# 1.17. PREVENTION: BLOOD CONSERVATION

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## QUESTION 1: Does allogeneic blood transfusion increase the risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. Allogenic blood transfusion is associated with an increased risk of SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

### RATIONALE

Allogeneic blood transfusion is a standard treatment to correct anemia in the setting of perioperative blood loss [1,2]. Data derived predominantly from retrospective studies have suggested that the administration of allogeneic blood transfusions may increase the risk of surgical site infection in arthroplasty and other surgical fields [1]. Postulated mechanisms for this occurrence include transfusion-associated immunomodulation (TRIM), in which infusion of circulating antigens present in the transfused blood product lead to a down-regulation of the host immune response [3]. Alternatively, this association may represent confounding factors such as hematoma formation, the presence of comorbid conditions or more prolonged, complex surgeries [4,5].

The association between allogenic transfusion and SSI and PJI has been explored in two recent meta-analyses. The meta-analysis conducted by Berríos-Torres et al. [4] for the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of surgical site infection examined the association between blood transfusions, including both allogeneic and autologous transfusions. When comparing allogeneic transfusion to no transfusion, they identified 4 observational studies (n = 5,737) that showed that allogeneic blood was associated with increased odds of infection compared with no transfusion (odds ratio (OR): 1.96, 95% confidence interval (CI) 1.46 to 2.63, $p < 0.01$, $I^2 = 0$) [2,4,6–8]. The second analysis compared allogeneic to autologous blood transfusions. This analysis also showed that allogeneic blood transfusions was associated with increased odds of infection when compared to autologous blood transfusion (OR: 4.53, 95% CI 2.37 to 8.65, $p > 0.01$, $I^2 = 0$) [6,8,9]. They concluded that there were uncertain tradeoffs between the benefits and harms of transfusion. However, the authors noted that there was no evidence to support withholding transfusion as a strategy to prevent surgical site infection in patients with anemia meeting transfusion criteria.

A second meta-analysis was published by Kim et al. [10]. This meta-analysis identified six studies (n = 21, 770) [5,6,8,11–13]. When patients who received allogeneic transfusion were compared to a combined group of patients who either received autologous or no transfusion, the patient cohort who received allogeneic transfusion was associated with increased odds of SSI (OR: 1.71, 95% CI 1.23 to 2.40; $p = 0.002$, $I^2 = 0.506$). The second component of the meta-analysis compared patients who received allogeneic transfusion to patients who received no transfusion. Patients who received allogeneic transfusions remained at increased odds of infection when compared to patients who received no transfusions (OR: 1.55, 1.11 to 2.17, $p = 0.01$, $I^2 = 0.110$). Therefore, the authors concluded that strategies that reduce the need for allogeneic transfusion should be considered in order to prevent SSI/PJI [10].

A review of the literature in electronic databases was performed (Table 1). In addition to the 2 meta-analyses, 20 studies met the inclusion criteria. Studies were published over a 20-year period (1997 to 2017). One study was a small (n = 100) randomized controlled trial and the remainder of the studies were observational studies. Most studies included lower extremity arthroplasty except two that included shoulder arthroplasty. A range of definitions for surgical site infection were applied. Data was analyzed using a random effects model to account for between-study heterogeneity.

#### Allogeneic Transfusion Versus No Transfusion

Fifteen observational studies were included in the meta-analysis comparing allogeneic transfusion to no transfusion [2,5–8,11–21]. One study by Llewelyn et al. [7] evaluated patients before and after transfusions with leukoreduced and non-leukoreduced allogeneic transfusions. These time periods were analyzed separately. The results show that patients who received allogeneic transfusions were associated with increased odds of surgical site infections when compared with patients who received no transfusions (pooled OR: 2.06, 95% CI 1.56 to 2.72, $p < 0.001$, $I^2 = 0.669$, Fig. 1).

#### Allogeneic Transfusion Versus Autologous Transfusion

Five observational studies were included in the meta-analysis comparing allogeneic transfusion to autologous transfusion [6,12,13,17,22]. Patients who received allogeneic transfusions were associated with an increased risk of surgical site infection when compared with patients who received autologous transfusions (pooled OR: 2.46, 95% CI 1.57 to 3.84, $p < 0.001$, $I^2 = 0.431$, Fig. 2).

#### Conclusion

Allogeneic blood transfusion is associated with an increased risk of SSI when compared to no transfusion or autologous transfusion. The data contained in the meta-analysis was derived from observational studies with significant heterogeneity. The underlying pathophysiological mechanism for this association has not been well-defined. In keeping with the conclusions drawn by Berríos-Torres et al. in the CDC guidelines, there is no data to support the withholding of allogeneic transfusion in patients with symptomatic anemia as a strategy to prevent SSIs [4]. Furthermore, the data presented supports that allogenic blood transfusion does increase the risk of SSI/PJI.

### TABLE 1. Characteristics of included studies

| Author | Year | Ref | Design | Population | Comparison | Allogeneic | | No Transfusion | | Autologous | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | SSI | No SSI | SSI | No SSI | SSI | No SSI |
| Shenolikar | 1997 | 14 | RCT | TKA | AL/AU | 1 | 39 | . | . | 0 | 42 |
| Levi | 1998 | 15 | OB | THA | AL/NIL | 11 | 145 | 20 | 519 | . | . |
| Borghi | 2000 | 16 | OB | THA + TKA | AL/AU | 4 | 274 | . | . | 13 | 2,593 |
| Rosencher | 2003 | 6 | OB | THA + TKA | AL/AU/NIL | 36 | 963 | 22 | 1,158 | 11 | 1,300 |
| Llewelyn | 2004 | 7 | OB | THA + TKA | NoLR AL/NIL | 43 | 563 | 31 | 840 | . | . |
| Llewelyn | 2004 | 7 | OB | THA + TKA | LR AL/NIL | 32 | 605 | 22 | 777 | . | . |
| Innerhofer | 2005 | 8 | OB | THA + TKA | AL/AU/NIL | 3 | 97 | 1 | 100 | 0 | 85 |
| Weber | 2005 | 2 | OB | THA | AL/NIL | 1 | 91 | 1 | 351 | . | . |
| del Trujillo | 2008 | 9 | OB | THA | AL/AU/NIL | 2 | 30 | 0 | 25 | 0 | 51 |
| Dowsey | 2008 | 11 | OB | THA | AL/NIL | 11 | 418 | 11 | 764 | . | . |
| Dowsey | 2009 | 17 | OB | TKA | AL/NIL | 8 | 292 | 10 | 904 | . | . |
| Pedersen | 2009 | 18 | OB | THA | AL/NIL | 5 | 2,249 | 5 | 2,249 | . | . |
| Basora | 2010 | 5 | OB | TKA | AL/NIL | 22 | 313 | 39 | 536 | . | . |
| Drosos | 2012 | 19 | OB | TKA | AL/AU/NIL | 13 | 58 | 6 | 79 | 8 | 84 |
| Friedman | 2014 | 12 | OB | THA + TKA | AL/AU/NIL | 108 | 3,854 | 123 | 6,190 | 33 | 1,869 |
| Frisch | 2014 | 20 | OB | THA + TKA | AL/NIL | 6 | 248 | 6 | 1,304 | . | . |
| Newman | 2014 | 13 | OB | THA + TKA | AL/AU/NIL | 14 | 822 | 12 | 1,594 | 6 | 904 |
| Smucny | 2015 | 21 | OB | TSA | AL/NIL | 110 | 31,577 | 310 | 332,607 | . | . |
| Tornero | 2016 | 22 | OB | THA | AL/NIL | 7 | 164 | 3 | 106 | . | . |
| Everhart | 2017 | 23 | OB | TSA | AL/NIL | 6 | 85 | 16 | 600 | . | . |

RCT, randomised controlled trial; OB, observational study; THA, hip arthroplasty; TKA, knee arthroplasty; TSA, shoulder arthroplasty; AL, allogeneic transfusion; AU, autologous transfusion; NIL, no transfusion; LR AL, leucoreduced allogeneic transfusion; NoLR AL, non-leucoreduced allogeneic transfusion; SSI, surgical site infection.

