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Systematic Review and Meta-Analysis To Estimate Antibacterial Treatment Effect in Acute Bacterial Skin and Skin Structure Infection

Jordan E. Cates,[a] Fanny S. Mitrani-Gold,[b] Gang Li,[c]* Linda M. Mundy[c]

University of North Carolina, Chapel Hill, North Carolina, USA[a]; GlaxoSmithKline (GSK), Research Triangle Park, North Carolina, USA[b]; GSK, Collegeville, Pennsylvania, USA[c]

A systematic literature review and meta-analysis were conducted to estimate the antibacterial treatment effect for linezolid and ceftaroline to inform on the design of acute bacterial skin and skin structure infection (ABSSSI) noninferiority trials. The primary endpoints included an early clinical treatment response (ECTR) defined as cessation of lesion spread at 48 to 72 h postrandomization and the test-of-cure (TOC) response defined as total resolution of the infection at 7 to 14 days posttreatment. The systematic review identified no placebo-controlled trials in ABSSSI, 4 placebo-controlled trials in uncomplicated skin and soft tissue infection as a proxy for placebo in ABSSSI, 12 linezolid trials in ABSSSI, 3 ceftaroline trials in ABSSSI, and 2 trials for nonantibacterial treatment. The ECTR rates at 48 to 72 h and corresponding 95% confidence intervals (CI) were 78.7% (95% CI, 61.1 to 96.3%) for linezolid, 74.0% (95% CI, 69.7 to 78.3%) for ceftaroline, and 59.0% (95% CI, 52.8 to 65.3%) for nonantibacterial treatment. The early clinical treatment effect could not be estimated, given no available placebo or proxy for placebo data for this endpoint. Clinical, methodological, and statistical heterogeneity influenced the selection of trials for the meta-analysis of the TOC treatment effect estimation. The pooled estimates of the TOC treatment response were 31.0% (95% CI, 6.2 to 55.9%) for the proxy for placebo, 88.1% (95% CI, 81.0 to 95.1%) for linezolid, and 86.1% (95% CI, 83.7 to 88.6%) for ceftaroline. The TOC clinical treatment effect estimation was 25.1% for linezolid and 27.8% for ceftaroline. The antibacterial treatment effect estimation at TOC will inform on the design and analysis of future noninferiority ABSSSI clinical trials.

Over the past decade, robust clinical, scientific, and regulatory debate has emerged for initiatives to improve the design, execution, and analysis of antibacterial clinical trials (1–4). New trials for acute bacterial skin and skin structure infections (ABSSSI), previously referred to as complicated skin and skin structure infections (cSSTI), remain important, given the rise in incidence of methicillin-resistant *Staphylococcus aureus* infections and reports of treatment failure (5–8). Per guidance from the U.S. Food and Drug Administration (FDA), patient eligibility for enrollment in ABSSSI trials should be restricted to those with erysipelas, cellulitis, major cutaneous abscesses, and wound infections having a minimal lesion surface area involvement of 75 cm^2 (9). For trial endpoints, the traditional test-of-cure (TOC) endpoint, with the treatment success defined as total resolution of the infection at 7 to 14 days posttreatment, remains aligned with the European regulatory guidance, yet the treatment success for the primary efficacy endpoint aligned with the FDA guidance is defined as cessation of lesion spread after 48 to 72 h of treatment (9–11). Revisions to the enrollment and endpoint criteria in recent regulatory guidance for ABSSSI trials necessitate reevaluation of the antibacterial treatment effect estimation calculated from across-trials comparisons of existing data for noninferiority trial design (4, 12–16).

To inform on future noninferiority ABSSSI trial design, we conducted a systematic review and meta-analysis of antibacterial treatment effect estimation. Linezolid and ceftaroline were *a priori* selected as drugs representative of potential active comparators for hospitalized adults with ABSSSI in a global phase 3 clinical development program. The trial data extracted for the systematic review were aligned with regulatory guidance for the enrollment and endpoint criteria in ABSSSI trials. A predefined meta-analysis plan defined the efficacy variables, primary endpoints of interest, and computational methods for antibacterial treatment effect estimation in ABSSSI historical trials for noninferiority margin justification.

MATERIALS AND METHODS

Study design. The systematic review and meta-analysis were designed and executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (17–19). Two independent reviewers conducted computer-based literature searches and a systematic review using the MEDLINE search engine (PubMed, U.S. National Library of Medicine, National Institutes of Health; http://www.ncbi.nlm.nih.gov). Ideally, treatment effect estimation for a noninferiority antibacterial trial should be calculated from placebo-controlled trials to allow for within-trial comparison of the antibacterial treatment response compared to the placebo treatment response (11, 14). Given a prior report that placebo-controlled trials were nonexistent for complicated skin infections (20), we partitioned the literature searches to identify placebo-controlled trials of any antibacterial treatment for ABSSSI (Appendix, search A1) as well as randomized clinical trials of active comparators in ABSSSI for linezolid (search B1) and ceftaroline (search B2). Due to nomenclature changes over time, studies that assessed ABSSSI, complicated skin and soft tissue infections (cSSTI), or complicated skin and skin structure infections (cSSSI) were included. While it was previously reported that there were no historical data for placebo-controlled trials of any antibacterial treatment in complicated skin infections, our search strategy, by design, would have captured any placebo-controlled ABSSSI trials, inclusive of

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Address correspondence to Fanny S. Mitrani-Gold, fanny.s.mitrani-gold@gsk.com.

* Present address: Gang Li, Pfizer, Collegeville, Pennsylvania, USA.

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trials for linezolid and ceftaroline. The placebo search was extended to include clinical trials reporting a placebo treatment response in uncomplicated skin and soft tissue infections (uSSTI) as a proxy for placebo in ABSSSI (search A2). This strategy, which comprised use of a proxy for placebo effect estimation, has been recommended in the FDA guidance for noninferiority trials and has been used for placebo treatment effect estimation for trials in complicated urinary tract infections (13, 21, 22). Given that historical studies published in 1937 reported relatively high response rates in the treatment of erysipelas with UV light, an additional search (search C) was conducted to identify clinical trials of nonantibacterial treatment in uSSTI and in ABSSSI (4, 23, 24). This search was *a priori* conducted to identify potentially informative data and not as a proxy for placebo treatment response estimation.

