Planned	Aspiration vs. frozen section
Lower	+/+	Not planned	Aspiration
Lower	+/–	Not planned	Reevaluate within 3 months
n/a	–/–	n/a	No further testing

[a]Adapted from AAOS Guidelines [1]

In addition to ESR and CRP, peripheral WBC counts are typically available when considering a diagnosis of PJI. Multiple studies have investigated the utility of WBC in diagnosis of PJI [8, 18, 63, 72, 77]. Despite differing thresholds among the studies, WBC count was not as consistently useful as ESR or CRP (particularly when these were used in combination) for the diagnosis of PJI. Furthermore, consideration of the peripheral neutrophil count (with a so-called left shift) did not improve the diagnostic value [77].

In summary, ESR and CRP can be used together as outstanding "rule out" test given their high sensitivity; when both are negative, PJI is extremely unlikely (negative likelihood ratio 0–0.06) [1]. As a result, these screening inflammatory markers should be the first step after history, physical, and radiographs in the work-up of potential PJI. If both are positive, further consideration of PJI is warranted (positive likelihood ratio 4.3–12.1) [1], and additional testing should be pursued, beginning with joint aspiration. If only one inflammatory marker is elevated and the other is normal, an algorithmic approach should be utilized depending on the probability of infection and the joint in question; these scenarios will be discussed below.

Preoperative Aspiration

An algorithmic approach to joint aspiration should be considered by the treating clinician when either the ESR or the CRP is elevated (Table 5.5). In patients with a suspected TKA infection, if the ESR and/or CRP is elevated, a joint aspiration should be performed given the ease with which a prosthetic knee joint can be aspirated. In patients with a suspected THA infection, if both ESR and CRP are elevated in a patient being considered for PJI, a joint aspiration should be performed. When only one of these markers is elevated in patients with a suspected THA infection, the clinician should rely on the clinical probability of infection as well as the planned reoperation status as hip aspirations are associated with more pain for the patient and a higher potential risk. In these cases, it is important to err on the side of caution to avoid missing the diagnosis of PJI and instituting treatment for another problem. If the clinical suspicion of PJI is high given the patient's risk factors or physical exam, an aspiration should be performed. If the clinical suspicion is low and revision surgery is planned, either an aspiration may be performed intra-operatively (assuming a result can be obtained with an hour) or frozen section results can be taken at the time of revision surgery. If the clinical suspicion is low and revision surgery is not planned, the patient should be reevaluated within 3 months for potential PJI. If the ESR and CRP are both within normal reference ranges for patients with a THA or TKA, given the extremely high sensitivity of these tests in combination for ruling out PJI, aspiration should generally not be attempted and no further testing is necessary in these patients unless the clinical suspicion for PJI is very high.

The variability in the recommendations for hip aspiration among the different scenarios is based largely on potential harm of joint aspiration [1] including the relative difficulty of hip aspiration compared to knee aspiration, patient pain or discomfort during the procedure, the possibility of false positive results (15–20 %), and the possibility of the introduction of bacteria into the joint during the procedure [2]. Cost of the aspiration may also be a factor [2], particularly if it involves another subspecialist or anesthesia. In a practice setting where the treating surgeon is able to perform a hip aspiration in a manner that minimizes or avoids these potential harms, including access to fluoroscopy (Fig. 5.3) or ultrasound, it may be worthwhile to obtain them more readily.

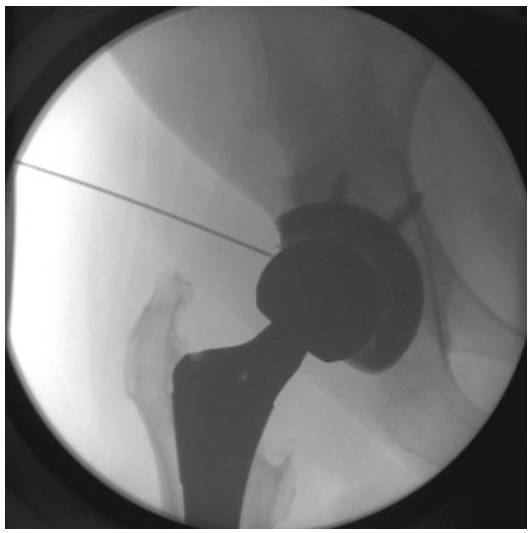

Fig. 5.3 Hip aspiration performed under fluoroscopic guidance through a lateral approach. An anterior approach can also be performed and may provide easier access to the joint in patients with a larger body habitus. Hip aspirations should be performed under image guidance whenever possible to ensure intra-articular placement of the needle

Whenever an aspiration is performed, the fluid obtained should be sent for several tests including the synovial fluid WBC count, percentage of neutrophils, as well as cultures for aerobic and anaerobic organisms. Elevated synovial fluid WBC count is highly suggestive of PJI. Multiple studies have demonstrated excellent sensitivity and specificity of synovial WBC for diagnosis of periprosthetic infection (Table 5.6), although sensitivity is lost when higher threshold values are used for diagnosis, such as that used by Spangehl et al. [77]. These studies have also demonstrated value of the percentage of neutrophils (i.e., the differential) present on WBC count, with values greater than 65 % (range 64–80 %) highly suggestive of PJI [17, 25, 74, 77, 80]. Two well-designed studies have addressed the diagnostic efficacy of aspiration cultures for diagnosis of PJI in TKA [17, 23]. In both these studies the specificity of bacterial culture was excellent (0.93–0.98), however, the sensitivity was not as reliable (0.78–0.80), demonstrating this test is better used to "rule in" PJI than "rule out" its presence. Likewise, meta-analysis [1] of seven Level-I studies in THA patients [2, 21, 26, 43, 50, 52, 85] demonstrated a similar value of aspiration culture as a "rule in" test for PJI in the hip (positive likelihood ratio 9.8) but demonstrated that it only had a small to moderate ability to "rule out" infection in these cases (negative LR 0.33).

A repeat aspiration should be performed when there is a discrepancy between the clinical probability of PJI and the initial aspiration culture result. In a study of 270 hips aspirated prior to revision surgery [2], 28 results conflicted with the clinical suspicion; repeat aspiration in these patients resulted in a specificity of 0.96. Similar results were found in smaller studies of both hip [77] and knee aspirations [3].

Table 5.6 Synovial white blood cell (WBC) threshold to diagnose PJI

Author	Joint	*N*	Threshold (WBC/μL)	Sensitivity	Specificity	PPV	NPV
Della Valle et al. [17]	Knee	105	>3,000	1.0	0.981	0.976	1.0
Ghanem et al. [25]	Knee	429	>1,100	0.907	0.881	0.872	0.915
Trampuz et al. [80]	Knee	133	>1,700	0.94	0.88	0.73	0.98
Spangehl et al. [77]	Hip	202	>50,000	0.36	0.99	0.91	0.90
Schinsky et al. [74]	Hip	201	>4,200	0.84	0.93	0.81	0.93

When intra-articular cultures are obtained, it is recommended that patients be off of antibiotics prior to performing the joint aspiration, as the yield has been shown to be lower (and false-negative rates higher) in patients who received antibiotics within 2 weeks of obtaining the fluid [81]. Although the precise amount of time needed to allow a "wash-out" of antibiotics from systemic circulation and the joint is unknown (and is likely variable for different antibiotics), in the absence of better evidence the AAOS work group on diagnosis of PJI accepted 2 weeks as the minimum time required [1].

In summary, aspiration of the joint in question is extremely valuable in reaching a diagnosis of PJI, and it should be attempted with an algorithmic approach as detailed in Table 5.5. Synovial fluid WBC count and percentage of neutrophils are excellent at both "ruling in" and "ruling out" active infection. Cultures taken from the joint are better at "ruling in" than "ruling out" PJI, assuming the patient has had a sufficient "antibiotic-free" period prior to aspiration. They also have the added advantage of identifying the infecting organism and its antibiotic sensitivities so appropriate antibiotic treatment can be initiated in a more timely manner or potentially even combined with cement at the time of revision surgery.

Intraoperative Tests

In the event that a patient comes to the operating room without a known diagnosis of PJI, there are several tests available to the orthopedic surgeon that may be helpful in determining the presence of active infection. These tests may also be used to confirm a previously established diagnosis of PJI. Intraoperative testing for PJI is covered in detail in Chap. 7.

Diagnosis of PJI in the Early Postoperative Period

The early postoperative period is a particularly difficult time to evaluate for PJI, as a certain degree of inflammation, edema, and pain are expected as part of the normal postoperative course. Fever is an unreliable clinical sign that has been shown to be costly and unnecessary to pursue in the early postoperative period [83]. Furthermore, inflammatory markers such as ESR and CRP are typically elevated in the early postoperative period [7, 44], which may complicate their interpretation.

Bedair et al. evaluated results of 146 knees that were aspirated within 6 weeks after TKA and compared the ESR, CRP, and synovial fluid WBC and differential between patients with and without a PJI [4]. The optimal synovial WBC count threshold to diagnose PJI, determined by receiver operating characteristic curves, was 27,800 WBC/μL (sensitivity, 0.84; specificity, 0.99; positive predictive value, 0.94; negative predictive value, 0.98). It is important to note that this value is considerably higher than the WBC count thresholds used outside of the early postoperative period (1,100–4,200 WBC/μL; Table 5.6). This study also found that CRP (optimal threshold 9.5 mg/dL; nl <0.8 mg/dL) and percentage of neutrophils in the synovial fluid aspirate (optimal threshold 89 %) were significantly higher in the infected group and can be useful parameters in diagnosing PJI in the early postoperative period.

AAOS Guidelines for Diagnosis of PJI of the Hip and Knee

A work group within the AAOS evaluated the available literature to determine the role of different diagnostic tests in order to devise a practical algorithm allowing clinicians to reach a diagnosis of PJI [16]. Through this effort, they developed an extensive guideline and evidence report entitled "The Diagnosis of PJIs of the Hip and Knee" in 2010 [1]. This report included 15 recommendations, with each graded on a scale from inconclusive (indicating insufficient or conflicting evidence) to strong (indicating good evidence); a fifth category of grading (consensus) was added where there was no supporting evidence. Based on these recommendations, diagnostic algorithms could be devised for patients at higher probability (Fig. 5.4) and lower probability (Fig. 5.5) of having a PJI.

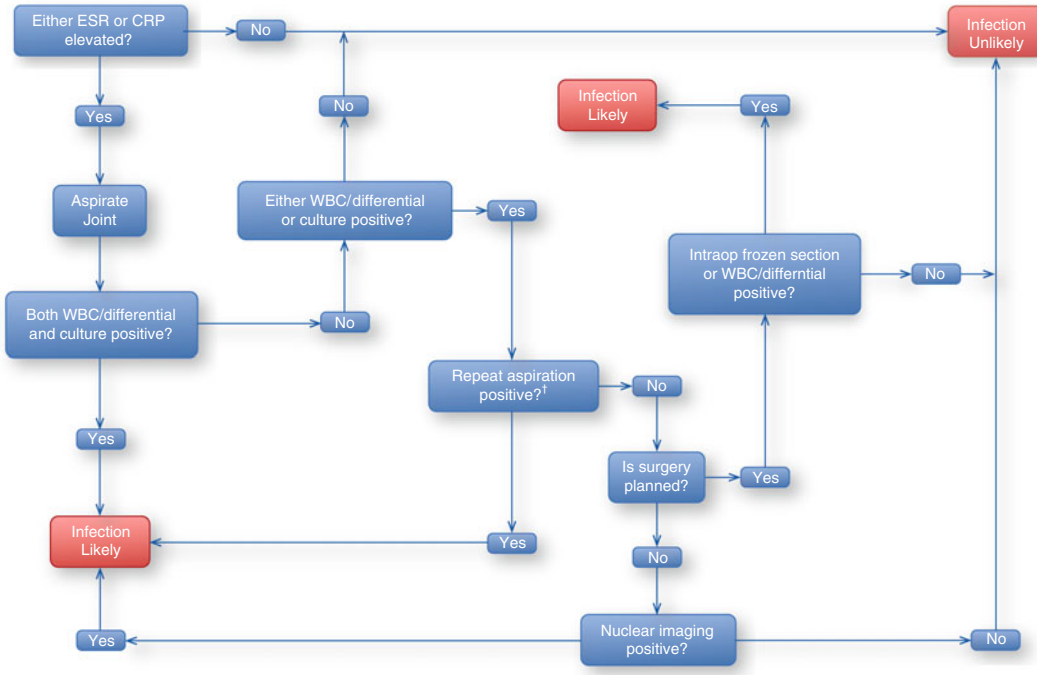

Fig. 5.4 Algorithm for patients with a higher probability of having a periprosthetic hip or knee infection. (Adapted from the AAOS clinical practice guideline [1].) †Repeat aspiration should be performed when a discrepancy exists between the probability of infection and the result of the initial aspiration culture

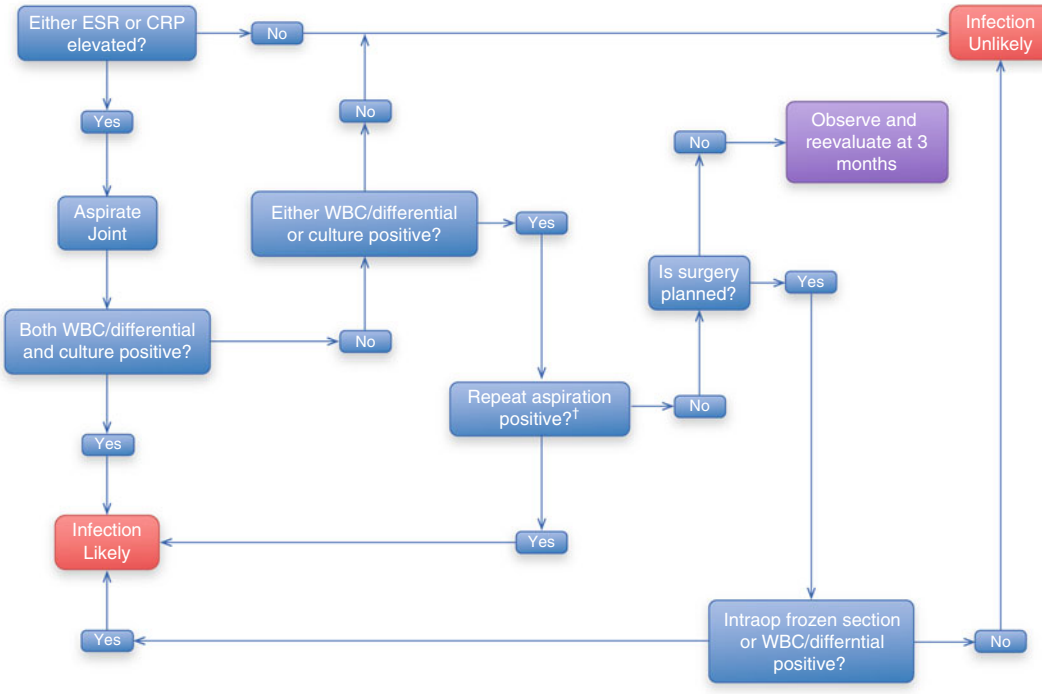

Fig. 5.5 Algorithm for patients with a lower probability of having a periprosthetic hip or knee infection. (Adapted from the AAOS clinical practice guideline [1].) †Repeat aspiration should be performed when a discrepancy exists between the probability of infection and the result of the initial aspiration culture

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6 Intraoperative Tests to Aid in Diagnosis of Periprosthetic Joint Infection

Gwo-Chin Lee and Raymond H. Kim

Introduction

Infection following joint replacement surgery is a catastrophic complication that can be costly to treat and cause significant pain and morbidity to the patient. Successful treatment of infection is dependent on accurate diagnosis of infection and on identification of the treating organism. In recent years, our understanding of what constitutes an infection has improved, and important criteria of what constitutes an infected joint replacement have been established. However, infection may not be easily identified in all cases of painful joint replacement prior to surgical intervention. Therefore, the purpose of this chapter is to review current and future methods of intraoperative infection detection, their effectiveness, and their role in the definition of an infected TJR.

Intraoperative Gram Stain

Gram staining is a common method for bacterial detection used to differentiate two large groups of bacteria based on their cell wall characteristics [1]. The three-step process involves (1) staining with crystal violet dye (water soluble), (2) decolorization, and (3) counterstaining. Due to the differences in thickness of the peptidoglycan cell layer in their outer walls, Gram-positive microorganisms will retain the crystal violet dye throughout the process, while Gram-negative bacteria lose the crystal violet stain during the decolorization process and be stained by the counterstain [2]. Gram stain is not infallible as some organisms are not susceptible to either stain used in the test [3, 4].

While this test is fast and inexpensive, The American Academy of Orthopaedic Surgeons (AAOS) clinical guidelines on diagnosis of periprosthetic joint infections (PJIs)of the hip and the knee recommend against the use of intraoperative Gram stain to rule out PJI [5]. In the committee's systematic review, they found that utilizing negative likelihood ratios, Gram stain is not a good "rule out" test (LR−, values >0.5) [5–7]. Furthermore, in a large multicenter study involving 945 revision total knee arthroplasties (TKAs), intraoperative Gram stain was found to have only a sensitivity of 27 % (poor) with a specificity of 99 %. The positive and negative predictive values were 98.5 % and 79 % (poor), respectively, with an accuracy rate of 80 %. Patients with positive tests had higher serum white blood cell (WBC), sedimentation rate and C-reactive protein, and higher cell counts in their preoperative aspirates. In no case was treatment altered by Gram stain results [8]. For these reasons, current data does not support the routine use of intraoperative Gram stain in the evaluation of PJI.

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Intraoperative Frozen Section

Tissue specimens can be helpful in the aid of diagnosis of infections. Various studies have looked at the predictive value of intraoperative frozen section in revision joint replacement surgeries [9–12]. The key variables in this test center around the number of neutrophils per high power field (HPF; ×400 magnification) and the minimum number of fields containing that concentration of inflammatory cells. In a meta-analysis of the published literature, Della Valle et al. determined that frozen section with a threshold of ten neutrophils per HPF is a good rule in test, meaning a positive result has a high likelihood of infection (LR+, 23), but that a negative result does not exclude infection (LR−, 0.23). Furthermore, when they analyzed studies using a lower threshold (i.e., five neutrophils per HPF), the authors found a similar sensitivity, but a lower specificity with a higher false positive rate. Therefore, the conclusion is that there is insufficient data to distinguish whether five or ten neutrophils per HPF is the best threshold needed for diagnosis of PJI [5].

More recently, the Musculoskeletal Infection Society, in establishing the definition for PJI, selected the threshold of five neutrophils per HPF in multiple frozen sections as a minor criterion as part of definition of PJI. In this setting, intraoperative frozen section needs to be considered along with other criteria such as serum serology (ESR, CRP), synovial cell count, purulence, isolation of microorganisms in one culture, and elevated synovial neutrophil percentage. When four out of six criteria are present, definitive infection exists. It is important to point out that the accuracy of histologic evaluation depends on the surgeon as well as the pathologists. Surgeons should take multiple samples from various areas of the hip and knee at the time of revision surgery, and histopathologists should not focus on PMNs found entrapped in superficial fibrinous exudate and surrounding vascular endothelium [13]. Consequently, the AAOS guidelines currently strongly recommend for the use of frozen section of peri-implant tissues in revision surgery of the hip and knee when PJI has not been excluded.

Synovial Cell Count

Joint aspiration can provide critical information with regard to the causes of failure in painful THA/TKA. Much has been written with regard to the inflammatory cells found in synovial aspirates as they relate to the presence of infection [14, 15]. Advantages of performing intraoperative joint aspirations include (1) confirmation of joint aspiration under sterile technique and (2) decreased likelihood of traumatic (i.e., bloody) aspirations. The main disadvantage is the variability in time when the results of the test can be returned to the surgeon in time for the surgeon to make a critical intraoperative decision. The AAOS clinical guidelines on diagnosis of PJIs recommend routine aspirations of all hips and knees undergoing revision surgery in the presence of abnormal serum serology (i.e., ESR, CRP). The aspirate should be sent for synovial fluid WBC count and differential WBC count. Routine aspirations of painful THA are not recommended unless there is a high index of suspicion for infection because preoperative hip aspirations have a high false positive rate (low sensitivity, low specificity), can introduce bacteria during the procedure into a prosthetic joint, and can cause significant pain or discomfort to the patient [5]. Consequently, while most revision TKAs will likely have a preoperative aspiration, intraoperative synovial cell counts can be most helpful with hips undergoing revision surgery.

The thresholds for numbers of WBCs found in the synovial aspirate depend largely on the timing of reoperation. For knees, subacute and chronic infections have been associated with WBC counts in the synovial aspirate ranging from 1,100 to 4,000 cells/μL with a differential threshold of PMNs ranging from 64 to 69 %. For hips, one study set the threshold for chronic infection at 3,000 cells/μL with a 80 % PMN differential [5, 13]. In the setting of infections occurring less than 3 months from the index surgical procedure, a WBC count in the synovial aspirate of greater than 27,800 cells/μL is associated with deep joint infection [16]. None of these studies have included patients with inflammatory arthropathies such as rheumatoid arthritis,

although a recent study by Cipriano et al. showed minimal differences in both the serum serology and synovial aspirates of infected THA/TKA in patients with inflammatory diseases compared to patients without [17]. Consequently, intraoperative synovial cell counts can provide additional data points in cases where preoperative aspiration results are not available or in cases when the line between septic and aseptic failures is not clearly defined.

Leukocyte Esterase

The qualities of an ideal intraoperative test include accuracy, expedience, and cost-effectiveness. The leukocyte esterase test looks for the esterase enzyme released by WBCs. Traditionally used to rapidly detect urinary tract infections, recent proposed applications of this test have included the possibility of rapid, accurate, and inexpensive way to detect PJI. Testing involves dipping a strip, commonly available, into the synovial aspirate looking for the presence of esterase released by WBC present in the synovial fluid. The hypothesis is that the higher the concentration of WBC in the synovial fluid, the more positive the test will become [18]. In a recent prospective study looking at the sensitivity and specificity of leukocyte esterase's ability to detect periprosthetic knee infections, Parvizi et al. compared findings of 30 infected TKAs and 78 noninfected TKAs and found that using a threshold of ++ on the strip, the test was 80.6 % sensitive (CI 61.9–91.9 %) and 100 % specific (CI 94.5–100 %) at detecting infection. The test had a positive predictive value of 100 % (CI 83.4–100 %) and a negative predictive value of 93.3 % (CI 85.4–97.2 %). In addition, leukocyte esterase strongly correlated with the percentage of PMNs found in the synovial aspirate, total WBC count, serum ESR, and C-reactive protein [19]. Consequently, while the role of this test continues to be defined, it can be a tool in the armamentarium for detection of PJI, particularly, if access to intraoperative cell counts and frozen sections are not readily available at the time of revision surgery.

Sonicates and Polymerase Chain Reaction

Correct identification of the infecting microorganism is crucial for proper management and eradication of PJI. However, in certain instances, deep joint infections remain culture negative. Berbari et al. reviewed a series of 897 PJIs and reported that in 60 patients (7 %), conventional microbiologic techniques failed to identify the causative organism [20]. Among the reasons for culture negative infections included recent use of antibiotics (within 14 days), low virulence atypical organisms, and potential biofilm protection. Strategies to maximize culture yields include the use of sonication and use of polymerase chain reaction (PCR).

Sonication involves placing the extracted implant into a solution which is then subjected to ultrasonic waves. The hypothesis is that the process is disruptive to the surface biofilm and, therefore, will improve culture yields and bacterial identification. Several studies have shown the effectiveness of process in improving bacterial ideals from joint resections [21, 22]. Holinka et al. looked at a series of 40 patients with infected prosthesis and the effects of sonication on culture yields. The authors reported higher yields of positive cultures in sonicates compared to routine methods of culture and, in particular, in patients receiving a recent course of antibiotics prior to revision surgery [23]. Therefore, this technique can help further define and identify infectious organisms in patients with PJI.

PCR works by amplifying the strains of bacterial DNA to allow detections of infectious bacteria. An advantage of PCR is that it can detect nonviable bacteria that do not grow on culture, bacteria lysed by sonication procedure, and it is unaffected by preoperative administration of antibiotics. Disadvantages of PCR are that it can be inaccessible and it can be overly sensitive yielding false positive results [24, 25]. However, under certain circumstances, PCR can be used in adjunct to sonication to improve culture yields and bacterial identification. Esteban et al. studied 258 retrieved implant components

(185 hip/knee prosthesis) and reported that PCR following sonication increased their positive culture yields by almost one-tenth compared to conventional microbiologic techniques [26]. Others have also shown the benefits of combining PCR in addition to sonication to improving bacterial identification in particular when antibiotic therapy had been instituted prior to resection of the infected implant [27]. Consequently, while PCR alone appears to be an overly sensitive diagnostic test for infection detection, using it selectively in conjunction with sonication can be helpful in identification of the infecting microorganism.

Gene Expression and Biomarkers

While our understanding and techniques for infection have improved over the years, our ability to distinguish between joint inflammation and joint infection remains imperfect. Current testing thresholds are determined with certain compromises in mind: maximize sensitivity while minimizing false positives. Therefore, as we continue to look to identify 100 % of true infections, we need more sophisticated testing modalities for infection detection. Gene expression and biomarkers represent this next frontier. The goal is to differentiate on cellular and molecular level immune reactions secondary to infection compared to those resulting from inflammation and wear. Deirmengian et al. introduced a novel way to identify infection by looking at the ribonucleic acid (RNA) expression of WBCs found in infection compared to gouty arthropathy. In their pilot study, they noticed that genes expressed during infection were significantly different compared to genes expressed during gouty attacks. The predominant genomic differences were in those found in the interleukin pathway, tumor necrosis pathway, and the antibacterial response [28]. Following their initial work, the same authors identified a panel of synovial fluid biomarkers that, when present, were predictive of joint infection. In a study of 51 patients (14 infected and 37 noninfected), they identified 12 biomarkers that were present at a significant higher concentration in infected knees compared to those without infection. Among them, synovial levels of interleukin (IL)-1 were 258 times higher in patients with infection, and together with IL-6 elevations had a 100 % sensitivity and specificity in distinguishing failures resulting from infection compared to failures from aseptic reasons [29]. Thus, one of the frontiers for infection detection lies at the genetic and molecular level. The information at this level has just begun to be abstracted and can potentially, someday, in addition to those with active joint infections, identify patients at risk for developing infections based on genetic profile.

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Biofilm-Related Periprosthetic Joint Infections

7

Dustin L. Williams and Roy D. Bloebaum

The Use of Planktonic Versus Biofilm Bacteria in Animal Models

Currently, the majority of animal studies that are used to model biofilm-related infections involve the use of an initial inoculum of planktonic bacterial cells from batch cultures [1–24]. The expectation has been that planktonic cells would attach to the surface of a biomaterial, medical device, or surrounding tissue and subsequently form a biofilm. Although valuable, data that has been derived from these experiments may not provide clinicians and biomaterials scientists additional clinical insight into how bacteria that reside in well-established, mature biofilms impact device-related and other human infections when they initially contaminate an implant site.

Following several decades of important observations from investigators that bacteria preferentially adhere to solid surfaces and to one another [25, 26], in 1978 Costerton et al. formally hypothesized that bacteria in nature reside primarily in the biofilm phenotype [27]. Strong support for this hypothesis continues to be shown in the literature that involves collecting, analyzing, imaging, and characterizing bacterial biofilms found in nature, human tissues, and clinically retrieved devices [28–34]. Additionally, since the initial hypothesis of Costerton et al., estimates have suggested that 99.9 % of bacteria in natural ecosystems reside in the biofilm phenotype [35]. Intriguingly, The Centers for Disease Control has estimated that biofilms cause 65 % of infections in the developed world [36]. A public announcement from The National Institutes of Health has stated, “Biofilms are clinically important, accounting for over 80 percent of microbial infections in the body” (see announcement PA-07-288).

Based on these observations and information, it is important to consider that when bacteria come in contact with wound sites, biomaterials, or portals of entry in humans, i.e., inoculate patients, there is strong evidence to suggest that the majority of these bacteria are inherently residing in well-established, mature biofilms. A specific example of this scenario is that of a patient who suffers from a Type IIIB open fracture, which is reduced with a fracture fixation device.

A Type IIIB severe fracture has been defined by Gustilo et al. [37] as having “Extensive soft-tissue injury loss with periosteal stripping and

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bone exposure" that "is usually associated with massive contamination." Rates of infection that accompany open fractures may reach as high as 50 [38–40] and 60 % in at least one reported instance [41]. The potential for open fractures to be massively contaminated is highlighted by the work of Bakken [42] and Torsvik et al. [43] who have shown that even 1 g of soil may contain between 10^7 and 10^{10} bacteria, the majority of which are estimated to reside in the biofilm phenotype [35]. These data indicate that biofilm-dwelling bacteria have the potential to initially contaminate open wound sites.

Limitations of Using Planktonic Cells as Initial Inocula

At least three proposed rationales can be given for why the use of planktonic cells has potentially limited investigators' abilities to detect clinically relevant outcomes of device biofilm-related infections. (1) Planktonic cells are more readily cleared by the immune system than cells residing in a biofilm [44–46]. Thus, when planktonic cells are used in in vivo models, it may be that a portion are eradicated before they can form biofilms. This may contribute to the low reproducibility for the induction of osteomyelitis, which has been suggested by Gaudin et al. [47] as a common problem with animal models of osteomyelitis. (2) It is well documented that planktonic bacterial cells are more susceptible to antibiotics than those residing in a biofilm [48, 49]. Therefore, if antibiotics are administered immediately following inoculation, they may affect planktonic cells more effectively than they would if bacteria in well-established biofilms were used as initial inocula. (3) When planktonic cells are added to an in vivo system, the possibility exists that they may be dispersed rapidly away from the site of initial inoculation, which would dilute the concentration of bacteria per given area—potentially making it easier for the body to handle the bacterial load and prevent attachment to a medical device.

In addition to these limitations that may accompany the use of planktonic cells as initial inocula, investigators have depended heavily on minimum inhibitory concentrations (MICs) to determine the dose of antimicrobial that should be delivered, either from a device coating or intravenously, to prevent and/or treat biofilm-related infections. The limitation of the MIC value in this specific instance is that it is based on data derived from planktonic cells from batch culture. Specifically, a MIC is defined by the Clinical and Laboratory Standards Institute (CLSI) as the dose of antimicrobial that is needed to result in a three log reduction ($10^5 \rightarrow 10^2$) of planktonic bacteria over a 24 h period (see CLSI standard M26-A). Antimicrobial efficacy tests as standardized by the Environmental Protection Agency (e.g., SOP Number: MB-09-04 and SOP Number: MB-06-05) are also based on planktonic bacterial responses. At least one standard of the American Society for Testing and Materials (ASTM E645-07) was found to recommend that microbicides be tested against biofilms. Citing these planktonic cell-based standards, Ceri et al. suggest that additional standards must be developed to treat and/or prevent recurring and untreatable infections that are the result of biofilm contamination and/or subsequent biofilm formation on medical devices [50].

The 10^5 Rule May Not Apply to Biofilm

Studies have shown that to prevent infection, bacterial loads must be kept below 10^5 cells/g of tissue [51–55]. This is a rule of thumb used by various clinicians as an indicator of infection [54]. However, this number is strain-dependent and is based on planktonic bacterial cell counts. Citing Bowler [56], Edwards and Harding have stated, "The clinical relevance of the theory that bacterial counts of over 10^5 represent clinical infection has been questioned" [52]. The work of Bernthal et al. [57] may provide support for this statement. They showed that low-grade infection developed in a mouse model of joint arthroplasty when 5×10^2, 5×10^3, or 5×10^4 planktonic bacteria

were used as initial inocula. Antoci et al. [58] found that infection developed in a rat model of periprosthetic infection (PPI) wherein 1×10^3 bacteria were used as initial inocula. It may be that even smaller numbers of cells are required to cause infection if they reside in the biofilm phenotype. Indeed, the ability of low number, mature biofilms to resist antimicrobial treatment and immune system components may enhance our understanding of how bacteria cause infection when initial inocula are on the order of tens, thousands, or tens of thousands of cells as opposed to the hundreds of thousands or hundreds of millions in planktonic form that are commonly used for in vivo studies.

Wolcott et al. [59] have recently undertaken a study wherein they showed that in the early stages of development, biofilms were more sensitive to antimicrobials when compared to biofilms that had matured for more than 24 or 48 h. Their data further suggested that even if similar numbers of cells were present, the maturity, and not so much the number of cells within the biofilm, had a significant influence on its ability to resist antimicrobial perturbations. Their work was designed to model a specific clinical application and effectively addressed those scenarios. Importantly, however, this work followed the predominant pattern of biofilm research wherein enormous numbers of cells accumulated over time within the biofilm growth system. Yet, it may not always be accurate to analyze biofilms as they undergo an increase in their number of cells. Though dynamic, biofilms in real life systems may not display the same growth rates as those generated under optimal conditions in the laboratory. Rather, in natural systems biofilms may increase in cellular number over a longer period of time, mature to a level of equilibrium, and, when challenged by modifications in their environment, respond appropriately.

The hypothesis is that these equilibrated, matured, slow growing biofilms are what primarily contaminate wound sites, surgical sites, parenteral routes, and medical devices within humans. Thus, to model contamination of a wound site with matured, equilibrated biofilms, similar to how they are found in nature, studies may benefit from growing biofilms to threshold levels, allowing them to mature, and then exposing them to wound sites, antibiotics, or other antimicrobial agents in in vitro and/or in vivo systems.

Limitations of Using Biofilms as Initial Inocula

While animal studies may benefit from utilizing biofilms as initial inocula, there are limitations to consider in doing so. First, current technologies for growing biofilms in a laboratory setting, i.e., in vitro, are largely unable to translate to in vivo applications. For example, if biofilms are grown on the surface of a polymeric slide within a Drip Flow Biofilm Reactor, it would be impractical to implant the biofilm-ridden slide in an animal. After a careful literature review, it appears that there is currently only one study in the literature wherein a biofilm reactor has been developed for the specific intent of growing biofilms on the surface of a polymeric membrane such that the biofilms could be used as initial inocula in an animal model (discussed in more detail below) [60, 61].

Second, the use of biofilms as initial inocula is application-dependent. If an infection is well known to be caused by planktonic bacterial cells, it would be inappropriate to use biofilms as initial inocula to model such an infection.

Third, repeatability has the potential to be a complicating aspect of using biofilms as initial inocula (this is also an important aspect of using planktonic bacteria as initial inocula). If biofilms are grown on the surface of a material and, for example, are scraped off, the scraping technique of one person may differ from another. This may further result in variable numbers of bacteria being used as initial inocula. If scraping of biofilms is to be performed, care would need to be taken to standardize the scraping procedure as has been done by Goeres et al. [62]. Similarly, if biofilms are grown on the surface of a material and not scraped off, the procedure for growing biofilms should be standardized and the repeatability confirmed as has been shown by Williams et al. [61].

Number of Bacteria in a Biofilm That May Be Used as Initial Inocula

It does not appear that all biofilms carry the same infectious potential and it is proposed that most have minimal pathogenicity. If the opposite were true, it is likely that many more people would suffer from infections including gingivitis, periodontitis, sinusitis, conjunctivitis, cellulitis, gastroenteritis, vaginitis, and/or colitis. Each human being is colonized with billions of bacteria, the majority of which appear to reside in well-established biofilms [63]. As such, infection may be considered an anomaly that extends beyond the normal host/bacterial relationship. Infection may also occur as humans are exposed to well-known pathogens that reside in biofilms from soil samples, on grocery carts, in food, within the human microbiome, on office desks, in shower heads, women's purses, grocery bags, and a plethora of other locations all over the world.

The number of bacteria that should be used as initial inocula in animal models of infection is application-dependent. Conditions may be considerably different in an animal that is intended to model a patient of total joint replacement or some other elective surgery. Elective surgeries are performed under scrupulously aseptic conditions, yet despite these efforts, rates of infection still range from 1 to 4 % and at times higher [64–71]. If an animal model were used to replicate an elective surgery scenario for biomaterial development, it may be more appropriate to use a low number biofilm as the initial inoculum than what might be used for a massively contaminated open fracture model. Additional consideration would also need to be given for the inclusion of organisms associated with human skin.

When biofilms are grown in the laboratory, it is common to see them reach incredibly high numbers—on the order of 10^7 or 10^{10} cells per given area. Biofilms that contain high numbers of cells can also be found in nature [25, 27, 29, 42, 43]. Similarly, bacterial cells that have been directly observed on and in the human body have been shown to reside in the biofilm phenotype [63, 72]. Biopsy punches of human skin have been estimated to contain ~10^6 cells/cm^2 and it is well documented that the hardy biofilm former, *Staphylococcus epidermidis*, comprises a large portion of these resident commensal bacteria [63, 73, 74]. In the large intestine, several hundred grams of bacteria can be found with numbers reaching an astounding 10^{11} or 10^{12} cells/g of tissue comprising hundreds of species [63, 75, 76]. Notably, 60 % of fecal solids have been shown to be comprising bacteria [77].

Although biofilms are ubiquitous and they tend to dwell in communities that can have very high numbers of cells, it may nevertheless be incorrect to assume that wound sites or surgical sites only become infected when they are contaminated with high number biofilms. To the contrary, a biofilm, or a portion of biofilm that has broken off, that contaminates a wound site may consist of as few as 10^2 or 10^4 cells, if not fewer.

Consider the paradigm of a patient who undergoes elective surgery, such as total joint replacement. After the patient's skin is prepped, 10^6 cells/cm^2 of normal flora may be reduced in number to less than 10^3 cells/cm^2 (a 99.9 % reduction, which is the most common claim of antiseptics). Note that the majority of these have been shown to reside in the biofilm phenotype. Importantly, groups have shown that even following antiseptic treatment, viable cells continue to reside several layers deep in skin [51, 78]. In an unpublished observation, the late Bill Costerton observed matrix-enclosed bacterial biofilms between stratified squamous cells in the distal 5–7 layers of human prepped skin (Fig. 7.1) [79]. While an incision is made during surgery, these viable, biofilm-dwelling bacteria may be transported from the deeper layers of skin through a patient's integument (Fig. 7.2). As such, they may have direct access to subdermal tissues, as well as to the surfaces of transcutaneous or other implanted biomaterials. As there is no data in the literature that involves small number biofilms contaminating wound and/or surgical sites, surgeons and investigators are left to wonder what effect these might have on the development of infection in these scenarios.

There are myriad other paradigms that could be considered with similar scenarios of low

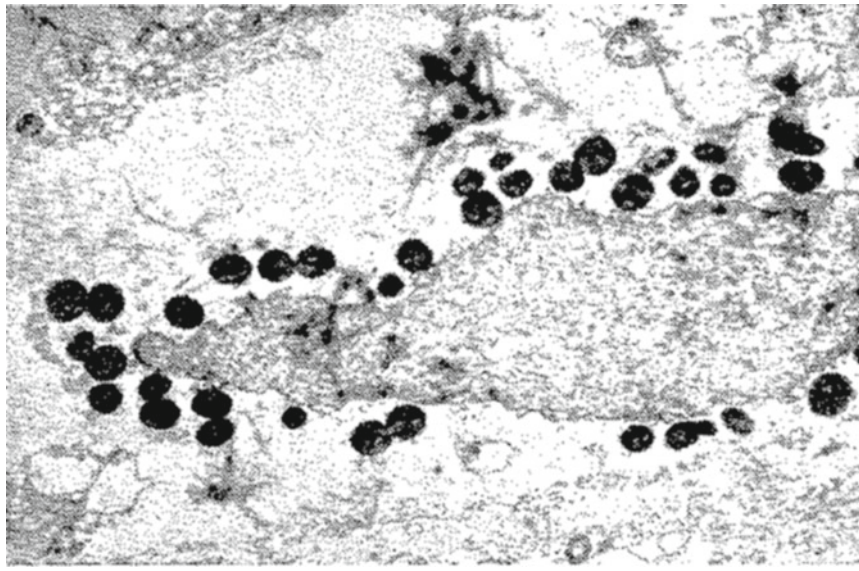

Fig. 7.1 Transmission electron microscope image of an extensive biofilm of Gram-positive bacteria on a skin cell deep (±70 μm) in a moist area between Bill Costerton's toes. Do not attempt this at home. Original image can be found on page 101 of "The Biofilm Primer," by Dr. Bill Costerton [81]. Image used with permission

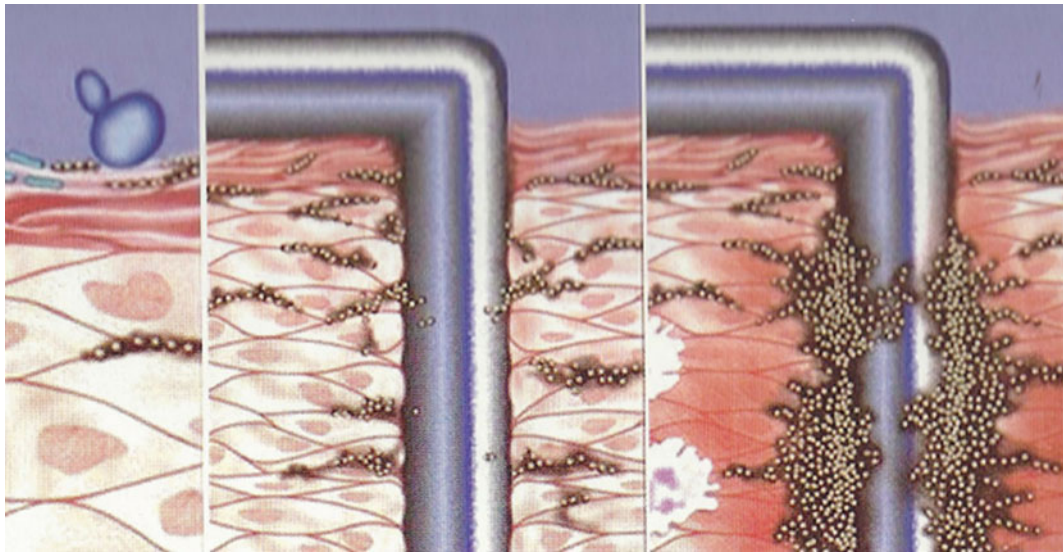

Fig. 7.2 Conceptual drawing of microbial colonization of human skin. In the *left panel* cells of *Staphylococcus epidermidis* (*black*) are seen to inhabit the deeper layers of skin, while cells of this species and of Gram-negative bacteria and fungi (*blue*) all occupy the distal layers of this squamous epithelium. The *central panel* shows that, when the skin has been prepared for surgery and a staple has been inserted, the surface of the skin is uncolonized, but living biofilms of *S. epidermidis* occupy the deeper layers in the vicinity of this foreign body. The *right panel* shows the development of an extensive *S. epidermidis* biofilm on the surfaces of the staple and the initiation of a mild inflammatory response involving the mobilization of leukocytes. Original image can be found on page 102 of "The Biofilm Primer," by Dr. Bill Costerton [81]. Image used with permission

numbers of cells within a biofilm contaminating wound and/or surgical sites. What remains is the fact that hypothesis-driven research needs to be undertaken to determine the impact that low number biofilms have on human health as they attach to and form on the surface of biomaterial devices. Furthermore, there does not appear to be a comparative study in the literature to determine the effect that fewer versus higher numbers of cells in a biofilm, which derive from the same bacterial strain(s), have on the formation of biofilms on biomaterials. For now, the understanding of critical doses required to cause infection is based solely on concentrations of planktonic bacteria.

Possible Methods of Growing Biofilm for Use as Initial Inocula

Connell et al. [80] have recently developed a remarkable method of growing biofilms in small numbers using micron-sized "lobster traps." Although countless possibilities exist for in vitro experimentation with these traps, they are currently limited in that they are adhered to a solid surface. However, modifications to the substrate could make it possible for them to be used as initial inocula in an in vivo model.

As was mentioned previously, a membrane biofilm reactor system has been developed with the specific intent of growing biofilms that could be used as initial inocula in an animal model of infection [61, 81]. Within this reactor, biofilms of methicillin-resistant *Staphylococcus aureus* (MRSA) were shown to develop into three-dimensional pillar-like structures on the surface of the membranes (Fig. 7.3). When used as initial inocula in an animal model of a simulated Type IIIB open fracture, these biofilms resulted in chronic infections that resembled biofilm-related infections that are seen clinically [60].

Importantly, despite the promising results of this work, there is one crucial factor to take into consideration. In the above study, biofilms were grown for a 48 h period, rinsed to remove loosely adherent or nonadherent cells, and transferred in a broth solution prior to using them as initial inocula. These steps were undertaken in an attempt to reduce the possibility of having planktonic cells present. However, the potential still existed that a portion of cells present could have been in the planktonic phenotype. As such, the question may arise; was it the biofilm bacteria or the planktonic bacteria that caused infection? Two responses can be given.

First, it is likely impossible with current technologies to separate all planktonic bacteria from those that reside in the biofilm phenotype such that an inoculum with biofilm bacteria alone is absolutely definitive. Yet, it is also unlikely that such a distinct separation exists between planktonic and biofilm bacteria in natural ecosystems. This may suggest that using an inoculum that has a mixture of the two, with those in the biofilm phenotype being more heavily selected, is clinically relevant.

Second, an additional animal model is currently being used to test the ability of the MRSA strain discussed above to cause infection when inoculated in the planktonic phenotype from batch culture. When the onset of infection was compared between these two animal models, there was a drastic difference in the rapidity and severity of infection that set in with the planktonic bacteria. In that instance, none of the animals survived past 11 days. In contrast, those that were treated with biofilms as initial inocula displayed signs of infection that were much less severe and which progressed at a much slower pace. More specifically, those animals displayed limited signs of pain or distress even out to 12 weeks, but each of them developed a significant osteomyelitic infection.

This contrast in the speed and severity of infection may provide clinical evidence that using biofilms as initial inocula is more correlative to biofilm-related infections that are present in patients. In patients, biofilm-related infections appear to be latent infections that develop slowly over time and which may persist for extensive periods [33]. So although these current animal models provide a promising step in the direction of using biofilms as initial inocula, there are many factors to take into account: a host's health, the pathogenicity of an organism, the ability for an organism to develop into a biofilm, the degree

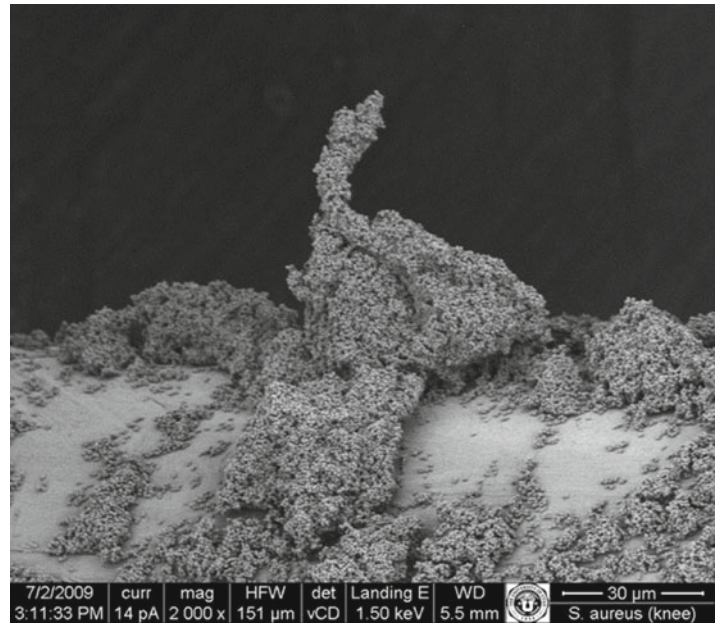

Fig. 7.3 Scanning electron microscope image of a methicillin-resistant *Staphylococcus aureus* (MRSA) biofilm that was grown on the surface of a PEEK membrane within a membrane biofilm reactor. Image used with permission [63]

of contamination, the ratio of cells in the planktonic phenotype to those in the biofilm phenotype, etc. Thus, this issue of planktonic versus biofilm infection is still a limitation and will require additional future testing to overcome the challenges of separating the bacterial phenotypes before more definitive statements can be made.

At this time, with the variety of biofilm reactor devices that are currently available, such as the CDC biofilm reactor, the modified CDC biofilm reactor, the Drip Flow Biofilm Reactor, and "lobster traps," the outlook is promising for a transition in biofilm investigation to occur from the in vitro paradigm to the in vivo setting.

Animal Models That Have Involved Biofilms as Initial Inocula

After a careful literature review, there appear to be two studies wherein well-established, mature biofilms have been used as initial inocula in animal models of infection. The first was published in 2010 by Zhao et al. [82]. To model chronic wounds in diabetic mice, Zhao et al. grew biofilms of *Pseudomonas aeruginosa* on the surface of polycarbonate membrane filters. Biofilms grew on the surface of filters as they were placed on agar that contained a lawn of *P. aeruginosa*. Each membrane was subsequently placed on a wound that had been created on the dorsal skin of a mouse. During the monitoring period, no mice showed signs of systemic infection, yet delayed wound healing was present in those that were treated with biofilm.

The second study wherein biofilms were used as initial inocula was mentioned previously and was performed by Williams et al. [60]. In this study, biofilms of MRSA were grown on the surface of PEEK membranes and placed in apposition to the proximal medial aspect of sheep tibiae. Each membrane was covered with a simulated fracture fixation plate in order to model the clinical scenario of a patient who has bacteria compressed between a fracture fixation and the surface of bone (Fig. 7.4). Infection developed in 100 % of animals exposed to biofilm and, as was mentioned, the infection cycle was similar to biofilm-related infections that are seen clinically.

Importantly, both of these models were developed with very high inocula of bacteria in biofilms. Thus, it remains to be determined if low number biofilms have a similar effect on the development of infection. Nevertheless, both of

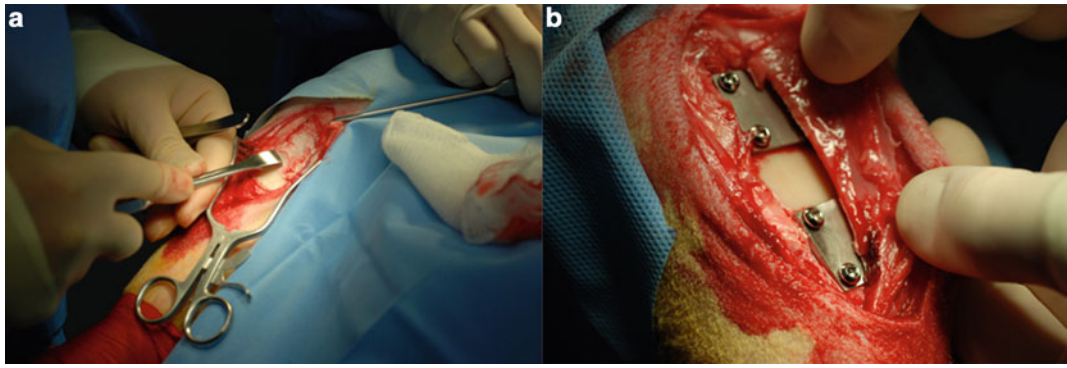

Fig. 7.4 Photographs taken during the surgical placement of PEEK membranes and stainless steel plates in the proximal medial aspect of a sheep tibia as published by Williams et al. [60]. (**a**) The periosteum of each sheep was removed in order to model a Type IIIB open fracture. (**b**) Two stainless steel plates, each of which had a PEEK membrane underneath it that was placed in direct apposition to the bone, were secured to the proximal medial aspect of the tibia

these studies provide an indication that using biofilms as initial inocula has the potential to result in infections that are chronic in nature. Furthermore, these models provide a platform for additional animal work to be performed with biofilms as initial inocula.

Future of Biofilm Studies

The impact of biofilm-dwelling bacteria on human health is becoming ever more apparent. Chronic wounds are now considered to be the result of acute infection that begins with biofilm contamination as opposed to a non-healing wound that is later contaminated and suffers from biofilm formation/infection [83–86]. Heart disease is now indicated to be compounded by biofilm-dwelling bacteria from oral plaque that enter the vasculature [87, 88]. Overall human health is believed to be significantly influenced by an intricate balance of biofilm-dwelling bacteria in gut flora [75]. In short, the impact of biofilms on human wellbeing and disease cannot be overestimated.

Looking to the future of biofilm and biomaterials research, additional approaches for in vitro analyses and design modifications to in vivo models that encompass the use of preformed, well-established, sessile communities of mature biofilms that model those found in nature, in patients, and within the environment can be envisioned. As studies are undertaken to analyze the impact of low number biofilms on infection outcomes, results may indicate that less than 10^5 cells/g of tissue, or per area, will be required to cause infection.

If the efficacy of antimicrobials is tested against high and low number biofilms, those on the order of 10^7–10^9 and 10^2–10^4 cells, respectively, we may uncover deeper insights into the concentrations of antimicrobial in, for example, antimicrobial eluting biomaterials, that are needed to prevent and eradicate biofilm-related infections from developing. We can only wonder at this time how many antimicrobials and antimicrobial eluting biomaterials have been prevented from progressing to clinical, home, industrial, and/or environmental use based on the fact that MIC values, which are primarily the result of planktonic cellular response, have been used to determine the amount that was needed to eradicate bacteria residing in well-established biofilms.

The opposite may be true as well. There is no indication that antibiotics that have been put into clinical use have shown efficacy against low and/or high number biofilms on implants. Although this trend may change as an understanding of the role of biofilm increases, this paradigm has potentially been a contributing factor to the development of antibiotic resistance. More specifically, in various systems, bacteria residing in

biofilms may have been exposed to lower concentrations than are needed to prevent their growth and eradicate them within in vitro and in vivo systems. However, a cavalier approach of simply increasing dosages of antimicrobials alone or used in eluting biomaterials could potentially lead to toxic effects in vivo and cause additional problems. Thus, future work will be needed to elucidate the efficacy and toxicity of antimicrobials used alone or in eluting biomaterials against biofilms in clinical studies.