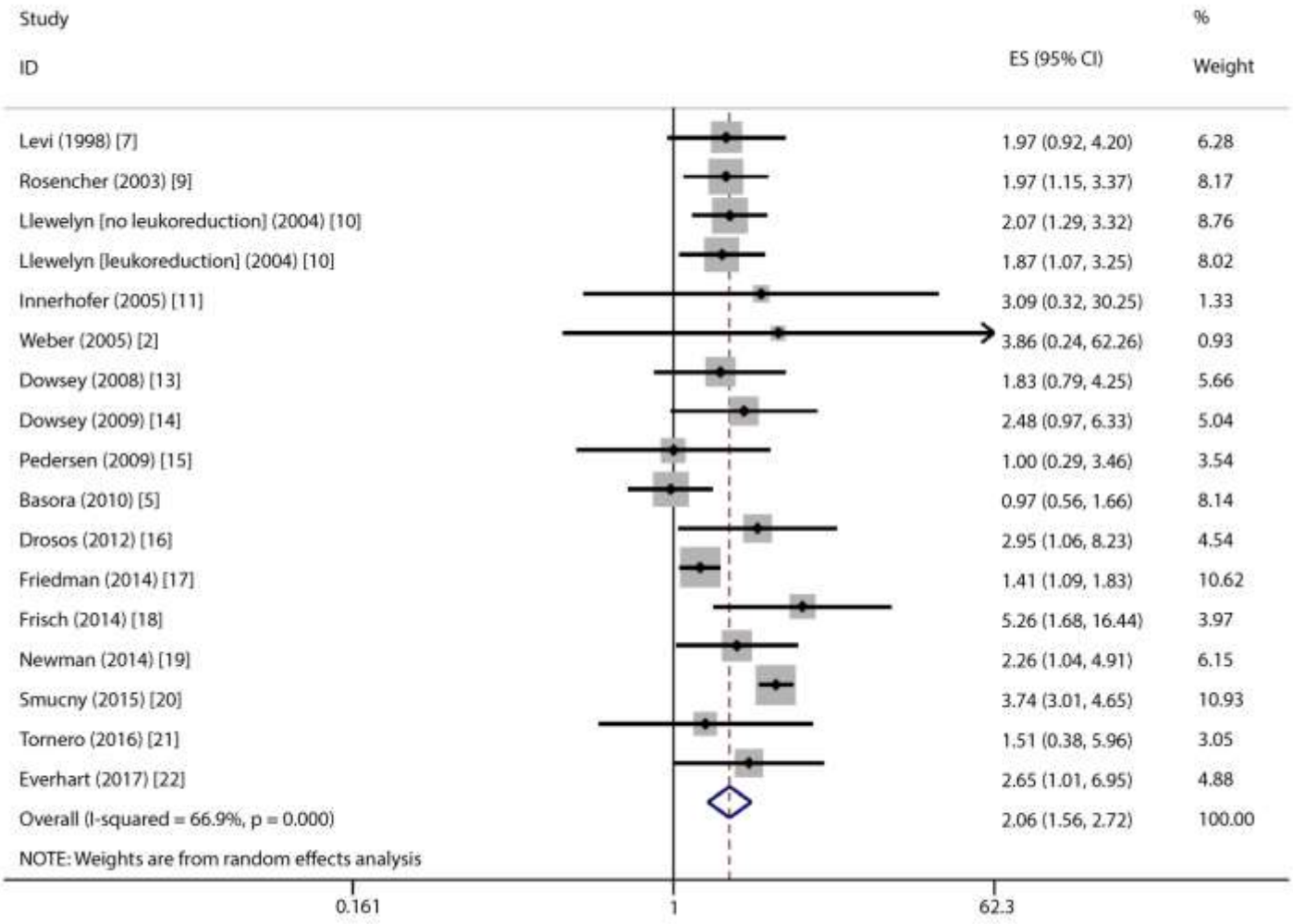


**FIGURE 1. Forest plot comparing allogeneic transfusion to no transfusion. (CI, confidence interval; ES, effect size).**

