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REVIEW ARTICLE

Meta-analysis of Cephalosporin Versus Penicillin Treatment of Group A Streptococcal Tonsillopharyngitis in Children

Janet R. Casey, MD,* and Michael E. Pichichero, MD‡

ABSTRACT. *Objective.* **To conduct a meta-analysis of randomized, controlled trials of cephalosporin versus penicillin treatment of group A β-hemolytic streptococcal (GABHS) tonsillopharyngitis in children.**

Methodology. **Medline, Embase, reference lists, and abstract searches were conducted to identify randomized, controlled trials of cephalosporin versus penicillin treatment of GABHS tonsillopharyngitis in children. Trials were included if they met the following criteria: patients <18 years old, bacteriologic confirmation of GABHS tonsillopharyngitis, random assignment to antibiotic therapy of an orally administered cephalosporin or penicillin for 10 days of treatment, and assessment of bacteriologic outcome using a throat culture after therapy. Primary outcomes of interest were bacteriologic and clinical cure rates. Sensitivity analyses were performed to assess the impact of careful clinical illness descriptions, compliance monitoring, GABHS serotyping, exclusion of GABHS carriers, and timing of the test-of-cure visit.**

Results. **Thirty-five trials involving 7125 patients were included in the meta-analysis. The overall summary odds ratio (OR) for the bacteriologic cure rate significantly favored cephalosporins compared with penicillin (OR: 3.02; 95% confidence interval [CI]: 2.49–3.67, with the individual cephalosporins [cephalexin, cefadroxil, cefuroxime, cefpodoxime, cefprozil, cefixime, ceftibuten, and cefdinir] showing superior bacteriologic cure rates). The overall summary OR for clinical cure rate was 2.33 (95% CI: 1.84–2.97), significantly favoring the same individual cephalosporins. There was a trend for diminishing bacterial cure with penicillin over time, comparing the trials published in the 1970s, 1980s, and 1990s. Sensitivity analyses for bacterial cure significantly favored cephalosporin treatment over penicillin treatment when trials were grouped as double-blind (OR: 2.31; 95% CI: 1.39–3.85), high-quality (OR: 2.50; 95% CI: 1.85–3.36) trials with well-defined clinical status (OR: 2.12; 95% CI: 1.54–2.90), with detailed compliance monitoring (OR: 2.85; 95% CI: 2.33–3.47), with GABHS serotyping (OR: 3.10; 95% CI: 2.42–3.98), with carriers eliminated (OR: 2.51; 95% CI: 1.55–4.08), and with test of cure 3 to 14 days posttreatment (OR: 3.53; 95% CI: 2.75–4.54). Analysis of comparative bacteriologic cure rates for the 3 generations of cephalosporins did not show a difference.**

Conclusions. **This meta-analysis indicates that the likelihood of bacteriologic and clinical failure of GABHS tonsillopharyngitis is significantly less if an oral cephalosporin is prescribed, compared with oral penicillin.** *Pediatrics* **2004;113:866–882;** ***meta-analysis, cephalosporin, penicillin, group A streptococcus, pharyngitis.***

ABBREVIATIONS. GABHS, group A β-hemolytic streptococcal/streptococci; OR, odds ratio; CI, confidence interval.

Penicillin has been the agent of choice for treatment of group A β-hemolytic streptococcal (GABHS) tonsillopharyngitis for the past 5 decades as advocated by the American Heart Association,[1] the American Academy of Pediatrics,[2] and the World Health Organization.[3] Since the early 1980s, there have been studies showing an increase in GABHS infection not cured by penicillin treatment.[4–6] In 2001, Kaplan and Johnson[7] published a meticulously designed study in which injectable benzathine penicillin failed to eradicate GABHS in 37% to 42% of children; oral penicillin failed in 35% of children.

Cephalosporins have been used successfully for the treatment of GABHS tonsillopharyngitis since the early 1970s. Two prior meta-analyses comparing cephalosporin and penicillin treatment for GABHS tonsillopharyngitis have been published.[8,9] Each of those meta-analyses concluded that cephalosporin treatment was superior in eradication of GABHS from acutely ill children. Since the publication of the last meta-analysis, 22 new randomized, comparative trials in children have been published. The objective of this study was to use updated and rigorous meta-analysis methods to compare the relative efficacy of cephalosporin and penicillin treatment of GABHS tonsillopharyngitis in children in all available randomized, controlled trials.[4,5,10–42]

METHODS

Trial Identification

Randomized, controlled trials comparing a cephalosporin and penicillin in the treatment of GABHS tonsillopharyngitis in children <18 years old were identified from Medline (1966–2000) and Embase (1974–2000) searches. The searches had no language restriction; the search terms used were streptococcal pharyngitis/tonsillitis, cephalosporin, and penicillin. Reference lists of relevant publications were reviewed to identify additional trials. Abstracts from Interscience Conference on Antimicrobial Agents and Chemotherapy and Society for Pediatric Research meetings were searched also to identify relevant trials that were unpublished.

Trial Selection and Quality

Trials comparing cephalosporin and penicillin treatment for GABHS tonsillopharyngitis infections were independently re-

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viewed for inclusion by us according to the following criteria: 1) patients <18 years old; 2) bacteriologic confirmation of GABHS tonsillopharyngitis with a positive rapid antigen detection test and/or a positive throat culture before treatment; 3) random assignment to antibiotic-therapy groups comparing an orally administered cephalosporin with an orally administered penicillin for a 10-day treatment duration; and 4) assessment of bacteriologic outcome using a throat culture after therapy. The Jadad scale was used to assess the quality of the included trials. The scale assigned scores from 0 to 5 (best quality trial) based on the following criteria: 1) study participants were allocated randomly to treatment by using an appropriate method such as a random-numbers table; 2) the intervention was double blinded; and 3) an accounting and description of study withdrawals was done.[43]

Data Abstraction and Definition of Terms

The primary outcomes of interest were: 1) bacteriologic cure, defined as a failure to isolate GABHS by throat culture obtained after completion of the antibiotic course; and 2) clinical cure, defined as the resolution of or improvement in the presenting signs and symptoms of GABHS infection after completion of the antibiotic course and continuing throughout follow-up. Sensitivity analyses were performed to assess the impact of careful clinical illness descriptions, compliance monitoring, GABHS serotyping, exclusion of GABHS carriers, and timing of the test-of-cure culture on the bacteriologic and clinical cure rates. We independently abstracted primary outcomes and sensitivity analysis data from each trial using a data-extraction form. Differences were settled by discussion, and consensus was reached. Additionally, where the published data allowed, an attempt was made to identify and eliminate GABHS carriers and recalculate the bacteriologic and clinical cure rates. For this purpose, GABHS carriers were defined as those patients who had isolation of GABHS on early or late follow-up cultures without GABHS tonsillopharyngitis symptoms.

Data Analysis

Meta-analysis was performed on the complete trial data set as well as trials grouped by decade: 1970–1979, 1980–1989, and 1990–1999. The meta-analysis was conducted using the Cochrane Collaboration's Revman 4.1 program (Cochrane Collaboration, Oxford, England). Differences in bacteriologic cure rates after cephalosporin treatment in comparison to penicillin treatment were calculated and expressed as an odds ratio (OR) with 95% confidence intervals (CIs). An OR >1 indicated a higher bacteriologic cure rate for cephalosporin treatment, as compared with penicillin treatment. ORs were calculated for individual trial outcomes, and a summary OR was determined for trials grouped by individual cephalosporin, by cephalosporin generation, by decade, and overall using 2 methods: the Peto fixed-effects model,[44] which assumes trial homogeneity, and the DerSimonian and Laird random-effects[45] model, which assumes trial heterogeneity. Statistical heterogeneity among trials was assessed by χ^2 analysis.[46,47] Investigation of possible clinical heterogeneity was performed by several stratified analyses: 1) grouping studies by decade; 2) grouping studies by individual cephalosporin generation; and 3) grouping studies by individual cephalosporins used. Sensitivity analyses were conducted to assess the robustness of the overall meta-analysis and to further investigate possible clinical heterogeneity among the trials by comparing summary ORs among groups redefined by 1) excluding all trials that were not double blinded, 2) excluding trials of a lower methodological quality (Jadad score ≤2), 3) excluding trials that did not give specific details of the clinical status of the patients, 4) excluding trials that did not monitor compliance, 5) excluding trials that did not perform serotyping or genotyping of the GABHS organism isolated on the initial and follow-up throat culture, 6) excluding trials that did not define carriers and eliminate them from analysis, 7) excluding trials that did not perform the test-of-cure follow-up culture 3 to 14 days after completion of the antibiotic treatment, and 8) including abstracts of trials for which peer-reviewed papers were not subsequently published. Bacterial cure rate trends between the 3 decades was calculated by using a z test for trends. A funnel graph of the standard effect versus the OR was plotted to determine whether publication bias existed.

