MAJOR ARTICLE

Meta-analysis of Cephalosporins versus Penicillin for Treatment of Group A Streptococcal Tonsillopharyngitis in Adults

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(See the editorial commentary by Bisno on pages 1535–7)

We conducted a meta-analysis of 9 randomized controlled trials (involving 2113 patients) comparing cephalosporins with penicillin for treatment of group A β-hemolytic streptococcal (GABHS) tonsillopharyngitis in adults. The summary odds ratio (OR) for bacteriologic cure rate significantly favored cephalosporins, compared with penicillin (OR,1.83; 95% confidence interval [CI], 1.37–2.44); the bacteriologic failure rate was nearly 2 times higher for penicillin therapy than it was for cephalosporin therapy ($P = .00004$). The summary OR for clinical cure rate was 2.29 (95% CI, 1.61–3.28), significantly favoring cephalosporins ($P < .00001$). Sensitivity analyses for bacterial cure significantly favored cephalosporins over penicillin in trials that were double-blinded and of high quality, trials that had a well-defined clinical status, trials that performed GABHS serotyping, trials that eliminated carriers from analysis, and trials that had a test-of-cure culture performed 3–14 days after treatment. This meta-analysis indicates that the likelihood of bacteriologic and clinical failure in the treatment of GABHS tonsillopharyngitis is 2 times higher for oral penicillin than for oral cephalosporins.

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]. Studies have shown an increase in the number of cases of GABHS infections that are not eradicated by penicillin treatment [4–7]. In 2001, Kaplan and Johnson [7] found that intravenous benzathine penicillin therapy failed to eradicate GABHS in 37%–42% of patients, whereas oral penicillin therapy failed in 35% of patients.

Cephalosporins have been used successfully for the treatment of GABHS tonsillopharyngitis since the early 1970's. Two prior meta-analyses comparing the efficacy of cephalosporin therapy with that of penicillin therapy for treatment of GABHS tonsillopharyngitis in children have been published [8, 9], and both showed that cephalosporin treatment was superior for eradicating GABHS. The objective of this study was to use rigorous methods of meta-analysis to compare the relative efficacy of cephalosporins with that of penicillin in the treatment of GABHS tonsillopharyngitis in adults in all available randomized controlled trials [10–17].

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METHODS

Trial identification. Randomized, controlled trials comparing cephalosporins with penicillin in the treatment of GABHS tonsillopharyngitis in adults were identified using searches of MEDLINE (date range, 1966–2002) and Embase (date range, 1974–2002) with no language restriction; search terms employed were "streptococcal pharyngitis/tonsillitis," "cephalosporins," and "penicillin." Reference lists of relevant publications were reviewed to identify additional trials. Abstracts from Interscience Conferences on Antimicrobial Agents and Chemotherapy were also searched to identify relevant trials that were unpublished.

Trial selection and quality. Trials comparing the efficacy of a cephalosporin with that of penicillin for treatment of GABHS tonsillopharyngitis were independently reviewed by us for the following criteria: (1) inclusion of adult patients (including those ⩾12 years old); (2) bacteriologic confirmation of GABHS tonsillopharyngitis, with a positive rapid antigen detection test result and/or positive results of cultures of throat swab specimens obtained prior to treatment; (3) random assignment to antibiotic therapy groups comparing an orally administered cephalosporin with orally administered penicillin over a 10-day treatment period; and (4) assessment of bacteriologic outcome using cultures of throat swab specimens obtained after completion of therapy. The Jadad scale was used to assess the methodological quality of the trials, assigning scores from 0 (worst quality) to 5 (best quality) according to the following criteria: randomization of patients to treatment groups using appropriate methods, use of double-blinded intervention, and description of reasons why patients withdrew from the study [18].

Data abstraction and definition of terms. Primary outcomes of interest were bacteriologic cure, defined as a failure to isolate GABHS in a culture of a throat swab obtained after completion of the antibiotic regimen, and clinical cure, defined as the resolution or improvement of the presenting signs and symptoms of GABHS infection upon completion of the antibiotic regimen and continuing throughout the follow-up period. Sensitivity analyses were performed to assess the impact of carefully made clinical illness descriptions, compliance monitoring, GABHS serotyping, inclusion 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 discussing them until a consensus was reached.

