



Efficacy and safety of vancomycin versus 13 alternatives in MRSA-confirmed skin and soft tissue infections: a meta-analysis of 39 randomized controlled trials

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Abstract

Purpose Vancomycin is the standard therapy for suspected or confirmed Methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infection (SSTI). Although newer anti-MRSA agents claim improved efficacy and safety, evidence in microbiologically confirmed MRSA-SSTI remains limited and heterogenous. Thus, this study aimed to systematically compare the efficacy and safety of alternative agents versus vancomycin in adults with confirmed MRSA-SSTI.

Methods Three databases were searched until August 05, 2025, to retrieve randomized controlled trials (RCTs) from published meta-analyses evaluating vancomycin versus alternatives involving patients with MRSA-confirmed SSTI. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated using random-effects model. The study is registered in PROSPERO (CRD420251119756).

Results From 28 meta-analyses, 39 RCTs ($n = 20,285$; 2,662 patients with MRSA-confirmed SSTI receiving alternative agents and 2,322 receiving vancomycin) were included. No significant difference in clinical success was observed between groups (RR: 1.012, 95% CI: 0.992–1.032; prediction interval: 0.994–1.030). Although alternatives showed modestly higher microbiological success (RR: 1.058, 95% CI 1.001–1.119; prediction interval: 0.895–1.250), the effect lost significance after publication bias adjustment. Alternative agents had significantly lower dermatologic but higher gastrointestinal and hematological risk. Tigecycline had higher adverse events (RR: 1.090, 95% CI: 1.019–1.166), and telavancin had higher drug discontinuation (RR: 1.405, 95% CI: 1.105–1.786).

Conclusion Despite the growth of newer anti-MRSA agents, vancomycin remains clinically comparable for MRSA-confirmed SSTI, with apparent microbiological advantages of alternatives tempered by potential publication bias. Varying safety and pharmacological profiles of these agents emphasize the importance of individualized treatment selection.

Keywords MRSA · SSTI · Vancomycin · Meta-analysis · Adverse event

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a predominant cause of skin and soft tissue infections (SSTIs) worldwide, contributing substantially to hospitalizations, prolonged therapy, and healthcare costs [1]. These infections range from localized abscesses and cellulitis to severe invasive manifestations such as deep tissue infections and necrotizing fasciitis. The pathogen's capacity for resistance, biofilm formation, and toxin production complicates treatment, particularly in severe or deep-seated infections [2].

Vancomycin has been the standard therapy for MRSA infections for decades due to its reliable bactericidal activity and clinical experience [3, 4]. However, its limitations,

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including slow bacterial killing and pharmacokinetic variability, reduced tissue penetration into abscesses and soft tissue compartments, nephrotoxicity, and emerging strains with elevated vancomycin minimum inhibitory concentrations (MIC “creep”), have raised concerns regarding its continued adequacy as a first-line therapy [4, 5]. Over the decades, several anti-MRSA agents, including linezolid, daptomycin, ceftaroline, lipoglycopeptides (telavancin, dalbavancin, oritavancin), and tigecycline—have been approved as potential alternatives to vancomycin. These newer agents demonstrate improved pharmacokinetics, enhanced tissue distribution, biofilm activity, more favorable safety profiles, and more convenient dosing regimens, potentially offering clinical advantages in SSTI management [3, 4]. Nonetheless, despite vancomycin’s narrow therapeutic index and the need for therapeutic drug monitoring, the adoption of AUC-guided dosing has improved exposure optimization and reduced nephrotoxicity while maintaining efficacy [6].

In this evolving therapeutic landscape, the current position of vancomycin against newer anti-MRSA agents in the management of MRSA-confirmed SSTIs remains uncertain. To establish an evidence-based hierarchy of efficacy and safety, comparative data should be derived from high-quality randomized controlled trials (RCTs) involving microbiologically confirmed MRSA cases, standardized clinical outcomes, and appropriate use of vancomycin as the definitive comparator. Moreover, existing evidence remains fragmented and inconsistent, as most systematic reviews and meta-analyses (SR-MA) have pooled heterogeneous study designs, included mixed-pathogen or empirically treated SSTIs, focused on limited interventions, and rarely assessed the impact of risk of bias or publication bias on pooled estimates, thereby limiting the reliability of their conclusions [7–9]. Without addressing these limitations, it remains unclear whether alternative agents truly provide a therapeutic advantage over vancomycin in confirmed MRSA infections.

Given these uncertainties, we conducted a comprehensive meta-analysis of RCTs identified from previously published SR-MAs to compare the efficacy and safety of vancomycin with alternative anti-MRSA agents in adult patients with microbiologically confirmed MRSA-SSTI, including assessing the influence of risk of bias and publication bias.

Materials and methods

Study design

We performed a systematic review and meta-analysis of individual RCTs involving confirmed MRSA cases in adult patients. Eligible RCTs were identified through previously published SR-MA. This re-analysis was performed at the

individual trial level using pre-defined inclusion criteria and outcome definitions. We reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Supplementary Table S1). The protocol is registered in PROSPERO (CRD420251119756).

Search strategy and study selection

PubMed, Embase, and Web of Science were searched until August 05, 2025, to identify eligible SR-MA evaluating vancomycin compared with other interventions for confirmed or suspected MRSA infections. The search strategy is detailed in Supplementary Table S2. Individual RCTs were subsequently identified by screening the trials included within the eligible SR-MA, and only those meeting the predefined eligibility criteria were included in the present meta-analysis. To enhance completeness, we manually checked the reference lists of these eligible RCTs and performed hand searching to identify additional relevant articles that may not have been captured within the included SR-MAs. Following consensus, two authors independently screened and selected the pooled studies, resolving any disagreements through discussion.

Eligibility criteria

Eligibility was assessed at two levels: (1) the SR-MA level for study identification and (2) the individual RCT level for quantitative synthesis. This approach was chosen to ensure comprehensive identification of relevant RCTs while minimizing duplication and inconsistency across multiple overlapping primary literature searches.

For the SR-MA, we included studies that compared vancomycin with other interventions for treating MRSA-confirmed or suspected infections. Studies with mixed comparators were excluded; however, adjunctive therapies targeting gram-negative or anaerobic bacteria (e.g., aztreonam) alongside vancomycin were permitted.

For the RCTs, we included those that met the following criteria:

1. **Population:** Adult patients with MRSA-confirmed SSTIs (complicated SSTI, complicated skin and skin structure infections, or acute bacterial skin and skin structure infections including cellulitis/erysipelas, wound infections, and major cutaneous abscesses)
2. **Intervention:** The treatment group received at least one antibiotic.
3. **Comparator:** Vancomycin (adjunctive therapies targeting gram-negative or anaerobic bacteria were permitted), if vancomycin was used in more than 75% of MRSA confirmed patients as a standard therapy, then the study was included in the analysis

4. **Outcome:** The primary outcomes were clinical success (resolution or improvement in clinical signs and symptoms without the need for further antibacterial therapy) and microbiological success (elimination or presumed eradication of MRSA isolates) at the test-of-cure visit, typically 7–14 days after end of therapy in microbiologically evaluable population with MRSA infections. Secondary outcomes included any adverse events, drug-related adverse events, serious adverse events, drug-related serious events, drug discontinuation due to adverse events, drug discontinuation due to drug-related adverse events, all-cause mortality, and organ-specific adverse events.

Data collection and extraction

After reaching a consensus on the extraction items, two authors independently extracted the data. Discrepancies were addressed through discussion with a third reviewer if necessary. Data extracted from SR-MA included the first author's name, publication year, publication type, total number of studies, funding, infection type, intervention, and comparator. Data extracted from eligible RCTs pooled from the eligible SR-MA included the first author, publication year, location, infection type, intervention and comparator, trial number, funding, age, sample size, MIC₉₀ values, efficacy outcomes (clinical and/or microbiological success), and adverse events.

If a test-of-cure visit was not specified, we extracted data in the following order: follow-up visit, end-of-study, or end-of-treatment evaluation conducted 5–30 days after the end of therapy. Additionally, if data for the microbiologically evaluable population were not available, data from clinically evaluable populations were sought, including per-protocol, modified, or microbial intention-to-treat populations having MRSA confirmed data. These exceptions were made due to variations in the outcome measures among individual studies per anti-MRSA interventions.

Risk of bias assessment

Two reviewers independently evaluated the methodological quality of SR-MA using the 'A MeaSurement Tool to Assess systematic Reviews' (AMSTAR2) tool. Similarly, RCTs were appraised using the revised Cochrane risk of bias tool for randomized trials (RoB 2).

Statistical analysis

Meta-analyses were conducted using the random-effects model in R Statistical Software (v4.5.1). For dichotomous efficacy and safety outcomes, the pooled results were

expressed as risk ratios (RR) with 95% confidence interval (CI). A fixed-effect model was applied when the included studies evaluated the same intervention using comparable study designs. Statistical significance was defined as $P < 0.05$. Between-study heterogeneity was assessed using τ^2 and I^2 and interpreted using 95% prediction intervals from random-effects models to estimate the expected range of treatment effect across future comparable studies. Sub-group analyses were performed for all outcomes based on the intervention type, with additional exploratory sub-group analyses conducted according to SSTI severity. For meta-analysis including more than ten studies, potential publication bias was evaluated using funnel plot asymmetry and Egger's regression test. When asymmetry was suspected or detected, the Duval and Tweedie trim-and-fill method (inverse-variance model) was applied to estimate the adjusted pooled effect after imputing potentially missing studies. Sensitivity analyses were conducted using the leave-one-out method and by stratifying studies at different levels of risk of bias to evaluate the robustness of the pooled results. Exploratory benefit–risk quadrant analyses were conducted by plotting pooled RRs for efficacy outcomes against RRs for selected safety outcomes that demonstrated statistically significant differences, to visually illustrate efficacy–safety trade-offs relative to vancomycin.

