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Efficacy and safety of optional parenteral antimicrobial therapy for complicated skin and soft tissue infections

A systematic review and Bayesian network meta-analysis

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Abstract

Background: Skin and soft tissue infections (SSTIs) carry significant economic burden, as well as morbidity and mortality, especially when caused by methicillin-resistant *Staphylococcus aureus*. This study aims to investigate the efficacy and safety of optional antimicrobial therapy for the treatment of complicated SSTIs (cSSTIs).

Methods: We searched PubMed, Medline (Via Ovid SP), Embase (Via Ovid SP), and the Cochrane Central Register of Controlled Trials from their inception to March 22, 2021 for randomized controlled trials (RCTs) that studied the use of optional antimicrobial therapy for cSSTIs. Citations' screening, study selection, data extraction, and risk of bias assessment were independently performed by 2 authors. The primary outcomes were clinical and microbiological treatment success, and adverse events (AEs) were also assessed.

Results: A total of 48 trials covering 24,381 patients assessing 20 types of antimicrobial treatment modalities were included. Overall, omadacycline was associated with the highest beneficial effect on clinical and microbiological treatment success and with the largest rank probability based on surface under the cumulative ranking curve values, avarofloxacin was closely followed. Both had, however, omadacycline was related to moderately safety profiles. Lefamulin ranked as the best option was associated with the lowest risk of severe AEs. Subgroup analysis showed similar results. The quality of primary outcomes was moderate to low.

Conclusions: The use of omadacycline was associated with higher rates of clinical and microbiological treatment success for the treatment of cSSTIs, with a relative low risk of AEs. Due to the limitations of the included RCTs, high-quality and well-designed RCTs are needed to further confirm the results.

Abbreviations: AEs = adverse events, CI = confidence interval, cSSTIs = complicated SSTIs, GRADE = Grading of Recommendation, Assessment, Development and Evaluation, ITT = intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, NMA = network meta-analysis, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomized controlled trials, SSTIs = skin and soft tissue infections, SUCRA = surface under the cumulative ranking curve.

Keywords: efficacy, meta-analysis, omadacycline, safety, skin and soft tissue infections, systematic review

1. Introduction

Skin and soft tissue infections (SSTIs) are a common reason for patients in-hospital treatment and mainly carry a high cost of hospitalization with more than 14 million outpatient visits a year, relate to a significant economic burden.[1–3] Currently diagnostics technologies limit pathogen isolation in SSTIs and influence host range differences and geographic factors, making physicians have difficulty in selecting the empiric antimicrobial therapy.[4–6] SSTIs that require complex management such as surgical procedures, or that accompany the setting of significant comorbidities are widely regarded as complicated SSTIs (cSSTIs).[5,7,8] In 2013, the US Food and Drug Administration released a new definition related to skin infections in terms of acute bacterial skin and skin structure infections. These infections contain cellulitis, erysipelas, major skin abscesses,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are publicly available.

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wound infections with a minimum lesion surface area of 75 cm^2 and are accompanied by signs of systemic inflammation or significant medical comorbidities. Oral antibiotic therapy for uncomplicated SSTIs with a higher rate of treatment success, however, cSSTIs typically need intravenous antibiotic therapy. Additionally, This has led to increased abuse of vancomycin and increased the risk of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[9,10] Therefore, there has been an emergence of newer antibiotics to meet the challenge of the potential increase in morbidity and mortality from multidrug resistant Gram-positive SSTIs.[11]

Vancomycin, linezolid, and daptomycin are the most common antibiotics for the treatment of cSSTIs, but there is still lack of evidence on their comparative clinical effectiveness. Recently approved newer antibiotics for the treatment of cSSTIs, such as oritavancin, dalbavancin, and tedizolid, further highlight the need for comparative effectiveness research. The majority of published randomized controlled trials (RCTs) have been compared to vancomycin or linezolid and the results did not achieve statistically significant differences. Current national guidelines on the treatment of SSTIs do not incorporate evidence on newer antibiotics and recently approved antibiotics, which may offer the advantage of outpatient treatment given their novel dosing regimens.[5]

Mullite-published meta-analyses have been conducted comparing the efficacy of vancomycin, linezolid, and other antibiotic agents. However, most of these considered only direct comparisons of 2 treatments and neglected the impact of indirect evidence. However, standard pairwise meta-analysis is only able to compare 2 drug classes that have already been evaluated in head-to-head or placebo comparison trials. In a complex condition with several options for treatment, of which some have not been directly compared in trials, a network meta-analysis (NMA) offers the potential to compare all therapeutic strategies simultaneously within a single framework and rank treatments per efficacy and safety. Here we compare the efficacy and safety of the optional antibiotics for the treatment of cSSTIs using the method of Bayesian NMA. Bayesian NMA is a statistical method used to combine the results from multiple studies and indirectly compare multiple treatments, thus incorporating all available direct and indirect evidence. Network analysis has been used to evaluate empirical therapy in the SSTIs, but results have been inconclusive due to relatively few included studies of newer antibiotics or reporting of adverse events (AEs) of antibiotics. Considering these limitations of the current evidence on the comparative efficacy of antibiotics, especially for evaluated novel antibiotics for the treatment of cSSTIs, we performed this systematic review and Bayesian NMA.

2. Methods

2.1. Study design

The study was approved by the ethics institutional review board of the People's Hospital of Guangxi Zhuang Autonomous Region. We performed a systematic review of the literature according to the recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct of NMA of intervention studies.[12] The protocol for the systematic review and NMA was preregistered in PROSPERO, CRD42021238391.

2.2. Literature review

PubMed, Embase (via Ovid SP), Medline (via Ovid SP), and Cochrane CENTRAL for all publications from inception up to May 2021 were systematically searched and the search strategy was described in Item S1 (Supplemental Digital Content, http://links.lww.com/MD/H40). We included articles regardless of the language of publication. The reference lists of all retrieved articles were also reviewed to identify additional articles missed by using these search terms. The authors approved all enrollment studies. We included in our review all RCTs that included adults with cSSTIs and that compared one of the optional antibiotics Gram-positive SSTIs.