RESULTS

Literature Search and Trial Inclusion

The Medline and Embase searches yielded 140 citations, 59 of which were randomized, clinical trials comparing cephalosporin treatment with penicillin treatment of GABHS tonsillopharyngitis. Two trials not identified by Medline or Embase were retrieved from reference listings, and 5 trials were identified from abstract searches. Sixty-six citations were assessed further according to inclusion criteria. Twenty six of these trials were excluded from the meta-analysis for the following reasons: 1) patient randomization could not be determined from the text of the article; 2) trial participants were predominantly or all adults; 3) bacterial cure was not a measured outcome; 4) the data presented were a republication of previous data already included in trials in the meta-analysis; or 5) the treatment was not for 10 days. This left 40 trials: 5 unpublished abstracts and 35 published trials for inclusion in the meta-analysis.

Methodologic Quality

The mean quality score for all trials was 2.3 (standard deviation: 1.3–3.3), of a maximum score of 5; 31% of the trials were of higher quality (Jadad score >2). The mean quality score increased each of the 3 decades: 1.8, 2.2, and 2.6 for 1970–1979, 1980–1989, and 1990–1999, respectively (Table 1). Of the 35 trials, 6 were double-blind studies.[18,20,28,29,31,40] The investigators were blinded to treatment allocation in 9 trials.[5, 21,22,27,33,34,37,39,41] Three quarters of the studies adequately described the reasons for patient dropouts for the overall study. Three trials provided individual dropout rates for each treatment group.[33,34,42] Nearly all patients who were dropped from studies were dropped because GABHS was not isolated on the initial throat culture.

Description of Trials

Twenty-six trials were conducted in the United States.[4,10–13,15–24,28,29,31–34,36–38,41,42] Twenty-four trials were conducted in private practices,[4,5,10–13,15–23,25,27–29,31,32,34,35,38,42] 7 trials were conducted in hospital emergency departments and clinics,[14,24,26,30,33,36,39] and 4 trials did not state the site at which they were conducted.[37,38,40,41] Six trials took place in the 1970s,[10–15] 11 took place in the 1980s,[4,16–25] and 18 took place in the 1990s[5,26–42] (Table 1). All trials required isolation of GABHS on a throat culture. Eleven trials[5,27,31,33,35–38,40–42] used a rapid antigen test at enrollment, but patients were dropped if GABHS did not grow from the throat culture. Early trials excluded patients with 1+ growth of GABHS on the initial throat culture in an attempt to avoid enrollment of carriers. These excluded patients represented a small proportion of those considered for enrollment. Two trials were conducted specifically with patients who had recurrent GABHS tonsillopharyngitis.[5,40] All other trials did not specify inclusion or exclusion of patients with recurrent GABHS infections. Eleven different cephalosporins and 1 carbacephem were compared with penicillin in the 35 trials: 16 first-generation, 14 second-generation, and

TABLE 1. Methodologic Description of Studies

Study	Ref No	Quality Score	Concealment of Treatment Allocation	No of ITT/Evaluable (% Dropouts)	No in Arm	Antibiotic	Clinical Status	Compliance Monitoring	Serotyping Performed	Details of Carriers*	Test of Cure Day†
1970–1979											
	10	2	Unblinded	193/180 (5%)	79 36	Cephaloglycin Penicillin V	No details	RC, TC UT	Yes	B	4–21 days
	11	2	Unblinded	150/140 (7%)	46 50	Cephalexin Penicillin V	Detailed Signs and symptoms	RC, TC UT	Yes	C	1–7 days
	12	2	Unblinded	Not given	89 76	Cephalexin Penicillin G	No details	No details	No	A	1–21 days
	13	2	Unblinded	117/114 (3%)	84 89	Cephalexin Penicillin V	Detailed Signs and symptoms	RC, TC, UT, S	Yes	B	4–21 days
	14	2	Unblinded	118/97 (18%)	43 54	Cephalexin Penicillin V or G	No details	UT	No	B	Exact date not given
	15	1	Unblinded	Not given	15 15	Cefaclor Penicillin V	No details	UT	Yes	A	4–25 days
1980–1989											
	16	2	Unblinded	110/96 (13%)	44 52	Cefadroxil Penicillin V	No details	No details	Yes	C	1–4 days
	17	2	Unblinded	99/99 (0%)	49 50	Cefadroxil Penicillin V	No details	UT	Yes	C	1–4 days
	18	3	Double Blinded	214/162 (24%)	79 83	Cefadroxil Penicillin V	No details	UT	Yes	C	Day 4
	19	2	Unblinded	Not given	224 226	Cefadroxil Penicillin V	No details	RC, TC, UT	No	B	1–21 days
	4	2	Unblinded	111/104 (6%)	51 53	Cefaclor Penicillin V	No details	RC, TC, UT	Yes	C	1–4 days
	20	4	Double Blinded	238/195 (18%)	96 99	Cefadroxil Penicillin V	No details	UT	Yes	C	4–21 days
	21	2	Investigator Blinded	110/93 (15%)	60 33	Cefuroxime Penicillin V	Detailed Signs and symptoms	TC, UT	Yes	B	3–7 days
	22	1	Investigator Blinded	150/137 (9%)	69 68	Cefadroxil Penicillin V	Detailed Signs and symptoms	TC	Yes	C	8–23 days
	23	2	Unblinded	133/115 (16%)	77 38	Cefuroxime Penicillin V	No details	TC, UT	Yes	B	2–7 days
	24	2	Unblinded	32/20 (38%)	12 8	Cefadroxil Penicillin V	No details	RC, TC	No	A	1–20 days
	25	2	Unblinded	300/239 (20%)	118 121	Cefadroxil Penicillin V	Detailed Signs and symptoms	No details	Yes	C	1–5 days

TABLE 1. Continued

Study	Ref No	Quality Score	Concealment of Treatment Allocation	No of ITT/Evaluable (% Dropouts)	No in Arm	Antibiotic	Clinical Status	Compliance Monitoring	Serotyping Performed	Details of Carriers*	Test of Cure Day†
1990–1999											
	26	2	Unblinded	108/71 (34%)	38 33	Cefetamet pivoxil Penicillin V	No details	No details	No	B	1 day
	27	2	Investigator Blinded	180/176 (2%)	95 81	Cefadroxil Penicillin V	No details	RC, TC	No	A	1–10 days
	28	5	Double Blinded	116/93 (20%)	47 46	Cefaclor Penicillin V	No details	No details	No	B	2 days
	29	5	Double Blinded	654/525 (20%)	263 262	Cephalexin Penicillin V	Detailed Signs and symptoms	TC	Yes	A	8–25 days
	30	3	Unblinded	117/100 (15%)	33 33	Cefetamet pivoxil Penicillin V	No details	TC	No	B	1 day
	31	4	Double Blinded	233/192 (18%)	104 88	Loracarbef Penicillin V	Detailed Signs and symptoms	UT	Yes	C	3–5 days
	32	3	Unblinded	110/95 (14%)	48 47	Cefixime Penicillin V	No details	RC, TC, UT	Yes	C	2–7 days
	33	2	Investigator Blinded	580/413 (29%)	275 138	Cefpodoxime Penicillin V	No details	No details	No	B	3–8 days
	34	3	Investigator Blinded	533/385 (28%)	259 126	Cefuroxime Penicillin V	No details	TC, UT	Yes	B	19–25 days
	35	3	Unblinded	409/323 (21%)	172 151	Cefprozil Penicillin V	No details	TC	Yes	B	1–12 days
	36	1	Unblinded	Not given	76 69	Cefprozil Penicillin V	No details	RC, TC	No	B	4–10 days
	37	1	Investigator Blinded	484/377 (22%)	121 130	Cefpodoxime Penicillin V	Detailed Signs and symptoms	RC, TC, UT	Yes	B	4–7 days
	5	2	Investigator Blinded	236/223 (6%)	114 109	Cefuroxime Penicillin V	No details	TC	Yes	B	2–5 days
	38	2	Investigator Blinded	617/426 (31%)	294 132	Ceftibuten Penicillin V	No details	No details	Yes	A	5–7 days
	39	1	Unblinded	No details	18 16	Cefetamet pivoxil Penicillin V	No details	No details	No	C	3–5 days
	40	3	Double Blinded	331/265 (20%)	135 130	Loracarbef Penicillin V	No details	TC	Yes	B	1–20 days
	41	2	Investigator Blinded	792/682 (14%)	455 227	Cefdinir Penicillin V	No details	No details	Yes	B	4–9 days
	42	3	Unblinded	462/374 (19%)	187 187	Cefadroxil Penicillin V	Detailed Signs and symptoms	RC, UT	Yes	A	2–12 days

ITT indicates intention to treat; RC, record card; TC, tablet count; UT, urine testing; S, serum antibiotic levels.
* A indicates carriers identified and excluded from analysis; B, carriers not identified; C, carriers identified and excluded from the recalculated analysis.
† Test of cure is reported as number of days after completion of antibiotic therapy.