There is evidence to suggest that bacteria dwelling in the biofilm phenotype have the potential to initially contaminate open wound sites and/or surgical sites of patients. These biofilms may attach to subdermal tissues or the surfaces of implanted devices resulting in chronic, biofilm-related infection. In addition, the impact that low number biofilms have on human infection as well as using well-established, mature biofilms as initial inocula for in vitro and in vivo models may help further the optimization of antimicrobial treatments, such as those used in coatings on biomaterials. In doing so, an understanding of the impact that biofilms from natural systems have as initial contaminants of wounds may also be increased. Most importantly, a shift in the use of biofilms for inoculation methods and analytical techniques may help biomaterial researchers take a step forward, and thus obtain the advantage in the battle against biofilm implant-related infections.

Relevance of Biofilms to the Field of Periprosthetic Infections

There are at least three methods by which bacteria may contaminate, colonize, and form biofilms on the surface of a total joint replacement device and ultimately cause biofilm-related PPI. The first is the possibility for bacteria from a surgeon, other healthcare worker, or the operating room itself to contaminate a surgical site during surgery. The second is for bacteria from the patient's own body to contaminate the surgical site/implant surface. As mentioned, it is hypothesized that biofilm-dwelling bacteria from the deeper layers of a patient's skin, which may not be killed by a surgical scrub, can migrate toward or inoculate the surface of an implant during surgery. The third possibility is for bacteria to spread hematogenously from one area of a patient's body to the surface of an implanted device. Though not yet well documented, this third method may be one cause of late onset PPI. Yet, late onset infections may also be the result of low number biofilms that take days, months, or perhaps even years to colonize an implant surface, reach an infectious dose, and cause PPI.

As our understanding grows of the role that biofilms play in multiple environments including PPI, clinicians and scientists will have the ability to better prevent and treat biofilm implant-related infections. In light of the many problems that accompany biofilm-related infections, such as antibiotic resistance, hospital-acquired infections, patient morbidity, and rising healthcare costs, there is significant motivation to address these issues. Using biofilms as initial inocula in clinically relevant and application-dependent animal models may provide the innovative and unique strategies that are necessary to prevent PPI.

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Microbiology of Periprosthetic Joint Infection

8

Farheen Tariq and John Segreti

Abbreviations

CA-MRSA	Community-acquired MRSA
CoNS	Coagulase-negative staphylococci
ESBL	Extended spectrum beta lactamase
ESR	Erythrocyte sedimentation rate
GBS	Group B streptococcus
GNRs	Gram-negative rods
HA-MRSA	Health care acquired MRSA
KPC	Klebsiella pneumoniae carbapenemase
M. chelonae	*Mycobacterium chelonae*
M. fortuitum	*Mycobacterium fortuitum*
MAC	*Mycobacterium avium* intracellulare
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MSM	Men having sex with men
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MTB	*Mycobacterium tuberculosis*
P. acnes	*Propionibacterium acnes*
PJIs	Prosthetic joint infections
PPD	Purified protein derivative
S. aureus	*Staphylococcus aureus*
S. typhimurium	*Salmonella typhimurium*

Introduction

Joint replacement surgery is now a commonly performed orthopedic procedure to alleviate immobility and to restore function. Almost any joint can and has been replaced, but the most common joints undergoing replacement are knees and hips. Clinical infection is often not clinically evident and low-grade infection may present as joint loosening or pain and can appear similar to aseptic mechanical failure. While mortality directly related to these infections is unusual, these infections also impose substantial morbidity for the patient and are a growing economic burden on healthcare systems. The management of these infections is complex and largely based on personal experience and expert opinion. It is imperative to understand the microbiology, pathogenesis, and risk factors of periprosthetic joint infections if we hope to improve patient outcomes.

The Pathogenesis of Periprosthetic Joint Infection

The pathogenesis of prosthetic joint infection involves interactions among the implant, the host's immune system, and the involved microorganism(s). Only a small number of

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microorganisms are needed to seed the implant at the time of surgery. The presence of a foreign body can reduce the number of *Staphylococcus aureus* cells needed to cause an infection by a factor of 100,000 in a guinea pig tissue cage model [1]. Organisms, typically skin flora, are dispersed in the operating room (OR) on squamous epithelial cells which then land in the open wound and adhere to the implant. The mechanism of adherence likely depends on the ability of the bacteria to produce surface adhesins as well as the conditioning of the prosthetic surface with host proteins such as collagen, fibrinogen, and fibronectin. Once attached to the implant, these organisms form a matrix-encased community of bacteria that is called a biofilm. This biofilm protects the colonizing bacteria from conventional antimicrobial agents and the host immune system. The matrix is quite variable and dynamic. It generally consists of polysaccharides, proteins and extracellular DNA. In vitro, it can take a day or more to develop an established biofilm, but the time of incubation required for biofilm formation in vivo is not clear. Bacteria growing within a biofilm are less metabolically active than bacteria in broth cultures. These colonies display more anaerobic characteristics and most exist in a stationary phase-like state, where transcription, translation, and cell division are markedly reduced thus making them less susceptible to most currently available antimicrobials [2]. Bacteria in biofilm may also be capable of cell-to-cell signaling which affect cellular attachment and detachment. Coagulase-negative staphylococci, *S. aureus*, enterococci, and *Pseudomonas aeruginosa* are a few organisms that have been isolated from biofilms on hip prostheses [3]. PCR amplification of the 16S rRNA gene has been utilized to identify bacteria on the surface of failed prosthetic joints in both clinically infected and noninfected hip joints [4, 5].

Microbiology

In primary joint replacement, the infection rate in the first 2 years has been shown to be generally <1 % in hip and shoulder prostheses, <2 % in knee prostheses and <9 % in elbow prostheses [6]. Jafari et al. found a failure rate of 18.7 % for 1,366 revision total hip arthroplasties with infection as the cause in nearly one-third [7]. Deep-implant skin and soft tissue infections following total hip arthoplasty have been reported to occur in 0.3–1.3 % of cases [8]. The two most common microorganisms responsible for infection are coagulase-negative staphylococci (CoNS) and *S. aureus* (see Tables 8.1 and 8.2) which cause approximately 50–65 % of cases [9–12]. Some organisms can have a long latency period and even though they are acquired perioperatively, they may remain dormant and do not manifest clinical infection until several years later. For infections that are acquired perioperatively, *S. aureus* and enterobacteriaceae usually cause infection within the first 4 weeks after arthroplasty. Coagulase-negative staphylococci, *Propionibacterium* species, and *Corynebacterium* usually present later [13]. Coagulase-negative staphylococci and *S. aureus* have been found in air samples in the operating room and next to the operative field. Nasopharyngeal shedding from operating room personnel was the source of many of these samples [14]. Gram-negative bacteria were isolated less often in comparison. This poses a potential risk for perioperative seeding of the joint prosthesis. Other sources for perioperative acquisition of infection include the patients own skin and nasal flora or a break in aseptic technique. This study also reported that the surgical mask was not effective in preventing nasal shedding into the air at 3 h after procedure onset. In general poorer outcomes have been reported for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) periprosthetic joint infections with a reported failure rate as high as 21 % in hip arthroplasties [15].

Staphylococcus aureus

S. aureus is either acquired via hematogenous dissemination or perioperative seeding of the joint. Additional risk factors described for *S. aureus i*nfection include dialysis dependence, trauma, bacteremia, and cancer. As mentioned

Table 8.1 Classification of microorganisms

Gram positive	Gram negative	Typical and atypical mycobacteria	Fungal
Staphylococcus aureus	*Pseudomonas aeruginosa* (PsAR)	*Mycobacterium tuberculosis* (MTB)	*Aspergillus* sp.
Coagulase-negative staphylococci (CoNS)	*E. coli*	MAC	*Histoplasma capsulatum*
	Klebsiella pneumoniae	*Mycobacterium kansasii*	*Sporothrix schenckii*
Streptococci (including GBS)		Rapid growing atypical mycobacteria (*Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium fortuitum*)	*Candida* sp.
Enterococci			
Corynebacterium sp.			
Anaerobes (*P. acnes*, *Peptostreptococcus* sp., Clostridial sp.)			

previously, rheumatoid arthritis is a strong risk factor for prosthetic joint infection with *S. aureus.* Sendi et al. in their study found that exogenous or perioperative infections were more frequent after knee arthroplasty (53 % vs. 27 %, $p=0.06$) and hematogenous infections were more frequent after hip arthroplasty (73 % vs. 47 %, $p=0.06$) [16]. Exogenous infections usually present more commonly with local signs as compared to hematogenous infections, which are more likely to manifest with systemic signs including sepsis. The source of bacteremia may not always be identifiable. The authors also reported that the median time interval from implantation to infection was 1 month (0.5–2) in the exogenous cases and 86 months (39–128) in the hematogenous cases. MRSA was first identified in the 1960s after the introduction of methicillin and has been associated with nosocomial infections since then [17]. In a United States surveillance report of 24,179 cases of hospital acquired *S. aureus* blood stream infections, methicillin resistance rates increased from 22 to 57 % between 1995 and 2001 [18]. There has been emergence of community-acquired MRSA (CA-MRSA) isolates which were first described in iv drug abusers in the 1980s. These infections were subsequently described in prisoners, men having sex with men (MSM), sports team members and other groups without typical risk factors for healthcare-acquired MRSA (HA-MRSA) including exposure to healthcare facilities, antibiotics, or MRSA colonized patients [19]. CA-MRSA isolates are generally more susceptible than HA-MRSA isolates to antimicrobials such as clindamycin, tetracyclines, trimethoprim-sulphamethoxazole, and rifampin, but this can vary based on local resistance rates in the community [20]. CA-MRSA clones have been identified in healthcare-associated infections making the distinction between CA-MRSA and HA-MRSA less clear [21]. Kourbatova et al. reported nine early prosthetic joint infections in the hip and knee out of 95 patients. Of these five were isolated as CA-MRSA and three as methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates [20]. Some studies have reported a higher rate of treatment failure with MRSA as compared to MSSA prosthetic joint infections [15, 22, 23].

Coagulase-Negative Staphylococci

Coagulase-negative staphylococci are etiologic agents mostly for delayed prosthetic joint infections occurring more than 3 months after joint replacement. *Staphylococcus lugdunensis* deserves special mention because it is a coagulase-negative staphylococcus that behaves like *S. aureus*. It has been described in case reports as causing late

Table 8.2 Microbiology of periprosthetic joint infection

Early onset prosthetic joint infection	More common	Overall frequency (%)
<3 months	*Staphylococcus aureus*	12–39
	Enterobacteriaceae and *Pseudomonas aeruginosa*	4–28.2
	GNRs	
	Less common	
	Mycobacterium fortuitum	
	Anaerobes (post-trauma)	2–10
Delayed onset prosthetic joint infection	More common	
3–24 months	Coagulase-negative staphylococci (CoNS)	22–43
	Propionibacterium sp.	
	Corynebacterium sp.	
	Streptococci (including GBS)	9–14
	S. aureus	
	GNRs	
	Enterococci	3–9.2
	Less common	
	Mycobacterium tuberculosis (MTB)	1–5
	Anaerobes	
Late onset prosthetic joint infection	More common	
>24 months (Hematogenous seeding)[a]	*S. aureus*	34 (hematogenous)
	GNRs	
	Streptococci (including GBS)	
	Streptococcus pneumoniae	
	Enterococci	
	CoNS sp.	
	Less common	
	MTB	
	Listeria monocytogenes	
	Atypical mycobacteria	
	Fungi	
	Anaerobes	
	Brucella sp.	

Data are from Trampuz et al. [9], Del Pozo et al. [50], Murdoch et al. [51], Lentino [52], Gomez et al. [53]
[a]Hematogenous infections can also appear early

infections with an acute presentation [24, 25]. The frequency of infection due to *S. lugdunensis* is likely underappreciated since many laboratories do not routinely speciate CoNS. Thus growth of CoNS in an otherwise virulent infection should prompt the clinician to ask the laboratory to do further speciation of the organism. Unlike other CoNS, it is typically susceptible to a variety of antibiotics, including beta-lactams.

Group B Streptococcus

The elderly and diabetic patients have been found to be at increased risk of invasive infection with group B streptococcus (*Streptococcus agalactiae*). Patients who develop group B streptococcus (GBS) prosthetic joint infection have been found to have multiple underlying comorbidities. In a study by Sendi et al., 75 % of prosthetic joint

infections with GBS occurred between 3 and 24 months after original implantation suggesting more hematogenous infection [26]. Also, onset of symptoms from time of prosthesis placement ranged from 2 weeks to 23 years. The majority of patients had an acute presentation of symptoms. They also had damaged periprosthetic tissue. The overall median frequency of GBS prosthetic joint infections at the participating centers was 3 % in this study. Debridement and implant retention with GBS infection can be undertaken if the duration of symptoms is short, the implant is stable and if there is minor soft tissue damage, which is the same practice also applied to other organisms. GBS infections are generally susceptible to penicillins. However, in patients with serious penicillin allergy, clindamycin, fluoroquinolones, and vancomycin have to be utilized. There are concerns about rising clindamycin resistance in GBS isolates. One study reported that out of 222 GBS strains from cervicovaginal-rectal swabs, 38 % were resistant to erythromycin and 21 % to clindamycin [27]. A previous study had found a 9 % rate of clindamycin resistance in 192 GBS isolates from patients with invasive disease including pediatric, pregnant, and nonpregnant adults [28]. *Streptococcus bovis*, *Gemella* species, *Abiotrophia* and *Streptococcus pneumoniae* have also been documented as causes of infected prostheses [24].

Gram-Negative Organisms

Gram-negative bacteria constitute approximately 6–23 % of prosthetic joint infections [10]. Hsieh et al. found that patients who had infection with gram-negative organisms tended to be older (mean age 68 vs. 59 years) and developed infection earlier after the index joint replacement surgery (median joint age, 74 vs. 109 days) as compared to gram-positive infections [10]. In this study *P. aeruginosa* was the most common pathogen, followed by *Escherichia coli* and then *Klebsiella pneumoniae*. Two-stage exchange and resection arthroplasty had a good outcome comparable to that of patients with gram-positive infections. However, prosthesis retention with debridement was associated with a less favorable outcome for patients with gram-negative infection. Retention of prosthesis was found to be more successful in patients with a shorter duration of symptom onset prior to surgery in this patient population. There is now concern for emergence of resistant gram-negative bacteria including extended spectrum beta lactamase (ESBL) and *Klebsiella pneumoniae* carbapenemase (KPC) producing organisms [29, 30]. Martinez-Pastor et al. reported 7 out of 132 prosthetic knee joint infections (5.3 %) involving ESBL-producing Enterobacteriaceae [31] such as *E. coli* and *K. pneumoniae*. ESBL-producing bacteria require treatment with carbapenems and KPC producing organisms are treated with tigecycline and colistin.

Mycobacteria: *Mycobacterium tuberculosis*

Prosthetic joint infection with *Mycobacterium tuberculosis* (MTB) can occur either by local reactivation of infection, extension from a contiguous site or hematogenous seeding as a result of disseminated infection. Tuberculosis involves the joints in 1–5 % of cases in endemic areas. These infections are mostly monoarticular and affect the hip and knee [32]. Risk factors include chronic steroid use and rheumatoid arthritis. There is some concern for reactivation of tuberculosis after arthroplasty ranging from 0 to 31 %, with a higher risk for a total knee vs. total hip arthroplasty [32, 33]. There are case reports describing the diagnosis of prosthetic joint tuberculosis made months to several years after arthroplasty. [32, 34–36]. The orthopedic surgeon should have a high clinical index of suspicion for these infections as they can be difficult to diagnose. Patients from tuberculosis endemic areas, prior history of tuberculosis, underlying HIV infection or on immunosuppressants may be at risk. Also, if special cultures are not sent for acid fast bacilli, the infection can be easily misdiagnosed with repeat negative routine bacterial cultures [35]. Systemic signs of infection are usually absent. Cold abscesses, draining sinuses and

fistulas have been described [33, 35]. PPD may not be positive and imaging studies are generally nonspecific. Histopathology from a synovial biopsy may reveal organisms or only granulomatous inflammation. Medical therapy alone often fails when the infection is discovered months or years after arthroplasty, in which case removal of the joint prosthesis has been suggested [34, 36]. Shanbhag et al. described a case report with review of literature including 22 cases of prosthetic joint infection with MTB. Six cases underwent a staged exchange with the use of antibiotic spacers implanted at the first surgery and an interval of 3–22 months before prosthetic joint replacement [37].

Fungal Infections

Fungi such as *Aspergillus fumigatus* involving knee arthroplasty has been described in relation to a history of immunosupression from steroids and underlying malignancy. *Histoplasma capsulatum* and *Sporothrix schenckii* are also uncommon causes of prosthetic joint infection [33]. These can occur in immunocompromised patients with endemic exposure to histoplasmosis or outdoor occupations and hobbies involving exposure to sporotrichosis. Prosthetic joint infection with *Candida* species is rare. Risk factors are similar to those for invasive candidiasis including immunosuppression, neutropenia, prolonged use of antibiotics and the presence of indwelling intravenous catheters. Diabetes mellitus, corticosteroids, parenteral nutrition, rheumatoid arthritis, history of multiple abdominal surgeries, history of renal transplantation, severe burns, and injection drug use are other known risk factors. However, cases have been described without any risk factors [38, 39].

Rare Microorganisms

Prosthetic joint infection by non-tuberculous atypical mycobacteria and *Mycobacterium bovis* is generally rare. Atypical mycobacteria reported to cause prosthetic joint infection include *Mycobacterium kansasii*, *Mycobacterium smegmatis*, and *Mycobacterium wolinskyi*. It also includes the rapid growing atypical mycobacteria such as *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum*. *M. fortuitum* causes more early postoperative infections as compared to *M. chelonae* [33]. The prosthesis has to be removed in most cases for adequate therapy. *Mycobacterium avium complex* (MAC) has been described with disseminated infection in an AIDS patient resulting in an infected prosthesis [40]. MAC prosthetic joint infection has also been reported in a renal transplant patient [41]. Immunosuppressed individuals are also at risk of developing infection many years after possible perioperative acquisition as a result of an altered immune response. Acquired or genetic defects in interferon-gamma production or diminished receptor expression are established risk factors for mycobacterial infection [42]. Immunosuppressants may lead to reduced interferon-gamma levels thereby increasing the risk of these infections. Another route of infection may be translocation from a genital or gastrointestinal source directly into the prosthetic joint. MAC can produce biofilm which may also enhances it role in pathogenesis. Periprosthetic isolation of MAC from culture may be considered a contaminant due to its ubiquitous presence in the environment, therefore, clinical correlation plays an important role [41]. Anaerobic prosthetic joint infection includes organisms such as *Bacteroides fragilis* group, *Fusobacterium* species, *Peptostreptococcus* species, *Clostridial* species, *Veillonella* species, and *Propionibacterium acnes* [43]. These infections often originate from an intraabdominal source, decubitus ulcers, and osteomyelitis. They can also occur in post-trauma patients. Most cases of anaerobic arthritis result from hematogenous spread. *Clostridial* species are known to infect penetrating wounds or foreign bodies. There have also been rare reported cases of *Clostridium difficile* causing infection in prosthetic joints [24]. Case reports with *Actinomyces* species have been associated with prosthetic joint infection after dental work, intrauterine device placement, and iv drug abuse [24]. These infections require long term treatment for up to 6–12

months. When these organisms are cultured, one needs to ascertain the source of the infection. *Propionibacterium acnes* has been associated with previous surgery and trauma [43]. *P. acnes* is a common contaminant of cultures especially when only a single specimen is positive. *P. acnes* requires anaerobic conditions and prolonged duration for growth. It has been shown to cause prosthetic shoulder joint infection as well as infection after rotator cuff repair. Lutz et al. reported an average time to positive culture of 11.4 days and Dodson et al. reported an average time of 9 days [44, 45]. *P. acnes* is susceptible to penicillin, clindamycin, and vancomycin but resistant to metronidazole. Levy et al. showed that *P. acnes* infection was higher among patients with a shoulder infection as compared to patients with a lower limb infection (9 of 16 patients with shoulder infection vs. 1 of 233 patients with lower limb infection; $p<0.001$ [46]. Five out of nine patients had an infected shoulder prosthesis in this study. *Corynebacterium jeikeium* has been diagnosed as a cause of late infected hip and knee arthroplasties. This organism is known to be penicillin resistant with variable susceptibilities to other antimicrobials. *Listeria monocytogenes* has been reported in the literature generally as a late infection occurring mostly in the elderly and immunocompromised patients, with most likely sources being unpasteurized milk/cheese, vegetables, and meat. *Nocardia* species which are usually opportunistic pathogens have been described in the literature [24]. *Bacillus* species (non-anthrax) have been implicated in case reports [24]. *Yersinia enterocolitica* has also been described as a rare cause of prosthetic joint infection associated with a gastrointestinal mode of acquisition and diarrheal illness [47, 48]. *Campylobacter* which is a commonly acquired food-borne illness has been found to cause prosthetic joint infections in immunucompromised as well as immunocompetemt patients [33]. *Salmonella* species, in particular *S. typhimurium* can present acutely as an early or late postoperative infection from an underlying bacteremia or gastroenteritis [24]. With the emergence of resistance to *Salmonella* species, it is important to obtain antimicrobial susceptibilities to target therapy. *Neisseria meningitides*, *Hemophilus influenza*, and *Moraxella catarrhalis* have also been linked to prosthetic joint infection. *Brucella* species have been implicated in prosthetic joint infections involving the hip and knee [33]. Modes of transmission include intake of unpasteurized milk and cheese and occupational exposure to source animals such as cattle, goat, sheep, and others. The median time from prosthesis implantation to diagnosis has been shown to be 48 months (range: 2 months–14 years). *Francisella tularensis* has also been isolated from an infected knee atrhoplasty [49]. *Pasteurella multocida* which normally causes skin and soft tissue infection has been linked to prosthetic joint infection associated with animal bites and animal contact. It has also been reported in immunocompromised patients. *Echinococcus* species infect the bone in 0.5–2 % of cases and usual sites of involvement are the pelvis, spine, humerus, and tibia [33]. This infection can be difficult to eradicate. *Tropheryma whipplei* can also be a challenging diagnosis as a cause for prosthetic joint infection. Culture-negative prosthetic joint infection Berbari et al. reported 60 of 897 (7 %) episodes of initial culture-negative prosthetic joint infection [12]. 32 of 60 (53 %) episodes were associated with antibiotic exposure in the 3 months prior to surgery and 23 % were receiving an antibiotic up to the time of surgery. Other possible reasons for culture-negative infection include fastidious organisms, bacterial pathogens trapped in biofilm or unusual microorganisms that do not grow on routine aerobic and anaerobic culture media. Death of bacteria prior to culture may also be a factor. They also reported that overall outcomes were similar as compared to prosthetic joint infections with positive joint cultures.

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Antibiotics in Treatment of Periprosthetic Joint Infections

9

Alex Soriano

Introduction

The infection rate after joint arthroplasty is about 1–3 % in spite of correct surgical techniques, aseptic measures, and antibiotic prophylaxis [1]. Taking into account the increasing number of arthroplasties performed each year in the developed world; a parallel increase in the number of prosthetic joint infections is expected. The management of these infections is complex due to the progressive increase in antibiotic resistant bacteria and the ability of bacteria to grow forming biofilms on the implant surface. The aim of the present chapter is to provide a general knowledge about antibacterial agents and the main characteristics of available antimicrobial families for treating the most frequent pathogens producing prosthetic joint infections. The description of each group of antibiotics includes the following aspects: mechanism of action, antibacterial spectrum, pharmacodynamic index predicting the efficacy, concentration achieved in bone, recommended dosages and way of administration, and the most relevant adverse events.

Bacteria, most especially *Staphylococcus aureus* have developed mechanisms to evade the immune system and to remain hidden but viable for a long period of time causing recurrent relapses. The most important mechanisms related with orthopedic implant infections are the ability to form biofilms [2] and the phenotypic switch to small colony variants (SCV) that are able to survive within osteoblasts [3, 4]. A summary of the data available about the activity of antibiotics against these bacteria is included in the description of each group of antibiotics.

General Concepts of Antibacterial Agents

Classically antibiotics have been divided in bactericidal or bacteriostatic and in general bactericidal agents are preferable to static ones, however, this distinction should not be taken as absolute. The definition of cidality is a laboratory concept. Bactericidal agents are those that kill bacteria rapidly (≥3 logarithms of colony forming units in 24 h) while bacteriostatic, also kill bacteria, but they do it slowly (Fig. 9.1). Bactericidal agents are preferred when host's defenses are insufficient like in neutropenic patients or when the infection is located in sites where neutrophil penetration is difficult like in meningitis or endocarditis. However, in other circumstances a bacteriostatic agent could be better. This is the case of necrotizing fasciitis due to *Clostridium perfringens* or *Streptococcus pyogenes* where animal models and some clinical data show that clindamycin or

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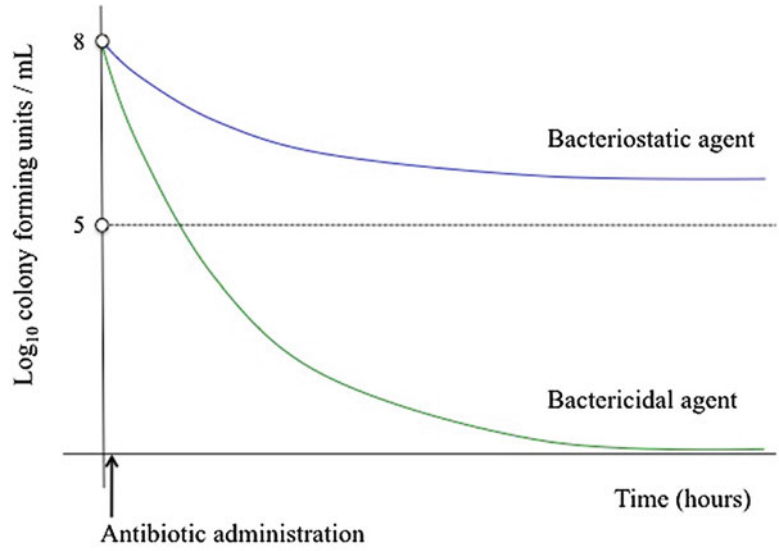

Fig. 9.1 Killing curve describing the activity of a bacteriostatic antibiotic (*blue*, reduction of <3 log of colony forming units after 24 h of exposure) and other bactericidal (*green*)

linezolid (static agents) prevent mortality better than betalactams (cidal agents). Protein synthesis inhibitors (clindamycin, linezolid, rifampin, tetracyclines) abruptly stop the production of toxins, critical in the pathogenesis of necrotizing fasciitis, while betalactams do not reduce or even increase the toxin production during the first 24 h [5].

The effectiveness of antibiotics depends on their in vitro activity well described by the minimum inhibitory concentration (MIC). The MIC is the minimal antibiotic concentration that inhibits the macroscopic growth of bacteria, therefore, the lower the MIC the higher the activity. Based on this information, microbiologist inform about the susceptibility or resistance of bacteria to each antibiotic. Although MIC is a useful tool for predicting the efficacy of antibiotics, experience from animal models and clinical studies has shown that the information provided by the MIC is limited. This test is performed in the laboratory using low bacterial inoculum in exponential growth phase and using static antibiotic concentrations while in patients, bacterial inoculum could be significantly higher and antibiotic concentration in serum and tissues is constantly changing. For this reason, during the last years infectious disease physicians, microbiologists, and pharmacologists have investigated in animal models and human beings the relationship between measurements of drug exposure (pharmacokinetics: absorption, distribution, and elimination) and antimicrobial effect (MIC), this interaction is called pharmacodynamics [6]. The development of pharmacodynamics has proven valuable for the design of appropriate regimens and to define more accurate susceptibility break points. It is possible to identify three patterns of antimicrobial activity (Fig. 9.2):

1. *Concentration-dependent antibiotics with prolonged post-antibiotic effect*. Higher serum concentration of these antibiotics kills microorganisms more rapidly than lower levels, and prolonged post-antibiotic effect allows for infrequent administration of large doses. The goal of a dosing regimen of these drugs would be to maximize concentrations over the MIC (Cmax/MIC). This pattern is observed with aminoglycosides.
2. *Time-dependent antibiotics with minimal or no post-antibiotic effects*. High antibiotic concentrations do not kill microorganisms better than lower levels and microorganisms regrowth very soon after serum levels fell below the MIC. This pattern is typical of

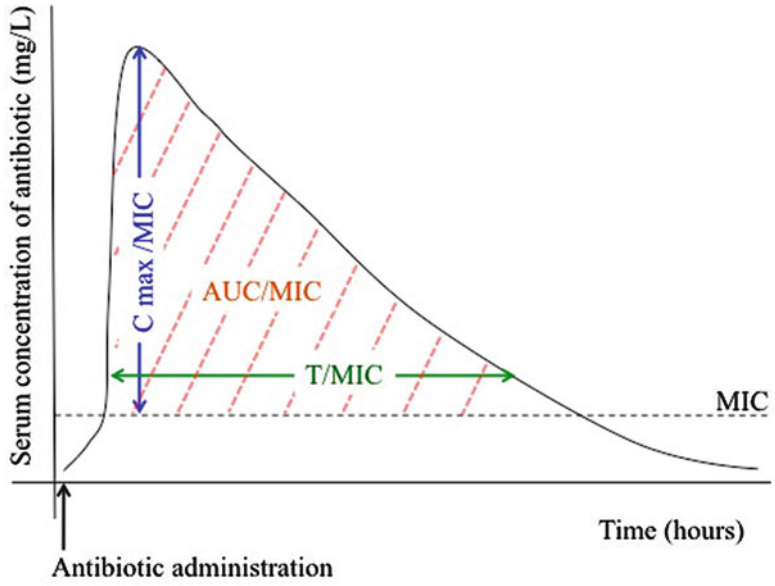

Fig. 9.2 Description of pharmakodynamic parameters predicting the antibiotic efficacy. *Cmax* peak serum antibiotic concentration, *MIC* minimum inhibitory concentration, *AUC* area under the concentration curve

betalactams and the goal of a dosing regimen is to maintain serum levels over the MIC for the entire period between two doses (T > MIC).

3. *Global exposure-dependent antibiotics*. These antibiotics are time-dependent with prolonged post-antibiotic effects preventing regrowth during the interval the serum concentration is below the MIC or concentration-dependent antibiotics with prolonged half-life. The goal of a dosing regimen is to optimize the amount of drug to ensure that killing occurs and the best parameter describing the global exposure is the area under the concentration curve for 24 h/MIC (AUC/MIC). This pattern is observed in the majority of antibiotics not included in the previous two groups: macrolides, clindamycin, metronidazol, glycopeptides, oxazolidinones, fluoroquinolones, daptomycin, or tetracyclines.

Significance of Antimicrobial Concentrations in Bone, Synovial Fluid, and Abscess

The majority of bacterial infections occur in the interstitial fluid of tissues (bone) or in other body fluids (synovial fluid); therefore, penetration into the extravascular space is highly important for antimicrobial therapy. Systemically administered antibiotics enter vascular circulation and diffuse (soft-tissue, skeletal muscle, bone, synovial fluid) or are secrete (urine, bile) into different human body sites. The concentrations achieved in these sites is the result of serum drug concentration, protein binding, half-life, lipid solubility, ionization, active transport, extravascular site geometric (big or small joints), and degree of inflammation. The extravascular sites of antibiotic distribution may be divided in four major categories that are described in Table 9.1.

Table 9.1 Categories of extravascular sites that have been evaluated for antibiotic distribution

Site description	Examples
Whole-body tissues	Skeletal muscle, skin, bone
Fluid-filled spaces of relatively large volume into which drug passively diffuses	Synovial fluid, abscesses, bursae, blisters
Fluid produced by the excretion or secretion of glands or organs	Urine, bile, sputum, saliva, sweat
Fluid-filled spaces with probable diffusion barriers or active excretory systems	Cerebrospinal fluid, vitreous humor

Over the last decades, several studies have been published on antibiotic penetration into bone [7]. Bone is a less vascularized tissue than, for example, the lungs or skin and it has a particular composition making difficult to predict whether agents showing good penetration into other tissues will also achieve high concentrations in bone. Bone tissue consists of an organic fraction (30–35 % of total bone mass, collagen fibrils, and extracellular fluid) and an inorganic fraction (65–70 %, hydroxyapatite crystals). In acute hematogenous osteomyelitis the microorganisn seed in the interstitial fluid (organic fraction) while in contiguous infections (diabetic foot or surgical infection) the microorganism colonize the inorganic and organic matrix. Since antibiotic concentration achieve in extracellular fluid is similar to that in serum [8], acute hematogenous osteomyelitis, without sequestrum or abscess, can be treated successfully with systemic antibiotics [9]. In contrast, inorganic matrix is poorly vascularized, antibiotic concentration is low and, therefore, contiguous infections frequently need surgical intervention to cure. According to this data, it would be desirable to identify the antibiotic concentration in the different bone compartments, however, techniques to separate a bone sample into, for example, extracellular fluid, collagen fibrils, bone cells, and hydroxyapatite are not available and virtually all published studies measure the total drug concentration in a bone homogenate (mix of organic and inorganic compartments). During the last years, the authors have made an effort to analyze separately cancellous bone, the inner part of the long bones that contains a higher proportion of extravascular fluid and a lower percentage of inorganic matter and cortical bone with a higher percentage of inorganic matter [7], and new techniques like microdialysis have been developed to measure the unbound (free) drug in the interstitial fluid of tissues. The majority of the articles describe the bone penetration as the ratio between bone and serum concentration, a review of the most relevant data available is provided in each antibiotic description.

Synovial fluid is produced by synovial membrane; this membrane is composed of vascularized connective tissue surrounded by a cuboidal

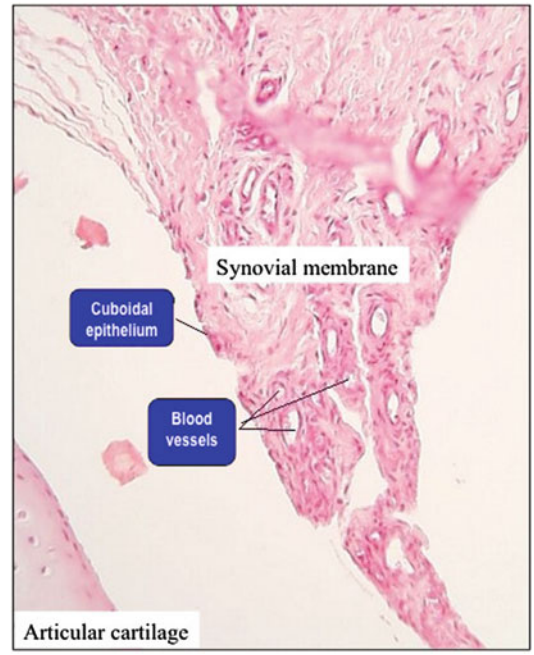

Fig. 9.3 A detail of the synovial fluid structure

epithelium that lacks a basement membrane (Fig. 9.3). Therefore, there are no barriers for antibiotic diffusion to synovial fluid as it is described in Table 9.2. However, the majority of these data were performed in subjects who underwent a joint surgery and not in patients with septic arthritis. In septic arthritis the volume of joint space is significantly higher than in non-septic arthritis. The ratio between interchangeable surface (synovial membrane) and volume of joint space determines the time needed to achieve the equilibrium between serum and synovial fluid (see below the details for antibiotic diffusion to abscess). It explains the need for immediate synovial fluid drainage in case of septic arthritis.

Abscess formation starts with the attraction of polymorphonuclear leukocytes that degrades infected tissue generating liquefaction necroses. Granulation tissue subsequently develops at the abscess border that is finally replaced by a fibrous capsule (Fig. 9.4). Animal model data suggested that the encapsulation phase occurs 10–14 days following infection. Permeability to antibiotics of the abscess wall varies depending on the stage of encapsulation. Three main factors determining

Table 9.2 Concentration of different antibiotics in synovial fluid

Antibiotic	Number of patients	Time from infusion (h)	Concentration in synovial fluid (μg/mL)	Ratio synovial fluid/ serum concentration
Gentamycin	6	1–3.5	3.2	80
Cefotaxime	22	2	29	116
Cloxacillin	29	0.75	105	87
Vancomycin	6	1–1.65	5.7	81
Linezolid	10	1.5	20.1	87

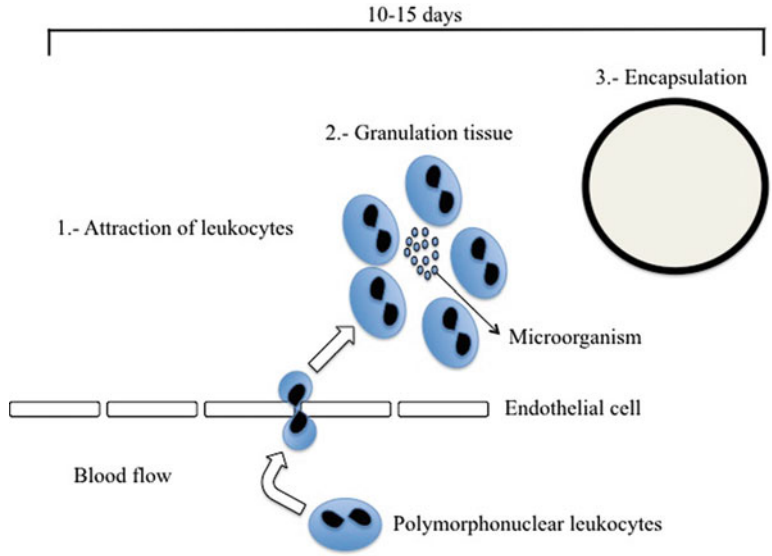

Fig. 9.4 Phases of abscess formation

the antibiotic concentration into abscess and the time needed to achieve the equilibrium between plasma and abscess are:

1. The permeability of the capsule that decreases in the course of abscess formation. Permeation is defined as the passive migration of a solute through a solid membrane and it is higher for low molecular weight, high lipid solubility, and non-dissociated antibiotics. This parameter is very difficult to evaluate in human beings and probably is the main reason to explain the variability reported by different authors.
2. The ratio between surface (A) and the total volume (V) of abscess. Equilibrium between plasma and abscess concentration is delayed in abscess with a low A/V ratio, as a drug enters and leaves more slowly.
3. Gradient of concentration between plasma and abscess. Higher free serum (unbound to proteins) antibiotic concentrations are necessary to obtain high antibiotic concentrations into abscesses.

Information about antibiotic diffusion to abscesses in human beings is scarce and some of the most relevant information is shown in Table 9.3. In addition, other factors like low oxygen availability, low pH of abscess fluid, and high bacterial inoculum determine a significant reduction in the efficacy of antibiotics against bacteria in abscesses. According to clinical data, success treating abscess without surgical drainage is strongly associated with an abscess size <5 cm and prolonged (>4 weeks) duration of antibiotics [10].

Table 9.3 Antibiotic levels measured in human abscess fluid

Antibiotic	Dose and interval	Doses until drainage	Plasma concentration (μg/mL)	Abscess concentration (μg/mL)
Cefotaxime	3 g/8 h i.v.	1–7	Conc. after 6 h of the last dose = 2 ± 1	Conc. after 6 h of the last dose = 2.1 ± 1.6
Amoxicillin	500 mg p.o.	1	Conc. after 1.5 h = 5.92 ± 2	Conc. after 1.5 h = 0.9 ± 0.3
Fosfomycin	8 g i.v.	1	Conc. max. (0.8 h) = 446 ± 128	Conc. max. (10.5 h) = 64.2 ± 66.9

Classification of Antibiotics and Principal Mechanisms of Resistance

For the present chapter, antibiotics are grouped according to the main mechanism of action:

1. Cell wall active antibiotics: betalactams and glycopeptides.
2. Antibiotics causing cytoplasmic membrane disruption: daptomycin.
3. Inhibitors of protein and RNA-synthesis machinery: aminoglycosides, clindamycin, tetracyclines, rifampin, and linezolid.
4. Inhibitors of folic acid synthesis: cotrimoxazole.
5. Inhibitors of the specific enzymes involved in DNA synthesis and supercoiling: fluoroquinolones.

Bacteria have developed mechanisms to circumvent the action of antibiotics. These mechanisms could be grouped in: (1) Antibiotic modification by breaking down the molecule using enzymes. For instance, betalactamases hydrolyze the betalactam ring of penicilins and are responsible of high penicillin-resistant in *S. aureus* (>90 %). (2) Modification of the target site preventing the binding of the antibiotic. An example is the acquisition of a protein binding penicillin (PBP) with a mutation in the betalactam binding site that makes *S. aureus* resistant to all betalactams including those resistant to the action of betalactamases like methicillin (MRSA). (3) Prevention of access to the target by inhibiting uptake. This mechanism is important for Gram-negatives since these bacteria have an outer membrane that has porins, which permit only the entry of small (≤700 Da) hydrophilic antibiotics. By loosening these pores, bacteria become resistant to those antibiotics that use this channel. (4) Prevention of access to the target site by increasing export of the drug using efflux pumps. These pumps have been described in Gram-positive and Gram-negative bacteria and are responsible for resistance to fluoroquinolones or tetracyclines.

Cell Wall Active Antibiotics

Betalactams

Betalactams block the transpetidase activity of PBP. These antibiotics are bactericidal and time-dependent. The maximum effect is obtained when free serum concentrations are fourfold the MIC for at least 40 % for carbapenems, 50 % for penicillins, and 60 % for cephalosporins of the interval between two consecutive doses (T>MIC). However, in severe infections the clinical evidence suggests that the maximum effect is achieved when the serum concentration of the betalactam is 100 % over the MIC. The antimicrobial spectrum of the main groups of betalactams including penicillins, cephalosporins, and carbapenems is shown in Table 9.4. The most active drugs against betalactam susceptible *S. aureus* are the penicillins resistant to the penicillase (methicillin, oxacillin, or flucloxacillin) followed by cefazolin that is widely used for treatment and prophylaxis. However, *S. aureus* produces four different types of penicillases (A, B, C, and D) and those producing type A are less susceptible to cefazolin. This fact has been associated with prophylaxis [11] and treatment [12] failure most especially in acute infections with high bacterial inoculum and when it is not planned to remove the implant. The recommended

Table 9.4 Description of antimicrobial spectrum of betalactams

Group	Antibiotic/s	Route	Predominant activity
Penicillins			
Naturals	Penicillin G	im-iv	GP
	Penicillin V	Oral	
Resistant to penicillase	Methicillin	im-iv	*S. aureus*
	Oxacillin	im-iv	
	(Flu) Cloxacillin	im-iv-oral	
Aminopenicillins	Ampicillin	im-iv-oral	GP, *Enterococcus faecalis*
	Amoxicillin	Oral	
	Combinations with clavulanic acid or sulbactam	im-iv-oral	GP, *E. faecalis*, GN, anaerobes
Carboxi and ureidopenicillins	Piperacillin-tazobactam	im-iv	GN, *Pseudomonas aeruginosa*, *E. faecalis*, anaerobes
Cephalosporins			
First generation	Cefazolin	im-iv	GP
	Cefalexin	Oral	GP
Second generation	(Axetil-) Cefuroxim	im-iv-oral	GP, GN
	Cefonicid[a]	im-iv	GP, GN
	Cefoxitin	im-iv	GP, GN, anaerobes
Third and fourth generation	Ceftriaxone[a]	im-iv	GN
	Ceftazidime	im-iv	GN, *P. aeruginosa*
	Cefepime	im-iv	GN, *P. aeruginosa*
Fifth generation	Ceftaroline[b]	iv	GN, GP, active against MRSA
Carbapenems			
Activity against *Pseudomonas aeruginosa*	Imipenem	iv	GP, GN, *P. aeruginosa*, ESBL-E, anaerobes
	Meropenem[c]	iv	
	Doripenem[c]	iv	
Without activity against *P. aeruginosa*	Ertapenem	iv	Idem, without activity for *P. aeruginosa*

GP Gram-positive (excluding methicillin-resistant staphylococci and *Enterococcus* spp.). *GN* Gram-negative (excluding *Pseudomonas* spp. and ESBL-E), *ESBL-E Enterobacteriaceae* (*Escherichia*, *Klebsiella*) producing extended spectrum betalactamases, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a]Antibiotics with long half-life

[b]The first betalactam with activity against MRSA

[c]Meropenem and Doripenem are more active than Imipenem for *P. aeruginosa*

dosages and way of administration for a selection of betalactams is shown in Table 9.5. The majority of betalactams has a short half-life and should be administered several times per day or in continuous infusion [13, 14] to achieve the pharmacodynamic index (T>MIC). The majority of studies of betalactams and betalactamase inhibitors (clavulanic acid, tazobactam, sulbactam) have reported a bone concentration of 10–30 % of the serum concentration and the rate of equilibration between bone and serum is relatively fast but penetration into cortical bone is low [7].

The activity of betalactams against Gram-positive or Gram-negative biofilms is limited. The activity of penicillins (penicillin and oxacillin), cephalosporins (cefazolin), and carbapenems (imipenem) against planktonic and biofilm of *S. aureus* and *P. aeruginosa* have been studied in the laboratory [15, 16]. The concentration needed to eradicate biofilms was in general more than 100-fold higher than the concentration needed for planktonic populations. The efficacy against SCV is limited most especially against intracellular cells [17]. Probably the lack of efficacy of betalactams is due to the low metabolic activity of bacteria in biofilms and SCV. These data suggest that betalactams are good drugs for acute infection due to susceptible Gram-positives

Table 9.5 Dose, route, and way of administration of the main betalactams

Antibiotic	Dose	Frequency	Route	Main coverage
(Flu) Cloxacillin	2 g	4 h	iv	MSSA
	LD: 0.5–1 g (10–30 min) +			
	CI 8–12 g	In 24 h	iv	
Cefazolin	1–2 g	8 h	iv	MSSA
	LD: 0.5–1 g (10–30 min) +			
	CI: 60–80 mg/kg	In 24 h	iv	
Ampicillin	2 g	4 h	iv	*E. faecalis*
Amoxicillin-clavulanate	875/125 mg	8 h	Oral	MSSA, GN, anaerobes
	1–2 g	8–6 h	iv	
Piperacillin-tazobactam	3/0.375 g	6 h	iv	*P. aeruginosa*
Ceftriaxone	1–2 g	24 h	iv	GN
Ceftazidime	2 g	8 h	iv	*P. aeruginosa*
	LD: 0.5–1 g (10–30 min) +			
	CI 6 g	In 24 h	iv	
Meropenem	1–2 g (first 500 mg in 10–30 min) infuse in 2–3 h (preferable)	8 h	iv	*P. aeruginosa* ESBL-E
Ertapenem	1 g	24 h	iv	ESBL-E

LD loading dose, *CI* continuous infusion, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *GN* Gram-negatives (excluding *Pseudomonas* spp. and ESBL-E), *ESBL-E* extended spectrum betalactamase *Enteroacteriaceae* (*E. coli*, *K. pneumoniae*,…)

or Gram-negatives where the rapidly growing bacteria is the dominant bacterial population but their efficacy is limited for eradicating biofilms and, therefore, other alternatives for long-term therapy would be preferable.

The most relevant adverse events are immediate allergic reactions mediated by IgE (angioneurotic edema, broncospasm, hypotension, urticaria) documented only in 0.01 % of the patients receiving penicillin derivatives. Late allergic reactions mediated by IgG are more frequent and characterized by skin rash. Ten percent of patients with penicillin allergy are also allergic to cephalosporins, therefore, are not recommended at least for those patients with antecedents of immediate reactions. Gastrointestinal alterations associated with oral betalactams like nausea, vomiting, and nonspecific diarrhea or *Clostridium difficile*-associated diarrhea. In patients receiving more than 10 days of treatment at dosages higher than 150 mg/kg/day neutropenia is a potential hematological adverse event. Betalactams, especially imipenem or cefepime at high dosages and in patients with renal failure, are associated with risk of convulsion.

Glycopeptides: Vancomycin

Vancomycin binds to D-Alanin-D-Alanine terminal residues of the monomeric component of peptidoglycan inhibiting the cell wall synthesis. Vancomycin is a time-dependent antibiotic with a slower bactericidal activity. This could explain clinical data showing that patients with osteomyelitis due to methicillin-susceptible *Staphylococcus aureus* (MSSA) treated with vancomycin had a worse outcome than those treated with betalactams [18], therefore, when vancomycin is selected as a first-line therapy but MSSA is finally the etiology of the infection, it would be better to switch therapy to a betalactam. From animal models and clinical experience in respiratory tract infections and bacteremia due to MRSA [19, 20], we have learnt that the best predictor of vancomycin efficacy is the AUC/MIC and the outcome is significantly better when this ratio is ≥400. Recent consensus recommends a trough vancomycin serum concentration ≥15 mg/L [21]. The dosage required for obtaining this target when the MIC of vancomycin is ≤1 mg/L is shown in Table 9.6. Clinical experience using vancomycin in patients

Table 9.6 Dose, route, way of administration and main coverage of different antibiotics

Antibiotic	Dose and frequency	Route	Main coverage
Vancomycin	15–20 mg/kg/12 h[a]	iv	MRSA MRCNS *E. faecium*
Daptomycin	6–10 mg/kg/24 h[a, b]	iv	MRSA MRCNS *E. faecium*
Aminoglycosides			
Gentamycin	5–7 mg/kg/24–12 h[a]	iv, im	GP, GN
Amikacin	15–20 mg/kg/24–12 h[a]	iv, im	GP, GN, *P. aeruginosa*
Clindamycin	300 mg/8 h 600 mg/8–6 h CI: 30–40 mg/kg in 24 h	Oral iv iv	GP, anaerobes
Tetracyclines[c]			
Doxicycline	200 mg (1 dose) 100 mg/12 h	iv, oral	GP, GN, anaerobes
Minocycline	200 mg (1 dose) 100 mg/12 h	iv, oral	GP, MRSA, GN, anaerobes
Tigecycline	100 mg (1 dose) 50 mg/12 h	iv	GP, MRSA, *Enterococcus* spp., GN, anaerobes
Rifampin	450–900 mg/24–12 h	iv, oral	GP, MRSA
Linezolid	600 mg/12 h	iv, oral	GP, MRSA, *Enterococcus* spp.
Cotrimoxazole (sulfamethoxazole/trimethoprim)	160/800 mg/12–8 h	iv, oral	MRSA
Fluoroquinolones			
Ciprofloxacin	400 mg/12–8 h 750 mg/12 h	iv, oral	GN, *P. aeruginosa*, GP
Levofloxacin	500 mg/24–12 h	iv, oral	GN, *P. aeruginosa*, GP
Moxifloxacin	400 mg/24 h	iv, oral	GN, GP, anaerobes

MRSA methicillin-resistant *S. aureus*, *MRCNS* methicillin-resistant coagulase-negative staphylococci, *GN* Gram-negatives (excluding *Pseudomonas* spp.), *GP* Gram-positives (excluding methicillin-resistant staphylococci and *Enterococcus* spp.), *CI* continuous infusion

[a]According to total body weight

[b]Doses higher than 6 mg/kg are recommended for severe infections and when the implant is not removed. In morbid obese patients do not give doses higher than 8 mg/Kg

[c]Minocycline and tigecycline are more active against *S. aureus* than doxicycline

with bacteremia due to staphylococci with a vancomycin MIC > 1 mg/L showed a higher failure and mortality rate [22]. Although there is no clinical experience in bone and joint infections, it is prudent to select an alternative anti-staphylococcal agent when vancomycin MIC > 1 mg/L.

In hip replacement patients, mean concentration of 7 % of the serum concentration has been reported in cortical bone and 13 % in cancellous bone, and only three of six bone samples from osteomyelitis patients had concentrations above the lower limit of detection [23]. The activity of vancomycin against biofilms, extra- and intracellular SCV in vitro as well as in animal models is very limited [15, 17]; however, biofilm activity improves when combining with rifampin or tetracyclines [24].

The most important adverse events are phlebitis (10 %), red-man syndrome during rapid intravenous infusion characterized by itching, skin rash, and nephrotoxicity. Red-man syndrome is avoided by slow infusion (1 h). Nephrotoxicity is associated with a trough serum concentration >15 mg/L, duration longer than 7 days or

concomitant nephrotoxic drugs (diuretics, aminoglycosides, anfotericin B) and in these situations is higher than 20 %.

Antibiotics Causing Cytoplasmic Membrane Disruption: Daptomycin

Daptomycin is a lipopeptide with a potent concentration-dependent bactericidal activity against Gram-positive cocci. The large hydrophobic cluster of the lipopeptide interacts with the acyl chain region of the bacterial membrane. Once inserted into the membrane, molecules of daptomycin form pores that disrupt the functional integrity of the cytoplasmic membrane allowing the release of intracellular ions and rapid cell death [25]. The pharmacodynamic index that predicts the efficacy of daptomycin is the AUC/MIC and the target value is ≥600. Although accepted doses (4–6 mg/kg/24 h intravenously) achieve high AUCs, clinical experience in patients with osteomyelitis or prosthetic joint infections demonstrated that low doses (4 mg/kg/24 h) were associated with significantly worse outcomes than higher doses [26, 27]. A recent open, randomized clinical trial in patients with a prosthetic joint infection due to staphylococci who underwent a 2-stage exchange were randomized to receive daptomycin 6 or 8 mg/kg or the comparator (vancomycin in the majority of the cases) for 6 weeks [28]. The clinical success rate was similar in the three groups, 88 %, 91 %, and 91 %, respectively. Considering also adverse events and microbiological failure, the success rates were 58 %, 61 %, and 38 %, respectively. These results suggest that for bone infections doses higher than 6 mg/kg are necessary (Table 9.6), probably because this antibiotic is highly protein bounded (92 %) and it has a large molecular weight. In poor vascularized areas where the interchangeable surface is small compared with the volume of infected tissue (i.e., devitalized tissue surrounding prosthesis, undrained abscesses) the promptness to achieve the desired tissue concentration of any drug depends on the speed of molecular diffusion. The speed of molecular diffusion depends, in turn, on the concentration gradient of free drug between capillaries and the center of the lesion and the physical and chemical properties of the molecule. Obtaining a high drug-free concentration gradient (high dose) allows to rapidly achieve, in the infectious foci, a concentration higher than the MIC. In addition, animal models have shown that results are better when combining daptomycin with rifampin [29, 30].

