8-1-2020

Contemporary Strategies to Prevent Infection in Hip and Knee Arthroplasty

Lachlan M. Batty
Epworth Hospital

Brent Lanting
London Health Sciences Centre

Current Reviews in Musculoskeletal Medicine (2020) 13:400–408
https://doi.org/10.1007/s12178-020-09653-9

HOT TOPICS

Contemporary Strategies to Prevent Infection in Hip and Knee Arthroplasty

Lachlan M. Batty[1] · Brent Lanting[2]

Published online: 16 June 2020

Abstract

Purpose of Review Prosthetic joint infection (PJI) remains a serious concern in lower limb arthroplasty. Despite the significant consequences of PJI, the assessment of the safety and efficacy of preventative measures is challenging due to a low event rate. Notwithstanding, enormous efforts have been made in this arena, and prevention strategies continue to evolve. This review provides an update on contemporary literature (published within the last 5 years) pertaining to infection prevention in primary hip and knee arthroplasty.

Recent Findings Patient optimization has been highlighted as a critical preoperative factor in mitigating PJI risk. Recent evidence emphasizes the importance of preoperative glycaemic control, nutritional status, weight optimization and smoking cessation prior to hip and knee arthroplasty. Perioperatively, attention to detail in terms of surgical skin preparation agent and technique as well as prophylactic antibiotic agent, spectrum, dose and timing is important with statistically and clinically significant differences seen between differing strategies. Intraosseous regional antibiotic administration is an emerging technique with promising preclinical data. Dilute betadine lavage also shows promise. Data supporting bundled interventions continues to grow.

Summary A multimodal approach is required in PJI prevention, and attention to detail is important with each element. Patient optimization is critical, as is the execution of the planned perioperative infection prevention strategy.

Keywords Arthroplasty · Hip · Knee · Infection · Prevention

Introduction

Infection prevention is a critical component in optimizing lower limb arthroplasty outcomes. Risk stratification is important for preoperative counselling, as is a structured approach in mitigating modifiable risk factors. This review provides an update and overview of contemporary literature pertaining to infection prevention in hip and knee arthroplasty divided into preoperative, perioperative and post-operative considerations.

✉ Lachlan M. Batty
Lachlan.batty@gmail.com

Brent Lanting
brent.lanting@lhsc.on.ca

[1] OrthoSport Victoria Research Unit, Epworth Hospital, 89 Bridge Rd, Richmond, Victoria 3121, Australia

[2] Division of Orthopaedic Surgery, University Hospital, London Health Sciences Centre, Western University, London, Ontario N6A 5A5, Canada

Preoperative Strategies

Screening and Threshold for Acceptable Preoperative Glycaemic Control

For diabetic patients, assessment of glycaemic control has long been considered important in risk stratification and prevention of prosthetic joint infection (PJI) [1]. The ideal marker of glycaemic control and threshold where PJI risk is increased continue to be refined. Cancienne et al. [2] queried a national administrative database and identified a group of 7736 patients undergoing total hip replacement (THR) who had a haemoglobin A1c (HbA1c) level within 3 months of surgery. HbA1c levels were stratified in 0.5 mg/dL increments, and the incidence of deep infection within 1 year of surgery was calculated for each HbA1c stratification. An exponential relationship between HbA1c and infection rate was demonstrated. Patients with an HbA1c level of 7.5 mg/dL or greater had a significantly higher risk of deep infection compared with patients below this threshold (odds ratio (OR) 2.6, $p < 0.0001$). A receiver operator characteristic inflexion point

corresponded to a HbA1c level between 7.0 and 7.5 mg/dL ($p = 0.001$, specificity 69%, sensitivity 47%). A similar HbA1c threshold of 7.7 mg/dL was suggested by Tarabichi et al. [3] after conduction of a multicentre retrospective study of 1645 diabetic patients undergoing hip and knee arthroplasty. With the primary outcome of PJI at 1 year diagnosed by Musculoskeletal Infection Society (MIS) criteria, a HbA1c over 7.7 mg/dL was predictive of PJI (area under the curve, 0.65; 95% CI, 0.51–0.78). Using this threshold as a cut off, PJI rates increased from 0.8% (11 of 1441) to 5.4% (11 of 204).

A growing evidence base supports serum fructosamine as an alternate, potentially superior measure of preoperative glycaemic control. Shohat et al. [4] reported on 829 patients undergoing primary total joint arthroplasty from a prospectively collected database. A serum fructosamine > 292 mmol/L outperformed a HbA1c > 7% in predicting deep infection, readmission and reoperation. Shohat et al. [5•] later reported results of a prospective multi-institutional study evaluating primary TKA patients from four academic institutions. PJI and wound complication were assessed in 1119 patients. Patients with serum fructosamine > 293 μmol/l were 11.2 times more likely to develop PJI compared with patients with fructosamine < 293 μmol/l ($p = 0.001$). Readmission and reoperation rates were 4.2 and 4.5 times higher in patients with fructosamine above this threshold. HbA1c at a threshold of 5.9%, 7% or 7.5% was unable to identify patients at higher risk of these complications. The authors concluded that serum fructosamine is better able to predict adverse events as compared with HbA1c in arthroplasty patients.