Identification of trials and full-screen review for eligibility. For each search, the publications were restricted to dates before 28 February 2013. Search terms included abbreviations and plural and full-phrase versions of the selected search terms (listed in Appendix 1) combined with Boolean operators (AND, OR) used in succession to narrow or widen the respective searches. Two reviewers independently assessed the identified publications for trial eligibility, data quality, and efficacy data. Eligible studies included randomized clinical trials for the respective searches of placebo-controlled trials (search A1), active comparator trials of linezolid (search B1) and ceftaroline (search B2) in ABSSSI, and trials of nonantibacterial treatment in uSSTI and ABSSSI (search C). Case series, observational studies, review papers, duplicate studies, and studies with incomplete data were not eligible for full-text review. The publications identified in searches A1, B1, B2, and C were excluded for one or more of the following criteria: pediatric exclusivity, lack of reported measure of endpoints of interest, >15% of subjects with either diabetic foot infections, animal or human bites, necrotizing fasciitis, decubitus ulcer infection, myonecrosis or ecthyma gangrenosum, and pooled treatment response rates for multiple infection types. Publications of uSSTI studies in search A2 were eligible for full review if the report was a placebo-controlled trial in impetigo, furunculosis, carbunculosis, folliculitis, ecthyma, erysipelas, or secondarily infected traumatic lesions (SITL). Publications of uSSTI studies were excluded for one of the following criteria: placebo add-on treatment, pediatric exclusivity, prevention or colonization trials, or inclusion of subjects with minor cutaneous abscesses treated via incision and drainage as surgical treatment. The latter group was excluded as any potential estimate of placebo effect could not be assessed independently of the surgical treatment effect (25–27).

Primary endpoints. For the meta-analysis, the two primary endpoints of interest were in the intention-to-treat (ITT) population and defined as the early clinical treatment response at 48 to 72 h after randomization and the TOC clinical treatment response. Outcome definitions of clinical success, cure, or treatment failure were evaluated from each of the published studies on the basis of criteria available and assessed for methodological and clinical heterogeneity. The early clinical treatment response was defined as the proportion of subjects who experienced cessation of spread or the reduction in the total surface area of the lesion at 48 to 72 h after randomization or after the first dose of the study drug (9). The TOC clinical treatment response varied in definition based on the location and year of the trial execution but was typically defined as the proportion of subjects who experienced total resolution of all signs and symptoms of the infection at 1 to 2 weeks after completion of the therapy (9). Studies that incorporated improvement in the definition of success were included in the meta-analysis, yet noted for this composite definition of success. Treatment was divided into three broad categories: placebo (with extension to a proxy for placebo), antibacterial, and nonantibacterial treatment for the ITT population unless otherwise noted.

Data extraction. Data were systematically extracted for general study characteristics, which included author, publication date, study drug and duration of therapy, active comparator, study population description, study years, countries or regions, study centers, and outcomes. Baseline demographic data were abstracted to assess age, gender, geographic region, proportion of baseline infection types, and lesion size when available. Methodological details were abstracted to assess randomization procedures, sequence generation, blinding in subjects and in investigators, eligibility criteria, inclusion and exclusion criteria, subject withdrawals, allocation concealment, primary outcome variable, secondary outcome variable, study definitions, timing of outcome assessment (including early clinical treatment response at 48 to 72 h after randomization and TOC clinical treatment response), incomplete reporting of outcomes, and other potential sources of bias.

Assessments of trial heterogeneity and publication bias. Publications reporting trials meeting the inclusion criteria were assessed for clinical, methodological, and statistical heterogeneity. Clinical heterogeneity was defined by patient selection, interventions, and outcomes, methodological heterogeneity was defined by study design and execution, and statistical heterogeneity was defined as a variation in the results beyond sampling variability (28–31). Given the qualitative decisions associated with clinical and methodological heterogeneity, each trial meeting the eligibility criteria was systematically assessed by each reviewer for inclusion and exclusion criteria, types and distributions of skin infections, timing of the outcome assessments, treatment duration, inclusion of lesion improvement as an indicator of success, and the proportion of subjects with methicillin-resistant *Staphylococcus aureus* (MRSA) pathogens. Each of two independent reviewers employed the Cochrane Risk of Bias Tool for assessment of publication bias, and any potential discrepancies were adjudicated via consensus with a third assessor (32).

Study selection for meta-analysis. Extensive clinical, methodological, and statistical heterogeneity influenced the selection of studies included in the meta-analysis (31). The proxy for placebo trials selected for inclusion in the meta-analysis was restricted to studies that did not exclusively enroll subjects with SITL, given the differential regulatory approval of antibacterial agents for this infection type. For the linezolid and ceftaroline trials, selection for inclusion in the meta-analysis was based on trial parameters in the historical data that approximated recent ABSSSI guidance to minimize the clinical and methodological heterogeneity of studies pooled in the meta-analysis (9, 31). These selection criteria were trials with total surface lesion area of >75 cm^2, a non-MRSA-specific population, and abscesses in <50% of the population. The trials reporting UV light treatment response were included in the meta-analysis as pooled nonantibacterial treatment (20, 23, 24).

