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PROSTHETIC JOINT INFECTION (S NODZO AND N FRISCH, SECTION EDITORS)

Intraoperative Considerations for Treatment/Prevention of Prosthetic Joint Infection

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Abstract

Purpose of Review Innovative measures have recently been proposed to prevent periprosthetic joint infection following total hip and knee arthroplasty. We sought to review these recent innovations to determine the reported reduction in periprosthetic joint infection.

Recent Findings The most recent literature demonstrates promising results in regard to hydrofiber dressings as an independent risk factor for primary prosthetic joint infection reduction, which in turn is also linked with cost savings. As our understanding of safe yet effective concentrations of antiseptic solutions develops, dilute betadine in particular has demonstrated encouraging efficacy which warrants continued investigation through controlled trials.

Summary In summary, we found that the application of a hydrofiber dressing may prove beneficial in decreasing the risk of prosthetic joint infection following primary total hip and knee arthroplasty. The gold standard for an infection prevention protocol continues to be explored and optimized.

Keywords Infection · Total hip arthroplasty · Total knee arthroplasty · Antiseptic solutions · Dressings · Antibiotic cement

Introduction

Periprosthetic joint infection (PJI) is a devastating complication following total hip and knee arthroplasty. There is a significant economic burden to the treatment of periprosthetic joint infection with a projected increase to $1.62 billion by 2020 [1]. With the introduction of bundled payment models, hospitals and surgeons will share in the financial costs of treatment of PJI. In addition to the economic burden, elderly patients with baseline comorbid conditions are at increased risk of postoperative morbidity and mortality when undergoing treatment of PJI [2]. Several intraoperative and postoperative considerations have been used to decrease the rate of infection. These innovations include the use of dilute betadine, chlorhexidine-based solutions, antibiotic cement, dissolvable beads, occlusive dressings, and portable incisional wound vacuum dressings. The aim of this paper was to evaluate the current literature on the use of these products in primary hip and knee arthroplasty.

This article is part of the Topical Collection on *Prosthetic Joint Infection*

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Antiseptic Solutions

Antiseptic solutions have been studied as a means to reduce intraoperative bacterial load during total joint arthroplasty. In a recent study by van Muers et al., five commercial antiseptics were explored looking at bactericidal as well as cytotoxic properties, in an effort to determine an optimal intraoperative irrigation. The five commercially available products used in this study were Lavasept 0.04%, hydrogen peroxide 3%, Octenisept 0.1%, povidone-iodine 10%, and chlorhexidine digluconate 20%. Of the five, dilute betadine provided the most optimal combination of being bactericidal while maintaining host cell viability [3]. Dilute betadine contains povidone-iodine, elemental iodine, and free iodine. Free iodine has bactericidal activity as it can enter cells and cause oxidation and deactivation [4, 5]. Dilute betadine had been used with efficacy, for infection reduction, in the irrigation of operative wounds in spine, cardiovascular, urologic, and general surgeries [6–9]. Recently, it has also been explored for use in the prevention of PJI following total joint

arthroplasty (TJA). Gilotra et al., utilizing a rabbit model to simulate a knee PJI, performed irrigation and debridement with a saline control as well as with a sterilized dilute betadine solution. They discovered a 20-fold decrease in bacterial counts at the implant ($p = 0.0003$) and > 10× reduction at the polyethylene interface ($p = 0.04$) with dilute betadine utilization. A landmark paper in the arthroplasty literature by Brown et al. found a statistically significant 6-fold reduction (0.97 vs 0.15%, $p = 0.04$) in acute PJI in utilizing dilute betadine irrigation in TJA cases [10]. Limitations of this study include its retrospective design and the potential that concomitant changes in practice over time may have influenced its results. However, the limited cost and ease of use of dilute betadine intraoperatively have increased its popularity in PJI prevention. Hofmann et al. reported a reduction in SSI from 2 to 0.7% ($p = 0.08$), including PJI (1.4 to 0.2% ($p = 0.02$)) following institution of a protocol of preoperative nasal mupirocin, addition of vancomycin to preoperative antibiotics, and incorporating an intraoperative betadine irrigation in their total joint arthroplasty patients. The clinical effect of betadine in particular was not clear given the other confounding variables [11•].

