

Clinical And Bacteriological Impact Of Clarithromycin In Streptococcal Pharyngitis: Findings From A Meta-Analysis Of Clinical Trials

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Introduction: Among the bacterial upper respiratory tract infections (URTIs), the most medically significant is pharyngitis due to Group A beta-hemolytic *Streptococci* (GABHS). A 2012 meta-review and a 2016 Cochrane systematic review reported favorably on the comparative efficacy and safety of clarithromycin in pediatric patients with URTIs and in adults with GABHS pharyngitis. In this paper, the evidence base for clarithromycin in patients with URTIs is augmented by a meta-analysis of comparative studies in GABHS pharyngitis.

Methods: A series of five outpatient trials of clarithromycin for the treatment of streptococcal pharyngitis from an internal database were subjected to meta-analysis. Active comparators comprised penicillin VK and erythromycin.

Results: Rates of clinical cure or improvement were very similar in all treatment assignments, but the rates of bacteriological cure were numerically higher with clarithromycin than with comparator antibiotics. Adverse events data indicated that clarithromycin was generally well tolerated in these studies, with a relatively low incidence of adverse events and few severe incidents.

Discussion: Though currently not advised as a first-line therapy for URTI in most guidelines, the results of the meta-analysis indicate that clarithromycin is nevertheless a valid, effective and largely well-tolerated treatment option for GABHS pharyngitis patients who cannot benefit from other agents.

Keywords: clarithromycin, erythromycin, amoxicillin, *Streptococcus*, pharyngitis, metaanalysis

Introduction

Upper respiratory tract infections (URTIs) such as acute pharyngitis generate many primary care consultations and are regarded by patients, their families and many physicians as a condition with a high initial nuisance impact and potential for substantial and serious sequelae. Among those with a bacterial origin, the most prominent category, and arguably the most medically significant, is pharyngitis due to Group A beta-hemolytic *Streptococci* (GABHS) (*S. pyogenes*), which may account for $\geq 20\%$ of sore throat-related clinic visits in pediatric patients aged >3 years and a smaller, but significant, percentage (5–15%) in adults.¹

Symptoms of acute sore throat are often self-limiting and the impact of antibiotic therapy on resolution of bacteria-attributable pharyngitis symptoms is relatively limited, although more pronounced in cases confirmed to be associated with GABHS infection.² Nevertheless, accurate diagnosis and effective treatment of

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streptococcal pharyngitis are important for preventing re-infection and spread and for the avoidance of longer-term complications of the initial infection, notably acute rheumatic fever, but also suppurative complications such as mastoiditis and cervical lymphadenitis, plus post-streptococcal glomerulonephritis and guttate psoriasis. In extreme instances, toxic shock syndrome or necrotizing fasciitis may ensue. Acute rheumatic fever is now uncommon in most developed countries, but it continues to be a significant cause of acquired heart disease in children in many middle- and low-income countries.³

The second-generation macrolide clarithromycin, which offers significant improvements over its predecessor, erythromycin, with an expanded spectrum of activity and enhanced tolerability,⁴ is regarded as a viable treatment option for patients with acute bacterial pharyngitis when penicillin V or amoxicillin is unavailable or for any reason inappropriate.^{1,5}

A meta-review in 2012 reported favorably on the comparative efficacy and safety of clarithromycin in pediatric patients with URIs,⁶ and a Cochrane systematic review in 2016 reported close equivalence of macrolides and penicillin for the resolution of GABHS pharyngitis in adults.⁷ The number of patients specifically treated with clarithromycin in that analysis was relatively small (N=499). We sought to augment the evidence base for clarithromycin in patients with URIs by conducting a meta-analysis of comparative studies in GABHS pharyngitis.