Identification and Optimization of Perioperative Malnutrition

Malnutrition has a spectrum of severity and can be difficult to diagnose. It can be subclinical and has been demonstrated to be common even in the setting of obesity [6]. There has been recent interest in the use of biochemical markers as a surrogate for nutritional status in joint replacement patients. Blevins et al. [7] conducted a retrospective investigation into the relationship between abnormal nutritional parameters and development of PJI as diagnosed by MIS criteria. Over a 16-year period, 30,863 patients undergoing hip or knee arthroplasty were assessed for PJI at 2 years. Multivariate logistic regression analysis demonstrated albumin < 3.5 g/dL (adjusted OR, 4.69, $p < .001$) and haemoglobin < 12 g/dL (adjusted OR, 2.718, $p = 0.018$) were independently associated with PJI, although albumin data were only available for 9001 patients. Similar findings were reported by Bohl et al., [8] who investigated the association between preoperative hypoalbuminemia (< 3.5 g/dL) and 30-day complication rates in 49,603 primary arthroplasties. After adjusting for demographic, comorbidity and laboratory factors, patients with hypoalbuminemia were at higher risk for SSI (2.29% vs 0.96%; adjusted relative risk (RR) 2.0, $p = 0.001$).

The efficacy of delaying arthroplasty to allow for nutritional optimization remains to be tested in clinical trials. However, in a 2016 review, Golladay et al. [9] made recommendations for arthroplasty patients on the basis of the existing arthroplasty and non-arthroplasty literature. The authors suggested the most common serologic markers to indicating preoperative malnutrition included a serum albumin of less than 3.5 g/dL, absolute lymphocyte count of less than 1500 and transferrin < 200. The authors recommended consideration of some simple preoperative interventions prior to arthroplasty (Table 1).

Management of the Patient with Obesity

Obesity has long been associated with increased perioperative complications in patients undergoing total joint replacement (TJR). Preoperative bariatric surgery is one potential intervention that has been investigated to mitigate this risk. A 2019 meta-analysis by Li et al. [10] investigated the influences of prior bariatric surgery on TJR outcomes in patients with a BMI > 40 kg/m2. The primary outcome of interest was complication (including PJI) and revision rates. Across 9 studies, a total of 38,728 patients were included with 5743 patients undergoing bariatric surgery prior to TJA and 32,985 morbidly obesity patients having TJA without bariatric surgery. The mean BMI prior to TJA in the control group was above 40, while it was below 40 in the bariatric surgery group. Six studies reported short-term (within 90 days) PJI rates. The bariatric surgery group tended to have a lower rate of PJI, with 159 of 5434 patients (2.9%) in this group and 1110 of 21,768 patients (5.1%) in the non-bariatric surgery group developing PJI (OR 0.70, $p = 0.09$). Although this difference was not significant, on subgroup analysis, a significant reduction in the risk of short-term PJI was seen in the bariatric surgery group undergoing TKA (OR 0.51, $p = 0.0009$). This was not evident for THA (OR 0.93, $p = 0.52$). Two of the included studies reported on short-term superficial wound infection; five of 237

Table 1 Considerations for nutritional optimization in arthroplasty patients as proposed by Golladay et al.

Nutritional element	Intervention/supplementation
Protein	Protein supplement, 1 g/kg daily for 10–14 days
Iron	324 mg TDS for 3–4 weeks
Vitamin D	1000 IU daily (increase if deficient)
Vitamin C	500 mg daily for 2 weeks
Zinc sulphate	220 mg daily

TDS three times per day *IU* international units

Table adapted from Golladay GJ, Satpathy J and Jiranek WA. Patient optimization—strategies that work: malnutrition. The Journal of arthroplasty. 2016;31(8):1631-4

knees (2.1%) in the bariatric surgery group and 42 of 11,068 patients (0.4%) in non-bariatric surgery group developed a superficial wound infection. The difference was not significant (OR 3.25, $p = 0.07$). Long-term (follow-up > 1 year) PJI rates were reported in 6 studies. There was no significant difference between groups, with 107 of 2006 patients (5.3%) in the bariatric surgery group and 612 of 18,210 patients (3.4%) in the non-bariatric surgery group developing PJI (OR 0.93, $p = 0.54$). The meta-analysis was limited by the heterogeneity of the included studies and smaller numbers for subgroup analyses. No recommendations were made in relation to when preoperative bariatric surgery should be considered. Optimal timing between bariatric surgery and TJR also need to be defined. The latter question was addressed in a study by Schwarzkopf et al. [11]. Patients undergoing THA more than 6 months after bariatric surgery were significantly less likely to be readmitted within 90 days for any cause; however, infection rates were not reported on. A further 2019 systematic review and meta-analysis on the efficacy of pre-arthroplasty bariatric surgery by Gu et al. [12] did not report rates of infection in isolation.

Arthroplasty After Intra-articular Injection

Using a nationwide insurance database, Richardson et al. [13•] assessed 58,337 patients undergoing primary TKR to assess the impact of preoperative corticosteroid or hyaluronic acid (HA) injections on the 6-month risk of PJI. Three thousand two hundred forty-nine patients (5.6%) received HA, and 16,656 patients (28.6%) received corticosteroid injections within the year prior to TKR. Multivariable logistic regression showed both corticosteroid (OR 1.21; $p = 0.014$) and HA (OR, 1.55; $p = 0.029$) given < 3 months of TKR were predictors of PJI independent of age, sex or comorbidities. There was no increased risk with injections > 3 months prior to TKR. There was no difference in PJI rates when based on type of injection (corticosteroid versus HA) or between single versus multiple injections. This large cohort adds to existing studies supporting delaying TKR for 3 months after intra-articular injection [14], although some series have suggested the infection risk may be elevated for as long as 6 months [15].

Smoking Status and Cessation

A 2019 meta-analysis by Bedard et al. [16] examined the effects of smoking status on PJI in hip and knee arthroplasty patients. Fourteen studies reporting on 227,289 primary THA and TKA were included in the meta-analysis. Strengths of this meta-analysis include assessment of overall wound complications as well as PJI specifically and the assessment of non-smoker, ex-smoker and current smoker groups. Weaknesses include the quality of the included studies which were comprised of entirely retrospective series with associated biases and heterogeneity. Nonetheless, the authors demonstrated that smokers had a significantly higher risk of both overall wound complications (OR 1.78) and PJI (OR 2.02). Compared with non-smoker users, there was an increased risk of PJI in both current smokers (OR 2.16) and former smokers (OR 1.52); however, only 6 and 10 of the studies reported on these groups, respectively. Current tobacco users also had a significantly increased risk of PJI compared with former tobacco users (OR 1.52). The study was unable to determine an optimum time frame between smoking cessation and arthroplasty surgery. No studies were identified that reported PJI rates after interventions to quit smoking.