Daptomycin cancellous bone concentrations were measured in eight diabetic patients using microdialysis [31]. Results showed that free plasma daptomycin concentration is equal to free bone concentration. According to in vitro data, daptomycin is one of the most potent antibiotics against biofilms [32], probably because the bactericidal activity of daptomycin is less affected by cell division or active metabolism [33]. Daptomycin is bactericidal against extracellular SCV at fourfold daptomycin MIC [34] but the activity against intracellular SCV is significantly reduce and only partially recovered when combining with rifampin and gentamycin [35].

The most important adverse event is a toxic myopathy that in general appears after 2 weeks of therapy and at high doses. According to different studies, using a mean dose of 8 mg/kg, 10 % of patients develop an increase of creatine phosphokinase (CPK) and 4–5 % symptoms of myopathy. It is recommended to stop daptomycin when there are clinical symptoms of myopathy or CPK levels ≥5 times the normal values.

Inhibitors of Protein and RNA-Synthesis Machinery

Aminoglycosides

Aminoglycosides bind to prokaryote ribosomes resulting in a measurable decrease in protein synthesis. The majority of antibiotics with a similar mechanism of action (tetracyclines, clindamycin, linezolid) are bacteriostatic; however, aminoglycosides are rapid bactericidal and concentration-dependent antibiotics. This suggests additional unidentified mechanisms of bactericidal activity.

Aminoglycosides are transported across the cytoplasmic membrane by an energy-dependent mechanism that is inhibited in low pH and anaerobic conditions that explain the reduced activity of these antibiotics against anaerobes and bacteria in abscesses. The spectrum of aminoglycosides includes aerobic and facultative Gram-negative bacilli (*Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter* spp.) and Gram-positives. MSSA remain susceptible but MRSA are frequently resistant. Streptococci and enterococci are resistant to aminoglycosides. In general, these antibiotics show synergy when combined with cell wall-active antibiotics (betalactams and vancomycin). Although the half-life of aminoglycosides is short, the rate of bacterial killing increases as the antibiotic concentration is increased (Cmax/MIC) and they have a prolonged post-antibiotic effect, therefore, the optimal regimen is a high dose once or twice daily (Table 9.6). The information about bone penetration of aminoglycosides is scarce. The activity against biofilms is limited since they are cationic molecules and extracellular matrix of biofilms contains anionic polysaccharides that probably do not allow aminoglycoside diffusion [32]. SCV are highly resistant to these antibiotics because the energy-dependent transport is blocked in SCV and aminoglycoside is not internalized [36]. In addition, a retrospective study of 50 episodes of enterococcal prosthetic joint infections analyzed the outcome among those receiving monotherapy (cell wall-active antibiotic) versus combination therapy with an aminoglycoside [37]. Groups did not differ with respect to outcome but nephrotoxicity and ototoxicity was higher in the aminoglycoside group. According to this information, the use of aminoglycosides is restricted to acute phase of severe infections in combination with cell wall-active antibiotics, for no longer than 3–5 days and for the treatment of multidrug-resistant Gram-negatives like *P. aeruginosa*.

The reported incidence of nephrotoxicity varies from 5 to 25 % range but concomitant use of other nephrotoxic drugs (diuretics, vancomycin), preexisting renal diseases, and >3 days of treatment have been significantly associated with a higher risk. It is recommended to measure peak and through serum levels to guarantee their efficacy and avoid toxicity. Other serious adverse events are ototoxicity and neuromuscular blockade.

Clindamycin

Clindamycin binds to 50S ribosomal subunit and blocks the protein synthesis in early chain elongation by interference with the transpeptidation reaction. The activity includes Gram-positives and anaerobes. It is important to mention that some Gram-positives (staphylococci) have inducible resistance to clindamycin. This mechanism of resistance is not captured by the standard MIC but there are reports showing clinical failure to clindamycin in patients with infections due to staphylococci with inducible resistance [38]. This mechanism of resistance should be suspected when a clindamycin-susceptible strain is resistant to erythromycin. In these cases, before giving clindamycin, it is necessary to apply for an additional test to rule out inducible resistance. Clindamycin is a time-dependent and bacteriostatic antibiotic and the recommended doses are shown in Table 9.6. Like other protein synthesis inhibitors, clindamycin rapidly reduces the synthesis of virulence factors that are critical in the pathogenesis of infection [5]. Studies of clindamycin bone penetration in humans were conducted in 1970s and the range of bone:serum ratio was 0.20–0.45, therefore, slightly higher than betalactams. Indeed, animal models of osteomyelitis showed that clindamycin was superior to cefazolin in the eradication of *S. aureus* from infected bone [39]. Combined with rifampin, clindamycin has shown a high success rate in short series of orthopedic implant infections [40]. Zeller et al. [41] described that patients treated concomitantly with rifampicin compared to patients with clindamycin monotherapy had a 40 % decrease in clindamycin serum concentration; however, they did not find differences in the clinical outcome.

The most important adverse events are gastrointestinal disturbances including diarrhea, nausea, vomiting, and abdominal pain that have been

reported in 10 % of the cases. Diarrhea associated with *Clostridium difficile* is a severe complication reported in <5 % of cases.

Tetracyclines

Tetracyclines inhibit bacterial protein synthesis by binding the 30S ribosomal subunit and are broad-spectrum, bacteriostatic, and time-dependent (T>MIC) antibiotics active against Gram-positive and Gram-negative bacteria. Since the 1970s the identification of an increasing number of tetracycline-resistant pathogens has limited their usefulness in clinical practice. Recently, a new generation of tetracyclines (tigecycline) that retains the broad spectrum of activity has been developed. The dosage of the main tetracyclines is shown in Table 9.6.

Modern analytical techniques for measuring bone concentrations of tigecycline have demonstrated a high bone penetration [7]. In vitro studies have shown that tetracyclins are active antibiotics against staphylococcal biofilms [42], most especially in combination with other antibiotic including rifampin, clindamycin, or vancomycin [24] and against intracellular SCV [17]. An animal model of chronic foreign-body infection due to MRSA demonstrated similar results for tigecyclin and vancomycin and both were significantly better than control [43]. Clinical experience in prosthetic joint infections is limited to the use of minocycline as suppressive therapy for a prolong period [44]. Tolerance was excellent and no relapse was observed in 50 % of cases at the last follow-up.

Gastrointestinal symptoms (nausea, vomiting) are common after oral administration of tetracyclines. The administration of food with doxycycline or minocycline may ameliorate some of these symptoms. A gray-brown to yellow discoloration of the teeth has been noted in children taking tetracyclines. The administration of less than 2 g/day IV is not associated with liver dysfunction or injury except in pregnant women. The tetracyclines aggravate preexisting renal failure. Hypersensitivity reactions, including anaphylaxis, urticaria, periorbital edema, fixed drug eruptions, and morbilliform rashes, and photosensitivity reactions are not common. Vertigo, a side effect unique to minocycline that usually begins on the second or third day of therapy, has been noted more frequently in women. The symptoms are reversible within several days after discontinuation of therapy, but this side effect has seriously limited the use of minocycline. Benign intracranial hypertension (pseudotumor cerebri) has been described in general associated with the medium- or long-term use of minocycline.

Rifampin

Rifampin exerts their antimicrobial activity by inhibiting the β-subunit of DNA-dependent RNA polymerase, which is highly conserved among prokaryotic organisms. Rifampin is a bactericidal and concentration-dependent (Cmax/MIC) antibiotic with potent activity against Gram-positives and mycobacteria. Rifampin maintains activity against bacteria in stationary phase [45], intracellular SCV, [17] and bacteria in biofilms [32]. The recommended doses are shown in Table 9.6; however, it is important to note that rifampin should never be administered in monotherapy since the selection of resistant mutants is common. Rifampin at 450 mg/12 h combined with ciprofloxacin was more effective than ciprofloxacin alone (curing percentages of 100 and 53 %) in orthopedic implant infections treated without removing the implant [46]. Since rifampin is a concentration-dependent antibiotic (Cmax/MIC) once daily administration (600–900 mg/24 h) is easier and also allows a higher Cmax/MIC than the 450 mg/12 h dosage. In addition, taking into account the long duplicative rate of biofilm bacteria, the administration of rifampin once a day could be sufficient. Bone serum concentration ratios of about 0.2–0.5 have been reported for rifampicin [7]. Many observational studies have demonstrated the efficacy of rifampin combinations (fluoroquinolones, linezolid, cotrimoxazole, tetracyclines) in prosthetic joint infections [47, 48]. Rifampin reduces the serum concentration of other antibiotics (linezolid, cotrimoxazole, or clindamycin), anticoagulants (acenocumarol), or

antiepileptic drugs (phenytoin); therefore, close clinical control is mandatory.

Gastrointestinal symptoms, such as abdominal pain or cramping, nausea, vomiting, and diarrhea, are relatively common. Elevations of serum hepatic transaminase levels can occur during therapy but the incidence is relatively low (1 %), being higher among individuals with chronic liver disease, alcohol abuse, or co-administration of other potentially hepatotoxic medications. Skin rash and other skin reactions are common reasons for discontinuation; however, antihistamines or desensitization therapy has allowed continuation of rifampin therapy in some patients. Mild thrombocytopenia, leukopenia, and granulocytopenia are relatively common during rifampin therapy. Acute renal failure has been described with highly intermittent dosing regimens or on reinstitution of rifampin after a drug-free interval.

Linezolid

Linezolid inhibits the protein synthesis by binding to the 50S ribosome at its interface with the 30S unit, thereby preventing the formation of the 70S initiation complex. Linezolid is a bacteriostatic and time-dependent (T>MIC) antibiotic with activity against the majority of clinically important Gram-positive organisms, including *S. aureus* (methicillin-susceptible and methicillin-resistant strains), coagulase-negative staphylococci, *E. faecium*, and *E. faecalis* (vancomycin-susceptible and vancomycin-resistant strains). The recommended doses are shown in Table 9.6. The reported mean bone:plasma concentration ratios were between 0.2 and 0.5 for linezolid [7]. Its oral formulation and activity against methicillin-resistant staphylococci makes this antibiotic an attractive alternative to intravenous glycopeptides. A review of the literature shows a high success rate with linezolid (85–90 %) in orthopedic implant infections when implant was removed [49–55]. The success rate when the implant was not removed varied from 72 % in acute to 43 % in chronic infections [53, 56].

The most important adverse events are nausea, vomiting, and diarrhea. Thrombocytopenia and anemia are frequent when treatment is longer than 2 weeks; however, these adverse events are less frequent when combined with rifampin. The reason for this fact is that rifampin reduces serum linezolid concentration. Peripheral neuropathy has been described in patients receiving linezolid courses longer than 3 months. Lactic acidosis is an uncommon adverse event. Linezolid produces a weak inhibition of monoaminoxidase and potentiates the action of serotoninergic drugs.

Inhibitors of Folic Acid Synthesis: Cotrimoxazole

Cotrimoxazole is the combination of sulfamethoxazole and trimethoprim. Each one inhibits a different enzyme in the bacterial process of thymidin biosynthesis. Cotrimoxazole proved to be bactericidal and more than 90 % of *S. aureus* (including MRSA) are susceptible and it is also active against Gram-negatives different from *P. aeruginosa*. It has a high oral bioavailability that makes this drug an attractive option for the treatment of prosthetic joint infections according to the doses shown in Table 9.6. However, it has been documented that pus inhibited sulfonamides. A major component of pus is polymerized DNA, released from inflammatory cells and injured tissues. *S. aureus* is able to obtain thymidine from DNA and this thymidine antagonizes the antistaphylococcal effects of both trimethoprim and sulfamethoxazole. Therefore, it is recommended to start cotrimoxazole after debridement of all necrotic tissue and pus and preferentially in combination [57, 58]. Information about activity of cotrimoxazole against biofilms is scarce, but several in vitro data showed that SCV are resistant to cotrimoxazole. The most important adverse events associated with sulfonamides are allergic reactions with skin rash, fever, serum sickness-like syndrome, or hepatic necrosis. Interstitial nephritis and tubular necrosis are rare events. More serious adverse reactions caused by sulfonamides may include acute hemolytic anemia

sometimes related to a deficiency in erythrocyte glucose-6-phosphate dehydrogenase (G6PD), aplastic anemia, agranulocytosis, thrombocytopenia, and leukopenia. It is recommended to avoid the combination with oral anticoagulants. In general, it is a well-tolerated drug and it has been used in chronic prosthetic joint infections as a suppressive therapy.

Inhibitors of the Specific Enzymes Involved in DNA Synthesis and Supercoiling: Fluoroquinolones

Fluoroquinolones inhibit bacterial DNA-gyrase (topoisomerase II) and topoisomerase IV. These antibiotics have a potent concentration-dependent bactericidal activity against Gram-negatives and Gram-positives. The pharmacodynamic index that predicts their efficacy is the AUC/MIC and the optimal value is ≥125; however, according to in vitro data a ratio of 250 is necessary to avoid the selection of resistant mutants. This target is achieved using the higher doses recommended in Table 9.6. The higher doses are especially recommended during the first 5–7 days of treatment and for treating infections due to *Pseudomonas aeruginosa*. The most active fluoroquinolones against Gram-negatives including *P. aeruginosa* are ciprofloxacin and levofloxacin. The experience in orthopedic implant infections due to Gram-negatives is scarce but in general is considered that the outcome is poor. However, recent experience suggests that when fluoroquinolones (ciprofloxacin or levofloxacin) are included in the antibiotic regimen (combined with a betalactam for the first 14 days) the success rate is higher [59]. Fluoroquinolones are probably efficacious for the treatment of implant infections and osteomyelitis due to Gram-negatives for two reasons: (1) their diffusion to synovial fluid and bone [60] and (2) their activity against biofilms. In an in vitro model of a *Pseudomonas* biofilm, Tanaka et al. [16] showed that the bactericidal action of betalactams against biofilm cells was affected by the low rate of cell growth inside the biofilm, while that of fluoroquinolones was considerably greater and independent of the growth rate. Unfortunately, the resistance rate to fluoroquinolones among *Enterobacteriaceae* family is increasing; therefore, it is necessary to further investigate new options for treating these infections.

Although ciprofloxacin associated with rifampin demonstrated a high success rate in a randomized trial in staphylococcal prosthetic joint infections, nowadays levofloxacin is superior to ciprofloxacin due to levofloxacin's better therapeutic index as a consequence of a lower MIC against *S. aureus* and a high serum concentration (higher bioavailability). Furthermore, its once-a-day administration facilitates the adherence to long-term treatment. The experience from our group shows that prolonged oral regimen with levofloxacin plus rifampin is well tolerated and has good results in prosthetic joint infections due to Grampositive cocci [61]. Moxifloxacin is more active than levofloxacin against staphylococci and it has moderate activity against intracellular SCV [62]; however, rifampin induces moxifloxacin metabolism reducing serum levels by approximately 30 % [63], therefore, moxifloxacin could be the best fluoroquinolone for staphylococci when rifampin cannot be administered.

The most important adverse events are gastrointestinal discomfort and diarrhea associated with *Clostridium difficile* in 1–5 % of cases. Headache, vertigo, dizziness, or convulsion (more frequent in patients with epilepsy or cranial trauma) has been described in less than 2 %. Tachycardia or other arrhythmia especially in patients with hypokalemia, hypocalcemia, and hypomagnesemia. Arthralgia and Achilles tendinitis in less than 1 % of cases.

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PMMA and Antimicrobial Delivery

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Biology of Biofilms

Common to all the organisms that cause prosthetic joint infection (PJI) is their ability to adhere to surfaces and form biofilm as an adaptive survival mechanism. Although the surfaces of current prosthetic implants are highly biocompatible, inciting minimal host response, protein deposition on these surfaces make them ideal surfaces for microbial attachment [1]. Following attachment, replication leads to colony formation. Exchange of soluble communicating factors in the colony, known as quorum sensing, leads to expression of the sessile phenotype. Glycoprotein and polysaccharide production, altered cell surface proteins, and a marked decrease in both metabolic activity and replication are features of sessile microbes, leading to a complex protective local environment, collectively called biofilm [2]. Sessile bacteria in biofilm no longer incite an immune response. They are not identified by host macrophages as pathogens and they no longer express the biology targeted by many antimicrobials [3]. Furthermore, they do not grow in routine culture [4]. Host defenses are ineffective and the microbes are resistant to antimicrobial levels that are hundreds of times greater than the usual minimum inhibitory concentration (MIC) for their planktonic form. The clinical implications are diagnostic and therapeutic. Successful isolation of the pathogens by conventional culture methods is only possible when planktonic phenotypes are shed from the biofilm. Culture negative infections can be a diagnostic challenge. Therapeutically, sessile microbes cannot be eradicated by parenteral antimicrobials. Surgical removal of biofilm is required. Unfortunately, intra-lesional resection that is performed for PJI leaves tissue debris in the surgical wound, including fragments of biofilm. Antimicrobial concentrations of 100× to 1,000× MIC are required to control the biofilm fragments that remain in the post-resection surgical wound [5, 6]. Local delivery is the only option that can achieve such high levels without exposing the host to unacceptable toxicity.

PMMA Physical Properties

Poly(methyl methacrylate) (PMMA) is a clear thermoplastic that forms by polymerization of liquid methyl methacrylate monomer. Orthopaedic bone cement is a two-part self-curing product in which PMMA powder is incorporated into polymerizing monomer during an exothermic reaction [7].

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Both components contain multiple additives. The powder contains 10–60 μm spheres of PMMA and copolymers, radio-opacifiers, polymerization initiators, and accelerators. Inhibitors in the monomer prevent premature polymerization. Some brands include coloring agents. Variations in the amounts of the minor components have important effects on the handling properties during polymerization. PMMA is hard, brittle, and insoluble in water (solubility coefficient 10^{-11} m^2/s). Its solubility is far less than would be necessary to permit meaningful delivery of any water-soluble drug contained within the substance of the PMMA. However, PMMA has intrinsic porosity with a few large pores that are 1 mm to 100 μm and greater (macroporosity) and many small pores that are less than 100 μm (microporosity). This intrinsic porosity is likely due to entrapment of air adjacent to particles that were not completely wetted during mixing and due to vaporization of the monomer during polymerization [8]. Although porosity in PMMA is generally considered a negative property, weakening the cement for mechanical applications [7], porosity is a positive property for drug delivery. Greater porosity increases permeability, allowing fluid penetration and release of deep drug by dissolution and diffusion. Minimizing porosity through vacuum mixing improves mechanical properties but is generally counterproductive for drug delivery. Even with its intrinsic porosity, absorption of water into PMMA is only 2–3 wt% [9]. Efforts to increase drug delivery from PMMA have focused on increasing porosity through the addition of poragens, understanding that this comes at the expense of decreasing mechanical strength.

Drug Delivery Principles

The release of drugs from local delivery vehicles is a highly studied phenomenon. Release mechanisms are well-understood phenomenon. The dominant mechanisms of drug release from antimicrobial-loaded bone cement (ALBC) are convection for fluid penetration into the cement and diffusion for transport of the antimicrobial out of the ALBC. When antimicrobial powder at the surface of the delivery vehicle dissolves in the surrounding fluid, immediate delivery termed "burst" occurs. Burst does not involve transport from within the ALBC. When fluid is absorbed into porous PMMA, drug in the pores dissolves. Diffusion delivers antimicrobial from the pores to the ALBC surface, transporting the antimicrobial down the concentration gradient, from near saturation at the dissolution site, to low concentration in the fluid adjacent to the ALBC. Drug release causes the concentration at the delivery site to increase, decreasing the concentration gradient, slowing diffusion. As fluid penetrates deeper into the ALBC, longer pore channels lead to increasing drag on fluid flow, slowing fluid penetration into the pores.

An important parameter characterizing ALBC performance is its antimicrobial release rate, measured in elution studies in which the contained antimicrobials are extracted, commonly using water as the eluent. The goal of elution studies is to quantify the maximum amount of drug that can be released at the fastest possible rate in optimized conditions. The mass of antimicrobial that is released by a specific time (M_t) is a reproducible metric used to compare release rates from different delivery vehicles. Typically the time is 30 days for ALBC. By 30 days in optimized conditions, the rate of release has generally fallen to near zero. A shorter time, as short as 24 h, can be used for vehicles that are water soluble and highly permeable such as hydrogels, collagen sponges, and calcium sulfate where the majority of available drug is released during the first 24 h in elution studies.

The rate of antimicrobial delivery from PMMA is highly dependent on the antimicrobial concentration in the surrounding fluid. Diffusion out of the ALBC into fluid with near-zero concentration is not limited by dissolved antimicrobial in the surrounding fluid. This is "infinite sink," an unlimited ability of the surrounding fluid to accept more antimicrobial. As antimicrobial is delivered to the surrounding fluid, the concentration increases, the concentration gradient decreases, and infinite sink conditions are lost. Delivery stops when the antimicrobial concentration in surrounding fluid is the same as the concentration in the pores. It is critical that infinite sink conditions are maintained in elution studies. Otherwise the amount of drug released in

the experiment would be dependent on the experimental conditions not the properties of delivery vehicle; comparison with the release from other vehicles would not be possible. By convention, drug delivery studies are done with continuous mixing of the eluent to prevent disproportionally high concentration in the fluid near the surface of the delivery vehicle. However, specifically for antibacterial elution from ALBC in water, the released antimicrobial is rapidly distributed throughout the eluent by convection, leading to negligible decrease in M_t without mixing. Diffusion is temperature-dependent, higher temperature leads to greater diffusion. By convention drug delivery experiments are done at 37 °C. By far the most important parameters controlled by the investigator in elution studies are eluent volume and eluent exchanges. Sufficient eluent volume with frequent total exchanges keeps the concentration low, maintaining infinite sink conditions. It should be understood that infinite sink is an experimental condition, not an intrinsic property of ALBC. It is highly unlikely that infinite sink occurs in a clinical delivery site. Intrinsic factors known to effect release of antimicrobials from ALBC are its porosity [10], and interaction of the antimicrobial with the PMMA [11, 12].

There are several nuances that should be considered while attempting to understand elution studies and how they apply to patient care.

1. Elution studies do not quantify antimicrobial levels in patients.
2. Release is surface area-dependent.
3. Increased porosity increases release.
4. Porosity is measured by volume fraction.
5. All poragens are not equal.
6. Antimicrobial powder is a poragen.
7. Mixing affects high-dose formulations.
8. Poragens may not produce interconnecting pores.
9. Monomer and water are immiscible.

Clinical Antimicrobial Levels

The in vivo environment in a surgical wound following a resection procedure, or at a cement-bone interface, is complex with an unknown volume of distribution and unknown fluid dynamics. Antimicrobial concentration, over location and time, is unknown. Infinite sink conditions are not present in post-resection surgical wounds. Fluid flow and diffusion of drug into surrounding tissues are unknown, likely varying considerably from location to location, even within a single delivery site. Reproducing in vivo delivery conditions during elution studies is not possible. It is important to restate that the concentration measured in eluent and the mass of released drug in elution studies do not quantify the levels achieved at local drug delivery sites clinically. The purpose of elution studies lies in determining the potential to deliver drug for comparison of one formulation to another, not to predict the levels that are actually achieved in a clinical delivery site.

Development of an in vivo model is underway to quantitatively image the actual concentrations of locally delivered antimicrobials, over location and time [13]. Intact fascial planes and bone have been seen to be barriers to diffusion. Although early results have confirmed that levels exceeding 100 μg/mL are achievable, further work is needed before imaging of antimicrobial concentrations can be performed in patients.

Surface Phenomenon

Antimicrobial release occurs at the surface of ALBC, dependent on the surface area that is exposed to the surrounding fluid. To compare one ALBC formulation to another, the release parameters should be expressed as a function of surface area or the test specimens must be a standardized size and shape (ASTM F451-08). Porosity increases the effective internal surface of the ALBC to which further interconnecting pores can deliver the contained drug, thereby increasing delivery per unit surface area from ALBC, over time.

Porosity Increases Release

Fluid must be able to get into the PMMA to dissolve the antimicrobial load and there must be continuity in the fluid between the dissolution

site and the exterior of the ALBC for dissolved antimicrobial to diffuse to the ALBC surface [10]. Increased porosity leads to increased fluid penetration. Antimicrobial release increases with increasing porosity.

Volume Fraction (vol%)

Particulate poragens can vary considerably in their density, often by several multiples. The combined volume of the pores that are generated by a certain weight of poragen varies in proportion, but opposite, to the density of the poragen. Most of the studies in the literature use the weight fraction (wt%) to quantify the antimicrobial load in ALBC. Vol% of poragen is considerably more accurate than wt% as a determinant for both drug release and compressive strength. This point is illustrated by large in vitro differences in drug release between ALBC made with identical weights of tobramycin sulfate from two different manufacturers; one is more than 3 times the volume of the other [14]. Important differences in release rates are likely to occur when wt% instead of vol% is used to formulate ALBC.

Poragen Properties

Solubility, particle morphology (size and shape), and interaction with the PMMA are all important factors affecting pore structure and resultant fluid penetration. Poragen must dissolve in the fluid to transform the space filled by poragen particles to pores thereby permitting fluid to flow into the pores. Particle size and shape determine how closely the particles can pack and the distance between the particles when they are suspended within the polymerized PMMA, thereby determining the amount of PMMA between pores [10, 15, 16].

Molecular interaction between PMMA and fluid penetrating into pores, known as interfacial tension and measured by contact angle (θ), is an important determinant of absorption, especially through very small pores. Absorption (how quickly the fluid penetrates) varies for different antimicrobial solutions. Molecular interaction between the antimicrobial and the PMMA can also lead to binding of the antimicrobial in the substance of ALBC [12] or affect antimicrobial diffusion through the pores [10]. An example is amphotericin B, a hydrophobic antifungal. Release is markedly less than expected for a similar dose of water soluble antibacterials, but compressive strength is increased [12]. Even when the chemical properties of an antimicrobial or an "inert" poragen are well known, release characteristics for each antimicrobial need to be documented in elution studies. Differences between water penetration in vitro and physiologic fluid penetration in vivo is also likely measurably different. However, it is expected that the relative rates for fluid penetration between different formulations of ALBC in vivo will be proportional to the in vitro data.

Antimicrobial Powder Is a Poragen

The particles of antimicrobial powder cause porosity in the PMMA and therefore are a consideration in the calculation for the volume fraction of poragen. Some antimicrobials (e.g., voriconazole [17]) have large volumes of non-antimicrobial components that have specific functions for clinical administration of the drug but are not included in the weight of the drug. These "inactive" components are also poragens.

Mixing

Adding low-dose antimicrobials to PMMA does not appreciably effect mixing or polymerization. The working time (non-sticky, dough consistency), the setting time (mix to hard), and handling characteristics are unchanged with up to 3 vol% poragen/antimicrobial. For low-dose formulations, antimicrobial release and compressive strength are not meaningfully changed by mixing method, even when no attempt is made to distribute the antimicrobial powder in the polymer powder before adding the monomer [18, 19]. Mixing under vacuum, desirable for implant fixation, is unaffected by low-dose antimicrobials.

When the poragen/antimicrobial content increases, the monomer is less able to wet the increased volume of powder Vacuum mixing becomes difficult and undesirable. The goal is to create porosity for fluid penetration and antimicrobial delivery, not to prevent porosity to maintain mechanical properties. Large air bubbles tend to disperse during mixing of high-dose ALBC, so major stress risers are unlikely. It is helpful to use your hands to knead the ALBC after about 2 min of aggressive stirring with a spatula. Wetting the gloved hands with water or saline helps prevent sticking and helps achieve a workable consistency. Alternatively the PMMA can be mixed first without adding the antimicrobial powder, then when the PMMA is polymerizing, the antimicrobial powder can be added and fully mixed (dough phase mixing). Dough phase mixing leads to higher antimicrobial release than dry powder mixing (antimicrobial powder + polymer powder before polymerization), but causes a more severe loss of compressive strength [15]. The antimicrobial powder, including lumps, is not dispersed homogeneously in the ALBC using dough phase mixing. There is considerable variation in both antimicrobial release and compressive strength. For nonstructural applications dough phase mixing is a good mixing method. However, the authors prefer dry powder mixing with finely ground antimicrobial powder, homogeneously mixed in the polymer powder before adding the monomer, to maximize release consistency and to minimize the detrimental mechanical effect. Antimicrobial release, although statistically less for dry powder mixing, is still extremely high and quite sufficient for therapeutic local delivery. The low viscosity phase that occurs in some PMMA brands will not occur while mixing high-dose ALBC although it will be sticky for the same time as without poragens. Setting time is not meaningfully changed and high-dose ALBC sets very hard. ALBC handling characteristics become less moldable as antimicrobial dose increases so that high-dose ALBC is difficult to inject into a mold for spacer fabrication. For that purpose an intermediate-dose ALBC of 5–6 vol% is used by many surgeons.

Monomer Is Not Miscible with Water

Water-soluble antimicrobial powder does not dissolve in monomer and aqueous antimicrobial solutions separate immediately after being mixed with monomer. Emulsions of antimicrobial solution in monomer also separate rapidly unless they are stabilized with a surfactant [20]. The use of aqueous antimicrobials in ALBC is limited to small volumes resulting in very low antimicrobial loads. It is possible to deliver liquid antibacterials from bone cement [20], but clinically impractical. Mixing aqueous antibacterial solutions in PMMA leads to separation of all but a few mL of the solution during polymerization. Because liquid antibacterial formulations are of limited concentration, it is not possible to entrap a therapeutic load of antibacterials without emulsifying a large volume of antimicrobial solution in the monomer. The emulsion needs to be stabilized with a surfactant to prevent separation during polymerization. Currently there is no suitable FDA approved surfactant available in the USA. Increased antimicrobial release has reported when a large volume of water-soluble antibacterial powder and a few mL of aqueous antibacterial solution are used to make ALBC [21, 22]. At present, combining powder and aqueous antibacterials in ALBC remains investigational, although it has potential and may make mixing high-dose formulations easier.

Interconnecting Pores

It is assumed that particulate poragens added to PMMA produce interconnecting pores. Without interconnecting pores fluid would not reach the depths to dissolve the contained drug and a route for diffusion out of the PMMA would not exist. A lack of interconnecting pores is the explanation why low-dose ALBC (<3 vol%) only releases 3–5 % of its antimicrobial load and only from very near its surface [23]. High-dose ALBC is known to be highly permeable. Fluid has been shown to reach the center of 7 mm high-dose ALBC beads in less than 30 days [10, 24]. Retrieved clinical spacers made from high-dose

ALBC more than a centimeter thick have signs of fluid present at their center, as quickly as 3 months [25] (Fig. 10.1).

Antimicrobial release from high-dose ALBC ranges from 30 to 75 % [15, 25] of its antimicrobial load, including the antimicrobial load from the depths of the ALBC.

It was assumed that the increased permeability and increased antimicrobial delivery is due to poragen particles touching other poragen particles in continuity. However, we have only demonstrated occasional instances of poragen particles touching each other on scanning electron microscopy (SEM) over multiple sections in all planes, for particles that are 250 μm or less. Interconnections caused by the antimicrobial particles touching each other are uncommon. Continuity between interconnecting pores throughout ALBC from the added poragen, has not been seen, even for high-dose amounts of 10 vol% and more.

The answer may lay at higher resolution and in permeability studies. At 10× higher magnification, many small pores, 10 μm and less can be seen connecting with all of the larger voids left by eluted poragen. These small pores are consistent with the intrinsic microporosity of the PMMA and are likely the route for fluid flow between the pores caused by the poragen powder. Penetration of fluid into ALBC likely occurs by absorption, a phenomenon that occurs in small capillary size channels. Absorption is distinctly different from fluid flow in large channels the size of arteries and veins. Washburn kinetics describe how pore diameter, interfacial tension between PMMA and the antimicrobial solution (measured by contact angle θ), and time, determine the absorption rate: $(t) = \sqrt{\sigma r t * \cos\theta / 2\eta}$. Fluid penetration into ALBC is driven by the surrounding hydrostatic pressure. As pore diameter decreases and length increases, drag along the pore walls becomes much more important. Flow slows with depth as drag increases.

Using standardized ALBC specimens (Fig. 10.2), we have recently illustrated that the rate of fluid penetration onto PMMA follows Washburn kinetics for fluid absorption in porous media [26].

The measured rate of fluid penetration into ALBC is proportional to the square root of time (Fig. 10.3) as illustrated by plots of "Depth vs. Time" for ALBC made with two different poragens.

Pore diameter calculated from this data using Washburn kinetics is in the range of PMMA's intrinsic microporosity, not the diameter of the poragen particles, supporting the concept that interconnections are likely from intrinsic microporosity in the PMMA not poragen particles touching. With more poragen, the amount of PMMA between antimicrobial particles decreases, leading to a shorter distance for fluid to flow in the small intrinsic pores. Fluid penetration increases, leading to increased antimicrobial release by diffusion.

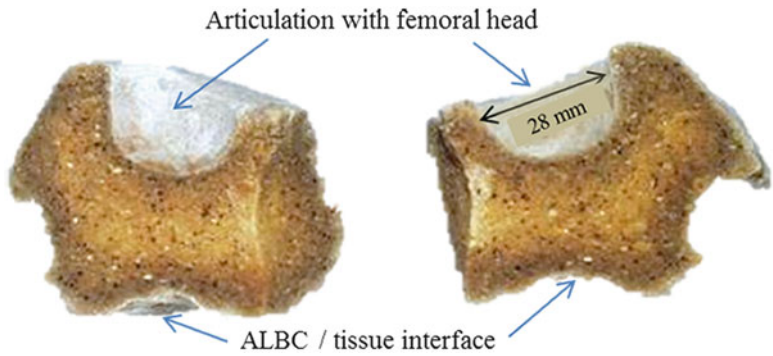

Fig. 10.1 Explanted acetabular spacer, split in half along its equator showing discoloration from fluid penetration at 3 months. The ALBC used to make this spacer started pure white and progressively turned yellow from fluid contact with the tobramycin sulfate, then brown from oxidation of protein in the extracellular fluid that penetrated

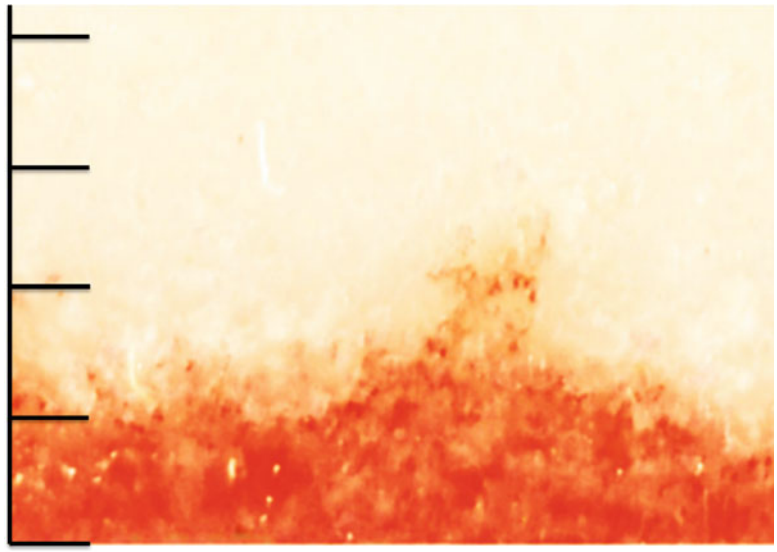

Fig. 10.2 Standardized ALBC sample, 10 mm thick, between two clear styrene sheets. Three of the edges were sealed with silicone leaving one edge open to absorb fluid. The edge at the bottom of the image was open to absorb fluid containing 5 wt% eosin stain. Fluid penetration is visualized as the irregular front of color proceeding perpendicular to the exposed edge. The scale, in mm, on the left measures the distance the fluid has penetrated. There is point-to-point variation in fluid penetration related to microscopic distribution of the poragen. This image represents fluid penetration into ALBC with 28 g of 250 μm particle size sucrose, over a period of 15 days

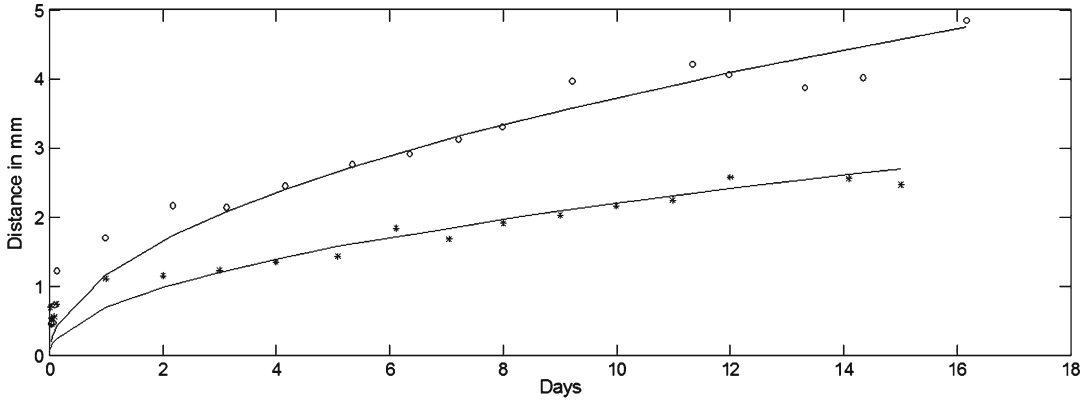

Fig. 10.3 Plot of fluid penetration into high-dose ALBC over time, comparing 28 g of sucrose (-+-) and 13.6 g of antimicrobials—vancomycin (4 g, tobramycin 3.6 g and cefazolin 6 g) (-o-), per batch of Cemex® cement. The antibacterial mixture is half the weight fraction of the sucrose but is a more effective poragen. Both display characteristic penetration rates proportional to $\sqrt{t}$. $r^2 = 0.97$

Mechanical Considerations

PMMA used for implant fixation should have a compressive strength greater than 70 MPa or higher (ISO 5833) [27]. Adding a large volume of antimicrobials to PMMA, >4 vol%, causes a decrease in mechanical properties rendering ALBC unacceptable for implant fixation. ALBC becomes weaker as the amount of poragen added increases, but the effect is not fully realized until the contained antimicrobial is solubilized. As the antimicrobial dissolves, the mechanical support from the solid particles is lost. Pre-elution

mechanical testing does not represent the mechanical properties of the ALBC that will exist throughout the time it is in situ. Although highly porous ALBC is not acceptable for implant fixation, even high-dose formulations function well in spacers that are reinforced with a metal core. To compare the mechanical properties of one ALBC formulation to another, standardized cylindrical test specimens, 6 mm diameter × 12 mm long are loaded in compression at the standardized loading rate of 24 mm/min (ASTM 451-08) [28]. Mechanical loading and articulation have additional considerations for spacers. Spacers which are subjected to cyclic loading consistent with daily activities increases aminoglycoside release up to 2× [29]. Surfaces subjected to motion can wear and smear, limiting release from sealed pores [30]. There is concern that motion between surfaces in articulating spacers will generate wear debris. Wear debris has been reported from articulating spacers even with a polished metal surface articulating on ALBC [31].

Pharmacodynamics

Elimination of bacteria is dependent on sufficient antimicrobial concentration for long enough duration, in concert with host defenses, for all the bacteria to die. The bug–drug interactions that successfully eradicate planktonic bacteria, typically antimicrobial levels above MIC by less than 10×, are unlikely to eradicated PJIs. Local delivery for sessile microbes in biofilm is aimed at concentrations 100× to 1,000× MIC. Bacterial load, replication rate, antimicrobial susceptibility for planktonic microbes and host immune status may play different roles for sessile bacteria in biofilm. The concept of bacteriostatic activity may not apply for concentrations that are far above the levels where bacteriostatic transitions to bacteriocidal [32]. Antimicrobial susceptibility of microbes in biofilm has been studied [33, 34] but the optimal duration of locally delivered antimicrobials after resection of a PJI has yet to be determined. The empiric 6 week duration for parenteral antimicrobial treatment of osteomyelitis has been applied to local delivery as the default duration. Extremely high local antimicrobial concentrations delivered to post-resection surgical wounds with healthy tissue boundaries may not require 6 weeks. In vitro planktonic bacteria are eradicated in 24–48 h at 1,000× MIC [35]. Unfortunately there are no in vitro or clinical data that specifically addresses required duration for locally delivered antimicrobials. Most clinical studies leave the ALBC in place for a minimum for 6 weeks, often much longer, sometimes permanent. Clinical reports of levels following local antimicrobial delivery are limited to a few days when post-op drains are in place or 12 weeks when joint fluid can be obtained at the time of ALBC spacer removal. Local levels generally fall below 100× MIC within a few days. Local delivery for 7 days or less using ALBC beads/sheets following debridement and implant retention has been associated with good results for acute infections [36].

Antimicrobial Agents Commonly Used in ALBC

Most antibacterials used in ALBC (gentamicin, tobramycin, vancomycin, cefazolin) are small, charged, water-soluble, salted molecules. These molecules are not soluble in monomer, and as such, are not incorporated in the substance of the PMMA as it forms. Numerous in vitro elution studies have been performed on many ALBC formulations, however, comprehensive in vitro and in vivo profiles do not exist to guide appropriate dosing. An empiric formulation used successfully by the senior author for 20+ years is tobramycin 3.6 g, vancomycin 4 g, cefoxitin 3 g, and cefazolin 3 g in each 40 g batch of Simplex P bone cement. Elution data [37], permeability data [24], and post-op drain fluid levels [38] are all consistent with the goals for local delivery to treat biofilm-based organisms. Until definitive data are available, a reasonable approach to dosing for culture-specific antimicrobials may be to use the equivalent of a 24 h IV dose added to enough poragen to make the ALBC porous, e.g., 24 h equivalent dose of therapeutic antimicrobial +10 g cefazolin, for high-dose formulations. For anaerobic coverage a second-generation cephalosporin (e.g., cefoxitin) for gm –ve or penicillin for gm +ve have satisfactory elution

characteristics. Metronidazole and clindamycin are not typically used, as they are not available in powder from.

Antifungal agents presented unique challenges for use in ALBC. Amphotericin B deoxycholate is hydrophobic. Extremely small amounts are released from ALBC and compressive strength is increased, likely due to covalent cross-linking during polymerization. However, effective amounts are released when amphotericin B deoxycholate is added with 10 g of poragen (cefazolin) per batch [12]. Voriconazole is also a hydrophobic antifungal, but it does not appear to cross link with PMMA. It is supplied with a large amount of hydrophilic carrier (4.8 g cyclodextran/300 mg voriconazole (6 % active). Release is high (>50 % in 7 days), but loss in strength is severe (>50 %) [17].

Systemic Toxicity

The use of high-dose ALBC is generally considered safe [39–41]. Locally delivered antimicrobials lead to very low serum levels during the first few days only. The incidence of systemic toxicity is very low. Gentamicin and vancomycin are nephrotoxic and ototoxic with additive toxicity systemically. However, levels associated with toxicity from systemic administration are rarely measured following local delivery form ALBC. Nonetheless, nephrotoxicity can occur when no other cause was identifiable (Table 10.1) [42, 43]. When this occurs, removal of the ALBC should be considered. Patients known to be allergic to an antimicrobial often do not have a reaction when the same drug is delivered in ALBC. This may be due to "desensitization" from the slow, uninterrupted increase in concentration that occurs following local delivery, similar to the kinetics used for rapid desensitization [44].

Local Toxicity

Toxicity has been observed in cell culture for high levels of water-soluble antibacterials (cephazolin, gentamicin, tobramycin, and vancomycin) [45–47] but wound healing and fracture healing in the presence of high-dose ALBC has not been a problem clinically. Clinical experience with local delivery of hydrophobic antifungals is far less than with hydrophilic antibacterials. Systemic toxicity from these agents is far greater. Amphotericin B deoxycholate is toxic in cell culture at levels less than 10× MIC [11], which raises the concern that wound healing could be effected in the presence of amphotericin B-loaded bone cement. Fortuitously, release is two orders of magnitude less than would expected for a similar dose of most water-soluble antibacterials [11], low enough to avoid clinically identifiable toxicity. The liposomal formulation of amphotericin B is released in much higher amounts [48] and is presumably less toxic due to less free amphotericin B. Voriconazole is far less toxic at much higher concentration than amphotericin B, both systemically and in cell culture [49]. Clinical experience with voriconazole-loaded bone cement is very limited.

Clinical Application

First described by Bucholz who added 0.5 g of gentamicin powder in Palacos R® cement for single-stage exchange [50], the use of locally delivered antimicrobials from ALBC has expanded progressively to virtually all types of established bone, joint and implant infections, as well as some recurrent soft-tissue infections in compromised hosts. The arthroplasty applications include:

1. Implant fixation: Low-dose
   (a) Second-stage reconstruction for PJI
   (b) Single-stage exchange for PJI
   (c) Aseptic revision
   (d) Primary arthroplasty
2. Dead space management: high-dose
   (a) Structural spacer in bone defects (intermediate dose for molds)
   (b) Nonstructural beads and sheets for bone and soft-tissue defects
3. Local delivery only: high-dose
   (a) to separate tissue planes
   (b) to extend delivery to the entire post-resection wound

Table 10.1 Reports of Nephrotoxicity

Paper	Cases	Age	Preexisting risk factors	Joint	Spacer/beads	Cement	Antimicrobial and load/ batch (g)	# Cement	Serum levels	Baseline SCr	Peak SCr (mg/dL)	Post-op day SCr peaked	Time post-op ARF developed	How ARF was treated	Outcome
Curtis (2005)	1	85	History of DM, renal insufficiency, beads with 3.6 g tobra placed prior to spacer	Knee	Spacer	Palacos	Tobra: 3.6 g Cefazolin: 3 g	120 g	On post-op day 16, after three dialysis sessions, random serum tobramycin was 2 μg/mL. Three dialysis sessions later tobra level was 1.5 μg/mL. Pt was not receiving IV tobra	1.3–1.7	7	15	11 days after placement of second spacer	Hemodialysis, exchange of spacer for spacer with 4 g vancomycin	Pt. discharged home on day 42 with creatinine of 3.5. No further hemodialysis was required
Dovas (2008)	1	61	DM type II, HTN	Knee	Spacer	Gentafix 1 (Teknimed S.A. Toulouse, France)	Gentamicin: 1 g Vancomycin: 2 g	Unknown	Gent: 0.28 Vanco: 5.68	0.69	6.1	14	1–3 days post-op	Dialysis. Spacer was retained	Serum creatinine returned to normal 102 months later
Patrick (2006)	2	82	Tobacco use, COPD	Hip	PROSTALAC	Unknown	Vanco and tobra: unknown doses	Unknown	Tobra: 5.5 Vanco: 0.6	1.2	2.9	Unknown	unknown	Spacer replace with PROSTALAC with 6 g Vanco, 9 g cefuroxime. Labs were normal 2 months later	
		79	Admitted from SNF for elective THA. CHF, CAD, HTN, OSA, nephrolithiasis	Hip	PROSTALAC	Unknown	Tobra: 3.6 g Vanco: 3 g Cefuroxime: 3 g	160 g	Tobra 2.9 (3–4 weeks post-op)	0.7	2.4	3–4 weeks post-op	3–4 weeks post-op	PROSTALAC explanted	10 days later serum CR was 1.7. 19 days later serum Cr was 1.1

Van Raaij (2002)	1	83	"On admission the laboratory test showed only minimal renal impairment"	Knee	Static spacer and beads	Palacos R-40 and Septopal beads	Gent: 0.33 g	240 g Palacos and 7 chains of 30 Septopal beads	2.1 (6 days post-op)	Unknown	410 µmol/L	3–4 days post-op	3–4 days post-op	Spacer was removed. New non-antimicrobial static spacer was placed	Three days after spacer removal serum gent concentration was 1.6. Pt admitted to ICU and required dialysis. One month later she underwent resection arthroplasty. Pt. left hospital with normal renal function
Springer (2004)	0		–	Knee	Static spacer	Simplex P	Vanco: mean 3.1 g Gent: mean 3.7 g	Mean: 136 g	–	–	–	–	–	–	–
Menge (2012)	14		–	Knee	Static and articulating spacers	Palacos, simplex P, and cobalt	*Amount range per entire spacer* Vanco: range: 1–16 g ($n=69$) Tobra: range: 1–12 g ($n=79$) Cefotaxime: range;: 2–8 g ($n=4$) Amikacin: 12.5 g ($n=1$) Amphotericin: 0.06 g ($n=1$)	*Mean* Articulating: 140 g Static: 116 g	–	–	Meand: 2.60 mg/dL	Median: 30 days	–	–	–

Palacos (manufactured by Heraeuse, marketed as Palacos, Palamed, Rifabocin, and Copal) and Simplex (manufacture by Stryker) are the two most commonly used and studied bone cements for antimicrobial delivery. While greater delivery can be measured from Palacos [33, 34], the delivery properties of the other cements are sufficiently similar to expect similar clinical performance. No brand of cement has been associated with superior clinical outcomes.

Implant Fixation with ALBC: Antimicrobial Levels

Low-dose ALBC is used therapeutically and prophylactically for implant fixation. Drug delivery is subordinate to implant fixation. Several low-dose formulations of ALBC are marketed worldwide (Table 10.2). In 2003, the US FDA approved low-dose ALBC for implant fixation only in the second-stage reconstruction following control of PJI; in the USA all other formulations and uses are surgeon directed off-label use, including prophylaxis for high-risk hosts, fixation in aseptic revisions and single-stage exchanges [51].

The most frequent use of low-dose ALBC has become prophylaxis during implant fixation in revision arthroplasty for aseptic failure and primary arthroplasties in high risk hosts. Some centers routinely use low-dose ALBC in all primary cemented total hip and total knee arthroplasties [52]. The rationale for using low-dose ALBC for implant fixation is to provide short-term protection from planktonic microbes before they become established on the implant surface, PMMA surface, or to adjacent bone. Typically 0.5–2 g of antimicrobial are mixed per batch of cement. Alternatively commercially available low-dose ALBC is available (Table 10.2). The cement mantle is a few millimeters thick with a high surface area to volume ratio. The antimicrobial levels

Table 10.2 Commercially Available ALBC and Antimicrobial

Brand	Company	Antimicrobial	Dose
Simplex T	**Stryker**	**Tobramycin**	**1 g**
Simplex P with erythromycin and colestin	Stryker Nordic-Europe, Middle East, Africa	Erythromycin glucoheptonate	0.5 g
		Colestin sulphomethate sodium	3,000,000 IU
Depuy CMW 1, 2, 3	**Depuy**	**Gentamicin**	**1 g**
SmartSet GMV and GHV	**Depuy**	**Gentamicin**	**1 g**
Palacos R+G	**Zimmer**/Heraeus Medical GmbH	**Gentamicin**	**0.5 g**
Cobalt G HV	**Biomet**	**Gentamicin**	**0.5 g**
Refobacin bone cement R	Biomet	Gentamicin	0.5 g
Refobacin plus bone cement R	Biomet	Gentamicin	0.5 g
Refobacin revision	Biomet	Gentamicin/clindamycin	1/1 g
Palamed G and MV+G	Biomet/Merck/ Heraeus	Gentamicin	0.5 g
COPAL G+V and G+C	Heraeus	Gentamicin/vancomycin	0.5/2.0 g
		Gentamicin/clindamycin	1/1 g
Cemex Genta HVand LV	**Exactec/**Tecres	**Gentamicin**	**1 g**
Vancogenex	Tecres	Gentamicin/vancomycin	1/1 g
GentaFix 1 and 3	Tecres/Mathys	Gentamicin	1 g
VersalBond AB	**Smith and Nephew**	**Gentamicin**	**1 g**
Cerafix Genta	Ceraver Osteal	Gentamycin	0.08 g
Septopal beads	Biomet	Gentamicin	0.500 g

Bold is available in the USA

at the bone/cement interface are unknown. Due to the low permeability of low-dose ALBC, most of the antimicrobial remains in the cement for the life of the implant but the extremely small fluid volume and limited flow in the cement/bone interface make the potential for very high levels. The vast majority of the ALBC used for fixation is completely contained by bone or implant. There is minimal exposure to the wound fluid. Data for post-op drain fluid levels are the levels that are present to protect the exposed extraosseous parts of the implants, not the intraosseous portions. Post-op joint fluid levels are reported generally to peak at less than 12 h, then decrease rapidly. In all of the reported studies, there was considerable variation in levels at each time point. Although the average drain fluid levels discussed here are generally above MIC for many of the formulations and above 10× for some, duration was short related to the time frame of wound healing or in many cases, undetectable. Even considering the goal is prophylaxis, not treatment, low-dose ALBC for fixation frequently fails to provide levels or duration that would be necessary to effect hematogenous or retrograde microbes, even 1 day after implantation. The effect if any is likely limited to contamination at the time of surgery. There is large variation in the ALBC loads and amounts used making comparison from one study to another difficult. Brien et al. implanted 40 cemented THAs using a combination of Simplex P cement or Palacos-R cement, 1.2 g tobramycin, and 500 mg vancomycin. Samples were taken from drains, serum, and urine at 6, 24, and 48 h post-op. Tobramycin levels in the drain fluid were above MIC levels at all time points. Vancomycin was undetectable in 30 % of cases [53]. Soto-Hall et al. mixed 500 mg tobramycin with 40 mg PMMA for fixation of ten revision THAs. Drain fluid tobramycin levels peaked about 10× MIC at 4 h, then declined to approximately 3× MIC by 30 h. Mean serum levels peaked near MIC at 12 h and remained there until post-op day 3 before they gradually declined [54]. Forsyth et al. reported results of THA fixation using Simplex T (1 g tobramycin/batch) in six patients with preexisting renal dysfunction compared to a control group of nine patients. Mean tobramycin drain fluid levels peaked at 1 h post-op, above 10× MIC in both groups. There was no correlation between peak serum tobramycin and peak serum creatinine levels. The group concluded that it was safe to use this ALBC formulation in patients with renal dysfunction [55]. Chohfi reported drain fluid, serum, and urine concentrations measured daily for 10 days after low-dose ALBC fixation of primary ten total hip arthroplasties using Cerafix-Vanco. Mean implanted cement mass was 88 g, loaded with 2.7 g of vancomycin. Peak drain fluid concentration was 10× MIC at 24 h post-op. The concentration steadily decreased to 0 by day 6. Urine concentrations were 5× higher than that in the drain fluid levels at 24 h and 1× MIC by day 10. Serum levels did not exceed 1× MIC and were undetectable by day 4 [56]. Bunetel et al. reported joint fluid, serum, and urine gentamicin concentrations after THA using 0.5 g gentamicin per batch of Palacos R cement. Mean joint fluid levels at 4 h were 10× MIC. At 48 h the mean joint fluid concentration was just above 1 MIC [57].