2.3. Study selection

We included RCTs that met the following criteria:

1. Population: We included people of any age or gender presenting with Gram-positive SSTIs (e.g., cellulitis, erysipelas, furuncles, simple abscesses, wound infections, and deeper infections such as necrotizing fasciitis, myositis [inflammation of muscles], and gas gangrene);
2. Intervention: treatment group must have received at least 1 antibiotics agent;
3. Comparison: the randomized comparator was placebo, no intervention, another class of antibiotics agent. Because we were interested in the class effects of antibiotics agents on clinical outcomes, we excluded studies comparing 2 agents from the same class of antibiotics drug, or the same compound tested at different doses;
4. Outcome: the primary outcome was the clinical and microbiological treatment success at the test-of-cure visit, commonly 7 to 14 days after the end of therapy, broadly defined as an improvement in the signs and symptoms associated with the cSSTI, secondary outcomes were AEs.
5. Design: RCTs.

2.4. Data extraction and quality assessment

A comprehensive search of databases was performed by 2 researchers (X.L. and H.L.), deleted duplicate records, screened the titles and abstracts for relevance, and identified each as excluded or requiring further assessment. We reviewed the full-text articles designated for inclusion and manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies. Any disagreement between the 2 investigators regarding the abstracted data was adjudicated by a third reviewer. The following data were extracted from each study: study design, first author, year of publication, number of patients, comparisons, and outcomes.

Two reviewers (X.L. and H.L.) independently evaluated the methodological quality of identified studies. The "risk of bias tool" referred to the Cochrane Handbook for Systematic Reviews of Interventions version 5.4 was used to assess methodological quality.[13,14] In terms of the assessment criteria, each trial was rated and assigned to 1 of the 3 following risk of bias: low, unclear, or high.[14]

2.5. Data synthesis and statistical analyses

We performed 2 types of meta-analysis. using the DerSimonian and Laird random-effects model[15] by "meta" (version 4.9-4)[16] package implemented in R software version 3.6.2. For dichotomous outcomes, the pooling results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). If 95% CIs of ORs did not include 1, the differences between the comparisons can be considered statistically significant. We measured between-study heterogeneity using the I^2 statistic.[17] We defined substantial heterogeneity as an I^2 statistic of ≥50%, which would imply that real differences exist between-study results that would not be explained by chance alone. In the presence of substantial heterogeneity, meta-analysis using the random-effects model was considered.[18] In consideration of the heterogeneity between included trials, we performed a random-effects NMA to combine direct and indirect evidence of

all treatment effects using WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) software In the WinBUGS program, the number of iterations was set to 100,000, and the first 10,000 iterations were regarded as burn-in for annealing to eliminate the impact of the initial value.[19] We ranked antimicrobials for each outcome by the surface under the cumulative ranking curve (SUCRA) probabilities and the posterior probabilities; SUCRA values of 100% and 0% were ranked as the best and worst treatments, respectively, and higher posterior probabilities in each simulation reveal the higher chance to be the best treatment agent.[20]

We performed a loop-specific method to systematically evaluate the inconsistency within every closed triangular or quadratic loop between direct and indirect sources of evidence.[21,22] We then considered the source of inconsistency to judge whether there is a significant difference between direct and indirect assessment for a specific interventions comparison in the loop.[21] The node splitting approach was used to evaluate inconsistency within the network by separating comparison into direct and indirect evidence.[23] When there were 10 or more trials, we evaluated small-study effects by using a comparison-adjusted funnel plot of treatments to detect the presence of any publication bias in NMA.[20,24] Subgroup analysis for the primary outcomes was performed based on the following subgroups:

1. based on a clinical modified intent-to-treat population or a microbiologically modified intent-to-treat population;
2. based on specific antimicrobials, source of infection, and isolated pathogens.

2.6. Grading the quality of evidence

We evaluated the quality of evidence from traditional pairwise meta-analysis, and NMA estimates comparisons for primary outcomes using the modified Grading of Recommendation, Assessment, Development and Evaluation (GRADE) tool for NMA.[25,26]

3. Results

3.1. Study identification and selection

In total, 10,750 records were obtained by literature search, and 630 duplicate papers were discarded and excluded. A selection of 10,120 studies remained for further analysis. After evaluation of the titles and abstracts, 9950 irrelevant articles were excluded. After reading the remaining 170 full-text papers, 121 studies were excluded for the following reasons: studies with an irrelevant study design (n = 46), non-RCTs (n = 16), lacking outcomes (n = 8), duplication of published articles (n = 6), and review and meta-analysis (n = 46). Finally, 48 studies[27–74] were included in the meta-analysis. The study selection process was performed in accordance with the PRISMA guidelines and Figure 1 showed the PRISMA flow diagram.

3.2. Characteristics of included studies

The main characteristics of the included studies are described in Table S1 (Supplemental Digital Content, http://links.lww.com/MD/H41, which illustrates the characteristics of included studies). Overall, 48 trials were included in the present NMA. The numbers of CSSTIs cover 2,4381 patients, ranging from 60 to 1897 per study. These studies were published from 2000 until 2020. Three studies adopted a 3-arm design, and the other 45 used 2-arm trial designs. Among the 99 arms in 48 trials, twenty types of antibiotics monotherapy or in combination were evaluated. Vancomycin was evaluated in 26 arms, linezolid was evaluated in 17 arms, vancomycin plus aztreonam was evaluated in