Data analysis. The meta-analysis was performed using Revman software, version 4.1 (Cochrane Collaboration). Bacteriologic cure rates after completion of cephalosporin treatment were compared with those of penicillin treatment and were expressed as ORs and 95% CIs. An OR >1 indicated a higher bacteriologic cure rate for the cephalosporin than for penicillin. ORs were calculated for individual trial outcomes, and a summary OR was determined for all trials using the Peto fixed-effects model [19], which assumes trial homogeneity, and the DerSimonian and Laird random-effects model [20], which assumes trial heterogeneity. Statistical heterogeneity among trials was assessed by χ^2 analysis [21, 22].

Possible clinical heterogeneity was examined using analyses in which cephalosporin groups were stratified by cephalosporin generation, by cephalosporin type, and by jack-knifing, wherein 1 study at a time was removed from the data set, and the data were reanalyzed. Sensitivity analyses assessed the robustness of the meta-analysis and further evaluated possible clinical heterogeneity by comparing summary ORs among groups redefined by excluding trials that (1) were not double-blinded, (2) had lower methodological quality (Jadad score ⩽ 2), (3) lacked specific details about the clinical status of patients, (4) did not note whether compliance was monitored, (5) lacked GABHS serotyping or genotyping data, (6) did not define carriers and eliminate them from analysis, and (7) did not perform test-of-cure culture between 3–14 days after completion of the treatment. The complements to these subsets were also analyzed. Logistic regression analysis was performed to evaluate the overall drug effect while adjusting for different sets of covariants from the sensitivity analysis. 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 reports of randomized clinical trials comparing cephalosporin with penicillin for treatment of GABHS tonsillopharyngitis. Two trials that were not identified by MEDLINE or Embase were retrieved from reference listings, and 5 trials were identified from abstract searches. Of the 66 citations, 57 were excluded for the following reasons: (1) the trial was published as an abstract only; (2) patient randomization criteria were not assessable; (3) most or all participants were children; (4) the adult data could not be separated from those of the children in studies that included equal numbers of adults and children; (5) bacterial cure rates were not measured; (6) data were from a study that was already included in our analysis; and (7) the treatment duration was <10 days. This left 9 trials in 8 published reports for inclusion in our analysis.

Methodological quality. The mean Jaded scale score ($\pm$SD) for all trials was 3.2 $\pm$ 1, out of a maximum score of 5 (table 1). Six of 9 trials were double blinded [10, 14–17], and 7 of 9 studies adequately described the reasons for patient withdrawal [10, 12–17]. Most patients were withdrawn from studies because GABHS was not isolated in the initial culture.

Description of trials. Six trials were conducted in the United States [10, 12, 14, 15, 17]. Five were multicenter outpatient studies [10, 12, 14, 17], 2 were performed in hospital emergency settings [11, 13], and 2 did not state the site of the trial [15, 16]. One trial took place in the 1980s [10], and 8 were performed in the 1990s [11–17] (table 1). All trials required isolation of GABHS in a throat swab culture. Seven trials

Table 1. Methodological description of studies.