In Vivo Elution Data from ALBC Beads

Few studies report fluid, tissue, and serum levels following local antimicrobial delivery using ALBC beads for arthroplasty infections. There is considerable variance in the data reported in each study (Table 10.3). Wound fluid levels are dependent on several uncontrolled factors including the number of beads implanted, the wound size, and wound fluid (blood/serum/edema) volume and flow. It is impossible to quantitatively compare one case to another or one report to another, however, data are consistent with moderate elevation of wound levels for a few days with minimal systemic exposure. Salvati et al. reported a prospective study that included 18 patients receiving Septopal® beads for the treatment of total hip periprosthetic infection. They reported peak synovial fluid levels above 10× MIC on postoperative day 1 and serum gentamicin levels that peaked at 0.1× MIC, a meaningful decrease in systemic exposure [58]. Anagnostakos et al. reported drain fluid results from 11 patients after implantation of intra-operatively fabricated low-dose antibiotic bead chains (40 g PMMA, 0.5 g gentamicin, 2 g vancomycin) (Refobacin: Merck,

Table 10.3 Antimicrobial In Vivo Elution

Paper	Application	*n*	Hip/knee	Bead/spacer	Cement	Antimicrobial	Dose g/batch	Amount cement used (g)	Mean peak joint fluid (range) (μg/mL)	Peak time post-op	Mean peak serum level (μg/mL)	Mean peak urine level	Mean last measure joint fluid (μg/mL)	Post-op day at time of last measurement	Complications/toxicity
Anagnostakos (2009)	Treatment	11	Hips	Beads	Refobacin-Palacos R	Gent/Vanc	0.5/2	~80	116 (12–371) 80 (21–198)	24 h			3.7/23	13d	None
		17	Hips	Spacers		Gent/Vanc	0.5/2		21.1 (0.7–39)/37 (3.3–72)	24 h			1.9/6.6	7d	None
Salvati (1986)	Treatment	18	Hips	Beads	Septopal	Gentamicin	0.5	2–5 chains	36.9 (19.6–69.5)	24 h	0.26 (0–1.0)	Max mean 24 h cumulative: 1.8 (0–4.7)			None
		38	Hips and knees	Spacers	Palacos-gentamicin	Gentamicin	0.5	3–5 batches	14.9 (2.7–38.9)	24 h	0.3 (0–3.8)	Max mean 24 h cumulative: 0.8 (0–3.1)			
Hsieh (2006)	Treatment	46	Hip	Spacers	Surgical Simplex	Vancomycin	4	86.7	1,538	24 h	0.58 (0.1–1.6)		571.9	7d	None
						Aztreonam	4		10,03.5	24 h	0.46(0.1–0.9)		313.6	7d	
Kelm (2006)	Treatment	10	Hips	Spacers	Refobacin-Palacos	Gentamicin	0.5	~80	~24 (5–40)	24 h			6 (2–8)	7d	None
						Vancomycin	2		~47 (3–72)	24 h			9 (8–10)	7d	
Mutimer (2009)	Treatment	12	Knees	Spacers	Spacer K	Gentamicin	Unknown	Unknown					0.46 (0.24–2.36)	99d (63–274)	None
Masri (1998)	Treatment	49	Hips and knees	Spacers	Simplex and Palacos	Tobramycin	≥3.6	Unknown					6.29	118d (42–340)	
						Vancomycin	≥1.5	Unknown					2.52	118d (42–340)	

Fink (2011)	Treatment	14	Hips	Spacer	Copal G+C	Gentamicin	1	Unknown	(1.02–50.93 μg/g)	6 weeks					n/a
						Clindamycin	1		(12.38–329.73 μg/g)	6 weeks					
						± Vancomycin	2		(15–177.24 μg/g)	6 weeks					
Bien (1993)	Prophylaxis	20	Hips	Fixation	Simplex	Tob or Vanc	1.2/0.5	Unknown	34.27/5.71	6 h	0.6/0.74	17.59/2.43	3.84/2.31	48 h	None
		20	Hips	Fixation	Palacos-R	Tob or Vanc	1.2/0.5	Unknown	22.16/5.48	6 h	0.32/0	14.76/2.36	8.12/1.62	48 h	None
Bunetel (1989)	Prophylaxis	10	Hips	Fixation	Palacos-R	Gentamicin	0.33	~60	31.8(9.3–82)	4 h	0.12		4.4 (0.02–12.9)	48 h	None
Forsyth (2006)	Prophylaxis	6	Hip patients with renal dysfunction	Fixation	Simplex	Tobramycin	0.5	~120	90.3	1 h	~1.1	~8	20.8	48 h	None
		9	Hip controls	Fixation	Simplex	Tobramycin	0.5	~120	103	1 h	~0.8	~23	15.8	48 h	None
Soto-Hall (1983)	Prophylaxis	10	Hips	Fixation	Simplex	Tobramycin	0.5	66.2	20	4 h	1.1	14.5	~6	48 h	None

Darmstadt, Germany; Vanco-cell: Cell-Pharm, Hannover, Germany) for the treatment of total hip periprosthetic infection [59]. Drain fluid levels were near 100× MIC on the first day and fell to <10× MIC by 7 days.

ALBC Spacers for PJI

High-dose ALBC is used for local antimicrobial delivery as adjuvant treatment following surgical resection. The rate of drug delivery is dependent on the surface area of the ALBC that is exposed to the wound; duration of drug delivery is dependent on the volume of ALBC. When ALBC is used in a structural location, it is generally molded into a load-bearing implant called a spacer. The mechanical role of an ALBC spacer is subordinate to drug delivery. Although spacer geometry does not provide as large a surface area as sheets or even multiple small beads, it does provide a surface for elution to the entire adjacent wound surface and the high-dose formulation provides sufficient release over that surface to exceed the clinical need. The larger volume of ALBC needed to make a spacer provides elution over a longer time period as drug from the depths is available for delivery in high-dose formulations. Due to a wide spectrum of bone deficiencies that follow resection, intra-operative fabrication of ALBC into a structural spacer is a custom process with the following goals:

1. Provide an elution surface to the entire post-resection surgical wound for antimicrobial delivery
2. Fill the entire volume of the bone/soft-tissue loss to control dead space and provide a working space for the secondary reconstruction
3. Maintain length for limb length and to prevent contracture of longitudinal structures (ligaments and muscle-tendon units)
4. Prevent soft-tissue sheer
5. Allow soft-tissue rehabilitation
6. Allow function and when possible weight bearing

PMMA is generally not strong enough to function mechanically as a load-bearing implant. Structural integrity of an ALBC spacer can be increased by reinforcing it with a metal core such as low demand femoral stems, rush rods, or conventional intramedullary fracture fixation rods [60, 61]. A continuous ALBC layer, 2 mm thick or more, is needed to ensure adequate antimicrobial delivery. In the setting of PJI, the goal is to deliver high antimicrobial levels to the resection margins, soft tissue and bone, and to the fluid in the wound, after a complete surgical resection has been performed. There is concern that microbes could colonize the surface of ALBC after local antimicrobial levels have fallen below the therapeutic level. Although reports of bacteria growing on ALBC spacers do exist, reinfection has not been a significant problem [62, 63]. More concerning is the potential for the development of antimicrobial resistance [64]. There are reports of resistant bacteria cultured from explanted ALBC spacers and beads [65, 66]. Choosing an alternate antimicrobial for a second course of local delivery might be prudent in that situation.

Fabrication of ALBC spacers must take specific considerations into account for each anatomic location, however, there are some general principles that apply to most applications. The implant must be stable at the spacer-bone interface in order to avoid motion can lead to bone destruction. Intramedullary extensions such as heavy Kirchner wires or Rush rods encased in cement are helpful in achieving a stable construct. A cement gun nozzle or chest tube of the appropriate diameter can be used for a mold. In addition to stability at the bone implant interface, skeletal stability is required in order to minimize soft-tissue shear and optimize wound healing. Mechanical stability provides pain control, and independent function between the stages. Finally, the spacer must have a shape and volume that will maintain appropriate soft-tissue tension and maintain adequate volume for a working space that will allow reimplantation of components and grafts at the second-stage reconstruction.

In addition to PJI treatment, spacers are useful for primary total joint arthroplasties in patients that have a history of septic arthritis or periarticular osteomyelitis when a staged protocol using a temporary spacer may be prudent to minimize the chance of developing PJI from occult infection [67]. For acute PJIs with high virulence organisms

such as MRSA, resection and antimicrobial spacer followed by a staged reconstruction is also a consideration [67–71].

There are two main varieties of spacers, static and articulating. Articulating spacers are typically used for the shoulder, elbow, hip, and commonly the knee. Static spacers are generally not indicated for major joints, with the exception of the knee, due to increased stress from long lever arms and functional demands. Articulating spacers can be intra-operatively fabricated custom devices, made from commercially available molds, or purchased as a prefabricated spacer. Custom-made spacers allow all structural issues to be addressed. In complex cases with significant bone loss or soft tissue compromise, spacer design and fabrication become more technically demanding. Prefabricated spacers and mold systems do not simplify the structural challenges of complex defects. Below is a brief overview of hip and knee spacers. Further details regarding the fabrication of use of spacers are discussed in the specific chapters on hip and knee spacers.

Hip Spacers

ALBC hip spacers can be non-articulating or articulating but generally not static. Non-articulating spacers fill the bone defects in the acetabulum and femur with ALBD independently, leaving the joint unstable, equivalent to a Girdlestone resection. These patients develop shortening and have limited function. The articulating spacers reconstruct the joint with three choices for the articulation surfaces. One is a large ALBC femoral head hemiarthroplasty that articulates directly in the acetabular defect. These are either made from silicone molds (Stage One Hip Cement Sparer Molds, Biomet, Warsaw, IN) or prefabricated from gentamicin-loaded bone cement (Spacer G, Tecres, Verona, Italy). They must be properly sized and used in a congruent acetabular fossa. These spacers should not be used in large acetabular defects that lack congruent stable articulation. Implant offset cannot be modified. There is concern about acetabular bone erosion with the use of large-head hip spacers; however, this has not been a significant problem in clinical use. An advantage of fabricating spacers intra-operatively over prefabricated spacers is that the antimicrobials and dosages loaded in the cement can be customized to the patient-specific needs. The second choice in articulation surfaces is a prosthetic metal head against a thin polyethylene component placed in the mass of ALBC that fills the acetabular defect. The femoral ALBC spacer is molded intra-operative around a metal core with the prosthetic metal head (PROSTALAC® Depuy, Warsaw IN). High-dose ALBC is to viscous to easily flow into the femoral mold used to fabricate a PROSTALAC, therefore intermediate-dose ALBC is typically used (e.g., 3.6 g of tobramycin and 1.5 g of vancomycin per batch of cement). The third option is a prosthetic metal head articulating against ALBC. This is typically achieved by custom intra-operative fabrication using a low-demand stem to reinforce the femoral spacer component. A nonstructural ALBC rod is made to place in the intramedullary canal distally. The femoral spacer is made by covering the prosthetic stem with ALBC by hand, leaving the neck and trunnion exposed. The acetabular spacer component is typically made by filling the acetabular defect with ALBC and molding the articular surface directly in the ALBC using the prosthetic femoral head. Stability can be enhanced by making the center minimally below the equator or by making a minimal posterior wall extension as part of the acetabular spacer. The femoral component is then grouted into place using a separate batch of ALBC placed in the metaphyseal region during the late-dough phase. Previously it was common practice to scrub and sterilize the implant that was removed during the debridement to be used as the metal reinforcement for the femoral ALBC spacer component. This practice has been criticized for the potential risk of residual glycocalyx that could be repopulated by hematogenous microorganisms. When bone defects are complex and extensive, additional constructs may be necessary to anchor or stabilize the spacer components [61, 72, 73]. Patients can be fully functional with sedentary activities. Most patients with well-made custom spacers progress to full weight bearing, many function well for more than a year, some permanently. Wear between the metal

femoral head and acetabular ALBC has been reported. Adverse local tissue response to this wear has not been reported. The wear particles seen in the synovium can be removed by synovectomy at the time of spacer removal and reimplantation [31].

Knee Spacers

Both static and articulating spacers are acceptable for knee spacers. A static knee spacer may be particularly preferable if the soft-tissue envelope is very tenuous or there is instability due to bone or ligament loss. When a static spacer (ALBC fusion) is employed in the knee, the soft-tissue envelope is not subject to shear from joint motion. Patients function independently and knee motion can be achieved reliably after reimplantation without the need for a quadricepsplasty. Articulating spacers are temporary ALBC components equivalent to a TKR, either molded intra-operatively (StageOne Knee®, Biomet Warsaw IN) or prefabricated (Spacer K, Tecres, Verona, Italy). Metal on poly articular surfaces for the spacer, similar to the PROSTALAC hip spacer, are not approved for use in the USA. Patients with cement on cement articulations will initially experience joint crepitus. With use, the spacer will develop smooth polished articular surfaces [74], resulting in decreased friction. Similar to the hip, wear debris is generated. Adverse local tissue response has not been a clinical problem, however, synovectomy to remove the wear particles at the time of spacer removal may be a consideration. Range of motion and function with articulating ALBC knee spacers have been good. ROM after reimplantation has been reported from −2° to 101° [75]. Weight-bearing protocols are surgeon specific and vary from non-weight bearing to weight bearing as tolerated. Infection control associated with both static and articulated knee spacers are generally reported about 90 % or higher. Articulating spacers have been reported to decreased bone loss [76, 77], increased range of motion [76, 78], increased functionality between stages [74, 79], and technically easier reimplantation [76] although most of these issues are mitigated in static spacers by making certain the spacer/bone interface is stable and by waiting until the soft-tissue envelope around a static spacer is fully healed with normal tissue mechanics before the second-stage reconstruction, usually by 6 months.

In Vivo Elution Data from ALBC Spacers

Antimicrobial delivery from spacers used clinically has been evaluated by measuring levels in the post-op drain fluid. Case-to-case and study-to-study variation is very large due to surgeon, extent of debridement, degree of wound closure, and the amount, formulation, and location of ALBC. Drain fluid from high-dose ALBC spacers containing tobramycin 3.6 g, vancomycin 4 g, and cefoxitin 6 g per batch of Simplex P cement has been reported by McLaren et al. to have tobramycin and vancomycin levels both about 500 μg/mL for the knee and about 220 μg/mL for the hip indicating that 100× to 1,000× MIC can be achieved clinically [38]. Hsieh et al. implanted custom-made hip spacers in 46 patients containing 4 g vancomycin and 4 g aztreonam per 40 g pack of PMMA (Surgical Simplex, Limerick, Ireland). Average mass of cement used in each spacer was 86.7 g. Serum and drain antimicrobial concentration was measured 7 consecutive days postoperatively. Joint fluid concentrations were also measured at the time of stage II reimplantation. No parenteral antimicrobials were administered during the period of data collection. Vancomycin drain levels decreased from a mean of 1,538 μg/mL on post-op day 1 to 572 μg/mL on post-op day 7. Aztreonam concentrations went from 1,004 to 314 μg/mL. Vancomycin and aztreonam serum levels did not exceed 1.6 and 0.9 μg/mL, respectively. At the time of second-stage reimplantation 30–160 days later, concentration values were well above the MIC for most microorganisms associated with periprosthetic infections. There were no cases of renal insufficiency [80]. Masri et al. reported joint fluid levels during the second-stage reimplantation after placement of spacers in the hip and knee. When at least 3.6 g of tobramycin and 1.5 g of vancomycin was used per package of cement, the

mean concentrations of tobramycin and vancomycin were 11.94 and 2.51 μg/mL, respectively, at a mean 118 days after implantation. These levels indicate continued release from the mass of the spacers but are 1–2 orders of magnitude below the goal of 100× MIC, an expected finding after 3 months and longer [81]. Fink et al. implanted hip spacers in 14 patients made with Copal cement loaded with gentamicin and clindamycin, with or without 2 g vancomycin. Tissue samples were taken at the time of reimplantation approximately 6 weeks later. All tissue samples contained antimicrobial levels greater than the MIC for the respective pathogen [31]. Kelm et al. implanted hand-made hip spacers in ten patients fabricated with 80 g PMMA, 1 g gentamicin, and 4 g of vancomycin. Drain fluid levels were measured every 24 h for 1 week. Gentamicin and vancomycin levels peaked on postoperative day 1 at values of approximately 22 μg/mL and 46 μg/mL, respectively, followed by a steadily declined thereafter. Spacers were explanted 4–14 weeks later. In vitro elution and bioactivity assays revealed persistent, low-level elution of antibacterials and the ability to inhibit epidermidis growth for at least 14 days after removal, independent of length of implantation period [82]. Anagnostakos reported drain fluid results from 17 patients after implantation of hand-molded hip spacers fabricated with 80 g PMMA, 1 g gentamicin, and 4 g vancomycin (Refobacin/Palacos: Merck, Darmstadt, Germany; Vanco-cell: Cell-Pharm, Hannover, Germany). Vancomycin concentrations were higher than those of gentamicin on day 1 (37 (3.3–72) vs. 21.1 (0.7–39) μg/mL) and remained higher over the entire length of the measurement period (max 7 days). Concentration of gentamicin and vancomycin at 7 days was 1.9 and 6.6 μg/mL, respectively.

Clinical Outcomes

There is minimal level 1 data to support the prophylaxis use of low-dose ALBC in routine joint replacements [5, 39, 83]. Confounding factors that may also have been instituted along with the ALBC are not always controlled. Even national registries with large numbers provide conflicting data. The reduction in PJI rates is small, in general a decrease of 0.5–1 %. Perioperative antimicrobials are still required; ALBC may be a synergistic modality with perioperative antimicrobials [84–88]. There have been reports of aminoglycoside-resistant bacteria isolated from patients with ALBC used for implant fixation as well as reports of bacteria growing on explanted antibiotic beads and spacers [63, 65, 89]. A study involving 91 patients undergoing revision arthroplasty for PJI caused by coagulase negative staphylococci reported an 88 % incidence of gentamicin-resistant organisms isolated in the patients receiving ALBC fixation at the time of primary implantation vs. a 15 % incidence in those receiving plain cement [90]. As a result, the routine use of ALBC for implant fixation in primary arthroplasty has been called into question [89, 91].

For aseptic revisions, there is better consistency in the data, albeit not level 1 data. Infection rates are decreased by about half, lower by 2–3 % when low-dose ALBC is used for fixation [85–87]. For established periprosthetic infection, infection after the second-stage reimplantation without ALBC is high, 1/4 to 1/3 of cases. When low-dose ALBC is used to reimplant, a TKA infection has been reported as low as 5 % [92].

For infection treatment, the trend has been increase the antimicrobial load. Bucholz increased from 0.5 to 3.0 g of gentamicin powder per batch over 20 years and 583 cases [37]. It is generally accepted that low-dose ALBC is not adequate for the treatment of established infection. High-dose ALBC used for treatment requires surgeon-directed formulation. It must be emphasized that local antimicrobial delivery is *adjuvant therapy*. Complete surgical resection is the primary treatment modality. Local antimicrobials cannot mitigate inadequate debridement. High-dose ALBC has been variably defined, ranging from any dose more than 1 g of antimicrobials per batch of cement up to 10 g or more. The key is that high-dose ALBC requires enough poragen to facilitate fluid penetration. This requires about 10 vol% poragen which corresponds to about 10 g of the commonly used antimicrobials. Although beads are frequently described to fill

nonstructural dead space, the senior author rarely uses beads, especially in the intramedullary locations or if they will be in place for an extended period of time. Making and stringing the beads is a technical nuisance, beads (spheres) have the worst (lowest) surface area to volume of all shapes and the tendency of beads to become encased in scar, all make beads less desirable than thin layers or sheets, 1–2 mm thick, of customized area/shape to match the wound requirements. ALBC sheets markedly increased the surface area available for drug delivery for the same volume of ALBC. The senior author commonly makes them 10–15 mm wide by 3–10 cm long. They can be placed in low volume tissue planes, molded to the shape of the wound surfaces while in the dough phase, and layered to fill complex volumes when dead space management is needed. ALBC sheets are also markedly less challenging to remove.

Most outcomes data for a two-stage protocol, resection, high-dose ALBC spacer, and delayed reimplantation with low-dose ALBC for established periprosthetic infection is low level data, generally reported to be about 90 % successful. Infection after reimplantation for TKA infection has been reported as low as 5 % [90]. When the second-stage reimplantation is performed without ALBC, infection rates are much higher, 1/4 to 1/3 of cases. There are two prospective clinical trials that looked local delivery using ALBC between resection and reconstruction [40, 93]. Nelson et al. reported 12 cases treated by local delivery using Septopal® beads, without systemic antimicrobials, compared with 13 cases treated by parenteral therapy without local delivery, the outcomes were not statistically different but likely underpowered: 15 % infection after local delivery and 30 % without local delivery. Of note is ALBC was not used for the second-stage reconstructions [93]. Cabrita et al. reported 38 patients treated with an ALBC spacer between stages and 30 patients without. The infection rate following the use an ALBC spacer was 10.9 %, and 33.3 % without [40].

In acute PJIs, postoperative or acute hematogenous (<4 weeks duration) when implant retention is planned, a staged protocol with local antimicrobial delivery is preferred. One protocol reported to have 90 % success, a thorough debridement is performed and modular components are sterilized in a betadine soak or with flash autoclave and reimplanted. Approximately 1/2–1 batch of ALBC as beads was placed throughout the wound in the gutters and suprapatellar pouch. Repeat debridement, ALBC removal and insertion of new modular components was performed approximately 4–7 days [36]. In a retrospective report there were 2 failures in 20 patients. Staphylococcal infections received rifampin combination therapy in that report [36]. With appropriate patient selection, successful direct exchange for the treatment of chronic PJI is similar to outcomes of two-stage exchange with success rates of 87 % and 90 %, respectively [87, 94].

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Prosthetic Retention: Treatment Options

11

David N. Vegari and Bryan D. Springer

Introduction

Infection following total knee arthroplasty (TKA) and total hip arthroplasty (THA) remains one of the most dreaded and difficult complications to treat. The overall incidence of infection in the literature ranges between 0.5 and 2 % for primary total joint arthroplasty (TJA) and 2–4 % for revision TJA. In 2005, 16.8 % of all revision TKA and 14.8 % of all revision THA were performed because of infection [1]. It is estimated that by the year 2030, 52,000 (65 %) of all revision knee procedures will be performed because of infection [2]. The economic impact of treating a patient with an infection after TJA is staggering. It is associated with costs ranging from $60,000 to $100,000 per treatment, longer hospital stays, and a higher complication rate [3–5]. Treating an infection following TJA is one of the most resource-consumptive procedures in orthopaedic surgery.

Several variables need to be considered when choosing a treatment option. These include the depth and timing of the infection, the status of the soft tissues, the fixation of the prosthesis, the involved pathogenic organism, the ability of the host to fight the infection, the resources of the physician, and the patient's expectations. Prosthetic retention is viewed as an attractive low-morbidity option for a patient with an infected total joint. Retention options include antibiotic suppression, arthroscopic irrigation and debridement (I&D), or open I&D with or without polyethylene exchange.

Based on the Tsukayama et al. classification system for infected TKA, a type I infection occurs in a patient with a positive culture at the time of surgery [6]. A type II superficial or deep infection occurs early within the first month after surgery. A type III infection is a late, acute, hematogenous infection that occurs after the TJA, with symptoms of greater than 4 weeks duration. A type IV infection is a late, chronic infection with symptoms that have persisted for more than 4 weeks.

Prosthetic Retention Options

Antibiotic suppression is recommended only in a patient who is medically debilitated and unable to undergo surgery. The infectious agent should be a low-virulence organism and the patient should be in stable condition, have well-fixed components, and treatable with a suitable oral antibiotic agent. The literature suggests that the success rate of antibiotic suppression-only treatment is approximately 20 % [7, 8].

Alternatively, a few studies have looked at long-term antibiotic suppression therapy in the

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post-I&D setting. Rao et al. found an 86 % success rate at 5 years [9]. One study by Zimmerli, which focused on rifampin in combination with ciprofloxacin, found a 100 % success rate when the two antibiotics were used in unison [10]. Although this study looked at both arthroplasty and non-arthroplasty patients, the results were encouraging. However, as Duncan points out in his review paper on periprosthetic joint infections (PJI), the role for antibiotic suppression is quite limited and data are lacking, particularly when antibiotic suppression is the sole treatment of infection [11].

Arthroscopic Irrigation and Debridement: Total Knee Arthroplasty

Arthroscopic knee I&D is sometimes an attractive option for patients with acute PJI. It is done through small arthroscopic portals with minimal disruption of the soft tissues. However, there are several other concerns regarding this technique. First, the overall examination of the joint, when done arthroscopically, is inferior to an open procedure because it limits the evaluation of the bone/cement and prosthetic interface. The polyethylene cannot be exchanged, precluding debridement in the posterior aspect of the knee, and a complete and thorough synovectomy cannot be performed. In addition, it is more difficult to remove debris through arthroscopic portals than with an open procedure. It is for these reasons that only in cases of significant extenuating circumstances should arthroscopic I&D be performed.

Therefore, the current literature on arthroscopic knee I&D is limited to a few studies with small numbers of patients. Waldman et al. reported on 16 patients with acute PJI. All patients who underwent arthroscopic knee I&D had fewer than 7 days of symptoms. At a mean follow up of 56 months, the success rate of eradicating infection was only 38 % [12]. Dixon et al. showed improved results; of 15 patients treated with arthroscopic knee debridement, 60 % had successful outcomes at follow-up, with a mean time of 55 months since primary TJA [13]. To date, no literature exists regarding the use of hip arthroscopy as a prosthetic retention option for treatment of an infected THA. As techniques continue to evolve, the ultimate role of hip arthroscopy is yet be determined. However, many of the same concerns regarding knee arthroscopy, such as limited visualization and debridement options, as well as inability to exchange the polyethylene, also exist for hip arthroscopy.

Open Irrigation and Debridement with Polyethylene Exchange

I&D is an attractive low-morbidity option. It allows the implant to be saved through a single surgery and limits the morbidity and functional limitations associated with resection arthroplasty. For the surgeon, implant removal can lead to bone loss and a complex reconstruction. In order for these benefits to be realized, however, the literature should support its use. Much of the current literature suffers from a lack of power and many uncontrolled variables such as medical comorbidities, surgical technique, length of antibiotics, and the definition of success.

Historically, it is generally agreed that open I&D for an infected TJA should be reserved for patients with an acute onset of infection as I&D and component retention for treatment of a chronic infection (signs and symptoms for more than 4 weeks) have been associated with high failure rates and poor outcomes for both THA and TKA and should not be considered [14, 15].

Surgical Considerations and Technique for Open Irrigation and Debridement

Once the diagnosis of acute PJI has been made, the decision to proceed to the operating room (OR) to perform an open I&D with polyethylene exchange should not be delayed. There are several important pieces of information that the operating surgeon should have to assist in guiding the treatment. The operative report from the

initial arthroplasty should be obtained because it allows the surgeon to determine the type and size of the prosthesis as well as the type and size of the polyethylene tibial insert or acetabular liner. The hospital should be notified to ensure that the proper polyethylene components are available. In addition, the surgical approach and any extensile approaches should be noted.

Antibiotics

The decision to give preoperative antibiotics should be based on several factors. If the preoperative aspirate has shown the type of bacteria present, it is reasonable to give prophylactic antibiotics based on the culture and sensitivity of the organism that is present. Culture results and sensitivities may take several days to be available and if suspicion is high for infection, the surgery should not be delayed in order for culture results to be available. If culture results are not known in the setting of high suspicion for infection, it is acceptable to hold antibiotics until surgical cultures are obtained.

Antibiotics should then be directed at the most likely source of infection (staphylococcus and streptococcus). In patients with suspected hematogenous spread from oral flora or genitourinary or gastrointestinal tract, broad spectrum coverage should be initiated to also cover gram-negative bacteria. Patients at high risk for resistant bacteria, such as methicillin-resistant staph aureus (MRSA) should also be give Vancomycin. These patients include those with a previous history of MRSA, institutionalized patients, and immunocompromised patients. Once the cultures have been taken in the OR, the appropriate antibiotics should be administered. The antibiotic regime can then be tailored to the patient once the final culture results from surgery have been obtained.

Operating Room Setup

It is important for the OR personnel to understand that the case is infected and treat it appropriately. While we prefer to use protective body exhaust suits and laminar flow ORs, there are conflicting data on the benefits of these procedures in reducing infection risks [16, 17]. We prefer to use two setups in the OR. A setup to perform the I&D is followed by a separate setup for placing the new polyethylene and closure. The surgeon and the OR team should change into new gown and gloves after the I&D. In addition, a separate set of clean, sterile instruments should be used to prevent reintroduction of infection into the joint once the debridement has been performed in order to reduce the risk of contamination to the joint from the previously used instruments.

It is generally recommended that between 3 and 5 surgical cultures be obtained during the procedure. This will improve the yield of culture results and also help to rectify issues of potential contamination. In addition, it is important that each culture is taken with a new instrument to prevent cross-contamination of cultures. Cultures should be sent routinely for aerobic and anaerobic cultures with sensitivities. Routine use of gram stain is not warranted as it suffers from a lack of sensitivity and specificity [18]. In addition, the routine use of cultures for acid fast bacilli and fungal cultures is warranted only in high suspicion or high risk patients. A frozen section may be useful in confirming the presence of infection based on the number of white blood cell in a high power field. It is generally accepted that somewhere between 5 and 10 white blood cells per high power field are consistent with a diagnosis of infection [19, 20]. This, however, is dependent on where the tissue is sampled and the experience and knowledge of the pathologist interpreting the sample.

Surgical Technique: Total Knee Arthroplasty

The surgical technique and approach are performed using the same standard principles that are used to perform a primary TKA. The patient is placed supine on the OR table and the operative leg is positioned free. We prefer to use a tourniquet, as the aggressive debridement and

synovectomy that is required can often lead to excessive bleeding. The prior incision is marked out and the leg is prepped and draped in the usual sterile fashion. Whenever possible, the incision that was used to perform the arthroplasty should be utilized for the I&D procedure. If skin flaps are required, they should be full thickness so as not to compromise the fragile blood supply to the skin.

We prefer to use a medial parapatellar approach for several reasons. Not only is it familiar to most surgeons, but it is readily extensile. One may often encounter a stiff knee or one that has scar tissue that may initially limit the exposure. A wide exposure allows for proper debridement of all infected tissue. An exposure through a medial parapatellar arthrotomy allows for the exposure to be extended either through a quadriceps snip or if needed a tibial tubercle osteotomy. The majority of knees can be exposed through a standard approach with an appropriate medial release and early lateral release to free up the lateral gutters. It is generally not necessary to avert the patella as this may increase the risk of patellar tendon avulsion.

The success of open I&D and polyethylene exchange is dependent on several factors. It is important to perform an aggressive debridement to remove as much infected tissue and synovium as possible. Once the arthrotomy has been performed, cultures should be taken and appropriate antibiotics administered. We prefer to take a minimum of 3–5 tissue cultures, which are taken from the synovium and peri-implant tissue.

A complete and thorough synovectomy should be performed, removing all infected-looking tissue and paying particular attention to the suprapatellar pouch and medial and latter gutters. It is equally important that a thorough debridement be performed in the posterior aspect of the knee; in order to do this correctly, the polyethylene must be removed.

It is important to inspect both the femoral and tibial component for loosening. In order to adequately assess for loosening, the implant interfaces must be exposed. Extraction devices specifically made for the components can be utilized to assess for component loosening. In addition many universal extraction tools are now available that allow for adequate testing of the components. A loose implant is a potential sign of chronic infection, and if encountered, the I&D should be abandoned in favor of a resection arthroplasty with placement of an antibiotic spacer.

Following a complete and thorough synovectomy, irrigation is then utilized. We prefer high-volume plain saline (approximately 9 L) with lavage. Little data exist on the efficacy of antibacterial solutions to improve outcome and can potentially lead to systemic toxicity [21–23]. Following the initial I&D, we prefer to perform a second-look debridement. New instruments are utilized to remove any additional tissue that is suspicious and the knee is irrigated with an additional 3–6 L of saline. Following completion of the irrigation, the surgical team should dispose of all instruments used during the I&D. Gown and gloves are changed and new instruments to be utilized during the closure are brought onto the field.

Trial polyethylene components can be used to determine appropriate thickness and stability of the joint. We prefer to release the tourniquet to obtain hemostasis prior to closure. A new polyethylene can then be inserted into the tibiofemoral articulation. Drains are used to help avoid hematoma formation postoperatively, given the aggressiveness of the debridement. The wound is then closed in layers with absorbable monofilament suture and a sterile compressive dressing is applied.

Surgical Technique: Total Hip Arthroplasty

Similar surgical principals are applied when I&D is performed for infection following THA. Specifically, copious irrigation with 9 L of fluids and a thorough debridement of devascularized tissues should be addressed. This should be done while maintaining the appropriate tissue planes. Often, scar tissue can obscure the tissue boundaries and care must be taken by the surgeon to tease out the appropriate planes depending on the approach to the hip. Intraoperatively, the components should be evaluated critically for signs of loosening or subsidence. Care must be taken to

remove the liner and that the locking mechanism is not damaged. Often times a modular head maybe replaced at this time as well.

Postoperative Care

Patients are typically mobilized on the first postoperative day, allowing them to be weight-bearing as tolerated and perform physical therapy. Cultures should be monitored daily. Antibiotics should continue to be administered intravenously and changed according to culture results and antimicrobial sensitivities. We prefer that all patients be managed in conjunction with an infectious disease specialist. A peripherally inserted central catheter line is placed to allow for long-term antibiotic administration. There is little consensus on the duration of antibiotic therapy following I&D. It is generally accepted that between 4 and 6 weeks of intravenous antibiotics be administered. A course of oral antibiotic therapy is then administered. Much debate exists about the duration of oral antibiotic therapy and no consensus has been reached regarding the use of chronic suppressive antibiotic therapy. In general, if the I&D is considered a curative procedure, then oral antibiotics are generally administered for a period of 3 months to a year. If the procedure is considered merely a suppression technique, then many advocate the use of chronic life-long suppression antibiotic therapy.

Results

Overall Results: Total Knee Arthroplasty

The overall results of I&D in the literature have been quite variable. Evaluating over 20 published articles in the scientific literature, the success of this procedure ranges from 19 to 83 % with the majority of studies showing a success rate of less than 60 %. A 2002 meta-analysis by Silva reviewed all available literature to date on 530 patients who underwent open I&D for treatment of acute PJI. This study included both acute postoperative infections as well as late acute hematogenous infections. The overall success was only 33.6 % [24]. Table 11.1 lists an overview of the results of literature on I&D for treatment of acute PJI. Because of the wide range of success and failure, there are clearly several variables that affect outcome, which include the timing of surgery, patient risk factors, surgical technique, and the infecting organism.

Timing of Surgery

The timing of surgery appears to be a critical factor in the success of I&D and polyethylene exchange. It has been well established that I&D with polyethylene exchange has high failure rates for patients, with the onset of symptoms at greater than 4 weeks. Schoifet et al. reported an overall failure rate of 77 % for I&D for PJI. All treatment failures occurred in patients with greater than 28 days of symptoms [14]. While several studies have shown that the time from onset of symptoms to surgical I&D was not a factor in outcome (<4 weeks), some authors have reported on improved success with shorter duration of symptoms. Brandt showed a higher probability of treatment failure for those patients treated with I&D when surgery was performed >2 days after onset of symptoms [25]. Marculescu et al. reported that duration of symptoms >8 days was associated with a greater risk of treatment failure by a factor of 2 [26]. Hsieh et al. found that a short duration of symptoms before surgery was the only identifiable risk factor associated with success of I&D for patients with a gram-negative prosthetic joint infection [27].

The role of multiple debridements was evaluated in a 1997 study published by Mont et al. Twenty-four patients who were within 30 days of surgery or presented with a late acute hematogenous infection with fewer than 30 days of symptoms underwent open I&D and polyethylene exchange. Success was achieved in 20 of 24 patients (83 %). Three of the four failures had debridement after on average onset of symptoms of 26 days, while the remainder of the knees had 10 days or fewer of symptoms. Ten of 12 patients

Table 11.1 Result of I&D for infected TKA

Author	Year	# patients	Follow up	Success	Comments
Koyonos [49]	2011	136	54 months	35 %	
Choi [50]	2011	32	36 months	31 %	
Odum [40]	2011	150 (THA/TKA)		31 %	No difference with organism or timing of I&D
Zmistowski [41]	2011			Gram(-) 70 %	
				MSSA 33 %	
				MRSA 49 %	
Azzam [51]	2010	104 (THA/TKA)	67 months	44 %	No relationship to timing, increase risk with: increased ASA, gross purulence, Staph aureus
Bradbury [39]	2009	19	min 24 months	16 %	Average duration to I&D is 5 days. All MRSA infections
Salgado [52]	2007	20		33 %	Average duration to I&D 14 days, included hip and knees (meta-analysis of literature)
Marculescu [26]	2006	99	24 months	60 %	
Deirmengian [53]	2003	31	48 months	35 %	92% failure with any staph, 44% failure with any other gram +, Increased age as risk factor, no difference with time to debridement
Silva [24]	2002	530		33.60 %	Factors success: < 4 months. surgery, < 4 weeks symptoms, Abx sensitive gram +, young age factors failure: sinus, wound drainage > 2 weeks, hinge components, immunocompromised
Segawa [54]	1999	10 Acute Post op	43 months	50 %	No difference in time to I&D, 4 of 5 failures immunocompromised
Wasielewski [55]	1996	10	32 months	75 % acute/50 % chronic	8 acute <2 weeks of symptoms 2 Chronic >2 weeks of symptoms
Kramhoft [56]	1994	27	NR	19 %	All successful outcomes had debridement within 1 week of symptoms
Teeney [57]	1990	21	48 months	29 %	Greater than 2 weeks duration of symptoms; had higher failure rates
Schoifet [14]	1990	31	36 months	23 %	Avg time to I&D for Failures: 32 days Success: 21 days

were successfully treated with a single debridement. An additional 12 patients showed persistent signs of infection and were treated with a second debridement (7 patients) or a third debridement (5 patients). The success rate in these patients with multiple debridements was 75 % [28].

In addition to the timing of surgical intervention, host factors appear to play a critical role in the success of open I&D to treat acute PJI. Several patient factors have been identified as either increasing or diminishing the success of the procedure. Table 11.2 lists specific risk factors that have been identified as variables in the success or failure of the procedure [29–33]. In addition, Table 11.1 also lists risk factors that were identified in those particular studies as influencing outcome.

Results Based on Organisms

The most common organisms associated with acute infections are *Staphylococcus aureus*, *Staphylococcus epidermidis*, or *streptococcus*.

Table 11.2 Risk factors for treatment failure

Increasing age
Duration of symptoms (> 2 weeks)
Presence of prolonged wound drainage
Staphylococcus aureus
Resistant organisms
Immunocompromised host
Rheumatoid arthritis
Diabetes mellitus
Malnourishment
Presence of sinus tract
Radiographic evidence of osteitis
Radiographic evidence of component loosening

It is clear from the literature that we are now also seeing an increase in resistant organisms as a cause of deep PJI. In fact, in many centers, MRSA has become the most common infecting organism in PJI [34–37]. It is a long-held belief that the virulence of the infecting organism affects outcome, with less virulent organisms (streptococcus) having improved success compared to more virulent resistant organisms.

In 1997, Brandt et al. looked specifically at the success of debridement and retention of components infected with *Staphylococcus aureus*. The 2-year probability of success for 33 patients (7 hips) was 31 %. Those patients who underwent I&D >2 days after the onset of symptoms had higher risk of failure [25]. Deirmengian et al. looked at treatment of acute postoperative and hematogenous infection in patients with gram-positive infections. All patients had open I&D with polyethylene exchange. The overall success rate was 35 %, with recurrence of infection as the endpoint. Only one of 13 patients (8 %) with acute staph aureus infection had eradication of infection compared to 56 % success when staph epidermidis or streptococcus was the infecting organism. This high failure rate led the authors to conclude that component removal should be considered in the face of an acute PJI with staph aureus [38].

MRSA infection poses a particular challenge because of its virulent nature and limited options for antibiotic therapy. Reports suggest that the overall incidence of MRSA infection in TJA is on the rise. Bradbury et al. looked at 19 cases of acute periprosthetic MRSA infections treated with open I&D and component retention. At minimum of 2 year follow-up, the failure rate was 84 %. The authors also summarized the current available literature on I&D for MRSA infections in their results. Of 34 studies, 13 patients were identified with an acute MRSA infection treated with open I&D and component retention. The reported failure rate was 77 % [39].

While *Staphylococcus aureus*, *Staphylococcus epidermidis*, and MRSA pose significant obstacles in the treatment of acute PJI, *Streptococcus* species have been considered to be of lower virulence, perhaps leading to improved success in the setting of an acute infection. Odum et al. however, reported on a multicenter series of 200 patients treated with open irrigation and component retention for acute PJI. The failure rate for streptococcal infection was 65 %. This was comparable to the failures rates of 71 % for all other organisms, indicating that even suspected lower virulent organisms such as streptococcus had equal failure rates to more virulent organisms [40].

Although gram-positive organisms account for 65–85 % of the infecting organisms in TJA, gram-negative organisms can pose a significant challenge due to the virulence of the organism and a growing resistance to antimicrobial agents. Hsieh et al. reported on 53 patients with gram-negative infection treated, 26 of which were treated with I&D and component retention. The 2-year cumulative probability of success of I&D was 27 %. This was statistically lower than those treated with a two stage exchange. In addition, those patients that had debridement after >11 days of symptoms had a higher failure rate compared with patients that had debridement with <5 days of symptoms [27]. In contrast, Zmistowski reported success in 7 of 10 patients (70 %) with gram-negative infections treated with open irrigation and component retention. This was compared to successful I&D in only 33 % of methicillin sensitive staph aureus (MSSA), 48 % of MRSA, and 57 % of polymicrobial infections [41].

Overall Results: Hip

There is substantially less literature on the success rates of I&D with polyethylene exchange for THA. Most studies combine TKA and THA and fail to discriminate between the two in their analyses. Tsukayama et al. have the largest reported series of I&D for THA. In this study they divide their results into duration from index procedure and duration of symptoms. They classify infections as early postoperative (less than 1 month after index procedure), acute hematogenous, late chronic (greater than 1 month after index procedure), and positive cultures (2 or more positive cultures in the revision). They treated only their early postoperative and acute hematogenous patients with I&D and polyethylene liner change. With this protocol they found that 25/35 (71 %) of early postoperative patients succeeded with I&D. Success was defined as no clinical evidence of infection for 2 years following completion of antibiotics dose and a functional hip with minimal or no pain [42].

Sukeik et al. found similar results when combining their early postoperative, and acute hematogenous cohort with success in 20/26 patients (77 %). Of note, 5 patients deemed a success required multiple debridements but components were ultimately retained. These patients remained infection-free at 5-year follow-up [43]. In addition, studies by both Lhotellier [44] and Klouche et al. [45] also seem to follow the aforementioned results when combining early postoperative and acute hematogenous infections with success in 47/59, (79 %) and 9/12 (75 %) of patients respectively. However, data from the Mayo Clinic demonstrated overall success rates of I&D at 29 % (6/21) for the combined acute hematogenous and early postoperative cohorts. Of note, I&D in the chronic setting was even more startling as 0/19 patients had their infection eradicated [46].

A few studies have analyzed the role of organism virulence as a potential variable for success or failure in the setting of I&D following THA. Meehan et al. found that 17/19 (89 %) of THAs and TKAs (4/6 THAs) 67 % succeeded with I&D in the setting of Penicillin-Susceptible Streptococcal Infections [47]. Estes et al. performed a staged I&D protocol 1 week apart. They were able to demonstrate success (defined as infection-free at 1 year follow-up) in 18/20 hips (90 %), and 4/4 knees (100 %). Of the 20 cases, 5/20 (25 %) were culture negative; 2/20 (10 %) were MRSA; 4/20 (20 %) were MSSA; 4/20 (20 %) were *streptococcus* species; 2/20 (10%) were *Escherichia coli*; 1/20 (5 %) were coagulase-negative staphylococcus; 1/20 (5%) were *Enterococcus faecalis* and 1/20 (5 %) were mixed species. The two failures included one from the Streptococcal group (*Streptococcus agalactiae*) and an MRSA infection [48].

Conclusion

Prosthetic retention options remain an attractive low-morbidity option for both patients and surgeons alike. However, this approach must be tempered by the sobering results that have been published on the limited success of I&D. It is clear that prosthetic retention options have no place in the treatment of a patient with a chronically infected TJA. The optimal timing, organism, and host factors that allow for a successful prosthetic retention is in evolution and much work needs to be done to better delineate those patients who may best be served with prosthetic retention.

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Single-Stage Exchange for Treatment of Periprosthetic Joint Infection

12

Daniel Kendoff and Thorsten Gehrke

Introduction

The general management of periprosthetic joint infections (PJI) after total joint arthroplasty (TJA) remains a challenge to any arthroplasty surgeon. PJI after primary joint replacement is still reported within a range between 0.5 and 2 %; however, it might increase above 10 % with revision arthroplasty [1–4].

The therapeutic goal in either one- or more staged revision of PJI is in general defined by the complete eradication of the infection and further maintenance of the joint function.

While it has been accepted worldwide that the treatment of a late chronic infection should be obtained by a multiple-staged revision technique, a distinct single-staged revision approach in infected total hip, knee, and shoulder arthroplasty has shown comparable results within the last 30 years in our clinical set-up [5–8].

Generally both revision techniques should be available depending on the clinical status of the patient, the local set-up, and the surgeon's expertise. In the most frequent clinical scenarios, an implant removal is followed by a 6–8 week course of systemic antibiotic treatment and delayed reimplantation of a prosthesis. The introduction of antibiotic-impregnated spacers in both knee and hip revisions seems to improve the functional outcome of the multiple-staged approach and has gained increasing popularity [9–11].

However, looking carefully at the current available literature and guidelines for the treatment of infected TJA, there is no clear evidence that a multiple-staged procedure has a clearly higher success rate than a one-staged approach. Although the two-staged approach has been described in a large number of studies as being the gold standard for infection eradication [14, 32, 33, 41], most of the herein mentioned recommendations, e.g., duration of antibiotic treatment, static vs mobile spacer, interval of spacer retention, cemented vs uncemented implant fixation, are based on level IV–III evidence studies or even expert opinions, rather than on prospective randomized or comparative data.

A one-stage exchange offers certain advantages with a comparative success rate of infection eradication. Obvious further advantages are the need for only one operative procedure (if no recurrence), reduced hospitalization time, and reduced relative overall costs [8, 12, 13, 35]. In order to achieve this potentially high success rate, there are pre-, peri-, and postoperative protocol that must be observed. The following therefore describes the authors' experience with and management strategies for a one-staged approach to PJI.

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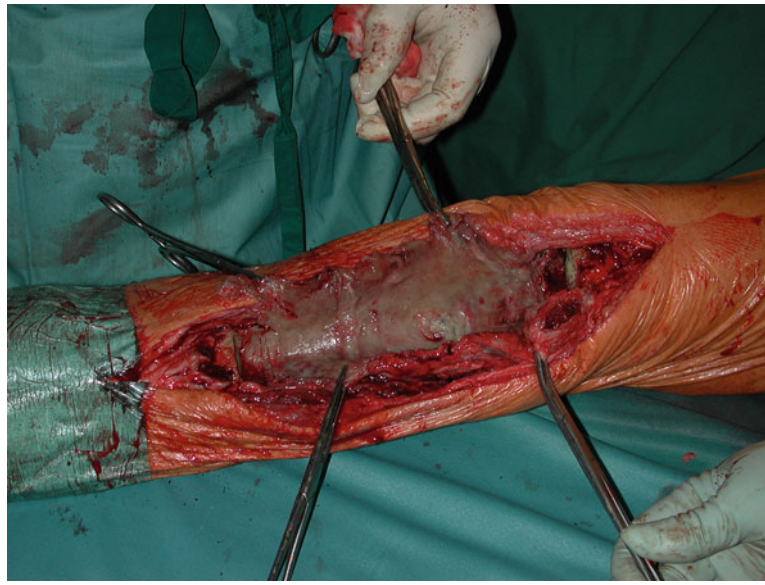

Fig. 12.1 Example of affected joint- capsule of a severely infected arthrodesis nail

Classification

The general period between colonization and clinically detectable infection may last for months or even years. Consequently, local signs of infection may occur very late. It is important to realize that PJI is not only an infection of the prosthetic interface, but an infection of the surrounding bone and soft tissues (Fig. 12.1). Infections occurring within the first three postoperative weeks should be considered as an acute infection and those occurring after the third postoperative week are referred to as late infections.

Consequently, we aggressively treat an acute infected TJA with a local debridement, soft tissue revision and lavage, and polyethylene liner exchange, including preservation of the initially implanted prosthesis. Systemic antibiotics in this scenario are adapted to the algorithm described by Zimmerli et al. [14]. Any late infection should always be treated with a complete implant removal.

Earlier classification guidelines mostly grouped stages of PJI into early, acute, and late infection types. Due to the advancements of diagnostic algorithms and further development of systemic and local treatment options, we adapted our classification system to that described by McPherson et al. [15, 16]. This includes type and timing of infection, the current systematic medical and immune status of the host patient, and the current local extremity grade based on all possible local compromising factors.

Diagnosis

According to our experience, current evidence, and recent clinical practice guidelines provided by the American Academy of Orthopaedic Surgeons, we defined the following mandatory preoperative testing in every single painful TJA patient [17].

- Laboratory monitoring of C-reactive protein and erythrocyte sedimentation rate [18, 19].
- Affected joint aspiration with prolonged microbiologic culture time of at least 14 days, with patients being off antibiotics for a minimum of 14 days [20].
- Synovial fluid analysis of white blood cell count and percentage of neutrophils [21–23].
- Repeated aspiration in cases of negative cultural results in combination with either

obvious infections signs or preexisting external positive cultural results.
- Biopsy of the joint in cases of persistent negative aspiration results with obvious sign of infection [24].

Joint Aspiration

If a single-staged exchange is planned, joint aspiration is used in order to identify the bacteria. The presence of a positive bacterial culture and respective antibiogramm is essential for the one-staged procedure. Specific antibiotic loaded acrylic cement (ALAC) is based on this diagnostic tool in order to achieve a high-topical antibiotic elution directly at the surgical site [26–29].

This strict aspiration-based diagnostic algorithm became standard for every planned TJA revision in our clinic, including all late or early aseptic loosening cases. Furthermore, we expanded this regime to all cases of unclear pain or malfunction after primary or revision TJA, based on an aspiration study, which showed that 4–7 % of patients who were initially planned for an aseptic TJA revision had evidence of a subtle low grade infection [30].

Indications

Very few arguments against a one-staged revision exist; consequently, we are able to perform around 85 % of all infected cases using this technique. The absolute mandatory infrastructural requirement is based on the clear evidence of the presence of bacteria in combination with a distinct patient-specific plan for the administration of topical and systemic antibiotic treatment.

Contraindications

We defined the following criteria for a two-staged procedure:
- Failure of ≥2 previous one-staged procedures.
- Infection spreading to the nerve-vessel bundle.
- Unclear preoperative bacteria specification.
- Nonavailability of appropriate antibiotics.
- High antibiotic resistance.

Preoperative Preparation and Planning

A positive bacterial culture and antibiogramm are absolutely mandatory prior to the one-staged approach. The proposed cemented fixation using ALAC is considered to be the treatment of choice in order to achieve a high-topical therapeutic level of antibiotic elution from the cement [25, 28, 29]. Future approaches might also include antibiotic local implant or silver coating alternatives for a one-staged approach.

The principal success of a one-staged approach not only depends on the removal of all hardware material (including cement and restrictors) in combination with the ALAC, but a very aggressive and complete debridement of any infected soft tissues and bone material. This includes a full synovectomy in the posterior aspects of the knee or radical debridement of the anterior and posterior capsule of the hip joint.

General Preoperative Planning

Specific Risks
- Risk of recurrent or new infection is between 10 and 15 %.
- Reoperation for haematoma, wound debridement, or persistent infection.
- Damage to the sciatic/peroneal nerve.
- Postoperative stiffness and loss of function (knee extensor mechanism).
- Risk of intra- and postoperative fracture.
- Increased risk of aseptic loosening.

Surgical Preparation

Implants and Cement
- The surgeon should be aware of the implant in situ and be familiar with its removal and disassembly (e.g., hinge mechanism in the knee).