Data analysis. Pooled treatment response rates and 95% confidence intervals (CI) were calculated for each treatment group using the DerSimonian-Laird methodology, a noniterative, random effects model to account for interstudy variability that utilized the metaphor package in R software (33). This method is commonly employed in meta-analyses of clinical trials, as it accounts for the heterogeneity of studies through a statistical parameter that represents the interstudy variation of the trials in the model (33). The proportion of total variation in the study estimates that was due to interstudy statistical heterogeneity was assessed using I^2 values and associated P values for trials included in the meta-analysis. Given the small number of the proxy for placebo and active comparator trials, meta-regression was not feasible. The indirect, across-trial comparisons to estimate the antibacterial treatment effect were calculated as the difference between the lower bound of the 95% CI of the response rate estimate for each antibacterial treatment and the upper bound of the 95% CI of the proxy for the placebo response rate estimate (14, 21). This methodology is aligned with the FDA guidance on the design of noninferiority trials and is acknowledged for yield of intrinsically conservative noninferiority margin estimates (14). Publication bias and heterogeneity were assessed using funnel plots (34).

RESULTS

Systematic review. No placebo-controlled trials of ABSSSI were identified (Appendix, search A1). There were 800 placebo records for uSSTI (search A2), 477 linezolid records (search B1), 73 ceftaroline records (search B2), and 2,390 records for trials defined as

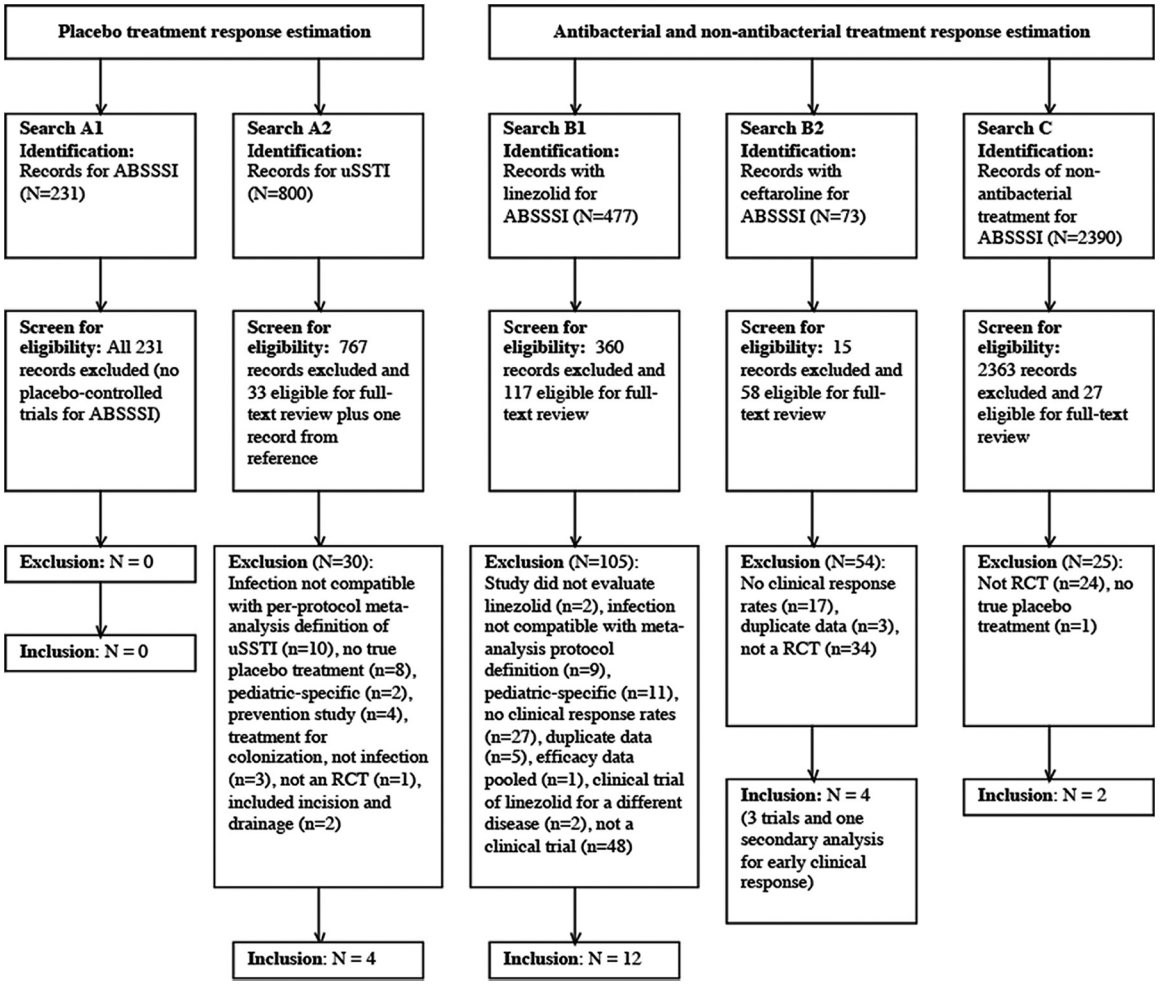

FIG 1 Flow chart depicting the systematic literature search for trials of treatment effect estimation in acute bacterial skin and skin structure infection (ABSSSI): publication identification, screening, eligibility, and trial inclusion. RCT, randomized clinical trial.

nonantibacterial treatments for skin infection (search C). The final selection of publications included 4 placebo-controlled uSSTI trials (35–38), 12 linezolid trials (39–50), 3 ceftaroline trials (51–53), 1 retrospective ceftaroline secondary analysis (54), and 2 nonantibacterial treatment trials of UV light for erysipelas (23, 24) (Fig. 1).

(i) Proxy trials of uSSTI for placebo treatment of ABSSI (searches A1 and A2). The four trials as proxy for placebo included 234 subjects with a range of uncomplicated infections reported as impetigo, folliculitis, SITL, and pyoderma (Table 1). Publication dates were from 1974 to 2013, three of the trials enrolled a subset of subjects <18 years of age, and one publication required certified translation from French to English (35–38). Each trial reported a TOC clinical treatment response; none reported an early clinical treatment response.