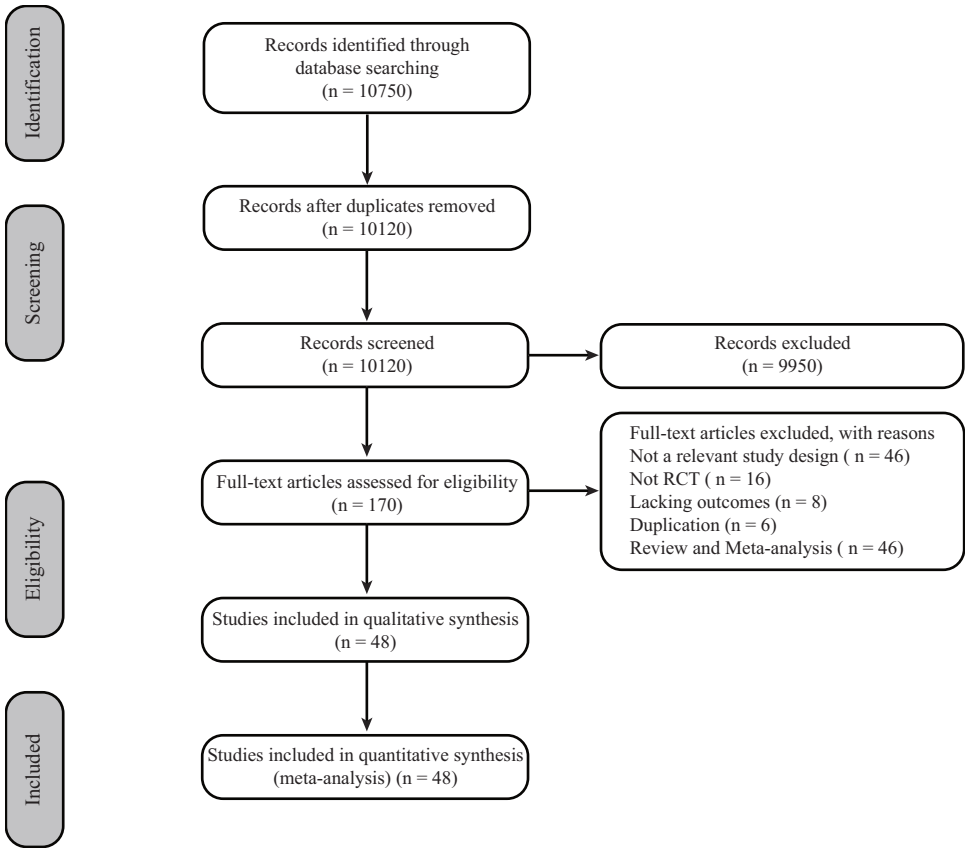

Figure 1. Identification process for eligible RCTs. RCTs = randomized controlled trials.

9 arms, daptomycin was evaluated in 8 arms, tigecycline and ceftaroline were evaluated in 5 arms, delafloxacin and tedizolid were evaluated in 4 arms, ceftobiprole, iclaprim, omadacycline, and oritavancin were evaluated in 3 arms, teicoplanin was evaluated in 2 arms, avarofloxacin, dalbavancin, lefamulin, oxacillin/dicloxacillin, TD-1792, telavancin and vancomycin plus ceftazidime were evaluated in 1 arm, respectively.

3.3. Risk of bias assessment

The risk of bias and methodologic quality of all included trials were assessed and summarized in Figure S1 (Supplemental Digital Content, http://links.lww.com/MD/H42, which illustrates the risk of bias graph). Almost half of the included RCTs were considered to have high methodological quality. The random sequence generation were reported in 24 studies. Twenty-one studies with a low risk of allocation concealment. Thirty-two studies adopted a double-blinded design and 5 studies adopted a single-blinded design. As for attrition bias, all trials had a low risk of bias for selective outcome reporting and a low risk of bias for incomplete outcome data reporting. In addition to other biases, most trials were judged to be at high risk of bias due to being funded by pharmaceutical companies.

3.4. Overview

Treatment networks plot for primary outcomes are shown in Figure 2 and for secondary outcomes are shown in Figure S2 (Supplemental Digital Content, http://links.lww.com/MD/H43, which illustrates the network of eligible treatment comparisons for secondary outcomes). The results of primary outcomes of the NMA are shown in Tables 1 and 2, and for subgroup analysis of primary outcomes are shown in Tables a–e of Supplemental Digital Content Item S2 (Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes). The results of secondary outcomes are shown in Table a-c of Item S3 (Supplemental Digital Content, http://links.lww.com/MD/H45, which illustrates the results of secondary outcomes). Treatment ranking based on the SUCRA values of primary outcomes are shown in Figure 3, subgroup analysis is shown in Figure S3 (Supplemental Digital Content, http://links.lww.com/MD/H46, which illustrates the rank probability curves for subgroup outcomes), and for secondary outcomes are shown in Figure S4 (Supplemental Digital Content, http://links.lww.com/MD/H47, which illustrates the rank probability curves for secondary outcomes). GRADE assessments for primary outcomes are provided in Table a-b of Item S4 (Supplemental Digital Content, http://links.lww.com/MD/H48, which illustrates the GRADE assessments for primary outcomes). There was no evidence of global inconsistency in any network (see Item S5, Supplemental Digital Content, http://links.lww.com/MD/H49, which illustrates the evaluation of inconsistency for primary and secondary outcome network).

3.5. Clinical treatment success

Clinical treatment success was evaluated in 45 trials with 18,585 cases, of whom 16,195 achieved treatment success. Network plots are shown in Figure 2. There was no evidence suggesting heterogeneity or inconsistency (Table 1). Omadacycline was related to a higher rate of clinical treatment success, compared with most of the evaluated antibiotics agents (Table 1). Clinical treatment success by linezolid was significantly higher compared with vancomycin with OR of 1.59 (95% CI 1.11–2.32). Similar results of Bayesian rank probability showed that omadacycline best treatment for clinical treatment success, followed by avarofloxacin and linezolid (Fig. 3).

In a subgroup analysis including the ITT populations, similar results showed that clinical treatment success by linezolid was significantly higher compared with vancomycin with OR of 1.54 (95% CI 1.08–2.16, see Table a of Item S2, Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes). Daptomycin was related to a lower rate of clinical treatment success, compared with vancomycin plus aztreonam, tigecycline, delafloxacin, and ceftaroline. Iclaprim was related to a lower rate of clinical treatment success, compared with vancomycin plus aztreonam, delafloxacin, ceftaroline, and omadacycline. Omadacycline was related to a higher rate of clinical treatment success. compared to ceftobiprole, oritavancin, and oxacillin/dicloxacillin. Similar results of Bayesian rank probability showed that omadacycline could be the best treatment for clinical treatment success in ITT populations (see Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/H46, which illustrates the rank probability curves for subgroup outcomes).

In a subgroup analysis including studies since 2010. Similar results showed that omadacycline was related to a higher rate of clinical treatment success compared to other treatments and ranked to be the best treatment option (see Table b of Item S2, Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes).