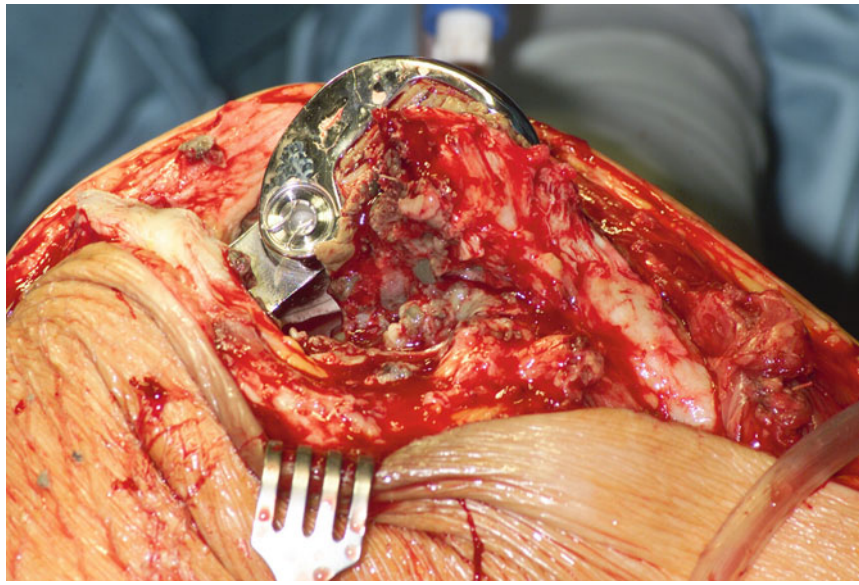

Fig. 12.2 Massive affected soft tissues including the collateral ligaments in a one-staged infected TKA revision

Occasionally the use of implant-specific instrumentation becomes necessary.

- Preexisting ligament deficiencies in the knee require constraint implants; however, ligament deficiency may also occur during intraoperative debridement–hence the need for rotating or fixed hinged implants in general (Figs. 12.2 and 12.3). Based on the above-described aggressive soft tissue debridement, this is the case in over 90 % of our one-staged knee revision cases.
- Inadequate bone stock and possible intraoperative complications such as acetabular/femoral or tibial shaft fractures, perforations of the cortex, osseous windows, and tibial/femoral disintegration must be taken into consideration when choosing an appropriate implant.
- Distal femoral or proximal tibial replacement implants may have to be chosen for patients with significant bone deficiency in the knee. Bone loss is usually significantly more extensive than radiographically evident. The potential need for total femoral replacement implants is rare.
- A significant damage to the extensor mechanism of the knee can require an arthrodesis nail, which should be available as a last option for some rare cases (patient consent).
- ALAC with additional antibiotics in powder form to be added intraoperatively is obligatory in every single case. Invariably at least 2–3 mixes of cement (80–120 g), including large mixing systems and appropriate cement guns, are required. In patients with a narrow diaphysis, extra narrow nozzles allow for appropriate retrograde cementing technique.
- Knowledge about the possible type of ALAC used at primary implantation, as resistance to the previously used antibiotics, must be expected.
- Industrially premanufactured ALAC cement may often be appropriate. As mentioned above, the antibiogramm for the final topic cement impregnation is absolute mandatory for the success of a one-staged procedure.

Operative Technique

Skin Incision and Debridement

- Old scars in the line of the skin incision should be excised. The prior incision from the last operative approach should be used.
- Fistulae should be integrated into the skin incision and radically excised to the joint capsule.

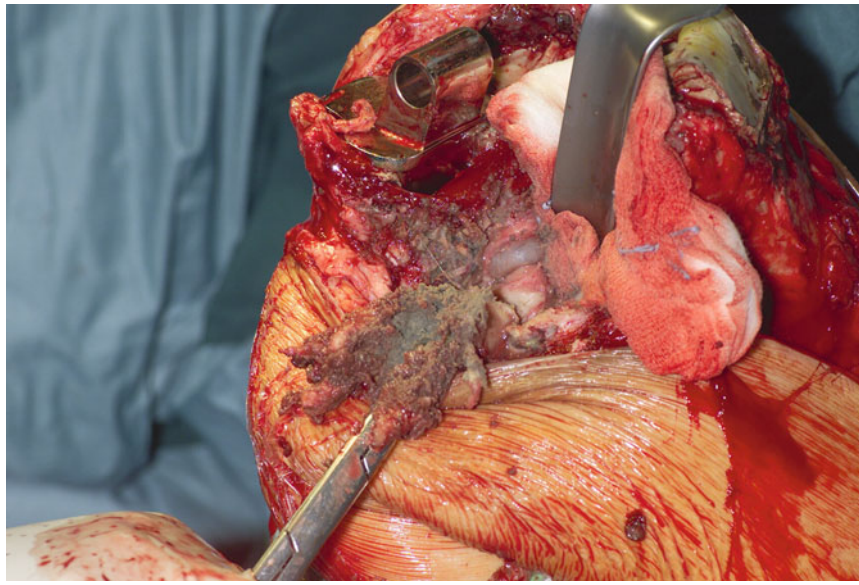

Fig. 12.3 Aggressive debridement also includes the posterior knee aspects in this case of combined metallosis. Consequently the collateral ligaments need to be sacrificed and a rotational hinge implant should be used

- An anticipated operative time exceeding 2 hours should include an above knee tourniquet, but not inflated. The knee procedure should begin without tourniquet; consequently, interfaces between infected tissue, scar, and surrounding healthy bleeding soft tissue can be distinguished more clearly during the debridement. All non-bleeding tissues and related bone need to be radically excised. After completion of debridement and implant removal, the tourniquet can be helpful for the final intramedullary cement removal as well as for the process of re-cementation at the knee site.
- Biopsy material, preferably 5–6 samples, should be taken from all relevant areas of the operation site as a routine measure for combined microbiological and histological evaluation [20, 24]. Only afterwards are the defined antibiotics administered systemically.

Implant Removal and Completion of Debridement

- Removing cemented implants might often be easier to remove and less invasive than removing ingrown cementless components.
- In cases of well-fixed uncemented components, cortical windows are required to gain access to the interface. High speed burrs and curved saw blades can aid the removal.
- Narrow straight osteotomes with symmetrically coned blades should remove all accessible bone cement, which can be removed without causing further loss of bone stock.
- A full range of narrow and wide osteotomes of various thicknesses (Lambotte osteotomes) should be available.
- Extraction of the implant necessitates special or universal extraction instruments, if available. Otherwise, general punches are required.
- Special curved chisels, long rongeurs, curetting instruments, long drills, and cement taps are used to remove the cement. In the hip joint retrograde chisels can be of relevant help in many cases.
- General debridement of bone and posterior soft tissues must be as radical as possible. It must include all areas of osteolysis and nonviable bone.
- Finalization of the aggressive debridement often exceeds the amount of resected materials than in a two-staged approach.

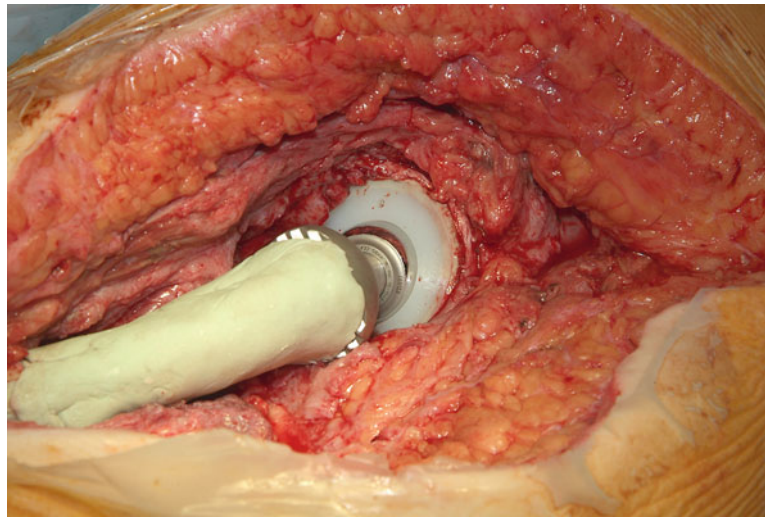

Fig. 12.4 Example of partial osseous proximal femoral resection, with implantation of a cemented long revision stem. The proximal additional cement mantle allows for a high topic therapeutic level of antibiotic elution, in combination with a cemented polyethylene cup

- We recommend the general use of pulsatile lavage throughout the procedure; however, after implant removal and debridement the intramedullary canals must be packed with polymeric biguanid-hydrochlorid (polyhexanid) soaked swabs.
- The complete team must re-scrub and new instruments used for reimplantation.
- A second dose of antibiotics must be given after 1.5 h operating time or if blood loss at this point exceeds 1 l.

Reimplantation

- Inadequate bone stock may require the use of allografts, although ideally this should be avoided. We even prefer to fill large defects with ALAC and do not favour the use of allograft (Fig. 12.4).
- Alternatively tantalum-based acetabular wedges and femoral and tibial cones have been implemented in our regular clinical use for some years. Variations of depth and width of those augments allow for a proper reconstruction of the resulting bone loss, including an excellent biocompatibility and related stiffness and cellular structure. Consequently, a combined fixation of the cement with the prosthesis and tantalum augment becomes possible. In addition, it has been postulated that tantalum should have some antibacterial potential; however, this has not yet been clinically proven.
- The ALAC is prepared in the meantime and it is mandatory to fulfil the following criteria:
  - Appropriate antibiotics (antibiogramm, adequate elusion characteristics).
  - Bactericidal (with the exception of clindamycin).
  - Powder form (never use liquid antibiotics).
  - Maximum addition of 10 % PMMA powder.
- Antibiotics (e.g., Vancomycin) might change the polymerization behavior of the cement, causing acceleration of cement curing.
- Generally current principles of modern cementing techniques should be applied. In order to achieve an improved cement–bone interface, the tourniquet should be inflated prior to cementing in total knee arthroplasty cases.

Postoperative Antibiotics

Postoperative systemic antibiotic administration is usually followed for 10–14 days (exception: streptococci). Although a prolonged administration of intravenous antibiotics for 6 weeks is common in the two-staged approach, the rationale for this prolongation has not been clarified in studies. In contradiction, there is evidence about possible relevant systemic and organ-specific complications after any prolonged antibiotic administration [13, 14].

Postoperative Care and Rehabilitation

Postoperative hospitalization ranges from 12 to 20 days (mean 14) in our set-up. The physiotherapeutic approach in any one-stage procedure cannot be generalised. An individual, patient-specific plan must be developed based on the condition of the soft tissue, bone damage, and extent of the infection. However, we recommend an early and aggressive mobilization within the first 8 days postoperatively. Weight bearing should then be adapted to the intraoperative findings and substance defects. In total knee patients, a similar mobilization strategy should help reduce associated muscular movement restrictions, stiffness, and fibrosis of the affected knee joint, and allows the patient to rehabilitate quickly. In a large number of patients, the adequate bone stock and relatively low soft tissue involvement allows for an immediate mobilization with full weight bearing.

Postoperative Complications

Persistence or recurrence of the infection remains the most relevant complication in the one-staged technique. Failure rates with a two-staged exchange have been described between 9 and 20 % in non-resistant bacteria and our unpublished data show comparative results after 8–10 years of follow up using the one-staged approach [31–34]. Consequently, we discuss a possible risk of recurrent or new infection of between 10 and 20 % at the time of patients' consent. Although we are unable to present general comparative data evaluating the functional outcome of a two- vs. one-staged approach, we believe that neither any articulating spacer nor partial or complete immobilization of the hip or knee joint will result in better functional outcome. We consider the risk for direct damage to the sciatic or peroneal nerve and main vessels as relatively low for an experienced surgeon, even with such an extended aggressive debridement, and relatively comparable to a two-staged exchange. The general risk of intra- and postoperative fractures is comparable to that of multiple-staged exchange.

Outcome

The two-staged approach for treatment of PJI has become the most used technique worldwide, with a reported reinfection rate between 9 and 20 % [31–34]. Although advocated as the gold standard, we established and have followed the above-described one-staged approach in our clinic for over 35 years in over 85 % of all infected TJA cases.

Accordingly, far more studies have been published that emphasize the multiple-stage revision technique. Very few studies or case series evaluating the one-stage exchange are currently available [5–8, 13, 36–38] Although most reports are from our institution, some international studies have had success rates between 90 and 75 % [13, 36–40].

A further benefit of a one-staged approach includes the significantly reduced duration of postoperative systemic antibiotics. This rarely prolongs more than 14 days in our current set-up. The rationale for a reduced antibiotic therapy has also been evaluated in a study by Hoad-Reddick et al., where the authors concluded that a prolonged course of antibiotics does not seem to alter the incidence of recurrent or persistent infection, even after a two-staged revision [41].

Summary

In summary, a distinct one-staged infected TJA approach is still very rarely used within the orthopaedic society. However, from our perspective the one-stage revision offers certain obvious advantages. This includes the need for only one operation, shorter hospitalization, reduced systemic antibiotic treatment, lower overall cost, and relatively high patient satisfaction. The key to success is based on well-defined and detailed hospital infrastructure, including a meticulous preoperative aspiration regime, planning, aggressive intraoperative surgical approach, and postoperative individualized patient care.

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Two-Stage Exchange Hip Arthroplasty: Static Spacers

13

Mathew E. Levine, Gregory K. Deirmengian, and Carl Deirmengian

Introduction

Periprosthetic hip infection (PHI) remains a devastating complication after hip arthroplasty. Of primary importance to any treatment plan is the successful eradication of infection before the reimplantation of components is attempted. The identification of the organism and its antibiotic sensitivities is critical in allowing for appropriate medical treatment of the infection. Additionally, a thorough debridement that minimizes the bacterial burden is necessary so that the patient's immune system, in combination with the antibiotic treatment, can be successful in eliminating the infection.

Historically, there are two strategies that have been used to treat PHI that are based on implant removal. A one-stage exchange completes the surgical debridement and reimplantation during one surgical intervention. Success of this technique is critically dependent on a radical debridement and reestablishment of a sterile field before reimplantation occurs. A two-stage exchange separates the debridement and reimplantation into two distinct surgeries, temporally divided by up to 12 weeks to allow for local and systemic antibiotic treatment and verification that the infection is eradicated. Both strategies have demonstrated substantial efficacy in the treatment of PHI [1–4].

Two-stage exchange is considered the standard of care for the treatment of chronic PHI by most surgeons in the United States [1, 2]. During the first stage, the infected prosthesis and involved tissues are removed, leaving behind a bed of non-infected tissue. Into this bed is implanted antibiotic-impregnated cement, with the purpose of providing ongoing local antibiotic treatment by elution from the cement. While some surgeons favor a static cement spacer, which does not articulate at the hip and is not intended to bear weight, other surgeons favor an articulating spacer that articulates at the hip joint and may provide integrity for weight bearing.

Antibiotic-impregnated static hip spacers provide local antibiotic delivery with a relatively low chance of local mechanical complications. Because there is no articulation designed into this strategy, dislocation of the spacer and femoral fracture around the cement spacer are less likely. However, static spacer strategies are not intended

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to provide weight-bearing properties for the patient and allow for some contraction of the tissues around the hip. They are most appropriate in cases of significant bone loss when an articulating spacer is less appealing. On the other hand, articulating spacer strategies preserve the space between the femur and acetabulum and also provide some hip functionality for the patient. While articulating spacer techniques are favored by many surgeons [5, 6], the potential for spacer dislocation [7] and fracture are certainly more likely with this strategy and may be difficult to achieve in cases of significant bone loss. Both types of two-stage strategies have been shown to result in over 90 % success in treating PHI [5, 7, 8].

The purpose of this chapter is to cover the topic of static hip spacers as part of a two-stage exchange strategy to treat PHI. While a static spacer technique is not the most functional treatment option, the relative ease of this technique, combined with its long history of success, gives it an important place in the armamentarium of any surgeon who treats PHI.

Indications

The diagnosis of periprosthetic infection is an evolving subject that depends on synovial fluid and systemic testing. While some tests, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and synovial fluid white blood cell count, measure the host response and degree of inflammation, other tests such as culture attempt to identify the organism. The presence of a soft tissue sinus is almost invariably associated with a chronic deep PHI. Additionally, the surgeon should have a high suspicion for infection whenever the start of symptoms correlates with a hospitalization or surgical technique. Finally, all hip arthroplasties undergoing revision for pain, especially in the setting of loose implants, should be considered possibly infected until proven otherwise.

The appropriate treatment of PHI has several important considerations. Antibiotic treatment alone is not an adequate treatment option when infection eradication is intended [9, 10]. The range of treatment options includes debridement with retention of components, a one-stage exchange, and a two-stage exchange. Debridement with retention of components is reserved for cases of acute postoperative or acute hematogenous infection, when it is the opinion of the surgeon that the infection has been present for fewer than 4 weeks. Even when debridement with retention of components is done under the appropriate indications, the resulting success in eradication of infection is less than optimal [2, 11].

Exchange arthroplasty is considered the most appropriate treatment when the infection has been present for more than 2–4 weeks. When the infection has been present for this amount of time, biofilm formation may be establishing, osteomyelitis may exist, and soft tissue sinus tracts may begin forming. All of these mechanisms of bacterial establishment cause dramatic reductions in the success of any strategy that does not include removal of implants. Removal of implants not only reduces the burden of bacteria that is established on the implants, but also improves the surgical exposure and allows access to the bone and tissues adjacent to the implant. The resulting debridement is more thorough and the reduction of bacterial load is improved.

Bacterial Identification

The most critical aspect of treating PHI is the identification of the organism and its relevant antibiotic susceptibilities. While no surgical debridement can create a truly sterile tissue field, appropriate antibiotic selection and treatment is a paramount step in eradicating the residual bacterial load.

In cases of possible PHI, a preoperative aspirate of the hip can be useful in driving the selection of the antibiotic included in the cement during exchange arthroplasty and used for systemic postoperative treatment [12]. Using sterile technique, ultrasound, or X-ray guidance may be utilized to aspirate the joint, attaining synovial fluid that can be analyzed for white cell count, differential cell count, and culture. Usually, exchange arthroplasty is performed in a stable patient with chronic pain, allowing some time for the identification of the organism before proceeding with the first stage.

Surgical Debridement and Removal of Implants: The First Stage

The successful removal of implants and tissue debridement require an adequate exposure to allow for tissue visualization and evaluation. Whichever the approach, it is usually necessary to extend the previous incision both proximally and distally. The creation of skin flaps should be minimized, as this creates dead space which may be occupied by blood and provide an environment for recurrent postoperative infection. Sinus tracts should be completely excised down to the joint. Those sinuses that are very close to the incision can be removed by incorporation into an elliptical incision that is slightly wider than the previous scar. A variety of strategies may be used to remove sinuses that are farther from the incision.

Upon entering the joint, a sample of the synovial tissue and capsule can be sampled and sent for frozen section histology to evaluate for acute inflammation. In cases where the preoperative workup is non-determinant, evaluation of this tissue can aid in the diagnosis of infection; however, the accuracy of this method requires high comfort and experience levels of the surgeon and pathologist. During the course of debridement and implant removal, at least five tissue samples from various anatomic locations should be sent to the laboratory for culture, especially when an organism was not identified preoperatively.

An adequate exposure for debridement often requires the incision or removal of scar and thickened capsular tissue surrounding the joint. The initial goal of the exposure is to dislocate the prosthetic femoral head and remove it, which provides access to the peri-acetabular tissues via retraction of the femur. At this point much of the synovium can be accessed, which is then thoroughly debrided and sent for culture. Debridement of the synovium also functions to provide appropriate access to the implants at their interface with the native bone, which is an important step for removal of implants. The importance of acquiring synovial tissue samples cannot be overemphasized, as they may harbor bacteria that are underrepresented in the synovial fluid.

Removal of the femoral implant can be a simple or very complex task depending on the shape and fixation of the component. Loose femoral implants are usually easy to remove. One of the most important considerations for removing a loose implant is to clear proximal bone, especially medial to the greater trochanter, to create a path for removal of the implant. If a clear path for femoral implant removal is not present, proximal femoral fracture, usually of the greater trochanter, may occur. For well-fixed implants, removal is highly dependent on the surgeon's preferred technique. For shorter tapered stems with a small area of fixation, a combination of flexible osteotomes and small burrs can be used to free the implant proximally for removal. For longer stems with a larger surface area of fixation, an extended trochanteric osteotomy [13] and transaction of the stem with a metal-cutting burr may be necessary for removal (Fig. 13.1a–c). Great care should be exercised in preserving the integrity of the femur for future reimplantation.

Debridement of the femur is generally accomplished in two steps. First is debridement of the bone that was adjacent to the joint space. A burr or saw can be used to remove any exposed bone of the proximal femur which was adjacent to the joint space. Second, the canal of the femur adjacent to the implant must be debrided to eliminate bacteria living at the interface. When a shorter tapered femoral stem is removed, there is often easy access to the proximal femur, allowing use of a rasp or burr to remove bone that was in contact with the implant (Fig. 13.2a–c). When debriding a femoral canal that has a longer femoral stem, a combination of reamers or reverse osteotomes can be utilized to access the bone that was in contact with the implant. Most importantly, there is often a thick adherent soft tissue layer at the interface that should be removed for appropriate debridement. Several tissue and bone samples should be sent for culture.

Removal of the acetabulum is generally free of complications when the correct instruments are available. The first step involves removing the acetabular liner and removing all acetabular screws. Then the acetabular shell can be removed with osteotomes. Osteotome systems are available

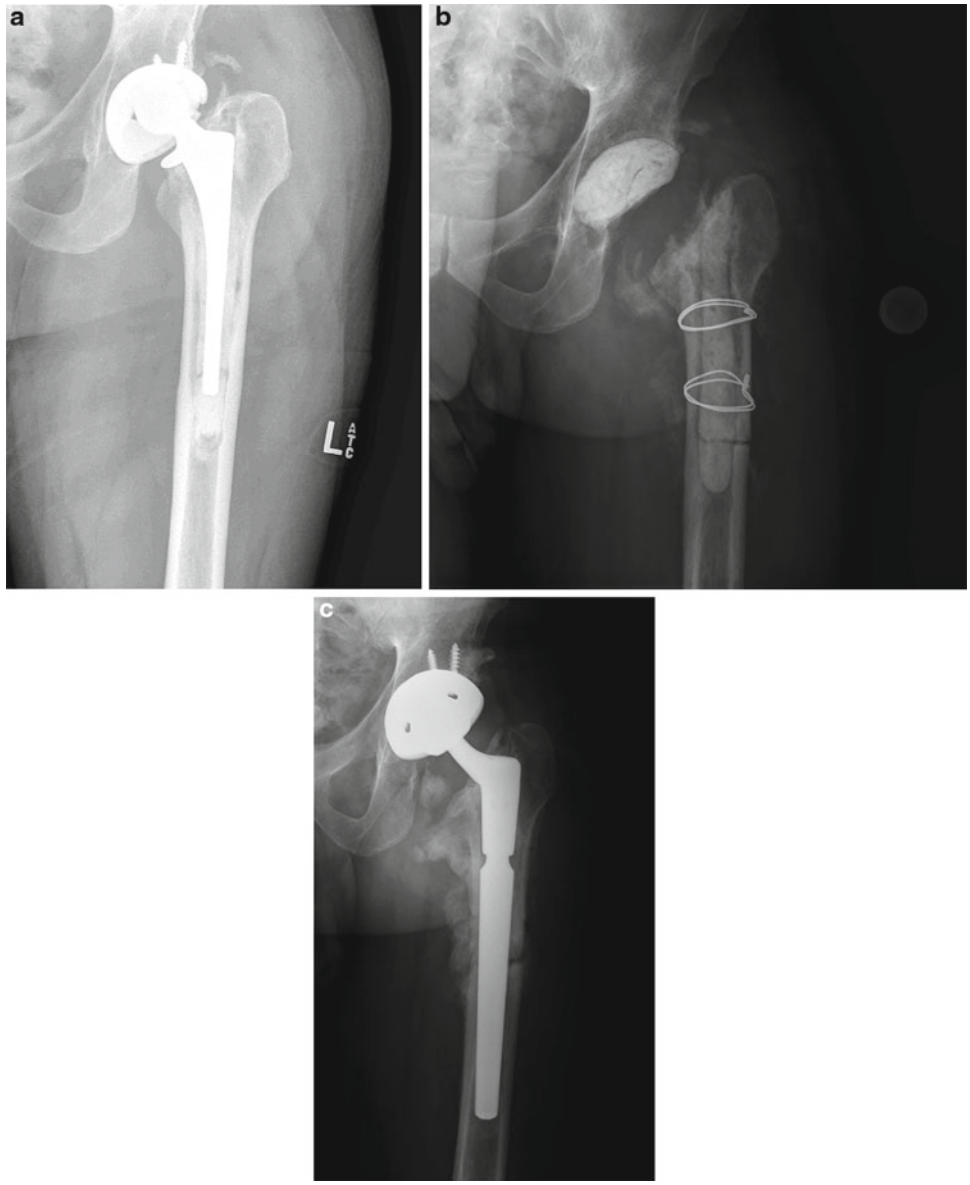

Fig. 13.1 (**a**) Preoperative views revealing a loose cemented femoral implant in the setting of deep infection. (**b**) An extended trochanteric osteotomy was utilized during the first stage debridement, allowing for adequate exposure and debridement of the canal. A static spacer was inserted. (**c**) A long modular tapered revision stem was utilized during the second-stage reimplantation. The trochanteric osteotomy was found to be stable

in a variety of sizes to match the sizing of acetabular shells. The best systems integrate curved short and long blades linked to a ball impactor, allowing the blades to move around the center of rotation of the shell [14, 15]. This usually results in removal of a well-fixed shell with negligible bone loss. Forced removal of an acetabular shell with screws must be avoided to limit bone loss and vascular injury.

Debridement of the acetabulum starts with a curette to clear all soft tissue from the acetabular inner surface and screw holes. Once bone is exposed, acetabular reamers may be used to further debride the acetabulum. Care must be taken

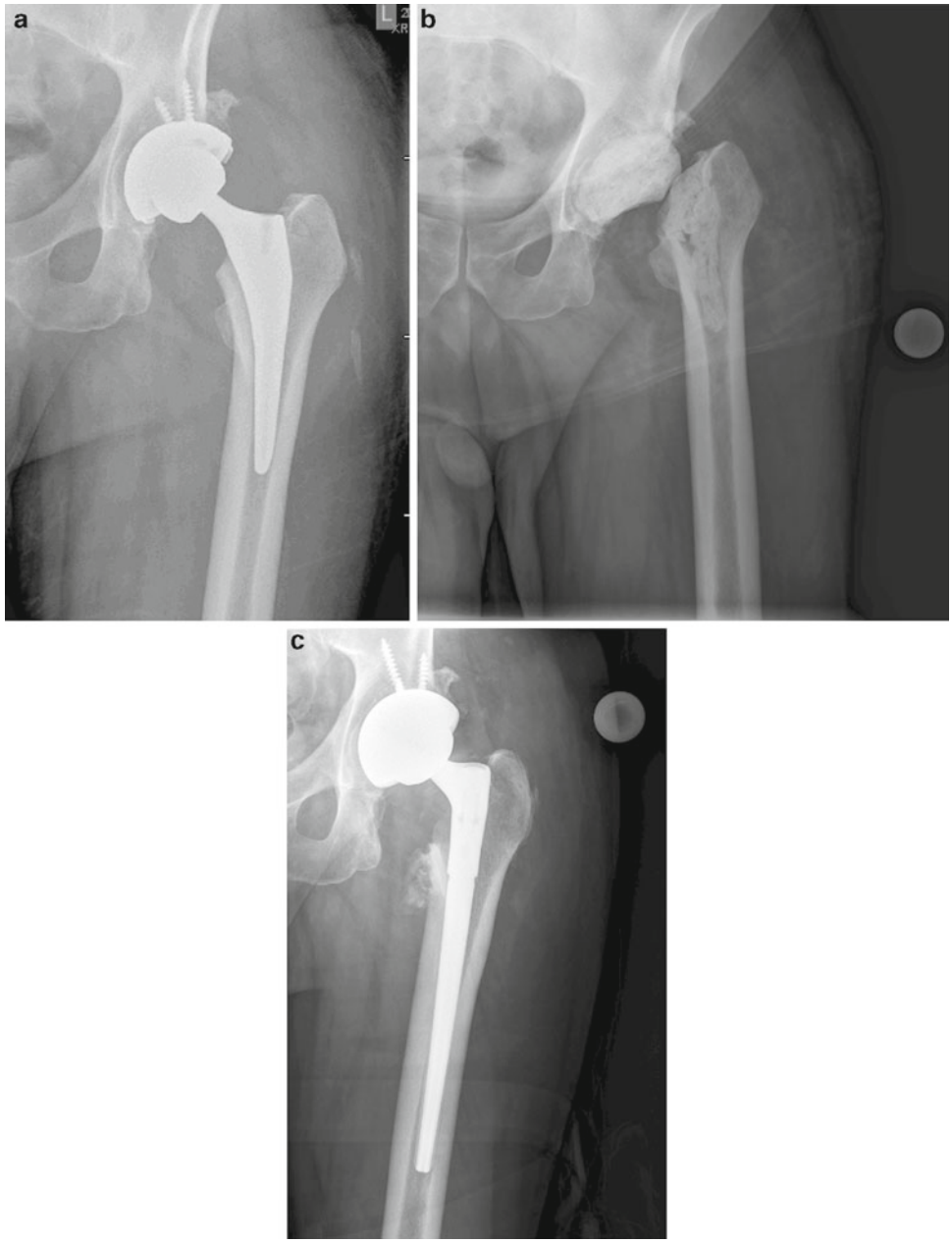

Fig. 13.2 (**a**) Preoperative views revealing a short tapered femoral stem in a patient with a deep infection. (**b**) Removal of the acetabular shell and femoral stem were followed by a static hip spacer. (**c**) A long modular tapered revision stem was utilized during the second-stage reimplantation

to preserve to acetabular integrity for future implantation. Several bone and soft tissue samples should be sent for culture of organisms. Additionally, the surgeon can take note of the acetabular bone loss to more confidently prepare for implant needs during reimplantation.

Once a thorough debridement has been accomplished, the surgical bed should be irrigated

with 6–9 L of sterile fluid. Pulse irrigators may provide for additional debridement via tissue agitation. There is controversy regarding the irrigator at this stage. While several studies have failed to show any advantage of the use of antibiotic irrigators [16], many surgeons continue to use such irrigators in an effort to eradicate the infection. Brown et al. [17] reported on the use of iodine-based irrigators after primary arthroplasty to decrease postoperative infection rates. Although this is an isolated retrospective study requiring further validation, many surgeons use various solutions in the hope of improving the eradication of organisms. At this point there are insufficient data to recommend a specific irrigation strategy, though a large volume of irrigation is recommended. Once the debridement is completed, it is advisable to redrape the patient and have the surgeon and assistants change gowns and gloves in order to avoid further contamination.

Construction and Insertion of the Static Cement Spacer

The purpose of the static cement spacer is to allow for ongoing antibiotic elution into the joint space and onto the bone surfaces. Although beads have been used in the past, most surgeons prefer solid spacer constructs, which are easier to remove at the time of reimplantation [18]. Furthermore, there is a lower risk of leaving retained cement at the time of reimplantation when the construct is a larger solid piece instead of several smaller beads.

The choice of cement to utilize for spacer block construction depends on several often interdependent variables. Antibiotic elution is the main consideration for a static spacer because mechanical strength is less important. Though several cement types may be combined with antibiotics to create a spacer block, the preference of most surgeons is to use Palacos cement (Zimmer, Inc., Warsaw, IN) given its superior antibiotic elution properties in most studies [19, 20]. However, it is important to note that antibiotic elution kinetics depend on many factors, including surface area and porosity of the cement spacer, in addition to the specific antibiotics chosen. The choice of optimal cement type may depend on these specific variables. In many studies, the elution kinetics one antibiotic is altered by the addition of another antibiotic.

The choice of antibiotics to mix with the cement is critically dependent on the organism sensitivity. Various combinations may be utilized, including compounds that provide antifungal activity. A common combination, especially when an organism has not been identified, is vancomycin and tobramycin. The amount of antibiotic to mix with the cement is another choice that is important. Establishing local concentrations well above the minimum inhibitory concentration of the organism is critical. It is important to note that the premixed antibiotic cements sold by manufacturers are for the purpose of prophylaxis, not treatment, and have far too little antibiotic to treat a PHI. In fact, several grams of antibiotic must be manually mixed with each 40 g bag of polymethylmethacrylate (PMMA) to allow for an appropriate level of elution into the joint space. While specific mixing ratios vary by surgeon, most utilize a combination of vancomycin and tobramycin when organisms reveal susceptibility to these drugs. Tobramycin has been shown to have better elution kinetics from PMMA than vancomycin in several studies [21–23]. A popular combination is to use 3.6 g of tobramycin powder and 3 g of vancomycin per every 40 g bag of PMMA [23]. Although mixing of the PMMA/antibiotic combination is more challenging than regular cement, it can be accomplished by either hand or mixing bowl techniques. Some surgeons add some extra liquid monomer to facilitate the mixing process. The effect of vacuum mixing on antibiotic elution varies depending on the cement type utilized.

Several types of static spacer constructs have been described, most of which include cement in the femoral canal and cement in the acetabulum. Some surgeons prefer shaping the cement constructs with commonly available operating room materials such as the nozzle of the cement gun or the bulb from a bulb irrigator. Others shape the cement by hand and insert it just before curing into the bone (Figs. 13.1a–c and 13.2a–c). However, it is important not to allow significant interdigitation

of the cement into the bone, as this may result in bone loss and other technical difficulties in removing the cement upon reimplantation.

Between Stages

After the first stage, the patient is usually limited to a toe touch weight-bearing capacity using a walker. Because the limb is significantly shortened, the patient usually has great difficulty controlling the hip during regular attempted activities.

Systemic antibiotics are started immediately and chosen to optimally treat the identified infection. Most surgeons favor 6 weeks of parenteral antibiotics immediately after the first stage. During this time, baseline and ongoing systemic tests such as CRP and ESR are measured to establish a trend of decreasing inflammation [24]. Additionally, the patient should be monitored carefully through this time for antibiotic toxicity and antibiotic levels may be monitored to avoid low and high systemic concentrations. Successful treatment with two-stage exchange arthroplasty may be related to maintenance of a post-peak serum bactericidal titer (SBT) of 1:8 dilution [25–27].

Once systemic antibiotic treatment is completed, a period of time ranging from 4 to 6 weeks off of antibiotics is observed to allow for any persistent infection to be identified. During this time, serial systemic tests such as CRP and ESR can be followed to demonstrate continued decline. If these tests show increasing systemic inflammation after antibiotics are stopped, the surgeon must be concerned about ongoing infection. Near the end of this antibiotic-free period, many surgeons proceed with a hip aspiration to attain a cell count and culture prior to reimplantation. Unfortunately, systemic tests often do not completely normalize before implantation and cell counts are difficult to interpret in the setting of a cement spacer. The presence of positive cultures, sinus tracts, or persistent drainage is almost invariable associated with persistent infection. Although there is currently no absolute test for the absence of infection before reimplantation, all efforts before reimplantation should focus on identifying possible persistent infection.

Reimplantation: The Second Stage

If the infection appears to be eradicated, the surgeon may choose to reimplant a prosthesis at about 10–12 weeks after the first stage. In cases where the patient is not fit for surgical intervention or chooses not to proceed with the risks of reimplantation, the static hip spacer may be left without removal indefinitely. However the surgeon should expect continued tissue contraction and thickening of the deep tissues as more time elapses, sometimes making reimplantation more difficult.

Again, the principles of tissue handling must be carefully observed upon exposure for reimplantation, avoiding the formation of skin flaps. Upon entering, the joint fluid and tissue samples should be sent for culture and analysis. Similar to the first stage, some surgeons prefer to also obtain a histological frozen section of tissue to provide additional data related to the diagnosis of infection, although this method has not been shown to be universally reliable. The hip is fully debrided and irrigated as if an infection were being treated, followed in many centers by a redraping of the patient and a changing of gowns by the operating staff.

The second-stage reimplantation then proceeds as a regular hip revision. Implants must be chosen based on the bone loss patterns of the femur and the acetabulum. Interestingly, one advantage of a two-stage procedure is that the bone adjacent to the cement is often well defined and somewhat sclerotic. After a first stage that utilizes a static spacer, the reimplantation often involves fibrotic and sometimes contracted capsular tissue that requires release or excision to create space for the implants.

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Two-Stage Exchange Hip Arthroplasty: Articulating Spacers

14

Glenn J. Kerr and Matthew S. Austin

Abbreviations

ETO	Extended trochanteric osteotomy
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSIS	Musculoskeletal Infection Society
MSSE	Methicillin sensitive *Staphylococcus aureus*
PJI	Periprosthetic joint infection
PROSTOLAC	Prosthesis of antibiotic loaded cement
THA	Total hip arthroplasty

Introduction

The incidence of primary total hip arthroplasty (THA) is estimated to increase 174 % to 552,000 procedures by the year 2030 and the demand for revision hip surgery may double by 2026 [1]. Periprosthetic joint infections (PJI) are estimated to occur in 1 % of primary THA and 4 % of revision THA procedures [2]. Thus, it can be extrapolated that the treatment of PJI will become much more common in the future [3, 4]. Once diagnosed, a chronic deep infection can be treated by one of several methods. Chronic suppression, irrigation and debridement, single-stage exchange, and two-stage exchange have all been described in the treatment of PJI [5–11]. Two-stage exchange is the generally accepted standard-of-care in North America [12–19].

Definition and Classification

A universal definition of PJI has been lacking until recently [20]. In an attempt to standardize the definition, the Musculoskeletal Infection Society (MSIS) endorsed the criteria outlined in Table 14.1. This set of criteria has subsequently been adopted by the American Academy of Orthopaedic Surgeons [21]. It is important to recognize that some PJI may not meet the strict criteria and clinical decision making is paramount in diagnosing and treating suspected PJI.

Classification of infection is based on the temporal relationship to surgery or to hematogenous seeding of the THA [22–24]. PJI may be stratified into four categories: Type I—early postoperative occurring within 4 weeks of surgery, Type II—late chronic infections which occur >4 weeks from surgery, Type III—acute hematogenous infections occurring at the site of a previously well-functioning prosthesis and Type IV—positive intraoperative cultures (two cultures) without clinical evidence of infection. Type I and III infections are treated with irrigation and debridement

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or two-stage exchange in North America, although controversy exists over the efficacy of irrigation and debridement [25]. Type II infections are treated with two-stage exchange and Type IV infections are treated with a prolonged course of antibiotics. The treatment of PJI depends on surgeon preference, infecting organism, patient comorbidities and a variety of other factors that are beyond the scope of this chapter.

Indications

A two-stage approach to an established PJI is indicated in most chronic infections, infection involving resistant or fungal pathogens and in immunocompromised hosts [15, 23, 26]. In North America, two-stage exchange may be indicated in acute infections involving resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and when gross purulence is present in the joint [15, 27, 28].

Table 14.1 MSIS definition of periprosthetic joint infection

Major
Sinus tract directly communicating with the prosthesis
A pathogen isolated from two separate soft tissue or fluid samples
Minor (must meet 4 of 6 below criteria)
Elevated serum ESR or CRP
Elevated synovial white blood cell count (WBC)
Elevated synovial neutrophil count (PMN%)
Presence of purulence in affected joint
Isolation of a pathogen in one soft tissue or fluid sample

Articulating Spacers

The goals of the interim construct during two-stage exchange are to enhance eradication of the infecting organism though drug elution, maintain limb length, facilitate exposure for revision surgery and improve functional mobilization [29]. Various types of cement spacers are described including static spacers (molded non-articulating cement fashioned to occupy space), antibiotic coated rods and nails used to roughly approximate the proximal femoral anatomy, preformed hemiarthroplasty devices, molds of hemiarthroplasty devices, and so-called PROSTALAC (Prosthesis of Antibiotic Loaded Acrylic Cement) implants (Fig. 14.1) [24]. A spacer may be composed of any type of cement however Palacos® (Zimmer, Warsaw, IN), which is radio-opaque with a high viscosity, has demonstrated the best antibiotic elution characteristics [30]. Other cement alternatives include Simplex® P (Stryker, Kalamazoo, MI) and Cobalt™ HV (BIOMET, Warsaw, IN). Antibiotics used in cement must be

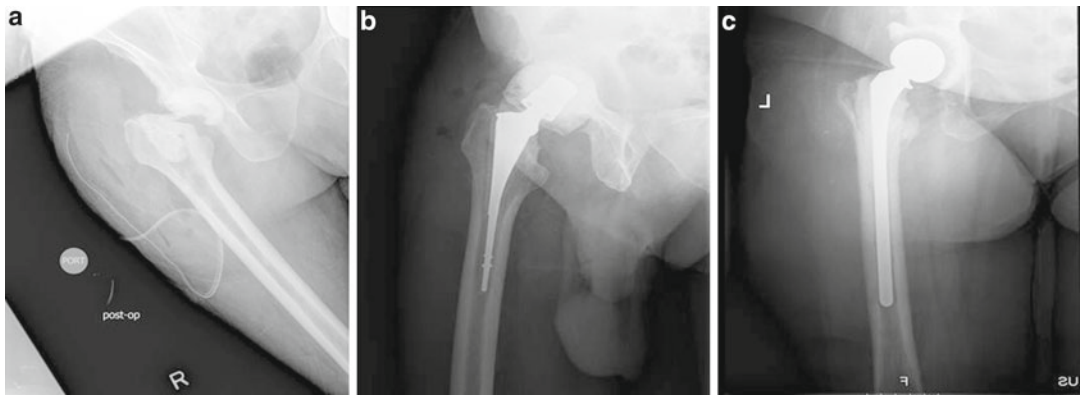

Fig. 14.1 (**a**) Static Spacer construct, (**b**) PROSTALAC with modular femoral head, (**c**) Cemented antibiotic coated stem and metal head with cemented poly

water soluble, heat stable, and elute at a bactericidal level for a prolonged period of time [22]. Masri et al. demonstrated a synergistic effect between tobramycin at a dose of 3.6 g and vancomycin at 1 g per 40 g packet of cement [31]. Tobramycin levels remained detectable after spacer explant at an average of 118 days; however Vancomycin levels were low or not detectable. Antibiotics are tailored to the infecting organism, when possible, and combinations such as vancomycin, gentamycin, and cefotaxime have been used successfully to eradicate infections [32].

In 1998 Younger et al. described the successful treatment of deep PJI of the hip using a two-stage articulating spacer with a success rate of 96 % [19]. A cement-on-cement spacer with a metal endoskeleton was initially utilized. This design later evolved into a metal on polyethylene articulation. Simplex or Palacos cement was used in combination with tobramycin, vancomycin, or penicillin. The authors endorsed the use of an articulating spacer to prevent limb shortening and to facilitate later revision. They recommended against the use of a cement hemiarthroplasty to avoid acetabular bone erosion.

Molds used to create an antibiotic coated implant, called the PROSTOLAC were subsequently developed and marketed commercially for the treatment of infection [29]. Wentworth et al. published on a series of 135 patients implanted with the PROSTOLAC using Simplex cement and a combination of 3.6 g of tobramycin and 1.5 g of vancomycin with an 82 % success rate. However, 38 patients withdrew from the study and 23 (17 %) did not undergo a second stage replantation or underwent resection arthroplasty. Others have published on modifications of this technique using different components for the endoskeleton and articulation [33, 34].

Surgical Technique

The process begins with preoperative planning, which is essential to the success of the articulating spacer. Patients may present with a wide variety of symptoms and infection should always be considered when evaluating a painful total hip. Patients commonly note lack of improvement following the index procedure. They may also have a history of prolonged drainage or wound healing issues [16]. Routine labs should be obtained including a C-reactive protein and erythrocyte sedimentation rate which have a demonstrated sensitivity of 97 % when used in combination [35]. Referral for hip aspiration follows if these markers are elevated [36]. It may be useful for patients to stop antibiotics for a minimum of 2 weeks prior to a planned aspiration to reduce the incidence of a false negative culture, if clinically appropriate. Other studies including radiographic evaluation should be obtained for planning purposes. Images of the femur should include the full implant, cement mantle and plug [19]. Bony involvement of the radiographic teardrop and migration of the acetabular component medial to Kohler's line is a contraindication for the use of a unipolar implant which could further migrate into the pelvis.

Surgical intervention for an infected total hip may be divided into three stages. The first stage begins with component removal, debridement, and spacer placement. This is followed by a minimum 6 week course of antibiotics, at least a 2 week antibiotic hiatus then further clinical and laboratory evaluation. Once the infection has been eradicated, the patient is returned to the operating room for spacer removal and revision arthroplasty. This approach may be modified based on specific patient and clinical circumstances which may prolong treatment or require repeat debridement. The timing of reimplantation surgery varies widely from a minimum of 6 weeks up to 9 months, depending on the infecting organism and the host [12–15, 19].

Knowledge of the in situ prosthesis should guide requests for instrument sets and implant specific extraction tools. Extensively coated cylindrical implants can be particularly difficult to extract and the surgeon should plan for an extended trochanteric osteotomy (ETO) [37]. An ETO can be quite useful and safe in this setting [38]. Morshed et al. reviewed 13 patients with a minimum of 2 years follow-up after an ETO in the setting of sepsis, noting union occurred in all

patients and eradication of infection was accomplished in 77 % of patients.

The prior incision should be used, when possible, to avoid skin compromise. The surgical approach depends upon surgeon preference but should be extensile. Following exposure, the acetabular component is exposed and removed. However, the femoral stem may need to be removed first in order to enhance acetabular exposure and facilitate cup removal.

A thorough debridement, including removal of all infected, nonviable tissue, draining sinus tracks, cement and metal debris should follow component removal [19, 28]. Sharp surgical dissection is recommended along with curettage of the acetabular bed and femoral canal. Finally, the hip is irrigated with a copious amount of saline solution. A gold standard for irrigation solution has not been established and fluid volume with dilution of the bacterial load should be the goal of this portion of the surgery.

The decision to proceed with an articulating spacer is based on the remaining host bone, particularly the acetabulum. Large cavitary defects involving the acetabulum, loss of supportive columns, and a thin or absent medial wall are relative indications for a static spacer or cemented metal on poly construct. The cement may be applied in a doughy state and molded to the contours of the acetabulum rather than pressurized. If there is adequate host bone a prosthetic mold or custom PROSTALAC can be safely employed (Fig. 14.2). A reamer or head trials can be used to gauge the appropriate head size. Provisional trials can be used to assess leg length and stability of the hip. Head and neck modularity is now commercially available and can assist with soft tissue tensioning and hip stability. A high-elution cement, impregnated with appropriate antibiotics, is recommended. The authors' preference is generally 3.2 g of tobramycin and 3 g of vancomycin per 40 g packet of cement. An extra vial of monomer may be helpful to reduce clumping with this large amount of antibiotic powder. The monomer may also be chilled to help with cement flow. The cement should be allowed to polymerize and harden ex-vivo in molded implants prior to insertion to facilitate later removal. Final range of motion and stability are then tested and the incision closed in layers. No deep drains are used to avoid diminution of antibiotic load from the wound bed [19].

The second stage of treatment usually involves parenteral antibiotics based on culture results in consultation with an infectious disease specialist. Antibiotics are continued for a minimum of 6 weeks or until there is a clear trend toward clinical improvement. The staged reimplant may be considered 2 weeks following cessation of antibiotics if the patient's incision and laboratory values (CRP and ESR) are trending toward normal [15]. Prior reports have explored the use of aspiration results, laboratory markers such as ESR and CRP and intraoperative frozen sections and surgical appearance of the hip [14, 15, 19, 37]. There is no universally accepted criteria for reimplantation and clinical judgment must be used on a individual basis. Patients infected with resistant organisms and fungal infections may require a more protracted course of treatment or repetitive debridement [14, 19, 26, 39].

Reimplantation surgery is the next stage of treatment. Surgical dissection and exposure may be challenging during this phase of the procedure. Tissue planes are often scarred with a proliferation of reactive and fibrous tissue, although this may be less prevalent with an articulating spacer [40]. Care should be taken to avoid fracture during hip dislocation and stem extraction. Intraoperative cultures and frozen sections may be obtained depending on institutional resources. Bony surfaces should undergo liberal curettage to remove biofilm followed by copious irrigation. Appropriate implants to address bone loss in the acetabulum and diaphyseal engaging stems for the femur should be on hand.

Postoperative Management

Following articulating spacer insertion, weight bearing is progressed according to surgeon and patient related factors. Weight bearing may be progressed with manufactured PROSTALAC implants, in some patients, as these devices are designed to provide greater durability and fatigue

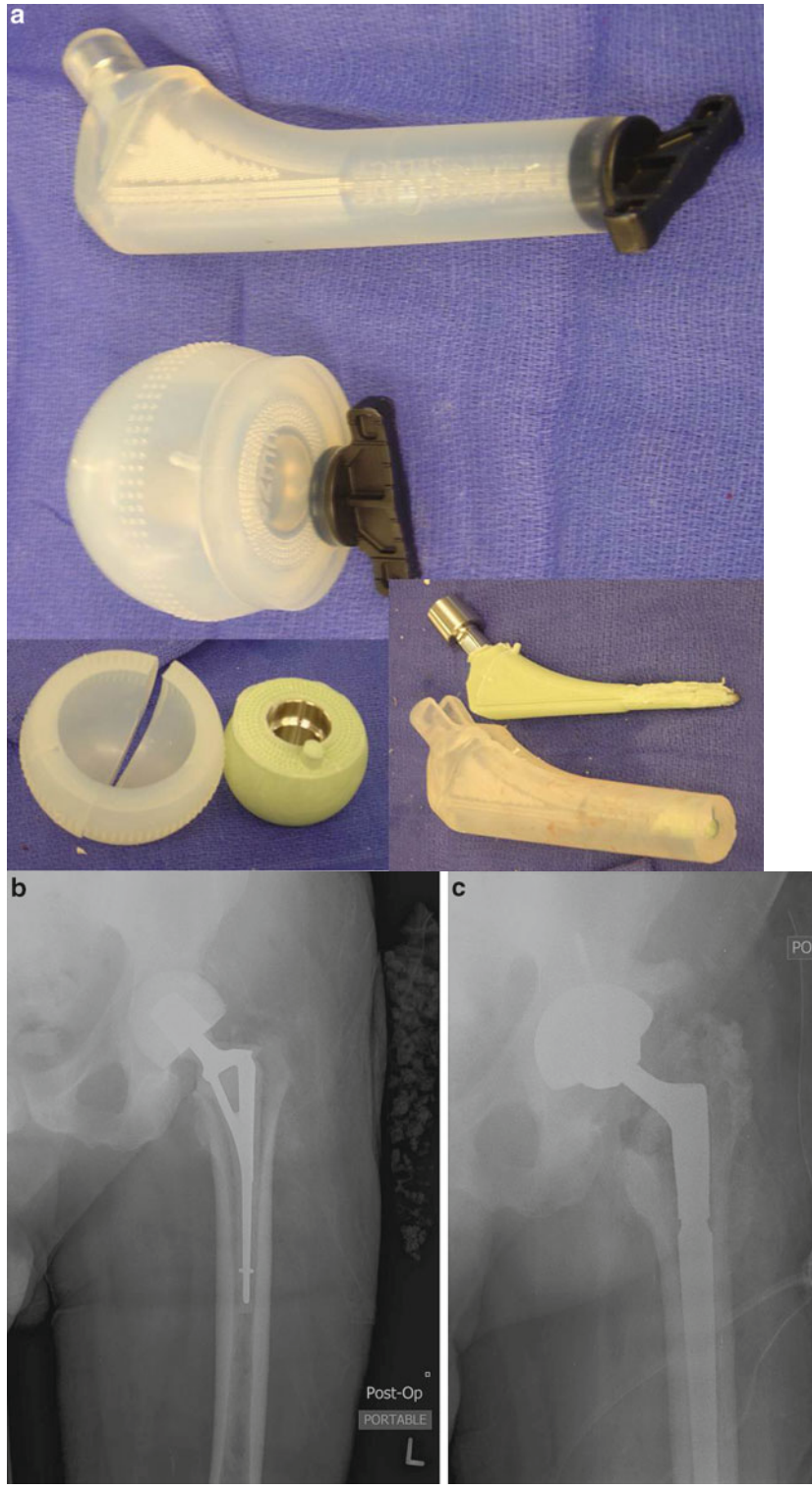

Fig. 14.2 (**a**) Monomer, cement and modular PROSTALAC molds (**b**) PROSTALAC following implantation (**c**) Successful revision to a modular femoral prosthesis and primary acetabular cup

strength as compared to fashioned implants using pins and wires [41]. The patient should be treated with venous thromboembolic prophylaxis. Therapy and activities may be progressed once the incision is healed, however, activities should be modified to decrease the incidence of implant or bone fracture, bone loss, or dislocation.

Pearls and Pitfalls

- Fascial planes should be recreated to facilitate exposure and closure for component explant and reimplantation.
- Extensive interdigitation of cement should be avoided if possible.
  - Cement and antibiotics are mixed by hand.
  - Apply cement in a doughy state prior to placement in non-molded articulating spacers.
  - Cement is molded around bony surfaces rather than pressurized.
- Explant of the antibiotic coated femoral stem may be challenging (Fig. 14.3).

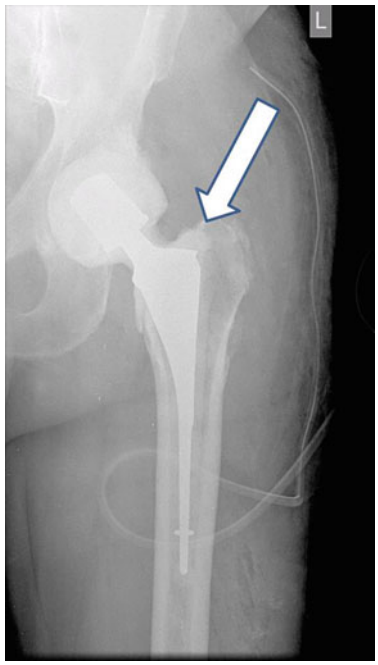

Fig. 14.3 Difficult revision following insertion of a PROSTALAC with significant cement at the shoulder of the implant interdigitating into the greater trochanter

  - Remove all soft tissue and cement around the shoulder of the implant to avoid damage to the greater trochanter.
  - A thin burr can be used to disrupt cement around the implant if there continues to be difficulty in removing the stem.
  - An extended trochanteric osteotomy may facilitate removal of the cemented spacer while allowing for improved visualization for preparation and implantation of the femoral component in some complex cases.
- Reverse curettes are extremely useful for removing biofilm and debris from the canal.

