EDITORIAL

Prevention of Periprosthetic Joint Infection in Total Knee Arthroplasty: Main Studies Reported Between November 2017 and January 2020

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Total knee arthroplasty (TKA) is one of the most successful surgical procedures performed in orthopedic surgery. Periprosthetic Joint Infection (PJI) is one of the most common mechanisms of failure and is the most feared of all the complications of TKA (1). When the most catastrophic sequellae of TKA – amputation and death – occur, they are usually the result of complications of infection. The prevention, detection, and treatment of infection are amongst the most important topics in orthopaedic research and great progress is being made in each of these areas.

In this Editorial we have reviewed the most important papers on prevention of infection associated with TKA, published between November 2017 and January 2020.

Preoperative Considerations

Preoperative Screening and Optimization

Optimization of the host is an important target for interventions to reduce the risk of PJI. Nussenbaum et al, in 2018 published their results after putting into effect strict preoperative assessment guidelines for TKA, including hemoglobin (Hb) A1c ≤7, Hb ≥11, body mass index (BMI) ≤35 and albumin ≥3.5 (2). They reported a statistically significant decline in the proportion of patients who developed a surgical site infection (SSI) or complications in general. The rates of total complications were reduced from 33.1% to 15% (*P<.01*) and the rates of SSI were reduced from 4.6% to 1.3% (*P=.01*) (2). Many of these factors (HbA1c and Hb, for instance) are easily modifiable in most cases but some (particularly BMI) are more challenging, and other recent studies have reported that the use of BMI cut-offs to deny surgery have the effect of denying successful surgery to many more patients than would have been spared a complication if surgery had been performed, suggesting that a more nuanced pre-operative assessment may be more discriminating (3).

Pre-operative screening and eradication of methicillin-resistant staphylococcus aureus (MRSA) prior to primary TKA has become routine practice in many countries. There is growing evidence that screening and eradication of sensitive staphylococci is a successful and cost-effective intervention for reducing the incidence of PJI. A cost-effectiveness analysis Kerbel et al in 2018 found all protocols of pre-operative screening and decolonization to be highly cost-effective (4). They analyzed the cost-effectiveness of various regimes from very inexpensive interventions (universal decolonization using intranasal mupurocin) to more expensive protocols including universal screening and

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AB&JS THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

Arch Bone Jt Surg. 2020; 8(4): 465-469. Doi: 10.22038/abjs.2020.48489.2403 http://abjs.mums.ac.ir

multimodal decolonization. They found that the cheapest intervention, universal decolonization, was the most cost-effective method for prevention of PJI, although concerns such as patient acceptability and the potential for mupurocin resistance remain.

In 2017, the meta-analysis published by Wang et al found that preoperative bathing with chlorhexidine on the evening before surgery could reduce the incidence of infection (5). Chlorhexidine was associated with a reduced total incidence of infection, corresponding to a reduction of 1.69% [risk ratio (RR)=0.22; 95% confidence interval (95% CI)=0.12-0.40; *P=0.000*]. However, the evidence and the number of included studies were insufficient; therefore, they concluded that more high quality randomized controlled trials (RCTs) were needed to better identify the effects of chlorhexidine in reducing the incidence of infection after TKA.

Risk Factors

Humidity and Temperature

The effect of environmental temperature and humidity on the incidence of PJI after TKA has not previously been investigated. Armit et al, in 2018, conducted a retrospective study of 1058 patients over 14 years, and linked outcomes to contemporaneous meteorological records to determine the relationship between the incidence of PJI and environmental humidity and temperature (6). Overall, 29 of the 1058 patients (2.7%) developed PJI. A trend was found suggesting that humidity >60% and apparent temperature >30°C may be risk factors for PJI (humidity, OR 1.4; 95% confidence interval (CI) 0.68-3.04; *P=0.221*; apparent temperature, OR 2.4; 95% CI 0.56-10.1; *P=0.174*). Whilst no statistically significant association was found, the authors reported that the relationship should be studied further.

Malnutrition

The systematic review and meta-analysis published in 2019 by Tsantes et al reported that, malnutrition is associated with PJI and surgical site infection (SSI) following TKA (7). The authors suggest that patients should be screened for malnutrition but stressed the need for further research. Aside from extreme cases, malnutrition is hard to identify clinically; a number of approaches to identify malnourished patients may be used, such as anthropometric tests, scoring systems and serological tests including albumin, transferrin, and total lymphocyte count. All included studies diagnosed malnutrition using serological markers, and the authors report uncertainty as to the validity of using these measures alone for diagnosing malnutrition. The authors suggested that the optimal method of treatment remains uncertain; it may include the use of high-protein drinks, vitamin and mineral supplementation, or high-calorie diets (7).