(ii) Antibacterial trials of ABSSSI (searches B1 and B2). Among the 12 linezolid trials published between the years 2000 and 2013, three were phase 2 trials, three restricted enrollment to subjects with MRSA infections (44, 46, 47), three were specific to China and the Asia-Pacific region (43, 44, 48), and one (45) reported only the treatment response rate for the clinically evaluable population (Table 1). The ceftaroline publications included one phase 2 trial, two registrational phase 3 trials, and a secondary subset analysis of the two phase 3 CANVAS (ceftaroline versus vancomycin in skin and skin structure infections) trials reporting an early clinical treatment response (51–54).

(iii) Nonantibacterial treatment trials (search C). The open-label controlled trials of subjects with erysipelas compared UV light to either prontosil or sulfanilamide (23, 24). The clinical data available did not specify lesion size, yet provided descriptive data for severely ill subjects with erysipelas and endpoints aligned with an early clinical treatment response at 48 to 72 h.

Meta-analysis. Data on the primary treatment response rate, lesion size, and treatment duration from the 21 trials and the one secondary analysis deemed eligible for the meta-analysis are summarized in Table 2.

(i) Treatment response at the TOC endpoint. The four proxy for placebo uSSTI trials reported TOC clinical treatment response rates ranging from 8% to 66% (Table 2) (35–38). Clinical and methodological heterogeneity was evident for lesion size, infection type, and timing of the TOC assessment (Table 3). For the meta-analysis, the trial that restricted enrollment to subjects with SITL was excluded (35), resulting in a pooled proxy for placebo TOC clinical treatment response rate of 31.0% (95% CI, 6.2% to

TABLE 1 Study design, population, and active comparator of 22 published trials identified in a systematic review for antibacterial treatment effect estimation for acute bacterial skin and skin structure infections[a]

Treatment and study	Trial and design[b]	Population age and infection type[c]	Comparator
Placebo in uncomplicated SSTI, $n = 4$			
Tomayko et al., 2013 (35)	Phase 3, RCT, DB	Age ≥9 mo with SITL	Topical retapamulin
Koning et al., 2008 (36)	RCT, DB	Age ≥9 mo with impetigo	Topical retapamulin
Colin and Avon, 1988 (37)	RCT, DB	Subjects with SSTI	Topical mupirocin
Zaynoun et al., 1974 (38)	RCT, DB	Age ≥4 mo with pyoderma[d]	Topical gentamicin
Linezolid, $n = 12$			
Prokocimer et al., 2013 (39)	Phase 3, RCT, DB	Adults with ABSSSI	Tedizolid
Noel et al., 2012 (40)	Phase 2, RCT, EB phase 2, RCT, EB	Age ≥18 yr with cSSSI	Omadacycline
Covington et al., 2011 (41)	Phase 2, RCT, EB	Age ≥18 yr with ABSSSI	JNJ-QR
Craft et al., 2011 (42)	Phase 2, RCT, EB	Age ≥18 yr with ABSSSI	CEM-102
Lin et al., 2008 (43)	Phase 3, RCT, DB	Age ≥18 yr in China with cSSTI or pneumonia	Vancomycin
Kohno et al., 2007 (44)	RCT, OL	Adults in Japan with cSSTI, pneumonia, or sepsis due to MRSA	Vancomycin
Jauregui et al., 2005 (45)	Phase 3, RCT, DB	Adults with cSSSI	Dalbavancin
Sharpe et al., 2005 (46)	RCT, OL	Age ≥18 yr with MRSA cSSTI	Vancomycin
Weigelt et al., 2005 (47)	RCT, OL	Adults with MRSA cSSTI	Vancomycin
Chen et al., 2004 (48)	One arm, OL	Adults with cSSTI in the Asia-Pacific region	No comparator
Stevens et al., 2002 (49)	RCT, OL	Age ≥13 yr with MRSA cSSTI, pneumonia, UTI, or bacteremia	Vancomycin
Stevens et al., 2000 (50)	RCT, DB	Age ≥18 yr with cSSTI	Oxacillin-dicloxacillin
Ceftaroline, $n = 4$			
Friedland et al., 2012 (54)	Secondary analysis phase 3 RCT, DB	Adults with ABSSSI	Vancomycin
Corey et al., 2010 (51)	Phase 3, RCT, DB	Age ≥18 yr with cSSSI	Vancomycin
Wilcox et al., 2010 (52)	Phase 3, RCT, DB	Age ≥18 yr with cSSSI	Vancomycin
Talbot et al., 2007 (53)	Phase 2, RCT, EB	Age ≥18 yr with cSSSI	Vancomycin
UV light, $n = 2$			
Snodgrass and Anderson, 1937 (23)	Clinical, OL	Subjects with erysipelas	Prontosil
Snodgrass and Anderson, 1937 (24)	Clinical, OL	Subjects with erysipelas	Sulfanilamide

[a] Intention-to-treat population assigned to linezolid, ceftaroline, placebo, or UV light for complicated skin and soft tissue infections (cSSTI), complicated skin and skin structure infections (cSSSI), or acute bacterial skin and skin structure infections (ABSSSI).
[b] RCT, randomized control trial; DB, double blinded; EB, evaluator blinded; OL, open label.
[c] Geographic region mentioned where relevant. SITL, secondarily infected traumatic lesion; MRSA, methicillin-resistant *Staphylococcus aureus*; UTI, urinary tract infection.
[d] Infections were impetigo, insect bites, and dermatitis.