5 third-generation trials. Nine trials gave detailed descriptions of patient signs and symptoms at enrollment.[11,13,21,22,25,29,31,37,42] Three trials provided no information on the clinical status of the patients at enrollment.[24,26,30] The remaining 23 trials stated that the patients were acutely ill with tonsillopharyngitis. Serotyping of the infecting streptococcal organism was performed in the majority of the trials (24 of 35 trials). Genotyping in lieu of serotyping was done in 1 trial.[41] When serotyping or genotyping was performed, true bacterial failures could be differentiated from reinfection with another serotype of GABHS. The true bacterial failure rates were used in the meta-analysis calculations. Carriers were specifically defined and eliminated from analysis by the authors in 7 trials.[12,15,24,27,29,38,42] Eleven additional trials had sufficient details of the data to allow carriers, defined as a patient with GABHS isolated on the test-of-cure throat culture and no tonsillopharyngitis signs and/or symptoms, to be identified and excluded from analysis and to allow recalculation of new bacterial and clinical cure rates.[4,11,16–18,20,22,25,31,32,39]

The timing of the test-of-cure follow-up culture varied among the trials. Most trials had an early and a late follow-up culture. Follow-up test-of-cure cultures were obtained between 3 and 14 days after antibiotic completion in 9 trials, which is considered the optimal timing.[18,21,31,33,36–39,41] When possible, bacteriologic and clinical cure rates used in this meta-analysis were taken from the early follow-up test-of-cure data to minimize the inclusion of GABHS reacquisitions or new infections in the final cure rates.

Specific compliance-monitoring methods used by 26 trials included tablet counts, record cards, urine tests, and serum drug levels. The remaining 9 trials provided no information on compliance monitoring or used parental or patient questioning only.[12,16,25,26,28,33,38,39,41]

Outcome of Bacterial and Clinical Cure Rates

The primary outcome analyzed was the bacterial cure rate, comparing cephalosporin with penicillin treatment. The summary OR for bacterial cure in all 35 trials, including 7125 patients, was 3.02 (95% CI: 2.49–3.67) favoring cephalosporin treatment ($P < .00001$) (Fig 1). The summary ORs for the trials performed in each of the 3 decades (1970s, 1980s, and 1990s) were 2.06 (95% CI: 1.27–3.34), 2.84 (95% CI: 1.97–4.09), and 3.25 (95% CI: 2.49–4.23), respectively. Cephalosporin treatment showed a trend toward increasing superiority over penicillin treatment over the past 3 decades; however, the trend did not reach statistical significance ($P = .09$). Of 35 studies, 33 had a point estimate that favored cephalosporins. In 19 trials, cephalosporin treatment was significantly superior to penicillin treatment. One trial had a point estimate favoring penicillin, but the results did not reach significance.[21] The bacterial cure rate did not favor either antibiotic in 1 trial.[15]

Five trials did not report the primary outcome of clinical cure. Therefore, the primary outcome of clinical cure rate comparing cephalosporin with penicillin treatment was assessed in 30 trials. The overall summary OR for clinical cure rate in those 30 trials, including 6448 patients, was 2.34 (95% CI: 1.84–2.97), favoring cephalosporin treatment ($P < .00001$) (Fig 2). The summary ORs for the 30 trials performed in each of the decades (1970s, 1980s, and 1990s) were 2.19 (95% CI: 1.25–3.85), 2.36 (95% CI: 1.65- 3.37), and 2.30 (95% CI: 1.62–3.26), respectively. The clinical cure rate consistently favored cephalosporin treatment over penicillin treatment; however, there was not a significant difference between the decades when trials were published ($P = .5$). Of 30 trials, 23 had a point estimate favoring cephalosporins. The clinical cure rate in 11 trials reached significance favoring cephalosporins as described in the report. Three trials had point estimates favoring penicillin, but the difference in the clinical cure rate did not reach significance in any trial.[17,28,31] The clinical cure rate in 1 trial did not favor either antibiotic.[15] Two trials did not have an OR calculated because of 100% clinical cure rate for both cephalosporin and penicillin treatment.[23,30]

Sensitivity Analysis

To test the robustness of the overall summary ORs, sensitivity analyses were conducted for the primary outcomes of bacterial and clinical cure rate (Tables 2 and 3). Bacterial cure rates significantly favored cephalosporin treatment when trials were grouped as 1) double-blinded trials ($P < .001$), 2) high-quality trials (Jaded score >2; $P < .00001$), 3) trials with well-defined clinical status at diagnosis ($P < .00001$), 4) trials with detailed compliance monitoring ($P < .00001$), 5) trials in which serotyping or genotyping occurred ($P < .00001$), 6) trials that eliminated carriers from analysis ($P < .0002$), and 7) trials with a test of cure 3 to 14 days after antibiotic completion ($P < .008$).

The robustness of the overall summary OR for clinical cure was assessed. Sensitivity analyses for the clinical cure rate significantly favored cephalosporin treatment when trials were grouped as trials with well-defined clinical status at diagnosis ($P < .03$), trials with detailed compliance monitoring ($P < .00001$), trials in which serotyping or genotyping occurred ($P < .00001$), trials that eliminated carriers from analysis ($P < .00005$), and trials with a test of cure 3 to 14 days after antibiotic completion ($P < .006$) (Table 3). When only those trials with a high-quality score were analyzed (10 trials, 2301 patients), the clinical cure rate significantly favored cephalosporin treatment by a small margin ($P < .04$). Additionally, when only the 6 double-blinded trials were analyzed (1432 patients), the clinical cure rate did not significantly favor either cephalosporin or penicillin treatment ($P = 0.5$).

Stratified Analysis of Cephalosporins

Eleven different cephalosporins (3 first generation, 4 second generation, and 4 third generation) and 1 carbacephem were included in 2 stratified analyses. First, each individual cephalosporin was analyzed compared with penicillin (Figs 3 and 4). Four cephalosporins (cephaloglycin, cefixime, ceftibuten, and cefdinir) had only 1 trial included in this analysis.

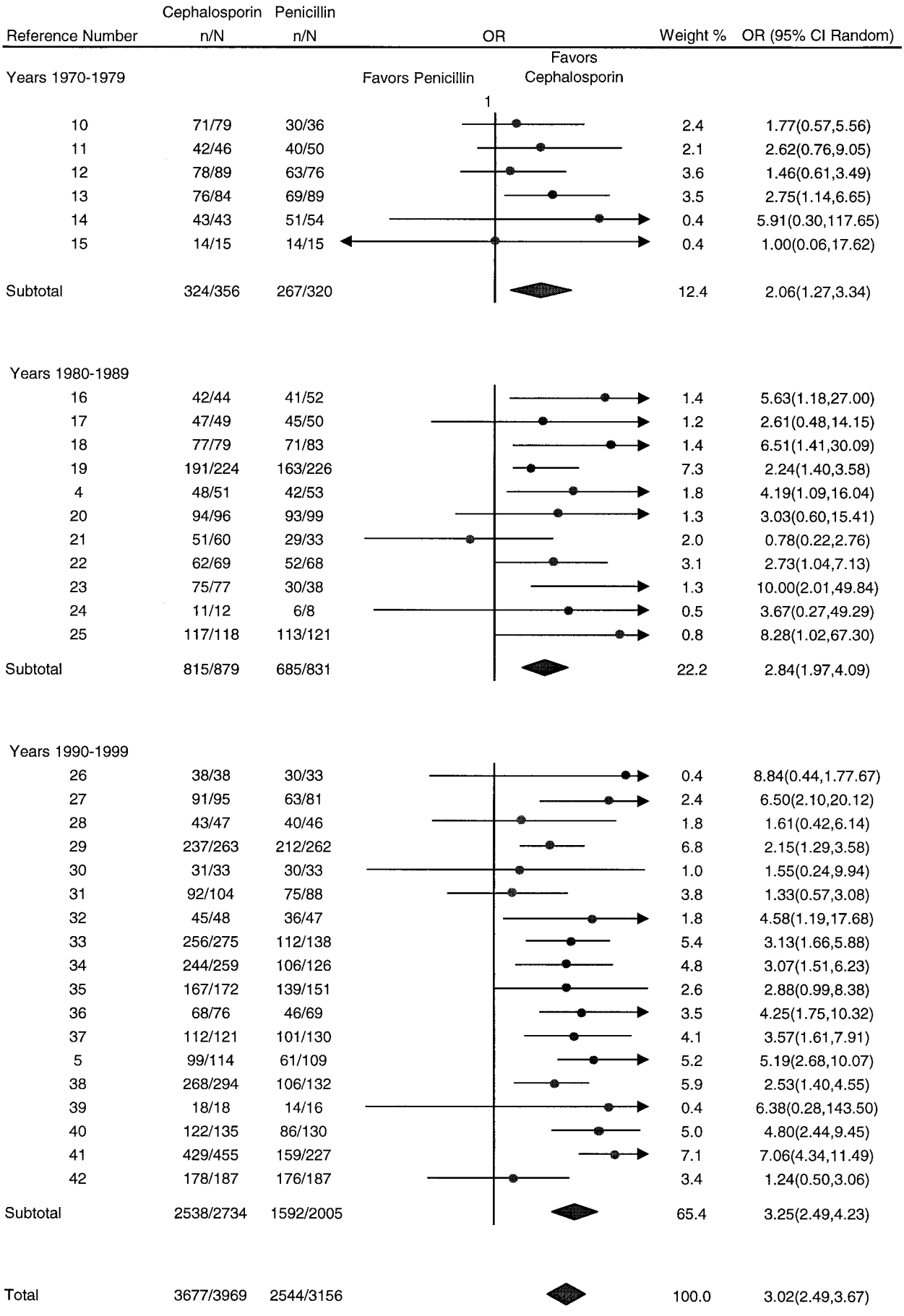

Fig 1. Bacterial cure rate analysis: cephalosporin versus penicillin in the treatment of GABHS tonsillopharyngitis.