Materials And Methods

Abbott's internal database was searched for all clinical trials with clarithromycin for the treatment of streptococcal pharyngitis. This database contains all trials conducted by Abbott Laboratories with clarithromycin after obtaining the international rights in 1985. Study quality was evaluated using the Jadad score scale, in which the range of possible scores is 0 (poor/weak) to 5 (good) (see [Appendix 1](#)).⁸

Five trials were identified. All five were randomized, multi-center outpatient trials, in which very similar protocols and case report forms were used. Three studies were double-blind, one study was single-blind and one study was an open-label study. Blindedness was maintained by producing study drugs and placebos in identical appearance and by having all patients comply with the same dosing regimen. All studies had appropriate endorsement from local ethics committees.

Patients who presented with a primary complaint of pharyngeal pain and an associated sign of streptococcal

pharyngitis provided two throat swabs. One swab was used to test for the presence of GABHS antigen using the rapid enzyme immunoassay Abbott Testpack™ Strep A (Abbott Laboratories, North Chicago, IL, USA), documented as having $\geq 90\%$ sensitivity and 97.4% specificity in the detection of Group A *Streptococci*.^{9,10} The second was used for culturing to confirm the diagnosis of GABHS pharyngitis. To that end, swabs were plated on two 5% sheep blood agar plates. The primary inoculum was cultured to permit isolation of beta-hemolytic organisms. The blood agar plates were stabbed in several areas to detect the organism's ability to produce streptolysin 0. One blood agar plate was incubated aerobically and the other incubated anaerobically, both at 35–37°C. All beta-hemolytic colonies were quantified, isolated and identified by Gram stain, bacitracin sensitivity and catalase reaction. Presumptive identification was confirmed using specific antisera. All tests were performed according to the provisions of the Clinical & Laboratory Standards Institute.¹¹

In each of the trials, four study visits were planned. At Visit 1 (day 1) informed consent was obtained, a medical history was recorded, a physical examination was performed, vital signs were checked and a pharyngeal swab was obtained for culturing.

Principal common inclusion criteria in these five studies comprised:

- age ≥ 12 years
- a complaint of sore throat accompanied by at least one sign of streptococcal pharyngitis
- infection with Group A *Streptococcus*, as indicated by a positive rapid immunoassay test or as determined clinically by the investigator. Patients were admitted to the studies at the time of rapid antigen testing, before culture test results were available.
- otherwise good health
- written informed consent (from the patient or his/her legal guardian).

Female patients were required to have been post-menopausal for ≥ 1 year or to have undergone a hysterectomy or tubal ligation. Use of contraceptive medication or a contraceptive device did not qualify a patient for enrolment in these studies.

Patients were randomized to study drug medication using schedules generated by the statistical department of the study sponsor. A separate randomization schedule was prepared for each investigator, generated in randomly

allocated blocks of either two, four or six. Patient numbers were assigned to the patients in order of enrolment. Further visits were scheduled at treatment days 5–7 (Visit 2) and at post-treatment days 4–5 (Visit 3) and 19–25 (Visit 4) for patients who completed the study drug treatment. At each visit, pharyngeal swabs were collected, adverse events were recorded and compliance with the study drug treatment was checked (not at Visit 4). Clinical response was scored by the responsible investigator at Visits 3 and 4.

The planned duration of study drug treatment was 10 days in all these trials.

The following assessment scales were used.

Clinical response at the end of the study drug treatment was scored using the following scale:

- Clinical cure: signs and symptoms of the infection resolved
- Clinical improvement: signs and symptoms of the infection improved but did not resolve
- Clinical failure: signs and symptoms of the infection did not improve, or worsened
- Recurrence: pre-treatment signs and symptoms of the infection resolved post-treatment but reappeared during follow-up (only in studies of streptococcal pharyngitis)
- Not evaluable: otherwise.

Clinical success at the end of the study drug treatment was defined as clinical cure or clinical improvement at that time.

Bacteriologic cure at the end of study drug treatment was scored using the following scale:

- Eradication: the initial pathogen(s) was/were eradicated at the end of study drug treatment and for the duration of follow-up
- Recurrence: eradication of the initial pathogen(s) at the end of study drug treatment with recurrence of the same pathogen(s) at any time during follow-up
- Re-infection: eradication of the pre-treatment pathogen at the end of study drug treatment with appearance of a new pathogen at any time during the follow-up period
- Persistence: otherwise.