Other antiseptics being investigated include those incorporating chlorhexidine. Chlorhexidine causes cell death via disruption of the osmotic equilibrium after it binds to bacterial membrane phospholipids [12]. There is a commercially available version of this at 0.05% concentration, Irrisept (IrriMax Corporation, Innovation Technologies, Inc., Lawrenceville, GA). A recent RCT found that chlorhexidine gluconate (CHG) at 0.05% added to splash basins was found to reduce contamination rates of the basin during arthroplasty cases (9 vs 0%, $p = 0.45$) though not at a statistically significant difference [13]. The possibility of reducing bacterial contamination in the wound itself with the use of CHG remains an area in need of further investigation. Frisch et al. were unable to find a statistical difference in SSI in primary TJA utilizing CHG 0.05% soaks compared to controls of saline and dilute betadine soaks at 1-year minimum follow-up [14]. They argue that since dilute iodine is not used in a manner that reaches its full antimicrobial potential, through drying and desiccation, and that it is deactivated by blood [15], CHG maintains some theoretical advantages. CHG 0.05% holds a potential advantage over dilute betadine as one in vitro study showed its effectiveness against 18 separate gram-negative and gram-positive strains of bacteria [16]. In the setting of established infections, concentrations of CHG over 2% have been found to be most optimal in decreasing biofilm [17]; however, concentrations over 0.4% are cytotoxic to surrounding fibroblasts, which is below the minimum bactericidal concentration of 0.78% [3].

The current evidence implies safety and efficacy in PJI reduction with the use of dilute betadine lavage [18]; however, there remains a need for randomized controlled studies to continue expanding the body of evidence of its efficacy. Taking an approach of combining antiseptics has also been explored and cautioned against due to the risk of causing harmful by-products [19]. Further randomized controlled studies are warranted for the use of CHG, as many of the proposed benefits in arthroplasty surgery remain theoretical and unproven.

Wound Dressings

Following completion of the surgical portion of the case, the surgeon is left with a variety of choices in surgical dressing selection. These decisions are best made while accounting for the cost, efficiency, and effectiveness in the prevention of wound complications and surgical site infections (SSIs), either superficial (sSSI) or deep (PJI). Historically, frequent postoperative dressing changes were performed prior to wound healing and epithelialization. However, exposure to an unsterile environment can place an unhealed wound at increased risk for SSI [20]. Therefore, dressings with the potential to minimize this, as well as to optimize wound environment, have been developed. Wound management options today range from glue-based dressings, hydrofiber dressings with or without silver impregnation, or negative pressure incisional wound vacuum technology (NPWT). Wound management is a major issue, particularly in the arthroplasty world, as wound healing problems increase the chance of PJI and the need for further surgery by up to 7.5-fold [21]. Carrol et al. in their retrospective review found 71% of deep PJIs were preceded by a superficial wound complication [22]. We compiled some of the most recent data over the past few years, to see if there has been any evidence-based paradigm shifts or trends in dressing usage.

Hydrofiber Dressing

Aquacel Ag (ConvaTec, Greensboro, NC) is a dressing which has been studied for its effectiveness following arthroplasty (Fig. 1). Termed as hydrofiber dressing, this dressing adheres via an adhesive hydrocolloid bordering a hydrofiber core [23]. Within the hydrofibers of the dressing, there are silver ions, which provide antimicrobial properties [24]. The hydrofiber core, once contacted by wound exudate, converts to a gel to form a barrier, locking in fluid to prevent lateral spread and minimizing skin maceration [25, 26].

Recent investigations with hydrofiber dressings have shown encouraging results. At least four randomized control trials have been performed since 2015 alone comparing a hydrofiber dressing to a control dressing. All four of these papers found statistically significantly less dressing changes required in the Aquacel group compared to their control groups [23, 26, 27, 28••]. Kuo et al. and Langlois et al. found higher peri-incisional blistering in the control groups than in the study groups, however neither achieved statistical

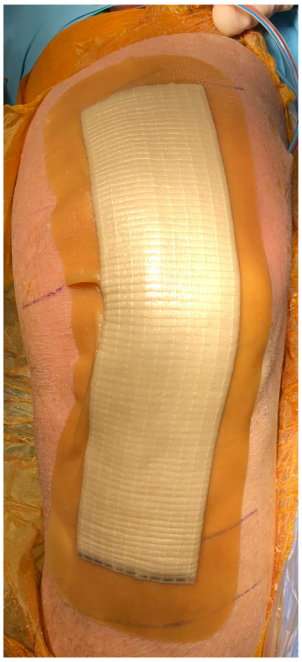

Fig. 1 Hydrofiber dressing (Aquacel Ag (ConvaTec, Greensboro, NC))