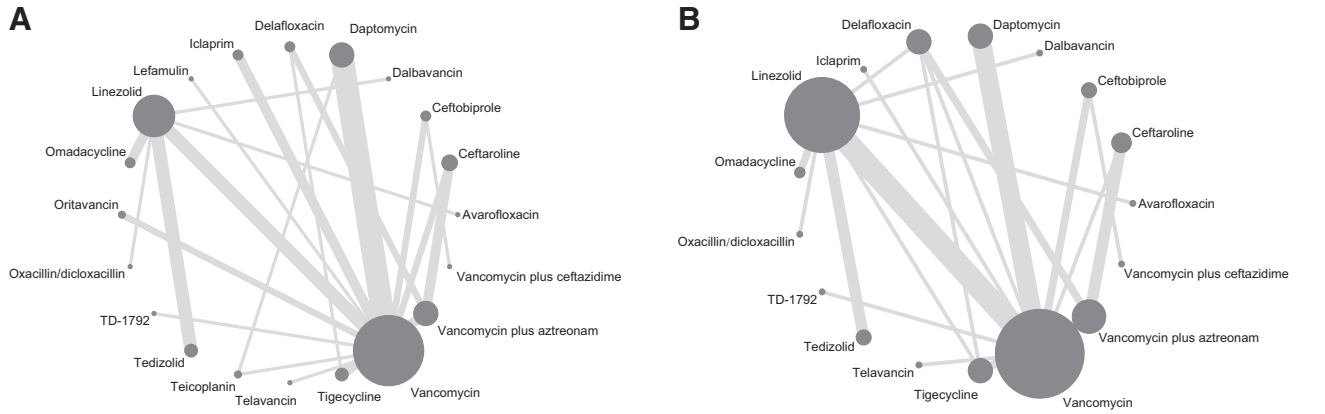

Figure 2. Graphic representation of treatment comparisons for the efficacy of optional parenteral antimicrobial therapy for complicated skin and soft tissue infections. Lines represent trials comparing 2 classes of drug or drugs for (A) clinical treatment success and (B) microbiological treatment success. The nodes indicate the drug treatments assessed in existing trials. The size of the node is proportional to the number of studies evaluating the treatment.

Table 1

OR and 95% CI for the comparative efficacy of optional antibiotics for the clinical treatment success of cSSTIs.

	Vancomycin	Vancomycin plus aztreonam	Vancomycin plus ceftazidime	Linezolid	Tedizolid	Daptomycin	Tigecycline	Delafloxacin	Ceftaroline	Ceftobiprole	Iclaprim	Omadacycline	Oritavancin	Avarofloxacin	Dalbavancin	Lefamulin	Oxacillin/ dicloxacillin	TD-1792	Teicoplanin	Telavancin
Vancomycin	NA			***1.62 (1.10–2.40)***		1.02 (0.70–1.49)			1.47 (0.52–4.21)	1.39 (0.59–3.24)	0.87 (0.65–1.17)		0.99 (0.61–1.62)			0.72 (0.22–2.36)		1.13 (0.39–3.26)	1.16 (0.21–6.43)	1.12 (0.82–1.53)
Vancomycin plus aztreonam	1.05 (0.44–2.34)	NA					0.85 (0.52–1.38)	0.89 (0.66–1.18)	1.27 (0.92–1.77)											
Vancomycin plus ceftazidime	1.27 (0.55–3.10)	1.27 (0.40–4.03)	NA							1.04 (0.62–1.75)										
Linezolid	***1.59 (1.11–2.32)***	1.55 (0.64–3.99)	1.23 (0.47–3.15)	NA	0.85 (0.62–1.16)							2.10 (1.17–3.75)		1.36 (0.57–3.25)	0.78 (0.45–1.35)		0.78 (0.48–1.26)			
Tedizolid	1.32 (0.79–2.22)	1.24 (0.47–3.44)	1.02 (0.38–2.94)	0.82 (0.56–1.21)	NA															
Daptomycin	1.01 (0.66–1.48)	0.97 (0.37–2.45)	0.80 (0.30–1.95)	0.63 (0.36–1.07)	0.77 (0.41–1.49)	NA													0.69 (0.15–3.15)	
Tigecycline	0.87 (0.32–2.14)	0.82 (0.54–1.31)	0.68 (0.18–2.21)	0.54 (0.18–1.41)	0.66 (0.21–1.86)	0.87 (0.30–2.34)	NA	1.35 (0.30–6.03)												
Delafloxacin	0.94 (0.37–2.20)	0.89 (0.61–1.24)	0.70 (0.21–2.29)	0.59 (0.21–1.45)	0.71 (0.24–1.96)	0.92 (0.33–2.58)	1.08 (0.62–1.79)	NA												
Ceftaroline	1.32 (0.62–2.78)	1.26 (0.88–1.85)	1.02 (0.33–3.19)	0.82 (0.35–1.86)	1.00 (0.40–2.53)	1.30 (0.56–3.21)	1.54 (0.89–2.69)	1.42 (0.86–2.44)	NA											
Ceftobiprole	1.30 (0.71–2.40)	1.26 (0.45–3.63)	1.01 (0.53–1.85)	0.82 (0.39–1.67)	1.00 (0.44–2.16)	1.29 (0.64–2.62)	1.49 (0.53–4.75)	1.44 (0.48–4.20)	0.99 (0.37–2.65)	NA										
Iclaprim	0.86 (0.57–1.26)	0.81 (0.32–2.12)	0.67 (0.25–1.71)	***0.54 (0.31–0.88)***	0.66 (0.34–1.22)	0.86 (0.49–1.48)	0.98 (0.37–3.11)	0.91 (0.35–2.44)	0.65 (0.29–1.51)	0.66 (0.32–1.32)	NA									