Results

A series of five studies were identified, all of which were conducted between 1985 and 1988. Summary particulars of all five studies are provided in [Table 1](#). Three studies used double-blind methodology, one was single-blind (investigator-blind) and one was open-label. Study MK86-008 has been published in the peer-reviewed literature.¹²

In all, 1184 patients with signs and symptoms of streptococcal pharyngitis were enrolled in the five studies, of whom 600 were randomized to treatment with clarithromycin 250

Table 1 Indication, Dosage And Format Details For The Analyzed Trials

Study Identifier	Indication	Clarithromycin Dose/Regimen/Duration	Comparator	Study Design	No. Of Patients (Clarithromycin/Comparator)	Jadad Score (see Appendix 1)
M86-008	Streptococcal Pharyngitis	250 mg twice daily for 10 days	Penicillin VK 250 mg four times a day	Double-blind, randomized, multicenter	108/98	4
M86-030	Streptococcal pharyngitis	250 mg twice daily for 10 days	Penicillin VK 250 mg three times a day	Phase III, single-blind, randomized, multicenter	226/227	2
M85-129	Streptococcal pharyngitis	250 mg twice daily for 10 days	Erythromycin stearate 500 mg twice daily	Phase III, double-blind, randomized, multicenter	49/53	4
M86-047	Streptococcal pharyngitis	250 mg twice daily for 10 days	Erythromycin stearate 500 mg twice daily	Open-label, multicenter	120/120	2
M88-165	Streptococcal pharyngitis	250 mg twice daily for 10 days	Erythromycin stearate 500 mg twice daily	Phase III, double-blind, randomized, multicenter	65/63	5

mg twice daily and 584 to treatment with penicillin VK (250 mg three or four times daily; n=412) or erythromycin (500 mg twice daily; n=172).

Exclusions from the statistical analysis, detailed in Table 2, arose primarily either because no pre-treatment pathogen was isolated (n=137) or because no streptococcal pathogen was isolated (n=36). A total of 960 streptococcal pharyngitis-causing pathogens were isolated pre-treatment, overwhelmingly comprising *S. pyogenes* (98.8% of isolates, n=996, including 507/514 evaluable patients treated with clarithromycin).

Median age was 30 years in both the clarithromycin group and the pooled control groups, with age ranges of 12–83 years for clarithromycin and 11–73 years in the pooled control groups. Most patients in both groups were aged ≥ 18 years (573/600 in the clarithromycin group; 555/584 in comparator groups) and two-thirds were male (n=394 for clarithromycin, n=381 for pooled comparators).

In all three treatment groups, the median total dose and the median duration of study drug treatment corresponded to the targeted total dose and treatment duration, respectively. Median compliance approached 100% in all three treatment groups.

Clinical and bacteriological outcome data at study Visit 3 (4–6 days after termination of study drug treatment) are summarized in Table 3 and Figure 1, respectively. Rates of clinical cure and clinical success (i.e., cured or improved) were very similar in all treatment assignments (Table 3) as well as in the individual trials (data not shown.) However, the rates of bacteriological cure were higher with clarithromycin than with either comparator agent (Figure 1).

Safety Data

In all, 287 of the 1184 patients reported a total of 457 treatment-emergent adverse events. Fifty-one of the 216

events (23.6%) recorded with clarithromycin 500 mg twice daily were considered probably related to the use of study medication, compared with 27/34 (79.4%) with erythromycin 500 mg twice daily, 9/64 (14%) with penicillin 250 mg four times a day and 7/117 (6%) with penicillin 250 mg three times daily.

Adverse events occurring with a frequency of $\geq 2\%$ in the patients assigned to the various study medications are summarized in Table 4.