significance [23, 26]. Springer et al. found statistical significance in regard to less wound complications (10 vs 22%, $p = 0.015$) and blistering (0.7 vs 6%, $p = 0.026$) in the Aquacel Ag group compared to their control Primapore (Smith and Nephew) [28••]. Interestingly, one study did find a 4.2% allergic reaction rate for patients to the Aquacel dressing itself leading to discontinuation of the dressing during their trial [23]. Another found a 6.9% blistering rate in the Aquacel group and a 3.4% skin maceration rate, both higher than the three other groups but not statistically significant ($p = 0.738$ and 0.626, respectively) [27]. In our experience, we would note it is important to place these dressings with limited to no tension (i.e., with the knee in flexion) to avoid blistering that can be caused during range of motion.

In regard to infection rates in these four RCTs, three of the studies found no SSIs in either group. This is limited by the fact they had short-term follow-up at 5 days [27], 4 weeks [28••], and 6 weeks [26]. Kuo et al. utilizing 2-year follow-up found superficial SSI was significantly lower in the Aquacel group (0.8 vs 8.3%, $p = 0.01$). There was also less deep PJIs in the Aquacel group, but this was not statistically significant (0 vs 0.8%, $p = 0.32$) [23].

Two of the largest studies to date on Aquacel Ag dressing in TJA were performed via a retrospective review with similar findings [29••, 30••]. Cai et al. reviewed Aquacel Ag usage in 903 patients versus a control of xeroform and gauze in 875 patients with an outcome of looking for acute PJI (< 3 months). They found a decreased rate of prosthetic joint infection in the Aquacel group (0.44 vs 1.7%, $p = .005$). This study did have several confounding variables including the institution of dual antibiotic prophylaxis with vancomycin and cefazolin and the use of dilute betadine lavage at wound closure in the Aquacel cohort [29••]. Grosso et al. performed a similar study looking for acute PJI within 3 months post arthroplasty, in which 605 Aquacel Ag dressings were compared to 568 sterile xeroform dressings. Similar to Cai et al., a significant lower incidence of PJI (0.33 vs 1.58%, $p = 0.03$) was again found in the Aquacel Ag group [30••].

Three review papers have also been written recently on the utilization of hydrofiber gel type dressings for TJA [30••, 31–33]. Chen et al. looked at five studies encompassing 3721 primary TJAs where 1487 gauze dressings, 1911 hydrofiber dressings, and 327 absorbent-style dressings were utilized. In regard to infection, there were 24/1487 (1.61%), 9/1911 (0.47%), and 6/327 (1.83%) total among the combined five studies for each of the three respective dressing types. Risk for PJI was found to be 4.16 times higher in gauze versus hydrofiber dressing (95% CI, 1.71–10.16) and 2.6 times higher in the absorbent dressing versus hydrofiber dressing (95% CI, 0.66–10.27) [33]. Chowdhry and Chen's review article look at nine papers on hydrofiber-type dressings in TJA [31]. They concluded that hydrofiber and hydrocolloid dressings require less dressing changes, have low blistering rates, and may reduce SSIs and that a decreased rate of PJIs compensates in terms of cost for the initial upfront expense of the dressing. Sharma et al.'s meta-analysis included 12 randomized trials and was unable to definitively conclude that hydrofiber dressings reduce PJI; however, they did find that the dressing has a higher fluid handling capacity as well as fewer wound complications versus conventional gauze dressings [32].

Multiple logistic regression models performed by Kuo et al. and Grosso et al. showed Aquacel Ag as an independent protective factor against PJI. Whether it is properties inherent to the dressing itself or simply the necessity for fewer dressing changes, Aquacel Ag shows merit in the prevention of prosthetic joint infection in primary TJA versus conventional gauze dressings. Given the prevention of prosthetic joint infection and potential associated long-term cost savings to the healthcare system of up to $375,000,000 with a reported 4-fold reduction in PJI [29••], the continued use of hydrofiber dressings is supported by the current body of evidence for arthroplasty surgery.