Results

There are no direct comparison studies evaluating the functional outcomes of static and dynamic hip spacers. A recent publication by Jaekel et al. found improved UCLA scores in patients with dynamic knee spacers compared to static spacers encouraging further research directed at articulating hip spacers [42]. In a study designed to address functional outcomes with articulating spacers, Scharfenberger reported on health-related quality of life compared to patients awaiting primary hip replacement [43]. Results in patients with a PROSTALAC demonstrated higher Western Ontario McMaster scores over patients awaiting hip replacement but inferior to patients 6 months out from primary total hip arthroplasty. In a study examining PROSTALAC function in patients with primary septic arthritis, Fleck et al. reported improvement of Harris Hip scores from 11 to 67 with the spacer and scores of 93 after definitive THA [40]. Others have reported functional Harris Hip scores between 56 and 70 with a PROSTALAC in place [16, 19]. Advocates for articulating spacers would stress improved quality of life and functional results compared to static spacers; however there is insufficient evidence at present.

There also continues to be controversy over single-stage exchange or direct exchange arthroplasty for chronic infections of the hip [10, 11, 44]. In one of the largest published series Buchholz et al. reported on over 583 cases with eradication of infection in 77 % and long term

Table 14.2 Results—two-stage exchange

Study	Prosthesis	Follow-up	# Hips	Success	Predominant organism	Comments
Durbhakula [13]	Molded Spacer	38 months	20	90 %	*Staph Aureus*	Spacer fracture was noted in 2 patients and the spacer was retained for definitive management in 2 additional patients
Hoffman [14]	Autoclaved spacer	76 months	42	94 %	*MSSA*	Large cohort lost to follow-up (36 %) making results questionable.
Kray [15]	Static spacer	2 years	32	96 %	*Staph Epidermidis*	Limited follow-up with only one recurrence. Used a molded static spacer.
Leung [40]	PROSTALAC	58 months	50 [38]	79 %	*MRSA*	Twelve patients died prior to follow-up evaluation. Substantially higher failure rate involving MRSA infections.
Lim [16]	Autoclaved spacer (48 %), handmade (37 %)	4.4 years	37	89 %	*MRSA*	Failures occurred only in the resistant group. Four patients did not clear the infection for the second stage.
Masri [17]	PROSTALAC	24–88 months	31	90.3 %	*MSSA*	Used hip aspiration results prior to proceeding with staged revision.
Sanchez-Sotello [18]	Handmade spacer (18 %) Resection arthroplasty (82 %)	2–16 years	169	92.9 %	*Coagulase Neg Staph*	Large cohort of patients treated with resection arthroplasty. No comment on functional outcomes and interim function.
Wentworth [30]	PROSTALAC	1–9 years	116	82.8 %	*Staph Aureus*	Looked exclusively at PROSTALAC implant, retrospective review.
Younger [20]	PROSTALAC	47 months	30	96 %	*Staph Epidermidis*	Original Study with only 3 weeks of IV antibiotics used in many patients. Provided functional outcomes between stages and following revision.

infection free rates of 50 % at 8 years [10]. A recent Markov decision-utility analysis favored direct exchange over two-stage exchange for both the surgeon and patient derived utilities [18]. Presently there are no published randomized controlled studies comparing the two approaches and such studies are unlikely to be conducted. Advocates for the direct exchange note the potential for decreased fiscal burden when successful and lower morbidity/mortality balanced against the risk of higher reinfection rates. The decision remains surgeon based and is largely regional.

Improved eradication and lower rates (82–96 %) of reinfection have been cited in multiple series examining two-stage exchange with the use of antibiotic cement [13–17, 23, 45]. Hofmann et al. report on a series of 42 patients with a 6 year follow-up and eradication of infection in 94 % of those available for review. Garvin and Hanssen noted an overall infection free rate of 91 % with two-stage exchange and 82 % with direct exchange in a review of multiple articles [24]. In one of the larger series, Sanchez et al. describe a 87.5 % infection free rate at 2–16 year follow-up in 169 hips [17]. Table 14.2 contains a

summary of 2-stage procedures. The treatment of drug resistant organisms, such as MRSA, may have increased failure rates with reported success in only 79 % of cases in a recent retrospective review of 50 patients [28].

Complications and pitfalls are often specific to the type of spacer used. Handmade spacers using a pin or small rod may be susceptible to spacer fracture or failure [33, 34]. Spacer instability has been reported in up to 15 % of cases and recurrent instability following revision surgery in up to 25 % of patients [46]. The large head of a hemiarthroplasty spacer should be appropriately sized during the surgery and offset, if possible, should be restored to appropriately tension the soft tissues. When using a cemented liner, particular attention should be given to the inclination and version of the implant and a large femoral head may reduce the risk of dislocation. Other pitfalls include the treatment of resistant organisms and the high morbidity of any infection. Lim et al. reported on the failure rates associated with a resistant organism (MRSA) with a 33 % failure rate in this group compared with no failures in the susceptible organism group [15, 27]. In his series, Fehring et al. noted 42 % mortality within 1–5 years following revision surgery and Leung et al. noted 24 % mortality with short-term follow-up, underscoring the serious implications of an infected prosthesis [28, 46].

Conclusion

Two-stage exchange using an articulating spacer has a high rate of treatment success with associated major complications including implant failure and interim instability. Spacers are designed to maintain limb length and promote patient mobility in the time between infected prosthesis removal and revision surgery. Combinations of antibiotics can be delivered in high concentrations at the site of infection improving treatment outcomes compared to results without an antibiotic spacer. There are no established criteria for the timing of reimplantation but it is generally performed between 6 and 12 weeks following implant removal in the setting of improved laboratory and clinical evaluation.

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Two-Stage Exchange Knee Arthroplasty: Static Spacers

15

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Two-stage exchange arthroplasty is currently the most commonly used treatment for infected total knee replacement in North America. Published reports have demonstrated a variable success rate for the procedure ranging from 67 to 91 % [1–5]. The procedure allows for placement of an antibiotic-cement spacer in the knee for local delivery of antibiotics, and at the same time provides a chance for systemic antibiotic therapy to effectively eradicate residual planktonic bacteria that remain in the knee after surgical debridement of the bacterial biofilm. Spacers also reduce dead space and maintain tension in the soft tissues to avoid contractures and potentially improve healing.

Cement and Antibiotic Elution

Elution of antibiotic from cement is a passive phenomenon in which antibiotics diffuse out of pores, cracks, and voids in the cement [6]. Elution rate and duration vary based on the type and dose of antibiotic used (first order kinetics) [7]. They also depend on the type and preparation of cement. Highly porous cement has been shown to have a higher and longer elution of antibiotics compared with its low porosity counterpart [8, 9]. A recent study [10] found that when antibiotic-impregnated polymethylmethacrylate (PMMA) products were mixed under atmospheric pressure, Palacos R+G (Zimmer, Warsaw, IN) produced a greater 5-day antimicrobial activity in vitro than Simplex P with tobramycin (Stryker, Kalamazoo, MI). This was attributed to the higher viscosity of Palacos [11, 12]. Further, vacuum-mixing increased their antimicrobial activity, with the highest increase seen with Palacos [10]. These findings corroborate the results of an earlier study showing higher antibiotic elution from vacuum-mixed Palacos [11]. The amount of antibiotics released from cement shows an exponential decline after day 1 of implantation [10, 11, 13]. Increasing the dose of the antibiotic leads to a higher and longer elution, not only due to the simple increase in concentration gradient for diffusion, but also by virtue of increased porosity of the cement [13]. In one study, low-dose antibiotics (1.0 g per 40 g of PMMA) resulted in an effective elution for an average of 2 days, intermediate-dose antibiotics (4 g per 40 g of PMMA) were effective for up to 21 days whereas high-dose antibiotics (8 g per 40 g of PMMA) had an elution that lasted for up to 60 days in vitro [14]. Therefore, hand-mixing of higher doses of antibiotics into the cement mixture is needed to treat prosthetic joint infections, whereas the low-dose antibiotics in commercial preparations are indicated for prophylaxis. They are currently FDA-approved for

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use in second-stage reimplantation when it is important to consider the mechanical strength of the cement-implant interface [10].

Antibiotic Types and Doses

Selection of antibiotics to be added to the cement spacer should be based on the type of the infecting organism. If the organism is unknown, antibiotics should be targeted against the most common pathogens causing prosthetic joint infection, namely methicillin-sensitive *Staphylococcus aureus*, coagulase-negative Staphylococci, *Staphylococcus* epidermidis, *Streptococcus*, *Enterococcus*, methicillin-resistant *S. aureus,* and Gram-negative bacteria [15–17]. Antibiotics used should also be heat stable, water soluble, and with a low allergenic potential [18]. The most commonly used antibiotics are vancomycin, tobramycin, gentamicin, and cephalosporins [18]. Vancomycin and tobramycin are commercially available in powder form and are therefore used most commonly. Gentamicin and tobramycin are also present in premixed commercial preparations. Fungal infections, although rare, require adding antifungal agents to the spacer, the type and dose of which remain yet to be determined. Recent studies have shown promising elution of voriconazole from cement in vitro [19, 20], whereas effectiveness of amphotericin B in cement is still questionable [21–23].

Doses of antibiotics should ideally be determined based on a resultant elution that will remain above the minimum inhibitory concentration (MIC) of most pathogens for the entire duration of spacer implantation. This aims at avoiding the development of drug resistance that may occur as a result of subinhibitory concentration of antibiotics and to minimize adherence of organisms to the surface of the spacer. For gentamicin, as low as 0.5 g per 60 g of cement has been shown to result in a local concentration that is above the MIC of most organisms for the first 48 h following surgery while maintaining a low serum concentration that avoids nephrotoxicity [24]. Adding 4 g of tobramycin or 4 g of vancomycin to 40 g of cement was reported to result in an in vitro elution that was above the MIC of *S. aureus* for 100 and 30 days respectively from Palacos, and for 20 and 15 days respectively from Simplex [13]. In cemented total hip arthroplasty using antibiotic-cement, measuring antibiotic concentration in hemovac fluid showed adequate elution of tobramycin over a 48-h period, and a less predictable elution of vancomycin. Tobramycin (1.2 g) or vancomycin (0.5 g) was hand-mixed with 40 g of cement [25]. In an in vivo study, Masri et al. [26] recommended that at least 3.6 g of tobramycin and 1 g of vancomycin should be added to each 40 g package of bone cement when antibiotic-loaded cement spacers are used to treat an infected total hip or knee arthroplasty. The authors noted that although it has been shown that adding higher doses of antibiotics resulted in higher and more sustained release in vitro [2, 14], increasing the dose of vancomycin from 1 to 2 g per package did not result in a significantly increased elution in their study [26]. However, increasing the tobramycin dose to 3.6 g per pack and using vancomycin in combination with tobramycin had a positive effect on vancomycin elution [26]. Another in vivo study demonstrated that using 4 g of vancomycin per 40 g of cement resulted in bioactive levels of the antibiotic at the time of second-stage surgery (average 107 days) [27]. Springer et al. showed that adding a total of 10.5 g of vancomycin and 12.5 g of gentamicin to a cement spacer made from Simplex bone cement did not result in systemic toxicity in a group of 34 patients with infected total knee arthroplasty. One patient had a temporary elevation in serum creatinine [17]. Despite these findings, systemic side effects of antibiotic-containing spacers have been reported in the literature [28, 29]. Spacers containing 2.9 g of gentamicin [28] and 3.6 g of tobramycin [29] resulted in acute renal failure in two elderly patients with mild preexisting renal impairment in two separate case reports. In both cases, serum antibiotic concentration measured 2 μg/mL [28, 29]. Two cases of tobramycin-induced acute renal failure have also been reported [30].

Surgical Technique

After thorough debridement and removal of components with special attention to minimizing bone loss, a cement mold of the extension gap is fashioned. Three to four packs of acrylic bone cement polymer is mixed with the antibiotic powder in a bowl followed by application of the liquid monomer. The mix is stirred with a spatula. The cement is allowed to cure until it is firm and is then placed in the extension gap while the knee is distracted. The cement block should be large enough to maintain adequate tension in the soft tissues and wide enough to rest on the cortical rim of the tibia [31]. The cement is allowed to harden with the knee in the extended position. Different techniques have been described to enhance fixation of the spacer block to the femur and tibia and to prevent migration. Superior and inferior pegs could be fashioned to fit into the femur and tibia, respectively [32]. Adding longer intramedullary extensions of the spacer has been described [31], with the advantage of antibiotic delivery into the medullary canal. Another technique with potential benefit in infected knees with deficient bone and collateral ligaments involves the use of an intramedullary nail inserted into the distal femur and proximal tibia. Cement is then introduced into the metaphyses, around the nail, and underneath the patella providing a state of "temporary knee fusion." This helps to achieve soft tissue healing, especially if a muscle flap is used in patients with chronically infected knees [33]. The surgeon must weigh the risk of using a metallic implant in the setting of chronic infection against the benefit of additional stability provided by the nail.

Indications for Static Spacers

Spacers were designed to facilitate reimplantation by minimizing soft tissue scarring and bone loss. In the 1980s, two-stage reimplantation was often done with no interim antibiotic spacer placed. In the 1990s, use of static cement spacers in the interim period became widespread [34]. Articulating spacers have been increasingly used since the late 1990s with the goal of improving quality of life in the period between stages as more knee flexion is permitted. Commercial molds, metal molds, implants, and hand-made spacers are used to create articulating spacers. They are designed to facilitate reimplantation by minimizing bone loss and soft tissue contracture and facilitating exposure. Another potential advantage is better ultimate knee flexion range following the second stage due to decreased immobilization between stages. However, an articulating spacer would not be the ideal choice in chronically infected knees with significant bone loss, extensor mechanism disruption, and collateral ligament insufficiency. It should also be avoided in patients with history of poor compliance and dementia [16]. In such cases, more stability is usually advantageous to allow healing, especially when plastic flaps are used. Joint immobilization has the added benefit of minimizing complications such as wound dehiscence, knee dislocation, fractures, spacer fracture, and particulate debris generation caused by the cement-on-cement articulation in a dynamic spacer [33, 35–37]. Complications related to static spacers are generally caused by displacement of an undersized static spacer block, which may result in significant bone loss, capsular contracture, and quadriceps scarring [31]. External bracing is also necessary with the use of static spacers.

Outcomes

Prospective randomized studies comparing the two spacer types are currently lacking. The vast majority of the studies citing improved range of motion [38], patient satisfaction [37], and ease of exposure at the time of reimplantation [39] with the articulating spacer report on individual case series with or without historical controls. Haddad et al. reported a 91 % success rate with the use of the PROSTALAC knee spacer in a group of 45 patients with infected knee arthroplasty. They noted decrease incidence of tibiofemoral dislocation in the group of patients that received a more constrained version of the PROSTALAC [35].

Another study showed a 12 % reinfection rate with the use of an all-cement articulating spacer. A femoral component fracture occurred in one case [40]. On the other hand, Haleem et al. reported a 16 % reoperation rate of two-stage knee arthroplasty revision using a static cement spacer. Nine knees (9 %) had component removal for reinfection and six knees (6 %) were revised for aseptic loosening [1]. One study showed an overall success rate of 74.5 % in treatment of infected total knee with a two-stage protocol using a static antibiotic spacer, with reinfection with same or different organism as the end-point [2]. Retrospective studies comparing the two spacer types showed a trend towards better function with articulating spacers but with no significant difference noted. Freeman et al. [34] found no statistically significant difference in reinfection rates or in postoperative total Knee Society scores between knees treated with static and articulating spacers. Knee Society functional scores showed a trend toward being better in patients in the articulating spacer group, however those patients were also significantly younger than patients in the static spacer group [34]. Another retrospective study comparing dynamic and static spacers showed similar reinfection rates, Knee Society scores, and range of motion between the two spacer groups [16]. Four patients in the dynamic spacer group experienced complications related to tibiofemoral instability and femoral component fracture. Emerson et al. [38] showed that patients with dynamic spacers had better average range of motion at follow-up compared with patients who had static spacers (107.8° compared with 93.7°). No clinical outcome scores were used. The reinfection rate was the same between the two groups [38].

Summary

Antibiotic spacers are an important tool in the management of periprosthetic joint infection. The concept of spacers has evolved from a static block in which the knee is immobilized in full extension to more conforming articulating surfaces that allow more knee motion, in an attempt to improve patients' quality of life before and after reimplantation. Static spacers are still indicated in knees with significant bone and soft tissue compromise to avoid complications related to mobility in the absence of the proper amount of constraint. Increasing the amount of antibiotics added to the cement results in a higher and longer elution but could lead to potential systemic toxicity. It also reduces the mechanical strength of cement which becomes a concern if mobility and weight bearing are to be permitted. The ideal dose of antibiotics to be mixed with cement remains unclear. Large doses have been demonstrated to be clinically safe, but have not shown to be cost-effective in providing better infection control.

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Two-Stage Exchange Knee Arthroplasty: Articulating Spacers

16

Jeremy Gililland, Walter Beaver, and J. Bohannon Mason

Introduction

Infection remains the primary biologic limitation of total knee arthroplasty (TKA), accounting for failure and complication in 1–2 % of total knees implanted [1–5]. The impact on patients and healthcare financing is undeniably harsh, with multiple surgeries and reinfections escalating the morbidity and cost. Despite sporadic reports to the contrary, irrigation and debridement with component retention has yielded inferior infection control [6]. Single-staged revision with removal of total knee components and replacement with new, sterile implants remains an attractive option as the patients are not exposed to a second surgery or a delay between surgical stages. The single-stage approach, though an improvement over debridement and retention, has been met with inconsistent success in infection eradication, ranging from 73 to 100 % [7]. Both surgical technique and bacterial speciation likely contribute to this variation and warrant further study.

For many years now the two-stage revision for infection control in TKA has remained the gold standard with reported successful infection control in 91–100 % [8, 9]. Interim treatment with a static, antibiotic-laden cement spacer helps maintain the joint space while delivering high-dose antibiotics locally. However, static spacers have been associated with interim bone loss due to extremity loading and spacer invagination into soft host cancellous bone, increased soft tissue scaring between stages, which may impact post-revision functional outcome, and contracture with lower knee range of motion (ROM) after revision [1, 9–12]. Articulating spacers were first introduced as an interim treatment for infected total knees in 1995 by Hofmann et al. in an attempt to improve patient function between revision stages and to address the issues with static spacers discussed above [13].

Benefits of Articulating Spacers

The documented benefits of articulating compared to static antibiotic spacers are numerous. The most obvious benefit derived from an articulating spacer may be ROM after the second-stage reimplantation. Several comparative studies have shown significantly improved ROM after an articulating antibiotic spacer [14–16]. In addition to improved ROM after articulating spacers, Choi et al. found less need for extensile exposures at the second-stage reimplantation procedure [15]. Chiang et al. also found significantly less patella baja along with improved ROM after articulating spacers in comparison to static spacers [14]. In addition to improved ROM, several studies have

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shown improved patient satisfaction after articulating spacers as compared to static spacers [14, 17–19]. Rogers et al. found that cyclical loading of antibiotic-laden cement spacers increased antibiotic elution from the cement [20]. This suggests that articulating antibiotic spacers may lead to increased local tissue antibiotic delivery as compared to static spacers; however, this has not yet been corroborated in in vivo studies, as eradication rates have been similar between static and articulating spacers. Fehring et al. found less bone loss between the spacer stage and the final reimplantation stage with articulating spacers compared to static spacers [12]. Taken together, these findings suggest that, when compared to static spacers, articulating antibiotic spacers may improve patient outcomes while simplifying the second-stage reconstruction.

Indications and Contraindications for Articulating Spacers

In the vast majority of instances when infection occurs following primary TKA and a two-stage spacer interval is contemplated, an articulating spacer can be used. Additionally, most revisions that become infected can also be managed with an interval articulating spacer. However, in order to utilize an articulating spacer several criteria must be considered.

First, adequate host bone must remain to accept the spacer. In cases of extreme bone loss it is important to control for rotational forces that will occur with knee flexion. This may require supplemental diaphyseal extension via antibiotic-coated rods or stems (Fig. 16.1). Second, sagittal plane control requires a functioning and centrally located extensor mechanism. Inability to centralize the extensor mechanism will lead to sagittal translation of the femur relative to the tibia and difficulty obtaining proper patellar localization at the time of subsequent reimplantation. Finally, relative stability of the collateral support of the knee between explantation and reimplantation is required for flexion. Patients without intact collateral ligaments can still receive an articulating spacer provided that the sleeve of scar tissue aids in inherent support of varus or valgus stress, or an external articulating brace is applied. In cases without collateral support, patients should not be allowed to weight-bear without external bracing.

Contraindications for articulating spacers are few, yet may reflect a bias toward use of non-articulating spacers in more extreme settings. Contraindications include extreme host bone loss where the ability to anchor a mobile spacer to host bone is questionable, extreme ligamentous laxity, absence of an extensor mechanism, and inadequate soft tissue coverage or viability to allow for motion of the articulating spacer. Finally, in end-stage infection management in which either the host is not considered a suitable candidate for subsequent reimplantation or if fusion is the next surgical step, a non-articulating spacer may be more appropriate.

Outcomes of Articulating Spacers

Articulating antibiotic spacers have been utilized successfully in the treatment of periprosthetic joint infections (PJIs). Several groups have documented success with articulating spacers in the treatment of septic TKAs, with success rates ranging from 71 to 100 % where success was defined as lack of recurrence of infection [5, 9, 10, 13, 17, 21–27]. Similar results have been shown with the use of articulating spacers for the treatment of septic total hip arthroplasty, with success rates ranging from 92 to 96 % [11, 22, 25]. In addition, several studies have been performed to directly compare the results of static and articulating antibiotic spacers for the treatment of PJI in TKA [12, 14–16, 19, 28].

In a retrospective review comparing static spacers to metal on polyethylene articulating antibiotic spacers, Choi et al. found no significant difference in the success of either treatment at mean 58-month follow-up with 71 % of the articulating group and 67 % of the static group having eradication of infection. They commented on the need for more extensile exposures at the time of reimplantation in the static spacer group [15]. Fehring et al. found no difference in the rate of infection eradication, HSS knee scores, operative

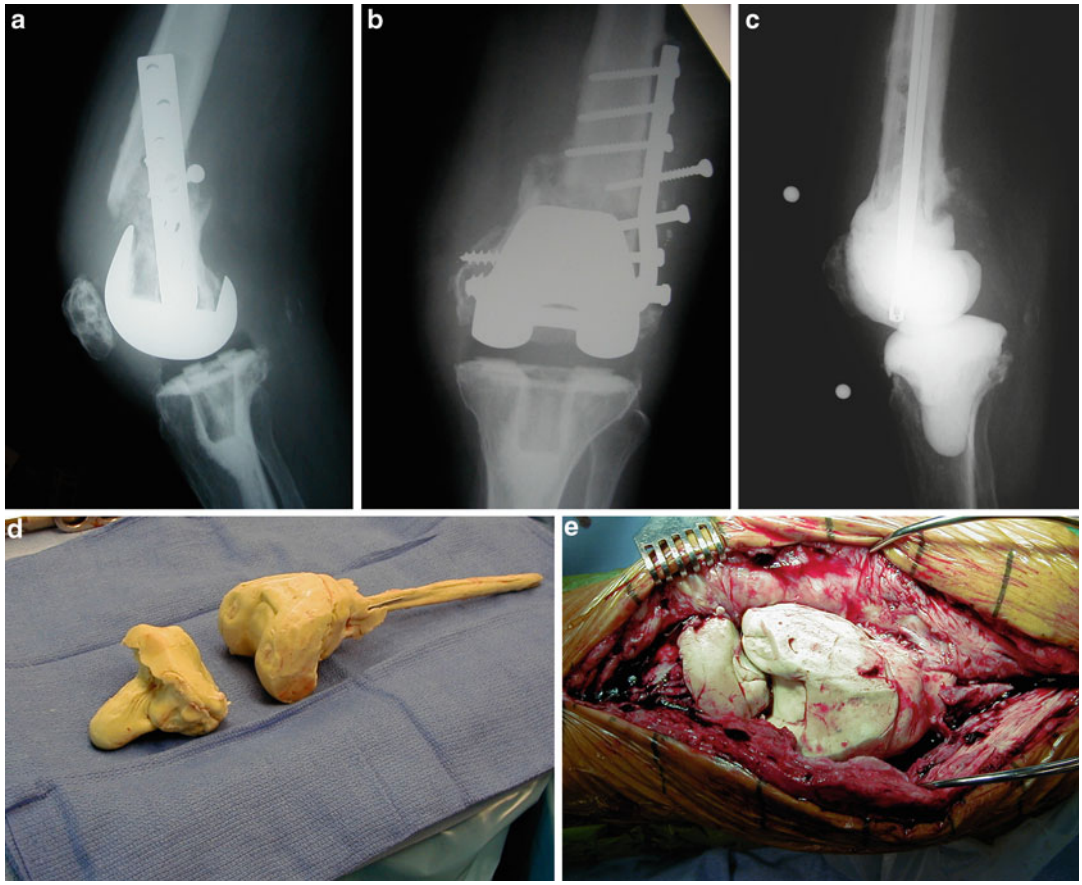

Fig. 16.1 Articulating antibiotic spacer in the setting of extreme bone loss. (**a**, **b**) Preoperative lateral and AP radiographs of infected nonunion of periprosthetic supracondylar femur fracture. (**c**) Postoperative lateral radiograph of implanted articulating antibiotic spacer with diaphyseal extension on the femoral side using an antibiotic coated rod. (**d**) Custom articulating antibiotic spacer. (**e**) Intra-operative photograph of implanted custom articulating antibiotic spacer

times, need for constraint at reimplantation, or need for extensile exposures in their retrospective comparative study of static and articulating antibiotic spacers. They also found a trend toward improved ROM in the articulating spacer group and significantly more bone loss after the spacer in the static group [12]. In a subsequent retrospective comparative study with longer follow-up, this same group again found similar success rates and Knee Society scores between the groups, while they did find that there were significantly more good to excellent scores in the articulating group [19]. In their 2007 retrospective comparison of articulating and static spacers, Hsu et al. found no difference in the eradication of infection with either technique, while they found improved ROM, better knee scores, and less bone loss in the articulating spacer group [28]. Similarly, in another retrospective comparative study, Park et al. found similar success rates with these two techniques with improved ROM and knee scores in the articulating spacer group [16]. However, very few prospective studies have been performed to compare articulating spacers to static spacers in the staged treatment of PJI.

In one of the only prospective randomized comparisons available, Chiang et al. compared the outcomes of 23 articulating antibiotic spacers to 22 static antibiotic spacers for the treatment of septic TKA. Similar to the retrospective literature,

they found no difference in the eradication of infection between groups with 86 % success in the static group and 91 % success in the articulating group. They found improved functional scores, satisfaction rate, and ROM after reimplantation in the articulating group. Additionally, one-third of the patients in the static group ended up with patella baja as compared to none in the articulating group [14].

Several retrospective comparative studies have been performed comparing septic and aseptic revision TKAs. Barrack et al. compared 28 two-stage septic revision TKAs with the use of static spacers to 99 aseptic revisions. At mean 36-month follow-up, they had a 93 % success rate for eradication of infection in the septic group. They found that postoperative ROM and Knee Society clinical and functional scores were lower in the septic group. Additionally, 23 % of the septic revisions were unable to return to ADLs as compared to only 7 % in the aseptic group. However, despite these inferior results in the septic group, they found an equal degree of patient satisfaction in both groups [29]. In contrast, Meek et al. compared 54 septic revision TKAs with the use of an articulating spacer to 57 aseptic revisions. At mean 41-month follow-up, they had a 96 % success rate for eradication of infection in the septic group. They found no difference in the degree of bone loss between the groups on either the tibial or femoral side. No differences were found between the groups in terms of preoperative and postoperative ROM HSS knee scores. However, the septic revisions were found to have significantly higher postoperative Oxford 12-item knee scores and WOMAC scores in terms of function, pain, and stiffness. In addition patient satisfaction was higher in the septic group [18].

Techniques for Articulating Spacer Construction

In their original description of the staged treatment of septic TKAs, Install et al. utilized a resection arthroplasty and splint for the first stage, followed by reimplantation after treatment with antibiotics. They described good success with this technique in terms of eradication of infection, but noted that reimplantation surgery required extensile exposure. Twenty percent of which had and extensor lag and another 20 % requiring a patellectomy in order to close the wound at the time of reimplantation [30]. From this experience, the concept of static antibiotic-laden block cement spacers arose. However, staged revisions with static spacers were still found to be complicated by the need for more extensile exposures at reimplantation, the development of patella baja, poor ROM after reimplantation, and bone loss secondary to the static spacer [12, 14, 15, 28, 29]. This led to the utilization of articulating spacers in the staged treatment of septic TKAs. A variety of techniques have been described in the literature for the construction of articulating antibiotic spacers for use in two-stage revision strategies for both the hip and the knee [9, 11–13, 15, 19, 25–28, 31, 32]. These techniques range from handmade cement spacers to the use of new arthroplasty components to optimize motion between stages.

Goldstein et al. described creating handmade articulating spacers by wrapping foil around the end of the femur and the proximal tibia, lubricating the foil, packing cement around the foil, and shaping this into a femoral and tibial component. The foil is then removed and the handmade femoral and tibial components are used to create an articulating spacer [31]. Villaneuva et al. have also described success using hand molded articulating spacers using a Homan retractor, a curved osteotome, and a burr to shape the components [27, 32].

Spacer molds, both commercially available and custom-made, have been utilized successfully for the construction of articulating antibiotic spacers [9, 12, 19, 26, 28]. Custom molds can be made from dental putty, polypropylene, or cast stainless steel [12, 26, 28]. In our institution, we have been utilizing custom cast metallic molds as well as commercially available molds for the creation of articulating antibiotic spacers (Fig. 16.2).

Hofmann et al. described success with autoclaving the explanted femoral component from a septic TKA and loosely cementing this component

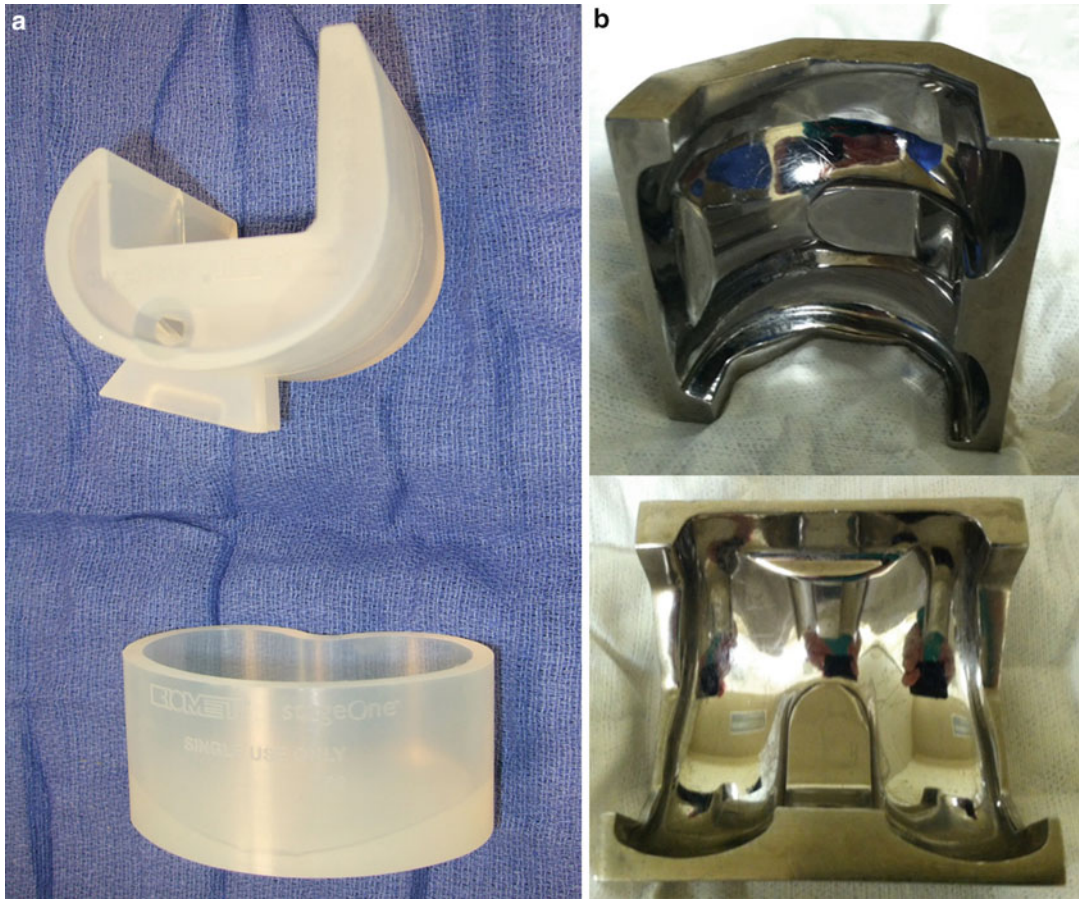

Fig. 16.2 (**a**) Photograph of commercially available spacer molds. (**b**) Photographs of custom made cast stainless steel spacer mold

and a polyethylene tibial insert with antibiotic cement [13, 24]. Choi et al. also described success with this technique and with the utilization of new femoral components in lieu of reused autoclaved femoral components [15].

The amount and type of antibiotics mixed into the cement for an antibiotic spacer is quite variable between different described techniques. However, Joseph et al. compiled a list of antibiotics that can be mixed with cement and the reported doses of those antibiotics that can be used in cement spacers (Tables 16.1 and 16.2) [33]. These lists can be very helpful when preparing to create an antibiotic spacer, especially if cultures have been obtained and the antibiotics can be targeted to treat the cultured organisms.

Articulating Antibiotic Spacer for Infected Total Knee Arthroplasty: Technique

Preoperative: Successful treatment of an infected TKA is dependent on isolation of the organism. Antibiotic treatment can then be organism-specific. Infectious disease specialists comanage the patient. PICC lines are initiated for ease of antibiotic delivery.

Operation: Once in the operating room (OR), the patient is placed in the supine position on the OR table. After proper anesthesia is given, the patient is properly positioned. The majority of the operation is performed with the knee in full extension

Table 16.1 Reported doses[a] of antibiotics used in antibiotic-impregnated cement

Antibiotic	Dose for prosthesis fixation	Dose for spacers and beads
Amikacin	1 g	2 g
Cefazolin	NR	4–8 g
Cefotaxime	3 g	NR
Cefuroxime	1.5–3 g	NR
Clindamycin	NR	4–8 g
Erythromycin	0.5–1 g	NR
Gentamicin	1 g	2–5 g
Ticarcillin	Not appropriate	5–13 g
Tobramycin	1.2 g	2.4–9.6 g
Vancomycin	1 g (vancomycin P)	3–9 g (vancomycin P or L)

P ultrafine powder, *L* lyophilized, *NR* not reported in the literature

[a]Per 40 g batch of cement

Table 16.2 Antibiotics used in antibiotic-impregnated cement

Can be mixed with cement				Decreased activity because of cement heat	Adversely affected by cement curing
Amikacin	Cefuzonam	Erythromycin	Penicillin	Chloramphenicol	Liquid gentamicin, clindamycin, etc. (because of aqueous content)
Amoxicillin	Cephalothin	Gentamicin (powder)	Polymyxin B	Colistimethate	Rifampin
Ampicillin	Ciprofloxacin	Lincomycin	Streptomycin	Tetracycline	
Bacitracin	Clindamycin (powder)	Methicillin	Ticarcillin		
Cefamandole	Colistin	Novobiocin	Tobramycin		
Cefazolin	Daptomycin	Oxacillin	Vancomycin		
Cefuroxime					

or 90° of flexion. A knee holding device is used to easily obtain these positions. A tourniquet is used for the procedure.

The knee is then prepped and draped in the usual sterile fashion. If possible, the old incision is used. Adequate length of the incision is paramount to obtain excellent exposure and to prevent damage to the soft tissues. Proper subcutaneous flaps are made to expose the extensor mechanism. A pin or short headed screw is placed at the top or the medial 1/3 tibial tubercle to help avoid infra-patella tendon avulsion. Releases are carried out in the usual fashion to gain exposure and again to avoid soft tissue damage. Cultures (both fluid and soft tissue) are sent.

After proper exposure to the knee, a synovectomy is performed and the polyethylene component is removed. This will remove tension on the soft tissues and aid in exposure. The knee is then flexed to 90°. A micro-sagittal saw is used around the exposed area of the femoral component. Thin osteotomes are also used to loosen the component. Care must be taken to loosen the component from the posterior condyles. This is the most difficult area to expose. The femoral component

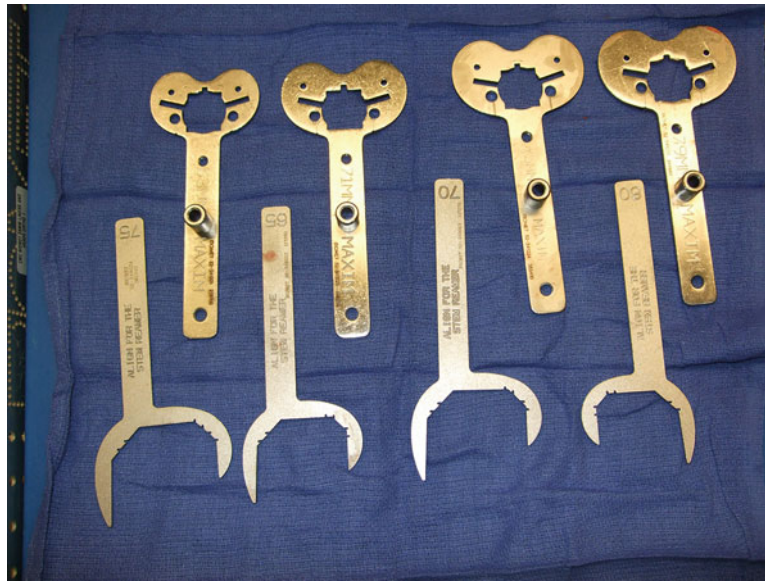

Fig. 16.3 Silhouettes used to size femur for appropriate mold selection

should then easily be removed with minimal bone loss.

After removal of the femoral component, exposure to the tibia is greatly improved. Again, using the micro-sagittal saw and thin osteotomes, the tibial component can be removed with minimal bone loss. A single-sided oscillating saw can be used to free the posterior-lateral side of the component from the bone and cement. This is the most difficult area to expose. The patella component is removed with a saw. The remaining pegs can easily be removed with a large drill or pencil-tipped burr.

A copious debridement to remove all necrotic tissue and retained cement is carried out. Hand reaming is then used to open the canals of both the tibia and femur. The saw is used to skim-cut the distal femur and proximal tibia. The tibia and femur are then sized for the proper molds. Using silhouettes (Fig. 16.3), the femur is sized, with tibial templates, the tibia is sized, the corresponding molds are then opened (Fig. 16.4).

Antibiotic cement rods are then made for insertion into the canals of both the femur and tibia. The type of cement and antibiotics are a personal choice (Fig. 16.5). Placement of a cut K-wire into the cement rods may aid in later removal. These are usually hand rolled to the proper length and diameter.

Cement and antibiotics are then mixed for the femoral component. Again, the type of cement and antibiotics are the surgeon's choice. A portion of an extra vial of monomer (liquid) is needed for mixing the cement when using antibiotics to obtain the proper consistency to inject into the mold. The cement for the femoral component is mixed for use in a cement gun (Fig. 16.6). The correct adaptor (Fig. 16.7) is needed to fit the opening in the mold. The antibiotic cement is injected into the mold (Fig. 16.8) until the mold is filled. Do not over-pressurize the mold. Once the cement has cured, a scalpel is used to score the midline of the mold (Fig. 16.9). The plastic mold is then easily removed (Fig. 16.10), leaving the cement femoral component ready to be inserted (Fig. 16.11).

The antibiotic cement component for the femur is placed on the femur without cement. Spacer blocks are then used to determine the thickness of the tibial cement spacer (Fig. 16.12). Once the thickness is determined, the antibiotic cement is placed into the tibial mold to the predetermined thickness and left to cure (Fig. 16.12). It is then easily removed for the mold using a

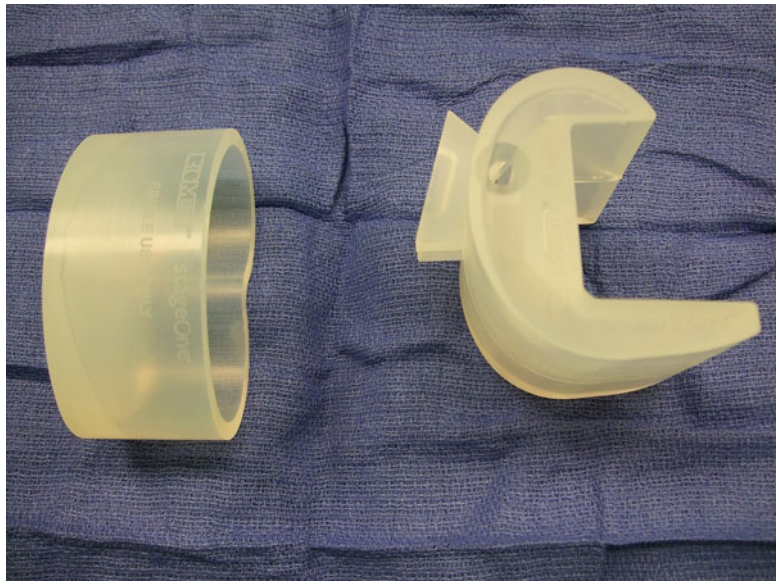

Fig. 16.4 Commercially available spacer molds for both the tibia and femoral components of the articulating spacer

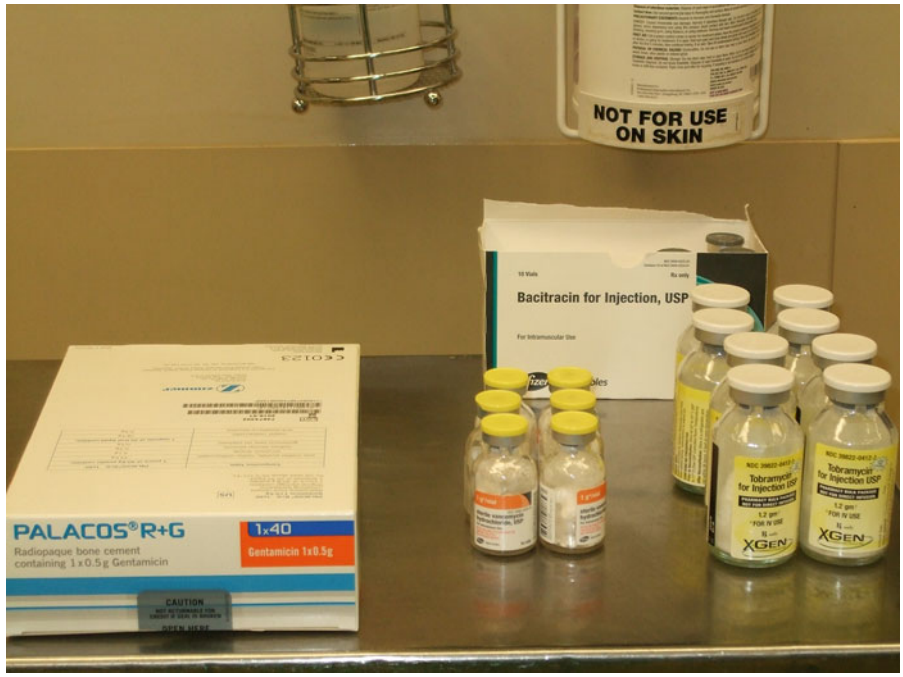

Fig. 16.5 Cement and powdered antibiotics

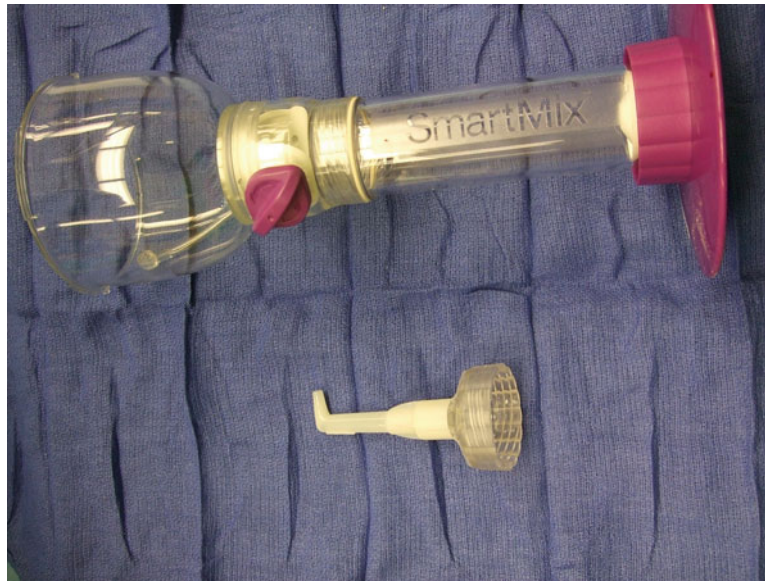

Fig. 16.6 Cement gun to be utilized for injection of antibiotic cement into molds

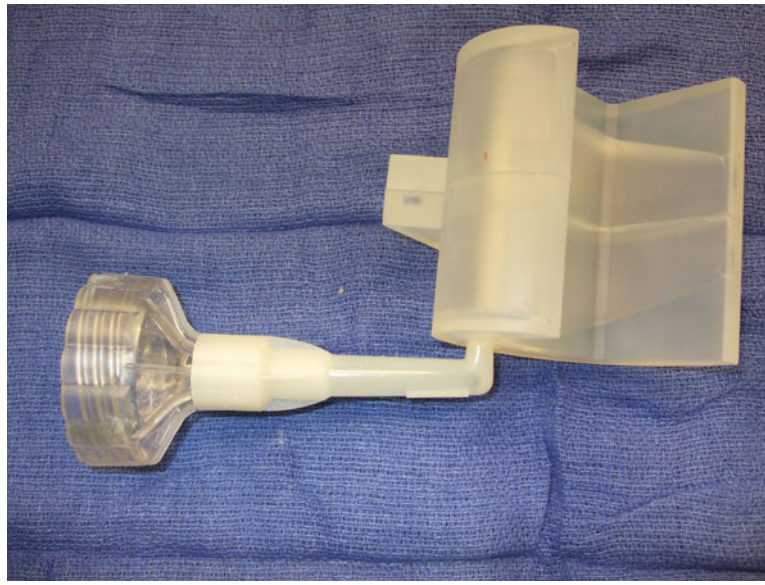

Fig. 16.7 Adapter connecting cement gun and spacer mold

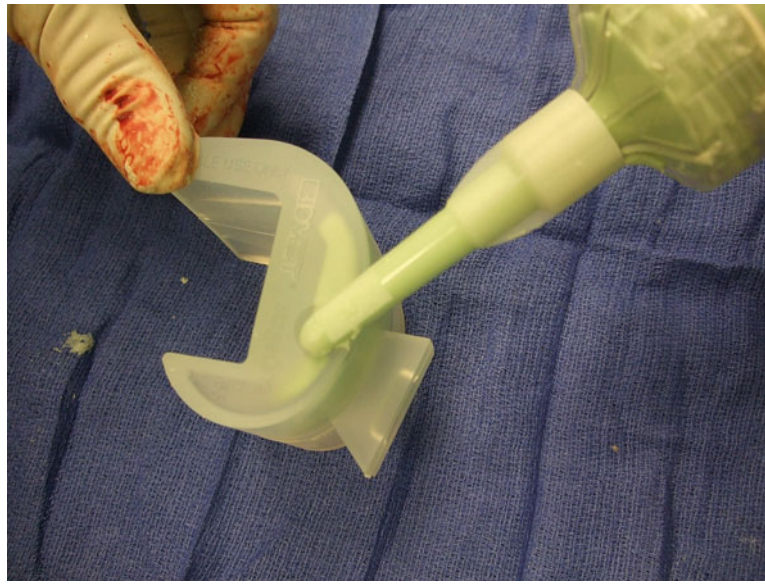

Fig. 16.8 Antibiotic cement being injected into femoral spacer mold

Fig. 16.9 Scalpel used to score the midline of the femoral mold in preparation for removal

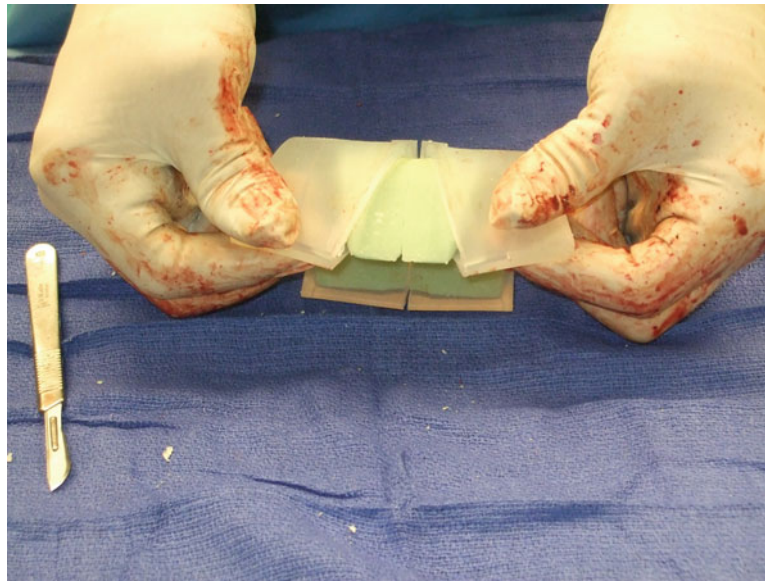

Fig. 16.10 Mold being peeled away from the underlying femoral component

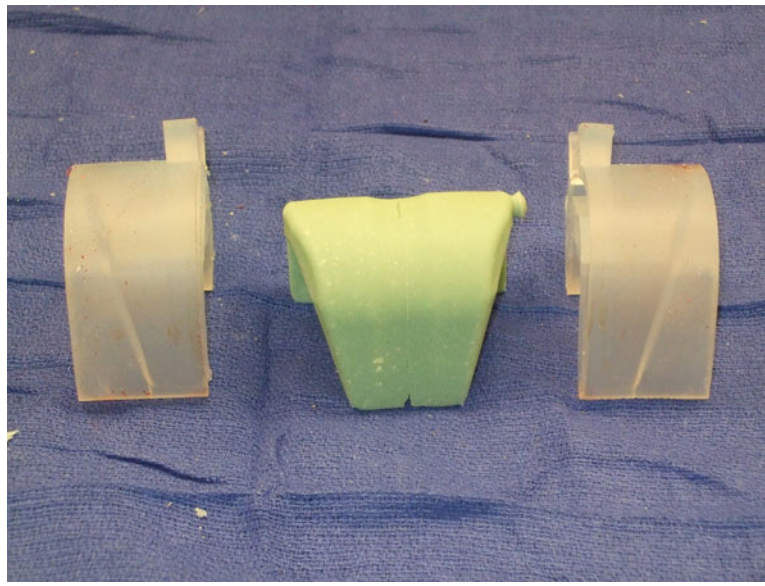

Fig. 16.11 The resulting femoral component

freer elevator (Fig. 16.13). The tibial component is ready for implantation (Fig. 16.14).

After the knee has been debrided and the cement spacers have been prepared, the tourniquet is released and bleeding is controlled with electrocautery. A final irrigation is accomplished and the final cement with antibiotics is mixed for implanting the components. The rods are placed in the canal of the femur. Cement is placed on the backside of the femoral component and the component is inserted on the femur with hand pressure. Excess cement is then removed. The

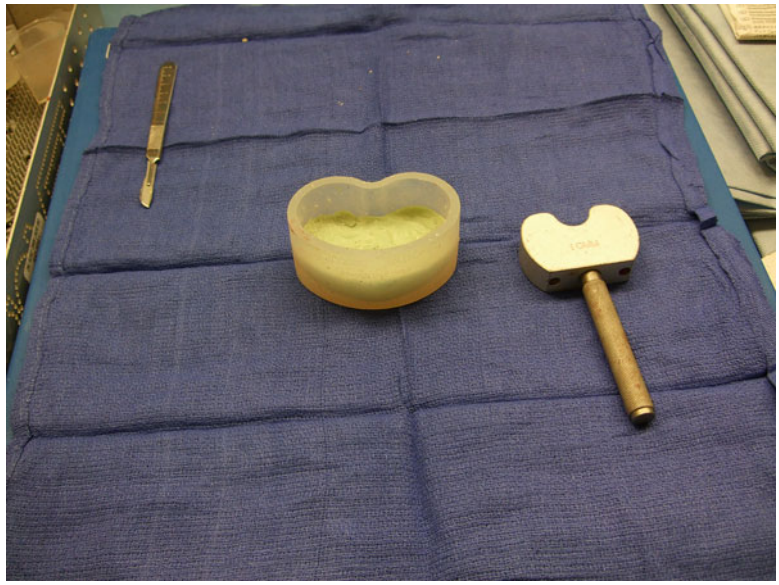

Fig. 16.12 A spacer block is used to determine the thickness needed for the tibial component and antibiotic cement is then placed into the tibial mold to the determined thickness and allowed to cure

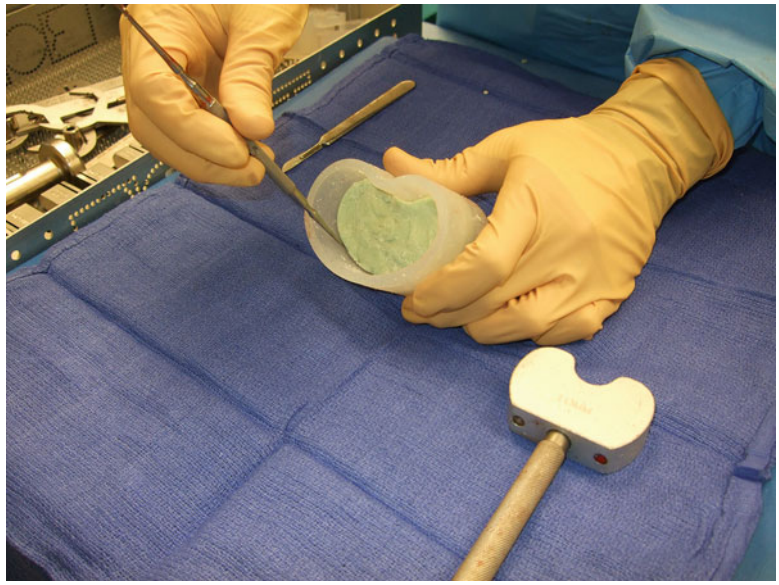

Fig. 16.13 Tibial component removed from the tibial mold using a freer elevator

cement rod is placed in the tibial canal and a small amount of cement is placed on the proximal tibia. Cement is placed on the backside of the tibial component and it is inserted with the knee in flexion. The knee is brought into extension and excess cement is removed (Fig. 16.15). The wound is irrigated. A drain is placed and the knee is closed in the usual fashion using non-braided, absorbable sutures. A dressing is placed along with a knee immobilizer.