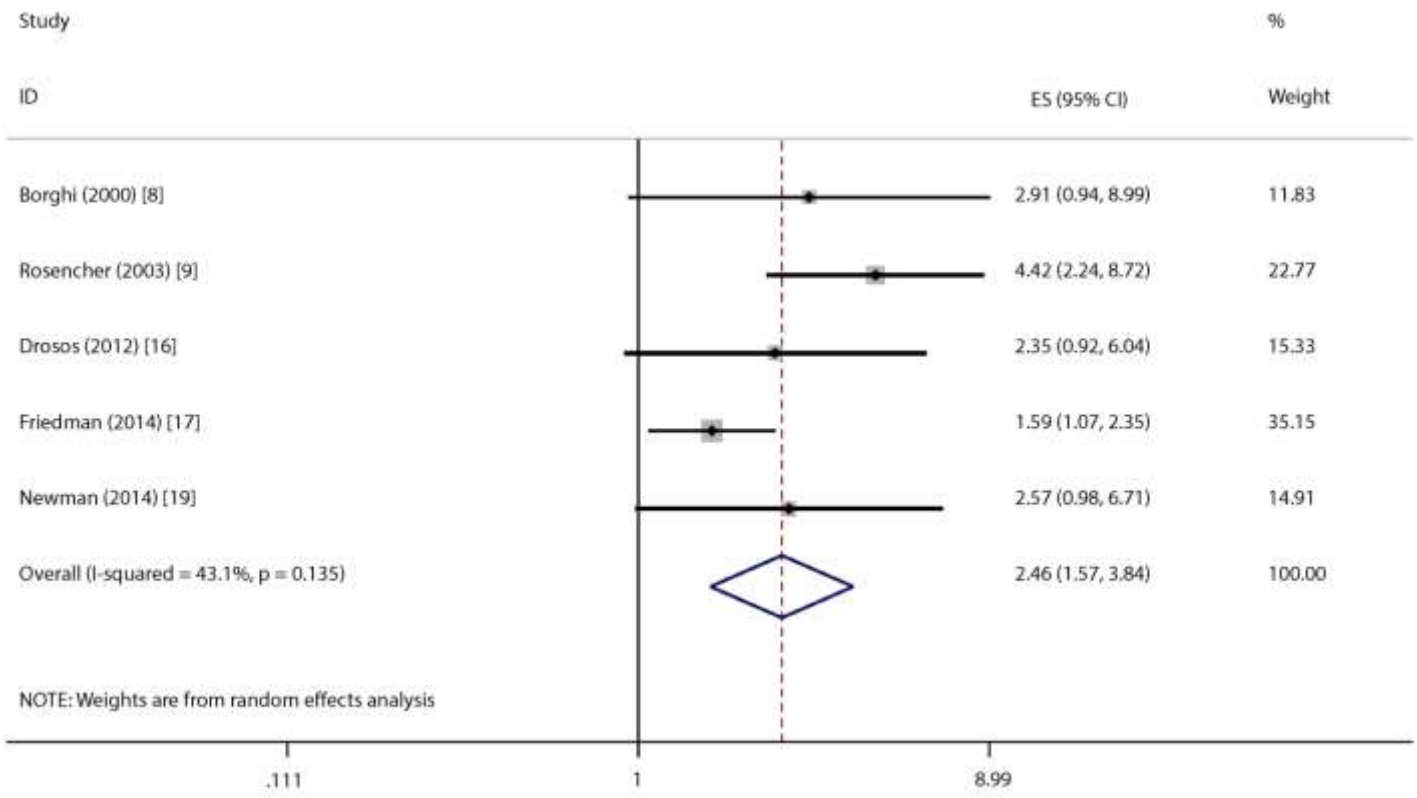


**FIGURE 2. Forest plot comparing allogeneic transfusion to autologous transfusion. (CI, confidence interval; ES, effect size).**

## REFERENCES


[1] Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011;114:283–292. doi:10.1097/ALN.0b013e3182054d06.

[2] Weber EWG, Slappendel R, Prins MH, van der Schaaf DB, Durieux ME, Strümper D. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. Anesth Analg. 2005;100:1416–1421, table of contents. doi:10.1213/01.ANE.0000150610.44631.9D.

[3] Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion–associated immunomodulation: fact or fiction? Blood. 2001;97:1180–1195.

[4] Berríos–Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152:784. doi:10.1001/jamasurg.2017.0904.

[5] Basora M, Pereira A, Soriano A, Martínez–Pastor JC, Sánchez–Etayo G, Tió M, et al. Allogeneic blood transfusion does not increase the risk of wound infection in total knee arthroplasty. Vox Sang. 2010;98:124–129. doi:10.1111/j.1423–0410.2009.01242.x.

[6] Rosencher N, Kerkkamp HEM, Macheras G, Munuera LM, Menichella G, Barton DM, et al. Orthopedic surgery transfusion hemoglobin european overview (OSTHEO) study: Blood management in elective knee and hip arthroplasty in Europe. Transfusion. 2003;43:459–469. doi:10.1046/j.1537–2995.2003.00348.x.

[7] Llewelyn CA, Taylor RS, Todd AAM, Stevens W, Murphy MF, Williamson LM, et al. The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery. Transfusion. 2004;44:489–500. doi:10.1111/j.1537–2995.2004.03325.x.

[8] Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell–filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion. 2005;45:103–110. doi:10.1111/j.1537–2995.2005.04149.x.

[9] del Trujillo MM, Carrero A, Muñoz M. The utility of the perioperative autologous transfusion system OrthoPAT in total hip replacement surgery: a prospective study. Arch Orthop Trauma Surg. 2008;128:1031–1038. doi:10.1007/s00402–007–0440–6.

[10] Kim JL, Park JH, Han SB, Cho IY, Jang KM. Allogeneic blood transfusion is a significant risk factor for surgical–site infection following total hip and knee arthroplasty: a meta–analysis. J Arthroplasty. 2017;32:320–325. doi:10.1016/j.arth.2016.08.026.

[11] Dowsey MM, Choong PFM. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res. 2008;466:153–158. doi:10.1007/s11999–007–0016–3.

[12] Friedman R, Homering M, Holberg G, Berkowitz SD. Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. J Bone Joint Surg Am. 2014;96:272–278. doi:10.2106/JBJS.L.01268.

[13] Newman ET, Watters TS, Lewis JS, Jennings JM, Wellman SS, Attarian DE, et al. Impact of perioperative allogeneic and autologous blood transfusion on acute wound infection following total knee and total hip arthroplasty. J Bone Joint Surg Am. 2014;96:279–284. doi:10.2106/JBJS.L.01041.

[14] Levi N, Sandberg T. Blood transfusion and postoperative wound infection in intracapsular femoral neck fractures. Bull Hosp Joint Dis. 1998;57:69–73.

[15] Dowsey MM, Choong PFM. Obese diabetic patients are at substantial risk for deep infection after primary TKA. Clin Orthop Relat Res. 2009;467:1577–1581. doi:10.1007/s11999–008–0551–6.

[16] Pedersen AB, Mehnert F, Overgaard S, Johnsen SP. Allogeneic blood transfusion and prognosis following total hip replacement: a population–based follow up study. BMC Musculoskelet Disord. 2009;10:167. doi:10.1186/1471–2474–10–167.

[17] Drosos GI, Blatsoukas KS, Ververidis A, Tripsianis G, Chloropoulou P, Iatrou C, et al. Blood transfusion and cytokines' changes in total knee replacement. Arch Orthop Trauma Surg. 2012;132:1505–1513. doi:10.1007/s00402–012–1567–7.

[18] Frisch NB, Wessell NM, Charters MA, Yu S, Jeffries JJ, Silverton CD. Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplasty. 2014;29:189–192. doi:10.1016/j.arth.2014.03.048.

[19] Smucny M, Menendez ME, Ring D, Feeley BT, Zhang AL. Inpatient surgical site infection after shoulder arthroplasty. J Shoulder Elbow Surg. 2015;24:747–753. doi:10.1016/j.jse.2014.12.024.

[20] Tornero E, Garcí–Ramiro S, Martínez–Pastor JC, Bori G, Bosch J, Morata L, et al. Prophylaxis with teicoplanin and cefuroxime reduces the rate of prosthetic joint infection after primary arthroplasty. Antimicrob Agents Chemother. 2015;59:831–837. doi:10.1128/AAC.03949–14.
[21] Everhart JS, Bishop JY, Barlow JD. Medical comorbidities and perioperative allogeneic red blood cell transfusion are risk factors for surgical site infection after shoulder arthroplasty. J Shoulder Elbow Surg. 2017;26:1922–1930. doi:10.1016/j.jse.2017.04.006.
[22] Borghi B, Casati A. Incidence and risk factors for allogenic blood transfusion during major joint replacement using an integrated autotransfusion regimen. The Rizzoli Study Group on orthopaedic anaesthesia. Eur J Anaesthesiol. 2000;17:411–417.

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## QUESTION 2: Can intraoperative or postoperative blood salvage be utilized in patients undergoing reimplantation for treatment of periprosthetic joint infectcion (PJI)?

RECOMMENDATION: Unknown. The limited published data on this subject suggests that the use of intraoperative or postoperative blood salvage in patients undergoing reimplantation for treatment of PJI may be beneficial, but also poses a potential risk of bacterial dissemination. Further studies are needed to evaluate the risks and benefits of this strategy.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

### RATIONALE

Different strategies have been used to avoid allogeneic red blood cell transfusion (ARBCT) in total joint arthroplasty due to its deleterious effects, including transfusion-associated lung injury, circulation overload and, most importantly, increased risk of PJI [1,2]. Cell salvage offers a safe, resource-saving and relatively inexpensive method to avoid ARBCT [1]. However, the main concern remains in its use in the setting of reimplantation given the possibility of persistent, undetectable infection.