One such intervention was studied by Schroer et al in a retrospective study of 4,733 patients in two hospitals, of which 543 (11.5%) were found to be malnourished (8). Patients at one hospital were enrolled into a newly-instituted nutritional intervention program, including a diet rich in high protein and anti-inflammatory foods. They demonstrated a significantly shorter length of stay when compared to similarly malnourished patients at the other hospital sites.

Preoperative Risk Calculator

A 2018 study from the Rothman Institute aimed to identify and validate the risk factors and their relative weights in predicting PJI after TKA, to develop a pre-operative risk calculator (9). Of the 42 risk factors analyzed, 17 were found to be significant risk factors for PJI, the most important being previous surgery on the same joint, intravenous drug abuse, and comorbidities including human immunodeficiency virus (HIV), coagulopathies and renal disease.

Intraoperative Considerations

Antimicrobial Incision Drape

In 2020 Hesselvig et al published a large randomized study of 1,187 patients to examine the use of iodine-impregnated adhesive incisional drapes versus no drape in primary TKA (10). The primary end point was wound contamination, as measured by wound swabs at the start and end of the procedure and a sample from the surgeon's gloves removed prior to implantation. Overall, 12% of patients demonstrated contamination, with contamination significantly more likely in the group without incisional drapes (OR 0.61 for contamination in the incisional drape group, 95% CI 0.43 to 0.87, *P=0.005*). It remains to be seen whether this translates to a difference in true rates of infection between the two groups, and the authors have committed to following their patients up for 10 years to determine whether such a difference exists.

Antibiotic-Loaded Bone Cement in Primary TKA

Whilst the use of antibiotic-loaded bone cement (ALBC) has become routine practice, there is some uncertainty over whether it produces a meaningful effect in reducing rates of infection. Turhan et al, in 2019, published a retrospective study of 506 patients comparing those who had received ALBC (n=85) to those who had not, finding no significant difference in infection between the two groups (11). However, the comparison was unadjusted for covariates and it is unlikely that it was powered to determine a difference if one did exist. In contrast, the registry study of Jameson et al studied a cohort of 731,214 patients, adjusted for multiple covariates using Cox regression (12). In the ALBC group, which comprised 98% of the cohort, a statistically significant reduction in all cause revision was demonstrated (HR 0.85, 95% CI 0.77-0.93, *P<0.001*); however, whilst there was a trend towards reduced revisions for infection in the ALBC group, this did not reach statistical significance (HR 0.84, 95% CI 0.67-1.01, *P=0.06*).

Wound Lavage with Povidone-Iodine

Lavage of the surgical wound with dilute povidone iodine (DPI) prior to closure is routine practice in

many centers and is a plausible intervention to reduce wound colonization following arthroplasty. At typical institutional prices, the use of DPI is so inexpensive that even if it led to a small absolute risk reduction (ARR) for PJI, it would be cost-effective. Kerbel et al, in 2019, calculated that at their hospital price ($2.54), dilute betadine lavage (0.35%) was cost-effective with an ARR as low as 0.01% for primary TKA (13). They examined this further with a range of potential costs, from a high of $40 per intervention (which would require an ARR of 0.16% for TKA) to a low of $0.50 at which point the intervention becomes so inexpensive as to be immediately cost-effective even without any discernible reduction in the risk of infection.

The evidence varies as to whether DPI lavage is clinically effective. The large, retrospective study of Hernandez et al in 2019 demonstrated no significant effect of DPI in reducing PJI in 6,024 patients undergoing TKA from an institutional registry. In fact, following propensity score matching, there was a trend to a higher rate of revision for infection in patients who had received DPI (HR 1.3, 95% CI 0.6 to 2.6, *P=0.5*) (14). The same group separately published the results of DPI lavage in 1,482 revision TKAs finding a similar trend (15). The authors recommended further study – in spite of the large numbers and high quality statistical matching, there remains the possibility of confounding by indication if DPI was used on patients felt to be of higher risk of infection.

The 2019 registry study of Slullitel et al. reached a different conclusion from the two studies outlined above (16). Of 9,466 arthroplasty cases, 3932, following exclusions, were TKA. Overall, there was no difference in the rate of reoperation of TKA for infection (1.01% with DPI vs 0.99% without, *P=0.930*). When the entire cohort [including TKA, total hip arthroplasty (THA), and hip resurfacing] was propensity score matched a statistically significant difference was reported favoring DPI (reoperation for infection 10/2268 (0.4%) v 22/2268 (1.0%), *P=0.33*) but this appeared to be largely due to an influential group of hip resurfacing cases where a large difference in infection rate was observed. When restricted to TKA and THA, no difference was reported (reoperation for infection 8/1850 in each group, *P=0.796*).