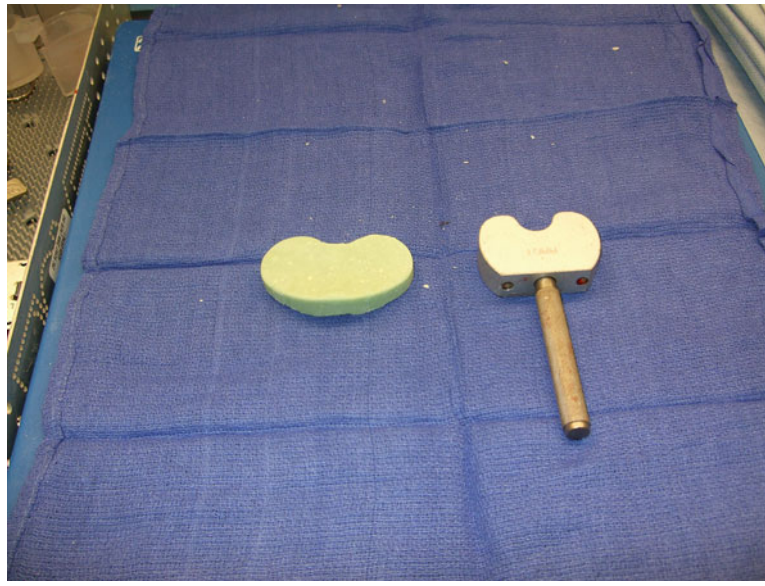

Fig. 16.14 Tibial component ready for implantation

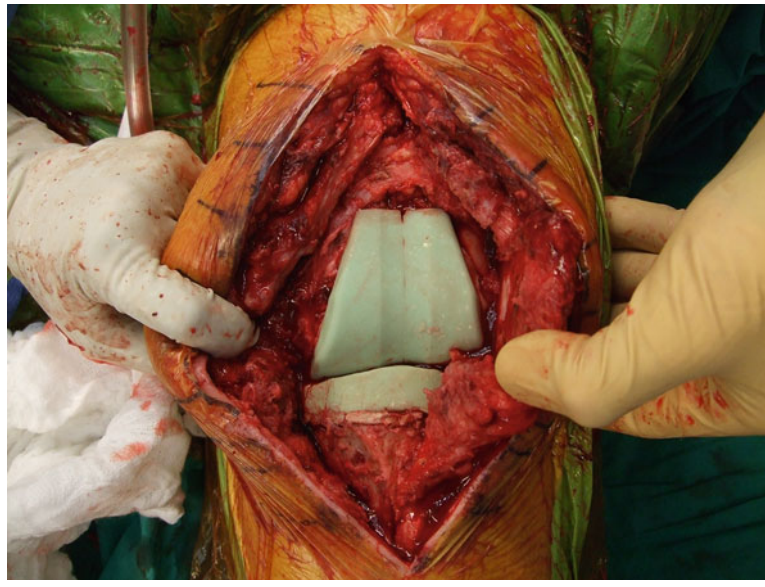

Fig. 16.15 Intra-operative photograph of implanted articulating antibiotic spacer

Postoperative care: The knee immobilizer is left for the first 3 weeks postoperatively to allow for the soft tissues to heal. Weight bearing is 1/3 to 1/2 depending on the weight of the patient. After 3 weeks, if the soft tissues are healed, the immobilizer is removed and the patient can begin ROM exercises.

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Knee Arthrodesis

17

Glenn J. Kerr and Javad Parvizi

Abbreviations

DBM	Demineralized bone matrix
PJI	Periprosthetic joint infection

Introduction

Since early descriptions of knee fusion by Hibbs in 1930 for tuberculosis, surgical techniques and indications for knee arthrodesis have evolved and narrowed [1]. Successful knee arthrodesis for primary septic arthritis approached fusion rates near 100 % [2–4]. Currently, the majority of knee fusions are salvage procedures for periprosthetic joint infections (PJIs) or oncologic procedures with higher failure rates [5–19]. Several methods of knee fusion are described including intramedullary devices, external fixators, and compression plating [3, 4, 20–26]. Charnley and Baker originally described compression arthrodesis for knee fusion which has evolved into the use of more modern external and ring fixators [3, 21]. Intramedullary fusion was initially described using long intramedullary nails such as the Kuntscher nail which spans from the greater trochanter to near the tibial plafond [6, 17, 18, 24, 27–38]. Current intramedullary implants are modular allowing for knee fusion through a single incision [20, 22, 39–44].

Techniques for Knee Arthrodesis

Fusion rates vary among the different techniques and the choice largely depends on surgeon preference, institutional experience, and patients-related factors. Fusion rates for the knee using intramedullary devices are reported between 80 and 100 % with successful fusion rates for PJI between 76 and 95 % [17, 20, 27, 32, 37, 43]. Lower rates of fusion have been reported for external fixation ranging from 43 to 71 % [9, 10, 14, 24, 45, 46] with improved results between 88 and 95 % when utilizing hybrid and Ilizarov frames [21, 47]. Arthrodesis using plate fixation is described and has a high rate of success in several limited series [23, 48]. Regardless of the method chosen, fusion is improved through adequate bone contact and elimination of the infection [43, 45].

Early intramedullary knee fusion techniques were very demanding often requiring intraoperative modifications and were associated with prolonged operative times and blood loss [6, 29, 30, 49]. Current techniques have higher fusion rates

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Table 17.1 Knee fusion alternatives

Author	Fusion type	Patients	Fusion rate (%)	Blood loss	Operative time (h)	Complications (%)	PJI (%)
First generation nails							
Donley [30]	Kuntscher, Sampson	20	85	1,574 nL	4.1	88	40
Incavo [34]	Long nail, custom nail, modular nail	21	80	748 mL	n/a	23	80
Lai [35]	Huckstep Nail	33	91	468 mL	1.73	21	91
Puranen [36]	Long nail	33	87	n/a	n/a	30	33
Talmo [37]	Long nail, Neff Nail	29	82	n/a	n/a	20	100
Modular nails							
Arroyo [39]	Neff Nail (Zimmer, Warsaw, IN)	21	90	865 mL	3.4	42	14
Barton [40]	Mayday Nail	12	100	n/a	n/a	30	83
Christie [41]	Witchita Fusion Nail (Stryker, Kalamazoo, MI)	53	96	n/a	n/a	n/a	56
McQueen [22, 42]	Witchita Fusion Nail	13	92	n/a	n/a	38	54
Waldman [43]	Neff Nail	21	95	n/a	n/a	0.04	100
White [44]	Mayday Nail	9	100	n/a	n/a	0	55
Yeoh [20]	Mayday Nail	11	91	n/a	n/a	45	100
External fixators							
Knutson [9]	External fixator	82	50	n/a	n/a	43	68
Kutscha [47]	External hybrid frame	17	88	n/a	n/a	18	100
Yeoh [20]	External fixator (monoaxial)	7	28	n/a	n/a	n/a	86
Hybrid external fixators							
Manzotti [71]	Ilizarov frame	6	83	n/a	n/a	n/a	100
Salem [21]	Ilizarov frame	21	90	n/a	n/a	42	75
Dual plating							
Pritchett [23]	Tension band plating	26	100	n/a	n/a	0	0
Nichols [48]	Compression plating	11	100	n/a	n/a	18	64

and implants which can be inserted through a single incision [20, 22, 39–44]. Table 17.1 contains a list of nail types, fusion rates, operative data, complications, and the number of PJI cases. Techniques were separated based on the type of nail with modular implants listed separately.

Alternatives to intramedullary fusion include resection arthroplasty, external fixation with uniplanar, bi-planar, or hybrid frames, and plating techniques [7, 11–14, 19, 21, 23, 47, 48, 50–58]. No single technique has been shown to be definitively superior to others regarding fusion rates, complications, or postoperative function. There are no prospective studies comparing techniques to the author's knowledge. Retrospective studies comparing intramedullary fusion with external fixation have demonstrated higher fusion rates using an intramedullary device, decreased complications, and length of hospital stay [9, 27, 44, 59].

Certain clinical situations may favor one method of arthrodesis over another such as intramedullary fusion for significant bone loss or hybrid fixators for single-stage fusion in septic knees (Table 17.2) [47, 57]. Rand et al. noted institutions performing more fusions may have greater success and surgeons should be facile with a variety of techniques particularly in

Table 17.2 Comparison of fusion methods

Fusion method	Advantages	Disadvantages
Intramedullary nail	Highest fusion rate	Reaming may spread infection into canals and implant remains following surgery
	Immediate weight bearing without casting	Some methods technically difficult with long operative times/EBL
	Internal device, which does not interfere with walking	Difficult to adjust for flexion angles and valgus
	Familiar operative technique similar to nail fixation for long bone fractures	True compression at the arthrodesis site is dependent on weight bearing
	Spacers may be used with bone loss	Removal of modular nails following fusion may be extremely difficult
	Can be successfully employed as a salvage procedure for failed arthrodesis using other techniques [27]	Retained hardware can become prominent leading to mechanical irritation
External fixation	All implants are removed once fusion is obtained, particularly in cases involving infection	Poor fusion rates in patients with significant bone loss
	Can be employed as a single-stage procedure with active infection	Limited weight bearing following surgery with most techniques. Bulky frames may discourage mobilization
	Less exposure required	Frequent clinical evaluations for adjustments and surveillance for pin tract infections
	Hybrid or ring fixator may allow for simultaneous fusion and bone transport in cases with severe bone loss	Technically difficult, particularly with Ilizarov frames
Dual or single plates	True compression through the arthrodesis site [48]	Retained plates may serve as a source of continued infection
	High fusion rates reported for noninfectious cases	Extra width of dual plates makes soft tissue closure difficult or impossible
	Technique allows for exact flexion and valgus angle positioning	Postoperative casting may be required
		Extensive dissection required particularly for dual plates [23]
		Not recommended with large areas of bone loss and active infection [48]
		Risk of fracture at the bone plate junction [38]
Resection arthroplasty	Limited operative exposure and times, particularly in sick or unstable patients	Many patients will remain non-weight bearing following the surgery
	No retained implants in infectious cases	Continued knee pain and instability following surgery
	Some arc of motion maintained in the knee following surgery. Patients may sit more comfortably [51]	Lowest functional outcomes among all techniques
		Poor results in patients with rheumatoid arthritis [56]

cases of revision fusion [13]. There are also reports of combined techniques such as intramedullary nailing combined with plate fixation or external compression devices which have not demonstrated a clear benefit over individual techniques [60, 61].

Indications/Contraindications

The incidence of primary and revision knee arthroplasty continues to increase and infection is the leading indication for revision surgery [62].

The most common current indication for knee arthrodesis is PJI after all treatment modalities have been exhausted [17, 43, 53, 63]. Other common indications included failed extensor mechanism reconstruction and tumor resection where a distal femoral replacement is not an option [64]. In cases involving infection, intramedullary nail fusion has demonstrated successful fusion rates, particularly when performed in a staged fashion [5, 17, 18, 27, 32, 35, 37, 43, 45]. External fixation has also been used successfully for knee fusion in the setting of infection [21, 57].

Knee arthrodesis is a salvage procedure and should not be considered in patients with other surgical alternatives. Although there are no absolute contraindications to knee arthrodesis, patients should be medically cleared for surgery and staged treatment is recommended for active infections.

Preop Planning

Historical data including the onset of symptoms, type of retained implants, infectious organism, and treatment to date should be recorded. Physical examination should include evaluation of previous incisions and the status of the soft tissue around the knee (Fig. 17.1). Plastic surgery should be consulted if there are concerns or if flap coverage is anticipated. Any leg length discrepancy should be noted prior to surgery and likely shortening of the extremity should be discussed. If peripheral pulses are not palpable a vascular surgery consultation is warranted.

Radiographic evaluation may include full length films from the hip to the ankle as well as dedicated views of the affected knee. Ipsilateral implants such as a total hip prosthesis may dictate the choice of implants, particularly with

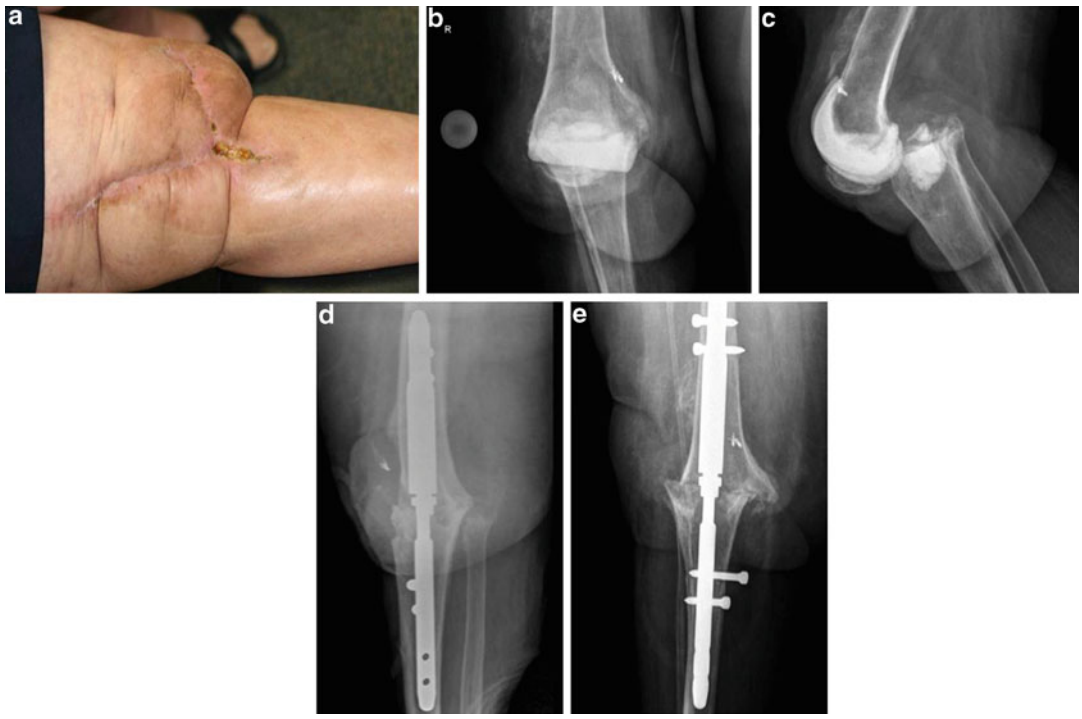

Fig. 17.1 (**a**) Sixty-seven year old male following placement of an antibiotic spacer for PJI with wound healing issues. (**b**, **c**) Preoperative X-rays with spacer subluxation. (**d**, **e**) Postoperative fusion X-rays

longer revision stems. In infected cases, violation of the medullary canal should be avoided which may lead to seeding of the hip prosthesis. External fixator or plate arthrodesis should be considered in this situation. Significant bone loss should be anticipated for conversion from stemmed revision implants and with tumor resection [8, 16, 64, 65]. Implants should be templated for anticipated sizes and lengths to be ordered prior to surgery.

Knee aspiration and routine labs (C-reactive protein and erythrocyte sedimentation rate) should be obtained on all patients awaiting knee arthrodesis. Ideally patients should stop antibiotics 2 weeks prior to aspiration to improve culture results. Medical clearance and optimization should be obtained on all patients prior to surgery.

A frank discussion detailing functional limitations and addressing patient expectations should also be undertaken. In the elective situation a trial with a range of motion brace locked in extension can provide significant insight into functional challenges following surgery.

Operative Technique: Intramedullary Nail Fusion

Surgical technique is critical for good fusion results and has been highlighted by Stewart and Bland and Woods and Lionberger [16, 25]. Woods et al. and Rand and Bryan have noted critical tenants of knee fusion including thorough debridement, adequate bone contact under compression, and early bone grafting once the infection has resolved [13, 14].

The previous anterior mid-line incision is used when possible with full thickness flaps developed both medially and laterally. Some surgeons prefer the use of transverse incision as it allows for better wound closure when the extremity has been shortened. We avoid transverse incision because of fear of wound necrosis at the junctions of new incision with previous longitudinal incisions(s). Medial and lateral full thickness skin flaps are developed and the patellar retinaculum is incised. More extensile exposure may be required particularly in stiff knees. Implants are removed if present and a thorough debridement of the knee including removal of all cement, infected granulation tissue, sinus tracks, and biofilm is performed.

Bone cuts of the distal femur and proximal tibia can be performed free hand or with traditional total knee guides. The maximal amount of native bone should be preserved to avoid excessive limb shortening. Neutral alignment of slight valgus is ideal with a small degree of flexion. Some nail designs such as the Mayday (Orthodynamics, Dorset, UK) may allow for slight valgus positioning and flexion.

Sequential reaming is next performed of the femur and tibia. For long intramedullary nails the final diameter is determined by the tibial final reaming diameter. In modular systems reaming for the femur and tibia may be done independently. An anterior cortical block of bone from the distal femur and proximal tibia is removed to accommodate the coupling system in some nails. Bone graft from aseptic reaming may be placed posteriorly and packed around the nail. Modular implants should thoroughly engage the isthmus by 4–6 cm or beyond. Nail passage or coupling is completed with care taken to ensure compression at the arthrodesis site and rotational control of the lower extremity. Rotation can be judged by palpating the femoral epicondyles, tibial tuburcle, and malleoli. Locking screws can be placed for modular implants while operative compression is maintained. In aseptic cases final bone grafting can be performed around the periphery of the fusion using reamings from the canals and/or cancellous allograft. An alternative is the use of demineralized bone matrix (DBM). We usually perform bone grafting and/or use DBM for patients with extensive bone loss in whom bone on bone contact is less than third of the surface of tibia and femur.

Although majority of previous literature point out the benefit of fusing the knee in slight flexion (5–10°), most of the available IM devices do not allow for such alignment (Fig. 17.2). We do however aim to place the knee in 5–7° of valgus to prevent potential for catching the contralateral foot during gait.

Full weight bearing is permitted following surgery with progressive mobilization

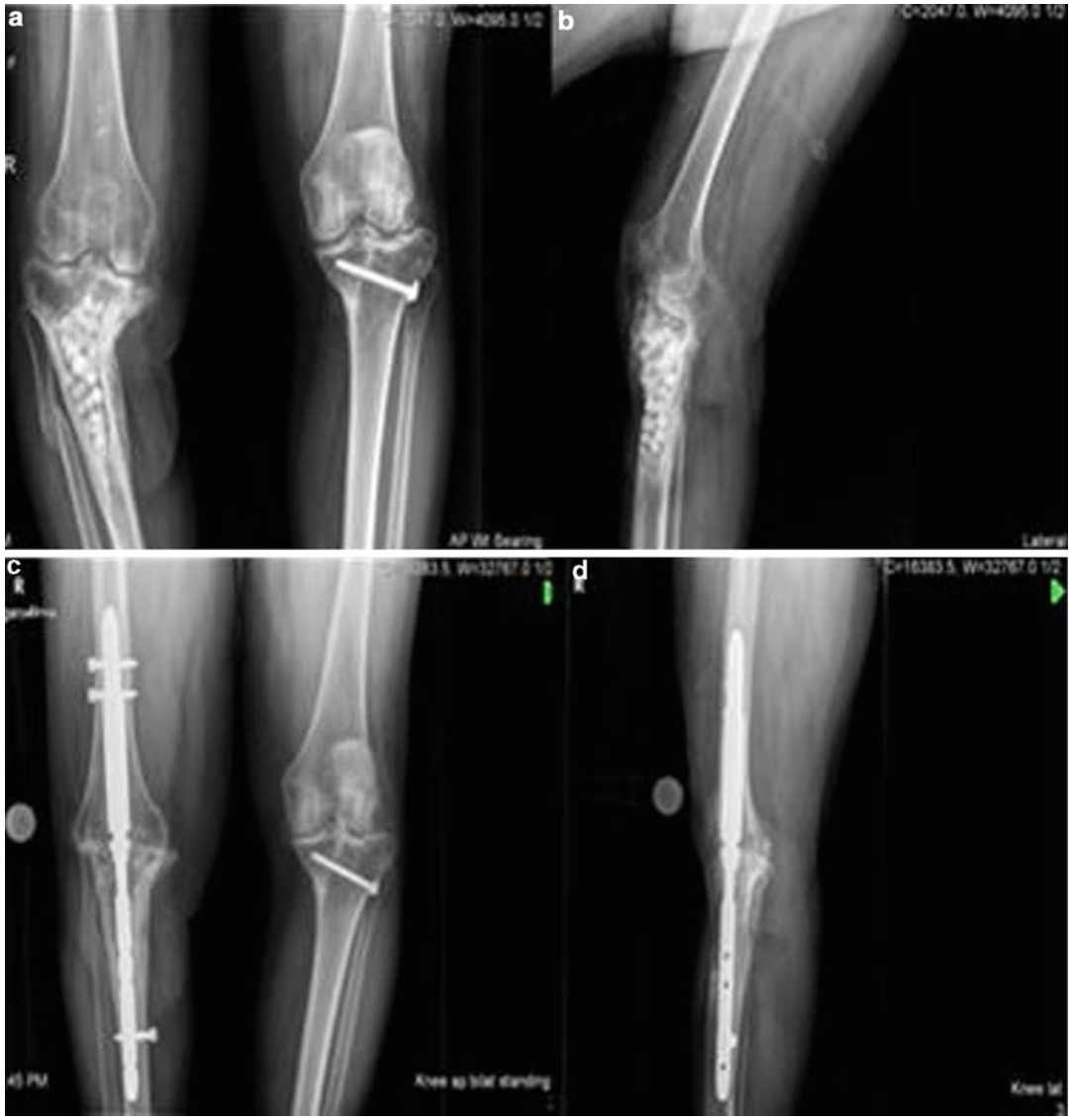

Fig. 17.2 (**a**, **b**) Sixty-seven-year-old female with chronic osteomyelitis and traumatic arthritis treated by a two-stage fusion (**c**, **d**) Postoperative X-rays following fusion

beginning postoperative day #1 [20, 39, 43, 44]. Mechanical and pharmacologic venous thromboprophylaxis are initiated following surgery. Parental antibiotics should be continued in cases with positive culture and duration guided by culture results and infectious disease recommendations. Regular follow-up with clinical and radiographic evaluation is recommended. Revision surgery with bone grafting should be considered if there is no evidence of fusion by 3–4 months.

Operative Considerations in Periprosthetic Joint Infection

Arthrodesis rates among isolated and staged fusions for failed PJI are encouraging with clearance of infection in the majority of cases. A staged revision is recommended for all infections with gross purulence and resistant or particularly virulent organisms [16, 32, 35, 36]. Single-stage fusions are the exception and should

only be attempted with nonresistant and low virulence organisms and in the absence of gross purulence at the time of surgery [35, 36]. Other considerations may include the patients' medical comorbidities and ability to accommodate a second surgery [27]. Even in the face of active infection an intramedullary fusion may be successful in a limited number of cases [66]. Use of a hybrid external fixator may also be considered in these cases with reasonable results.

If one-stage arthrodesis is to be performed, there should be a dirty (initial) and clean (final) setup in the OR. During the initial setup debridement and cleaning of the joint is performed. Bone cuts and reamings to be used later are saved. After extensive irrigations (9 L) the wound is covered and redraping performed. All dirty instruments are removed, cautery tip, suction tip, and gauze swabs exchanged for clean set. All personnel change gloves and may consider rescrubbing. Only when the clean setup is available the device to be used is opened and the bone graft is placed in the knee joint.

Complications

A number of major complications have been associated with knee fusion including wound dehiscence, nonunion, and persistent infection. Minor complications such as hardware migration, irritation, and postoperative fractures have also been reported. Complications may vary by technique such as pin site infection with external fixation. Complications unique to long intramedullary nail arthrodesis include proximal migration at the hip and mechanical irritation. Modular nails may be extremely difficult to remove or revise following fusion [34, 35, 43]. This may require anterior fenestration of the femur and special cutting equipment to remove the nail. There are also isolated reports of proximal and distal fractures at the distal and proximal ends of the nail [67].

Failure of the arthrodesis or nonunion has been reported in almost all series. Identifying the causative issues is paramount and repeated attempts at fusion are warranted if these issues can be corrected. Rand et al. have demonstrated the value of repeat attempts at arthrodesis and bone grafting if the first attempt is not successful [13]. In their series they were successful in 50 % of the cases on their second, third, and fourth attempts at fusion.

Functional Results

While primary arthroplasty can address pain with maintenance of motion, arthrodesis sacrifices motion of the knee to address pain [63]. Physical function following fusion is significantly worse compared to age-matched controls [29]. In addition to loss of motion, progression of arthritis in ipsilateral joints such as the hip and ankle may be anticipated [52]. A patient's ability to sit comfortably in a vehicle or public transportation, use the restroom, and navigate stairs or inclines can be profoundly affected by knee arthrodesis. The use of walking aids following arthrodesis has been reported in up to 92 % of patients following surgery [27]. Talmo et al. reported on 29 patients following intramedullary fusion and noted 14 % required a wheelchair, 24 % continued to have knee pain at the fusion site, and 24 % developed pain involving the ipsilateral hip [37].

Harris et al. noted patients with knee arthrodesis walk less efficiently and with a slower gait compared to age-matched controls. They also have unique limitations including difficulty with sitting in vehicles, increased need to maneuver the limb, and difficulty walking where foot clearance is required such as in heavy snow [68]. In their series comparing patients with arthrodesis to those with amputation, Harris et al. demonstrated near equivalent function and walking efficiency. Waters et al. reported on traumatic and vascular above the knee amputations with a significant increased cost of walking between 37 and 63 % [69]. This compares with 35 % increased energy cost following arthrodesis.

Wang's series of 26 patients highlights the value of knee arthrodesis to relieve pain but underscores the poor functional results compared to a functioning total knee arthroplasty [58]. Outcomes are uniformly lower compared to

primary and even revision total knee arthroplasty [27, 63, 68]. In a series of eight rheumatoid patients, Figgie et al. highlight the neutral range for successful fusion between 7° ± 5° valgus and 15° ± 15° of flexion. Fusions outside of these parameters led to poor functional results and loss of ambulation. There was no clinical progression or arthritic change in the 11 patients fused within this range.

Some degree of leg length discrepancy is associated with nearly all arthrodesis procedures. Following fusion for failed knee arthroplasty leg length discrepancies between 1 and 8 cm have been reported, particularly with hinged implants [27, 29–32, 65]. The energy cost associated with minimal leg length discrepancies of 2 cm or less is negligible [70]. However, both oxygen consumption and perceived exertion increase significantly with 3 and 4 cm leg length discrepancies [70]. Consideration should be given to knee fusion in full extension versus flexion if large amounts of bone loss are anticipated [19, 22].

Conclusion

The most common indication for knee arthrodesis is salvage of a failed arthroplasty procedure. Arthrodesis may be accomplished in a variety of ways and should only be considered after other alternatives have been exhausted. Surgical outcome and satisfaction may be improved through preoperative discussion regarding functional limitations, demands, and expectations.

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Resection Arthroplasty and Hip Joint Fusion

18

Thomas L. Bradbury

History of Excision Arthroplasty of the Hip

The earliest and most rudimentary form of arthroplasty involved the surgical removal of the articulating surfaces of the joint. Professor James Syme of the University of Edinburgh reported some of the earliest accounts in his 1831 publication *The Excision of Diseased Joints*. The first report on surgical resection of proximal portion of the femur was published in The Lancet in 1849 [3]. The account is delineated in the obituary of Mr. Anthony White, an English surgeon with a local reputation for dexterity and successful surgical outcomes. The operation was performed on a 13-year-old boy who had developed infection around the hip joint from wounds sustained during a fall 3 years earlier. The infection proved resistant to contemporary treatments and threatened the boy's life. After the surgery, per White's report, "the wound quickly healed, the various sinuses soon ceased to discharge and the health of the patient rapidly improved." As antibiotics and safe anesthesia would not be available for years to come, this heroic type of surgery was dangerous and utilized only as a last resort.

Decades later, G.R. Girdlestone published two reports on the technique that now often bears his epitaph. His initial report appeared in 1928 and described the technique he had devised for treatment of tuberculous hip arthrosis in children [4]. The second report, published in The Lancet in 1943, described a similar operation for the treatment of chronic, pyogenic infection involving the hip [5]. Both reports emphasized the same treatment principles: namely, wide exposure of the joint afforded by debridement of the abductors and femoral head and/or femoral neck, removal of all necrotic and infected bone from the acetabulum, debridement of intra-pelvic sinus tracts and subsequent traction on the extremity to prevent enclosure of any remaining infection. The gapping wound was always left open, facilitated by various packing techniques. The operation was often successful not only in saving lives, but also the eradication of local infection. By his report, "the great gapping wound becomes a narrow scar" within a few months.

Years later, Robert Taylor expanded the indication for resection arthroplasty. In 1950, he published a report on the outcome 93 patients who underwent operative excision of the femoral head and neck with subsequent postoperative traction to produce *pseudarthrosis of the hip joint* [6]. The primary indication for the surgery was osteoarthritis in the older patient. Taylor emphasized the importance of beveling the walls of the acetabulum and femoral neck to allow a large, smooth zone of contact between the pelvis and femur. He reported favorable outcomes: 83 patients (90 %) were classified as having a good result as indicated by complete relief of pain and

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the ability to ambulate with a cane. He reported that seven patients were left with a poor result and three died from the surgery.

In 1955, Milch published the results of a "resection-angulation operation" for treatment of hip arthrosis [7]. Milch argued that his combined procedure would allow the same improvement in pain reported by Taylor with additional improvement in stability and function as a result of a valgus producing osteotomy in the subtrochanteric region. It was his opinion that his resection-angulation operation would provide more reliable results in the treatment of hip arthrosis.

At the time of Milch's publication, early forms of prosthetic arthroplasty (i.e., cup arthroplasty and resurfacing arthroplasty) were considered experimental and the early results had been disappointing. However, by 1960, Sir John Charnley had made significant progress with the development of low-friction arthroplasty. As time passed, it was evident that Charnley's technique would provide dramatic improvements in hip pain and function over the short term. Vital to the early success of his technique included the development of a bearing couple that allowed low-friction articulation. The low-friction properties of the bearing reduced the transfer of stress to implant-bone interface. In addition, fixation of the implant with acrylic cement provided a robust means of fixation. Charnley's technique gained popularity across Europe and was later used in the United States after the FDA approved the use of polymethylmethacrlate as a means of prosthetic fixation. Despite the early success of Charnley's technique, long-term results were unknown. Patient candidacy for the surgery was limited to the older, less active patient cohort who had relatively uncomplicated primary arthrosis of the joint. In cases in which patient candidacy was uncertain, the clinician would often use the *Girdlestone pseudarthrosis test* to help determine the feasibility for performing low-friction hip arthroplasty. The premise of the test being that if the patient was sufficiently disabled by their hip arthrosis that a resection arthroplasty would allow improvement in pain, they would be a candidate for total hip arthroplasty. The success of Charnley's technique opened the door for improvements in hip pain, hip function, and overall quality of life for those with hip arthrosis. As such, the primary treatment of hip arthrosis with femoral head resection with or without angulation osteotomy of the femur was essentially abandoned. The technique of femoral head resection as a primary operation would again be relegated to treat the sequelae in hip sepsis and for treatment of painful, dislocations in the setting of spasticity.

Although commonly used to reference surgical removal of the femoral head and neck, it should be understood that the terms "Girdlestone resection" or "Girdlestone procedure" refer specifically to the techniques Girdlestone described in which the wound is left open for healing by secondary intent. "Excision arthroplasty" and/or "Resection arthroplasty" are better used to describe the more contemporary operation in which the surgeon removes the femoral head or arthroplasty components and primarily repairs the soft tissues and skin.

Indications and Outcomes: Resection Arthroplasty for Failed Hip Arthroplasty

The indications for resection arthroplasty of the hip include destruction of the hip joint associated with pain and deformity that cannot be safely managed with operations capable of producing more robust functional outcomes. This situation can occur as a result of intrinsic hip joint pathology or, more commonly, in the setting of failed previous surgical intervention.

At present, the primary indication for resection arthroplasty remains a means of eradicating infection and limb salvage in the setting of recurrent or resistant periprosthetic infection. Throughout the 1960s and 1970s, resection arthroplasty was used as a salvage measure to address failure of various early forms of hip arthroplasty including *cup arthroplasty*, the Judet femoral head replacement and McKee-Farrar replacements [8, 9]. As the use of acrylic cement to affix arthroplasty components to host bone became more widespread, reports of removal of infected low-friction arthroplasty component

fixed with cement began to appear. Charnley was among the earliest to report on removal of prosthetic components and cement for treatment of infection [10].

Since Charnley's initial report, there have been multiple retrospective series reporting on the outcomes of removal of failed total hip arthroplasty components. Needless to the say, the results have been quite variable. In 1964, Murray et al. published the results of resection arthroplasty for multiple conditions [11]. Included in their series was a subgroup of 12 patients who underwent the procedure for the treatment of periprosthetic hip infection. The procedure produced a pain-free result in this subgroup. As a whole, ambulatory capacity improved and no patient had residual evidence of infection after final healing.

Among the earliest reports dedicated to the result of removal of arthroplasty component and cement in the setting of periprosthetic infection by published by Clegg in 1977 [12]. The report included a series of 30 hips in 29 patients treated with removal of arthroplasty components. Pain and function after resection arthroplasty to treat infection were compared to the pre-arthroplasty state. Twenty-six (90 %) patients reported improvement in pain in comparison to the pre-arthroplasty state. In contrast, functional outcomes declined for all but three patients in comparison to pre-arthroplasty function. The procedure eradicated evidence of infection in 80 % of patients. The authors implicated retained cement as the cause of residual infection after component removal.

Kantor et al. evaluated a series of 41 patients managed with resection of arthroplasty components for treatment of periprosthetic hip infection [13]. Thirty-nine percent of patients continued with chronic drainage. Retained polymethylmethacrylate was identified as a principle risk for continued infection and drainage. Ninety-seven percent of patients had persistent pain, which was not further quantified. Average limb shortening was 6 cm. The magnitude of leg length inequality was not improved with postoperative traction. Ambulatory velocity evaluated by foot switch gait analysis and energy requirements during ambulation measured by oxygen consumption was recorded and compared to both normal controls and those who had undergone above knee amputation. On average, patients with above knee amputations walked with a velocity 68 % normal while patient with hip resection walked at a pace 46 % normal. Oxygen consumption during ambulation for above knee amputation patients averaged 166 % normal while those with hip resection averaged 273 % normal.

The largest series in the literature was published in 1987 by Marchetti et al. [14]. The series included the outcome of 104 failed total hip arthroplasties managed by removal of components. As a result of limb shortening, hip muscle weakness and altered associated with resection arthroplasty, the authors argued that traditional outcome measures to evaluate hip performance after hip arthroplasty were inappropriate. Based on a modified outcome scoring system, they reported satisfactory results in 72 % of patients. Younger age, arthroplasty failure as a result of periprosthetic infection and restricted motion after surgery resulted in worse outcomes.

Petty et al. reported on the outcome of 21 patients who underwent removal of total hip arthroplasty components for treatment of periprosthetic hip infection. The results were noted to be poor: five patients (23 %) continued with chronic drainage despite removal of the components, all patients reported moderate to severe pain during activity or rest, all patients required assistive devices to ambulate, and 18 of the 21 patients were dissatisfied with the results of the resection arthroplasty. The authors concluded that the results of resection arthroplasty for treatment of infected total hip arthroplasty were inferior to the results of resection arthroplasty for other diagnoses.

In summary, review of the literature reveals significant variability in the outcomes of resection arthroplasty for the treatment of infected and/or failed hip arthroplasty [15]. Results regarding pain after resection arthroplasty are highly variable and range from *no or minimal pain* to pain severe enough to preclude quality of life. Functional results are also difficult to assimilate, but on average, about 80 % of patient can walk a "reasonable distance" with the use of an

assistive device. The pace and efficiency of ambulation after resection arthroplasty is markedly reduced, even in comparison to above knee amputation patients. Success regarding eradication of infection averages about 80 % and is likely related to the quality of the surgical debridement.

Indications and Outcomes: Revision Hip Arthroplasty After Resection Arthroplasty

Reports on the outcome of revision total hip arthroplasty following resection arthroplasty are limited. Schröder et al. compared the outcome of 32 patients with a long-standing pseudarthrosis to a group of 16 patients who underwent reimplantation of hip arthroplasty components at an average of 3 years after resection arthroplasty [16]. Harris Hip Scores in the pseudarthrosis group averaged 58 compared to 64 in those who had undergone reimplanation. Although patients who underwent revision hip arthroplasty had better personal satisfaction and more easily accomplished activities of daily living, the improvement was marginal. The authors concluded that resection arthroplasty remained a viable option for treatment of failed total hip arthroplasty.

Charlton et al. reported on a series of 44 hips treated with revision total hip arthroplasty after resection arthroplasty [17]. The indications for resection arthroplasty included infected primary hip arthroplasty, infected revision hip arthroplasty, infected hemiarthroplasty, and infected hardware around the hip joint. The average time between resection and remiplantation was 11 months. After minimum follow up of 2 years, Harris Hip Scores improved from 40 to 78. Leg length inequality was equalized in 50 % of patients. Leg length inequality was improved to an average discrepancy of 6 mm in the other 50 %. Complications after hip reimplantation included dislocation in 11 %. Thirty-nine percent of patients ambulated with a persistent limp. However, recurrent infection occurred in only one patient (2.3 %). The authors concluded that although complications are relatively frequent, the procedure carries a low rate of infection recurrence and provides the opportunity for significant improvement in functional capacity.

Rittmeister et al. reported on a series of the 39 hips treated with revision hip arthroplasty after a period of resection [18]. The indication for resection was infection in all but one patient who All patients who underwent revision surgery had a normal ESR and CRP. At an average follow up of 12 months, the average Harris Hip Score was 62. Complication occurred in 66 % of patients. Seventeen of thirty-nine hip required revision surgery. The most common complication was "soft tissue revision" for concern of recurrent infection. The authors found that the duration of resection arthroplasty, patient age, and the number of previous surgeries had no influence on overall outcome. The results of this study are in stark contrast to the results reported by Charlton. The authors cite the failure to identify the infecting organism at the time of resection arthroplasty as a reason for the high rate of recurrent infection after reimplantation.

In summary, revision hip arthroplasty after a previous resection arthroplasty should be approached with caution. Although successful outcomes are possible, the risk of recurrent infection, instability, persistent leg length inequality, and abductor dysfunction should be considered.

The radiographs in Figs. 18.1, 18.2, and 18.3 show a case example of revision hip arthroplasty after long-standing resection.

Technique: Resection Arthoplasty for Failed Total Hip Arthroplaty

As the most common current indication for resection arthroplasty remains persistent infection after revision total hip arthroplasty, eradication of infection is often a primary goal. As such removal of all prosthetic material and debridement of all necrotic, infected tissue is of utmost importance. All antibiotics should be stopped at least 3 weeks prior to surgery to improve the chance of culturing offending organisms. This approach will allow the

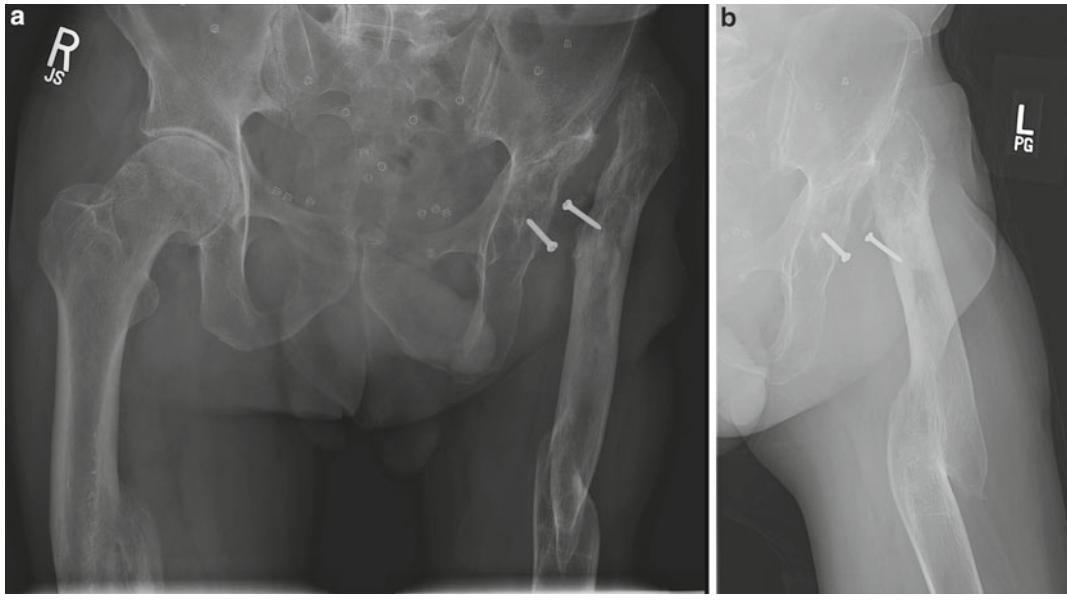

Fig. 18.1 (**a**, **b**) AP Pelvis and lateral hip radiographs of a 58-year-old man who sustained multiple bilateral lower extremity fractures in a truck vs. motorcycle accident at the age of 18. Attempts at internal fixation of a left femoral neck fracture were complicated by chronic hip sepsis which was ultimately treated with resection arthroplasty; the screws were evidently not encountered during the resection. Forty years after resection arthroplasty, he rated his hip pain at a 1–2 on a VAS scale of 10, but complained of progressive low back pain and difficulty with activities of daily living because of his leg length inequality and hip instability. However, he remained ambulatory for short distances with one cane

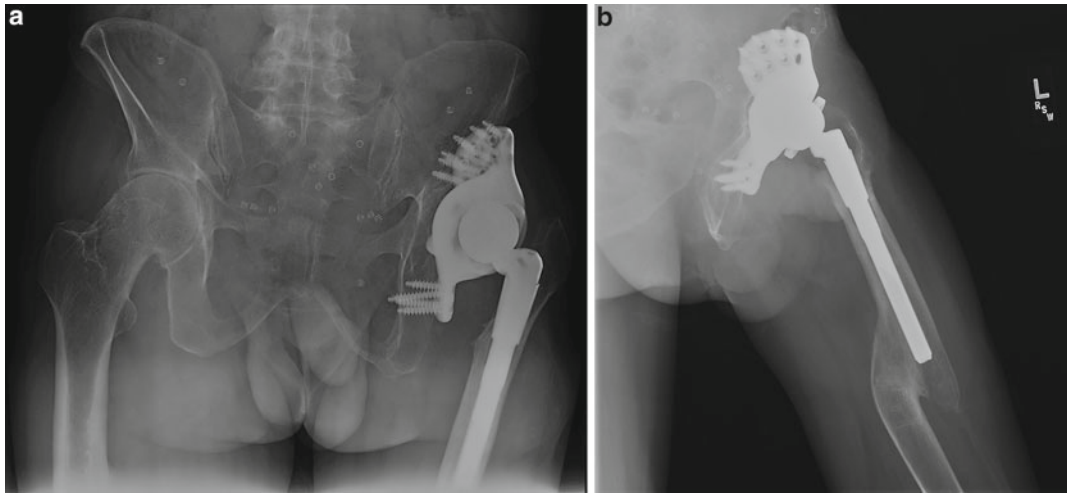

Fig. 18.2 (**a**, **b**) AP pelvis and lateral hip radiographs after conversion to total hip arthroplasty. Preoperative serum sedimentation rate and C-reactive protein value were normal. Attempts at aspiration of the hip were unsuccessful. Given the global, segmental acetabular bone deficiencies, a custom, porous-coated acetabular component was utilized. The femur was reconstructed with a modular stem allowing versional control. The malunion in femoral diaphysis was ignored. A constrained acetabular insert was used to address concerns for postoperative instability

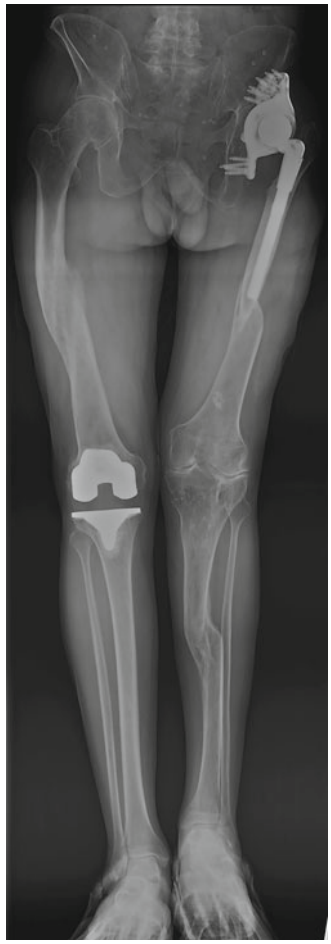

Fig. 18.3 AP long leg view demonstrating improved, but persistent leg length inequality. After recovery, the patient reported no change in hip pain, but a marked improvement in low back pain and ambulatory capacity. The surgical wound healed uneventfully

most appropriate post-debridement selection of antibiotic therapy. Although controversial, withholding preoperative, prophylactic antibiotics may also be considered as there less need to protect against further periprosthetic infection. Incorporating previous incision lines into a surgical approach that allows extensile exposure is necessary. A posterior approach to the hip allows maximal access to both the femur and pelvis. Instrumentation allowing removal of well fixed components and salvage of remaining, viable bone stock are essential. A pneumatic, high-speed burr with a router tip is invaluable in establishing a dissection plane between host bone and the porous surface of ingrown components. For removal of ingrown acetabular components, modular, curved osteotomes attached to a trial femoral head ball of appropriate size allows easy removal of most hemispherical designs while preserving remaining acetabular bone stock. The technique for removal of uncemented, osseointegrated femoral component depends on the design of the stem. Tapered, proximally coated implants can often be removed safely by establishing a proximal plane between the implant and bone with a high-speed router tip. The distal aspect of the ingrowth surface can be carefully divided with flexible osteotomes. However, the surgeon should have a low threshold for extending the exposure of the femoral implant with an extended trochateric osteotomy when attempts at removal from the proximal direction threaten the integrity of the remaining femoral bone stock. The technique used to perform the osteotomy should allow preservation of the attachments of both the abductor and vastus musculature to the trochanteric fragment. The length of the osteotomy distally should allow adequate access to the component while preserving maximal diaphyseal integrity for possible future reconstruction. In cases where components are cemented, the availability of cement removal osteotomes and curettes, cement drills and taps, and ultrasonic cement removal devices can prove invaluable. After removal of all prosthetic and foreign material, the quality of the remaining acetabular and femoral bone should be assessed. Ideally, all nonviable, non-perfused bone should be debrided. This is best accomplished with a high-speed, saline cooled spherical burr. Debridement can be considered complete when the debridement surface demonstrates uniform punctate Haversian bleeding (aka "the paprika sign"). Although local beveling of the proximal femoral bone at the future site of articulation with the pelvis is advisable, osteotomy or osteoplasty techniques designed to improve functional outcomes after resection arthroplasty likely have little to no value.

Surgical dead space created by debridement must be actively managed. Transfer of viable local muscle tissue is ideal when available. The use of non-articulating, antibiotic impregnated

polymethymethacrylate spacers in both the acetabulum and proximal femur can be used to both eliminate dead space and provide a vehicle for high dose local antibiotic delivery. However, after elution of antibiotics, retained polymethylmethacrylate can theoretically provide a nidus for continued or recurrent infection. Negative pressure therapy can be used to manage dead space until wound contraction and maturation allows delayed primary closure over conventional drains or healing by secondary intent.

Postoperative management after resection arthroplasty begins with organism directed IV antibiotic therapy. Instruction on ambulation with protected weight bearing until the surgical wound and soft-tissue envelope around the hip has matured is advisable. Progression to weight bearing as tolerated is allowed thereafter. Traction of any sort provides no benefit. Both active and passive range of motion to patient tolerance is encouraged. Leg length inequality will often be significant and can be improved with external shoe lifts.

Hip Joint Arthrodesis

The long-term results of total hip arthroplasty have narrowed the indications for primary hip joint fusion. As a result, few orthopaedic surgery residents have been exposed to the technique over the past decade. However, primary arthrodesis is still indicated in the young, potentially active patient with end stage arthrosis of the joint who is otherwise not a good candidate for hip arthroplasty. Long-term outcomes have demonstrated durable pain relief with only mild to moderate decline in function. Acceleration of degenerative changes in the ipsilateral knee, low back, and contra lateral hip are recognized drawbacks. Although complications are more frequent, patient satisfaction with hip arthroplasty after hip fusion is on par with satisfaction levels after primary arthroplasty of the hip.

Hip joint arthrodesis for salvage of failed or infected total hip arthroplasty has limited application. In 1984, Kostuik and Alexander reported on a series of 14 hips treated with fusion after failed total hip arthroplasty [19]. Prosthetic loosening was the mode of failure in all hips. Fifty percent of the cases were also infected. The fusion technique utilized a lateral approach with osteotomy of the greater trochanter. After removal of the prosthesis and cement, the A-O fusion technique was accomplished with a cobra plate. Supplemental fixation with another plate along the anterior aspect of the fusion site was utilized in the majority of cases. Four of the seven cases involving infection were treated in one stage. The remaining three cases were treated in a two stage fashion after an initial debridement operation. Successful arthrodesis occurred initially in 13 of 14 cases. The single psuedoarthrosis was successfully fused after supplemental one grafting. The authors reported surprisingly acceptable outcomes. Hip pain was relieved in all patients. All patient were ambulatory after healing and only three used a cane for assistance. All but a single patient returned to their previous occupation. Average leg length inequality measured 4.6 cm. Low back pain was not a significant issue, although average follow up was of short duration. The authors recommended fusion for treatment of failed total hip arthroplasty in young patient with unilateral hip disease. As follow up was of short duration and the measures used to evaluate outcomes were rudimentary, this recommendation should be viewed with skepticism. Present day infection management protocols and revision implant options allow reconstruction options with the potential for more robust outcomes than is possible with fusion after failed total hip arthroplasty.

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Above-Knee Amputation

19

Antonia F. Chen, Catherine J. Fedorka,
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Introduction

Above-the-knee amputation (AKA), or a transfemoral amputation, is a removal of the lower extremity at the level of the femur. It is one of the oldest performed surgical procedures, with the earliest performed procedure noted in Hippocrates's *De Articularis* and Plato's *Symposium* in 385 BC, and the first successful AKA performed by Dr. William Cloves in 1588 [1]. The word amputation is derived from the Latin word *amputare*, which is a combination of *ambi-* (around) and *putare* (to prune). AKAs were initially performed for some tribal rituals or as a method of punishment; after the development of gunpowder, they were later used to treat traumatic limb wounds when the number of amputations increased. Today, AKAs are used to treat limb-threatening medical conditions such as infections, tumors, diabetes, and vascular disease, in addition to trauma. In total knee arthroplasty (TKA), AKAs may be performed to treat periprosthetic joint infections (PJIs), especially when other methods of treatment such as two-stage revision arthroplasty and arthrodesis have failed. This chapter provides a comprehensive look at the role of AKAs in TKA, including the history of AKAs, indications for surgery, surgical technique, stump care, various prostheses, functional status, and long term follow up.

Indications for Surgery

AKA is a last-resort treatment option in patients with an infected TKA who have exhausted all other treatment options and who are not candidates for two-stage exchange arthroplasty or arthrodesis. Failure rates between 9 and 31 % after an initial two-stage procedure for infection have been reported [2–5]. As these failure rates continue to rise, much attention has been paid to risk factors for failure. It has been shown that infections due to resistant gram-positive and gram-negative organisms have a higher rate of failure with two-stage exchange arthroplasty [4–9]. Patients infected with these difficult pathogens may therefore require multiple procedures to eradicate the infection.

With each subsequent procedure, the patient's risk for complications increases. For each revision procedure, the patient may require a more

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constrained component with augments and stems to accommodate for bone loss and ligamentous instability. Progressive bone loss, damage to surrounding soft tissue stabilizers of the knee, and wound complications can all occur with multiple revision attempts [10, 11]. With each procedure, the surgeon's options become more limited with regards to available prostheses, until amputation may be the only viable option to remove the entire prosthesis, as retaining implants may allow recurrent infections. In previous studies of AKA after TKA, the average number of procedures after index TKA has been cited between 2.8 and 6 [11–13]. Amputation may therefore be indicated in these patients who have had multiple procedures in unsuccessful attempts to eradicate infection.

Presentation

Patients who present with chronic infections have often undergone multiple procedures and may have marked scar tissue or inadequate soft tissue coverage for a revision AKA (Fig. 19.1). In many of these patients, a flap may not be a viable option for coverage secondary to chronic infections and/or vascular disease, and an AKA would be indicated to get adequate soft tissue closure.