Omadacycline	***3.45 (1.79–7.28)***	***3.35 (1.1–10.38)***	2.74 (0.83–7.92)	***2.16 (1.20–3.98)***	***2.60 (1.33–5.52)***	***3.44 (1.53–7.88)***	***4.00 (1.22–13.82)***	***3.74 (1.17–12.44)***	2.66 (0.91–7.43)	***2.66 (1.03–6.97)***	***3.97 (1.90–9.10)***	NA								
Oritavancin	1.00 (0.62–1.53)	0.96 (0.38–2.51)	0.77 (0.27–1.98)	0.62 (0.34–1.04)	0.76 (0.39–1.42)	0.98 (0.54–1.71)	1.13 (0.41–3.32)	1.06 (0.40–2.97)	0.75 (0.31–1.79)	0.76 (0.36–1.56)	1.14 (0.62–2.03)	***0.29 (0.12–0.63)***	NA							
Avarofloxacin	2.16 (0.71–5.65)	2.07 (0.54–8.56)	1.67 (0.42–6.14)	1.35 (0.52–3.38)	1.67 (0.59–4.51)	2.15 (0.73–6.62)	2.50 (0.61–10.84)	2.32 (0.58–10.23)	1.65 (0.42–6.16)	1.66 (0.50–5.30)	2.52 (0.80–7.55)	0.63 (0.21–1.85)	2.18 (0.72–6.79)	NA						
Dalbavancin	1.23 (0.58–2.59)	1.17 (0.39–3.58)	0.93 (0.29–2.80)	0.76 (0.38–1.47)	0.93 (0.44–1.98)	1.21 (0.51–2.94)	1.38 (0.43–4.59)	1.32 (0.41–4.25)	0.94 (0.33–2.54)	0.94 (0.34–2.36)	1.41 (0.60–3.40)	***0.35 (0.14–0.88)***	1.24 (0.51–2.79)	0.56 (0.18–1.80)	NA					
Lefamulin	0.68 (0.17–2.42)	0.64 (0.15–2.94)	0.51 (0.11–2.42)	0.42 (0.11–1.62)	0.52 (0.12–2.10)	0.67 (0.16–2.58)	0.75 (0.17–3.84)	0.72 (0.17–3.59)	0.50 (0.12–2.34)	0.51 (0.12–2.04)	0.78 (0.19–3.35)	***0.20 (0.04–0.87)***	0.69 (0.16–2.67)	0.32 (0.06–1.83)	0.54 (0.12–2.56)	NA				
Oxacillin-dicloxacillin	1.23 (0.63–2.61)	1.19 (0.41–3.85)	0.96 (0.29–3.24)	0.78 (0.40–1.39)	0.94 (0.44–1.92)	1.23 (0.56–2.97)	1.40 (0.48–5.09)	1.34 (0.45–4.55)	0.94 (0.35–2.69)	0.95 (0.39–2.52)	1.44 (0.68–3.16)	***0.36 (0.15–0.83)***	1.23 (0.56–2.83)	0.57 (0.17–1.64)	1.00 (0.41–2.59)	1.80 (0.41–8.23)	NA			
TD-1792	1.14 (0.35–3.62)	1.09 (0.26–4.61)	0.88 (0.19–3.57)	0.69 (0.21–2.47)	0.86 (0.25–3.15)	1.10 (0.33–3.90)	1.30 (0.28–5.93)	1.22 (0.28–5.44)	0.84 (0.20–3.51)	0.85 (0.25–3.36)	1.30 (0.41–4.66)	0.31 (0.09–1.23)	1.12 (0.35–3.88)	0.52 (0.11–2.36)	0.96 (0.23–3.71)	1.71 (0.28–8.76)	0.91 (0.24–3.52)	NA		
Teicoplanin	0.90 (0.22–4.45)	0.88 (0.16–5.22)	0.70 (0.13–4.40)	0.55 (0.13–3.02)	0.67 (0.15–4.11)	0.87 (0.23–4.36)	1.04 (0.19–6.55)	0.98 (0.18–5.97)	0.70 (0.13–3.95)	0.67 (0.15–3.79)	1.06 (0.24–5.66)	0.26 (0.05–1.63)	0.92 (0.22–4.55)	0.42 (0.07–2.82)	0.75 (0.15–4.44)	1.33 (0.21–9.58)	0.72 (0.14–4.28)	0.81 (0.12–5.35)	NA	
Telavancin	1.14 (0.72–1.80)	1.07 (0.43–3.05)	0.87 (0.34–2.23)	0.70 (0.39–1.23)	0.88 (0.42–1.71)	1.10 (0.62–2.09)	1.31 (0.48–4.09)	1.20 (0.43–3.60)	0.84 (0.35–2.21)	0.87 (0.41–1.96)	1.32 (0.74–2.39)	***0.33 (0.14–0.72)***	1.13 (0.63–2.22)	0.52 (0.16–1.68)	0.92 (0.38–2.28)	1.69 (0.42–6.57)	0.93 (0.38–2.10)	0.99 (0.28–3.61)	1.28 (0.23–6.04)	NA