Triclosan-Coated Sutures

Triclosan (5-Chloro-2-(2,4-dichlorophenoxy)phenol) is a non-antibiotic anti-bacterial and anti-fungal agent in widespread use. The introduction of Triclosan-coated ('Plus', Ethicon, West Lothian, United Kingdon) sutures was intended to reduce the risk of PJI. The quasi-randomized trial of Sprowson et al (17) examined 2,546 patients undergoing THA and TKA and found no difference in the rate of infection (rate of infection 0.7% in the triclosan group and 0.8% in the control group, *P=0.65*).

Postoperative Considerations

Extended Oral Antibiotic Prophylaxis

Whilst routine perioperative antibiotic prophylaxis has been the standard of care for many years, there is some data suggesting that, in high risk patients, extending the course to seven days following surgery may have an effect on the rate of PJI. Inabathula et al introduced a protocol to use extended oral antibiotic prophylaxis for 7 days after hospital discharge in high risk patients. Comparing the rates of infection in high risk TKA patients prior to (10/468) and following introduction of extended prophylaxis (2/439) they found a statistically lower rate of infection in the extended prophylaxis group (18). However, as outlined by DeFrancesco et al in their review of Inabathula's paper, heterogeneity of groups and protocols and issues with the design of the study limit the conclusions that can be drawn (19).

Non-Cefalosporin Antibiotics

First generation cefalosporins are the standard choice of antibiotic for perioperative prophylaxis. However, a proportion of patients receive an alternative antibiotic, either due to true cefalosporin allergy, out of caution when a patient is allergic to penicillin (due to the risk of cross-reactivity), or because of positive MRSA screening. The use of non-cefalosporin antibiotics may not be entirely benign – a retrospective study of 29,685 arthroplasites (17,026 of which were TKAs) by Wyles et al demonstrated an increase in adjusted rate of infection of 32% when non-cefalosporin antibiotics were used (20). They found a low rate of true penicillin allergy and suggested that the negative impact of using non-cefalosporin antibiotics was great enough to justify allergy testing in the cohort of patients who were believed to be allergic to penicillins.

Table 1 summarizes recommendations based on the presented papers. To prevent infection, it is critical to identify high-risk patients and control those risks prior to surgery. Action must be taken at every step of the surgical process, from preoperative to postoperative protocols, including intraoperative measures. In this Editorial some recent issues that surgeons should explore to try to prevent infection after TKA have been reviewed. Our goal must be to lower the current rate of infection following TKA.

Table 1. Recommendations based on the presented papers

FACTORS	FINDINGS
PREOPERATIVE	
S. Aureus screening and decolonization	Likely to lower risk of PJI
Bathing with clorhexidine	Weak evidence but likely effective
Risk factors	
Humidity and temperature	May increase PJI risk
Malnutrition	Likely increases PJI risk. Optimize nutrition prior to surgery
Preoperative risk calculator	Increased risk if: Prior open surgery, drug abuse, revision arthroplasty, HIV, AIDS
INTRAOPERATIVE	
Antimicrobial incision drape	Reduces bacterial wound colonisation
Antibiotic-loaded bone cement in primary TKA	Controversial
Povidone iodine irrigation prior to wound closure	Limited evidence but cost-effective even with small effect
Triclosan-coated sutures	Unlikely to be effective
POSTOPERATIVE	
Extended oral antibiotics prophylaxis	Possible effect in high risk patients
Use of alternative antibiotics to cefalosporins	Avoid if possible: if patient-reported allergy, test and use cefalosporin if possible

PJI = Periprosthetic joint infection; HIV = Human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; TKA = Total knee arthroplasty