There is limited data available in literature specific to the use of intraoperative or postoperative blood salvage to be utilized in patients undergoing reimplantation for the treatment of PJI. A systematic review was performed specifically evaluating if it is safe to re-infuse these products in this setting. Several level III and IV studies have examined the incidence of bacterial contamination of blood salvage equipment in elective non-orthopaedic surgery and have demonstrated little if any evidence of bacterial dissemination from blood salvage devices [3–6].

The use of intraoperative cell salvage has been supported in aseptic revision and primary hip and knee arthroplasty. It has been seen as efficacious in reducing the need for ARBCT and demonstrated cost-effectiveness [7]. A systematic review by Carless et al. evaluated 75 studies that investigated the effectiveness of cell salvage in different surgical specialties including orthopaedics [8]. They concluded that there is sufficient evidence to support the use of cell salvage. Furthermore, with advances in washing and filtration technology, new cell salvage devices continuously improve and provide a high-quality blood product for re-infusion [9].

Few absolute contraindications have been clearly stated for blood salvage [10]. Anything that results in lysis of the red blood cells is defined as an absolute contraindication. Blood that has been mixed with fluids such as sterile water, hydrogen peroxide, alcohol or any hypotonic solution will result in red cell destruction. The reason for this contraindication is end-organ damage as a result of administering lysed red blood cells [11,12]. In terms of blood contamination or infection, it has been thought that administration of this contaminated blood will lead to bacteremia or sepsis and has been established as a relative contraindication. Studies have found that contamination of processed and re-administered units obtained intraoperatively range from 9 to 30% without clinical implications [3,13].

No evidence has been found in favor or against the use of blood salvage in the setting of reimplantation beyond the fact that it reduces ARBCT. Other specialties have shown it to be a safe procedure in contaminated scenarios. ARBCT increases the risk of PJI, and thus a careful evaluation should be performed before deciding to use intraoperative or postoperative blood salvage in these patients.

### REFERENCES

[1] Cone J, Day LJ, Johnson GK, Murray DG, Nelson CL. Blood products: optimal use, conservation, and safety. Instr Course Lect. 1990;39:431–434.
[2] Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008;466:1710–1715. doi:10.1007/s11999–008–0209–4.
[3] Bland LA, Villarino ME, Arduino MJ, McAllister SK, Gordon SM, Uyeda CT, et al. Bacteriologic and endotoxin analysis of salvaged blood used in autologous transfusions during cardiac operations. J Thorac Cardiovasc Surg. 1992;103:582–588.
[4] Verwaal VJ, Wobbes T, Koopman–van Gemert AW, Buskens FG, Theeuwes AG. Effect of perioperative blood transfusion and cell saver on the incidence of postoperative infective complications in patients with an aneurysm of the abdominal aorta. Eur J Surg. 1992;158:477–480.
[5] Nessly ML. Infection and Cell–Saver use. Ann Thorac Surg. 1990;50:509–10.
[6] Schwieger IM, Gallagher CJ, Finlayson DC, Daly WL, Maher KL. The incidence of Cell–Saver contamination during cardiopulmonary bypass. Ann Thorac Surg. 1989;48:51–53.
[7] Dusik CJ, Hutchison C, Langelier D. The merits of cell salvage in arthroplasty surgery: an overview. Can J Surg. 2014;57:61–66.
[8] Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimizing perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010:CD001888. doi:10.1002/14651858.CD001888.pub4.
[9] Xie H, Pan JK, Hong KH, Guo D, Fang J, Yang WY, et al. Postoperative autotransfusion drain after total hip arthroplasty: a meta–analysis of randomized controlled trials. Sci Rep. 2016;6:27461. doi:10.1038/srep27461.
[10] Esper SA, Waters JH. Intra–operative cell salvage: a fresh look at the indications and contraindications. Blood Transfus. 2011;9:139–147. doi:10.2450/2011.0081–10.
[11] From the Centers for Disease Control and Prevention. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. JAMA. 1999;281:1076–1077.
[12] Pierce LR, Gaines A, Varricchio F, Epstein J. Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. Am J Health Syst Pharm. 1998;55:1057, 1062, 1070.

[13] Kang Y, Aggarwal S, Pasculle AW, Freeman JA, Martin LK. Bacteriologic study of autotransfusion during liver transplantation. Transplant Proc. 1989;21:3538.

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# QUESTION 3: Do antiplatelet drugs need to be withheld preoperatively to reduce the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Aspirin should not be withheld preoperatively. There is no evidence that withholding aspirin affects SSI/PJI rates and the cardiac and stroke risk associated with discontinuing aspirin outweighs any unproven, theoretical benefit with respect to SSI/PJI.

Clopidogrel should be withheld a minimum of five days preoperatively to reduce the risk for subsequent SSI/PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

## RATIONALE

Antiplatelet drugs are commonly prescribed to reduce the risk of major vascular complications [1]. These medications interfere with one or more steps in platelet release and aggregation [2], causing a measurable decrease in the risk of thrombosis which cannot be dissociated from an increased risk of bleeding [3]. Because of the potential increased risk of bleeding, as well as concern for possible increased risk of SSI/PJI, the question whether to discontinue such medications perioperatively is an important topic in surgical care.

### Irreversible Cyclooxygenase Inhibitors (i.e., Aspirin)

Aspirin, an antiplatelet agent widely used for its cardio-protective features, is taken by many total joint arthroplasty (TJA) patients preoperatively. It is an irreversible inhibitor of cyclooxygenase (COX), thus preventing the formation of thromboxane A2 (TxA2), a substance used in platelet aggregation [4]. It is rapidly absorbed, reaching peak levels in approximately 2 hours and has a dose-dependent half-life between 2 and 15 hours. Aspirin reduces mortality in patients undergoing cardiac and vascular surgery [4–7] and several studies have shown that aspirin therapy should never be discontinued after a coronary or cerebrovascular event [4,8–11]. Withholding aspirin increases the incidence of myocardial infarction, mortality and drug-eluting stent thrombosis and is an independent predictor of major ischemic events and death [4,12–15].

Deveraux et al. investigated the effects of aspirin versus placebo in non-cardiac surgery, including orthopaedic procedures. In this randomized controlled trial, 10,010 patients were grouped according to their aspirin use [16]. Use of aspirin significantly increased the risk of major bleeding, compared to placebo. However, there were no significant differences in infection rates between the aspirin and placebo groups. In a prospective cohort study of 139 TJA patients, Cossetto et al. found no difference in superficial wound infection or PJI between patients who continued aspirin perioperatively versus those who did not take aspirin [17]. In a retrospective cohort study of 175 TJA patients, Meier et al. demonstrated no difference in PJI between patients who discontinued aspirin 10 days preoperatively versus those who continued aspirin in the perioperative period [18]. Additionally, these two TJA studies found no significant difference in rates of bleeding in those taking aspirin before hip or knee surgery compared to those not taking antiplatelet drugs [17,18].

There is no evidence that withholding aspirin affects SSI/PJI rates. Because the cardiac and stroke risk associated with discontinuing aspirin outweighs any unproven, theoretical benefit for SSI/PJI risk, aspirin should not be withheld preoperatively.