A total of 23 treatment-emergent adverse events were classified as severe (clarithromycin: nine cases, 1.5%; erythromycin: seven cases, 4.1%; penicillin 250 mg four times a day: five cases, 2.7%; penicillin 250 mg three times daily: two cases, 0.9%). The seriousness of events was not documented. No deaths occurred in any of these studies.

Discussion

The results of this analysis indicate that clarithromycin, while currently not identified as a first-line therapy for URTI in most guidelines, is nevertheless a valid, effective and largely well-tolerated treatment option for GABHS pharyngitis patients who, for whatever reason, cannot benefit from other agents.

The number of patients accrued in the pharyngitis contingent was substantial: we believe that our cohort of >1000 patients (across both treatment assignments) is the largest such population reported for clarithromycin in that indication. These factors lend a degree of resilience to our central conclusion. Most of the patients enrolled were adults (96.0%) and, to that extent, our findings of high rates of clinical and, in particular, bacteriological cure with clarithromycin may be seen as extending to adult URTI patients the findings of the meta-analyses of Gutiérrez-Castrellón et al⁶ and the earlier results of Abad-Santos et al,¹³ who concluded that clarithromycin is an effective alternative for the treatment of URTIs in

Table 2 Reasons For Exclusion From Statistical Analysis In Trials Of Streptococcal Pharyngitis. Values Shown Are Numbers Of Patients

Reason For Exclusion	Clarithromycin (N=600)	Erythromycin (N=172)	Penicillin VK (N=412)	Total (N=1184)
No pre-treatment pathogen	66	10	61	137
No streptococcal pharyngitis pathogen	18	3	15	36
No pre-treatment specimen	1	–	–	1
Other reason	1	1	–	2
Total	86	14	76	176
Net evaluable patients	514	158	336	1008

Table 3 Clinical Outcomes In Streptococcal Pharyngitis Studies At Visit 3 (4–6 Days Post-Treatment)

Outcome	Clarithromycin 250 mg b.i.d./10 Days	Comparator
Versus penicillin VK 250 mg TID or QID		
Cured	84.9%	83.6%
Improved	7.5%	9.3%
Failure	2.3%	2.8%
Not evaluable	5.2%	4.3%
Relative clinical cure rate=0.849/0.836=1.02		
Versus erythromycin 500 mg b.i.d.		
Cured	81.9%	79.6%
Improved	15.4%	15.0%
Failure	2.0%	2.7%
Not evaluable	0.7%	2.7%
Relative clinical cure rate=0.819/0.796=1.03		
Pooled relative clinical cure rate*: 1.02 (0.96, 1.08)		

Notes: *Mantel-Haenszel analysis; () 95% confidence interval.

Abbreviations: b.i.d., twice daily; t.i.d., three times daily; q.i.d., four times daily.

pediatric patients. Our own data also corroborate the views of those authors as to the effectiveness of clarithromycin in pediatric patients but, with limited numbers (n=57), our findings should be regarded as supplementary, not definitive.

The numerical findings for bacteriological cure are notably in favor of clarithromycin. In the largest of the studies in our dataset (M86-030), the intergroup difference in bacteriologic cure rate in pharyngitis patients was determined a priori and significantly favored clarithromycin over penicillin VK (95% vs 87%; p=0.009). The bacteriological superiority of clarithromycin over erythromycin may reside in part in the drug's pharmacokinetics and metabolism, including tissue penetration and the formation

of a bacteriologically relevant 14-hydroxy metabolite, and findings from pharmacodynamic modeling, which suggest that clarithromycin has a lower potential for encouraging the emergence of unrecognized resistant strains within an overall susceptible isolate.^{13–18}

While a large proportion of pharyngitis cases may resolve without treatment, antibiotic use is necessary for pathogen eradication to prevent spread and re-infection and to minimize potential sequelae of the index infection. Complications of pharyngitis are rare in many of the high-income countries where clinical trials are often conducted but different considerations may apply in lower-income areas of the world,¹⁹ where poverty in its broad sense plus particular environmental proxies for poverty, such as overcrowding and shared housing, can promote the spread of infection and cycles of re-infection. Effective use of clarithromycin in that context may have a positive and long-lasting impact on the health of both URTI patients and their contacts.