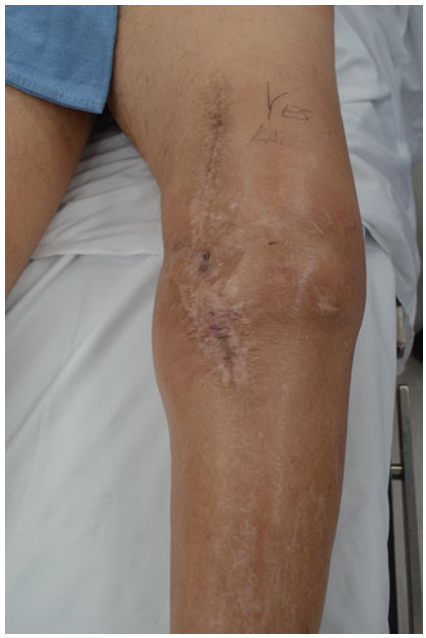

Fig. 19.1 Total knee arthroplasty periprosthetic joint infection

Patients that present with recurrent PJI after multiple procedures after TKA should still receive the standard workup for infection, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, and cell count from joint aspiration. If the patient is septic, performing an AKA could be a life-saving measure. Patients should also receive radiographic imaging to determine the amount of remaining bone stock and to determine the level at which the AKA should be performed.

Comorbidities

Previous studies have shown that patients undergoing AKA for infected TKA have high Charlson comorbidity index scores [14] and ASA scores [13, 15, 16], which put them at increased risk for multiple procedures. Many of these patients are also immunosuppressed. This poses a significant problem when their TKA becomes infected, because it could lead to life-threatening sepsis. Progressive infection that is unable to be suppressed with antibiotics is therefore an indication for amputation because reimplantation is contraindicated in these patients. Amputation may be the only viable option for treatment in these very sick patients.

Finally, one also must consider the overall well being of the patient as amputation may be the best option to control their pain and help them recover without multiple operations. A patient may choose not to undergo another salvage procedure secondary to their pain or perceived risk of undergoing revision or arthrodesis. With the improvement in prosthetic choices available, patients may have better function with an AKA than with a chronically stiff, painful, and debilitated knee.

Surgical Technique

Performing an AKA after TKA for PJI has special considerations because of the existing implant and knee infection. A radiograph obtained prior to surgery can indicate the level of bone that needs to

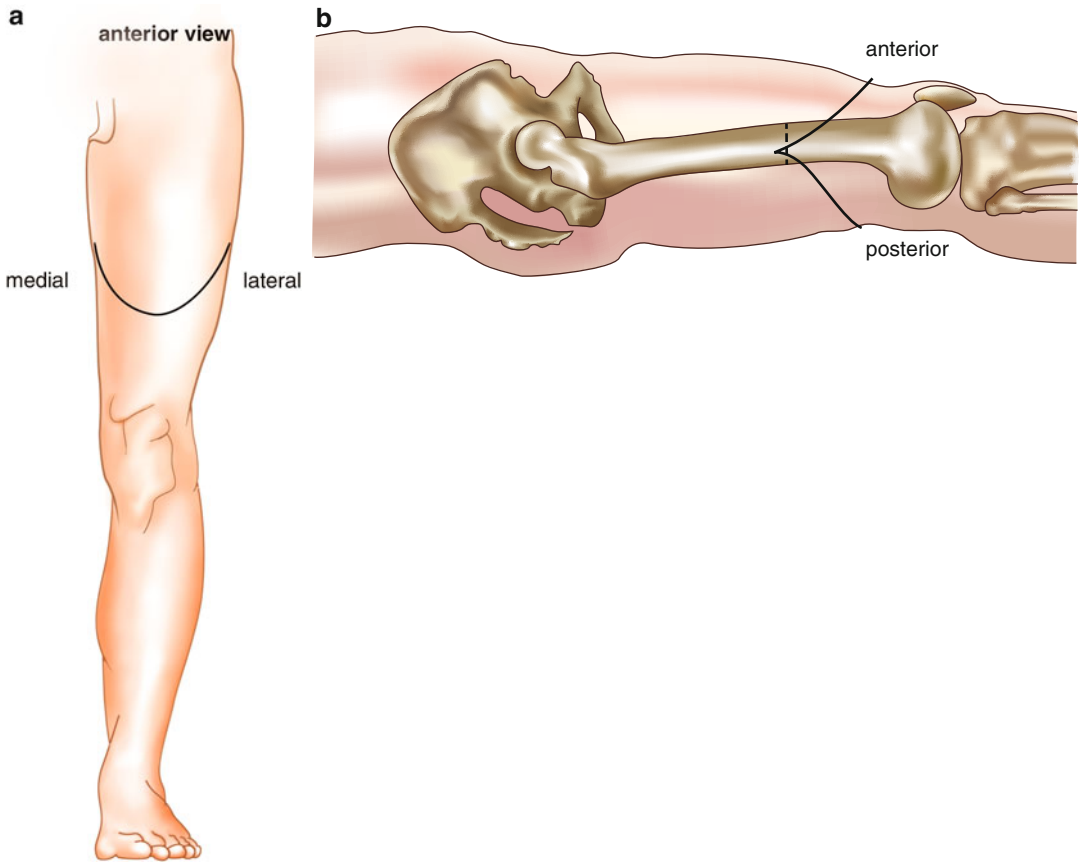

Fig. 19.2 Fish mouth incision for above-knee amputation. (**a**) Anterior view. (**b**) Lateral view

be resected in order to remove the existing prosthesis, to remove all infected bone, and/or to provide an adequate bone stock for walking on a prosthesis. If the AKA is being performed electively, the patient should receive standard medical clearance prior to proceeding with surgery.

Operative Approach

The patient is positioned supine on the operating table and a bump is placed under the buttocks of the involved extremity to elevate the leg and allow access to the posterior leg. The limb should be prepped and draped high, as if to do a hip procedure, and then a sterile tourniquet applied. If a high AKA is being performed, it may be impossible to use a tourniquet as the tourniquet may be on top of the surgical field. Because the patient's leg is infected, an Esmarch bandage should not be used to exsanguinate the limb. The limb can be elevated for 5 min to exsanguinate.

For the incision, most AKAs are performed 4–6 in. proximal to the joint line. However, the size of the existing prosthesis must be considered before determining the level of amputation. In cases where there is a distal femoral replacement or a long-stemmed prosthesis, the distal bone may be absent or in bad condition. If a prosthesis has a long stem, it should be removed prior to performing the AKA. In many cases, the prosthesis can be removed with the limb distal to the amputation. Additionally, the level of amputation has to be performed above skin with irreversible ischemic changes and to provide adequate soft tissue coverage for the end of the stump.

Traditionally, a fish mouth incision is made at the level of the amputation (Fig. 19.2). This is a U-shaped incision curved anteriorly and posteriorly that meets at the medial and lateral corners

of the thigh. The location of the final incision is not as crucial as the soft tissue coverage on the stump. It is important that adequate padding is present on the distal bone and that the skin not be allowed to scar down to the bone. If the tissue coverage is poor, there will be issues with ulcers and breakdown on the stump. Traditionally, the anterior flap is longer so that the incision will be posterior. If the extremity has to be removed quickly due to medical reasons, a guillotine incision, or amputating the leg with a straight cut, can be performed and the wound closed secondarily when the patient is more stable. The guillotine amputation is also used when there is infection, such as gas gangrene or necrotizing fasciitis, or when soft tissues are necrosing at the tissue edges. With time, healthy tissue margins will declare themselves and the wound can eventually be closed.

Anterior Anatomy

The first incision should be made over the anterior leg. Sharp dissection should be carried through fat, taking care to cauterize blood vessels contained in the fat, specifically the great saphenous vein. The anterior musculature (quadriceps) should be sharply transected with a scalpel blade or electrocautery. Care should be taken to dissect out the superficial femoral artery and vein, which should be clamped and tied off with 2-0 silk ties. Small muscle perforating vessels can similarly be tied or cauterized. Nerves (branches of the femoral nerve) can be placed on gentle stretch and sharply transected with a scalpel. Dissection is carried all the way down to the femur to allow for the femoral bone cut.

Implant Removal

Once the femur is exposed and it is determined that the prosthesis needs to be explanted, it is important to have the necessary tools to remove the implant. Knowing the existing prosthesis prior to surgery is important in order to have the correct extraction tools specific to the implant. Additionally, it is key to have other tools that may be necessary for implant explantation, including osteotomes, cement extraction tools (e.g., reverse curettes), ultrasonic cement removal devices, and flexible trephine reamers. Removal of the femoral implant should proceed as if one were performing a knee revision. Removing all the cement, the implant, and debriding the femoral canal is important to eradicating the infection.

Femoral Transection

Transection of the femur early in the case allows easier access to the posterior neurovascular bundle. To ease retraction of tissues from the femur, a cobb or other periosteal elevator is used to elevate the periosteum off the femur. Once the femur is prepared, a malleable is placed on the posterior cortex of the femur. This will serve to retract the tissues while the femur is being cut and to protect the posterior soft tissues. A rake or other retraction device is used to keep the cut anterior musculature out of the path of the saw. A sagittal electrical saw is used to transversely cut the femur from anterior to posterior (Fig. 19.3a), or a Gigli saw (a flexible wire saw) can be used to transversely cut the femur from posterior to anterior. Bone wax can be applied to the end of the femur to reduce any bony bleeding. Once the femur is transected, a large bone hook may be placed within the medullary canal to retract the femur and allow access to the posterior structures.

Posterior Anatomy

The deep femoral artery and vein should be located immediately posterior to the femur. Attention must be paid to identifying these vessels and tying them off with 2-0 silk ties. The posterior musculature can then be dissected with electrocautery, scalpel, or amputation knife. The adductor musculature, specifically the adductor magnus, can be preserved for performing an adductor myodesis, which is covered below. Care should be placed on identifying the sciatic nerve, which is posterior to the adductor magnus muscle.

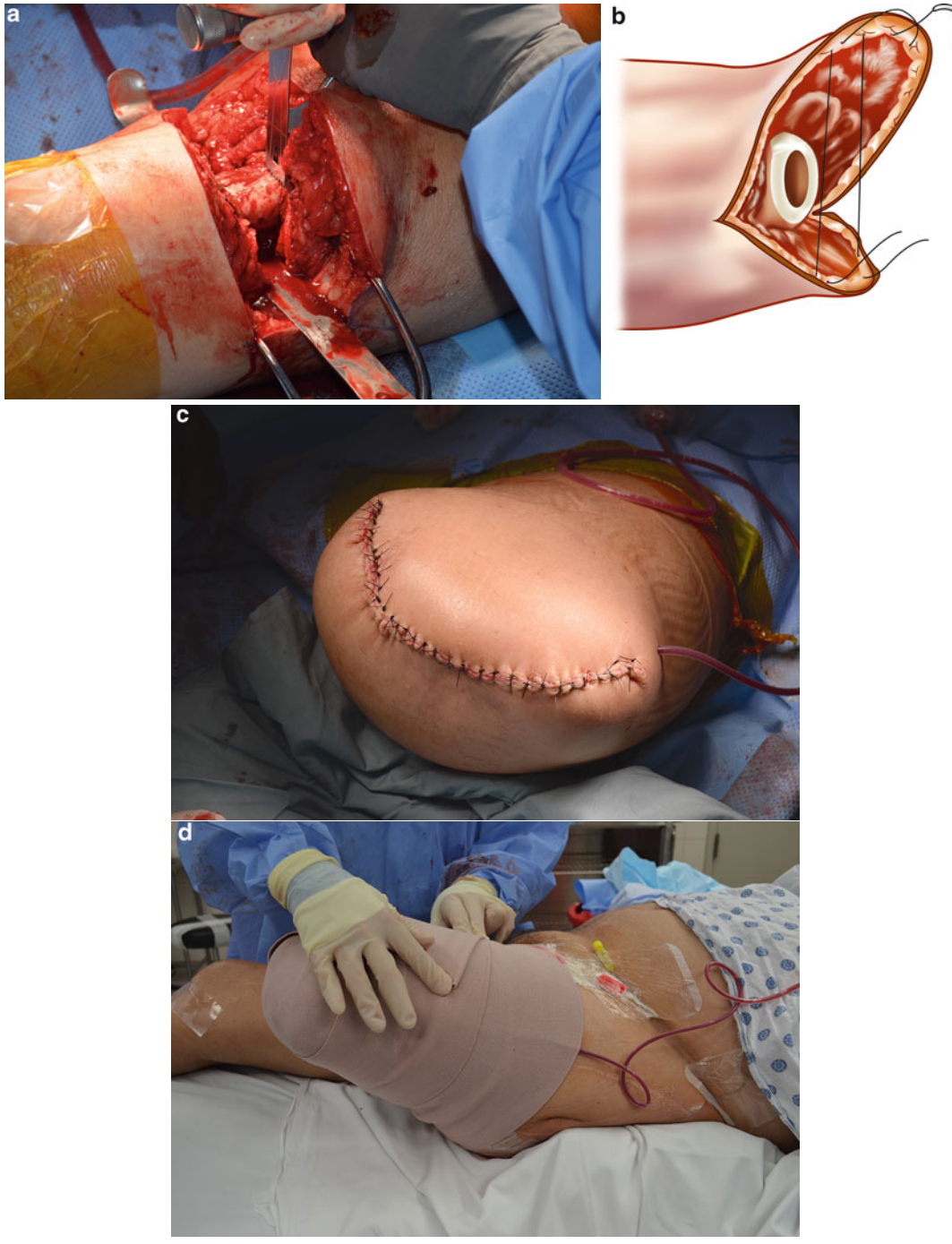

Fig. 19.3 Above-knee amputation surgical approach. (**a**) Femoral exposure. Transverse incision, expose femur, cut with oscillating saw. (**b**) Completed amputation with a fish mouth incision. (**c**) Wound closure with nylons and a drain. (**d**) Application of dressing

Once the sciatic nerve is identified, it should be placed on gentle stretch and ligated with electrocautery or a scalpel. This will allow the nerve to retract and not irritate the stump of the amputation site. Once the posterior musculature of the hamstrings has been transected, attention should be turned to the skin incision. Using the marks made at the beginning of the case for the second part of the fish mouth incision, a scalpel should be used to sharply dissect through the skin and subcutaneous fat to complete the amputation (Fig. 19.3b).

Once the amputation has been completed, the tissues are debrided and irrigated. The surgeon should feel comfortable that all major vessels have been ligated and then the tourniquet should be deflated. This allows for final inspection to cauterize and/or ligate vessels as needed. Then the closure of tissues can proceed.

Because the knee is infected, instruments used for performing the amputation should be removed from the operative field once the limb distal to the amputation is removed. Fresh instruments should be used for closing the wound, especially after a thorough irrigation has been performed.

Myodesis and Myoplasty

Function after AKA can be improved by stabilizing distal muscle by performing myodesis (attaching muscle to bone) or myoplasty (attaching muscle to muscle). The senior author prefers to use a myoplasty technique in his patient population. The most commonly performed myodesis is the adductor myodesis, where the adductor magnus is attached to the femur to provide maximum adduction of the remaining limb and to prevent flexion-abduction of the stump. To perform this, a drill hole is placed approximately 3/8 in. above the distal cut femur and the adductor flap is sutured through the bicortical hole. This also removes tension from the anterior myocutaneous flap created from the amputation.

Alternatively, a quadriceps myodesis or myoplasty can be performed to reduce the chance of a hip flexion contracture. A quadriceps myoplasty is performed by suturing the quadriceps to the adductor muscle and a quadriceps myodesis is performed by anchoring the quadriceps muscle to the posterior femur through holes drilled in the femur.

Closure

A drain is placed exiting laterally from the thigh. The ends of the anterior and posterior skin flaps should be brought together to approximate the location of closure and to ensure that there is adequate soft tissue padding over the distal end of the transected femur. Closure of the stump should occur in layers, starting with closing the deep fascia with absorbable sutures. The subcutaneous tissue can also be closed with absorbable suture and the skin can be closed with simple, interrupted nylons (Fig. 19.3c). Care must be taken to avoid any redundant tissues or dog ears at the corners of the wound. If redundant tissue remains, it can later cause skin irritation and wound breakdown on the stump. The incision should be covered with a nonstick sterile dressing, 4×4 fluffed gauze, and a gentle compression dressing should be applied with an ace wrap placed around the distal stump (Fig. 19.3d).

Stump Care

Stump care is variable and needs to be considered on a case-by-case basis. The population of patients who receive AKA after TKA infections are mostly an unhealthy group of patients [13, 16] that often have excessive scar tissue and soft tissue damage. These patients often fought infection for a prolonged period of time and have rather poor nutritional status. Thus, wound healing is commonly slow and the stump sutures should be maintained for a minimum of 3 weeks. Close observation of the wound with daily dressing changes is essential, as wound breakdown needs to be addressed in the immediate postoperative period.

Our protocol recommends that the patient lie prone several times daily to prevent the hip from developing a hip flexion contracture. If there is concern that a contracture is developing, a physical

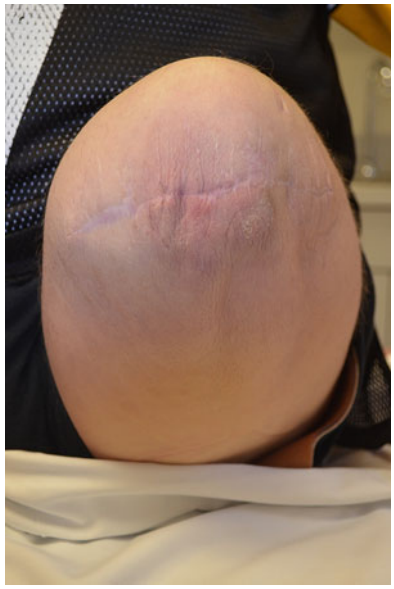

Fig. 19.4 Healed stump

therapist can be consulted to work on stretches and exercises.

Once the wound has completely healed, stump shrinking should commence [17]. Stump shrinking is the process by which either an elastic compression stocking or an elastic bandage is applied to the stump and is worn at all times to help taper the stump and reduce edema. Elastic bandages are advantageous because they can be used to control the location and amount of pressure in specific areas, but they are more difficult to apply. Elastic compression stump shrinkers are easier to apply and uniformly compress the stump but are more expensive and less customizable. Stump shrinking is applied until the volume of the stump is unchanged for a week. Once this volume is constant, the first prosthesis can be fit (Fig. 19.4).

Prostheses

It is crucial that a physician who specializes in physical medicine and rehabilitation is involved in the process of ordering and evaluating the prosthetic limb. The choice of prosthetic is tailored to the individual patient and their functional demands. A prosthetist who will be involved with fitting the prosthesis is also crucial to the process

The socket is the component of the prosthesis that mates with the stump. It is responsible for transferring the weight of the body to the prosthesis. Most current sockets are made of rigid plastic and are held in place by suction, which is called a suction socket. Most times, a sock is worn over the stump and a Silesian bandage holds the socket in place. However, there are times when nothing is worn between the stump and the socket. Over the first 18 months, there may be as many as two socket changes. For this reason, most initial prostheses are made in a modular fashion [17].

There are four main types of AKA prosthetic knees that will be discussed: variable friction (cadence control), polycentric (4 bar linkage), fluid control (hydraulic knee), and constant friction knee.

1. Variable friction (cadence control) knees have a number of staggered friction pads to provide increasing resistance to knee flexion as the knee extends. This design allows for variable gait speed, but is not durable.
2. Polycentric (4 bar linkage) knees have a variable center of rotation. The knee has different stability characteristics during the gait cycle (Fig. 19.5).
3. Fluid control (hydraulic knee) contains a piston that allows an adjustment of cadence response. The fluid hydraulics provides the varying resistance in the swing phase. The stiffness can be adjusted to meet patient needs and is preferred by young, active patients. The knee is heavier than others. The most advanced knees will have a microprocessor that provides for increased functional abilities. The microprocessor electronically controls the prosthesis through the stance and the swing phase using information from gait analysis and biomechanical studies. The sensors can sense and react to various stimuli. For instance, the knee can stiffen in response to a stumble in order to prevent a fall. The prosthesis allows for increased safety and speed on even and uneven surfaces, as well as on stairs. However, many insurance companies will not provide this high tech device to patients without documentation

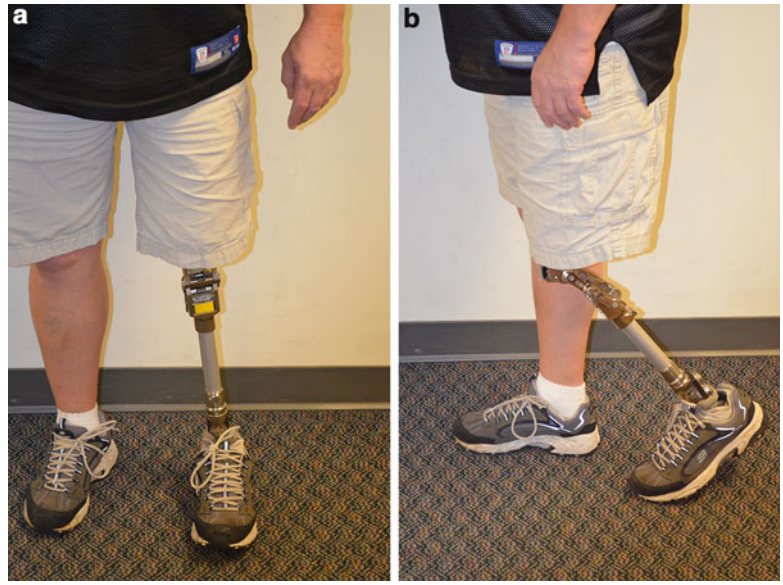

Fig. 19.5 Prosthesis—this AKA patient is shown ambulating with four-bar polycentric constant friction knee: (**a**) AP and (**b**) lateral

demonstrating that the patient will place the high demands on the prosthesis that require this level of expense.

4. The most common type of knee used in children is the constant friction knee. This knee is not recommended for older, weaker patients. This is a simple hinge that utilizes a rubber pad to dampen knee swing with friction to the knee bolt. It is a general utility knee that can be used on uneven terrain. The major drawback of the constant friction knee is that it allows only single-speed walking and relies on alignment alone for stance phase stability.

Complications

Amputations have a high risk of wound complications, especially when they are being performed for PJI. In terms of local complications after AKAs, there is the risk of wound dehiscence, poor healing, skin necrosis from wearing a prosthesis, bone erosion, hematoma, edema, and pain (postoperative, neuromas, and phantom pain) [18]. Patients also have increased risk of developing heterotopic ossification after AKA. Increased trauma to the surrounding soft tissues predisposes patients to the formation of excessive bone, which results in pain and may require revision amputation to remove bone [19].

Recurrent infections are common complications after performing an AKA to treat a PJI. Isilkar et al. reported one deep and one superficial infection after performing nine AKAs [11]. Sierra et al. found eight total complications in 25 patients: five deep infections (two of which required revision amputations), one superficial infection, one episode of skin necrosis, and one perioperative death [16]. In our previous study of AKA for infected TKAs, nine patients required irrigation and debridement of the stump for infection and two patients required a revision amputation. Two patients also died in the immediate postoperative period [13]. As these studies demonstrate, AKA patients have a higher chance of dying in the postoperative period compared to the general population, as they have greater medical comorbidities and are less mobile.

Functional Status

Previous studies on AKA after TKA have demonstrated poor functional outcomes with regards to use of a prosthesis and ambulatory status. This is often due to the exponential increase in the

energy required to ambulate after an AKA. The energy expenditure necessary for ambulating with a unilateral AKA, as measured by mean oxygen costs, is 49 % higher than unimpaired patients [20]. The speed of ambulation is dramatically decreased and the rate of oxygen consumption is increased in AKA patients [21].

Pring et al. was the first to examine the functional status of patients after AKA. Twenty-three patients with an average follow up of 48 months were evaluated for their functional status postoperatively. All patients were initially fitted with a prosthesis; however, only 15 patients were able to ambulate in the immediate postoperative period. Ten of these were able to walk for the first 2 years, but only seven were regular daily walkers at follow up. Of these, only three were able to walk more than 30 min, and only one was able to shop for themselves. Twenty of the twenty-three patients in this study required a wheelchair at some point during their day. Furthermore, ten had to change their housing situations as they required a higher level of care postoperatively than they did preoperatively [12].

Isiklar et al. studied nine AKAs after TKA in eight patients who were operated on between 1983 and 1992 and followed them for an average of 2.5 years after AKA. At last follow up, only two of eight patients were ambulatory with a walker and only one used a prosthetic device [11]. Sierra et al. studied 25 AKAs performed after TKA, 19 of which were done to treat infection. The patients were followed for an average of 8.6 years. Nine patients were fitted with a prosthesis, but only five were wearing the prosthesis at last follow up. One patient was able to ambulate unlimited distances, while three could walk less than five blocks outside of the house with the use of an assistive aid. Two patients were able to ambulate within the household and required assistive devices [16]. Patients who were fitted with a prosthesis and were ambulating were younger than those who could not ambulate.

Finally, we recently performed a retrospective review of 35 AKAs for treating PJI after TKA over a 15 year period at two tertiary care centers. Prior to AKA, only nine patients lived independently. Five were able to walk unlimited distances, three could walk fewer than five blocks outside the home, and twenty-seven were homebound. Fourteen of the patients were fitted with a prosthesis postoperatively, with only seven wearing it for greater than 1 h each day. Postoperatively, eight of fourteen patients were able to walk outside the home, with four patients able to walk unlimited distances and four patients only able to walk fewer than five blocks. All but three of these patients required an assistive device for ambulation and two patients were able to ambulate within the household. Twelve patients remained in their own homes and eight patients resided in assisted living facilities after their surgeries. Patients who were fitted with a prosthesis were younger and had fewer comorbidities than those who did not receive a prosthesis. Patients with prostheses also had higher ADLS scores [22] and SF-12 scores [13, 23, 24].

Overall, patients who undergo amputation for TKA have limited functional capabilities, but many of these patients were already limited preoperatively. AKA should be considered as an absolute last resort unless the patient is younger and healthier, as these patients have a better chance of functioning independently postoperatively with a prosthesis [13, 16].

Follow Up

In addition to compromised activity after AKA, there are also increased costs associated with AKAs compared to limb salvage procedures. A study by MacKenzie et al. demonstrated that the costs for limb reconstruction and amputation with regards to acute and postoperative care were similar. However, with the addition of the prosthesis, the projected lifetime costs were 3 times greater for amputation patients compared to limb salvage patients [25].

There is a high rate of mortality for patients who undergo amputation for complications after TKA. Sierra et al. reported 10 deaths in 25 patients [16] and our study had 15 deaths out of 35 patients at final follow up. We were unable to determine the cause of death in many of our

patients and could therefore not determine if their deaths were related to infection. However, as most patients survived the initial perioperative period, we concluded that infection was not the immediate cause of death.

As demonstrated in the literature, many patients undergoing AKA for infected TKA have significant health problems that confound their ability to function with an AKA. Many of the patients were homebound prior to their amputation [13]. As preoperative functional status is one of the best determinants of postoperative functional status, lack of significant functional improvement postoperatively is not unexpected. Therefore, amputations should only be used as a last resort in the treatment of PJI.

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Postoperative Management of Periprosthetic Joint Infection

20

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Introduction

Prosthetic joint infections (PJIs) of the knee and hip are a significant cause of morbidity due to pain and loss of function. On average, 0.8–1.9 % of prosthetic knee joints become infected [1–3] and 0.3–1.7 % of prosthetic hip joints become infected [3–5]. Although the rate of infection is relatively low, the total number of PJIs is increasing as the number of replacements performed per year increases.

The goals of treating PJIs are to control pain, to preserve function of the joint, to maintain quality of life, to cure or suppress the infection, and to prevent recurrence [6]. Management generally requires a multidisciplinary approach involving both surgical intervention and medical therapy with the use of antimicrobials. There has been a lack of standardization of the approach to PJIs due to a lack of randomized controlled trials [7]. The Infectious Diseases Society of America recently released its clinical practice guidelines, but management of PJIs still varies from clinician to clinician [8, 9]. Methods of treatment have been suggested previously in the literature and yielded better patient outcomes when they were followed [7, 10, 11].

The postoperative management of PJI involves administration of antimicrobials, monitoring for drug toxicity and adverse effects, management of patient comorbidities, and monitoring for relapse of infection. Antimicrobial choice and duration depend on the surgical approach that is taken. Many factors influence the aggressiveness of the overall approach, including virulence of the infecting organism, the organism's resistance patterns, presence of bacteremia, the patient's surgical risk functional status and wishes, the number of prior failed treatment attempts, bone condition, and the surgeon's experience [6]. The longer the infection has been present, the more likely a biofilm has developed and the longer the treatment should continue if the hardware with the biofilm is not removed [12]. Management options include debridement with antimicrobial therapy and retention of the prosthesis, two-stage exchange, single-stage exchange, implant removal with antimicrobial therapy without replacement of hardware, palliative long-term suppressive antimicrobial therapy, or amputation.

Debridement with Retention of Hardware

Patients with acute PJI who meet certain criteria may be treated with wound debridement and antimicrobial therapy without removal of the

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hardware. Patients must present within 3 weeks of symptom onset and within 3 months of implantation or have an infection from a hematogenous source [8]. These patients are less likely to have difficult-to-treat biofilms. The implant must be stable with no abscess or sinus tract present [8]. The patient must also have an organism that is relatively easy to treat with antimicrobial therapy. Thus, patients with an infection caused by a multidrug-resistant organism, *Enterococcus*, quinolone-resistant *Pseudomonas aeruginosa*, or a fungus are not candidates for this approach [6, 10, 11].

A microbiologic diagnosis is necessary to guide the choice of antimicrobials. Therapy is usually initiated with intravenous antimicrobials and later switched to oral therapy. The duration of the intravenous portion of antimicrobial therapy used at different medical centers varies from 2 to 6 weeks, with 6 weeks being more common in the United States [8, 13, 14]. Oral antimicrobials with good bioavailability, such as quinolones, can be used as initial therapy in some cases [6]. Although clear data are lacking, it has been suggested to continue with oral therapy for 3 months for prosthetic hip infection and 6 months for prosthetic knee infection based on the duration used in a single randomized controlled trial [11, 13]. Some clinicians opt for lifelong antibiotic suppression, especially in patients with very poor bone stock or unable to tolerate further surgery [9]. In general, knee infections are treated longer because the surrounding tissue is less favorable [11].

The inclusion of rifampin in the antimicrobial regimen should be considered with retained hardware if the infection is due to a susceptible *Staphylococcus* [15]. Although it cannot be used as monotherapy due to the high risk of development of resistance during therapy [16], rifampin has been shown to be efficacious in treating adherent, stationary-phase staphylococci associated with biofilms [17]. In a 1998 randomized controlled trial, staphylococcal PJI treated with ciprofloxacin and rifampin fared better than infections treated with ciprofloxacin alone [13]. However, the use of rifampin should be considered on a case-by-case basis because its use is often limited by drug toxicities and drug–drug interactions. It should be avoided in patients with underlying liver disease, heavy alcohol use, and significant drug interactions. If bacteremia is present, rifampin should not be added until the bloodstream has cleared.

Patients should be monitored for signs of recurrent infection both throughout treatment and after. Patients whose hardware is retained are at a higher risk of treatment failure than patients whose hardware is removed. Although it is not standard practice, one author suggests considering the use of oral suppressive therapy after completing treatment in patients who are at high risk for relapse [18]. However, continuing antibiotics past 6 months has been shown to delay relapse and not improve the chance of cure [14]. In general, the risk of relapse is highest within 4 months after discontinuation of antimicrobial therapy [14] and patients should be instructed to watch for symptoms that may herald recurrence of infection.

Two-Stage Approach

The most common approach to PJI in the United States is to remove the infected hardware and then treat the patient aggressively with antibiotics prior to reimplantation [8]. Many centers also implant an antibiotic-impregnated cement spacer during the first surgery to provide localized antimicrobial therapy while maintaining the length of the limb. The two-stage surgical approach allows time for identification of the causative organisms, optimization of targeted antimicrobial therapy, and sterilization of the joint space prior to placement of new hardware. The drawbacks of this method are temporary loss of mobility for the patient and the need for two major surgeries instead of one.

After the removal of hardware, treatment with intravenous antimicrobials is preferred. In the setting of antibiotic allergies, desensitization should be considered to allow the patient to receive first-line treatment for the causative organism. Various durations of antimicrobials have been used prior to reimplantation, ranging from 2 to 8 weeks or longer [6, 11]. A duration of 4–6 weeks is commonly used [6]. Most infectious diseases clinicians in the United States favor

6 weeks [9, 10]. A prolonged antimicrobial course may be required for difficult-to-treat infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant organisms, enterococci, and fungi [11]. In contrast, two recent studies successfully used 2 weeks or even no systemic antimicrobials in patients with antimicrobial spacers and longer delays prior to reimplantation [19, 20].

Although there is currently no consensus on the optimal duration of the antibiotic-free period prior to reimplantation [9], antimicrobials should be stopped at least 2 weeks prior to reimplantation. The joint space is often aspirated after the discontinuation of antimicrobials to assess for persistent infection. If the aspiration suggests infection, patients may require a spacer block exchange and another course of targeted antimicrobial therapy. If the aspiration is negative for infection, patients may proceed to implantation of new hardware with repeat cultures obtained in the operating room. If the cultures taken in the operating room remain negative, the patient usually does not require further antimicrobials. Some clinicians advocate the continued use of antimicrobials targeted against the initial pathogen, but data to support this practice are lacking. Some practitioners may choose to give the patient oral suppression for 3–6 months or even lifelong in patients who are at high risk of recurrent infection. If, however, an organism is isolated from the cultures taken at the time of reimplantation, targeted intravenous antimicrobials should be resumed for approximately 6 weeks followed by oral suppressive antimicrobials for at least 3 months for hip replacement patients and at least 6 months for knee replacement patients.

Single-Stage Exchange

A single-stage exchange may be done if the patient has no severe comorbidities, if the organism is not difficult to treat, and if the surrounding soft tissue is in satisfactory condition [11, 21]. In this approach, the old hardware is removed, the surrounding infected tissue is thoroughly debrided, and new hardware is placed. If the patient is not systemically ill, antimicrobials can be withheld until after cultures are obtained in the operating room. Although there is wide variability in the duration of antimicrobial used [22], it has been suggested that treatment should begin with anywhere from 2 to 6 weeks of parenteral therapy followed by oral therapy for a total of 3 months for prosthetic hip infections and for 6 months for prosthetic knee infections [11].

Palliative Options

In some cases, new hardware is not replaced if the surgical risk of repeat arthroplasty outweighs the expected benefit [11]. The infected hardware may be removed without the intention to place new hardware. Some practitioners will administer 4–6 weeks of antimicrobials after resection arthroplasty of an infected prosthetic joint [12]. In severe cases, the infected limb may require amputation. In other cases, the infected hardware may be left in place, and chronic antimicrobial therapy is given with the goal to suppress the infection. Oral antibiotics such as trimethoprim-sulfamethoxazole, doxycycline, or minocycline may be used if the organism is susceptible, as these antimicrobials are better tolerated for long-term use. Rifampin is not necessary as an adjunctive in these cases because the goal is only to suppress the infection.

Antimicrobial Selection

There are few randomized controlled trials to guide the choice of antimicrobial therapy for PJI. However, the basic concept is to achieve adequate concentrations of antibiotic to kill organisms that may be residing on avascular prosthetic material or within difficult-to-penetrate biofilms. Cultures should be obtained during surgery to guide antimicrobial choice. Although susceptibility testing is helpful, caution must be taken when applying this information to the treatment of a PJI because of the presence of biofilms [13, 17, 23–25]. In vitro susceptibility does not always correlate with clinical outcomes.

Table 20.1 Suggested antimicrobial options by causative organism

Organism	Antimicrobial agent	Alternative(s)
Methicillin-susceptible *Staphylococcus aureus*	Cefazolin or nafcillin ± rifampin	Vancomycin or daptomycin
Methicillin-resistant *Staphylococcus aureus*	Vancomycin ± rifampin	Daptomycin, linezolid, ceftaroline
Coagulase-negative *Staphylococcus*	Vancomycin	Daptomycin
Enterococcus and *Streptococcus agalactiae*	Penicillin G or ampicillin ± aminoglycoside	Vancomycin, daptomycin
Other streptococci	Penicillin G or ceftriaxone	Vancomycin
Enterobacteriaciae	Ciprofloxacin	Carbapenem, tigecycline, colistin (if multidrug-resistant)
Pseudomonas	Ceftazidime or cefepime	Ciprofloxacin
Bacteroides	Metronidazole	
Propionibacterium acnes	Penicillin G	Vancomycin, clindamycin

Choice should be guided by susceptibility testing

The type of organism found varies somewhat according to time from implantation [26, 27]. Within 3 months of implantation, virulent organisms such as *S. aureus* and Gram-negative rods are more common. Delayed infections occurring between 3 months and 2 years after implantation tend to be caused by less virulent organisms such as coagulase-negative staphylococci and *Propionibacterium acnes*. Late infections arising more than 2 years after implantation are usually due to hematogenous seeding from a skin, respiratory, urinary, or dental source. The organisms isolated reflect the pathogens commonly found in the location from which the infection originated, and source control should be assessed aggressively.

Empiric antimicrobial therapy should cover the most common pathogens, including staphylococcus. Cefazolin usually provides adequate coverage, although vancomycin may be used if there is a high local incidence or high risk of MRSA in the patient [12]. In choosing between the use of intravenous and oral antimicrobials, the bioavailability of the oral drug must be taken into account. Some clinicians use intravenous antimicrobials only during empiric therapy and switch to susceptible oral agents once the organism has been identified and susceptibility data are available [18]. Other clinicians will use a longer course of intravenous agents prior to switching. Table 20.1 lists suggested antimicrobials for common bacteria that cause PJI.

Gram-Positive Bacteria

More than half of all PJI are due to Gram-positive bacteria [6]. The most common organisms in this category are coagulase-negative staphylococci, *S. aureus*, and streptococci, including enterococcus. The preferred treatment for methicillin-sensitive *Staphylococcus aureus* (MSSA) is cefazolin or nafcillin with the addition of rifampin if indicated and if tolerated by the patient. The long-term use of nafcillin is often precluded by gastrointestinal upset or nephrotoxicity [28]. In patients with a severe immediate-type penicillin allergy, alternatives include vancomycin and daptomycin. Although there are currently no clinical trials supporting the use of daptomycin in this setting, this drug has been used with success anecdotally.

The drug of choice for MRSA is vancomycin dosed at 15–20 mg/kg/dose every 8–12 h with normal renal function and consideration of the addition of rifampin [11]. Use of rifampin has been shown to increase the ability to penetrate biofilms [13, 29]. As seen in the treatment of MSSA, an alternative to vancomycin that is being used more frequently for the treatment of MRSA is daptomycin, dosed at 6 mg/kg/dose intravenously once daily [30]. In patients intolerant to vancomycin and daptomycin, or for MRSA isolates found to be intermediate or resistant to vancomycin and daptomycin, alternative therapies include linezolid or ceftaroline [31]. Options for

long-term oral suppression of MRSA include trimethoprim-sulfamethoxazole, doxycycline, minocycline, or clindamycin [30].

Antimicrobial choices for the treatment of coagulase-negative Gram-positive bacteria, such as *Staphylococcus epidermidis*, are the same as for *S. aureus*. *Staphylococcus epidermidis* is usually resistant to methicillin, requiring the use of vancomycin or daptomycin. However, *Staphylococcus lugdunensis* can often be treated with cefazolin if susceptible.

Enterococci and *Streptococcus agalactiae* are treated with penicillin G or ampicillin [11]. The addition of an aminoglycoside can be considered, but one recent study of enterococcal PJI showed that the use of combination therapy did not improve outcome [32]. Furthermore, patients who received aminoglycoside therapy were more likely to experience adverse effects from the medication, such as nephrotoxicity or ototoxicity [32]. Other streptococci are treated with penicillin G or ceftriaxone [11].

Gram-Negative Bacteria

For enterobacteriaciae, ciprofloxacin should be used if susceptible due to its good bioavailability, tolerability, and long history of use. *Pseudomonas* should be treated with agents such as ceftazidime, cefepime, or ciprofloxacin if susceptible. Unfortunately, many bacteria have become increasingly resistant to traditional choices of antimicrobials. Bacteria with extended-spectrum beta-lactamase and/or carbapenemase production cannot be treated with certain commonly used antibiotics. Other mechanisms of resistance have further limited antimicrobial options. Alternative antimicrobials, including carbapenems, aminoglycosides, tigecycline, and colistin, may be necessary. Control of the source of the infection becomes increasingly important in cases where medical therapies are limited.

Anaerobic Bacteria

Treatment of anaerobic bacteria should be guided by susceptibility testing, if available. In general, *Bacteroides* infections can be treated with metronidazole. Other anaerobic bacteria, such as *P. acnes*, can be treated with penicillin, clindamycin, or vancomycin [33]. *P. acnes* is more common in shoulder joint infections than in infections of the lower extremity joints.

Fungi

Fungal PJI is rare. *Candida* species are the most common fungi isolated, making up about 1 % of all PJI. In the past, many of these infections have been treated with permanent resection arthroplasty in conjunction with antifungal agents due to heightened concern for recurrent infection. However, some cases have been successfully treated with a delayed two-stage procedure [34]. Amphotericin is often preferred for the treatment of deep-seated fungal infections; however, current recommendations for *Candida* PJI are to treat with 400–800 mg (6 mg/kg) daily of fluconazole or 3–5 mg/kg daily of lipid formulation amphotericin B (LFAmB) for at least 2 weeks followed by fluconazole 400 mg daily [35]. Fluconazole has been shown to achieve high levels within synovial fluid [34]. Alternative agents include echinocandins or amphotericin B-deoxycholate dosed at 0.5–1 mg/kg daily for at least 2 weeks followed by fluconazole 400 mg daily [35]. Different *Candida* species have different susceptibility patterns; for example, *Candida glabrata* is sometimes resistant to fluconazole or may require high doses to be treated successfully [35]. Total treatment duration should be at least 6 weeks and, in some cases, very prolonged courses of 9 months to a year have been used [34]. Documentation of clearance of infection is required prior to placement of a new prosthesis [35]. If the prosthesis cannot be removed, the patient should receive chronic suppression with fluconazole if the *Candida* is susceptible [35]. Amphotericin or voriconazole may be added to the cement used for placement of the spacer.

Rare Pathogens

There is a wide range of rare pathogens that can cause PJI. Diagnosis often requires a high index of suspicion, as these organisms often require

specialized media for identification. Removal of hardware is preferred in these cases because medical treatment is often challenging. Some rare pathogens include *Mycobacterium tuberculosis,* non-tuberculosis mycobacteria, *Brucella melitensis*, *Francisella tularensis*, *Yersinia enterocolitica*, *Pasteurella multocida*, *Campylobacter* species, *Haemophilus influenza*, *Echinococcus*, *Gemella*, *Listeria monocytogenes*, *Mycoplasma*, mold infections, and others. These infections should be managed with the assistance of an infectious diseases specialist.

Polymicrobial Infections

Polymicrobial infections are often found in patients with soft tissue defects, wound dehiscence, drainage, or prior irradiation [36]. Antimicrobial treatment should be guided by susceptibility patterns of the pathogens involved. Many polymicrobial infections include the presence of MRSA and anaerobic bacteria. If MRSA is not present, treatment can be initiated with agents such as ampicillin-sulbactam or a carbapenem for 2–4 weeks and then narrowed based on susceptibilities.

Culture-Negative Infections

In some cases, cultures taken from an infected prosthetic joint may not reveal the causative organism. Diagnosis of infection is made on the basis of periprosthetic purulence seen in the operating room, acute inflammation present in periprosthetic tissue samples, or presence of the organism in the sinus tract [37]. If there are low numbers of the organism in the collected samples or if the organisms are lodged in a biofilm, they may not appear in the culture. In other instances, the pathogen may not grow in the culture due to recent antibiotics given to the patient or the use of antimicrobial cement. Problems with the culture technique, such as an inappropriate culture medium, inadequate incubation time, or prolonged transit time from the operating room to the microbiology laboratory, can also affect the yield of cultures. Finally, certain pathogens, such as slow-growing, small-colony staphylococcus variants, can sometimes be missed on routine solid media cultures [38]. One recent study showed that when cultures were held for 2 weeks, most initial culture-negative infections were found to be due to Gram-positive bacteria such as *P. acnes* and coagulase-negative *Staphylococcus* [39].

If the prosthesis is removed from the patient, some institutions may be able to sonicate the hardware to release organisms from the biofilm and increase the yield of cultures [40]. Polymerase chain reaction (PCR) testing of surgical specimens can detect the presence of pathogens without requiring the organism to grow for identification. However, because PCR testing is so sensitive, it may detect organisms that are not clinically relevant.

Optimal management of culture-negative infections is not well defined. Use of broad-spectrum antimicrobials has not been shown to improve outcomes compared to use of cephalosporins. However, when choosing an empiric regimen, the spectrum of activity of recently administered antimicrobials, including local antimicrobial agents found in cement, should be taken into account. Treatment is usually initiated to target Gram-positive organisms with agents such as vancomycin or daptomycin. Local antimicrobial resistance patterns and patient drug allergies also influence antimicrobial choice. Despite the lack of objective guidance in these cases, outcomes have not been shown to be worse than in cases with a known pathogen and antimicrobial susceptibilities [37].

Patient Monitoring

Patients being treated for PJI should be monitored closely for antimicrobial efficacy, toxicity, and adverse reactions. The most common adverse effect of antimicrobial therapy is rash, which may even require discontinuation of therapy or switching to another agent [41]. Patients may also develop diarrhea or *Clostridium difficile* enterocolitis. Patients are monitored for treatment

failure by assessing for clinical signs and symptoms of infection and by obtaining regular blood tests, including complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) [42]. Although abnormal laboratory parameters are helpful for detecting treatment failure during therapy, normal values do not ensure that the patient will not experience recurrence of infection after antimicrobials are stopped [42]. The patient's white blood cell count should remain within the normal range, and if it was elevated at the time of surgery, it should normalize as treatment progresses.

ESR and CRP are useful for monitoring the progress of PJIs [8, 43]. CRP rises in response to tissue destruction, including from surgery or infection [44]. An elevated CRP has a sensitivity of 73–91 % and specificity of 81–86 % for prosthetic knee infection if a cut-off of 13.5 mg/dL is used [6, 45, 46]. The sensitivity and specificity for prosthetic hip infection are 95 % and 62 %, respectively, if a cut-off of 5 mg/dL is used [47]. Surgery will cause the CRP to rise and peak 2–3 days after surgery [44]. The CRP should then decrease rapidly to a normal range if there are no complications [44]. The ESR peaks about 5 days after surgery before gradually returning to normal range or slightly above normal range [43]. ESR and CRP are expected to gradually return to a normal range throughout the course of treatment. Clinicians often use inflammatory markers to guide therapy and may choose to extend treatment if clinical or laboratory parameters are not yet normalized at the end of the planned course of treatment [8, 42, 48].

Antimicrobial Toxicities

Patients on long-term antimicrobials should receive regular blood testing to monitor for signs of toxicity or side effects. Many antibiotics can cause cytopenias, and following the patient's creatinine level is often important for dosing of the antimicrobial agent and for monitoring for nephrotoxicity. Patients should be counseled on potential side effects of the medications they will receive. Although beta-lactam antibiotics are most commonly implicated, any antibiotic can potentially cause a hypersensitivity reaction with rash. Most antibiotics can also cause gastrointestinal upset and diarrhea. Table 20.2 lists some of the common adverse reactions related to antimicrobial agents commonly used for the treatment of PJI.

Table 20.2 Adverse reactions associated with antimicrobial agents commonly used to treat prosthetic joint infections

Antimicrobial agent	Adverse effects
Cefazolin	Drug rash, cytopenias
Daptomycin	Myositis, eosinophilic pneumonia
Doxycycline, minocycline	Gastrointestinal upset, photosensitivity, pill esophagitis
Fluoroquinolones	QT prolongation, Achilles tendon rupture
Linezolid	Myelosuppression, peripheral neuropathy
Nafcillin	Gastrointestinal upset, cytopenias, nephritis
Rifampin	Discoloration of bodily fluids, hepatotoxicity
Trimethoprim-sulfamethoxazole	Drug rash, cytopenias
Vancomycin	Nephrotoxicity, Red man syndrome

Vancomycin serum levels should be monitored regularly throughout treatment. Elevated levels greater than 15 μg/mL are associated with higher incidence of nephrotoxicity. Although kidney injury was originally due to impurities in older formulations of the drug, recent studies still report a significant incidence of renal dysfunction associated with trough levels greater than or equal to 15 μg/mL [49]. Patients with underlying risk factors for renal insufficiency such as hypertension or diabetes may benefit from treatment with an alternative agent such as daptomycin. Vancomycin can also cause infusion-related reactions such as phlebitis and Red man syndrome, a reversible rash due to the release of histamine.

Despite its higher cost, daptomycin is sometimes favored due to its once-a-day dosing, which may be easier to administer in the ambulatory setting. It may also be easier to dose than vancomycin in patients with fluctuating renal function or a BMI >30 kg/m^2. The main adverse reaction

of daptomycin is reversible skeletal muscle toxicity. Eosinophilic pneumonia has also been reported [50]. Patients should be forewarned to notify their physician if they develop soreness in their muscles or respiratory symptoms. Patients should have a baseline creatine phosphokinase (CPK) measured prior to initiation of daptomycin, weekly CPK levels should be monitored during treatment, and patients receiving concurrent statin therapy should have the statin held temporarily if possible [8].

Linezolid treats most Gram-positive bacterial infections and has good oral bioavailability [51], but its long-term use is limited by side effects of the drug. Forty percent of patients experience a reversible myelosuppression, and some patients develop irreversible peripheral and optic neuropathy [52]. Tongue and dental discoloration have also been reported. The use of linezolid in patients who are also taking selective serotonin reuptake inhibitors places them at risk for serotonin syndrome.

Patients given rifampin should be warned that the drug may cause bodily fluids such as urine, saliva, sweat, and tears to appear orange in color. Soft contact lenses may be stained as a result. Because rifampin is metabolized by the cytochrome P450 system, it can cause drug interactions with many medications metabolized by the same system. In particular, patients who are on warfarin must have their prothrombin time followed closely. Rifampin can also cause hepatotoxicity, and liver function tests should be monitored while patients are on this medication.

Fluoroquinolones may rarely cause QT interval prolongation and predisposal to cardiac arrhythmias, such as torsade de pointes, in patients taking other QT-prolonging medications, such as amiodarone [53]. Fluoroquinolones are also rarely associated with risk of Achilles tendon rupture in patients, particularly in patients over 60 years of age, on corticosteroid therapy, or recipients of organ transplantation [54]. This class of drugs can also lower the seizure threshold and should be given with caution in patients with seizure disorders. Patients should also be counseled on the risk of developing *C. difficile* colitis while on this medication and instructed to notify their physician if they develop diarrhea.

Trimethoprim-sulfamethoxazole use is often limited by allergic reactions and the development of drug rash. Trimethoprim-sulfamethoxazole can cause leukopenia, thrombocytopenia, and granulocytopenia when taken for prolonged periods of time [55]. The drug can also cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Creatinine should be monitored regularly because this medication can cause nephrotoxicity and a rise in serum creatinine [56].

The tetracyclines, including doxycycline and minocycline, often cause gastrointestinal upset. Patient should also be warned that these medications can cause photosensitivity and pill esophagitis.

Patients treated with metronidazole should be counseled to avoid alcohol intake until after completion of therapy because the medication can cause a disulfiram-like reaction. Patients may also experience an unpleasant metallic taste in their mouth. Metronidazole has also been reported to cause peripheral neuropathy, though this adverse reaction is generally reversible.

Outpatient Parenteral Therapy

Because of the long duration required to treat most cases of PJI, many patients complete their course of intravenous antimicrobials in the outpatient setting. With the development of specialized equipment for infusion of antibiotics at home, many patients can be trained to administer antimicrobials at home, often with the assistance of a visiting nurse or family members. Other patients may receive outpatient antimicrobials in an outpatient infusion center or in a nursing facility. The implementation of outpatient parenteral antimicrobial therapy requires coordination between the physician and other members of the healthcare team, including social services, pharmacy, and home nursing. Issues such as dosing frequency, drug stability, and insurance coverage may limit or influence the selection of antimicrobial agents. The physician must also determine the appropriate type of long-term vascular access the patient requires and manage problems that may arise with its use [41]. Complications of vascular lines

include clotting of the lumens of the line, deep venous thrombosis septic thrombophlebitis, and bleeding or infection at the line site.

Chronic Suppression

Chronic suppressive antibiotics are used when infected hardware is not removed, such as when patients are unable or unwilling to undergo surgery. Chronic suppression may sometimes be used for patients after debridement with hardware retention or if signs of inflammation are still present at the time of reimplantation during a two-stage approach. The use and duration of chronic oral antimicrobial suppression continues to be a controversial topic [8]. Patients who are on antibiotics indefinitely must be counseled and monitored regarding side effects of the medications with long-term use.

Management of Comorbidities

Patients with PJI often have comorbidities that should be addressed on an outpatient basis. Diabetics should have their blood glucose levels well controlled. Patients with peripheral vascular disease may need interventions to improve blood flow in the infected limb to aid healing and to allow systemic therapies to reach the infected site. Optimizing the patient's nutritional status may also aid wound healing.

Conclusion

With an aging population, more joint replacement procedures will continue to be performed each year. The management of PJI is a challenging component of care requiring the collaborative efforts of orthopedic surgeons, infectious diseases physicians, and other healthcare providers. Careful selection of antimicrobial therapy and close monitoring of patients in follow-up are crucial to fully treating PJIs, preventing treatment failures and complications, and optimizing the goal of a successful outcome for each patient.

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