Closed Incision Negative Pressure Wound Therapy

Another technology investigated to assist with wound care is negative pressure incisional wound therapy (NPWT) (Fig. 2). NPWT devices, developed in the 1980s [34], have been used more predominantly in general surgery, plastic surgery, cardiothoracic surgery, vascular surgery, obstetrics, and trauma surgery than in arthroplasty [35••]. Multiple benefits of NPWT devices have been described including a decreased rate of seromas/hematomas [36, 37], stimulation of angiogenesis at

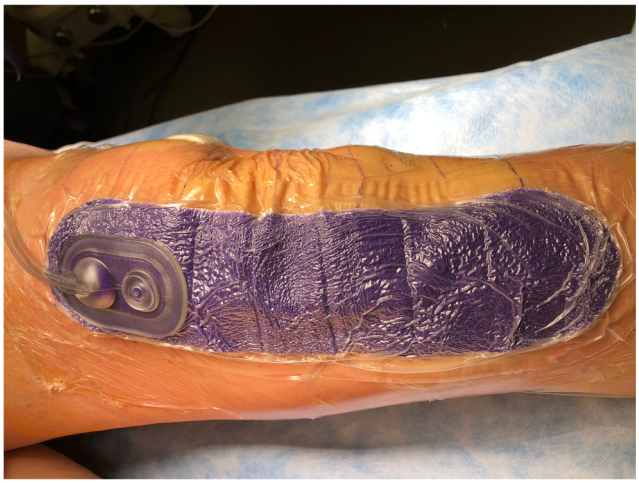

Fig. 2 Negative pressure wound therapy (PREVENA™ system; KCI, San Antonio, TX)

wound edges [38], and decreased shear stress leading to less wound dehiscence [37, 39]. Multiple recent studies in orthopedics have investigated the reported benefits of these NPWT devices. Shohat et al. in summarizing the recent guidelines on PJI prevention noted that the WHO and the CDC support that there is evidence in favor of the use of NPWT in high-risk arthroplasty patients; however, this was graded as weak [40•]. Willy et al., in a 2017 paper with an international multidisciplinary consensus, make recommendations that NPWT should be used in patients deemed high risk for developing surgical site complication or patients with one or more medical comorbidities [41]. Risk factors listed include diabetes mellitus, ASA > 2, advanced age, obesity, active tobacco use, hypoalbuminemia, corticosteroid usage, alcoholism, male sex, chronic renal insufficiency, chronic obstructive pulmonary disease, and hematoma [41]. Though primary or revision hip and knee arthroplasty were not listed in particular as surgeries specifically at risk, incision-related risk factors pertinent to arthroplasty included the following: areas of high tension, repeat incisions, mechanically unfavorable site, excessive undermining, traumatized soft tissue, edema, and prolonged operative times [41]. A recent meta-analysis by Semsarzadeh et al. investigated NPWT on closed incisions (non-arthroplasty) and found a relative reduction in surgical site infection of 29.4% and wound dehiscence of 50% compared to control dressings [42]. There is a paucity of data in the arthroplasty literature, most of which are limited on size or control of variables or have significant bias due to industry relations.

Four recent randomized controls (RCT) [33, 34, 43•, 44, 45] and one prospective cohort in comparison to a historical control [46] have been published recently in regard to primary TJA cases, with one other investigation reporting on hip hemiarthroplasties for femoral neck fracture [44]. Of the four RCTs, none found a statistically reduced rate of infection in the NPWT group as compared to the control. Karlakki et al. found a 4-fold reduction in wound complications in the NWPT group (2 vs 8.4%, $p = 0.06$) and two patients in the control group required formal washouts. However, wound complications were gathered via phone calls as opposed to direct inspection post-discharge limiting the utility of this finding [45]. An additional limitation was that the method of wound closure was not standardized among all the cases. Gillespie et al. also found a non-significant reduction in SSIs (5.7% NPWT vs 8.6% control (hydrocolloid dressing), $p = 0.65$); however, they found that there was a statistically significant higher absolute number of any complications (68.5 vs 42.8% ($p = 0.04$)) in the NPWT group [43•]. Manoharan et al. had two wound complications, one in the conventional dry dressing group and one in the NPWT. They found no benefit to wound healing in their 12-day follow-up period. One readmission necessitating IV antibiotics was attributed to severe blistering from the NPWT [34]. Lastly, Pauser et al. in their 10-day follow-up on 21 patients who had a hemiarthroplasty placed for hip fracture comparing NPWT ($n = 11$) (PREVENA™ system; KCI, San Antonio, TX) to standard dressings ($n = 10$) demonstrated that NPWT patients had statistically less postoperative seromas (measured with ultrasound) along with less days overall in which the wound was secreting (0.9 vs 4.3 days, $p = 0.0005$) [44].