The lower triangle shows summary ORs (95% CIs) derived in network meta-analysis (taking into account both the direct and indirect evidence) for the comparison of the drug in the row versus the drug in the column as reference. In contrast, the upper triangle shows summary ORs (95% CIs) derived in traditional pairwise meta-analysis (taking into account direct evidence only) for the comparison of the drug in the column versus the drug in the row as reference. White spaces indicate lack of direct evidence for the given comparison. The statistically significant values are described bold italic.

CI = confidence interval, cSSTIs = complicated skin and soft tissue infections, NA = not available, OR = odds ratio.

Table 2

OR and 95% CI for the comparative efficacy of optional antibiotics for the microbiological treatment success of cSSTIs.

	Vancomycin	Vancomycin plus aztreonam	Vancomycin plus ceftazidime	Linezolid	Tedizolid	Daptomycin	Tigecycline	Delafloxacin	Ceftaroline	Ceftobiprole	Iclaprim	Omadacycline	Avarofloxacin	Dalbavancin	Oxacillin-dicloxacillin	TD-1792	Telavancin
Vancomycin	NA			***2.11***		1.32 (0.78–2.21)	0.88	1.79	3.33	1.17	2.16					1.27	1.27
				(1.41–3.17)			(0.29–2.63)	(0.51–6.24)	(0.51–21.71)	(0.71–1.95)	(0.70–6.66)					(0.33–4.97)	(0.87–1.86)
Vancomycin plus aztreonam	1.34 (0.53–3.95)	NA					1.79 (0.82–3.90)	0.92 (0.37–2.30)	0.87 (0.54–1.42)								
Vancomycin plus ceftazidime	1.32 (0.40–4.60)	0.99 (0.21–4.36)	NA							0.91 (0.53–1.56)							
Linezolid	***2.14***	1.58	1.60	NA	0.76		2.28	1.64				2.30	1.36	1.22	1.20		
	(1.17–3.68)	(0.47–4.64)	(0.40–5.72)		(0.22–2.63)		(0.19–26.72)	(0.44–6.18)				(0.92–5.72)	(0.57–3.25)	(0.66–2.26)	(0.60–2.37)		
Tedizolid	1.46 (0.49–4.29)	1.09 (0.23–4.15)	1.13 (0.22–5.23)	0.68 (0.28–1.75)	NA												
Daptomycin	1.27 (0.66–2.35)	0.97 (0.28–3.05)	0.97 0.24–3.78)	0.60 (0.26–1.40)	0.86 (0.25–3.21)	NA											
Tigecycline	1.89 (0.77—4.97)	1.45 (0.72—2.56)	1.46 (0.35—6.15)	0.89 (0.32—2.65)	1.31 (0.36—5.84)	1.49 (0.52–4.99)	NA	1.70 (0.45–6.39)									
Delafloxacin	1.87 (0.73–5.68)	1.39 0.63–3.16)	1.41 (0.31–6.77)	0.88 (0.32–2.96)	1.28 (0.32–6.10)	1.44 (0.48–5.05)	1.00 (0.42–2.36)	NA									
Ceftaroline	1.24 (0.43–4.01)	0.92 (0.53–1.68)	0.93 (0.20–4.70)	0.58 (0.18–1.98)	0.82 (0.21–4.38)	0.96 (0.27–4.12)	0.64 (0.30–1.59)	0.66 (0.25–1.77)	NA								
Ceftobiprole	1.19 (0.57–2.48)	0.87 (0.25–2.70)	0.89 (0.33–2.26)	0.55 (0.24–1.55)	0.79 (0.24–3.04)	0.91 (0.33–2.69)	0.61 (0.19–1.97)	0.62 (0.18–2.22)	0.94 (0.24–3.53)	NA							
Iclaprim	2.17 (0.48–9.53)	1.66 (0.22–9.37)	1.65 (0.26–9.99)	1.03 (0.21–4.78)	1.46 (0.25–9.21)	1.73 (0.34–8.24)	1.11 (0.18–6.09)	1.17 (0.18–6.84)	1.77 (0.23–10.28)	1.85 (0.38–8.93)	NA						
Omadacycline	***5.07***	3.88	3.91	2.39	3.52	3.97 (0.97–17.27)	2.65	2.67	4.18	4.36	2.28	NA					
	(1.39–18.21)	0.70–17.9)	(0.69–21.13)	(0.82–7.58)	(0.88–13.91)		(0.57–11.54)	(0.48–11.74)	(0.76–18.26)	(0.99–16.46)	(0.35–15.88)						
Avarofloxacin	2.88 (0.90–9.70)	2.22 0.44–9.26)	2.18 (0.47–11.91)	1.37 (0.46–4.51)	2.00 (0.50–9.08)	2.27 (0.56–8.83)	1.54 (0.33–6.83)	1.56 (0.35–7.16)	2.42 (0.42–10.9)	2.44 (0.65–9.87)	1.37 (0.18–10.5)	0.60 (0.13–2.77)	NA				
Dalbavancin	2.63 (0.85–8.78)	1.96 (0.37–7.17)	1.91 (0.32–10.83)	1.23 (0.49–3.58)	1.73 (0.44–7.16)	2.05 (0.53–8.16)	1.38 (0.32–5.33)	1.39 (0.30–5.81)	2.07 (0.40–8.45)	2.14 (0.53–8.55)	1.18 (0.18–8.13)	0.51 (0.12–2.54)	0.87 (0.20–4.13)	NA			
Oxacillin-dicloxacillin	1.76 (0.52–5.52)	1.31 0.26–5.77)	1.31 (0.25–6.27)	0.83 (0.29–2.32)	1.19 (0.27–4.59)	1.39 (0.36–5.23)	0.90 (0.21–4.07)	0.92 (0.19–3.73)	1.39 (0.27–6.99)	1.47 (0.33–5.34)	0.80 (0.13–5.22)	0.35 (0.07–1.47)	0.59 (0.12–2.64)	0.66 (0.15–2.79)	NA		
TD-1792	1.26 (0.24–8.24)	0.99 (0.16–7.19)	0.95 (0.14–7.38)	0.60 (0.11–4.85)	0.87 (0.12–8.27)	0.99 (0.20–7.31)	0.69 (0.11–5.30)	0.70 (0.12–5.05)	1.06 (0.16–8.31)	1.06 (0.20–8.41)	0.64 (0.07–5.69)	0.26 (0.04–2.45)	0.44 (0.06–4.04)	0.49 (0.07–4.32)	0.74 (0.11–6.33)	NA	
Telavancin	1.27 (0.51–2.91)	0.95 (0.22–2.97)	0.96 (0.18–4.03)	0.59 (0.20–1.81)	0.84 (0.23–3.78)	0.98 (0.34–2.98)	0.66 (0.20–2.17)	0.68 (0.15–2.21)	1.03 (0.21–3.98)	1.06 (0.28–3.23)	0.59 (0.10–3.43)	0.24 (0.06–1.26)	0.42 (0.09–1.82)	0.47 (0.11–2.03)	0.72 (0.17–3.12)	0.98 (0.12–5.28)	NA

The lower triangle shows summary ORs (95% CIs) derived in network meta-analysis (taking into account both the direct and indirect evidence) for the comparison of the drug in the row versus the drug in the column as reference. In contrast, the upper triangle shows summary ORs (95% CIs) derived in traditional pairwise meta-analysis (taking into account direct evidence only) for the comparison of the drug in the column versus the drug in the row as reference. White spaces indicate lack of direct evidence for the given comparison. The statistically significant values are described bold italic.

CI = confidence interval, cSSTIs = complicated skin and soft tissue infections, NA= not available, OR = odds ratio.