Evidence accrued from a range of clinical studies and in experimental research indicates that clarithromycin exerts wide-ranging anti-inflammatory and immunomodulatory effects that may be pertinent in this context. Mechanisms involved may include inhibiting the production of microbial toxins and other virulence factors, so attenuating the pro-inflammatory host response; suppression of immune cell activity; and modulation of the cytokine profile toward a less pro-inflammatory/more anti-inflammatory balance.^{20–23}

Limitations of our research must be acknowledged. Ours should be construed as a convenience sample: it is possible that either the patient populations or the response of those populations to treatment is not fully representative of the wider population that might be candidates for clarithromycin therapy for GABHS pharyngitis. The dosages of

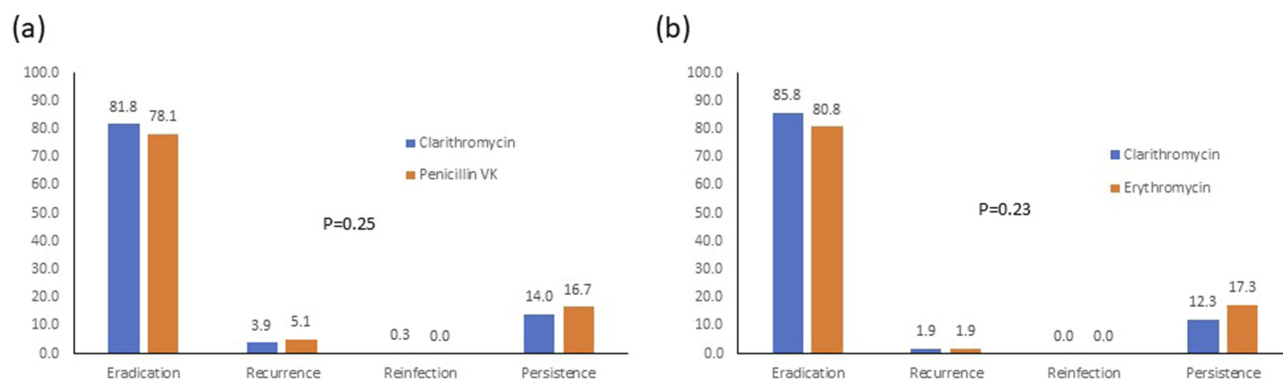


Figure 1 Bacteriological outcomes in the five GABHS pharyngitis studies at Visit 3 (4–6 days post-treatment). (A) Clarithromycin versus penicillin VK; (B) clarithromycin versus erythromycin. P-values are for comparison of outcome trend across all four categories.

Table 4 Adverse Events Recorded In $\geq 2\%$ Of Patients

Study Drug	Event
Clarithromycin 500 mg b.i.d.	Headache (n=23, 3.8%), nausea (n=19, 3.2%), diarrhea (n=18, 3.0%), abdominal pain (n=14, 2.3%), dyspepsia (n=13, 2.2%)
Erythromycin 500 mg b.i.d.	Dyspepsia (n=8, 4.7%), nausea (n=8, 4.7%), vomiting (n=4, 2.3%)
Penicillin VK 250 mg q.i.d.	Nausea (n=8, 4.3%), headache (n=6, 3.2%), infection (n=5, 2.7%), SGPT increased (n=4, 2.2%)
Penicillin VK 250 mg t.i.d.	Headache (n=13, 5.7%), abdominal pain (n=9, 4.0%), rhinitis (n=7, 3.1%), diarrhea (n=6, 2.6%), back pain, cough and infection (each n=5, 2.2%)
Amoxicillin 1000 mg b.i.d.	Not applicable
Amoxicillin 500 mg t.i.d.	Not applicable

Abbreviations: b.i.d., twice daily; t.i.d., three times daily; q.i.d., four times daily; SGPT, serum glutamate pyruvate transaminase.

penicillin V were somewhat lower than might be prescribed today. Jadad scores ranged from 2 to 5, with three of the five studies registering scores of 4 or 5 (see [Appendix 1](#)). The range of scores nevertheless indicates methodological variability in the conduct of these studies and highlights the desirability of corroborating our central conclusions with additional studies that apply consistent contemporary standards of randomization and blinding.