The lone recent study on primary TJA to find a statistically significant reduction of SSI in a NPWT group was by Redfern et al. with rates of 1% with NPWT versus 3.5% with gauze ($p = 0.04$). However, this did not translate to any statistical difference in deep PJI reduction (1% NPWT vs 1.25% gauze). Overall complication rates were also statistically less in the NPWT group (1.5 vs 5.5%, $p = 0.02$) including hematoma, edema/swelling, and surrounding soft tissue appearance [46]. Limitations of this study include the use of a historical control and inability to account for other potential confounding variables that may be responsible for the reduction in surgical site complication rates.

In the realm of revision arthroplasty, NPWT seemingly has shown greater promise in regard to SSI prevention. Cooper and Bas investigated 138 revision hip and knee arthroplasties. Thirty patients, chosen at the discretion of the surgeon to be high risk for wound complication issues, were given a NPWT and 108 were treated with an Aquacel. Despite a group generally deemed higher risk in the NPWT, they were able to demonstrate statistically significant less wound complications (6.7 vs 26.9%, $p = 0.024$) and surgical site infections (3.3 vs 18.5%, $p = 0.045$). There were also trends, though non-significant, towards less reoperations, as well as deep and superficial infections among the NPWT group. Cooper et al. published on NPWT versus Aquacel Ag in patients with periprosthetic fractures [47••]. These cases were managed with both ORIF and revision arthroplasty. Similar to their prior investigation, the NPWT group had statistically reduced wound

complications (4 vs 35%, $p = 0.002$), but also saw a decrease in deep prosthetic joint infections (0 vs 25%, $p = 0.004$) and reoperations related to wound issues (4 vs 25%, $p = 0.021$) [47••]. However, limitations of this study included differences between the cohorts in the use of betadine lavage.

There is a lack of high-quality randomized evidence supporting the routine use of NPWT in hip and knee arthroplasty [48]. There has yet to be convincing evidence of the utility in NPWT in the setting of primary arthroplasty although it remains difficult to adequately power a study demonstrating a difference in SSI. There is the potential that NPWT may prove beneficial for use in "high-risk" patients although this exact cohort must still be defined. NPWT may prove more effective in the revision arthroplasty setting given the inherently increased risk of perioperative wound complications, although additional randomized investigations are necessary for confirmation.

Antibiotic Cement

Antibiotic-loaded bone cement (ALBC) has been widely employed in both primary total knee and hip arthroplasties. Utilization of ALBC has been widely adopted in Europe for decades and particularly has become the standard of care in northern European countries [49–52]. However, in the USA, the use of antibiotic cement in primary total knee and hip arthroplasties remains controversial due to the potential development of drug resistance, toxicity, and alterations in the mechanical properties of the cement. In prophylactic use of ALBC, a low dose of bone cement is used and defined as < 1 g of powdered antibiotic per 40 g of polymethylmethacrylate (PMMA) [53]. There are six low-dose ALBCs that are commercially available and approved by the Food and Drug Administration; however, they are only approved for use during the second-stage surgery of a two-stage exchange for PJI [53]. ALBC is not approved for prophylaxis use in primary or revision total hip and knee arthroplasty. Although there is a perceived decrease in infection rates [54, 55], two historical studies have reported increased costs with the use of ALBC [53, 56]. Gutowski et al. retrospectively reviewed the rate of infection in 3048 total knee arthroplasties (TKAs) performed without ABLC over a 3-year period compared to the prevalence of infection in 4830 TKAs performed with tobramycin-loaded cement. They reported an added $200–$500 per patient with the use of ALBC and overall low incidence of periprosthetic joint infection. They found that with the introduction of ALBC in TKA, the rate of infection increased from 0.75 to 0.83% within 2 years. Most recently, Sanz-Ruiz et al. sought to assess the value and cost-effectiveness of ALBC for the prevention of periprosthetic joint infection in total hip and knee arthroplasty [57••]. A total of 2518 hip and knee replacements were retrospectively reviewed. The initial cohort of patients did not have routine use of ALBC before 2010, whereas the second cohort of patients had the routine use of ALBC following 2011. This is the largest cohort of patients and most recent publication with the routine use of ALBC in primary hip and knee arthroplasty. They found a 57% overall decrease in PJI ($p = 0.001$) with the use of ALBC. More specifically, they found a decrease of 60.6% ($p = 0.019$) in PJI with respect to TKA, and 72.6% ($p = 0.009$) in cemented hip arthroplasty. In addition to the decrease in the rate of PJI, this retrospective study reported a total cost saving of $1,123,846 with the use of ALBC when comparing it to the overall cost of treatment of PJI. These findings contradict a prior retrospective review of 22,889 patients from a knee registry by Namba et al. in 2009 that reported the infection rate in the ALBC group was 1.4% compared to 0.7% in the non-ALBC group [58]. Their results are similar to historical data reported by Jiranek et al. who did not recommend routine use of ALBC and in fact recommended its use only to high-risk patients or in revision surgery [53]. In the current literature, there are three prospective randomized studies that have evaluated the efficacy of ALBC [54, 59, 60]. Both McQueen et al. and Josefsson et al. demonstrated no statistical significant difference in superficial or deep infection with the use of ALBC in primary joint arthroplasty. Chiu et al. compared the use of ALBC in 178 versus 162 patients with no ALBC. There were no infections in the ALBC group but five PJIs in the non-ALBC group, which was statistically significant ($p = 0.0238$). However, the five infected patients in the non-ALBC group were diabetic patients. Once removing the diabetic patients from the non-ALBC cohort, there was no statistical difference in the efficacy of ALBC. Given the conflicting literature on the use of antibiotic-loaded cement, there is a commonality in that high-risk patients complicate this data. To our knowledge, Qadir et al. is the only study to identify high-risk patients and separate them into another cohort [61]. They created three cohorts of patients that were classified into plain bone cement (cohort I), ALBC (cohort II), and high-risk stratified patients (cohort III). The infection rate at 1 year was 0.78, 0.61, and 0.64% respectively ($p = 0.550$, $p = 0.564$, $p = 0.933$). Even after risk stratifying patients, they found no statistically significant decrease in PJI in the first year. At their institution, they noted a significant hospital overhead cost with the use of ALBC compared to plain bone cement, costing $350–$400 per batch compared to $60–70 per batch of plain bone cement.