55.9%); the variance across trials ($I^2 = 90.6\%$, $P < 0.0001$) was high (Fig. 2a) (36–38). Eleven of the 12 linezolid trials reported TOC clinical treatment response rates ranging from 50% to 95% (Table 2) (39–44, 46–50). These trials, published over a 13-year interval, had evidence of clinical and methodological heterogeneity for lesion size, type of infection, geographic region, MRSA etiology, per-protocol treatment duration, definition of clinical success, and timing of TOC assessment (Tables 2 and 3). For the meta-analysis, the selection of the three linezolid trials comprised subjects with total surface area lesion size of ≥75 cm^2, non-MRSA-specific populations, and <50% of subjects with abscesses (39, 41, 42). The pooled linezolid TOC clinical treatment response rate was 88.1% (95% CI, 81.0% to 95.1%) (Fig. 2b), with evidence of variation across the trials ($I^2 = 80.4$, $P = 0{\cdot}006$). The three ceftaroline trials had consistent distributions of infection types, durations of treatment, definitions of clinical success, and timing of TOC assessment (Tables 2 and 3). The pooled ceftaroline TOC clinical treatment response rate was 86.1% (95% CI, 83.7% to 88.6%) (Fig. 2c), with no evidence of clinical, methodological, and statistical heterogeneity ($I^2 = 0$, $P = 0.74$) (51–53). The TOC endpoint was not reported in the trials of UV light (23, 24).

(ii) Treatment response at the early clinical endpoint. No early clinical treatment response was reported in the proxy for placebo uSSTI trials. The early clinical treatment response for linezolid in the ITT population was reported in three trials, with a pooled estimate of 78.7% (95% CI, 61.1% to 96.3%); a high variance across trials ($I^2 = 96.7\%$, $P < 0{\cdot}0001$) was evident (39, 41, 42). This response rate approximated the early clinical treatment response rate of 79.4% (95% CI, 75.1% to 83.7%) reported in the most robust of the three linezolid trials with these data, as well as the early clinical treatment response of ceftaroline at 74.0% (95% CI, 69.7% to 78.3%) reported in one trial (39, 54). The pooled UV light treatment response in erysipelas at the early endpoint was 59.0% (95% CI, 52.8% to 65.3%), with low variance between the two trials ($I^2 = 0$, $P = 0.482$), as well as low methodological and

TABLE 2 Trial parameters and treatment response estimates for placebo treatment in uncomplicated skin and soft tissue infection and antibacterial and nonantibacterial treatment for acute bacterial skin and skin structure infection

Treatment and study	Skin infection lesion size	Mean (SD) Rx[a] duration (days)	Intention-to-treat response (no. events/total [%])	
			Early	TOC
Placebo in uncomplicated SSTI, $n = 4$				
Tomayko et al., 2013 (35)	Total area ≤100 cm^2	NA[b]	NA	75/113 (66.4)
Koning et al., 2008 (36)	Total area ≤100 cm^2	NA	NA	28/71 (39.4)
Colin and Avon, 1988 (37)	Subgroups: 1–2, 2–4, 4–6, >6 cm^2	NA	NA	2/25 (8.0)
Zaynoun et al., 1974 (38)	NA	NA	NA	12/25 (48.0)
Linezolid, $n = 12$				
Prokocimer et al., 2013 (39)	≥75 cm^2	NA	266/335 (79.4)	288/335 (86.0)
Noel et al., 2012 (40)	13.5 cm (14.2)[c]	9.6 (4.4)	NA	82/108 (75.9)
Covington et al., 2011 (41)	≥75 cm^2	NA	45/78 (57.7)	64/78 (82.1)
Craft et al., 2011 (42)	≥100 cm^2	11.5 (NA)	63/65 (97)	73/77 (94.8)
Lin et al., 2008 (43)	NA	12.2 (5.4)	NA	30/33 (90.9)
Kohno et al., 2007 (44)	NA	10.9 (5.0)	NA	9/17 (52.9)[d]
Jauregui et al., 2005 (45)	NA	NA	NA	NA[e]
Sharpe et al., 2005 (46)	NA	NA	NA	15/30 (50.0)[d]
Weigelt et al., 2005 (47)	NA	11.8 (4.9)	NA	439/583 (75.3)
Chen et al., 2004 (48)	NA	NA	NA	72/77 (93.5)
Stevens et al., 2002 (49)	51.2% with lesions ≥28 cm^2	12.6 (7.1)	NA	37/53 (69.8)[d]
Stevens et al., 2000 (50)	NA	13.4 (5.4)	NA	279/400 (69.8)
Ceftaroline, $n = 4$				
Friedland et al., 2012 (54)	≥75 cm^2	NA	296/400 (74·0)	NA
Corey et al., 2010 (51)	83.5% had ≥1 dimension >5 cm	Median, 7	NA	304/351 (86.6)
Wilcox et al., 2010 (52)	94.3% had ≥1 dimension >5 cm	Median, 6.5	NA	291/342 (85.1)
Talbot et al., 2007 (53)	NA	Median, 7.8 (range, 0.4–19.5)	NA	59/67 (88.1)
UV light, $n = 2$				
Snodgrass and Anderson, 1937 (23)	NA	2.6 exposures[f]	64/104 (61.5)	NA
Snodgrass and Anderson, 1937 (24)	NA	1.4 exposures[f]	77/135 (57.0)	NA

[a] Values are mean (SD) unless otherwise specified. Rx, treatment.
[b] NA, not available.
[c] Mean maximum linear dimension (SD).
[d] Microbiological ITT (MITT) reported for Sharpe et al., 2005 (46), and Stevens et al., 2002 (49), but microbiological evaluable (ME) was the only outcome available in Kohno et al., 2007 (44).
[e] Jauregui et al., 2005 (45), report results for the clinically evaluable (CE) and microbiological evaluable (ME) population at TOC.
[f] Exposures per case.

clinical heterogeneity in the trial design or execution (Tables 2 and 3) (23, 24).

Antibacterial treatment effect estimation for ABSSSI. Given the biological plausibility of UV light treatment against bacteria, the response rates to UV light treatment in erysipelas were considered inappropriate as proxy for placebo responses (23, 24, 55). Given no available proxy for placebo early clinical treatment response data, an early clinical treatment effect estimate could not be calculated for linezolid or ceftaroline. In contrast, the available proxy for placebo uSSTI treatment response rate (31.0%; 95% CI, 6.2% and 55.9%) permitted calculation of the TOC clinical treatment effect estimate for linezolid and ceftaroline. This across-trials comparison, defined as the difference between the upper bound of the 95% CI for the proxy for placebo treatment response and the respective lower bound of the 95% CI for the treatment response in linezolid (81.0%) and in ceftaroline (83.7%), resulted in TOC clinical treatment effect estimation of 25.1% for linezolid and 27.8% for ceftaroline (Table 4).