Certainty of the evidence assessment

The quality of evidence for each meta-analysis was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, considering risk of bias, consistency, directness, precision, and publication bias.

Results

Study identification and selection

This study involved 28 SR-MA with a total of 157 unique studies targeting MRSA suspected or confirmed infections. After applying eligibility criteria, we screened 50 unique publications, of which 34 that had efficacy data on MRSA confirmed SSTI patient were included. References screening of the 50 publications added two unique publications, thus, in total 39 RCTs from 36 publications were included in the meta-analysis. Figure 1 illustrates the PRISMA flow diagram. Supplementary Table S3 list excluded articles, along with the reasons for exclusion for SR-MA and RCTs, respectively.

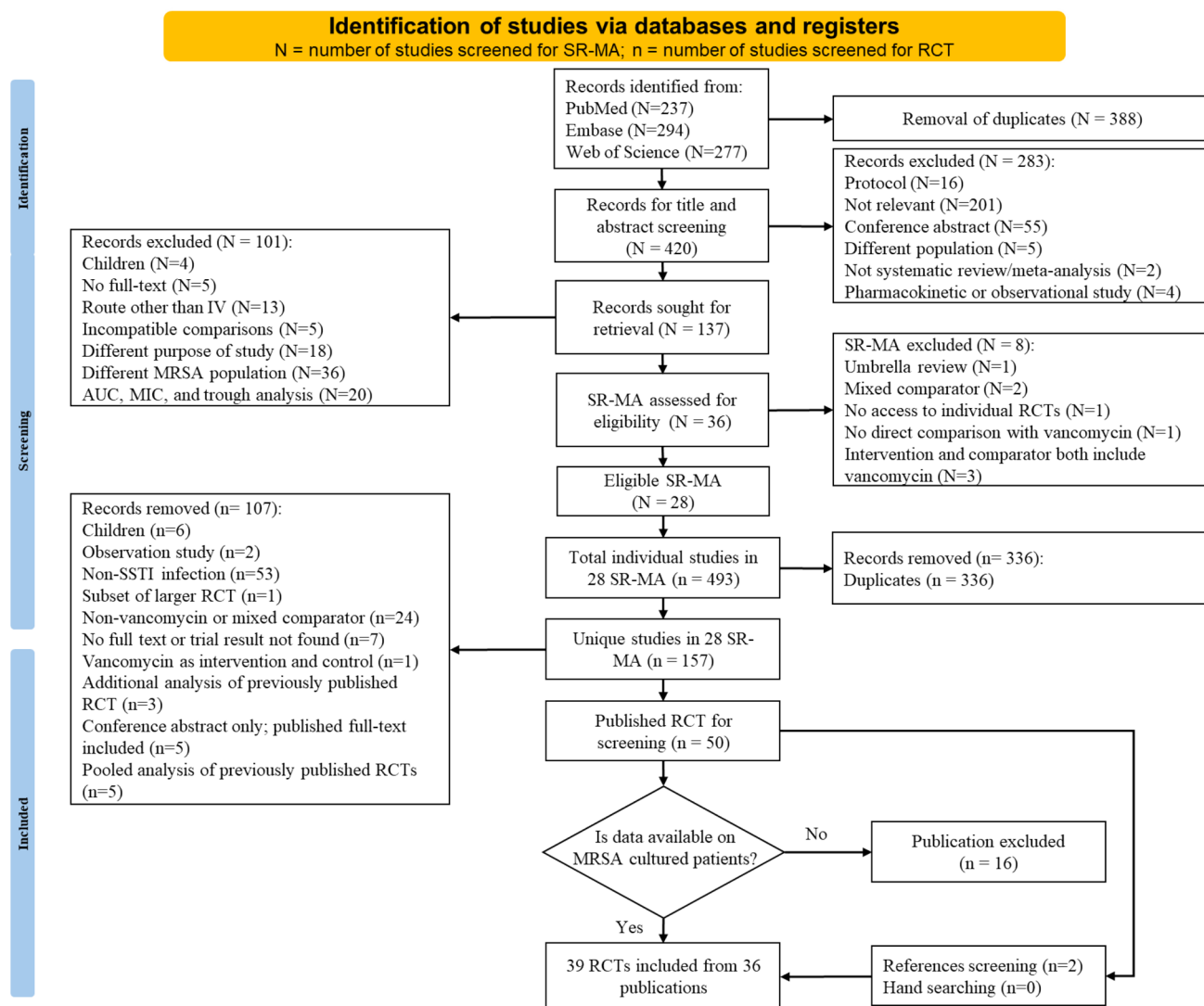


Fig. 1 PRISMA flowchart. IV, intravenous; SR-MA, systematic review and/or meta-analysis; RCT, randomized controlled trial

Characteristics of included studies

Of the 28 included SR-MAs published between 2009 and 2025, only one conducted a GRADE assessment and six had pre-registered protocols (Supplementary Table S4). The RCTs, published between 1996 and 2021, compared vancomycin with BC-3781 (Lefamulin, $n = 1$) [10], cefilavancin (TD-1792, $n = 1$) [11], ceftaroline ($n = 4$) [12–15], ceftobiprole ($n = 3$) [16–18], dalbavancin ($n = 2$) [19], daptomycin ($n = 4$) [20–23], delafloxacin ($n = 3$) [24–26], Iclaprim ($n = 3$) [27–29], linezolid ($n = 7$) [24, 30–35], oritavancin ($n = 2$) [36, 37], quinupristin/dalfopristin ($n = 2$) [38], telavancin ($n = 4$) [39–41], and tigecycline ($n = 4$) [42–45] (Table 1). One RCTs compared vancomycin with both linezolid and delafloxacin [24]. The total sample size was 10,647 in the intervention groups and 9,638 in the vancomycin groups,

with 2,662 and 2,322 microbiologically confirmed MRSA cases, respectively. MIC_{90} values for MRSA were reported in only 55% of the studies for both treatment groups. Several alternative agents exhibited MIC_{90} values ranging from 0.06 to 0.5 mg/L, lower than vancomycin, which was almost always 1 mg/L. Notably, weight-based vancomycin dosing was commonly utilized in recently published RCTs. Among the 39 included RCTs, 28 enrolled patients with complicated SSTI/SSSI, one enrolled uncomplicated SSSI, and 10 did not classified infections as complicated or uncomplicated.

Risk of bias in included studies

Supplementary Table S5 presents AMSTAR 2 ratings for the included SR-MA. The quality of the SR-MA was suboptimal, with 23 of the 28 rated as critically low and five as low.

Table 1 General characteristics of 39 randomized controlled trials from 36 publications

First author, year	Infection	Trial design	Study period	Clinical trial number	Location	Participants (Intervention/Vancomycin)		Dosage regimen		MIC ₉₀ , mg/L (range)		Therapy duration, days	Sponsor
						Sample size	MRSA sample	Mean age ± S.D., years	Intervention (+aztreonam)	Vancomycin (+aztreonam)	Intervention		
BC-3781													
Prince et al., 2013 [10]	ABSSSI (unSSSI)	Phase 2, DB	NI	NI	United States	141/66	66/39	41.9 ± 13.2/ 40.4 ± 13.7	100 or 150 mg IV q12h	1 g IV q12h	NI	NI	Nabriva Therapeutics AG
Ceflavancin													
Stryjewski et al., 2012 [11]	cSSSI	Phase 2, DB	NI	NCT00442832	United States	101/102	38/36	40.0 ± 11.2/ 40.0 ± 11.3	2 mg/kg IV q24h	1 g IV q12h	0.015 (0.008–0.015)	1 (0.5–1.0)	Theravance, Inc
Ceftaroline													
Corey et al., 2010 [12]	cSSSI	Phase 3, DB	Feb–Nov 2007	CANVAS 1 NCT00424190	Multi-region	351/347	108/120	47.2 ± 17.0/ 49.2 ± 17.2	600 mg IV q12h	1 g (+1 g) IV q12h	1	1	Forest Laboratories, Inc
Dryden et al., 2016 [13]	cSSTI	Phase 3, DB	May 2012–Jun 2014	COVERS NCT01499277	Multi-region	506/255	25/15	52.6 ± 16.5/ 53.6 ± 16.3	600 mg IV q8h	15 mg/kg IV q12h (+1 g IV q8h)	0.5	1	AstraZeneca
Talbot et al., 2007 [14]	cSSSI	Phase 2, OB	NI	NI	Multi-region	67/32	6/6	41.6/44.0	600 mg IV q12h	1 g IV q12h (± 1 g IV q8h)	NI	NI	Cerexa, Inc
Wilcox et al., 2010 [15]	cSSSI	Phase 3, DB	NI	CANVAS 2 NCT00423657	Multi-region	348/346	86/71	47.8 ± 17.0/ 47.5 ± 16.1	600 mg IV q12h	1 g (+1 g) IV q12h	0.5	1	Forest Laboratories, Inc
Ceftobiprole													
Noel et al., 2008 [16]	cSSSI	DB	Oct 2004–Dec 2005	NI	Multi-region	397/387	90/87	48.0 ± 16.1/ 46.7 ± 16.3	500 mg IV q12h	1 g IV q12h	2 (0.5–2)	1 (0.5–2)	Johnson & Johnson
Noel et al., 2008a [17]	cSSSI	Phase 3, DB	Sep 2005–Oct 2006	NCT00210899	Multi-region	547/281	160/90	52.9 ± 15.5/ 51.9 ± 15.65	500 mg IV every 8 h	1 g IV q12h (+1 g IV q8h) ^b	NI	NI	Johnson & Johnson