The transatlantic paradigm with respect to the use of ALBC in routine primary hip and knee arthroplasty remains controversial. The cost efficiency profile seems to be different in the USA compared to Europe. There are

wide variations between hospital system cost profiles in the USA compared to universal hospital-wide cost assessments in European countries.

Dissolvable beads

Calcium sulfate beads have recently been advocated as a delivery method for local antibiotic delivery in treatment of PJI. Historical use of non-dissolvable PMMA allowed for rapid elution of antibiotics within the first 24 h; however, there were concerns that when leaving the beads in place, they would be colonized by bacteria and form a biofilm [62, 63]. In order to address this problem, calcium sulfate beads provide a high concentration of antibiotic delivery and for a longer time period without the formation of biofilm [63–66]. Flierl et al. sought to evaluate the use of dissolvable beads in the treatment of acute PJI. In this series of 33 patients treated with irrigation and debridement with the addition of antibiotic-impregnated calcium sulfate beads, 16 patients failed and went on to a two-stage exchange or chronic antibiotic suppression [67••]. However, calcium sulfate beads are not without complications. Complications that have been reported include wound drainage, typically seen with use of higher volumes of calcium sulfate beads, and heterotopic ossification [65]. Other options include the use of calcium phosphate beads; however, they have only been reported in the treatment of PJI [68]. Use of calcium phosphate beads is not without risk to the patient. Kallala et al. reported 3 of the 15 patients in their small series to have hypercalcemia post operatively [68]. At this time, we do not recommend routine prophylactic use of dissolvable beads in primary or revision arthroplasty, as well as for the treatment of acute or chronic periprosthetic joint infection.

Conclusion

Several intraoperative and postoperative considerations have been used to decrease the rate of infection. These innovations include the use of dilute betadine, chlorhexidine-based solutions, antibiotic cement, dissolvable beads, occlusive dressings, and portable incisional wound vacuum dressings. There is compelling evidence for the use of hydrofiber dressings in prevention of PJI in primary hip and knee arthroplasty. We propose that the data presented in this review in addition to our own experience demonstrates supportive evidence in their ability to decrease the rate of PJI following hip and knee arthroplasty. The gold standard for an infection prevention protocol continues to be explored and optimized.

Compliance with Ethical Standards

Conflict of Interest Denis Nam reports Paid Consultant: Acelity Inc., ZimmerBiomet Inc., Stryker Inc. Research Support: Acelity Inc., ZimmerBiomet Inc. Stock Options: OrthoAlign Inc.

The other authors declare that they have no conflict of interest.

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.

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- • Of importance
- •• Of major Importance

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