Risk of bias assessment. From the assessment of publication quality and risk of bias, the four placebo-controlled trials of uSSTI all had low or uncertain bias scores, 7 of the 16 active comparator trials had one or more high bias scores, and the 2 nonantibacterial trials of UV light had high bias in three of the six categories (Table 5). Funnel plots were assessed (data not shown) to determine potential publication bias; however, the assessment was inconclusive, given the small number of trials and the heterogeneity in treatment response rates.

DISCUSSION

The findings from this systematic review and meta-analysis of the antibacterial treatment effect estimation in ABSSSI inform on future trial designs for this group of infections. The early clinical

TABLE 3 Evidence of methodological and clinical heterogeneity in 22 treatment trials representing proxy for placebo, antibacterial, and nonantibacterial UV light treatment for acute bacterial skin and skin structure infection

Treatment and study	Study design and definitions				Infection type distribution (%)[a]							
	Assessment											
	Early	TOC	Duration	Improvement[b]	Impetigo	Folliculitis	SITL	Other	Abscess	Cellulitis/erysipelas	Wound/other	MRSA
Proxy for placebo												
Tomayko et al., 2013 (35)	NA[c]	12–14[d]	5	No	0	0	100	0				
Koning et al., 2008 (36)	NA	14[d]	5	Yes	100	0	0	0				
Colin and Avon, 1988 (37)	NA	7[d]	5	No	28	36	0	36				
Zaynoun et al., 1974 (38)	NA	7–10[d]	7	No	48	0[e]	0	52				
Linezolid												
Prokocimer et al., 2013 (39)	48–72[d]	7–14[f]	10	No					29.3	41.5	29.3	43.1
Noel et al., 2012 (40)	NA	10–17[g]	NA	No					67	9	24	50.8
Covington et al., 2011 (41)	48–72[h,i]	2–14[g]	7–14	No					35.9	34.6	29.5	NA
Craft et al., 2011 (42)	At 72[h]	7–14[d]	10–14	No					0	64	36	76
Lin et al., 2008 (43)	NA	7–28[g]	7–21	Yes					NA	NA	NA	NA
Kohno et al., 2007 (44)	NA	7–21[g]	7–21	No					NA	NA	NA	100
Jauregui et al., 2005 (45)	NA	14 ± 2	14	Yes					30	30	40	50.5
Sharpe et al., 2005 (46)	NA	10[f]	7–21	No					NA	NA	NA	100
Weigelt et al., 2005 (47)	NA	7[f]	4–21	No					26.7	47.6	25.7	41.3
Chen et al., 2004 (48)	NA	14–21[g]	7–28	Yes					NA	NA	NA	3.2
Stevens et al., 2002 (49)	NA	15–21[g]	7–14	No					33.7	13.0	53.3	100
Stevens et al., 2000 (50)	NA	15–21[g]	10–21	Yes					14.6	44.8/10.3	30.3	NA
Ceftaroline												
Friedland et al., 2012 (54)	48–72[d]	NA	5–14	NA					28.7	54.2	17.1	42.3
Corey et al., 2010 (51)	NA	8–15[g]	5–14	Yes					28.2	34.5	37.4	34.3
Wilcox et al., 2010 (52)	NA	8–15[g]	5–14	Yes					40.6	30.1	29.3	32
Talbot et al., 2007 (53)	NA	8–14[g]	7–14	Yes					44.8	34.3	20.9	NA
UV light												
Snodgrass and Anderson, 1937a (23)	72[j]	NA	NA	NA					0	100	0	0
Snodgrass and Anderson, 1937b (24)	72[j]	NA	NA	NA					0	100	0	0

[a] SITL, secondarily infected traumatic lesions defined as abrasions, lacerations, and wounds; MRSA, methicillin-resistant *Staphylococcus aureus*.
[b] Improvement: successful treatment response at test of cure (TOC).
[c] NA, not available.
[d] After the first dose of study drug.
[e] Folliculitis cases enrolled yet not possible to discern the case number assigned to the placebo arm.
[f] At the end of the treatment visit.
[g] After last dose of study drug.
[h] Postrandomization.
[i] Also includes the assessment from 36 to 84 h.
[j] Hours after initiation of therapy.

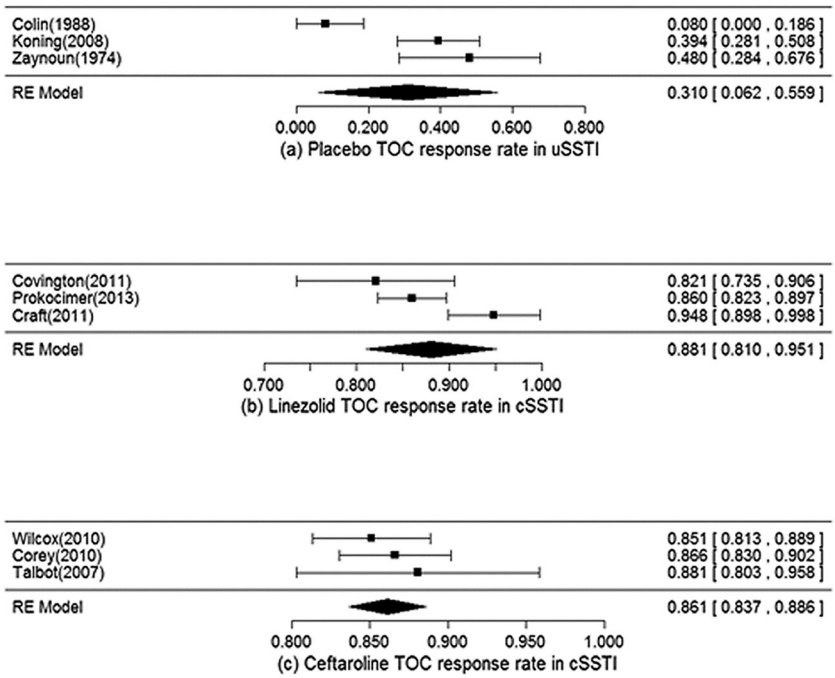

FIG 2 Forest plots of the primary meta-analysis for clinical response at test of cure for proxy-for-placebo treatment (a), linezolid treatment (b), and ceftaroline treatment (c). RE, random effects.