Women of child-bearing age and potential were excluded from the studies in our dataset. This reflected the application of the contemporary ethical balance of advantage versus risk in the treatment of URTIs with antibiotics. Similar considerations still prevail and the clarithromycin SPC cautions that use in pregnancy requires a careful assessment of risk versus benefit.²⁴ The outcomes of such deliberations may be different in high-income countries and low- or middle-income territories where rheumatic heart disease remains a substantial contributor to maternal death rates, and where there are also hazards from toxic shock syndrome and necrotizing fasciitis.^{25,26} There is no a priori reason to imagine that clarithromycin would have been anymore or less effective in this sector of the general population and there are no data from later experience to indicate such a difference in response. However, our data can offer no first-hand proof of that supposition.

Adverse events data indicated that clarithromycin was generally well tolerated in these studies, with a relatively low incidence of adverse events and few severe incidents. These findings should be contextualized by the acknowledgement that macrolide therapy has been associated increased rates of gastrointestinal adverse events (vs placebo) and with some increase in the risk of hearing loss.²⁷ A Cochrane review of 2016 reported that the odds ratio for

adverse events with “macrolide” was higher than with “penicillin” (OR 2.33, 95% CI 1.06 to 5.15) but that conclusion was based on a single study that compared azithromycin with penicillin V²⁸ and it is not clear whether and to what extent that finding is an accurate reflection of a whole-of-class effect of macrolides. A more recent Cochrane assessment found no evidence that macrolides caused more cardiac disorders, hepatobiliary disorders or changes in liver enzymes nor any indications that less serious events such as dizziness, headache, itching or rashes were reported more often with macrolides than with placebo. The overall standard of evidence underpinning these conclusions was, however, deemed weak.²⁷

These considerations notwithstanding, our findings indicate that clarithromycin can be an effective option for patients with GABHS pharyngitis who are candidates for antibiotic therapy. In reaching these conclusions it must be acknowledged that the studies in our dataset can offer no insights into longitudinal trends in antibiotic resistance. Any substantial assessment of global trajectories of antibiotic resistance is beyond the scope of this report but the existence of such trends is indisputable and some of those trends are not favorable to the use of macrolides in URTIs. Over-prescription or inappropriate use of antibiotics is one factor contributing to this state of affairs^{29–35} and we would firmly endorse the views of Mohan et al³⁵ (writing from a low- to middle-income perspective) on the need to restrict inappropriate antibiotic use in URTIs. Additional recent perspectives on this issue have been provided in a series of reports from the Survey of Antibiotic Resistance program,^{36–38} the CARTIPS Antimicrobial Surveillance Program in People’s Republic of China³⁹ and other initiatives.³⁰ Antibiotic resistance is not a problem confined to a single agent or class, however, and the extent that effective use of clarithromycin

adds to the variety of effective treatment options for URTIs, we regard our findings as evidence that clarithromycin can indeed play a useful and effective role in the treatment of GABHS pharyngitis in pediatric and adult patients.

Data Access

The accessed data is not freely available.

Ethics Approval

Ethics approval for all five studies was obtained by the investigators.

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Disclosure

Dr Nauta is a salaried full-time employee of Abbott Healthcare Products B.V., Weesp, The Netherlands, and owns company stock. Dr Hoban has in the past received grant support from Abbott and currently sits on Abbott Advisory boards and lectures for Abbott. This research was supported financially by Abbott Products Operations AG, Allschwil, Switzerland. The authors report no other conflicts of interest in this work.

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