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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.

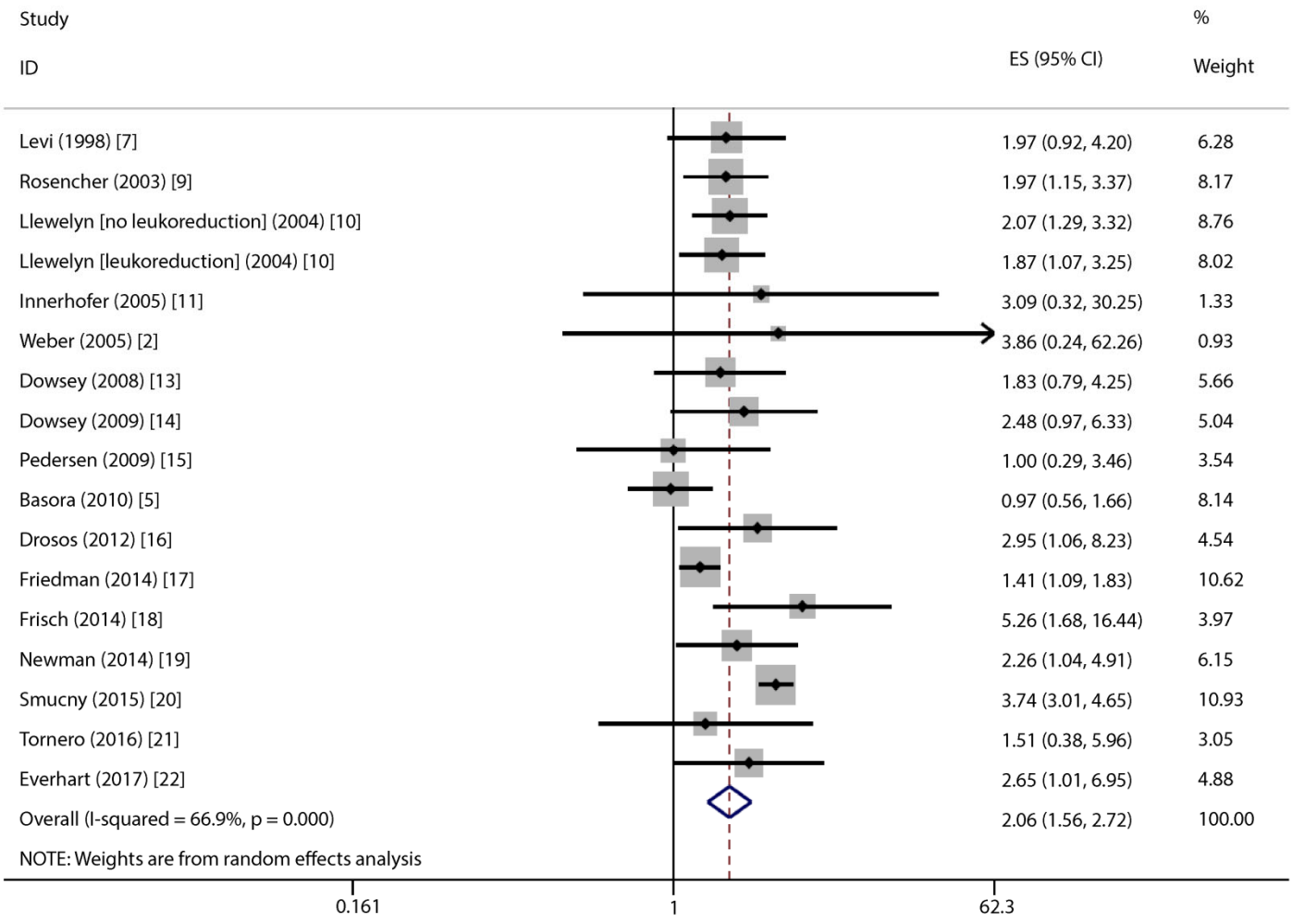

FIGURE 1. Forest plot comparing allogeneic transfusion to no transfusion. (CI, confidence interval; ES, effect size).