Table 1 (continued)

First author, year	Infection	Trial design	Study period	Clinical trial number	Location	Participants (Intervention/Vanco-mycin)			Dosage regimen		MIC ₉₀ , mg/L (range)	Therapy duration, days	Sponsor
						Sample size	MRSA sample	Mean age ± S.D, years	Intervention (+aztreonam)	Vanco-mycin (+aztreonam)			
Overcash et al., 2021 [18]	ABSSSI (cSSSI)	Phase 3, DB	Feb 2018–Feb 2019	TARGET NCT03137173	Multi-region	335/344	82/73	*51 (18–89)/50 (20–87)	500 mg IV q8h	1 g or 15 mg/kg (+1 g) IV q12h	1	5–14	Basilea Pharmaceutica International Ltd
Dalbavancin													
Boucher et al., 2014 [19]	ABSSSI	DB	2011–2012	DISCOVER 1 NCT01339091, DISCOVER 2 NCT01431339	Multi-region	659/653	74/50	48.9/50.3	1 g IV on day 1 → 500 mg IV on day 8	1 g or 15 mg/kg q12h	0.06	1	Durata Therapeutics
Daptomycin													
Aikawa et al., 2013 [20]	SSTI	Phase 3, OL	2008–2010	NCT00770341	Multi-region	88/22	55/19	*69 (22–92)/70 (29–82)	4 mg/kg IV q24h	1 g IV q12h	0.5 (0.25–1)	1 (0.5–2)	Merck
Katz et al., 2008 [21]	cSSTI	Single blind	Feb–Sep 2007	NCT00426933	Multi-region	48/48	37/35	*44 (18–77)/41 (18–86)	10 mg/kg IV q24h	1 g IV q12h	NI	NI	Cubist Pharmaceuticals
Kauf et al., 2015 [22]	cSSSI	OL	Sep 2011–Oct 2012	NCT01419184	United states	118/106	39/27	47.2 ± 15.2/50.0 ± 13.5	4 mg/kg IV q24h	1 g IV q12h	NI	NI	Merck & Co., Inc
Pertel et al., 2009 [23]	cSSSI	Single blind	NI	NCT00295178	Multi-region	28/22	3/2	*54 (25–79)/48 (18–86)	4 mg/kg IV q24h	Standard of care	0.25 (0.12–0.5)	1 (0.5–1)	Cubist Pharmaceuticals
Delafloxacin													
Kingsley et al., 2016 [24]	ABSSSI	Phase 2, DB	NI	NCT01283581	United States	81/98	34/35	39.7 ± 14.3/44.8 ± 15.5	300 mg IV q12h	15 mg/kg IV q12h	0.12	0.5	Melinta Therapeutics
O’Riordan et al., 2018 [25]	ABSSSI	Phase 3, DB	May 2014–Jan 2016	NCT01984684	Multi-region	423/427	78/91	51.2 ± 15.9/50.2 ± 16.0	3*300 mg/d IV, then 450 mg PO q12h	15 mg/kg (+1–2 g) IV q12h	0.25	NI	Melinta Therapeutics
Pullman et al., 2017 [26]	ABSSSI	Phase 3, DB	Apr 2013–Jun 2014	NCT01811732	Multi-region	331/329	66/50	46.3 ± 13.9/45.3 ± 14.4	300 mg IV q12h	15 mg/kg (+2 g) IV q12h	0.25 (0.004–0.5)	NI	Melinta Therapeutics

Table 1 (continued)

First author, year	Infection	Trial design	Study period	Clinical trial number	Location	Participants (Intervention/Vanco-mycin)		Dosage regimen		MIC ₉₀ , mg/L (range)		Therapy duration, days	Sponsor
						Sample size	MRSA sample	Mean age ± S.D., years	Intervention (+aztreonam)	Vanco-mycin (+aztre-onam)	Interven-tion		
Iclaprim													
Holland et al., 2018 [28]	ABSSSI (cSSSI)	Phase 3, DB	Apr 2016-Aug 2017	REVIVE-2 NCT02607618	Multi-region	295/305	69/69	50.0 ± 15.6/ 50.8 ± 15.0	80 mg IV q12h	15 mg/kg IV q12h	0.5	1	Motif Bio-sciences plc
Huang, et al., 2018 [29]	ABSSSI (cSSSI)	Phase 3, DB	Apr 2016-Jan 2017	REVIVE-1 NCT02600611	Multi-region	298/300	73/61	46.4 ± 13.3/ 48.2 ± 14.8	80 mg IV q12h	15 mg/kg IV q12h	0.5	1	Motif Bio-sciences plc
Krievins et al., 2008 [27]	cSSSI	Phase 2, DB	NI	NI	Multi-region	62/30	4/1	49.7 ± 14.1 or 45.6 ± 14.3/ 43.5 ± 14.1	0.8 or 1.6 mg/ kg IV (30 min) q12h	1 g IV q12h	(≤0.06–1)	10	Arpida Ltd
Linezolid													
Itani et al., 2010 [30]	cSSTI	Phase 4, OL	Oct 2004-Jul 2007	NCT00087490	Multi-region	537/515	322/318	49.7/49.4	600 mg IV or PO q12h	15 mg/kg IV q12h	NI	NI	Pfizer Inc
Kingsley et al., 2016 [24]	ABSSSI	Phase 2, DB	Feb-Nov 2011	NCT01283581	United States	77/98	37/35	44.8 ± 14.9/ 44.8 ± 15.5	600 mg IV q12h	15 mg/kg IV q12h	2	0.5	Melinta Thera-peutics
Kohn et al., 2007 [31]	MRSA (cSSTI)	OL	Oct 2001-Jan 2004	NI	Japan	100/51	18/10	68.4 ± 16.4/ 67.5 ± 16.3	600 mg IV or PO q12h	1 g IV q12h	(0.5–2)	(0.5–1)	Pfizer Inc
Sharpe et al., 2005 [32]	MRSA- cSSTI	OL	NA	NI	Unites States	30/30	30/30	66/76	600 mg PO q12h	1 g IV q12h	NI	NI	Pfizer Inc
Stevens et al., 2002 [33]	MRSA	OL	Jul 1998-Jul 1999	NI	Multi-region	240/220	53/43	63.9 ± 16.1/ 59.8 ± 20.2	600 mg IV or PO q12h	1 g IV q12h	NI	NI	Pharmacia Corpora-tion
Weigelt et al., 2005 [34]	cSSTI	OL	Oct 2002-Mar 2003	NI	Multi-region	592/588	176/185	52.0 ± 18.0/ 52.0 ± 18.0	600 mg IV or PO q12h	1 g IV q12h	NI	NI	Pfizer Inc

Table 1 (continued)

First author, year	Infection	Trial design	Study period	Clinical trial number	Location	Participants (Intervention/Vanco-mycin)		Mean age ± S.D, years	Dosage regimen		MIC ₉₀ , mg/L (range)		Therapy duration, days	Sponsor
						Sample size	MRSA sample		Intervention (+aztreonam)	Vanco-mycin (+aztreonam)	Intervention	Vanco-mycin		
Wilcox et al., 2009 [35]	cSSSI	OL	May 2002–May 2005	NI	Multi-region	363/363	48/39	53.7 ± 18.1/ 53.8 ± 17.6	600 mg IV q12h	1 g IV q12h	2	1	7–28	Pfizer Inc
Oritavancin														
Corey et al., 2014 [36]	ABSSSI	Phase 3, DB	Jan 2011–Nov 2012	SOLO I NCT01252719	Multi-region	475/479	104/100	46.2 ± 14.20/ 44.3 ± 14.50	1200 mg (SD) IV → placebo q12h	1 g or 15 mg/kg q12h	NI	NI	7–10	Medicines Company
Corey et al., 2015 [37]	ABSSSI	Phase 3, DB	Jan 2011–Jun 2013	NCT01252732	Multi-region	503/502	100/101	45.0 ± 13.4/ 44.44 ± 14.3	1200 mg (SD) IV → placebo q12h	1 g or 15 mg/kg q12h	0.12	1	7–10	Medicines Company
Quinupristin/dalfopristin														
Nichols et al., 1999 [38]	cSSSI	Two phase III OL	Feb 1995–Apr 1996 & Jun 1995–Jul 1996	NI	Multi-region	289/273	9/6	55.3 ± 17.8/ 55.5 ± 17	7.5 mg/kg IV q24h	1 g IV q12h or 2 g q6h (oxacilin) or 1 g q8h (cefazolin)	NI	NI	3–14	Research grant from Rhone-Poulenc Rorer
Telavancin														
Stryjewski et al., 2005 [39]	cSSTI	Phase 2, DB	NI	FAST-1	Multi-region	84/83	22/26	44.6 ± 13.9/ 44.3 ± 13.5	7.5 mg/kg IV q24h	1 g IV q12h	0.25 (0.03–0.25)	1 (0.25–1)	4–14	Theravance, Inc
Stryjewski et al., 2006 [40]	cSSSI	Phase 2, DB	NI	FAST-2	Multi-region	100/95	26/19	44.7 ± 13.7/ 42.3 ± 10.9	10 mg/kg IV q24h	1 g IV q12h	0.25 (0.06–1.0)	1 (0.25–1)	4–14	Theravance, Inc
Stryjewski et al., 2008 [41]	cSSSI	Phase 3, DB	Jan 2005–Jun 2006	ATLAS 1 NCT00091819, ATLAS 2 NCT00107978	Multi-region	928/939	348/369	48.8 ± 16.6/ 48.7 ± 16.6	10 mg/kg IV q24h	1 g IV q12h	0.5 (0.12–1.0)	1 (0.5–2.0)	7–14	Theravance, Inc