References

1. Papas PV, Congiusta D, Scuderi GR, Cushner FD. A modern approach to preventing prosthetic joint infections. The journal of knee surgery. 2018; 31(07):610-7.
2. Nussenbaum FD, Rodriguez-Quintana D, Fish SM, Green DM, Cahill CW. Implementation of preoperative screening criteria lowers infection and complication rates following elective total hip arthroplasty and total knee arthroplasty in a veteran population. The Journal of arthroplasty. 2018; 33(1):10-3.
3. Giori NJ, Amanatullah DF, Gupta S, Bowe T, Harris AH. Risk reduction compared with access to care: quantifying the trade-off of enforcing a body mass index eligibility criterion for joint replacement. The Journal of bone and joint surgery. American volume. 2018; 100(7):539.
4. Kerbel YE, Sunkerneni AR, Kirchner GJ, Prodromo JP, Moretti VM. The Cost-Effectiveness of Preoperative Staphylococcus aureus Screening and Decolonization in Total Joint Arthroplasty. The Journal of arthroplasty. 2018; 33(7):S191-5.
5. Wang Z, Zheng J, Zhao Y, Xiang Y, Chen X, Zhao F, et al. Preoperative bathing with chlorhexidine reduces the incidence of surgical site infections after total knee arthroplasty: A meta-analysis. Medicine. 2017; 96(47).
6. Armit D, Vickers M, Parr A, Van Rosendal S, Trott N, Gunasena R, et al. Humidity a potential risk factor for prosthetic joint infection in a tropical Australian hospital. ANZ journal of surgery. 2018; 88(12):1298-301.
7. Tsantes AG, Papadopoulos DV, Lytras T, Tsantes AE, Mavrogenis AF, Korompilias AV, et al. Association of malnutrition with periprosthetic joint and surgical site infections after total joint arthroplasty: a systematic review and meta-analysis. Journal of Hospital Infection. 2019; 103(1):69-77.
8. Schroer WC, LeMarr AR, Mills K, Childress AL, Morton DJ, Reedy ME. 2019 Chitranjan S. Ranawat Award: Elective joint arthroplasty outcomes improve in malnourished patients with nutritional intervention: a prospective population analysis demonstrates a modifiable risk factor. The bone & joint journal. 2019; 101(7_Supple_C):17-21.
9. Tan TL, Maltenfort MG, Chen AF, Shahi A, Higuera CA, Siqueira M, et al. Development and evaluation of a preoperative risk calculator for periprosthetic joint infection following total joint arthroplasty. JBJS. 2018; 100(9):777-85.
10. Hesselvig AB, Arpi M, Madsen F, Bjarnsholt T, Odgaard A, ICON Study Group. Does an Antimicrobial Incision Drape Prevent Intraoperative Contamination? A Randomized Controlled Trial of 1187 Patients. A Publication of The Association of Bone and Joint

Surgeons®| CORR®. 2020; 478(5):1007-15.
11. Turhan S. Does the Use of Antibiotic-Loaded Bone Cement Have an Effect on Deep Infection in Primary Total Knee Arthroplasty Practice? Surgical infections. 2019; 20(3):244-6.
12. Jameson SS, Asaad A, Diament M, Kasim A, Bigirumurame T, Baker P, et al. Antibiotic-loaded bone cement is associated with a lower risk of revision following primary cemented total knee arthroplasty: an analysis of 731 214 cases using National Joint Registry data. The bone & joint journal. 2019; 101(11):1331-47.
13. Kerbel YE, Kirchner GJ, Sunkerneni AR, Lieber AM, Moretti VM. The cost effectiveness of dilute betadine lavage for infection prophylaxis in total joint arthroplasty. The Journal of arthroplasty. 2019; 34(7):S307-11.
14. Hernandez NM, Hart A, Taunton MJ, Osmon DR, Mabry TM, Abdel MP, et al. Use of povidone-iodine irrigation prior to wound closure in primary total hip and knee arthroplasty: an analysis of 11,738 cases. JBJS. 2019; 101(13):1144-50.
15. Hart A, Hernandez NM, Abdel MP, Mabry TM, Hanssen AD, Perry KI. Povidone-Iodine Wound Lavage to Prevent Infection After Revision Total Hip and Knee Arthroplasty: An Analysis of 2,884 Cases. JBJS. 2019; 101(13):1151-9.
16. Slullitel P, Dobransky J, Bali K, Poitras S, Bhullar R, Kim PR, Group TO. Is there a Role for Pre-closure Dilute Betadine Irrigation in the Prevention of Postoperative Infection following TJA? The Journal of Arthroplasty. 2019.
17. Sprowson AP, Jensen C, Parsons N, Partington P, Emmerson K, Carluke I, et al. The effect of triclosan-coated sutures on the rate of surgical site infection after hip and knee arthroplasty: a double-blind randomized controlled trial of 2546 patients. Bone Joint J. 2018; 100(3):296-302.
18. 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.
19. DeFrancesco CJ, Fu MC, Kahlenberg CA, Miller AO, Bostrom MP. Extended Antibiotic Prophylaxis May Be Linked to Lower Peri-prosthetic Joint Infection Rates in High-Risk Patients: An Evidence-Based Review. HSS Journal®. 2019; 15(3):297-301.
20. Wyles CC, Hevesi M, Osmon DR, Park MA, Habermann EB, Lewallen DG, 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. The bone & joint journal. 2019; 101(6_Supple_B):9-15.