Intraoperative Strategies

Selection of Surgical Skin Site Preparation

Peel et al. [17•] conducted a cluster randomized, assessor-blinded, superiority trial in patients undergoing elective TJR comparing chlorhexidine gluconate 0.5% in 70% ethanol to 1% iodine in 70% ethanol. At a university teaching hospital, 780 participants were included with 390 participants randomized to each group. Standard preoperative protocols included MRSA screening and eradication, preadmission chlorhexidine body wash, urine screening and prophylactic antibiotics. The primary outcome was superficial incisional SSI and/or clinically significant wound ooze within 30 days. The secondary outcome was any surgical site infection, including PJI. There was no difference in the rate of superficial wound complications (4.9% vs 3.8%, $p = 0.50$). There was, however, an increased rate of SSI in the chlorhexidine alcohol group compared with iodine alcohol (3.1% vs 1.0%, $p = 0.014$). The odds of PJI were also increased in the chlorhexidine alcohol arm compared with iodine alcohol (1.8% vs 0.5%, $p = 0.022$). The authors concluded that alcohol-based iodophor preparations are a reasonable choice for surgical site skin preparation. Contradictory findings from a recent World Health Organization meta-analysis in the non-arthroplasty population were acknowledged by the authors [18]. Selection of chlorhexidine-tolerant bacteria due to the pre-hospital body wash or a potential preferential role for iodine alcohol for procedures involving implantation of prosthetic material was hypothesized as explanations by the authors.

Single Versus Repeat Surgical Site Skin Preparation

In a randomized control trial of 600 patients undergoing TKR or THR, Morrison et al. [19] investigated the effect of repeat surgical site skin preparation on the incidence of surgical site infection. Both groups were initially prepped with a 7.5% povidone-iodine scrub, 75% isopropyl alcohol and then 10% iodine paint. In addition, the intervention group received an

additional preparation of iodine povacrylex and isopropyl alcohol over the incision site prior to adhesive draping. Mean follow-up was in excess of 37 months for both groups. There was a significant reduction in the incidence of superficial SSI for the intervention group (1.8% vs 6.5%, $p = 0.02$). Similar rates of PJI were reported between groups (0.7% vs 0.7%, $p = 1.00$). The authors recommend that a second surgical preparation solution be applied to the skin after draping and before making a surgical incision.

Knee Flexion Angle During Surgical Site Skin Preparation

Knoll et al. [20] describe a skin preparation technique where the knee is positioned in maximum flexion to allow superior exposure of the extensor surface. A case example highlighted inadequate skin preparation being revealed upon knee flexion when the limb had been prepped in extension. The authors acknowledge a lack of objective evidence demonstrating a decreased rate of surgical site infection associated with this technique and, however, emphasize a low institutional infection rate of under 1%.

Intra-articular Dilute Betadine Lavage

Brown et al. [21] investigated the effects of a 500 ml, 0.35% betadine lavage for 3 min on the 90-day incidence of deep infection following hip and knee arthroplasty in a before and after comparative study. A retrospective cohort of 1862 consecutive patients (630 THA, 1232 TKA) was compared with a prospective cohort of 688 consecutive patients (274 THA, 414 TKA) following introduction of this protocol. The betadine lavage group also had betadine applied to the skin surrounding the incision which was not done in the control group; however, both groups had a 1 L normal saline pulse lavage prior to closure. Patient demographics in each group were similar. Eighteen early post-operative infections were identified before the use of dilute betadine lavage, and 1 was identified following (0.97% vs 0.15%, $p = 0.04$).

The senior author from the paper by Brown et al. [21] later reported results of a randomized control trial investigating whether the same protocol reduces the rate of acute post-operative periprosthetic joint infection in aseptic revision hip and knee arthroplasty [22]. Although the focus of this review is on primary arthroplasty, this trial adds to the emerging evidence for the efficacy of this strategy which potentially applies in the primary arthroplasty setting also. Patients were randomized to either 0.35% dilute betadine lavage for 3 min (144 knees, 79 hips) or normal saline lavage (153 knees, 81 hips). Operative procedures and patient demographics were similar between the randomized groups. Within 90 days post-operatively, there were eight infections in the saline group and 1 in the betadine group (3.4% vs 0.4%, $p = 0.038$). There was no difference in wound complications between groups (1.3% vs 0%, $p = 0.248$). Of note, the senior author does not use dilute betadine lavage when performing unicompartmental knee arthroplasties due to concerns of the impact on the articular cartilage in the non-resurfaced joint compartments.

Glove Changing

As highlighted in a 2019 systematic review by Kim et al. [23], evidence regarding the efficacy of intraoperative glove changing to reduce the risk of PJI in arthroplasty surgery remains weak. The search found no data measuring a direct effect of glove change on PJI rate. The authors therefore summarized the available literature examining glove microbiological contamination and perforation rate as a surrogate marker. Eight studies evaluated microbiological contamination of surgical gloves, with rates ranging from 3.4 to 30%. Two of these studies were randomized trials. Pooled results of these two studies showed reduced contamination rates in the glove change group (OR 0.37, $p < 0.0001$). Acknowledging the limitations of the available data, the authors concluded that changing gloves significantly reduces contamination rates. Based on this, the authors recommend gloves should be changed after draping, before handling implants, if visible perforation is seen as well as every hour if the aforementioned criteria are not met.