Table 1 (continued)

First author, year	Infection	Trial design	Study period	Clinical trial number	Location	Participants (Intervention/Vancomycin)		Dosage regimen		MIC ₉₀ , mg/L (range)		Therapy duration, days	Sponsor
						Sample size	MRSA sample	Mean age ± S.D, years	Intervention (+aztreonam)	Vancomycin (+aztreonam)	Intervention		
Tigecycline													
Breidt et al., 2005 [42]	cSSSI	Phase 3, DB	Nov 2002–Dec 2003	NI	Multi-region	274/269	6/6	48.8 ± 17.0/ 50.1 ± 17.8	100 mg/day (SD) → 50 mg IV q12h	1 g (+2 g) IV q12h	0.25	2	Wyeth Research
Ellis-Grosse et al., 2005 [43]	cSSSI	Phase 3, DB	Aug 2001–Feb 2004	NI	Multi-region	422/411	32/33	48.5 ± 16.4/ 48.5 ± 17.2	100 mg/day (SD) → 50 mg IV q12h	1 g (+2 g) IV q12h	0.25	2	Wyeth Research
Florescu et al., 2008 [44]	MRSA (cSSSI)	Phase 3, DB	Nov 2003–Aug 2005	NCT00079976	Multi-region	117/39	117/39	^a 51/51	100 mg/day (SD) → 50 mg IV q12h	1 g IV q12h	(0.12–0.5)	NI	Wyeth
Sachidanand et al., 2005 [45]	cSSSI	Phase 3, DB	NI	NI	Multi-region	292/281	21/21	49.4 ± 15.4/ 48.4 ± 16.6	100 mg/day (SD) → 50 mg IV q12h	1 g (+2 g) IV q12h	0.25	1 (1–4) (0.12–1)	Wyeth

SD standard deviation, NI no information, DB double blind, OB observer blinded, OL open label, IV intravenous, PO oral; mg milligram, g gram, kg kilogram, L liter, MRSA methicillin-resistant *Staphylococcus aureus*, ABSSSI acute bacterial skin and skin structure infection, unSSSI uncomplicated skin and skin structure infection, cSSSI complicated skin and skin structure infection, SSSI skin and skin structure infection, cSSSTI complicated skin and soft tissue infection, SSSTI skin and soft tissue infection, SD single dose

q6h means every 6 h, q8h means every 8 h, q12h means every 12 h, q24h means every 24 h

^aMedian (range)

^bceftazidime

^cgentamicin

The risk of bias assessment for the published RCTs is shown in Supplementary Figure S1. Seventeen of 36 publications were rated as of high methodological quality. Twenty-five studies adopted a double-blind design, while two used a single-blind design. Funding information was reported for 35 publications, all sponsored by the pharmaceutical industry.

Clinical success in MRSA-induced SSTI

For clinical cure, data were available for 12 different interventions compared with vancomycin across 32 RCTs involving patients with MRSA-induced SSTI [10–22, 24–33, 35–37, 39–41, 44]. In total, 88.93% ($n=1,728/1,943$) of patients infected with MRSA-SSTI treated with alternative agents achieved clinical success, compared with 86.02% ($n=1,421/1,652$) in the vancomycin group. The pooled

analysis showed no significant difference in clinical success between interventions and vancomycin (RR: 1.012, 95% CI: 0.992–1.032), with the prediction interval (95% CI: 0.994–1.030) and subgroup analyses also indicating no significant differences across intervention type (Fig. 2a).

Leave-one-out sensitivity analysis demonstrated that removal of individual studies did not alter the overall effect estimate, indicating good stability of the findings (Supplementary Figure S2). When stratified by study quality, meta-analyses restricted to trials with low or high risk of bias showed no significant difference between groups, whereas inclusion of studies rated as having some concerns yielded a higher clinical success rate with linezolid compared with vancomycin (Supplementary Figure S3). Assessment of publication bias showed no evidence of funnel plot asymmetry, and Egger's regression test was non-significant ($p=0.390$)

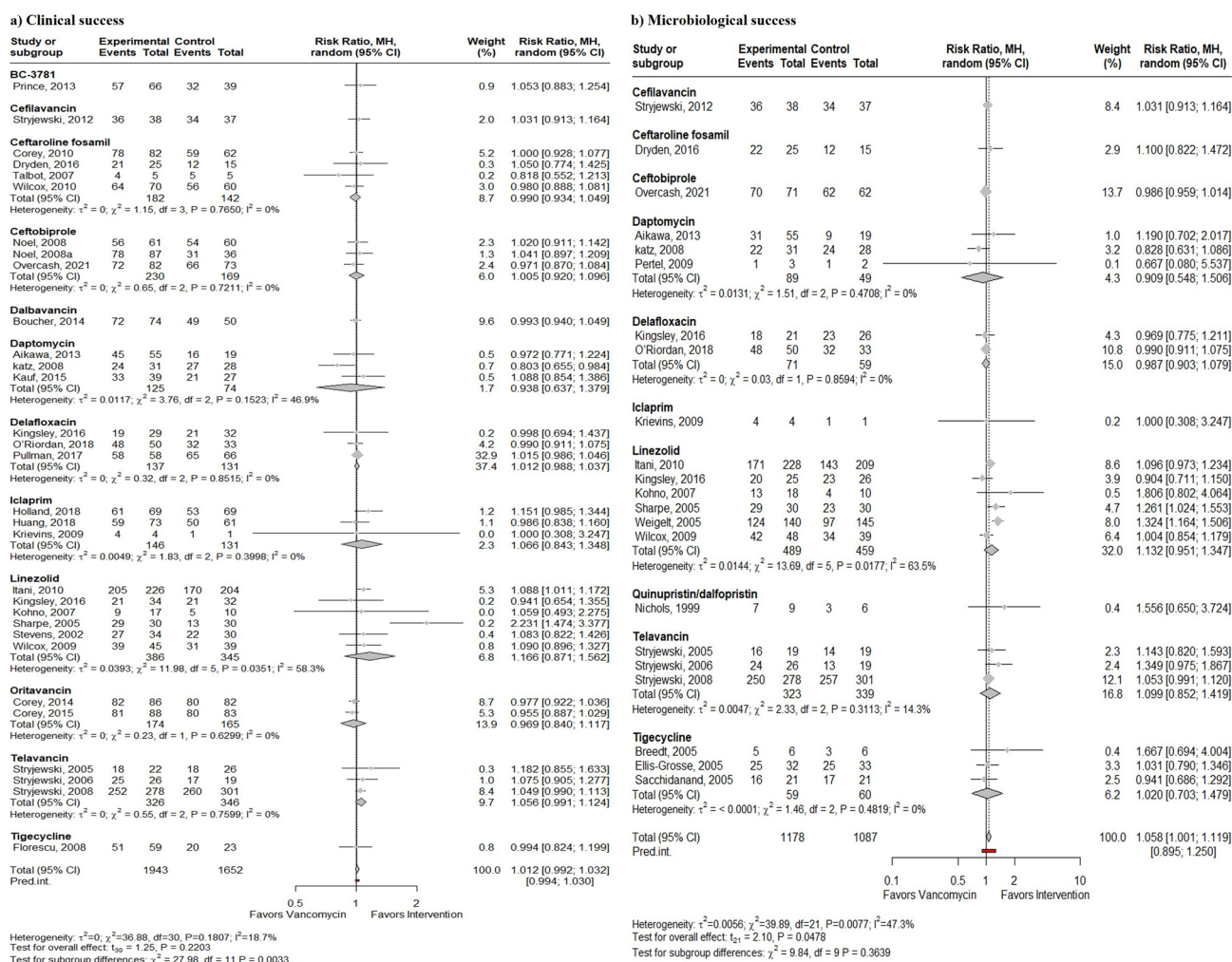


Fig. 2 Forest plot showing meta-analysis of clinical and microbiological success of vancomycin versus alternative agents in microbiologically confirmed MRSA-SSTI. **a** Clinical success between vancomycin and alternative agents. **b** Microbiological success between

vancomycin and alternative agents. CI, confidence interval; MRSA, Methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infections

(Supplementary Figure S4). After adjustment using the Duval and Tweedie trim-and-fill method, four studies were imputed, yet the pooled estimate remained non-significant (Supplementary Figure S5). Exploratory subgroup analyses by SSTI severity showed no significant differences between interventions and vancomycin (Supplementary Figure S6).