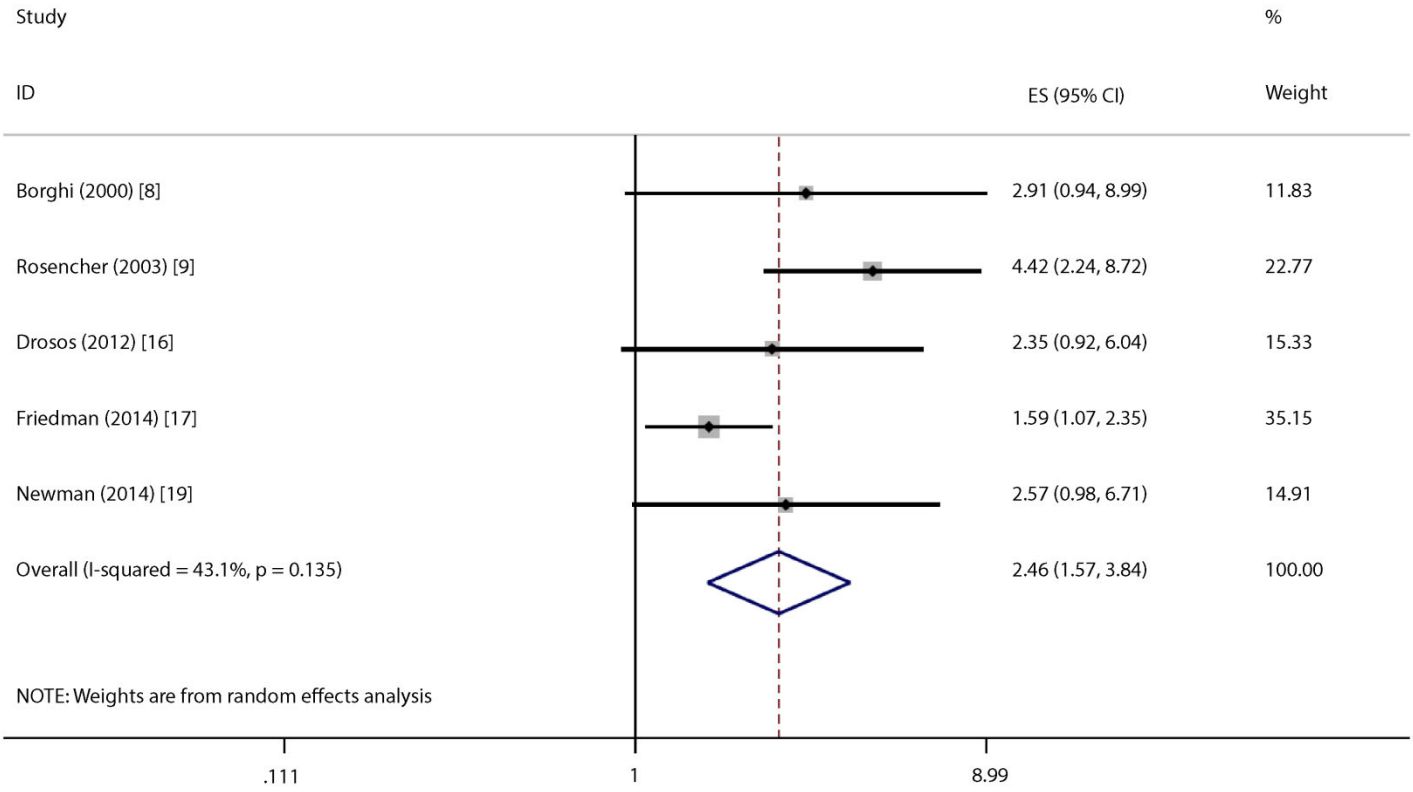

FIGURE 2. Forest plot comparing allogeneic transfusion to autologous transfusion. (CI, confidence interval; ES, effect size).

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