Reference	Jaded scale score	Treatment allocation blinding	No. of patients in ITT analysis/no. evaluable (% who dropped out)	Antibiotic received (no. of patients)	Clinical status	Method(s) of compliance monitoring	Serotyping performed	Carriers eliminated from data analysis	Time TOC culture performed, days[a]
[10]	3	Double	ND	Cefadroxil (88), penicillin V (79)	No details given	Urine tests	No		4–21
[11]	2	None	ND	Cefetamet pivoxil (35), penicillin V (40)	No details given	Tablet counts; urine tests[b]	No	Yes	20–30
[12]	2	None	93/63 (32)	Cefpodoxime proxetil (30), penicillin V (33)	Detailed signs and symptoms	Record cards	No	ND	3–8
[13]	2	None	514/489 (5)	Cefadroxil (246), penicillin V (243)	No details given	Tablet counts	No	Yes	10
[14]	4	Double	218/171 (22)	Loracarbef (89), penicillin V (82)	Detailed signs and symptoms	Urine tests	Yes	Yes	3–5
[15]	4	Double	116/90 (22)	Loracarbef (47), penicillin V (43)	Detailed signs and symptoms	Urine tests	Yes	Yes	3–5
[16]	4	Double	344/239 (31)	Loracarbef (115), penicillin V (124)	Detailed signs and symptoms	No details given	No	Yes	3–5
[17]	4	Double	615/427 (31)	Cefdinir q.d. (210), penicillin V (217)	Detailed signs and symptoms	No details given	No[c]	ND	4–9
[17]	4	Double	614/434 (19)	Cefdinir b.i.d. (217), penicillin V (217)	Detailed signs and symptoms	No details given	No[c]	ND	4–9

NOTE. ITT, intent-to-treat analysis; ND, no data given; TOC, test-of-cure.

[a] Days after completion of treatment.

[b] Tablet counts were used for the cefetamet pivoxil group, and urine tests were used for the penicillin V group.

[c] Genotyping was performed.

Study	Cephalosporin group, *n/N*	Penicillin group, *n/N*	Weight %	OR (95% CI)
Beisel, 1980 [10]	58/63	55/62	6.3	1.48 (0.44–4.93)
Cerstelotte, 1990 [11]	35/35	39/40	0.7	2.70 (0.11–68.34)
Brown, 1991 [12]	29/30	30/33	1.4	2.90 (0.28–29.51)
Holm,1991 [13]	232/246	213/243	17.4	2.33 (1.21–4.52)
McCarty, 1992 [14]	78/89	74/82	13.6	0.77 (0.29–2.01)
McCarty, 1992 [15]	41/47	43/43	8.8	0.07 (0.00–1.34)
Muller, 1992 [16]	108/115	106/124	8.8	2.62 (1.05–6.53)
Nemeth, 1999 [17]	192/210	181/217	21.7	2.12 (1.16–3.87)
Nemeth, 1999 [17]	199/217	181/217	21.4	2.20 (1.21–4.01)
Total	972/1052	922/1061	100	1.83 (1.37–2.44)

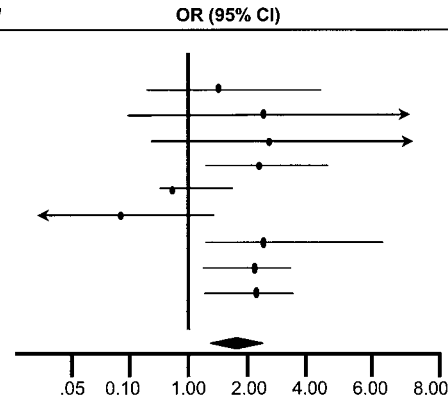

Figure 1. Bacterial cure rate analysis comparing cephalosporins with penicillin in the treatment of group A β-hemolytic streptococcal tonsillopharyngitis. *Dots,* point estimate OR for each trial; *horizontal plot lines,* 95% CIs; *arrows,* CIs that extend beyond the x-axis scale. Proportion data *(n/N)* are total number of patients cured/total number treated; the weight percentages represent the weight each individual trial has on the overall outcome, expressed as a percentage of the total.

used rapid antigen tests at enrollment but excluded patients from analysis if GABHS was not isolated in a throat swab culture [12–17]. One trial excluded patients with 1+ growth of GABHS at enrollment in an attempt to exclude carriers [10].

Four different cephalosporins and 1 carbacephem were compared with penicillin in the 9 trials. Two trials involved first-generation agents [10, 13], 4 involved second-generation agents [11, 14–17], and 3 involved third-generation agents [12, 17]. Six trials gave detailed descriptions of patient signs and symptoms at enrollment [12, 14–17]. The remaining 3 trials stated that the patients were acutely ill with tonsillopharyngitis [10, 11, 13].