Microbiological success in MRSA-induced SSTI

Data on microbiological success were available for 10 interventions compared with vancomycin across 23 RCTs involving patients with MRSA-induced SSTI [11, 13, 18, 20, 21, 23–25, 27, 30–32, 34, 35, 38–43, 45]. Overall, 84.38% ($n=994/1,178$) of patients infected with MRSA-SSTI treated with alternative agents achieved microbiological success, compared with 78.56% ($n=854/1,087$) treated with vancomycin. Pooled analysis demonstrated higher microbiological success with alternative agents (RR: 1.058, 95% CI: 1.001–1.119), with prediction interval (95% CI: 0.895–1.250), while subgroup analyses indicated no significant differences among the interventions type (Fig. 2b).

Leave-one-out sensitivity analysis indicated that the overall effect lost statistical significance upon exclusion of certain studies. (Supplementary Figure S7). When stratified by risk of bias, no significant differences were observed among studies with low or high risk, while inclusion of studies with “some concerns” introduced a significant effect (Supplementary Figure S8). Examination of funnel plot asymmetry and Egger’s regression test ($p=0.046$) indicated potential small-study effects (Supplementary Figure S4). After adjustment using the Duval and Tweedie trim-and-fill method, five studies were imputed, and the adjusted pooled estimate became non-significant (Supplementary Figure S9). In exploratory subgroup analyses by SSTI severity, alternative agents demonstrated a modestly higher rate of microbiological eradication than vancomycin among patients with complicated SSTIs (RR: 1.081, 95% CI: 1.012–1.156; Supplementary Figure S10).

Adverse events

Among the interventions, the risk for any adverse events was higher for tigecycline (RR: 1.090, 95% CI: 1.019–1.166), while telavancin had higher risk for drug discontinuation due to adverse events (RR: 1.405, 95% CI: 1.105–1.786) (Fig. 3). There was no significant difference between intervention and vancomycin for the drug-related adverse event, drug discontinuation due to drug-related adverse event, serious adverse event, drug-related serious adverse event, and all-cause mortality (Supplementary Figures S11–S15). Supplementary Figure S16 illustrates the publication bias of safety outcomes. A summary of the meta-analysis results for all

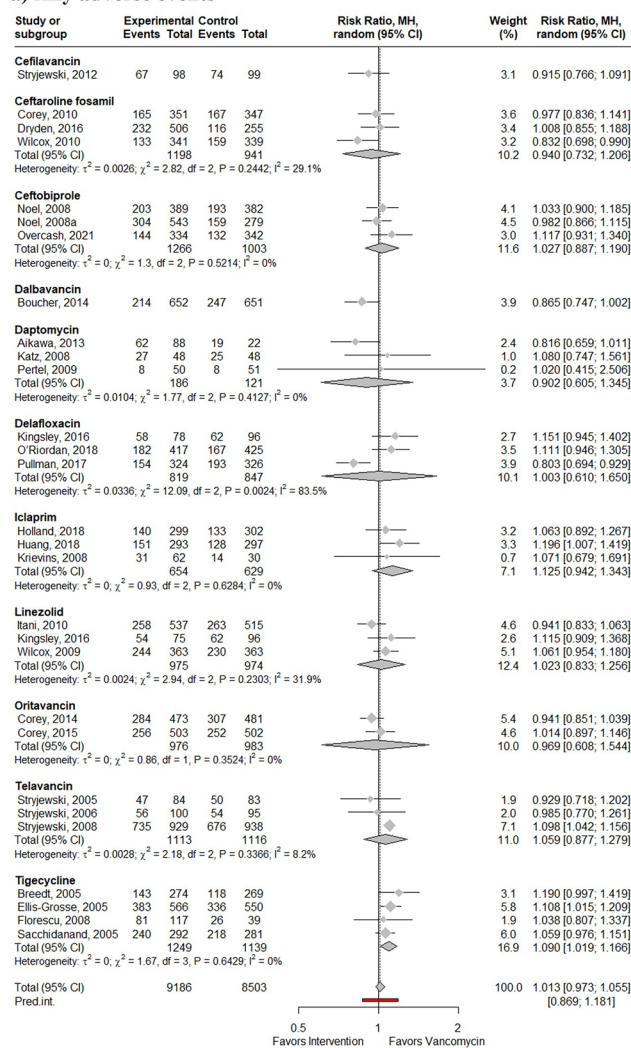
organ-specific adverse events across the different treatment regimens is presented in Fig. 4.

Skin and subcutaneous tissue disorders

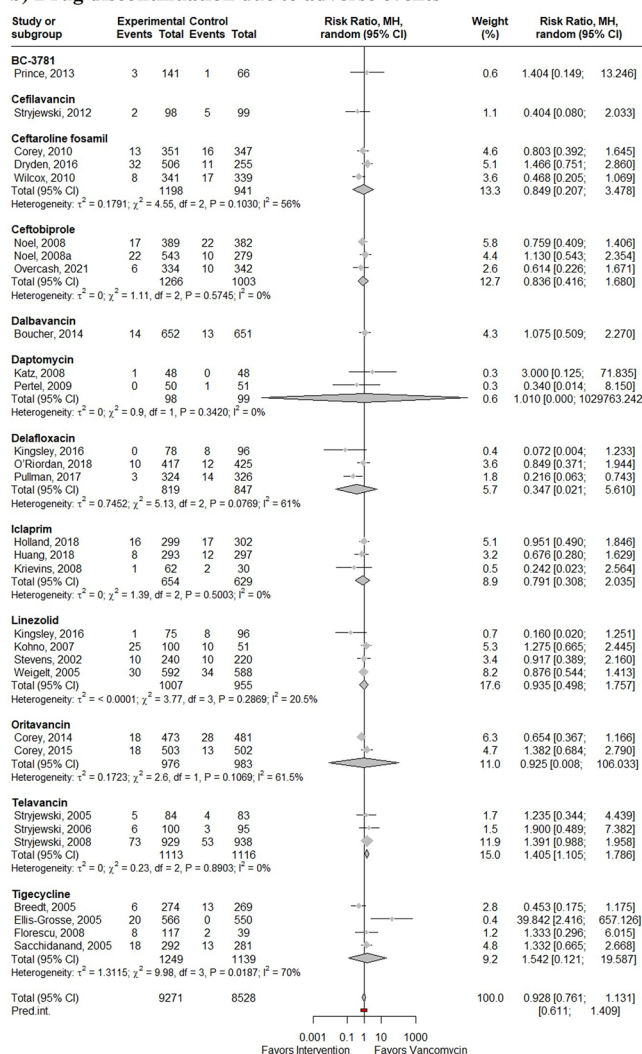
Daptomycin was associated with a lower risk of erythema than vancomycin (RR: 0.109, 95% CI: 0.014–0.824) (Supplementary Figure S17). The overall pooled effect favored intervention, showing a lower risk than vancomycin for pruritus (RR: 0.448, 95% CI: 0.376–0.533; prediction interval 0.370–0.543), with no significant difference among intervention subgroups (Supplementary Figure S18). Similarly, alternative agents had lower risk for rash (RR: 0.597, 95% CI: 0.415–0.857; prediction interval 0.267–1.331), with tigecycline (RR: 0.334, 95% CI: 0.283–0.394) showing significantly lower risk than vancomycin among interventions (Supplementary Figure S19). No significant difference was observed for generalized pruritus and infusion/injection site extravasation (Supplementary Figures S20 and S21).

Gastrointestinal disorders

Overall, intervention had a higher risk for diarrhea (RR: 1.435, 95% CI: 1.161–1.774; prediction interval 0.718–2.870), with ceftobiprole (RR: 1.309, 95% CI: 1.137–1.506), delafloxacin (RR: 2.643, 95% CI: 1.632–4.280), linezolid (RR: 2.323, 95% CI: 1.446–3.732), and tigecycline (RR: 1.647, 95% CI: 1.029–2.637) demonstrating significantly higher risk than vancomycin across interventions (Supplementary Figure S22). Interestingly, tigecycline has higher risk than vancomycin for anorexia (RR: 7.499, 95% CI: 2.660–1.140) and dyspepsia (RR: 3.579, 95% CI: 1.793–7.146) (Supplementary Figures S23 and S24). Alternative agents also had higher risk for dysgeusia (RR: 6.041, 95% CI: 1.792–20.363), with ceftobiprole showing significantly higher risk than vancomycin among interventions (RR: 14.853, 95% CI: 12.016–18.360) (Supplementary Figure S25). Furthermore, interventions were associated with higher risk for nausea (RR: 1.625, 95% CI: 1.336–1.978; prediction interval 0.636–4.153), with ceftobiprole (RR: 1.731, 95% CI: 1.269–2.360), linezolid (RR: 2.001, 95% CI: 1.536–2.606), telavancin (RR: 1.754, 95% CI: 1.214–2.533), and tigecycline (RR: 4.020, 95% CI: 2.977–5.430) showing a significantly higher risk than vancomycin among alternatives (Supplementary Figure S26). Additionally, alternative interventions showed significantly higher risk for vomiting (RR: 1.634, 95% CI: 1.274–2.096; prediction interval 0.576–4.637), and among them, telavancin (RR: 1.838, 95% CI: 1.271–2.659) and tigecycline (RR: 5.383, 95% CI: 5.334–5.432) had significantly higher risk than vancomycin (Supplementary Figure S27). No significant difference in abdominal pain and constipation was

a) Any adverse events

Heterogeneity: $\tau^2 = 0.0052$; $\chi^2 = 54.17$, $df = 28$, $P = 0.0021$; $I^2 = 48.3\%$
 Test for overall effect: $I_{95} = 0.66$, $P = 0.5122$
 Test for subgroup differences: $\chi^2 = 26.18$, $df = 10$, $P = 0.0035$

b) Drug discontinuation due to adverse events

Heterogeneity: $\tau^2 = 0.0341$; $\chi^2 = 41.57$, $df = 29$, $P = 0.0614$; $I^2 = 30.2\%$
 Test for overall effect: $I_{95} = -0.78$, $P = 0.4444$
 Test for subgroup differences: $\chi^2 = 25.04$, $df = 11$, $P = 0.0090$

Fig. 3 Forest plot showing meta-analysis of adverse events and drug discontinuation between vancomycin versus alternative agents. **a** Any adverse events. Tigecycline was associated with higher risk for adverse events compared to vancomycin. **b** Drug discontinuation due

to adverse events. Telavancin had a higher risk for drug discontinuation due to adverse events compared to vancomycin. CI, confidence interval

found between vancomycin and alternatives (Supplementary Figures S28 and S29).