### Adenosine Diphosphate (ADP) Receptor Inhibitors (i.e., Clopidogrel, Prasugrel)

Clopidogrel is a platelet inhibitor indicated for use in patients with acute coronary syndrome, stroke or peripheral arterial disease. It is a thienopyridine antithrombotic agent, which prevents adenosine diphosphate (ADP)-mediated platelet aggregation, leading to the inhibition of fibrinogen binding to glycoproteins GPIIb and GPIIIa on the platelet surface [4]. The half-life of clopidogrel is approximately eight hours [19], but the effects of clopidogrel can be seen for up to seven days after discontinuation because there can be individual variation in recovery of platelet function, which depends more on the amount of initial inhibition by the drug and previous duration of therapy than on the number of days since cessation of the medication [4,12,20–23].

Several retrospective studies have found greater bleeding and/or increased risk of bleeding events in those taking clopidogrel before TJA or hip fracture surgery [24–26]. Patients who continued clopidogrel in the preoperative period were also significantly more likely to receive a blood transfusion within 24 hours of surgery and during hospitalization [27]. In a retrospective cohort study of 116 patients, Nandi et al. found that patients who stopped clopidogrel 5 or more days before TJA had lower rates of bleeding events, as well as significantly lower rates of reoperation for infection and antibiotics prescribed for the surgical wound when compared to those who stopped clopidogrel for 1 to 4 days, or 0 days before surgery [25]. Postoperative events did not vary with timing of clopidogrel resumption after surgery. In a case series of seven TJA patients by Shubert et al., 12.5% of patients developed a PJI and 25% of patients required antibiotics for the surgical wound when clopidogrel administration was uninterrupted in the perioperative period [26]. In a retrospective cohort study of 142 primary or revision TJA patients, Jacob et al. did not find a difference in rate of PJI between patients that discontinued clopidogrel more than seven days preoperatively versus those who discontinued clopidogrel less than 7 days preoperatively [27]. These findings do not refute those of earlier studies, as the selection of the seven-day time point may have limited the ability of this study to detect a difference between groups.

Because of the increased risk of SSI/PJI with continuation of clopidogrel, it should be withheld a minimum of five days preoperatively to reduce the risk for subsequent SSI/PJI. It appears that clopidogrel may be resumed as early as the day of surgery, although the evidence for when to restart is limited [25].

## REFERENCES


[1] Harty JA, McKenna P, Moloney D, D'Souza L, Masterson E. Anti–platelet agents and surgical delay in elderly patients with hip fractures. J Orthop Surg (Hong Kong). 2007;15:270–272. doi:10.1177/230949900701500304.

[2] Kroll MH, Reséndiz JC. Mechanisms of platelet activation. Thrombosis and Hemorrhage. 3rd ed., Baltimore, MD: Williams & Wilkins; 2002.

[3] Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet–active drugs: the relationships among dose, effectiveness, and side effects: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:234S–264S. doi:10.1378/chest.126.3_suppl.234S.

[4] Dundon JM, Trimba R, Bree KJ, Woods CJ, Laughlin RT. Recommendations for perioperative management of patients on existing anticoagulation therapy. JBJS Rev. 2015;3. doi:10.2106/JBJS.RVW.N.00105.

[5] Mangano DT, Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. N Engl J Med. 2002;347:1309–1317. doi:10.1056/NEJMoa020798.

[6] Dacey LJ, Munoz JJ, Johnson ER, Leavitt BJ, Maloney CT, Morton JR, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. Ann Thorac Surg. 2000;70:1986–1990.

[7] Neilipovitz DT, Bryson GL, Nichol G. The effect of perioperative aspirin therapy in peripheral vascular surgery: a decision analysis. Anesth Analg. 2001;93:573–580.

[8] Smith SC, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention–summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/SCAI Writing Committee to update the 2001 guidelines for percutaneous coronary intervention). J Am Coll Cardiol. 2006;47:216–235. doi:10.1016/j.jacc.2005.11.025.

[9] Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006;113:2363–2372. doi:10.1161/CIRCULATIONAHA.106.174516.

[10] Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Coll Cardiol. 2007;49:734–739. doi:10.1016/j.jacc.2007.01.003.

[11] Popma JJ, Berger P, Ohman EM, Harrington RA, Grines C, Weitz JI. Antithrombotic therapy during percutaneous coronary intervention: the seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:576S–599S. doi:10.1378/chest.126.3_suppl.576S.

[12] Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non–cardiac surgery—a prospective outcome study. Br J Anaesth. 2006;96:686–693. doi:10.1093/bja/ael083.

[13] Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug–eluting stents. JAMA. 2005;293:2126–2130. doi:10.1001/jama.293.17.2126.

[14] Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation. 2004;110:2361–2367. doi:10.1161/01.CIR.0000145171.89690.B4.

[15] Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol. 2005;45:456–459. doi:10.1016/j.jacc.2004.11.041.

[16] Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso–Coello P, Kurz A, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370:1494–1503. doi:10.1056/NEJMoa1401105.

[17] Cossetto DJ, Goudar A, Parkinson K. Safety of peri–operative low–dose aspirin as a part of multimodal venous thromboembolic prophylaxis for total knee and hip arthroplasty. J Orthop Surg (Hong Kong). 2012;20:341–343. doi:10.1177/230949901202000315.

[18] Meier R, Marthy R, Saely CH, Kuster MS, Giesinger K, Rickli H. Comparison of preoperative continuation and discontinuation of aspirin in patients undergoing total hip or knee arthroplasty. Eur J Orthop Surg Traumatol. 2016;26:921–928. doi:10.1007/s00590–016–1830–7.

[19] Owens CD, Belkin M. Thrombosis and coagulation: operative management of the anticoagulated patient. Surg Clin North Am. 2005;85:1179–1189, x. doi:10.1016/j.suc.2005.09.008.

[20] Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost. 1999;25 Suppl 2:15–19.

[21] Kam PCA, Nethery CM. The thienopyridine derivatives (platelet adenosine diphosphate receptor antagonists), pharmacology and clinical developments. Anaesthesia. 2003;58:28–35.

[22] Weber AA, Braun M, Hohlfeld T, Schwippert B, Tschöpe D, Schrör K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. Br J Clin Pharmacol. 2001;52:333–336.

[23] Price MJ, Teirstein PS. Dynamics of platelet functional recovery following a clopidogrel loading dose in healthy volunteers. Am J Cardiol. 2008;102:790–795. doi:10.1016/j.amjcard.2008.02.109.

[24] Chechik O, Thein R, Fichman G, Haim A, Tov TB, Steinberg EL. The effect of clopidogrel and aspirin on blood loss in hip fracture surgery. Injury. 2011;42:1277–1282. doi:10.1016/j.injury.2011.01.011.

[25] Nandi S, Aghazadeh M, Talmo C, Robbins C, Bono J. Perioperative clopidogrel and postoperative events after hip and knee arthroplasties. Clin Orthop Relat Res. 2012;470:1436–1441. doi:10.1007/s11999–012–2306–7.

[26] Shubert D, Bono J, Nandi S. Uninterrupted perioperative clopidogrel and bleeding–related events after total joint arthroplasty: a case series. J Surg Orthop Adv. 2015;24:115–119.

[27] Jacob AK, Hurley SP, Loughran SM, Wetsch TM, Trousdale RT. Continuing clopidogrel during elective total hip and knee arthroplasty: assessment of bleeding risk and adverse outcomes. J Arthroplasty. 2014;29:325–328. doi:10.1016/j.arth.2013.06.008.