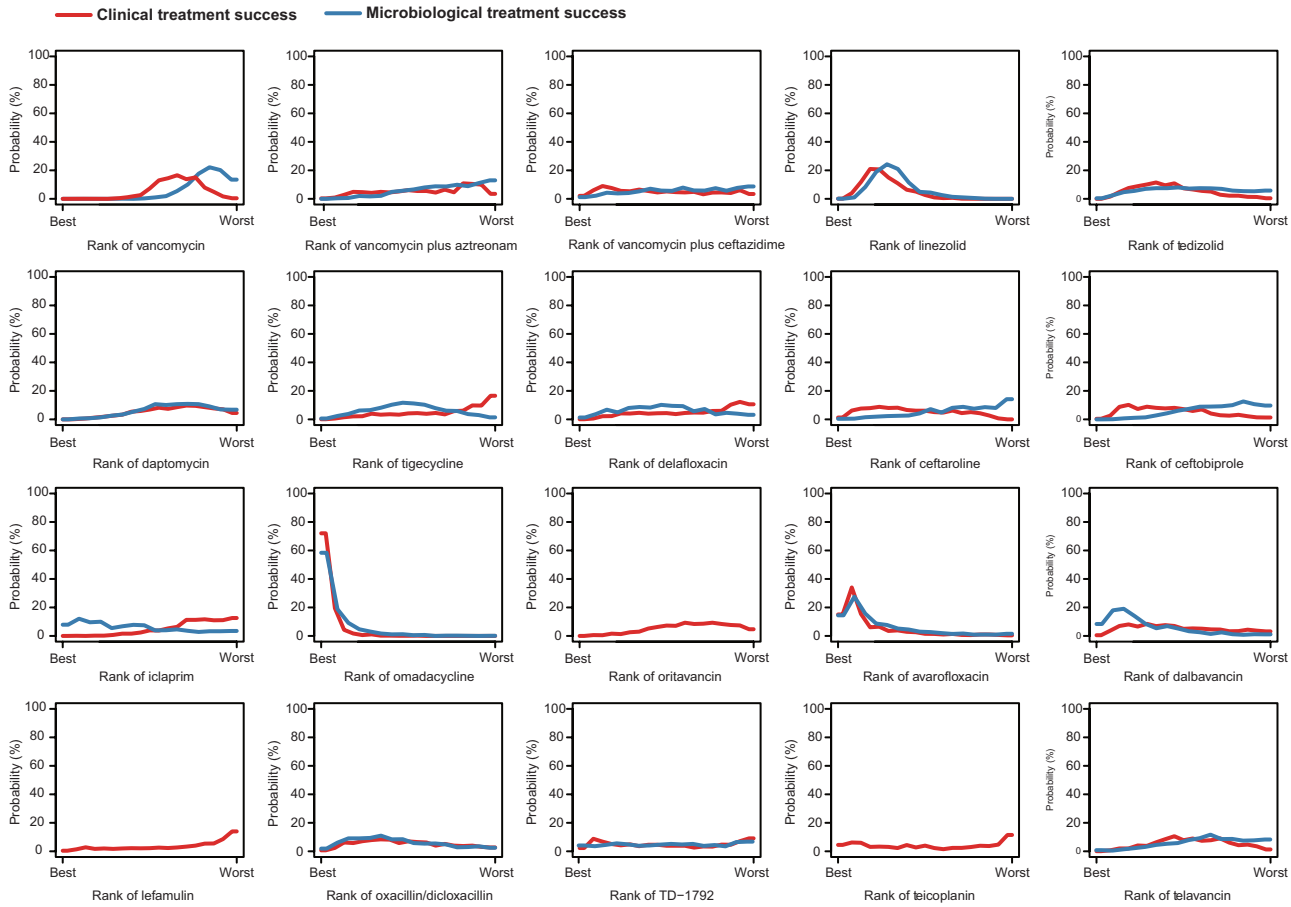

Figure 3. Rank probability curves for primary outcomes. The graphs display the distribution of probabilities for each treatment ranking from best through worst at different positions for each outcome. Ranking indicates the probability that drug class is first "best," second "best," etc.

3.6. Microbiological treatment success

Microbiological treatment success was evaluated by 1003 investigators in the 34 trials, although explicit definitions of microbiological treatment success were only reported for some trials. The network geometry was shown in Figure 2. Compared with vancomycin, linezolid (OR 2.14, 95% CI 1.17–3.68, Table 2) and omadacycline (OR 5.07, 95% CI 1.39–18.21, Table 2) were associated with significantly higher microbiological treatment success. The rank probability of treatments based on SUCRA values, which were shown in Figure 3, omadacycline can be considered the best treatment for microbiological treatment success, followed by avarofloxacin and dalbavancin.

In a subgroup analysis including the ITT populations, the results revealed no significant difference among any comparisons (see Table c of Item S2, Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes). Similar results of treatments ranking based on SUCRA values showed that omadacycline can be considered the best treatment for microbiological treatment success, followed by avarofloxacin and linezolid (see Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/H46, which illustrates the rank probability curves for subgroup outcomes).

In a subgroup analysis including patients infection caused by MRSA, linezolid, tedizolid, and omadacycline were related to a higher rate of MRSA treatment success, compared with vancomycin (OR 2.07, 95% CI 1.22–3.37, OR 2.70, 95% CI 1.10–5.82, OR 2.64, 95% CI 1.05–6.27, respectively, see Table d of Item S2, Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes). The rank probability of treatments based on SUCRA values revealed that tedizolid was the best treatment for MRSA, followed by omadacycline, iclaprim (see Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/H46, which illustrates the rank probability curves for subgroup outcomes).

In a subgroup analysis including studies since 2010, the results revealed no significant difference among any comparisons (see Table e of Item S2, Supplemental Digital Content, http://links.lww.com/MD/H44, which illustrates the results of subgroup analysis of primary outcomes). Bayesian rank probability showed that omadacycline could be the best treatment for microbiological treatment success, followed by avarofloxacin (see Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/H46, which illustrates the rank probability curves for subgroup outcomes).

3.7. Adverse events

3.7.1. Any AEs. A total of 41 trials with 23,552 patients, which were compared to 19 treatments provided the dates of any AEs. Lefamulin was related to a lower risk of any AEs compared with other treatments with significant (see Table a of Item S3, Supplemental Digital Content, http://links.lww.com/MD/H45, which illustrates the results of secondary outcomes). However, the risk of any AE was higher in the tigecycline and telavancin arms compared with most of the other treatment arms. SUCRA ranking revealed that lefamulin, dalbavancin, and oxacillin/dicloxacillin had a lower risk of any AEs (see Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/H47, which illustrates the rank probability curves for secondary outcomes), but tigecycline and telavancin were related to the highest risk of any AEs.

3.7.2. Serious AEs. Thirty-five trials with 20,701 participants reported results for serious AEs, 952 patients had experienced serious AEs. TD-1792 was related to a lower risk of serious AEs compared with other treatments with significant (see Table b of Item S3, Supplemental Digital Content, http://links.lww.com/MD/H45, which illustrates the results of secondary outcomes). However, the risk of serious AEs was higher in the telavancin arms compared with most of the other treatment arms. SUCRA ranking showed that TD-1792, avarofloxacin, and oxacillin/dicloxacillin had a lower risk of serious AEs (see Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/H47, which illustrates the rank probability curves for secondary outcomes), but telavancin and telavancin were related to the highest risk of serious AEs.