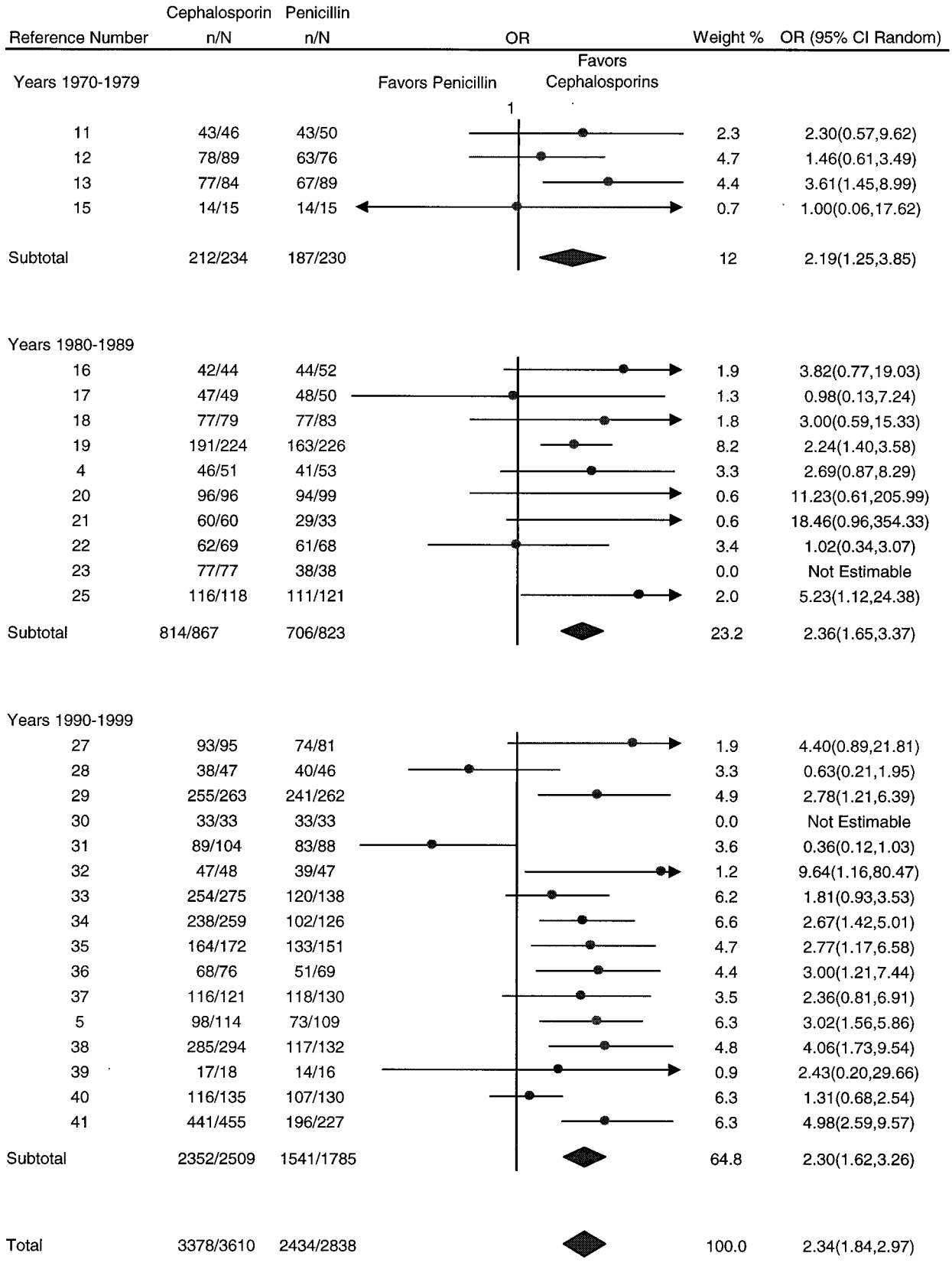

Fig 2. Clinical cure rate analysis: cephalosporin versus penicillin in the treatment of GABHS tonsillopharyngitis.

Cephalexin (5 trials), cefadroxil (10 trials), cefaclor (3 trials), cefuroxime (4 trials), cefetamet (3 trials), cefprozil (2 trials), loracarbef (2 trials), and cefpodoxime (2 trials) had >1 trial to combine and calculate individual and summary ORs. When compared with penicillin treatment, cephalexin, cefadroxil, cefuroxime, cefprozil, cefpodoxime, cefixime, ceftibuten, and cefdinir were statistically superior in bacterial

TABLE 2. Sensitivity Analysis of Primary Outcome: Bacterial Cure Rate

Description	Ref Nos of Included Studies	No of Trials	No of Participants	OR (95% CI)
All trials	4, 5, 10–42	35	7125	3.02 (2.49–3.67)
Double-blinded studies	18, 20, 28, 29, 31, 40	6	1432	2.31 (1.39–3.85)
Quality score >2	18, 20, 28–32, 34, 35, 40, 42	11	2673	2.50 (1.85–3.36)
Clinical status defined	11, 13, 21, 22, 25, 29, 31, 37, 42	9	2080	2.12 (1.54–2.90)
Compliance monitoring detailed	4, 5, 10, 11, 13–15, 17–24, 27, 29–32, 34–38, 40, 42	26	4906	2.85 (2.33–3.47)
GABHS typing performed	4, 5, 10, 11, 13, 15–18, 20–23, 25, 29, 31, 32, 34, 35, 37, 38, 40–42	24	5395	3.10 (2.42–3.98)
Carriers eliminated	12, 15, 24, 27, 29, 38, 42	7	1716	2.51 (1.55–4.08)
Follow-up test of cure 3–14 days after therapy	18, 21, 31, 33, 36–39, 41	9	2398	3.53 (2.75–4.54)

TABLE 3. Sensitivity Analysis of Primary Outcome: Clinical Cure Rate

Description	Ref Nos of Included Studies	No of Trials	No of Participants	OR (95% CI)
All trials	4, 5, 11–13, 15–23, 25, 27–41	30	6448	2.33 (1.84–2.97)
Double-blinded studies	18, 20, 28, 29, 31, 40	6	1432	1.33 (0.62–2.83)
Quality score >2	18, 20, 28, 29–32, 34, 35, 40	10	2301	1.82 (1.03–3.21)
Clinical status defined	11, 13, 21, 22, 25, 29, 31, 37	8	1706	2.08 (1.06–4.06)
Compliance monitoring detailed	4, 5, 11, 13, 15, 17–23, 27, 29–31, 34–37, 40	22	4300	2.27 (1.73–2.97)
GABHS typing performed	4, 5, 11, 13, 15–18, 20–23, 25, 29, 31, 32, 34, 35, 37, 38, 40, 41	22	4906	2.55 (1.88–3.46)
Carriers eliminated	12, 15, 27, 29, 38	5	1322	2.62 (1.65–4.16)
Follow-up test of cure 3–14 days after therapy	18, 21, 31, 33, 36–39, 41	9	2398	2.49 (1.83–3.38)

and clinical eradication of GABHS. Second, the trials were grouped by cephalosporin generation and analyzed to assess a treatment effect and assess heterogeneity among the trials. The first-generation cephalosporins, based on 16 trials (3119 patients) evaluating bacterial cure rate, were statistically superior to penicillin therapy (OR: 2.41; 95% CI: 1.90–3.06; $P < .00001$); for 12 trials (2513 patients) evaluating clinical cure rate the OR was 2.36 (95% CI: 1.76–3.16; $P < .00001$). The second-generation cephalosporins showed similar results, with bacterial cure rate superiority based on 14 trials (2139 patients; OR: 2.68; 95% CI: 1.74–4.13; $P < .00001$); for 13 trials (2275 patients) evaluating clinical cure rate the OR was 2.36 (95% CI: 1.78–3.13; $P < .00001$). Last, the third-generation cephalosporins were evaluated in five trials (1867 patients), and these too showed higher bacterial cure rates compared with penicillin (OR: 3.93; 95% CI: 2.52–6.13; $P < .002$); for clinical cure the OR was 3.28 (95% CI: 1.99–5.41; $P < .00001$).