Serotyping of the infecting streptococcal organism was performed in 2 trials [14, 15], and genotyping was done in 2 trials [17], thereby permitting differentiation between true treatment failures and new infections. True treatment failure rates were used in the calculations. Carriers were defined and eliminated from analysis in 6 trials [10, 11, 13–16]. Specific compliance monitoring methods used by 6 trials included tablet counts, record cards, and urine tests [10–15]; the remaining trials provided no information or used patient questioning only [16, 17].

The timing of test-of-cure culture varied among the trials, but most performed such cultures during the early and late stages of follow-up. Test-of-cure cultures were performed 3–14 days after completion of the antibiotic regimen in 7 trials [12–17]. When possible, bacteriologic and clinical cure rates used in this meta-analysis were taken from data on test-of-cure cultures performed during the early stages of the follow-up period to minimize the inclusion of patients with reacquisition of GABHS or with new infections in the final cure rate analysis.

Study	Cephalosporin group, *n/N*	Penicillin group, *n/N*	Weight %	OR (95% CI)
Biesel, 1980 [10]	61/63	61/62	4.6	0.50 (0.04–5.66)
Brown, 1991 [12]	29/30	32/33	2.4	0.91 (0.05–15.16)
Holm, 1991 [13]	232/246	213/243	28.7	2.33 (1.21–4.52)
McCarty, 1992 [14]	86/89	77/82	6.3	1.86 (0.43–8.05)
McCarty, 1992 [15]	46/47	43/43	3.3	0.36 (0.01–8.98)
Muller, 1994 [16]	108/115	106/124	14.6	2.62 (1.05–6.53)
Nemeth, 1999 [17]	199/210	193/217	23.4	2.25 (1.07–4.72)
Nemeth, 1999 [17]	209/217	193/217	16.7	3.25 (1.43–7.40)
Total	970/1017	918/1021	100	2.29 (1.61–3.28)

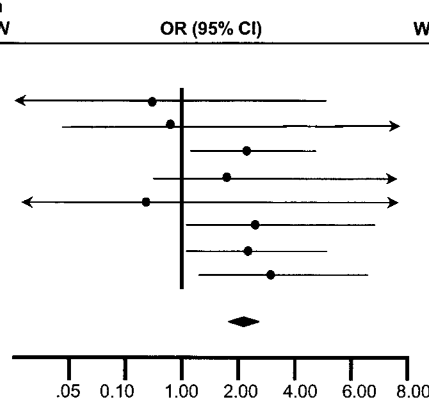

Figure 2. Clinical cure rate analysis, cephalosporin versus penicillin in the treatment of group A β-hemolytic streptococcal tonsillopharyngitis. *Dots,* point estimate OR for each trial; *horizontal plot lines,* 95% CIs; *arrowheads,* CIs that extend beyond the x-axis scale. Proportion data *(n/N)* are total number of patients cured/total number treated; the weight percentages represent the weight each individual trial has on the overall outcome, expressed as a percentage of the total.

Table 2. Sensitivity analysis of primary outcome for patients with group A β-hemolytic streptococcal tonsillopharyngitis: bacterial cure rate.

Description, by category	References	No. of trials	No. of patients	OR (95% CI)
General				
All trials	[10–17]	9	2113	1.83 (1.37–2.44)
Double blinded	[10, 14–17]	6	1486	1.70 (1.22–2.35)
Quality score >2[a]	[10, 14–17]	6	1486	1.70 (1.22–2.35)
Clinical status defined	[12, 14–17	6	1424	1.74 (1.24–2.43)
Compliance monitoring	[10–15]	6	1013	1.39 (0.89–2.16)
Detailed				
Serotyping performed	[14, 15, 17]	4	1122	1.59 (1.10–2.30)
Carriers eliminated from analysis	[10, 11, 13–16]	6	1189	1.55 (1.04–2.31)
TOC culture performed 3–14 days after therapy	[12–17]	7	1913	1.85 (1.37–2.49)

NOTE. TOC, test-of-cure.

[a] Based on the Jaded scale.