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## QUESTION 4: Is there a role for the administration of erythropoietin, hemotinics or other agents for patients with orthopaedic infections?

RECOMMENDATION: Yes. Erythropoietin used preoperatively in infected revision arthroplasty results in higher preoperative hemoglobin levels and lower allogeneic transfusion rates without compromising eradication of infection.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 9%, Abstain: 9% (Super Majority, Strong Consensus)

## RATIONALE

The use of erythropoietin to reduce transfusion requirements in primary arthroplasty is widely known, although as transfusion rates have decreased, the cost-effectiveness of this treatment has been questioned [1]. Similarly, the effect of tranexamic acid in reducing transfusion requirement has been firmly established in primary arthroplasty [2], however much less is known about the effects of these agents in the case of orthopaedic infection. Although a recent paper has suggested that transfusion alone is not a risk factor for infection, the incidence of infection seems associated with other factors predictive of transfusion such as complexity or preoperative anemia, with all cause revision exhibiting much higher transfusion rates than primary arthroplasty [3]. As concurrent infection precludes autogenic transfusion, allogenic transfusion becomes the most common method of treating postoperative anemic, which carries with it inherent risk.

Only two case control studies have been found studying the effect of erythropoietin in infected arthroplasty, one in revision hip and one in revision knee for infection [4,5]. Both studies use an Epoetin alpha 40,000 unit dose administered between first- and second-stage revision, with different administration regimes. In both cases, transfusion rate and pre-reimplantation hemoglobin were used as primary end-points and both studies showed significant improvements in both metrics, without any noticeable increase in complications. It is notable, however, that both studies are at least 15 years old with no obvious follow-up work, since.

Several studies in the early 2000s examined the effects of the ani-fibrinolytic Aprotinin in the reduction of bleeding in studies including orthopaedic surgery for infection [6–8]. However, despite its effectiveness and widespread use in cardiothoracic surgery, Aprotinin was withdrawn from the market in 2008 due to concerns over increased mortality and renal failure. In light of this, the effects of Aprotinin have not been reviewed.

The beneficial effect of tranexamic (TXA) acid has been extensively reviewed in arthroplasty, but little research exists for patients with orthopaedic infections [9]. Only one small retrospective review examined the effects of topical TXA on infected arthroplasty patients undergoing two-stage revision. Those treated with TXA had lower hemoglobin droops and lower transfusion rates, with no increase in complications than those treated without TXA. However, it is not possible to form definitive conclusions from only one small retrospective study.

Only two studies were found examining the effects of erythropoietin in orthopaedic infections. Both case-control series indicate reduced transfusion rates and improved hemoglobin before re-implantation in two-stage revision for infection [4,5]. It must be noted that both studies are historic, with debatable relevance of comparing practice in the early 1990s (the time of the control cohorts) with contemporary care. However, the compelling success of these studies suggests that further investigation is required.

We note that a somewhat similar question from the 2013 International Consensus Meeting (ICM) resulted in strong consensus towards treatment of anemia with iron with or without erythropoietin to reduce the risk of transfusion. However, for this question the evidence is different from the 2013 ICM question. The current available literature does not appear to strongly support the same conclusion, primarily because the previously-referenced studies did not focus on infected cases [10,11].

## REFERENCES


[1] Voorn VM, van der Hout A, So–Osman C, Vliet Vlieland TP, et al. Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty. Vox Sang. 2016;111:219–225. doi:10.1111/vox.12412.

[2] Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta–analysis of 2720 cases. Transfus Med. 2015;25:151–162. doi:10.1111/tme.12212.

[3] George J, Sikora M, Masch J, Farias–Kovac M, Klika AK, Higuera CA. Infection Is not a risk factor for perioperative and postoperative blood loss and transfusion in revision total hip arthroplasty. J Arthroplasty. 2017;32:214–219.e1. doi:10.1016/J.ARTH.2016.06.046.

[4] Lee G–C, Pagnano MW, Jacofsky DJ, Hanssen AD. Use of erythropoietin in two–stage reimplantation total hip arthroplasty. Clin Orthop Relat Res. 2003;414:49–54. doi:10.1097/01.blo.0000084405.53464.5e.

[5] Cushner FD, Locker JR, Hanssen AD, Jacofsky DJ, Scott WN, Scuderi GR, et al. Use of recombinant human erythropoietin in two–stage total knee arthroplasty for infection. Clin Orthop Relat Res. 2001;392:116–123.

[6] Capdevila X, Calvet Y, Biboulet P, Biron C, Rubenovitch J, d'Athis F. Aprotinin decreases blood loss and homologous transfusions in patients undergoing major orthopedic surgery. Anesthesiology. 1998;88:50–57.

[7] Jeserschek R, Clar H, Aigner C, Rehak P, Primus B, Windhager R. Reduction of blood loss using high–dose aprotinin in major orthopaedic surgery. J Bone Joint Surg Br. 2003;85:174–177. doi:10.1302/0301–620X.85B2.13303.

[8] Samama CM, Langeron O, Rosencher N, Capdevila X, Rouche P, Pegoix M, et al. Aprotinin versus placebo in major orthopedic surgery: a randomized, double–blinded, dose–ranging study. Anesth Analg. 2002;95:287–293, table of contents.

[9] Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta–analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br. 2011;93–B:39–46. doi:10.1302/0301–620X.93B1.24984.

[10] Delasotta LA, Rangavajjula A, Frank ML, Blair J, Orozco F, Ong A. The use of preoperative epoetin–α in revision hip arthroplasty. Open Orthop J. 2012;6:179–183. doi:10.2174/1874325001206010179.

[11] Delasotta LA, Rangavajjula A V, Frank ML, Blair JL, Orozco FR, Ong AC. The use of epoetin–alpha in revision knee arthroplasty. Adv Orthop. 2012;2012:595027. doi:10.1155/2012/595027.



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# QUESTION 5: Does the use of tranexamic acid (TXA) reduce blood loss and need for allogeneic blood transfusion during primary total joint arthroplasty (TJA)?

RECOMMENDATION: Yes. The administration of intravenous (IV), topical and/or oral TXA is an effective strategy for reducing blood loss and the need for allogeneic transfusion during primary TJA.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

## RATIONALE

Blood loss in primary TJA, especially total hip arthroplasty (THA), can be significant and is often under-estimated due to hidden blood loss [1–3]. Postoperative blood transfusion rates due to blood loss is estimated to be about 11% for total knee arthroplasty (TKA) and 18% for THA [1]. Therefore, several methods have been utilized to help reduce the risk of blood loss and need for allogeneic transfusion.

After discovery of the antifibrinolytic properties of TXA in the early 1960s by Shosuke and Utako Okamoto, TXA has become widely used in many medical specialties [4,5]. Benoni et al. were the first to publish on the blood conserving properties of TXA in orthopaedic surgery [6]. Ever since their original publication, a growing body of literature has been published on the use of intravenous, topical and oral TXA in primary hip and knee arthroplasty. The overwhelming results from these studies and subsequent meta-analyses have demonstrated that TXA is a safe and effective method for reducing blood loss and the need for allogeneic blood transfusion.

IV TXA has been the most popular and widely-studied formulation in total joint arthroplasty with a recent literature search identifying more than 40 randomized clinical trials comparing intravenous TXA and placebo in primary TJA. Meta-analysis by Sukeik et al. and Yang et al. have proven the effectiveness of intravenous TXA compared to placebo in the setting of primary hip and knee arthroplasty [7,8].