Heterogeneity

Tests for statistical heterogeneity were performed for both primary outcomes by χ^2 analysis. There was no heterogeneity among the 35 trials for bacterial cure rate ($P = .086$), but heterogeneity was present among the 30 trials for clinical cure rate ($P = .004$). The summary and individual trial ORs were calculated by using both a fixed-effects model, which assumes trial homogeneity, and a random-effects model, which accounts for trial heterogeneity. Results are reported using the random-effects model, because trial heterogeneity was present for 1 of the primary outcomes but both methods yielded similar results with no significant change in any of the ORs (data not shown).

To further assess possible clinical and statistical heterogeneity among the 35 trials, stratified and sensitivity analyses were performed. We performed stratified analyses for the trials grouped by the 3 past decades, the 3 different generations of cephalosporins, and trials of individual cephalosporins. Neither of the primary outcomes (bacterial and clinical cure rates) showed any statistical heterogeneity in the 1970s and 1980s, but heterogeneity was found among the trials published in the 1990s (Figs 1 and 2).

Second, we examined statistical heterogeneity among the trials involving individual cephalosporins and found it among the 2 trials involving loracarbef and in the 3 trials involving cefuroxime therapy (Figs 3 and 4). In 1 of these 3 trials,[21] the average dose of cefuroxime was 7 mg/kg per day, compared with the recommended and approved dose of 30 mg/kg per day (ie, cefuroxime was given at approximately one quarter of the standard dose). Regrouping the trials by specific confounders for sensitivity analysis allowed additional evaluation of the presence of statistical heterogeneity. Heterogeneity was present when only those trials performing serotyping were analyzed. Third, we analyzed the data set for heterogeneity among the trials of the 3 generations of cephalosporins and found none among the first- and third-generation cephalosporins, but heterogeneity was found among the 14 trials involving second-generation cephalosporins.

Publication Bias

The symmetrical, inverted funnel-shaped plot of the ORs versus standard effect (Fig 5), as shown by the wide scattering of ORs from small studies and narrowing to a peak among large studies, suggests no evidence of publication bias. Additionally, a sensitivity analysis was performed that included 5 abstracts of trials that were never published. The sum-

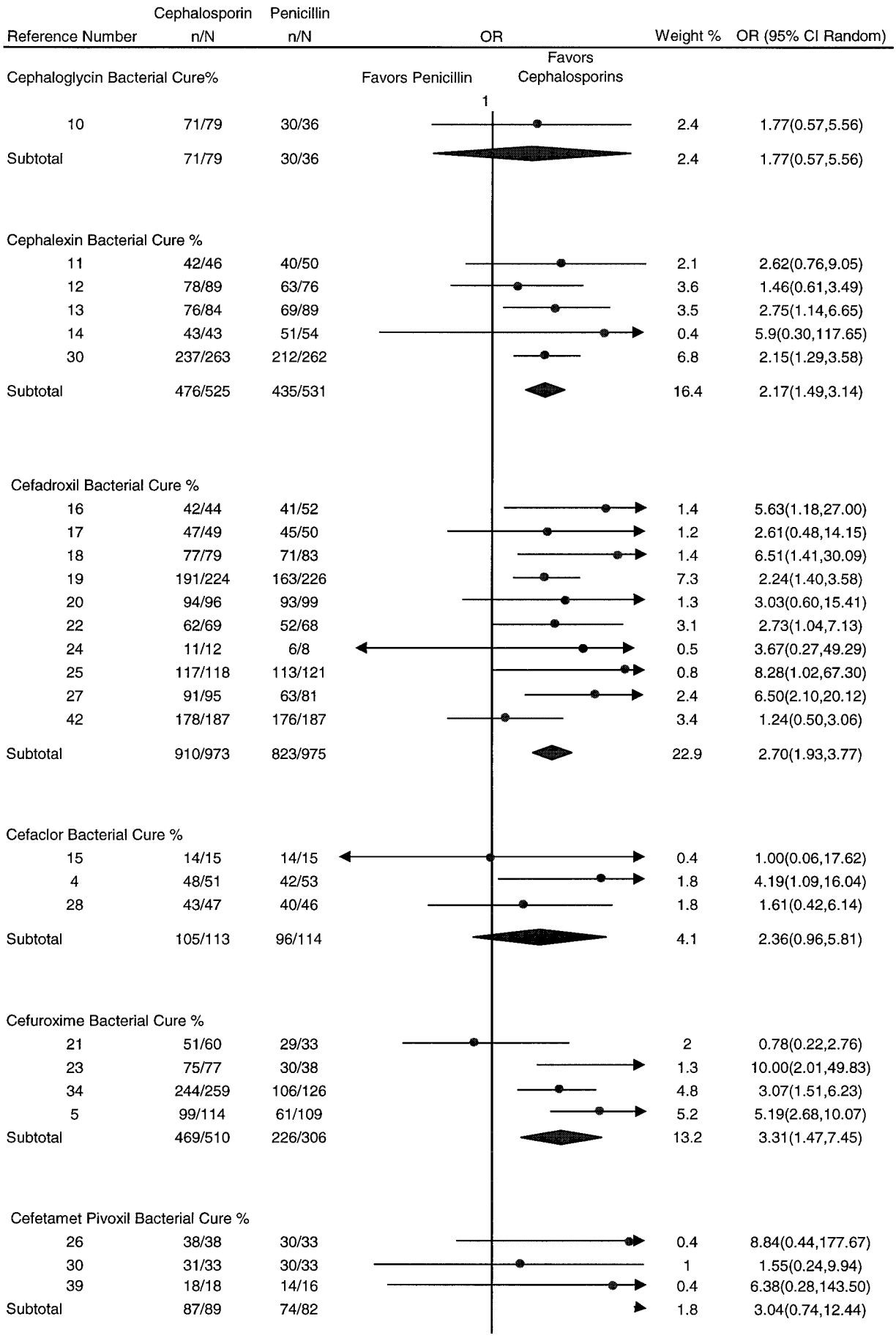

Fig 3. Bacterial cure rate analysis: individual cephalosporin analysis.