Nervous system and psychiatric disorders

Tigecycline had a significantly higher risk for headache (RR: 1.285, 95% CI: 1.126–1.468) compared to that of vancomycin (Supplementary Figure S30). There were no significant differences in experiencing dizziness or insomnia between vancomycin and alternatives (Supplementary Figures S31 and S32).

Laboratory abnormalities

Overall, interventions had higher risk for thrombocytopenia than vancomycin (RR: 3.523, 95% CI: 1.150–10.794; prediction interval 0.372–33.339) (Supplementary Figure S33). Tigecycline showed a significantly lower risk for anemia (95% CI: 0.486, 95% CI: 0.400–0.591) and elevating both alanine transaminase (RR: 0.221, 95% CI: 0.149–0.329) and aspartate transaminase (RR: 0.330, 95% CI: 0.198–0.550) enzymes than vancomycin (Supplementary Figures S34–S36). No significant differences were observed in the incidence of hypokalemia, elevation of creatine phosphokinase

level, leucopenia, and renal dysfunction between vancomycin and alternatives (Supplementary Figures S37–S40).

Cardiovascular and general systemic disorders

Tigecycline had lower risk than vancomycin for hypertension (RR: 0.545, 95% CI: 0.430–0.691) and pyrexia (RR: 0.484, 95% CI: 0.302–0.776) (Supplementary Figures S41 and S42). No significant differences between vancomycin and alternatives were observed for the incidence of abscess limb and chills (Supplementary Figures S43 and S44).

Benefit-risk quadrant analyses

Efficacy–safety trade-offs across alternative anti-MRSA agents relative to vancomycin were illustrated using exploratory benefit–risk quadrant analyses, complementing the meta-analysis findings. Cefilavancin appeared in the quadrant representing higher efficacy and lower risk of any adverse events and adverse events leading to drug discontinuation based on pooled estimates compared with vancomycin (Fig. 5); however, this finding was derived from a single RCT (Fig. 2 and 3). Corresponding analyses for other outcomes are shown in Supplementary Figures S45–S49.

Certainty of evidence using GRADE

In adult patients with confirmed MRSA, the certainty of evidence assessed using GRADE for the pooled primary and secondary outcomes comparing vancomycin with alternative treatments was predominantly rated as moderate or low, downgraded mainly due to risk of bias, particularly in studies involving linezolid and daptomycin, and smaller MRSA subsets (Table 2). Details of the GRADE assessment for all pre-specified sub-group analysis of primary and secondary outcomes are presented in Supplementary Table S6.

Discussion

This comprehensive meta-analysis, integrating data from 39 RCTs across 36 publications and 28 previously published SR-MA, represents one of the largest comparative syntheses assessing 13 anti-MRSA therapies versus vancomycin in microbiologically confirmed MRSA SSTI.

Vancomycin has long been the standard treatment for both suspected or confirmed MRSA-related SSTI, alongside teicoplanin, with linezolid, daptomycin, and telavancin strongly recommended as alternatives [3, 4]. The lack of clinical superiority for any intervention in our analysis, despite several alternative agents showing lower MIC₉₀ values relative to vancomycin, including subgroup and sensitivity analysis, reinforces the continued relevance of current

guideline recommendations. Although recent evidence have suggested possible advantages of linezolid or daptomycin in MRSA-related infections [7–9, 46], our findings, limited to microbiologically confirmed MRSA SSTI, suggest that earlier conclusions may have been confounded by study design heterogeneity, inclusion of mixed-pathogen infections, or empirically treated populations.

Interestingly, in risk-of-bias-stratified analyses, higher clinical success with linezolid was observed in studies rated with “some concerns” of bias, which were mostly open-label and industry-funded. This underscores how methodological quality and funding sources can distort comparative efficacy. Industry-funded open label trials have been shown to report more favorable efficacy outcomes, potentially due to selective outcome reporting, comparator dosing strategies, or trial design optimization [47, 48]. Moreover, in some included RCTs, the MIC₉₀ values for linezolid were higher than those of vancomycin [24, 35]. Importantly, differences in clinical success between vancomycin and alternative agents remained non-significant even after adjustment for publication bias, and the prediction intervals were narrow and centered around null value, strengthening confidence in vancomycin’s therapeutic equivalence. While newer agents showed slightly higher pooled microbiological eradication rates, particularly in industry funded trials rated with “some concerns”, this effect was inconsistent in sensitivity analysis and lost significance after publication bias correction. Furthermore, the wide prediction interval crossing the null value suggests that the apparent microbiological advantage is not consistently reproducible and likely reflects small-study effects or selective reporting in smaller, industry-funded trials rather than true pharmacodynamic superiority in MRSA-SSTIs.

Safety profiles varied substantially across interventions, making tolerability a crucial factor in clinical decision-making. Consistent with prior findings [46], our analysis demonstrated that alternative agents were associated with a lower risk of dermatologic reactions, but a higher incidence of gastrointestinal adverse events and thrombocytopenia, compared with vancomycin. The lower incidence of pruritus and rash among alternative agents may reflect reduced histamine release and cytokine-mediated hypersensitivity reactions compared with vancomycin, which is known to trigger “red man syndrome” via non-IgE-mediated histamine release, particularly during rapid infusion [49].

Conversely, the higher rates of gastrointestinal disturbances with newer agents are mechanistically consistent with their pharmacologic classes. The increased risk of dysgeusia with ceftobiprole may be linked to the release of diacetyl, a flavoring agent, during conversion of its prodrug to active compound [50]. Tigecycline, a glycycline derivative of minocycline, is well recognized for its high incidence of gastrointestinal intolerance due to activation of gut motilin