Body Exhaust Suits and Surgical Helmet Systems

A 2016 systematic review by Young et al. [24] evaluated the efficacy of body exhaust suits (BES) and surgical helmet systems (SHS) as compared with conventional surgical gowns in arthroplasty infection prevention. The authors differentiated between the 2 systems highlighting that BES are characterized by aspiration tubing and a negative intra suit pressure, while SHS are typically characterized by a fan on a helmet with a positive pressure within the suit. The authors acknowledged differing designs, materials, constructions and filtering systems amongst the various SHS available. Four studies totalling 3990 patients compared PJI rates between BES and conventional surgical gowns. At a mean 2.5-year follow-up, PJI rates were 0.17% (3 of 1795) in the BES group and 1.0% (16 of 1604) in the conventional surgical gown group ($p < 0.01$). Three registry-based investigations including 175,018 patients compared deep infection rates between SHS and conventional surgical gowns. SHS was associated with an increase in deep infections (RR 1.67) after adjustment for major covariates; however, this was not statistically significant ($p = 0.09$). The authors concluded that "In contrast to BES, modern SHS designs were not shown to reduce contamination or deep infection during arthroplasty".

Vijaysegaran et al. [25] proposed a mechanism by which infection rates may be increased in association with SHS. An

airtight flow through chamber was used as a simulated surgical environment. The authors compared the particle and microbiological emission rates of space suits and standard surgical attire. Particle and microbiological emission rates were detected using an optical particle counter and an ultraviolet aerodynamic particle sizer. The authors demonstrated that in 4 of the 5 experiments performed, there was a statistically significant increase in both particle and microbiological emission rates when SHS are used compared with standard attire.

Antibiotic Administration

The optimal choice, timing and dose of prophylactic antibiotic remain to be determined. Data regarding risks and benefits of alternate and extended spectrum prophylaxis continues to grow. Wyles et al. [26•] examined the effect of substituting a first-generation cephalosporin for an alternate antibiotic (vancomycin or clindamycin) due to allergy. Between January 2004 and May 2017, 29,695 arthroplasties were performed with 28,174 (94.9%) received cefazolin and 1521 (5.1%) received non-cefazolin antibiotics. The PJI rate was 32% lower in patients given cefazolin after adjusting for ASA score and BMI ($p < 0.001$). Survivorship free of PJI in the cefazolin group compared with the non-cefazolin groups was 99.40% vs 99.34% at 1 month, 99.11% vs 98.55% at 2 months, 98.83% vs 98.22% at 1 year, and 98.15% vs 96.96% at 10 years. The authors commented that the early divergence was supportive of the efficacy of a first-generation cephalosporin perioperatively. Cross-referencing their institutional Allergy Testing Registry, 2576 patients were tested for a patient provided history of penicillin or cephalosporin allergy. Of these, 96.8% were cleared by the allergist to use cephalosporins.

The role of extended spectrum antibiotics such as the addition of vancomycin continues to be debated. Burger et al. [27] demonstrated that when vancomycin is added, timing of administration is important. One thousand nine hundred seventy-seven consecutive primary TJR patients were reviewed retrospectively with 1044 given cefazolin and 953 given cefazolin with a single dose of vancomycin. Vancomycin administration was surgeon dependent and either given selectively to high-risk patients or as standard. All patients received 1 g. The addition of a single dose of vancomycin did not significantly reduce PJI rates when compared with cefazolin alone (1.6% vs 2.1%, $p = 0.32$). However, when initiated 45 min or earlier before incision, the infection rate was lower (0.2%) when compared with cefazolin and vancomycin within 45 min of incision (2.9%, $p < 0.01$) or to cefazolin alone (2.1%, $p < 0.01$). The addition of vancomycin is not without risk. Courtney et al. [28] retrospectively evaluated 1828 patients undergoing primary TJA over a 2-year period who received cefazolin ($n = 500$) or cefazolin and vancomycin ($n = 1328$). Patients receiving vancomycin were more likely to develop an acute kidney injury (AKI) compared with those receiving cefazolin alone (13% vs 8%, $p = 0.002$). The chance of a higher severity AKI was also greater in the vancomycin group (3% vs 0%, $p = 0.003$). There was no difference in the rate of SSI surgical site (1.4% vs 1.1%, $p = 0.636$) in this study.

Kheir et al. [29] highlighted the importance of appropriate weight-based dosage of vancomycin. They reviewed 1828 patients given prophylactic vancomycin prior to TJA. This choice of antibiotic prophylaxis was made due to penicillin allergy or MRSA colonization. Only 28% (518 of 1828) were adequately dosed according to weight-based dosage recommendations of 15 mg/kg. Ninety-four percent (1726 of 1828) of patients received a fixed 1-g dose of vancomycin, and of these, 64% (1105 of 1726) were underdosed. Of the patients who were underdosed with vancomycin, 2 of 20 PJI were caused by MRSA. No patients with appropriate or overdosed vancomycin developed PJI with MRSA. Similar findings regarding underdosing have been reported in relation to cefazolin dosing. Rondon et al. [30] assessed adequacy of dosing of cefazolin based on guidelines for 1 g if a patient weighs less than 60 kg, 2 g if patient weights between 60 kg and 120 kg and 3 g if patient weight over 120 kg. Of 17,393 primary total joint arthroplasties, the vast majority of patients weighing greater than 120 kg were underdosed (95.9%, 944/984). Underdosed patients had a higher rate of 1-year PJI compared with adequately dosed patients (1.51% vs 0.86%, $p = 0.002$).