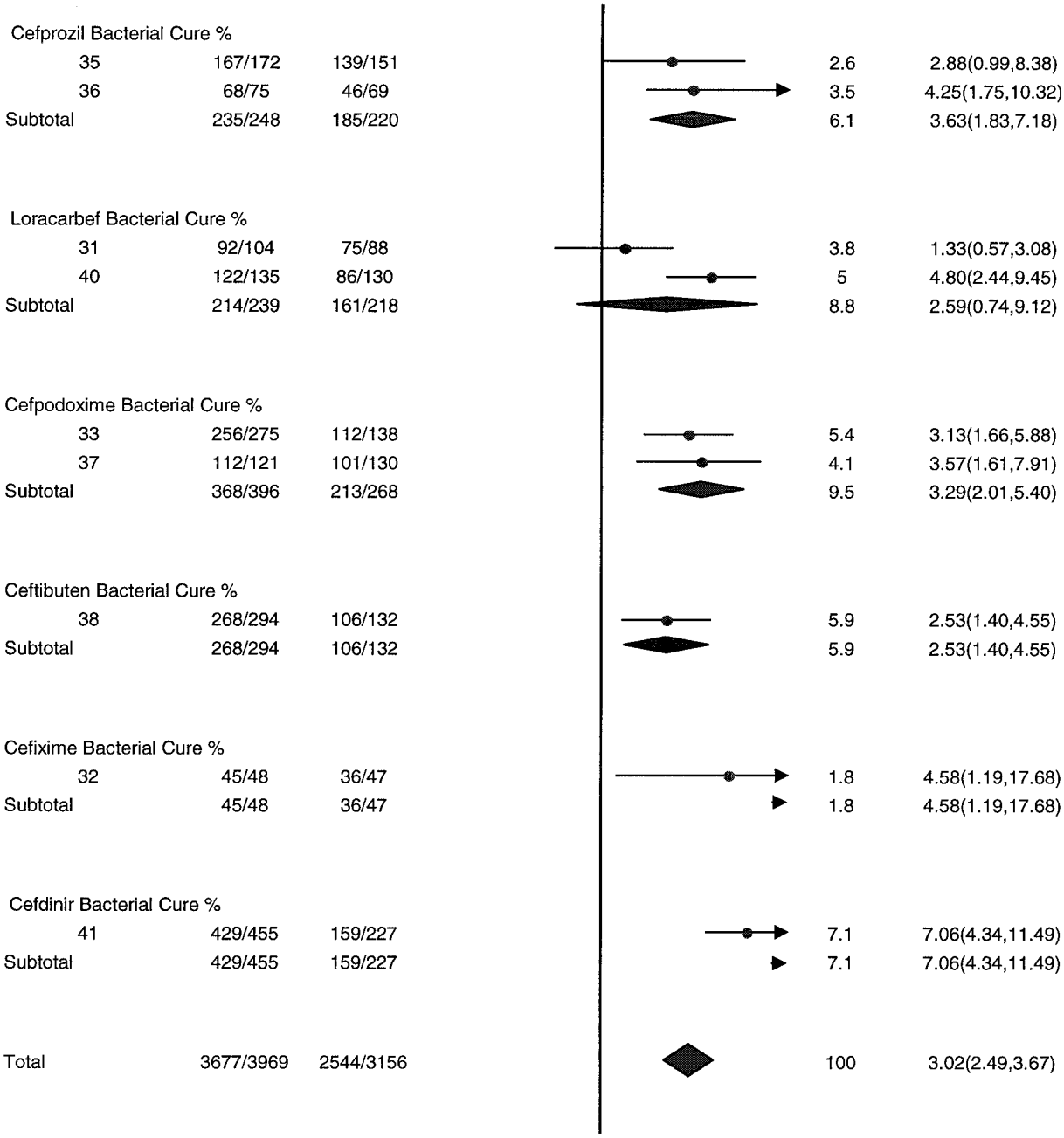

Fig 3. Continued.

mary OR for bacterial cure rate with the 5 abstracts included[48–52] (40 trials, 7880 patients) was 3.11 (95% CI: 2.61–3.70). Inclusion of unpublished trials did not result in a significant change in the overall summary OR for all trials. Of the 5 unpublished trials, 3 reported a clinical cure rate outcome.[50–52] When those 3 trials were analyzed along with the 30 published trials (6992 children), the summary OR for clinical cure rate was 2.39 (95% CI: 1.91–2.99), which was not a significant change from the overall summary OR for clinical cure.

Secondary Analysis

Seven trials specifically described elimination of carriers from their analysis. Eleven additional trials (1452 children) had sufficient data in the text to allow identification of probable posttreatment carriers, as defined by those patients with isolation of GABHS on any throat culture after completion of antibiotic therapy and no signs or symptoms of acute GABHS infection. Thus, 18 trials[4,11,12,15–18,20,22,24,25,27,29,31,32,38,39,42] (3168 patients) were grouped together for a secondary analysis to determine bacterial and clinical cure rates under circumstances in which, as best as possible, carriers were eliminated from analysis. The overall summary OR for recalculated bacterial cure rate was 2.65 (95% CI: 1.96–3.57), which still significantly favors cephalosporin treatment ($P \leq .00001$). Sixteen[4,11,12,16,18,20,22,24,25,27,29,31,32,38,39,42] of 18 trials had point estimates that favored cephalosporin treatment, with 6 trials[18,25,27,29,32,38] independently reaching significance. One trial's[17] point estimate favored

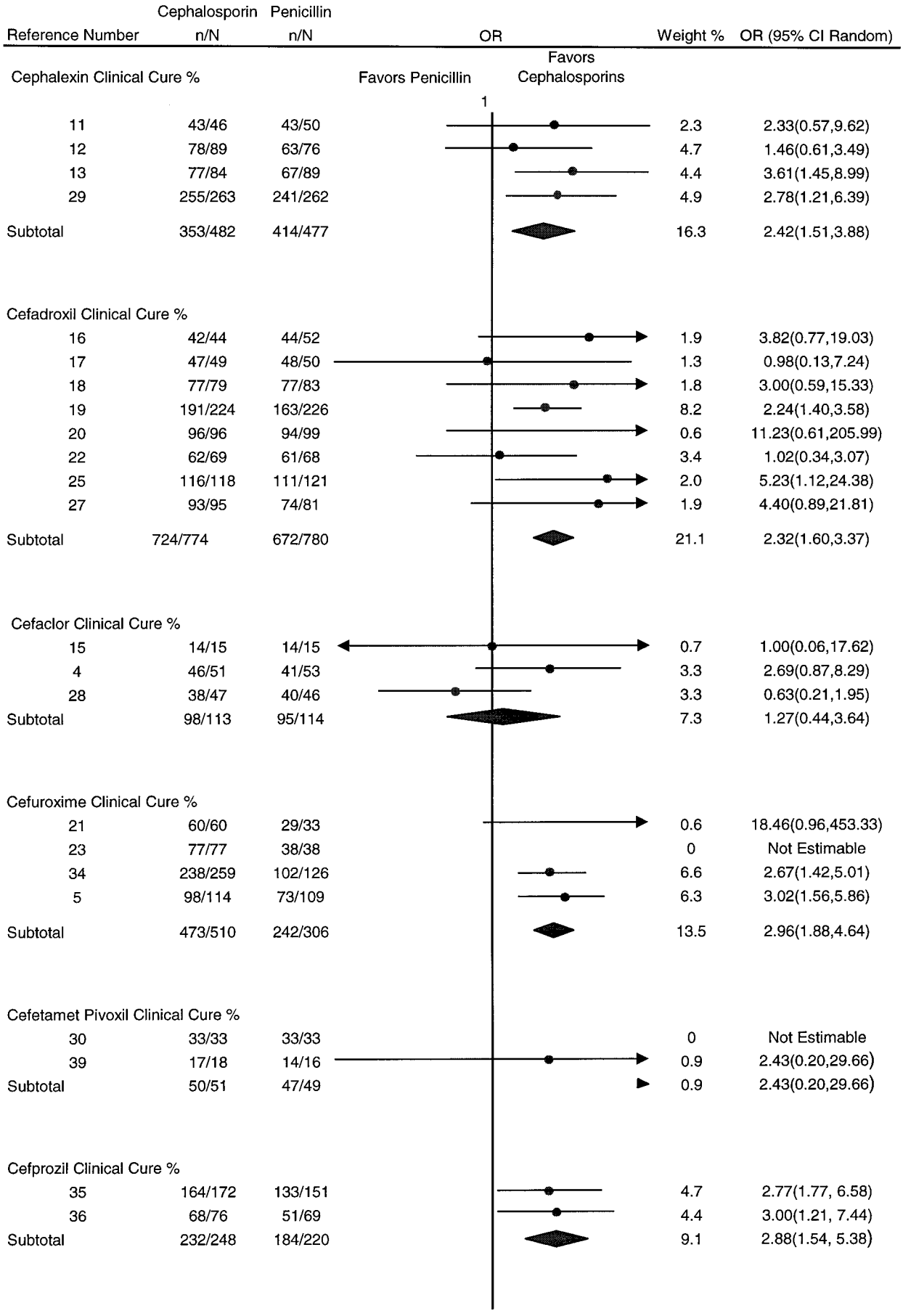

Fig 4. Clinical cure rate analysis: individual cephalosporin analysis.