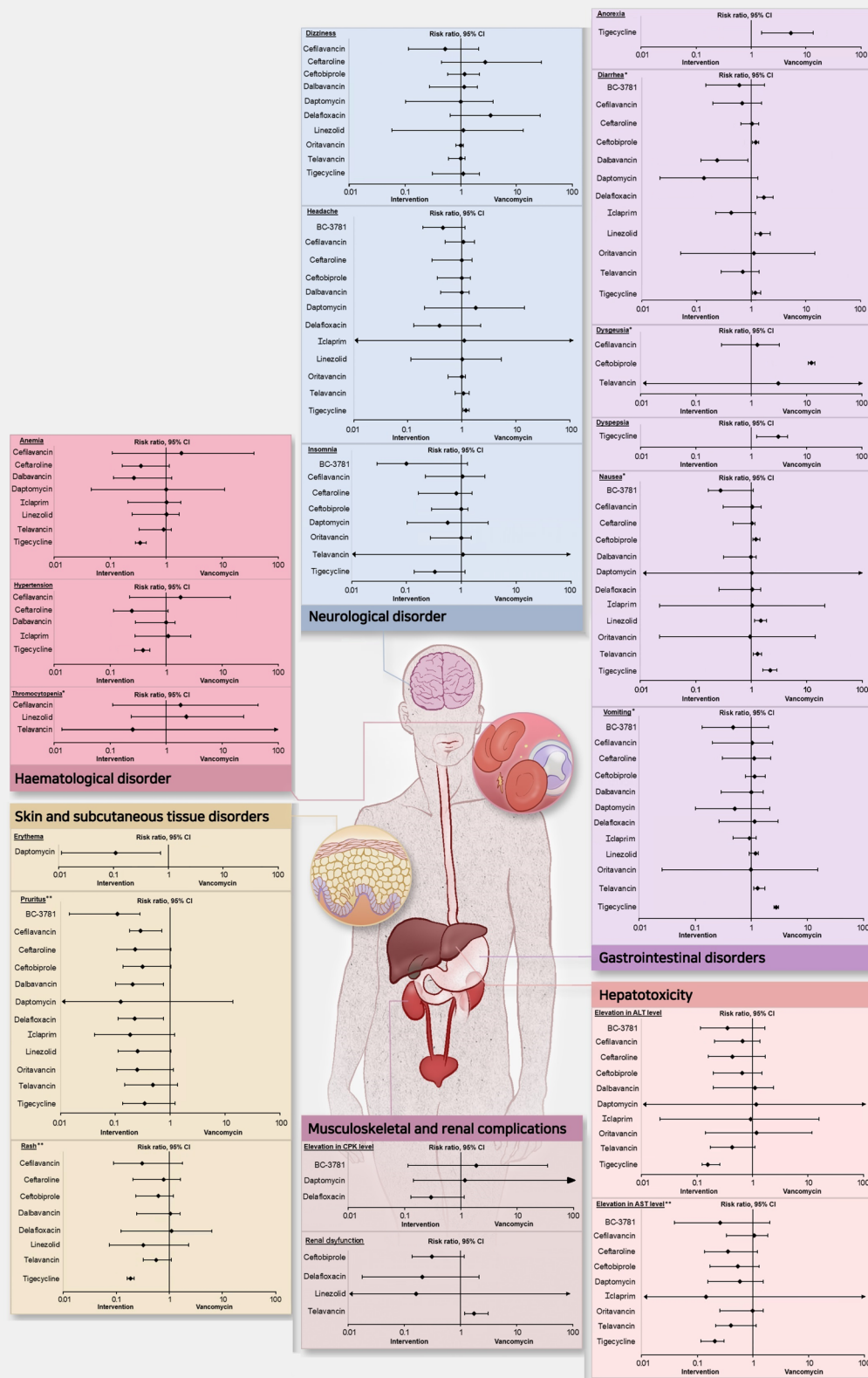


Fig. 4 Summary of meta-analysis results for organ-specific safety outcomes. An asterisk (*) indicates that the pooled estimate showed a higher risk of specific adverse events for interventions compared with vancomycin, while double asterisk (**) indicates a lower risk for alternative agents compared with vancomycin. ALT, alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase; CI, confidence interval

receptors and local mucosal irritation [51]; consistent with our findings of increased diarrhea, nausea, vomiting, anorexia, and dyspepsia. Despite its broad-spectrum activity and excellent tissue penetration, tigecycline exhibited a consistently higher overall adverse event burden, limiting its routine clinical use. However, its lower risk of rash, anemia, hypertension, and hepatic enzyme elevation indicates potential suitability for patients with glycopeptide hypersensitivity, cardiovascular instability, anemia, or hepatic impairment.

Although pooled analysis indicated a higher overall risk of thrombocytopenia with alternative agents, subgroup analysis did not show significant differences among intervention. Linezolid, an oxazolidinone, is known to induce thrombocytopenia during prolonged use [8]. Non-significant signal likely reflects the short treatment durations of linezolid in the included trials. Nonetheless, clinicians should remain alert for hematologic toxicity during oxazolidinone therapy. Telavancin, while offering once-daily dosing convenience, showed higher discontinuation and renal event rates, restricting its use in patients with renal impairment. Given its nephrotoxic potential [41], baseline renal assessment and regular monitoring of renal function during therapy are essential. Furthermore, the lack of a significant difference in renal events between alternative agents and vancomycin may be explained by the relatively short treatment duration in SSTIs compared with pneumonia or bloodstream infections, where prolonged or high-exposure therapy increases renal risk [52]. These findings suggest that, in short-course SSTI treatment, vancomycin does not confer a higher risk of nephrotoxicity than alternative agents when contemporary dosing and monitoring practices are applied. The increasing adoption of AUC-guided vancomycin dosing likely contributed to mitigating nephrotoxicity by optimizing drug exposure while minimizing renal toxicity [6]. Understanding these risk–benefit trade-offs is crucial for optimizing therapy, particularly in elderly or comorbid patients where adverse event profiles may influence adherence, healthcare costs, and overall quality of life.

This study has some limitations. First, approximately 32% of RCTs ($n = 16/50$) existing in the literature did not stratify efficacy outcomes (either clinical or microbiological success) by microbially confirmed MRSA-SSTI, resulting

in their exclusion, particularly important anti-MRSA agent like teicoplanin from our analysis. Second, MIC_{90} data were inconsistently reported for MRSA-SSTI and not available at the individual patient level, preventing analysis of the relationship between antimicrobial susceptibility and clinical or microbiological outcomes. Furthermore, nearly all trials were industry funded. Although trial-level risk-of-bias assessments and publication-bias adjustments did not suggest material inflation of treatment effects, the potential influence of sponsorship-related design and reporting biases cannot be fully excluded, emphasizing the need for independent, high-quality head-to-head trials using standardized MRSA definitions, uniform outcome measures, and pharmacokinetic-guided dosing. Additionally, although we provided scatter plots distributing the efficacy and safety value with CI for each intervention, for the individualization of treatment selection, ranking of safety events using network meta-analysis could address this limitation. Finally, our approach for identifying primary studies relied on previously published SR-MA instead of performing an extensive review of the primary literature. Although every effort was made to ensure completeness, including reference screening of all RCTs and manual searches for recent publications, some studies may still have been missed. Such omissions could influence pooled estimates if missing studies differed systematically by drug class or study size. Nonetheless, sensitivity analyses, prediction intervals, and publication-bias adjustments suggest that any such impact is unlikely to materially alter the overall conclusion.

Conclusions

In this meta-analysis of RCTs identified from existing SR-MAs, vancomycin remains comparable in clinical efficacy to newer anti-MRSA agents for SSTI, with some alternatives showing marginal microbiological advantages that diminish after bias correction. Safety profiles vary significantly across drug classes, emphasizing the need for individualized therapy guided by patient characteristics, infection severity, and risk factors. Importantly, no significant difference in nephrotoxicity risk was observed between vancomycin and alternative agents among SSTI patients. In the era of AUC-guided vancomycin dosing and antimicrobial stewardship initiatives, optimizing rather than replacing vancomycin, a widely accessible and cost-effective therapy, represents the most rational strategy for improving outcomes while minimizing toxicity and resistance.

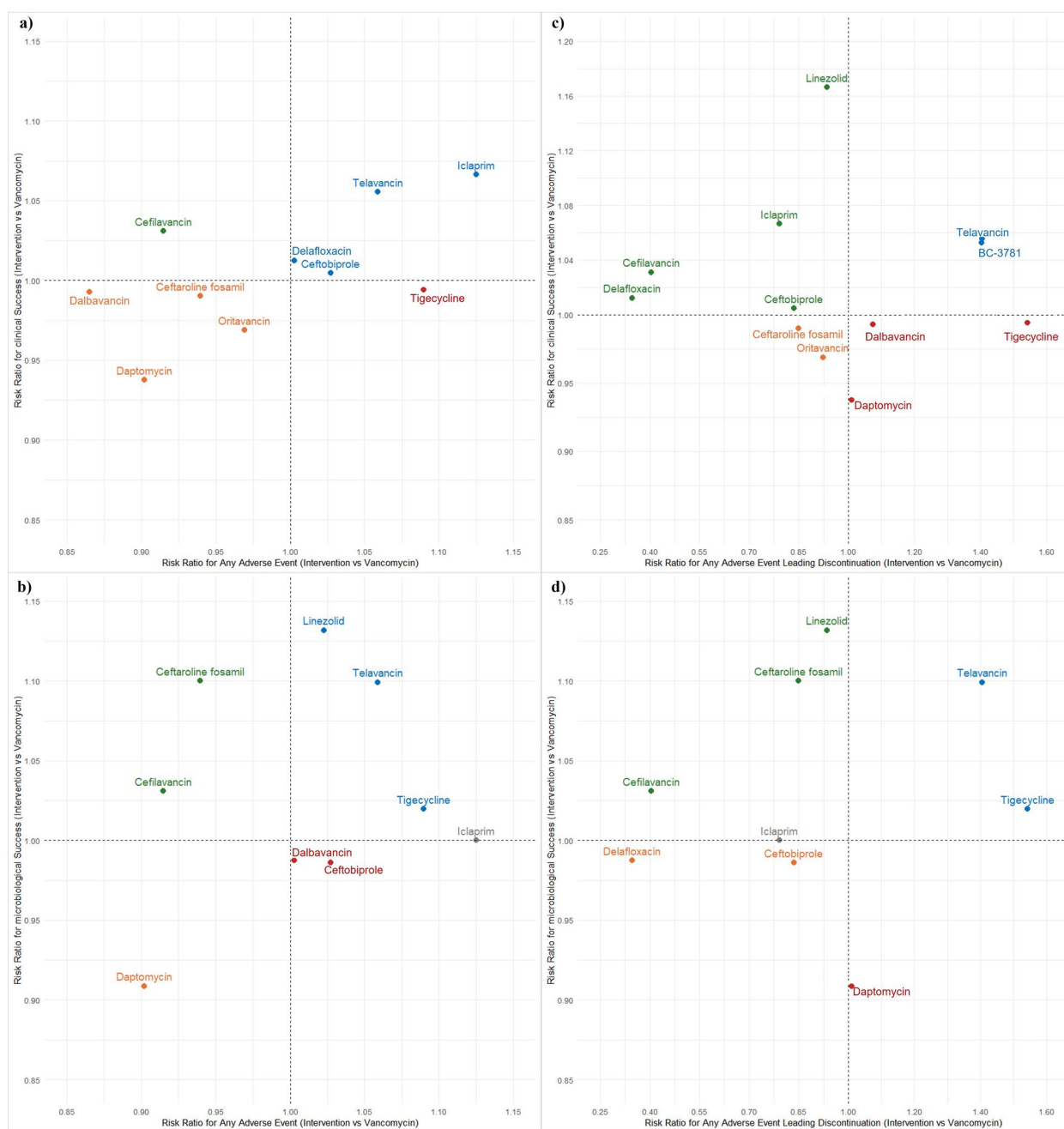


Fig. 5 Benefit–risk quadrant analysis illustrating efficacy outcomes plotted against any adverse events and adverse events leading to treatment discontinuation for alternative anti-MRSA agents relative to vancomycin. **a** Clinical success versus any adverse events, **b** microbiological success versus any adverse events, **c** clinical success versus adverse events leading to drug discontinuation, and **d** microbiological success versus adverse events leading to drug discontinuation. Each point represents the pooled risk ratio of an individual agent compared with vancomycin. Agents are classified into four

color-coded quadrants based on relative efficacy and safety profiles: blue indicates higher efficacy with higher risk of safety events, green indicates higher efficacy with lower risk of safety events, orange indicates lower efficacy with lower risk of safety events, and red indicates lower efficacy with higher risk of safety events. Grey-colored agents had effect estimates close to the null value, indicating borderline or neutral effects relative to vancomycin. The quadrants provide a visual, descriptive comparison of efficacy–safety trade-offs and do not imply formal ranking or indirect comparisons among agents