Topical TXA is seen as an alternative to intravenous and oral routes of administration to provide local drug delivery. In two parallel-randomized control trials, Alshryda et al. investigated topical TXA in the setting of primary hip and knee arthroplasty by administering intra-articular 1 gm TXA or an equivalent volume of saline placebo [9,10]. Both studies provided evidence that topical TXA reduces the absolute risk for blood transfusion and reduces blood loss in primary hip and knee arthroplasties [9,10]. A systematic review and meta-analysis of 14 studies demonstrated similar results of a significant reduction in blood loss and need for transfusion when topical TXA was used compared to placebo, without an increase risk of complications [11]. When topical and intravenous TXA have been compared in a randomized clinical trial, Gomez-Barrena et al. found topical TXA in primary TKA demonstrated noninferiority to intravenous TXA [12].

The use of oral TXA during primary TJA was explored recently. The study by Irwin et al. reports on the use of oral TXA during a national shortage of IV TXA. The comparison of the data in their retrospective cohort demonstrated a lower odds ratio for transfusion when oral TXA was used [13]. Fillingham et al. and Kayupov et al. performed similar randomized clinical trials in primary hip and knee arthroplasties comparing a dose of 1 gm IV to 2 gm oral TXA, which demonstrated statistical equivalence with regard to reduction in blood loss and the need for allogeneic blood transfusion [14,15]. A systemic review and meta-analysis by Zhang et al. of six studies demonstrated lower hemoglobin drop, blood loss and transfusion rate in patients receiving oral TXA compared to the placebo group without increasing the risk of complications [16]. Another meta-analysis by the same author Zhang et al. comparing oral versus IV application of TXA concluded that oral TXA is cost efficient and convenient and has similar effects on reducing blood loss and transfusion rate as IV TXA [17].

More recently, the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society and American Society of Regional Anesthesia and Pain Medicine worked together to create a clinical practice guideline on the use of TXA in TJA [18]. The efficacy recommendations of the clinical practice guidelines found with a strong recommendation that all formulations (IV, topical and oral) TXA are superior to placebo and equivalent amongst each other in terms of blood sparing properties [18]. Additionally, the clinical practice guidelines cited with a strong recommendation that higher doses and/or multiple doses of any formulation of TXA does not provide reduced blood loss and/or risk of transfusion [18]. The only moderate strength recommendation regarding the efficacy of TXA in primary TJA was the recommendation in favor of the pre-incision dosing of IV TXA [18].

Given the overwhelming literature supporting the blood conservation properties of TXA, we conclude that all formulations and dosing regimens are effective in minimizing blood loss and reducing the need for allogeneic blood transfusions in primary hip and knee arthroplasties.

## REFERENCES


[1] Carling MS, Jeppsson A, Eriksson BI, Brisby H. Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study. J Orthop Surg Res. 2015;10:48. doi:10.1186/s13018–015–0188–6.

[2] Liu X, Zhang X, Chen Y, Wang Q, Jiang Y, Zeng B. Hidden blood loss after total hip arthroplasty. J Arthroplasty. 2011;26:1100–1105.e1. doi:10.1016/j.arth.2010.11.013.

[3] Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty?. Correct blood loss management should take hidden loss into account. Knee. 2000;7:151–155.

[4] Okamoto S, Okamoto U. Amino–methyl–cyclohexane–carboxylic acid: AMCHA. Keio J Med. 1962;11:105–115. doi:10.2302/kjm.11.105.

[5] Okamoto S, Sato S, Takada Y, Okamoto U. An active stereo–isomer (trans–form) of AMCHA and its antifibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med. 1964;13:177–185.

[6] Benoni G, Carlsson A, Petersson C, Fredin H. Does tranexamic acid reduce blood loss in knee arthroplasty? Am J Knee Surg. 1995;8:88–92.

[7] Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta–analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br. 2011;93:39–46. doi:10.1302/0301–620X.93B1.24984.

[8] Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta–analysis. J Bone Joint Surg Am. 2012;94:1153–1159. doi:10.2106/JBJS.K.00873.

[9] Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Maheswaran S, et al. Topical (intra–articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX–K). J Bone Joint Surg Am. 2013;95:1961–1968. doi:10.2106/JBJS.L.00907.

[10] Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H, et al. Topical (intra–articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX–H). J Bone Joint Surg Am. 2013;95:1969–1974. doi:10.2106/JBJS.L.00908.

[11] Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM. A systematic review and meta–analysis of the topical administration of tranexamic acid in total hip and knee replacement. Bone Joint J. 2014;96–B:1005–1015. doi:10.1302/0301–620X.96B8.33745.

[12] Gomez–Barrena E, Ortega–Andreu M, Padilla–Eguiluz NG, Pérez–Chrzanowska H, Figueredo–Zalve R. Topical intra–articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double–blind, randomized, controlled, noninferiority clinical trial. J Bone Joint Surg Am. 2014;96:1937–1944. doi:10.2106/JBJS.N.00060.

[13] Irwin A, Khan SK, Jameson SS, Tate RC, Copeland C, Reed MR. Oral versus intravenous tranexamic acid in enhanced–recovery primary total hip and knee replacement: results of 3000 procedures. Bone Joint J. 2013;95–B:1556–1561. doi:10.1302/0301–620X.95B11.31055.
[14] Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL, Della Valle CJ. The James A. rand young investigator's Award: a randomized controlled trial of oral and intravenous tranexamic acid in total knee arthroplasty: the same efficacy at lower cost? J Arthroplasty. 2016;31:26–30. doi:10.1016/j.arth.2016.02.081.
[15] Kayupov E, Fillingham YA, Okroj K, Plummer DR, Moric M, Gerlinger TL, et al. Oral and intravenous tranexamic acid are equivalent at reducing blood loss following total hip arthroplasty: a randomized controlled trial. J Bone Joint Surg Am. 2017;99:373–378. doi:10.2106/JBJS.16.00188.
[16] Zhang LK, Ma JX, Kuang MJ, Zhao J, Lu B, Wang Y, et al. The efficacy of tranexamic acid using oral administration in total knee arthroplasty: a systematic review and meta–analysis. J Orthop Surg Res. 2017;12:159. doi:10.1186/s13018–017–0660–6.
[17] Zhang LK, Ma JX, Kuang MJ, Zhao J, Wang Y, Lu B, et al. Comparison of oral versus intravenous application of tranexamic acid in total knee and hip arthroplasty: a systematic review and meta–analysis. Int J Surg. 2017;45:77–84. doi:10.1016/j.ijsu.2017.07.097.
[18] Fillingham YA, Jevsevar DS, Yates AJ, Sayeed SA, Sah AP, Bini SA, et al. Tranexamic acid in total joint arthroplasty: the clinical practice guides of the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society, American Society of Regional Anesthesia and Pain Medicine. 2017.

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## QUESTION 6: Does the use of tranexamic acid (TXA) reduce blood loss and need for allogeneic blood transfusion during revision total joint arthroplasty (TJA)?