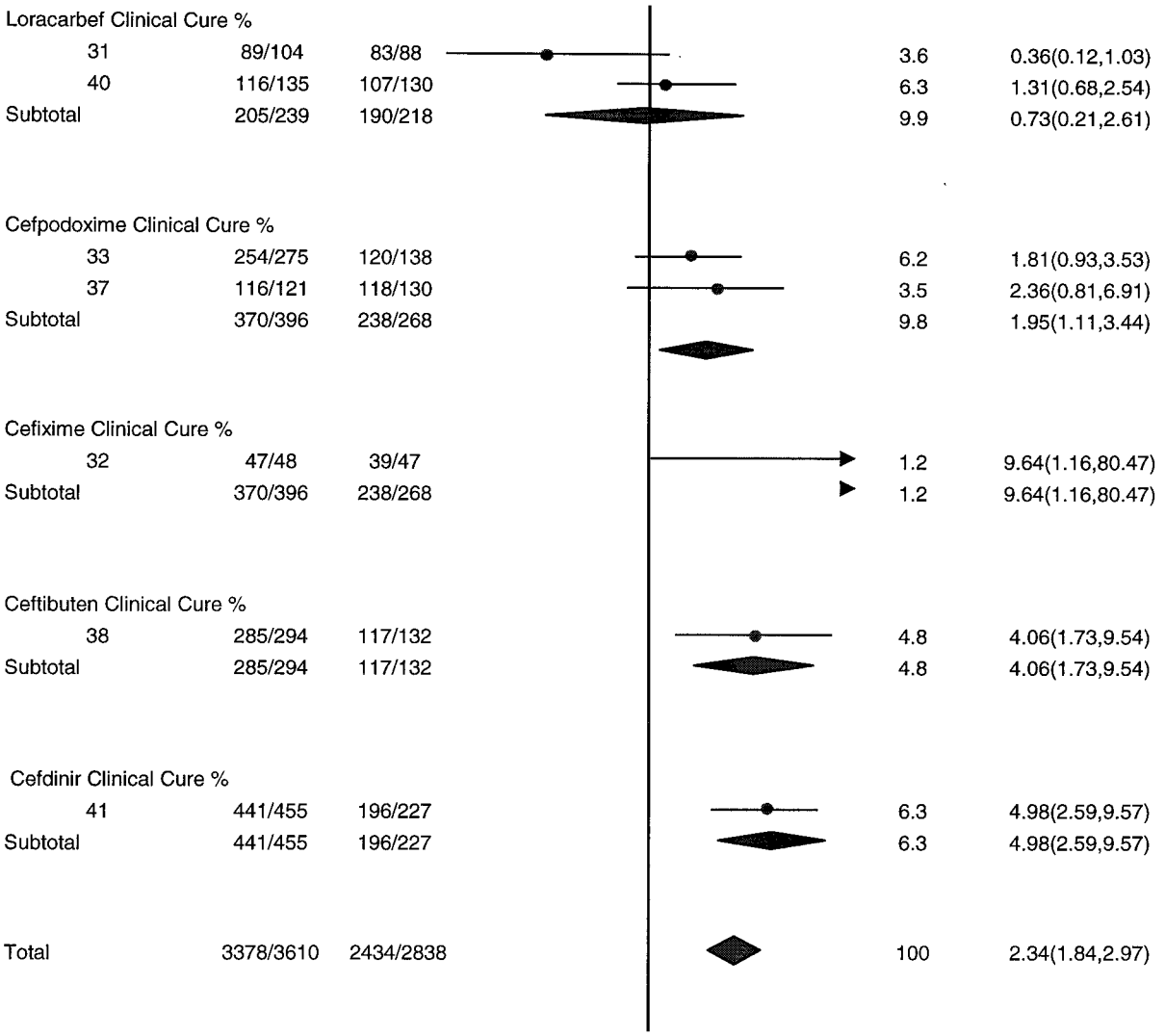

Fig 4. Continued.

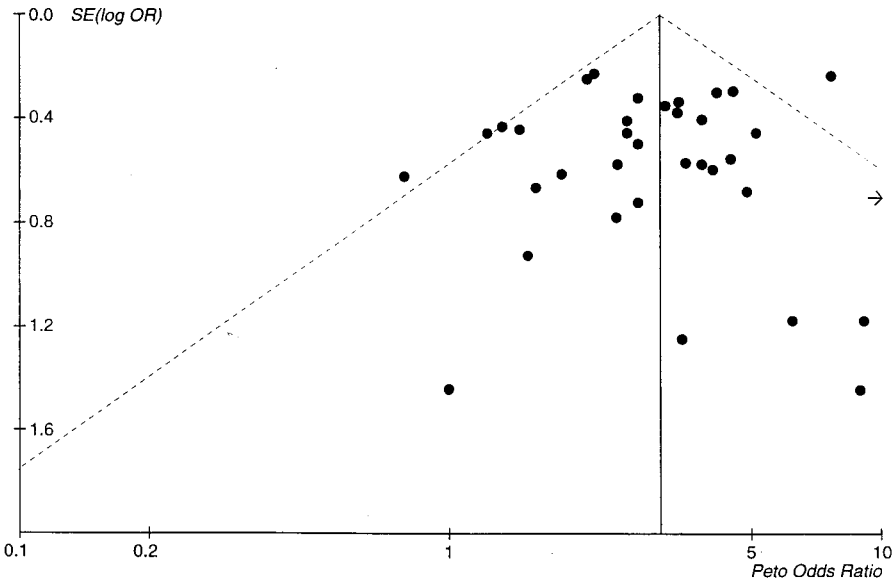

Fig 5. Funnel plot of OR versus standard effect for studies included in the meta-analysis of primary outcome of bacterial cure.

penicillin treatment, and 1 trial's[15] point estimate favored neither cephalosporin nor penicillin treatment.

A similar procedure was followed for a secondary analysis of the clinical cure rate with carriers eliminated from analysis. Sixteen trials[4,11,12,15–18,20,22,25,27,29,31,34,38,39]

(2774 patients) were included in this analysis. The overall summary OR for clinical cure rate was 2.61 (95% CI: 1.86–3.65), which significantly favors cephalosporin treatment ($P < .00001$). Fourteen[4,11,12,16,18,20,22,25,27,29,31,34,38,39] of 16 trials had point estimates that favored cephalosporin treatment, with results of 4 trials[25,29,34,38] independently reaching significance. One trial's[17] point estimate favored penicillin treatment, and 1 trial's[15] point estimate favored neither cephalosporin nor penicillin treatment. Tests for heterogeneity among the 18 trials used for the secondary analysis of bacterial cure rate ($P = .46$) and the 16 trials used for the clinical cure rate ($P = .8$) were not significant.

Sensitivity analyses were performed to assess the robustness of the summary ORs for the secondary analysis data set. In the sensitivity analysis for bacterial cure rate, cephalosporin treatment was favored significantly over penicillin treatment when the trials were grouped as double-blinded trials (5 trials, 1448 patients; $P = .006$), high-quality trials (5 trials, 1169 patients; $P = .00002$), trials with well-defined clinical status at diagnosis (6 trials, 1563 patients; $P = .005$), trials with detailed compliance-monitoring strategies (13 trials, 2205 patients; $P = .00001$), trials with GABHS typing performed (14 trials, 2770 patients; $P < .00001$), and trials with follow-up culture 3 to 14 days after therapy (3 trials, 491 patients; $P = .008$) (data not shown). The results from the sensitivity analysis of the clinical cure rates were similar, ie, cephalosporin treatment was favored significantly over penicillin treatment in all groupings except the 3 trials (491 patients) with follow-up culture 3 to 14 days after therapy ($P = .12$) (data not shown).

DISCUSSION

This meta-analysis indicates that the likelihood of bacteriologic failure of GABHS in children with tonsillopharyngitis is significantly less ($P < .00001$) if an orally administered cephalosporin antibiotic (specifically cephalexin, cefadroxil, cefuroxime, cefpodoxime, cefprozil, cefixime, ceftibuten, or cefdinir) is used for treatment compared with an orally administered penicillin. This likelihood of a higher success rate has increased over the 3 decades since cephalosporins were first studied as therapy; the observed trend occurred as a consequence of more frequent penicillin failures over time, in agreement with other studies.[53] Using the rigorous methodology of the Cochrane Collaboration meta-analytic approach currently available, this conclusion confirms, strengthens, and extends similar conclusions in prior meta-analyses,[8,9] studies,[6,8,54] and reviews.[54–57]

This meta-analysis demonstrates that oral cephalosporins, when grouped together as an antimicrobial class, are superior to penicillin in the eradication and clinical cure of GABHS. However, clinicians do not prescribe a class of antibiotics when treating GABHS tonsillopharyngitis; therefore, it was important to evaluate each of the cephalosporins individually. Eight of the 11 individual cephalosporins were statistically superior in the eradication and clinical cure of GABHS tonsillopharyngitis. Three cephalosporins (cefaclor, cephaloglycin, and cefetamet proxetil) and loracarbef were statistically equivalent to penicillin in bacterial eradication and clinical cure of GABHS, although there is a trend toward their superiority. The sample size in each of the trials involving these 4 drugs was small, and the studies may not have had the statistical power to demonstrate differences.