Table 2 GRADE summary findings table for primary and secondary outcomes

Outcomes	Number of participants (publication)	Risk ratio (95% CI)	Anticipated absolute effects		Certainty of the evidence (GRADE)
			Risk with vancomycin	Risk with interventions (95% CI)	
Primary outcome					
Clinical success	3595 (31)	1.012 (0.992–1.032)	860 per 1000	870 per 1000 (853–888)	⊕ ⊕ ⊕ ○ Moderate ^a
Microbiological success	2265 (22)	1.058 (1.001–1.119)	786 per 1000	831 per 1000 (786–879)	⊕ ⊕ ○ ○ Low ^{a,c}
Secondary outcomes					
AE	17,689 (29)	1.013 (0.973–1.055)	540 per 1000	547 per 1000 (525–569)	⊕ ⊕ ⊕ ○ Moderate ^a
Drug-related AE	12,975 (23)	0.985 (0.902–1.075)	239 per 1000	235 per 1000 (215–257)	⊕ ⊕ ⊕ ○ Moderate ^a
Drug discontinuation due to AE	17,799 (30)	0.928 (0.761–1.131)	42 per 1000	39 per 1000 (32–48)	⊕ ⊕ ⊕ ○ Moderate ^a
Drug discontinuation due to drug-related AE	3130 (5)	0.963 (0.371–2.498)	25 per 1000	24 per 1000 (9–63)	⊕ ⊕ ○ ○ Low ^{a,d}
Serious AE	14,279 (27)	0.991 (0.865–1.135)	56 per 1000	56 per 1000 (49–64)	⊕ ⊕ ○ ○ Low ^{a,c}
Drug-related serious AE	5701 (8)	0.812 (0.434–1.518)	9 per 1000	8 per 1000 (4–14)	⊕ ⊕ ○ ○ Low ^{a,d}
All-cause mortality	16,738 (23)	1.096 (0.855–1.403)	13 per 1000	15 per 1000 (12–19)	⊕ ⊕ ⊕ ○ Moderate ^a
Erythema	206 (2)	0.109 (0.014–0.824)*	58 per 1000	6 per 1000 (1–47)	⊕ ○ ○ ○ Very low ^{a,d,e}
Pruritus	12,387 (20)	0.448 (0.376–0.533)	61 per 1000	27 per 1000 (23–52)	⊕ ⊕ ⊕ ○ Moderate ^a
Rash	10,535 (14)	0.597 (0.415–0.857)	34 per 1000	20 per 1000 (14–29)	⊕ ⊕ ⊕ ○ Moderate ^a
Infusion/Injection site extravasation	4052 (5)	0.922 (0.586–1.451)	49 per 1000	45 per 1000 (28–71)	⊕ ⊕ ⊕ ⊕ High
Generalized pruritus	4487 (5)	0.615 (0.343–1.105)	36 per 1000	22 per 1000 (12–40)	⊕ ⊕ ⊕ ⊕ High
Diarrhea	18,485 (27)	1.435 (1.161–1.774)	43 per 1000	62 per 1000 (50–76)	⊕ ⊕ ⊕ ○ Moderate ^a
Anorexia	1689 (2)	7.499 (2.660–21.140)*	5 per 1000	36 per 1000 (13–102)	⊕ ⊕ ○ ○ Low ^{d,e}
Dyspepsia	1689 (2)	3.579 (1.793–7.146)*	12 per 1000	43 per 1000 (22–86)	⊕ ⊕ ○ ○ Low ^{d,e}
Dysgeusia	3706 (5)	6.041 (1.792–20.363)	37 per 1000	221 per 1000 (66–746)	⊕ ⊕ ⊕ ○ Moderate ^d
Nausea	19,434 (31)	1.625 (1.336–1.978)	74 per 1000	120 per 1000 (98–146)	⊕ ⊕ ○ ○ Low ^{a,b}
Vomiting	17,200 (26)	1.634 (1.274–2.096)	37 per 1000	60 per 1000 (47–78)	⊕ ⊕ ○ ○ Low ^{a,b}
Abdominal pain	4636 (6)	0.919 (0.323–2.612)	24 per 1000	22 per 1000 (9–63)	⊕ ⊕ ○ ○ Low ^{a,d}
Constipation	11,735 (18)	0.831 (0.650–1.061)	43 per 1000	36 per 1000 (28–46)	⊕ ⊕ ○ ○ Low ^{a,e}
Headache	17,845 (26)	1.098 (0.955–1.262)	56 per 1000	61 per 1000 (53–70)	⊕ ⊕ ⊕ ○ Moderate ^a
Dizziness	8988 (12)	1.215 (0.984–1.502)	28 per 1000	34 per 1000 (28–42)	⊕ ⊕ ⊕ ○ Moderate ^a
Insomnia	6742 (10)	0.991(0.755–1.302)	53 per 1000	52 per 1000 (40–69)	⊕ ⊕ ⊕ ○ Moderate ^a
Thrombocytopenia	4457 (8)	3.523 (1.150–10.794)	6 per 1000	22 per 1000 (7–66)	⊕ ⊕ ○ ○ Low ^{a,d}
Increase in ALT level	10,345 (16)	0.688 (0.447–1.059)	33 per 1000	23 per 1000 (15–35)	⊕ ⊕ ○ ○ Low ^{a,b}
Increase in AST level	7947 (13)	0.641 (0.427–0.964)	34 per 1000	22 per 1000 (14–33)	⊕ ⊕ ⊕ ○ Moderate ^a
Anemia	8069 (14)	0.772 (0.589–1.011)	34 per 1000	26 per 1000 (20–34)	⊕ ⊕ ⊕ ○ Moderate ^a
Hypokalemia	4111 (7)	1.099 (0.543–2.227)	19 per 1000	21 per 1000 (10–43)	⊕ ⊕ ○ ○ Low ^{a,d}
CPK increase	1305 (5)	1.135 (0.222–5.813)	21 per 1000	23 per 1000 (5–120)	⊕ ⊕ ○ ○ Low ^{a,d}
Leucopenia	2575 (6)	1.042 (0.442–2.460)	12 per 1000	12 per 1000 (5–29)	⊕ ⊕ ○ ○ Low ^{a,d}
Renal dysfunction	4216 (5)	0.562 (0.126–2.517)	18 per 1000	10 per 1000 (2–46)	⊕ ○ ○ ○ Very low ^{a,b,d}
Hypertension	5094 (7)	0.670 (0.428–1.048)	32 per 1000	21 per 1000 (14–33)	⊕ ⊕ ⊕ ⊕ High
Pyrexia	9353 (13)	0.836 (0.655–1.067)	35 per 1000	29 per 1000 (23–37)	⊕ ⊕ ⊕ ⊕ High
Abscess limb	3804 (6)	1.189 (0.397–3.562)	16 per 1000	19 per 1000 (6–56)	⊕ ○ ○ ○ Very low ^{a,b,d}
Chills	5482 (6)	1.568 (0.966–2.543)	18 per 1000	28 per 1000 (17–45)	⊕ ⊕ ⊕ ○ Moderate ^d

AE adverse event, ALT alanine transaminase, AST aspartate aminotransferase, CPK creatine phosphokinase, CI confidence interval, GRADE grading of recommendations, assessment, development, and evaluation

Table 2 (continued)

An asterisk (*) denotes that a fixed-effect model was applied, since the included studies assessed the same intervention with comparable study designs

^aRisk of bias

^bInconsistency

^cIndirectness

^dImprecision

^ePublication bias

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s15010-026-02745-7>.

Authors' contributions S.P. and E.K. conceptualized and designed the study. S.P. conducted the literature search, reviewed the literature, extracted data, performed data analysis and interpretation, and writing (original draft, review and editing). Y.E. contributed to data extraction and revised the draft. E.K. revised the manuscript critically for important intellectual content and provided resources. All authors contributed to the final version of the manuscript and approved its submission.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Not applicable. This study is a systematic review and meta-analysis of previously published data and did not involve any direct interaction with human participants or access to individual-level patient data.

Consent to participate Not applicable. No new data were collected from human participants for this study.

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