RECOMMENDATION: Yes. The administration of TXA during revision TJA reduces blood loss and the need for allogeneic blood transfusion.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 0%, Abstain: 3% (Unanimous, Strongest Consensus)

### RATIONALE

It is well-known that revision TJA cases are more complex and are associated with a greater amount of blood loss and an increased need for allogeneic blood transfusion compared to primary TJA. Despite the vast body of literature investigating TXA following primary TJA, only a limited number of studies exist on the use of TXA after revision TJA. Among the nine published studies, seven are retrospective comparisons with one prospective non-randomized study and only a single randomized clinical trial [1–9]. All seven retrospective comparison studies and the single prospective non-randomized study have shown that intravenous (IV) TXA decreased both the rate of blood transfusion and the amount of blood transfused when compared to controls [1–8]. Wu et al. performed a randomized clinical trial comparing IV verses combined IV and topical TXA in revision total hip arthroplasty (THA), which demonstrated improved blood sparing properties for combined IV and topical TXA [9].

Despite the lack of multiple randomized clinical trials, several retrospective studies have supported the use of TXA to reduce blood loss and transfusion during revision TJA. Despite the known efficacy of TXA in primary TJA, the literature lacks robust evidence in revision TJA. As a result, the recommendation is only provided a moderate level of strength.

### REFERENCES

[1] Aguilera X, Videla S, Almenara M, Fernandez JA, Gich I, Celaya F. Effectiveness of tranexamic acid in revision total knee arthroplasty. Acta Orthop Belg. 2012;78:68–74.
[2] Kazi HA, Fountain JR, Thomas TG, Carroll FA. The effect of bolus administration of tranexamic acid in revision hip arthroplasty. Hip Int. 2012;22:615–620. doi:10.5301/HIP.2012.10143.
[3] Noordin S, Waters TS, Garbuz DS, Duncan CP, Masri BA. Tranexamic acid reduces allogenic transfusion in revision hip arthroplasty. Clin Orthop Relat Res. 2011;469:541–546. doi:10.1007/s11999–010–1441–2.
[4] Ortega–Andreu M, Talavera G, Padilla–Eguiluz NG, Perez–Chrzanowska H, Figueredo–Galve R, Rodriguez–Merchán CE, et al. Tranexamic acid in a multimodal blood loss prevention protocol to decrease blood loss in revision total knee arthroplasty: a cohort study. Open Orthop J. 2016;10:439–447. doi:10.2174/1874325001610010439.
[5] Park KJ, Couch CG, Edwards PK, Siegel ER, Mears SC, Barnes CL. tranexamic acid reduces blood transfusions in revision total hip arthroplasty. J Arthroplasty. 2016;31:2850–2855.e1. doi:10.1016/j.arth.2016.05.058.
[6] Phillips SJ, Chavan R, Porter ML, Kay PR, Hodgkinson JP, Purbach B, et al. Does salvage and tranexamic acid reduce the need for blood transfusion in revision hip surgery? J Bone Joint Surg Br. 2006;88:1141–1142. doi:10.1302/0301–620X.88B9.17605.
[7] Samujh C, Falls TD, Wessel R, Smith L, Malkani AL. Decreased blood transfusion following revision total knee arthroplasty using tranexamic acid. J Arthroplasty. 2014;29:182–185. doi:10.1016/j.arth.2014.03.047.
[8] Smit KM, Naudie DDR, Ralley FE, Berta DM, Howard JL. One dose of tranexamic acid is safe and effective in revision knee arthroplasty. J Arthroplasty. 2013;28:112–115. doi:10.1016/j.arth.2013.05.036.
[9] Wu YG, Zeng Y, Yang TM, Si HB, Cao F, Shen B. The efficacy and safety of combination of intravenous and topical tranexamic acid in revision hip arthroplasty: a randomized, controlled trial. J Arthroplasty. 2016;31:2548–2553. doi:10.1016/j.arth.2016.03.059.

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# QUESTION 7: Does the use of tranexamic acid (TXA) reduce the incidence of surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures?

RECOMMENDATION: The administration of TXA potentially reduces the incidence of SSI and/or PJI following total joint arthroplasty (TJA) by limiting postoperative anemia and the need for allogeneic blood transfusion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 5%, Abstain: 6% (Super Majority, Strong Consensus)

## RATIONALE

Allogeneic blood transfusions are associated with an immunomodulating effect on the host. The immunomodulation properties of allogeneic blood was recognized in 1970s when patients undergoing renal transplant had a better survival if they had received an allogeneic blood transfusion prior to transplantation [1]. By extrapolation one would expect a higher rate of infection in patients who receive allogeneic blood transfusion. A clear link between allogeneic transfusions and infection following primary TJA has not been demonstrated. There are conflicting findings amongst various studies [2–5].

The published studies do, however, support a connection between preoperative anemia and the increased risk of SSI and PJI after TJA [6–8]. Although the literature demonstrates preoperative anemia as a risk factor for allogeneic blood transfusion, we are uncertain about the root cause of the association between anemia and infection [9]. The increased infection risk in patients with preoperative anemia could be related to higher rate of allogeneic transfusion in this cohort and may be many other factors. It is also possible that preoperative anemia could be a marker of poor host status. However, no literature is available to support a relationship between postoperative anemia and an increased risk of SSI or PJI. It remains uncertain whether a patient with a normal preoperative hemoglobin concentration who experiences postoperative anemia without receiving a transfusion is at an increased risk of SSI or PJI.

Although no studies exist directly linking the use of TXA with a reduction in SSI or PJI after TJA, it is well-established the use of TXA reduces the risk of blood loss and the need for allogeneic blood transfusion. Based on the potential links between allogeneic transfusions or anemia with infection, we extrapolate that any method of blood sparing could assist with reducing the incidence of SSI and PJI.

## REFERENCES


[1] Opelz G, Sengar DP, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. Transplant Proc. 1973;5:253–259.

[2] Friedman R, Homering M, Holberg G, Berkowitz SD. Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. J Bone Joint Surg Am. 2014;96:272–278. doi:10.2106/JBJS.L.01268.

[3] Frisch NB, Wessell NM, Charters MA, Yu S, Jeffries JJ, Silverton CD. Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplasty. 2014;29:189–192. doi:10.1016/j.arth.2014.03.048.

[4] Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty–day complication rates. J Bone Joint Surg Am. 2014;96:1945–1951. doi:10.2106/JBJS.N.00077.

[5] Newman ET, Watters TS, Lewis JS, Jennings JM, Wellman SS, Attarian DE, et al. Impact of perioperative allogeneic and autologous blood transfusion on acute wound infection following total knee and total hip arthroplasty. J Bone Joint Surg Am. 2014;96:279–284. doi:10.2106/JBJS.L.01041.

[6] Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, et al. Patient–related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am. 2012;94:794–800. doi:10.2106/JBJS.K.00072.

[7] Greenky M, Gandhi K, Pulido L, Restrepo C, Parvizi J. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res. 2012;470:2695–2701. doi:10.1007/s11999–012–2435–z.

[8] Viola J, Gomez MM, Restrepo C, Maltenfort MG, Parvizi J. Preoperative anemia increases postoperative complications and mortality following total joint arthroplasty. J Arthroplasty. 2015;30:846–848. doi:10.1016/j.arth.2014.12.026.

[9] Maempel JF, Wickramasinghe NR, Clement ND, Brenkel IJ, Walmsley PJ. The pre–operative levels of haemoglobin in the blood can be used to predict the risk of allogenic blood transfusion after total knee arthroplasty. Bone Joint J. 2016;98–B:490–497. doi:10.1302/0301–620X.98B4.36245.