Bosco et al. [31] retrospectively reviewed their SSI rates before and after routine-extended gram-negative antibiotic prophylaxis to THR patients in response to high proportions of gram-negative organisms in their PJI patients. Before July 2012, all patients were administered 1 g of cefazolin, and after this period, gentamicin or aztreonam was given in addition. Of 5389 primary THR, 4122 received cefazolin only, and 1267 were given weight-based high-dose gentamicin in addition. The SSI rate dropped from 1.19 (49/4122) to 0.55% (7/1267) ($p = 0.05$). During the study period, there was no change in TKR SSI rates which were not given extended gram-negative prophylaxis.

Duration of Antibiotic Prophylaxis

Determining the optimum duration of antibiotic prophylaxis after arthroplasty remains challenging. A 2019 meta-analysis by Siddiqi et al. [31] investigated the efficacy of single-dose preoperative antibiotic administration with or without extended post-operative prophylaxis. The primary outcome was SSI/PJI within 2 years. Thirty-two studies including 23 randomized controlled trials were included reporting on 51,627 patients. The pooled effect for the comparison between a single preoperative dose versus additional post-operative prophylaxis was 0.96 (95% CI, 0.73 to 1.26). Despite the large numbers

of included patients, the authors felt the analysis was "drastically underpowered" and that definitive conclusions could not be drawn. They noted an overall poor quality of the included studies. Eight studies compared post-operative antibiotics given for < 24 h versus > 24 h. There was no significant difference in infection rates between these subgroups with rates of 2.2% (56 of 2498) vs 1.3% (41 of 3080) respectively ($p = 0.36$). Similar findings were reported in another 2019 meta-analysis examining efficacy of post-operative antibiotics is any orthopaedic procedure where an implant was placed [32].

In a retrospective cohort study examining 2181 arthroplasties, Inabathula et al. [33] investigated whether extended oral antibiotic prophylaxis reduced PJI in high-risk patients. Classification as high risk was determined at a coordinated care conference based on factors including BMI > 35, diabetes, smoking, chronic renal failure, autoimmune disease and colonization with MRSA. Extended oral antibiotic prophylaxis consisted of cefadroxil, 500 mg twice daily for 7 days, or 300 mg of clindamycin 3 times daily for 7 days if they were allergic to cephalosporins. Patients who tested positive for MRSA received Bactrim DS twice daily for 7 days. Infection rates before and after the oral antibiotic intervention were compared as well as infection rates in high-risk patients who did not receive extended oral antibiotics. High-risk patients without extended antibiotic prophylaxis were 4.9 ($p = 0.009$) and 4.0 ($p = 0.037$) times more likely to develop PJI after TKA and THA, respectively, than high-risk patients with extended prophylaxis.

Intraosseous Regional Administration of Antibiotics

Intraosseous regional administration (IORA) of antibiotics for TKR has been evaluated in the preclinical and clinical settings. Young et al. [34] used a mouse model with an intra-articular knee prosthesis, followed by *Staphylococcus aureus* inoculation to demonstrate that IORA prophylactic cefazolin and vancomycin were more effective in reducing the number of colony-forming units as compared with the same dose of antibiotic given systemically.

The same group subsequently investigated the efficacy of IORA in the setting of single-stage aseptic revision TKR [35]. Twenty patients were randomized to 1 g systemic IV prophylactic vancomycin or a 500 mg vancomycin bolus injection into the tibial via an intraosseous cannula under tourniquet control prior to skin incision. Subcutaneous fat and bone samples were taken at regular intervals with tissue vancomycin concentrations measured. IORA administration resulted in vancomycin tissue concentrations 5 to 20 times higher than systemic IV administration. High tissue concentrations were maintained throughout the procedure despite periods of tourniquet deflation. There were no infections in either group. IORA has also been investigated into context of primary TKR for the obese patient. Chin et al. [36] using similar investigative methods randomized 22 patients with a BMI > 35 undergoing TKA to receive either 15 mg/kg (maximum 2 g) IV vancomycin or 500 mg vancomycin via tibial IORA. Mean concentrations in subcutaneous fat were measured with 39.3 mg/g in the IORA group and 4.4 mg/g in the IV systemic group ($p < 0.01$). Mean tissue concentrations in bones were 34.4 mg/g in the IORA group and 6.1 mg/g in the IV systemic group ($p < 0.01$). Two patients in the systemic group developed superficial infections, and no deep infections were recorded. Despite these promising results, as highlighted in a 2018 review, the effect of IORA on prosthetic joint infection rates remains to be seen [37].

Intra-articular Dilute Antibiotic Lavage

The efficacy of topical antibiotics administered in irrigation solution was investigated in a preclinical investigation by Goswami et al. [38]. Cultures of *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) were exposed for 1 and 3 min to irrigation solutions combined with polymyxin and bacitracin, vancomycin or gentamycin. These solutions were compared against dilute betadine, chlorhexidine, Castile soap and sodium hypochlorite. After exposure, surviving bacteria were counted, and cytotoxicity was also assessed. Irrigation with dilute polymyxin-bacitracin was ineffective against both bacteria, vancomycin irrigation was effective against *S. aureus* but not against *E. coli*, and gentamicin irrigation showed partial efficacy against *E. coli* but none against *S. aureus*. Povidone-iodine, chlorhexidine and sodium hypochlorite irrigation were effective against both *S. aureus* and *E. coli*. Povidone-iodine showed the least cytotoxicity of the efficacious solutions, and chlorhexidine lavage conferred the greatest in vitro cytotoxicity. The authors concluded that dilute lavage with polymyxin-bacitracin adds little value and that povidone-iodine lavage may be a better wash due to lower levels of cytotoxicity and potential antimicrobial resistance associated with antibiotic lavage.