In tonsillopharyngitis, the primary outcome and antibiotic treatment goal of interest is eradication of GABHS. Eradication is necessary to prevent nonsuppurative and suppurative sequelae,[58] to eliminate contagion,[59] and to produce a more rapid symptomatic resolution of the illness.[60] Because of the ease with which a throat swab can be obtained, we have the advantage in studies of this illness of being able to measure the primary outcome of interest clearly. Nevertheless, there are trial design complexities that need to be addressed in a meta-analysis of GABHS tonsillopharyngitis trials that were not addressed in either of the 2 meta-analyses published previously.[8,9] Also, sensitivity analyses were not included in those previous papers. To overcome these shortcomings, we adopted the Cochrane Collaboration meta-analysis methodology and performed sensitivity analyses for identified confounders.[61]

In this meta-analysis, we included only studies that had randomized allocation of therapy, which resulted in 2 studies being dropped that had been included in a prior meta-analysis.[8] Second, abstracts were dropped from the primary analysis but included in a sensitivity analysis to account for publication bias that might have been introduced by not including unpublished data in the primary analysis.[62] To determine whether the statistically superior bacterial cure rates produced by the cephalosporins compared with penicillin would hold true when specific trial methodologic designs were grouped and analyzed, sensitivity analysis was done. We analyzed the subset of higher quality studies: those that had randomized, double-blinded treatment allocation ($n = 6$) and those with Jadad scores >2 ($n = 11$). Cephalosporin therapy was more likely to result in GABHS eradication for both trial subsets. Not all trials gave details of the patient's signs and symptoms, and it is important to know that patients being studied in the trials had acute pharyngitis; thus we analyzed only those trials that fully detailed the patient's clinical status at enrollment. For those 9 trials, the odds of bacterial cure were more likely with cephalosporin treatment. Compliance with the assigned therapy is an important variable when assessing a treatment's effects, especially when there is a compliance barrier such as taste in the case of penicillin V. Twenty-six trials reported detailed compliance-monitoring methods and included only compliant patients in the analysis. In those trials, cephalosporin treatment was significantly superior to penicillin treatment. Serotyping of the GABHS organisms at the time of inclusion in the study and at failure allows for the differentiation of failures from reinfections. Without these data, failure rates could be elevated falsely. Serotyping was performed in 24 trials, and for those trials, cephalosporin treatment resulted in bacterial cure more often than penicillin

treatment. Test-of-cure timing is an important variable in the interpretation of cure rates, because if the follow-up culture is done too soon, the persisting bacteriostatic effect of prior antibiotic therapy might allow the false conclusion that eradication has occurred. Or, if the follow-up culture is done too long after completion of therapy, intercurrent new infections contaminate the outcome analyses. It has been suggested that the test-of-cure evaluation should optimally take place within 3 to 14 days of completion of therapy. Nine trials had the test-of-cure cultures obtained in the optimal window, and for those trials, the OR favoring cephalosporin treatment was more likely to result in bacterial cure from penicillin treatment. As with the bacteriologic outcome, sensitivity analysis was undertaken for clinical cure rate data to address issues of differing methodology among the included trials. The overall results and conclusions were nearly identical.

The failure to exclude or the unintentional enrollment of GABHS carriers in clinical trials comparing cephalosporins with penicillin is a concern. In the clinical setting in which comparative tonsillopharyngitis antibiotic trials occur, the incidence of GABHS carriers is ~2% to 10%.[63–65] Penicillin is poorly effective in eradication of GABHS carriers,[66–69] whereas cephalosporins are effective.[65,70,71] Therefore, the inclusion of a high proportion of carriers would yield a more favorable outcome with cephalosporins, although the clinical importance would be lessened because carriers generally are less contagious to others and usually are not harmed by the GABHS. Because this issue is so important and contentious, we approached it with special attention by using 3 separate analyses.

First, a sensitivity analysis was performed including only those trials for which the investigators stated in the methods that they specifically attempted to exclude carriers. In those 7 trials, involving 1716 patients, bacteriologic eradication was more likely to be achieved with the cephalosporins compared with penicillin. Second, to increase the robustness of the data set, we derived from tables and/or figures of the trial results that subset of patients with positive GABHS throat cultures plus signs and symptoms of acute pharyngitis at the test-of-cure visit; these symptomatic patients would most likely have bona fide persisting infection. Typically, these data were not in the abstract and sometimes not stated explicitly by the authors. This undertaking allowed the addition of 1452 patients from 11 additional trials to the 7 trials described above. Virtually identical results favoring cephalosporins were obtained.

Third, the clinical cure rates reported in the trials were subjected to meta-analysis. Patients with GABHS tonsillopharyngitis clinically improve over time with or without antibiotic therapy. Therefore, measurement of clinical response during the 10-day treatment is largely meaningless in antibiotic trials. However, after completion of therapy, some patients relapse or recur with symptoms and signs of tonsillopharyngitis and GABHS are recovered on a throat swab. Those patients more likely have bona fide renewed risks for suppurative and nonsuppurative sequelae and are less likely to be GABHS carriers. The likelihood of clinical cure (plus bacteriologic eradication of GABHS) was higher after cephalosporin than penicillin treatment.

Meta-analysis incorporates existing biases and introduces new biases.[72,73] To minimize bias during trial selection, we used predetermined inclusion criteria. Publication bias was assessed by a funnel plot,[74] and no bias was evident. A recent study suggested that publication bias may also be present if unpublished abstracts are not included in the analysis of a new treatment versus an older treatment.[75] As such, we searched, found, and included abstract publications of trial results that did not later become full, published papers in a sensitivity analysis, and no changes in results or conclusions occurred. We used the Jadad scale to assess study quality.[43] Most of the trials scored <3 because of the lack of double blinding, and a lack of double blinding may lead to larger estimates of differences in treatment effects,[76] especially for subjective outcomes such as clinical response. Many trials failed to account for dropouts fully in terms of numbers and explanations, and many did not state the method of randomization.

Statistical and clinical heterogeneity is a potential concern in this meta-analysis. Therefore, the more conservative random-effects model, which takes into account trial heterogeneity, was used in all statistical analyses. To explore possible sources of clinical heterogeneity, we performed stratified analysis of the individual cephalosporins and of the 3 generations of cephalosporins. A third stratified analysis on the time frame during which the trials were conducted (1970–1999) identified a trend for larger differences between cephalosporins and penicillin for bacteriologic cure in recent years. Generally, no significant heterogeneity was found.

We and others have speculated that cephalosporins may be more effective than penicillin in eradication of GABHS from the tonsillopharynx for 3 reasons: 1) the presence of β-lactamase-producing copathogens that inactivate penicillin but not cephalosporins in vivo[8,77–82]; 2) penicillin is more effective in eradicating α-streptococci in the tonsillopharynx than cephalosporins, and these commensals represent ecological competitors with GABHS in the throat[83–86]; and 3) cephalosporins achieve sustained adequate bactericidal drug levels in the tonsillopharynx throughout the course of therapy because of their improved pharmacokinetic and pharmacodynamic profile compared with penicillin, the pharmacokinetic and pharmacodynamic profile of which suggests rapidly diminishing tissue levels as inflammation subsides over time.[87–92]

The difference between the cephalosporins and penicillin bactericidal cure rates for GABHS tonsillopharyngitis seems to be increasing. We have described and documented this phenomena previously,[53,57] and in this meta-analysis, the same observation occurred. There is no evidence to explain why this drop in penicillin cure rate has occurred; however, it has been observed by multiple investigators, in multiple countries, and in multiple studies.[5,6,7,54,90]

It may be that the presence of β-lactamase copathogens is increasing with time as a consequence of ongoing widespread use of antimicrobials and the increased selection of β-lactamase-producing oropharyngeal flora, leading to their increased prevalence.

Injudicious antimicrobial use is a growing concern and has produced a circumstance under which selection of resistant strains and clonal spread has occurred. There is no clear evidence that cephalosporins are more effective in selecting resistant strains than other β-lactam antibiotics, but the broader spectrum of the cephalosporin class has been noted as a concern. If cephalosporins were to join penicillin as a treatment of choice for GABHS tonsillopharyngitis, it is unclear whether this would increase selection pressure. In addition, there is a concern of acquisition costs, because many of the cephalosporin antibiotics are more expensive than penicillin or amoxicillin. In this regard, we did undertake an analysis of the various generations of cephalosporin antibiotics. Because penicillin bacteriologic failure rates have increased over time, there is an appearance that more expensive third-generation cephalosporins may have higher efficacy. The fact that the third-generation cephalosporins were evaluated more recently (when penicillin failure rates were higher) gives the appearance of higher efficacy. Actually, our analysis suggests that the bacteriologic eradication rate of the different generations of cephalosporins is not significantly different. This finding in part may address the acquisition-costs issue, because first-generation cephalosporins are of narrower spectrum and lower acquisition cost than second- and third-generation agents.

CONCLUSIONS

Our findings clearly show that the likelihood of a bacteriologic and clinical cure of GABHS tonsillopharyngitis in children is significantly higher after 10 days of oral cephalosporin therapy with cephalexin, cefadroxil, cefuroxime, cefpodoxime, cefprozil, cefixime, ceftibuten, or cefdinir than after 10 days of oral penicillin. These findings do not apply to adults, nor was the analysis extended to shortened course therapies.[93,94] The trend for a more frequent oral penicillin treatment failure over the past 3 decades is of concern. Penicillin is inexpensive, narrow in spectrum, and endorsed by many treatment guidelines as the sole agent of choice.[1–3] Cephalosporins are more expensive and have a broader spectrum of antibacterial activity. On the other hand, the acquisition cost of the antibiotic represents a very small percentage of the total cost of management of a patient with GABHS tonsillopharyngitis.[95] Additional medical visits and loss of school and work productivity represent the largest cost of treatment failure. We would advocate the addition of cephalosporins as a treatment of choice for GABHS tonsillopharyngitis based on our finding that these agents more often produce bacteriologic eradication and clinical cure compared with penicillin.

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