treatment responses for linezolid (78.7%), ceftaroline (74.0%), and UV light (59.0%), provide reference data for the recently recommended primary endpoint in ABSSSI trials (9). The TOC treatment effect estimations for linezolid (25.1%) and ceftaroline (27.8%) provide historical data for noninferiority margin justification in future noninferiority trial designs and for superiority trial designs that may include adaptive models and futility stopping criteria (56, 57). Overall, our findings provide historical evidence of the sensitivity to drug effect (HESDE) at the TOC endpoint for ABSSSI and are consistent with prior estimations of the treatment effect (13).

These TOC treatment effect estimations are conservative, yet are based on the calculations recommended in the FDA guidance (9). These estimates are conservative for two reasons. First, the definition of the antibacterial treatment effect as the difference between the upper bound of the 95% CI for the proxy for placebo treatment response and the respective lower bound of the 95% CI for the antibacterial treatment response is intrinsically conservative. An alternative calculation based on the difference in the point estimates of the placebo and treatment group response rates would yield treatment effect estimations of 57.1% for linezolid and 55.1% for ceftaroline (Table 4). Second, these estimates are further conservative, given that the placebo treatment response for uSSTI, assumed to be higher than the placebo treatment response in ABSSSI, was used as a proxy for the placebo response in ABSSSI. As in most antibacterial trials involving serious infection indications, where there is existing effective therapy as the standard of care, placebo treatment is medically and ethically inappropriate and historically not reported. Hence, randomized, parallel-group noninferiority trials are employed to demonstrate drug efficacy and meet the regulatory guidance for approval of a new test or antibacterial agent in serious infection indications (7–9, 12). To inform on noninferiority margins, we followed the FDA guidance for use of a proxy for placebo in the absence of a true placebo response for ABSSSI. While the placebo response rate in uSSTI should not be interpreted as the true placebo response rate

TABLE 4 Summary of meta-analysis results for the clinical treatment response at the test-of-cure endpoint for placebo in uncomplicated skin and soft tissue infection, linezolid, and ceftaroline, and estimated antibacterial treatment effect estimation for acute bacterial skin and skin structure infection

Treatment group (no. of trials)[a]	Point estimate response rate (% [95% CI[b]])	Treatment effect estimate (%)[c]	Alternate treatment effect estimate (%)[d]
Placebo in uSSTI (3)	31.0 (6.2–55.9)		
Linezolid in ABSSSI (3)	88.1 (81.0–95.1)	25.1	57.1
Ceftaroline in ABSSSI (3)	86.1 (83.7–88.6)	27.8	55.1

[a] uSSTI, uncomplicated skin and soft tissue infection; ABSSSI, acute bacterial skin and skin structure infection.
[b] CI, confidence interval.
[c] Calculated as the difference between the lower bound of the 95% CI of the response rate estimate for each antibacterial treatment and the upper bound of the 95% CI of the proxy for placebo response rate estimate (13, 20).
[d] Calculated as the difference in the point estimate of the response rate between each antibacterial treatment and placebo.

TABLE 5 Assessment of publication bias in 22 publications of placebo treatment for uncomplicated skin and soft tissue infection and antibacterial and nonantibacterial treatment for acute bacterial skin and skin structure infection[a]

Treatment and study	Selection bias		Performance and detection bias: blinding[b]	Attrition bias: incomplete outcome data	Reporting bias: selective reporting	Other biases
	Random sequence generation	Allocation concealment				
Placebo in uncomplicated SSTI, $n = 4$						
Tomayko et al., 2013 (35)	L	L	L	L	U	U
Koning et al., 2008 (36)	U	U	L	L	U	U
Colin and Avon, 1988 (37)	U	U	L	L	U	U
Zaynoun et al., 1974 (38)	U	L	L	L	U	U
Linezolid, $n = 12$						
Prokocimer et al., 2013 (39)	L	L	L	L	L	U
Noel et al., 2012 (40)	L	L	L	L	U	U
Covington et al., 2011 (41)	U	U	L	L	U	U
Craft et al., 2011 (42)	U	L	L	U	U	U
Lin et al., 2008 (43)	U	U	L	U	U	U
Kohno et al., 2007 (44)	U	H	H	L	L	U
Jauregui et al., 2005 (45)	L	L	L	L	H	U
Sharpe et al., 2005 (46)	U	H	H	L	L	U
Weigelt et al., 2005 (47)	U	H	H	U	U	U
Chen et al., 2004 (48)	H	H	H	L	L	U
Stevens et al., 2002 (49)	U	H	H	L	U	U
Stevens et al., 2000 (50)	U	L	L	L	U	U
Ceftaroline, $n = 4$						
Friedland et al., 2012 (54)	L	L	L	L	L	U
Corey et al., 2010 (51)	L	L	L	L	U	U
Wilcox et al., 2010 (52)	L	L	L	L	U	U
Talbot et al., 2007 (53)	U	L	H[c]	L	U	U
UV light, $n = 2$						
Snodgrass and Anderson, 1937 (23)	H	H	H	L	U	U
Snodgrass and Anderson, 1937 (24)	H	H	H	L	U	U

[a] Cochrane Risk of Bias Tool and PRISMA guidelines. H, high bias; U, uncertain bias or unable to determine; L, low bias.
[b] Blinding of participants, personnel, and outcome assessment.
[c] Evaluator blinded only.

in ABSSSI, we assumed that the use of this proxy for the placebo treatment response, resulting in an overestimation of the ABSSSI placebo treatment response, is a conservative approach in estimating antibacterial efficacy relative to that of placebo. Based on the uncertainty of the true placebo effect and the use of the FDA guidance, each ABSSSI treatment effect estimate is conservative, given that the overestimation of the ABSSSI placebo treatment response results in a conservative underestimation of the ABSSSI treatment effect (14, 22, 58).