Wound Closure

Two recent meta-analyses have studied the rates of SSI with staple as compared with suture skin closure. In a 2017 meta-analysis, Kim et al. [39] included RCTs and high-quality observational cohort studies evaluating skin closure with sutures or staples in primary TKR. Deep tissue closure techniques were not considered. In terms of superficial infection rates, 7 studies reporting on 561 TKR were included. Of 232 knees closed with sutures, 12 superficial infections were reported (5.2%), compared with 8 events observed in 339 TKAs closed with staples (2.4%). The difference was not statistially significant (RR, 1.78, $p = 0.22$). In terms of deep infection, 677 knees were included. There were 3 cases in 294 knees (1.0%) closed with sutures and 1 in the 383 knees (0.3%)

closed with staples. This was not statistically significant (RR, 3.78, $p = 0.91$). There were higher rates of prolonged wound discharge in the staple group. The authors concluded that staples may have subtle clinical advantages over suture closure. In a 2019 meta-analysis of RCTs by Krishnan et al. [40], the authors included any study comparing compared sutures with staples for skin closure after any orthopaedic surgery. Although not specific to TJR, 6 of the 17 trials included only patients undergoing elective THA or TKA. The authors concluded that the existing RCTs do not provide definitive evidence of a difference in SSI risk with staple or sutures skin closure.

Post-Operative Strategies

Silver-Impregnated Dressings

Ionic silver has been proposed as a topical antimicrobial by preventing the growth of microorganisms. Its use in surgical dressings has been explored in the arthroplasty setting. Grosso et al., [41] retrospectively reviewed a single surgeon series of 1173 consecutive patients undergoing TKR or THR over an 8-year period. After 4.5 years, sterile xeroform/gauze dressings were changed to AQUACEL® Ag SURGICAL Dressing, with no other major change in infection prevention. PJI within 3 months of surgery was diagnosed in 9 of 568 patients (1.58%) managed with a sterile xeroform dressing and 2 of 605 patients (0.33%) with the use of AQUACEL® Ag SURGICAL Dressing. Multiple logistic regression with consideration to demographic factors, procedure factors and patient comorbidities found AQUACEL® Ag SURGICAL Dressing as a protective factor for PJI (OR 0.092, $p = 0.005$). Similar results have been reposted by Cai in a 2014 retrospective series [42]. In a prospective RCT by Kuo et al. [43], 240 patients were randomized to receive either AQUACEL Ag Surgical Dressing or a Sofra-Tulle dressing after TKR. Demographics were similar between groups. The incidence of superficial SSI in the AQUACEL group was 0.8% (1 of 120) compared with 8.3% (10 of 120) in the control group ($p = 0.01$). Only one patient in the Sofra-Tulle group developed a deep infection. Multivariate logistic regression demonstrated that AQUACEL Ag Surgical Dressing was protective against PJI with an odds ratio (OR 0.07, $p = 0.01$).

Outcomes of Bundled Infection Prevention Interventions

The synergistic effect of combining multiple of the aforementioned interventions has also been highlighted. Matsen Ko et al. [44] reduced 12-month PJI rates in primary TJR from 1.4 to 0.37% over a 5-year period with implementation of a bundled prevention strategy. This bundled package was progressively implemented and included staff education regarding PJI, minimization of operating room traffic (all required items made available in theatre, no intraoperative staff breaks), eliminating of lint-producing materials; antimicrobial dressing left intact for 5 days, addition of vancomycin to cephalosporin prophylaxis, universal nasal mupirocin decolonization, preoperative chlorhexidine wipes, post-operative bleeding reduction strategies (routine tranexamic acid and aspirin venous thromboembolism prophylaxis where appropriate) and dilute betadine irrigation. Surgery was also postponed for patients at high PJI risk (HbA1c > 7.5, BMI > 40, laboratory evidence of malnutrition) to allow for modification of these risk factors or a proven effort to do so. Using a bundled intervention with similar elements, Bullock et al. [45] compared 90-day infection rates before and after implementation. Comparing the 2 years before and after implementation, there was a reduction in the THR infection rate from 1.56 (10 of 641) to 0.59% (4 of 675); however, this reduction was not statistically significant ($p = 0.09$). There was, however, a statistically significant reduction in TKR infection rate from 1.43 (13 of 908) to 0.11% (1 of 890) ($p = 0.0016$).

Conclusions

Strategies for infection prevention continue to evolve, and the optimal infection prevention strategy in hip and knee arthroplasty surgery is yet to be defined. The studies highlighted in this review need to be interpreted within the context of previous literature, and their limitations and biases need to be carefully considered. Evolving strategies need to be continually tested rigorously in the clinical environment, but a multimodal approach and attention to detail are critical factors in the prevention of prosthetic joint infection.

Authors' Contributions All authors made substantial contributions to the conception or design of the work, drafted the work or revised it critically for important intellectual content and approved the version to be published.

Data Availability Not applicable.

Code Availability Not applicable.