3.7.3. AE leading to discontinuation. Thirty-two trials with 19,673 participants were assessed for AE leading to discontinuation and 703 had valid results on AE leading to discontinuation. There were no significant differences in AE leading to discontinuation between 18 interventions (see Table b of Item S3, Supplemental Digital Content, http://links.lww.com/MD/H45, which illustrates the results of secondary outcomes). SUCRA showed that TD-1792 had a lower risk of AE leading to discontinuation (see Fig. S4, Supplemental Digital Content, http://links.lww.com/MD/H47, which illustrates the rank probability curves for secondary outcomes).

3.8. GRADE evaluation

We used the GRADE approach to further assess the certainty of evidence. GRADE assessments for primary outcomes are provided in Item S4, (Supplemental Digital Content, http://links.lww.com/MD/H48, which illustrates the GRADE assessments for primary outcomes). Due to some unclear nature of the risk of bias and indirectness, the quality of most comparisons of primary outcomes was moderate to low. The other outcomes of GRADE evaluations probably had equivalent or worse quality.

4. Discussion

We conducted this NMA involving RCTs for evaluating the efficacy and safety of optional antimicrobial therapy for cSSTIs, a comprehensive literature search was performed with no restriction for publication date and language, to ensure maximum coverage of existing published trials. To our knowledge, this study is the largest NMA in the field of cSSTIs, as we considered and evaluated systematic treatment strategies and a larger number of outcomes in detail and undertook separate subgroup analyses for patients with different conditions and published time. The results of NMA showed that omadacycline was associated with a higher rate of clinical and microbiological treatment success for the treatment of patients with cSSTIs compared to another optional antimicrobial, avarofloxacin was closely followed. In addition, omadacycline was associated with moderate rank of AEs, compared to another optional antimicrobial. Furthermore, lefamulin was related lower risk of AEs. This finding was also true for cSSTIs caused specifically by MRSA.

There were several systematic reviews and meta-analyses that evaluated the effects of optional antibiotics monotherapy or in combination for the treatment of SSTIs.[75–78] However, this NMA is the first one that altogether considered clinical and microbiological treatment success and AEs as outcomes. A recently published study evaluated 3 novel glycopeptides antibiotics for the treatment of cSSTIs, and the results showed that dalbavancin and oritavancin could offer more efficacy and safety comparable to standard care. However, comparator regimens of standard care in this study were also different, and the heterogeneity and imprecise nature may exist in the results, and only 3 novel glycopeptides antibiotics were evaluated.[77] Previously published study included 33 trials that compared the efficacy of 19 antibiotics for the treatment of acute bacterial skin and skin structure infections, and the results suggest equivalence of clinical efficacy among vancomycin, daptomycin, linezolid, and novel antimicrobial agents including oritavancin for the treatment of acute bacterial skin and skin structure infections.[78] This study did not evaluate microbiological treatment success and AEs as outcomes. On the other hand, the most recently published RCTs and novel treatment strategies were not included and the results were uncertain.

Several strengths of our NMA should be mentioned. Different from the previously published meta-analysis, our study had some remarkable innovations. Firstly, the previous traditional pairwise meta-analysis usually focused on comparisons of 2 treatments, but this study used an NMA method, which can offer the potential to compare all therapeutic strategies into a single framework, enabling computation of treatments per efficacy and safety from both direct and indirect comparisons with multiple treatments that cannot be evaluated in traditional pairwise meta-analysis. Secondly, all the published NMA studies did not use the SUCRA method to rank the probability per treatment for efficacy and safety. It is the first study that employed SUCRA values to rank the relative efficacy and safety of each antimicrobial. The SUCRA results showed the percentage of efficacy and safety per treatment compared to a hypothetical optimal intervention, which was considered the best treatment without uncertainty.[79–81] Hence, NMA can provide the highest strength of evidence for the draft of clinical guidelines. Thirdly, previously published studies did not involve the latest RCTs, due to the time of publication; moreover, the sample sizes and novel treatment strategies were not large enough for the accurate evaluation of these interventions. Incomplete inclusion of studies and inadequate sample size could substantially influence the results of NMA. In this study, we performed a comprehensive evaluation of the various treatment strategies with higher precision and a larger number of patients. Other strengths of this NMA included a comprehensive search of the literature and using the GRADE approach to evaluate the quality of evidence.

This NMA included a total of 20 different antimicrobials monotherapy or in combination for the treatment of cSSTIs. Bayesian NMA was used to assess the comparative efficacy and safety of those antimicrobials, aiming to evaluate the most preferable agent for the treatment of cSSTIs. Meanwhile, more evidence-based information on the selection of the most optimal antimicrobial for cSSTIs was attempted to present. Taking all outcomes into consideration, omadacycline was the best option for the clinical and microbiological treatment success, with reality the moderate risk of AEs. Omadacycline has a potential role as a part of an antimicrobial stewardship program in the treatment of patients with infections caused by antibiotic-resistant and multidrug-resistant Gram-positive pathogens, including MRSA.

This study still had some limitations. Firstly, by the method of meta-analysis in general, the results of this study were dependent on the quality of available included trials. Some included trials were small samples and single-centered designs. The results and conclusions should therefore be interpreted with caution, because of the limitation of the included trials. Another potential limitation is that most of the included RCTs were funded by pharmaceutical companies. In addition, our study is limited to cases of suspected or confirmed Gram-positive pathogens infection cSSTI. Future research should evaluate the efficacy and safety of these drugs in patients with cSSTI. Finally, NMA offers the potential to compare direct and indirect interventions, which contributed to the reduced statistical power and uncertainty of ranking results. More trials are thus expected to help accurately estimate the efficacy and safety of antimicrobials for the treatment of cSSTI.

5. Conclusion

Omadacycline demonstrated superior clinical and microbiological efficacy compared to other evaluated antimicrobials for the treatment of cSSTI where a Gram-positive pathogen is suspected or confirmed and related to moderate rank probability risk of AEs. Considering the quality of evidence, to further confirm the conclusion of the current study, high-quality, larger sample size, and well-designed RCTs are an urgent requisite.

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