Outcome of bacterial and clinical cure rates. The primary outcome analyzed were the bacterial cure rates for cephalosporin and for penicillin treatment. The summary OR for bacterial cure in all 9 trials, which included 2113 patients, was 1.83 (95% CI, 1.37–2.44), and favored cephalosporin treatment ($P < .00004$) (figure 1). Seven of 9 studies had a point estimate that favored cephalosporins [10–13, 16, 17]. In 4 trials, sample size was sufficient to show that cephalosporin treatment was significantly superior to penicillin treatment [13, 16, 17]. Two trials had a point estimate favoring penicillin, but the results did not reach statistical significance [14, 15].

One trial did not report the primary outcome of clinical cure; therefore, 8 trials were included in our analysis. The overall summary OR for clinical cure rate, which included data for 2038 patients, was 2.29 (95% CI, 1.61–3.28), favoring cephalosporin treatment ($P < .00001$) (figure 2). Five of 8 trials had a point estimate favoring cephalosporins [13, 14, 16, 17]. The clinical cure rate in 4 trials reached statistical significance and favored cephalosporins [13, 16, 17]. Three trials had point estimates favoring penicillin therapy, but the difference did not reach statistical significance [10, 12, 15].

Sensitivity analysis. To test the robustness of the overall summary ORs, sensitivity analyses were conducted (tables 2 and 3). Bacterial cure rates significantly favored cephalosporin treatment when trials were grouped as double-blinded trials (OR, 1.70; 95% CI, 1.22–2.35), high-quality trials (Jaded score, >2) (OR, 1.70; 95% CI, 1.22–2.35), trials in which a well-defined clinical status was specified at diagnosis (OR, 1.74; 95% CI, 1.24–2.43), trials in which serotyping or genotyping was done (OR, 1.59; 95% CI 1.10–2.30), trials in which carriers

Table 3. Sensitivity analysis of primary outcome for patients with group A β-hemolytic streptococcal tonsillopharyngitis: clinical cure rate.

Description, by category	References	No. of trials	No. of patients	OR (95% CI)
General				
All trials	[10, 12–17]	8	2038	2.29 (1.61–3.28)
Double blinded	[10, 14–17]	6	1486	2.33 (1.52–3.57)
Quality score >2[a]	[10, 14–17]	6	1486	2.33 (1.52–3.57)
Clinical status defined	[12, 14–17]	6	1424	2.40 (1.56–3.70)
Compliance monitoring	[10, 12–15]	5	938	1.86 (1.08–3.22)
Detailed				
Serotyping performed	[14, 15, 17]	4	1122	2.41 (1.46–3.97)
Carriers eliminated from analysis	[10, 13–16]	5	1114	2.09 (1.30–3.37)
TOC culture performed 3–14 days after therapy	[12–17]	7	1913	2.38 (1.66–3.42)

NOTE. TOC, test-of-cure.

[a] Based on the Jaded scale.

Table 4. Bacterial cure rate summary ORs and statistical heterogeneity for individual cephalosporins.

Cephalosporin (generation)	Reference(s)	No. of trials	No. of patients	Summary OR (95% CI)	*P*	
					Compared with penicillin	Test for heterogenicity
Cefadroxil (1st)	[10, 13]	2	614	2.11 (1.18–3.75)	.01	.51
Cefetamet pivoxil (2nd)	[11]	1	75	2.70 (0.11–68.34)	>.05	Not done[a]
Loracarbef (2nd)	[14, 15]	3	500	1.10 (0.62–1.96)	.8	.025[b]
Cefpodoxime (3rd)	[12]	1	63	2.90 (0.28–29.51)	.05	Not done[a]
Cefdinir (3rd)	[17]	2	861	2.16 (1.41–3.30)	.0004	.93

[a] Because only 1 trial was in the analysis group.
[b] Statistically significant.

were eliminated from the analysis (OR, 1.55, 95% CI, 1.04–2.31), and trials with a test-of-cure culture performed 3–14 days after completion of antibiotic treatment (OR, 1.85; 95% CI, 1.37–2.49). The complements of the sensitivity analysis groups had similar results (data not shown).