Compliance with Ethical Standards

Conflicts of Interest LB, not applicable. BL, personal fees from Smith & Nephew, Stryker, DePuy, Integra and Intellijoint and institutional support from Smith & Nephew, DePuy, Stryker and Zimmer, all outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Shohat N, Muhsen K, Gilat R, Rondon AJ, Chen AF, Parvizi J. Inadequate glycemic control is associated with increased surgical site infection in total joint arthroplasty: a systematic review and meta-analysis. J Arthroplast. 2018;33(7):2312–21.e3.
2. Cancienne JM, Werner BC, Browne JA. Is there a threshold value of hemoglobin A1c that predicts risk of infection following primary total hip arthroplasty? J Arthroplast. 2017;32(9):S236–S40.
3. Tarabichi M, Shohat N, Kheir MM, Adelani M, Brigati D, Kearns SM, et al. Determining the threshold for HbA1c as a predictor for adverse outcomes after total joint arthroplasty: a multicenter, retrospective study. J Arthroplast. 2017;32(9):S263–S7.e1.
4. Shohat N, Tarabichi M, Tischler EH, Jabbour S, Parvizi J. Serum fructosamine: a simple and inexpensive test for assessing preoperative glycemic control. JBJS. 2017;99(22):1900–7.
5.• Shohat N, Tarabichi M, Tan T, Goswami K, Kheir M, Malkani A et al. 2019 John Insall Award: Fructosamine is a better glycaemic marker compared with glycated haemoglobin (HbA1C) in predicting adverse outcomes following total knee arthroplasty: a prospective multicentre study. Bone Joint J. 2019;101(7_Supple_C):3–9. **A prospective multicentre study demonstrating that serum Fructosamine, an inexpensive and available test better predicts adverse outcomes in total knee arthroplasty as compared to HbA1c which has been traditionally used to assess perioperative glycaemic control.**
6. Courtney PM, Rozell JC, Melnic CM, Sheth N, Nelson C. Effect of malnutrition and morbid obesity on complication rates following primary total joint arthroplasty. J Surg Orthop Adv. 2016;25(2):99–104.
7. Blevins K, Aalirezaie A, Shohat N, Parvizi J. Malnutrition and the development of periprosthetic joint infection in patients undergoing primary elective total joint arthroplasty. J Arthroplast. 2018;33(9):2971–5.
8. Bohl DD, Shen MR, Kayupov E, Della Valle CJ. Hypoalbuminemia independently predicts surgical site infection, pneumonia, length of stay, and readmission after total joint arthroplasty. J Arthroplast. 2016;31(1):15–21.
9. Golladay GJ, Satpathy J, Jiranek WA. Patient optimization—strategies that work: malnutrition. J Arthroplast. 2016;31(8):1631–4.
10. Li S, Luo X, Sun H, Wang K, Zhang K, Sun X. Does prior bariatric surgery improve outcomes following total joint arthroplasty in the morbidly obese? A meta-analysis. J Arthroplast. 2019;34(3):577–85.
11. Schwarzkopf R, Lavery JA, Hooper J, Parikh M, Gold HT. Bariatric surgery and time to total joint arthroplasty: does it affect readmission and complication rates? Obes Surg. 2018;28(5):1395–401.
12. Gu A, Cohen JS, Malahias M-A, Lee D, Sculco PK, McLawhorn AS. The effect of bariatric surgery prior to lower-extremity total joint arthroplasty: a systematic review. HSS J. 2019;1–11.
13.• Richardson SS, Schairer WW, Sculco TP, Sculco PK. Comparison of infection risk with corticosteroid or hyaluronic acid injection prior to total knee arthroplasty. JBJS. 2019;101(2):112–8. **The first study to differentiate risk of PJI by the type of medication given with a pre-operative intra-articular injection. Both corticosteroid and hyaluronic acid injection <3 months of total knee arthroplasty increased the risk of periprosthetic joint infection.**
14. Cancienne JM, Werner BC, Luetkemeyer LM, Browne JA. Does timing of previous intra-articular steroid injection affect the postoperative rate of infection in total knee arthroplasty? J Arthroplast. 2015;30(11):1879–82.
15. Bedard NA, Pugely AJ, Elkins JM, Duchman KR, Westermann RW, Liu SS, et al. The John N. Insall Award: do intraarticular injections increase the risk of infection after TKA? Clin Orthop Relat Res. 2017;475(1):45–52.
16. Bedard NA, DeMik DE, Owens JM, Glass NA, DeBerg J, Callaghan JJ. Tobacco use and risk of wound complications and periprosthetic joint infection: a systematic review and meta-analysis of primary TJA procedures. J Arthroplast. 2018.
17.• Peel TN, Dowsey MM, Buising KL, Cheng AC, Choong PF. Chlorhexidine–alcohol versus iodine–alcohol for surgical site skin preparation in an elective arthroplasty (ACAISA) study: a cluster randomized controlled trial. Clin Microbiol Infect. 2019;25(10):1239–45. **A cluster randomised control trial including 780 patients comparing two differing surgical skin preparations in a lower limb arthroplasty specific population.**
18. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16(12):e276–e87.
19. Morrison TN, Chen AF, Taneja M, Küçükdurmaz F, Rothman RH, Parvizi J. Single vs repeat surgical skin preparations for reducing surgical site infection after total joint arthroplasty: a prospective, randomized, double-blinded study. J Arthroplast. 2016;31(6):1289–94.
20. Knoll PA, Browne JA. Prepping the knee in maximal flexion: getting into every nook, cranny, and fold. Arthroplast Today. 2017;3(2):99–103.
21. Brown NM, Cipriano CA, Moric M, Sporer SM, Della Valle CJ. Dilute betadine lavage before closure for the prevention of acute postoperative deep periprosthetic joint infection. J Arthroplast. 2012;27(1):27–30.
22. Calkins TE, Culvern C, Nam D, Gerlinger TL, Levine BR, Sporer SM, et al. Dilute betadine lavage reduces the risk of acute postoperative periprosthetic joint infection in aseptic revision total knee and hip arthroplasty: a randomized controlled trial. J Arthroplast. 2019.
23. Kim K, Zhu M, Munro JT, Young SW. Glove change to reduce the risk of surgical site infection or prosthetic joint infection in arthroplasty surgeries: a systematic review. ANZ J Surg. 2019;89(9):1009–15.
24. Young SW, Zhu M, Shirley OC, Wu Q, Spangehl MJ. Do 'surgical helmet systems' or 'body exhaust suits' affect contamination and deep infection rates in arthroplasty? A systematic review. J Arthroplast. 2016;31(1):225–33.
25. Vijaysegaran P, Knibbs LD, Morawska L, Crawford RW. Surgical space suits increase particle and microbiological emission rates in a simulated surgical environment. J Arthroplast. 2018;33(5):1524–9.
26.• Wyles C, Hevesi M, Osmon D, Park M, Habermann EB, Lewallen D et al. 2019 John Charnley Award: Increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin: the value of allergy testing for antibiotic prophylaxis. Bone Joint J. 2019;101(6_Supple_B):9–15. **This study highlights that among patients with a potential allergy to Cephalosporins, in 96.8% of cases Cefazolin was deemed safe to use after formal allergy testing. This is important due to the higher efficacy of Cefazolin as compared to alternate prophylactic antibiotics.**