The second major finding from our study is the evidence and assessment of heterogeneity in these historical clinical trials as relevant and informative to future ABSSSI clinical trials. For the meta-analysis, all data from the ceftaroline trials were included, given minimal evidence for clinical, methodological, and statistical heterogeneity. For the linezolid trials, data from the maximum number of trials ($n = 12$) offered the potential benefit of increased robustness for the treatment effect estimate, but this was offset by significant evidence of clinical, methodological, and statistical heterogeneity (31). The meta-analysis trial selection process for the linezolid TOC clinical treatment response was prioritized to identify the historical trials aligned with the recent FDA regulatory guidance for future ABSSSI trials. This process yielded a selection of just three trials and represented the best reproducibility for the linezolid treatment response to be observed in future noninferiority trials, along with the potential to minimize the deviations in the study operating characteristics, inclusive of type I error and power.

As with all systematic reviews and meta-analyses, we acknowledge the potential bias inherent in our study design and reported findings. First, the publications identified in the systematic review were contingent upon the search terms used, and the inclusion of open-label studies may have introduced bias to the reported outcomes of effectiveness (59). Second, other active comparator treatment effect estimations are plausible for ABSSSI and can be assessed in future meta-analyses. Tedizolid, as an example, was in late-stage development for ABSSSI during the conduct of our systematic review and meta-analysis. Active comparator data for the linezolid treatment response, from the tedizolid phase 3 trial, was included in our meta-analysis (Fig. 2b), and a recent safety summary of tedizolid suggests supportive evidence of preclinical and clinical data for tedizolid treatment in ABSSSI (39, 60). Given the recent approval for use of tedizolid in ABSSSI, the tedizolid treatment effect estimation can be systematically examined for future trials that utilize tedizolid as the active comparator agent. Third, debate continues for the primary endpoint measures in ABSSSI clinical trials (9–11, 13, 15, 16, 20, 60–63). In alignment with the

regulatory guidance, we have categorized the early clinical treatment response at 48 to 72 h, when available, as well as the TOC clinical treatment response, when available. Both the timing of the TOC endpoint and the characterization of the clinical treatment response at this endpoint were limited by nonstandardized definitions across studies (Table 3). Fourth, the early outcome measure for ABSSSI recommended by the Foundation of the National Institutes of Health, of at least 20% reduction in total surface area at day 2 or day 3 versus baseline was not definitely reported in the trials that met our final inclusion criteria, and, therefore, cessation of spread at 48 to 72 h was substituted for this endpoint (20, 62, 63). The comparative early endpoint analysis for cessation of spread versus at least 20% reduction in total surface areas was, therefore, beyond the scope of our systematic review. Fifth, only three linezolid studies and one ceftaroline study reported the 48- to 72-h early clinical treatment response, and, hence, the small sample size affects the robustness of this measure of treatment response. Sixth, it is plausible that successful early clinical treatment responses in ABSSSI subjects (48 to 72 h) might potentially become failures at later efficacy time point measurements (7 to 14 days posttreatment). Future clinical trials and nonrandomized studies are needed to assess subjects at both early and later endpoints, in order to further understand the potential discordances between early successes and late failures and subsequent clinical implications (39, 45). Seventh, publication bias may exist, but assessment using funnel plot analysis was inconclusive for such bias. Last, we acknowledge potential secular changes in the standard of medical care and hygiene practices, which may have influenced treatment effect estimates from these historical studies.

In summary, the results of this systematic review and meta-analysis for the antibacterial treatment effect estimation for ABSSSI inform the design, execution, and analysis of future ABSSSI trials. The across-trials comparison enables noninferiority margin justification in the absence of placebo-controlled trials for ABSSSI. We have characterized the vast amount of clinical, methodological, and statistical heterogeneity for ABSSSI as reported in trials of proxy for placebo treatment as well as trials of linezolid and ceftaroline.

APPENDIX

Search terms for the systematic review for antibacterial treatment effect estimation for acute bacterial skin and skin structure infection. Publications were restricted to dates before 28 February 2013. Searches included abbreviations, plural, and full-phrase versions of the terms.

Search A1. For placebo-controlled trials for ABSSSI, the search terms were "placebo" combined with "SSTI," "SSSI," "ABSSSI," "cellulitis," "abscess," "wound infection," "burn infection," and "erysipelas."

Search A2. For uSSTI publications, the search terms were "placebo" combined with "SSTI," "SSSI," "ABSSSI," "impetigo," "abscess," "cellulitis," "furunculosis," "carbunculosis," "folliculitis," "traumatic lesion," "erysipelas," and "ecthyma."

Searches B1 and B2. The searches for linezolid and ceftaroline were conducted separately, with each drug name, respectively, combined with "SSTI," "SSSI," "ABSSSI," "cellulitis," "abscess," "wound infection," "burn infection," and "erysipelas."

Search C. For trials reporting nonantibacterial treatment response, the terms included all previously listed skin infection terms, along with a review of the available reports of nonantibacterial treatment in skin infections.

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The research study was conducted by all authors within our defined research, epidemiology (J.E.C., F.S.M.-G., L.M.M.), and statistical (G.L.) roles and scope of work for Quantitative Sciences and our antibacterial development program at GlaxoSmithKline (GSK). J.E.C. is a GSK-UNC research assistant, F.S.M.-G, is a GSK consultant, L.M.M. is a GSK employee and eligible for stock ownership, and G.L. was an employee at GSK, with stock options during the study execution; he is currently an employee at Pfizer.

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