Sensitivity analyses for the clinical cure rate significantly favored cephalosporin treatment when trials were grouped as double-blinded trials (OR, 2.33; 95% CI, 1.52–3.57), high-quality trials (Jadad score >2) (OR, 2.33; 95% CI, 1.52–3.57), trials in which a well-defined clinical status was specified at diagnosis (OR, 2.40; 95% CI, 1.56–3.70), trials with detailed compliance monitoring (OR, 1.86; 95% CI, 1.08–3.22), trials in which serotyping or genotyping was done (OR, 2.41; 95% CI, 1.46–3.97), trials in which carriers were eliminated from the analysis (OR, 2.09; 95% CI, 1.30–3.37), and trials with a test-of-cure culture performed 3–14 days after completion of antibiotic treatment (OR, 2.38; 95% CI, 1.66–3.42). The complements of the sensitivity analysis groups had similar results (data not shown).

All multilogistic regression analysis models confirmed that cephalosporin treatment had bacterial and clinical cure rates that were significantly superior to those of penicillin therapy (P values, <.0001–.0003). Unlike the sensitivity analysis, with logistic regression when the antibiotic and compliance variables were included in the regression model, the bacterial and clinical cure rates of cephalosporin remained statistically significant ($P < .0001$ and $P < .0004$, respectively).

Stratified analysis of cephalosporins. One first-generation cephalosporin (cefadroxil), 1 second-generation cephalosporin (cefetamet), 2 third-generation cephalosporins (cefdinir and cefpodoxime), and 1 carbacephem (loracarbef) were included in a stratified analysis. The trials were grouped by cephalosporin generation (the second-generation cephalosporin and the carbacephem were grouped together) and analyzed. In 2 trials ($n = 614$), the first-generation cephalosporins were statistically superior to penicillin with respect to bacterial cure rate (OR, 2.11; 95% CI, 1.18–3.75; $P = .01$) and clinical cure rate (OR, 2.08; 95% CI, 1.11–3.09; $P < .02$). In 4 trials ($n = 500$), the second-generation cephalosporins had bacterial cure rates that were equal to those of penicillin ($n = 575$; OR, 1.18; 95% CI, 0.64–2.00; $P = .7$), but in 3 trials, clinical cure rates of second-generation cephalosporins were superior (OR, 2.11; 95% CI, 1.01–4.39; $P < .05$). In 3 trials ($n = 924$), the third-generation cephalosporins had bacterial cure rates (OR, 2.18; 95% CI, 1.44–3.31; $P < .0003$) and clinical cure rates (OR, 2.57; 95% CI, 1.50–4.39; $P < .0006$) that were statistically superior to those of penicillin.

Analysis of comparative cure rates for each of the individual cephalosporins was undertaken. Each cephalosporin had a statistically higher cure rate than did penicillin, with the exception of loracarbef (table 4).

Heterogeneity. Tests for statistical heterogeneity were performed for both primary outcomes. There was no heterogeneity among the 9 trials for bacterial cure rates ($P = .28$) and clinical cure rates ($P = .77$) and no heterogeneity among the trials of the 3 generations of cephalosporins. There was heterogeneity among the trials involving individual cephalosporins because 2 trials studied loracarbef. We performed 7 different sensitivity analyses (only double-blinded trials, etc.), and statistical heterogeneity was present in 1 subset (i.e., trials in which serotyping or genotyping was performed). Cephalosporin treatment remained significantly superior to penicillin treatment when analyzing each trial's effect on the overall analysis. Elimination of trials 4 [13] and 9 [17] individually caused the largest change in the bacterial cure rate; the ORs ranged from 1.83 when all 9 trials were included (95% CI, 1.37–2.44) to 1.56 when trial 4 was removed (95% CI, 1.14–2.14) and 1.56 when trial 9 was removed (95% CI, 1.13–2.15).

Publication bias. A symmetrical inverted funnel-shaped plot of the ORs versus standard effect (as shown by the wide scattering of ORs from small studies and narrowing to a peak among large studies) was observed, which suggested no evidence of publication bias.