27. Burger JR, Hansen BJ, Leary EV, Aggarwal A, Keeney JA. Dual-agent antibiotic prophylaxis using a single preoperative vancomycin dose effectively reduces prosthetic joint infection rates with minimal renal toxicity risk. J Arthroplast. 2018;33(7):S213–S8.
28. Courtney PM, Melnic CM, Zimmer Z, Anari J, Lee G-C. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. Clin Orthop Relat Res. 2015;473(7):2197–203.
29. Kheir MM, Tan TL, Azboy I, Tan DD, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. Clin Orthop Relat Res. 2017;475(7):1767–74.
30. Rondon AJ, Kheir MM, Tan TL, Shohat N, Greenky MR, Parvizi J. Cefazolin prophylaxis for total joint arthroplasty: obese patients are frequently underdosed and at increased risk of periprosthetic joint infection. J Arthroplast. 2018;33(11):3551–4.
31. Bosco JA, Tejada PRR, Catanzano AJ, Stachel AG, Phillips MS. Expanded gram-negative antimicrobial prophylaxis reduces surgical site infections in hip arthroplasty. J Arthroplast. 2016;31(3):616–21.
32. Ryan SP, Kildow BJ, Tan TL, Parvizi J, Bolognesi MP, Seyler TM. Is there a difference in infection risk between single and multiple doses of prophylactic antibiotics? A Meta-analysis. Clin Orthop Relat Res. 2019.
33. Inabathula A, Dilley JE, Ziemba-Davis M, Warth LC, Azzam KA, Ireland PH, et al. Extended oral antibiotic prophylaxis in high-risk patients substantially reduces primary total hip and knee arthroplasty 90-day infection rate. JBJS. 2018;100(24):2103–9.
34. Young SW, Roberts T, Johnson S, Dalton JP, Coleman B, Wiles S. Regional intraosseous administration of prophylactic antibiotics is more effective than systemic administration in a mouse model of TKA. Clin Orthop Relat Res. 2015;473(11):3573–84.
35. Young SW, Zhang M, Moore GA, Pitto RP, Clarke HD, Spangehl MJ. The John N. Insall award: higher tissue concentrations of vancomycin achieved with intraosseous regional prophylaxis in revision TKA: a randomized controlled trial. Clin Orthop Relat Res 2018;476(1):66, 74.
36. Chin SJ, Moore GA, Zhang M, Clarke HD, Spangehl MJ, Young SW. The AAHKS clinical research award: intraosseous regional prophylaxis provides higher tissue concentrations in high BMI patients in total knee arthroplasty: a randomized trial. J Arthroplast. 2018;33(7):S13–S8.
37. Symonds T, Parkinson B, Hazratwala K, McEwen P, Wilkinson M, Grant A. Use of regional administration of prophylactic antibiotics in total knee arthroplasty. ANZ J Surg. 2018;88(9):848–53.
38. Goswami K, Cho J, Foltz C, Manrique J, Tan TL, Fillingham Y, et al. Polymyxin and bacitracin in the irrigation solution provide no benefit for bacterial killing in vitro. JBJS. 2019;101(18):1689–97.
39. Kim KY, Anoushiravani AA, Long WJ, Vigdorchik JM, Fernandez-Madrid I, Schwarzkopf R. A meta-analysis and systematic review evaluating skin closure after total knee arthroplasty—what is the best method? J Arthroplast. 2017;32(9):2920–7.
40. Krishnan RJ, Crawford EJ, Syed I, Kim P, Rampersaud YR, Martin J. Is the risk of infection lower with sutures than with staples for skin closure after orthopaedic surgery? A meta-analysis of randomized trials. Clin Orthop Relat Res. 2019;477(5):922–37.
41. Grosso MJ, Berg A, LaRussa S, Murtaugh T, Trofa DP, Geller JA. Silver-impregnated occlusive dressing reduces rates of acute periprosthetic joint infection after total joint arthroplasty. J Arthroplast. 2017;32(3):929–32.
42. Cai J, Karam JA, Parvizi J, Smith EB, Sharkey PF. Aquacel surgical dressing reduces the rate of acute PJI following total joint arthroplasty: a case–control study. J Arthroplast. 2014;29(6):1098–100.
43. Kuo F-C, Chen B, Lee MS, Yen S-H, Wang J-W. AQUACEL® Ag surgical dressing reduces surgical site infection and improves patient satisfaction in minimally invasive total knee arthroplasty: a prospective, randomized, controlled study. Biomed Res Int. 2017;2017:1–8.
44. Ko LJM, Yoo JY, Maltenfort M, Hughes A, Smith EB, Sharkey PF. The effect of implementing a multimodal approach on the rates of periprosthetic joint infection after total joint arthroplasty. J Arthroplast. 2016;31(2):451–5.
45. Bullock MW, Brown ML, Bracey DN, Langfitt MK, Shields JS, Lang JE. A bundle protocol to reduce the incidence of periprosthetic joint infections after total joint arthroplasty: a single-center experience. J Arthroplast. 2017;32(4):1067–73.