DISCUSSION

This meta-analysis indicates that the likelihood of bacteriologic failure in adults with GABHS tonsillopharyngitis is 2 times higher for oral penicillin therapy than for oral cephalosporin therapy ($P = .00004$). Using the Cochrane Collaboration meta-analytic approach, this conclusion confirms, strengthens, and extends similar conclusions in prior meta-analyses [8, 9], studies [6, 8, 23], and reviews [23–26].

In tonsillopharyngitis, the primary outcome and antibiotic treatment goal of interest is eradication of GABHS. Eradication is necessary to prevent nonsuppurative and suppurative sequelae [27], to eliminate contagion [28], and to produce a more rapid symptomatic resolution of the illness [29]. Because of the ease with which a throat swab specimen can be obtained, we have the advantage in studies of this illness of being able to clearly measure the primary outcome of interest. Nevertheless, a meta-analysis of GABHS tonsillopharyngitis studies must address complexities involving the design of trials that were not addressed in either of the 2 meta-analyses previously published involving children [8, 9], including sensitivity analyses for suggested confounders [30]. The overall result, which showed the superiority of cephalosporin therapy for eradicating GABHS, did not change after sensitivity and multilogistic regression analyses of the important confounding variables.

Meta-analysis incorporates existing biases and introduces new biases [31, 32]. To minimize bias during trial selection we used predetermined inclusion criteria. Publication bias was assessed by a funnel plot [33] and none was evident. Clinical and statistical heterogeneity is a potential concern in this meta-analysis. Statistical heterogeneity was not significant among the trials for bacteriologic outcomes ($P = .28$) and clinical outcomes ($P = .77$), suggesting that the included trials were similar enough so as not to introduce bias.

We and others have speculated that cephalosporins may be more effective than penicillin in eradication of GABHS from the tonsillopharynx for 3 reasons: (1) β-lactamase–producing coinfecting pathogens that inactivate penicillin but not cephalosporins may be present in vivo [8, 34–39]; (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 [40–43]; and (3) cephalosporins achieve sustained adequate bactericidal drug levels in the tonsillopharynx throughout the course of therapy because of their improved pharmacokinetic and pharmacodynamic (PK/PD) profile compared with penicillin, which has a PK/PD profile that suggests rapidly diminishing tissue levels as inflammation subsides over time [44–49], and 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, where comparative trials of antibiotics for the treatment of tonsillopharyngitis are undertaken, the incidence of GABHS carriers is ∼2%–10% [50–52]. Penicillin is poorly effective in eradication of GABHS carriage [53–56], whereas cephalosporins are effective [52, 57, 58]. Therefore, the inclusion of carriers in a trial might impact the relative cure rates for penicillin therapy and cephalosporin therapy.

Injudicious use of antimicrobials is a growing concern and has produced a circumstance where selection of resistant strains and clonal spread has occurred. There is no clear evidence that cephalosporins are more effective in selecting resistant strains than are 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 if this would increase selection pressure. In addition, the cephalosporin antibiotics are more expensive than penicillin. However, the bacteriologic eradication rate of the different generations of cephalosporins was not significantly different; and first-generation cephalosporins have a narrower spectrum and a lower acquisition cost than second- and third-generation agents.

In conclusion, our findings clearly show that the likelihood of a bacteriologic and clinical cure of GABHS tonsillopharyngitis in adults is significantly higher after 10 days of therapy with an oral cephalosporin than with oral penicillin. The analysis was not extended to shortened courses of therapy [59]. The trend toward more-frequent oral penicillin treatment failure over the past 3 decades is of concern [4–7, 60]. Yet penicillin is inexpensive, has a narrow spectrum, and is endorsed by treatment guidelines as the sole agent of choice [1–3]. However, antibiotic acquisition cost is a very small percentage of the total cost of management of a case of GABHS tonsillopharyngitis [61]. The absolute difference in bacteriologic failure rates between cephalosporins and penicillin was 5.4%; thus, one would need to treat 19 adults with a cephalosporin to see 1 additional bacteriologic cure, compared with penicillin. We would advocate a case-by-case assessment for use of cephalosporins as a treatment of choice for GABHS tonsillopharyngitis.

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