RIC

ARTÍCULO ORIGINAL

Efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections: a systematic review with meta-analysis

Pedro Gutiérrez-Castrellón,* José Luis Mayorga-Buitron,* Vanessa Bosch-Canto,* Guillermo Solomon-Santibañez,* Agustín de Colsa-Ranero**

* Centro Cochrane de análisis de pruebas,
** Departamento de Enfermedades Infecciosas, Instituto Nacional de Pediatría, Secretaría de Salud.

ABSTRACT

Purpose. Upper respiratory infections (URIs) are one of the most common infectious diseases in children. Macrolides had been considered one of the best options of treatment. Instead of clarithromycin is one of the macrolides most used, meta-analysis about the safety and efficacy of this drug has not been published. **Materials and methods.** A systematic review with meta-analysis of randomized controlled trials (RCTs) was conducted. Studies in subjects ≤ 12 years of age with URIs were included. Central Cochrane Registry, MEDLINE, EMBASE, Lilacs and Artemisa from 1966 to January of 2011 were reviewed. Clinical cure, clinical success, bacteriological eradication, relapse risk and adverse events risks were analyzed. Risks ratios (RR) with 95% confidence intervals (CI 95%) were calculated, using a fixed effects model. **Results.** 24 studies, from a total of 76 RCTs were included. Clarithromycin was therapeutically equivalent to other antibiotics studied with respect to clinical cure [RR 1.02 (0.98 to 1.06), p NS], clinical success [RR 1.01 (0.99 to 1.03), p NS] and relapse risk [RR 1.34 (0.81 to 2.21), p NS], but was associated with a better bacteriological eradication [RR 1.06 (1.02 to 1.09), p 0.001], and a lower risk for related adverse events [RR 0.77 (0.65 to 0.90), p = 0.001]. **Conclusions.** High quality evidence showed that Clarithromycin is a safe and effective alternative for the treatment of URIs in pediatric patients. Is superior to other antibiotics in relation to bacterial eradication. Its equivalence profile related to clinical cure, clinical success and relapse risk, let to consider it as an important alternative.

Key words. Clarithromycin. Upper respiratory infections. Children.

Eficacia y seguridad de la claritromicina en pacientes pediátricos con infecciones respiratorias superiores: una revisión sistemática con metaanálisis

RESUMEN

Justificación. *Las infecciones respiratorias (IRAs) son uno de los procesos infecciosos más frecuentes en niños. Los macrolidos se han considerado como una de las mejores opciones para su tratamiento. La claritromicina es el macrolido más utilizado. No se ha publicado ningún metaanálisis sobre la eficacia y seguridad de la claritromicina en niños.* ***Material y métodos.*** *Se realizó una revisión sistematizada de la evidencia con metaanálisis de ensayos clínicos controlados (RCTs), efectuados en sujetos de ≤ 12 años con IRAs. Se efectuó búsqueda de la evidencia publicada en Central Cochrane Registry, MEDLINE, EMBASE, Lilacs y Artemisa de 1966 a enero 2011. Se analizaron como variables de desenlace la curación clínica, tasa de éxito, erradicación bacteriológica, riesgo de recaída y presencia de eventos adversos. Se efectuó cálculo de razón de riesgos (RR) con intervalo de confianza a 95% (IC95%), utilizando un modelo de efectos fijos.* ***Resultados.*** *Se incluyeron 24 estudios de un total de 76 RCTs evaluados. La claritromicina fue equivalente a otros antibióticos en relación con la curación clínica [RR 1.02 (0.98 a 1.06), p NS], tasa de éxito [RR 1.01 (0.99 a 1.03), p NS] y riesgo de recaída [RR 1.34 (0.81 a 2.21), p NS], asociándose con una mayor erradicación bacteriológica [RR 1.06 (1.02 a 1.09), p 0.001], y con un riesgo menor de eventos adversos relacionados [RR 0.77 (0.65 a 0.90), p = 0.001].* ***Conclusiones.*** *La evidencia de calidad demuestra que la claritromicina es una alternativa eficaz y segura para el tratamiento de las IRAs en niños. Es superior a otros antibióticos en relación con la erradicación bacteriana. Su perfil de equivalencia con otros antibióticos para la curación clínica, tasa de éxito y riesgo de recaída la soportan como una alternativa significativa.*

Palabras clave. *Claritromicina. Infecciones respiratorias. Niños.*

BACKGROUND

Acute pharyngitis

Acute pharyngitis, a commonly occurring illness, is responsible for 1 to 2% of all visits to outpatient departments, emergency rooms and physician offices.[1] The etiology includes bacteria, viruses and atypical organisms (i.e. chlamydia, mycoplasma). The most common cause of bacterial pharyngitis is group A betahemolytic streptococcus (GABHS) *(Streptococcus pyogenes)*, which is responsible for 15-30% and 5-10% of all cases in children and adults, respectively.[1-4] Antibiotic therapy is recommended for pharyngitis caused by GABHS, but not for any of the other forms of the infection.[5] Although GABHS pharyngitis is typically self-limiting, antibiotic therapy initiated early in the course of illness can hasten the resolution of clinical symptoms[1,6,7] and is utilized to prevent the occurrence of non-suppurative sequelae such as rheumatic fever.[8,9] Penicillin for 10 days is considered the regimen of choice for the treatment of GABHS pharyngitis.[4,5,10] Other beta-lactams (e.g. ampicillin, amoxicillin, cephalosporins), macrolides and clindamycin, have also been shown to be effective in the management of this infection.[5] Although a 10-day course of antibiotics is considered standard therapy, data suggest that short course regimens of clarithromycin, azithromycin, or a cephalosporin (e.g. cefuroxime, cefixime, cefdinir, ceftibuten, cefpodoxime) are equally effective.[11–17] Obvious advantages to shorter courses include improved adherence, more favorable patient/parent acceptance, and, in some circumstances, decreased direct and indirect costs.[18,19]

Acute otitis media

Acute otitis media (AOM) is the most common childhood infection for which antibiotics are prescribed in the United States.[20-22] A study using 2006 Medical Expenditure Panel Survey data demonstrated an average expenditure of $350 per child with AOM, totaling $2.8 billion.[23] Timely and accurate diagnosis and appropriate management of AOM may have significant consequences for ambulatory health care utilization and expenditures. Multiple systematic reviews on AOM diagnosis and management have been conducted,[24-29] including 2001 study by Takata GS[30] which was the basis for the 2004 American Academy of Pediatrics and American Academy of Family Physicians joint practice guidelines.[31] Since then, new trials have been published, the heptavalent pneumococcal conjugate vaccine (PCV7) has become widely used, and clinician practice has changed regarding antibiotic choice for AOM.[32] Since the introduction of PCV7, there have been significant shifts in AOM microbiology, with *S pneumoniae* becoming less prevalent and *H. influenzae* becoming more prevalent. A recent study of a single pediatric practice found evidence suggesting that this balance may be shifting again because of an increase in the proportion of AOM with nonvaccine *S. pneumoniae* serotypes.[33] These data and the introduction of PCV13 support the need for ongoing surveillance of AOM isolates. Immediate ampicillin/amoxicillin treatment has a modest benefit compared with placebo or delayed antibiotics but also may be associated with more diarrhea and rash. Of 100 average risk children with AOM, approximately 80 would likely get better within about 3 days without antibiotics.[34] If all were treated with immediate ampicillin/amoxicillin, an additional 12 would likely improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM. Most antibiotics used to treat uncomplicated AOM in children at normal risk have similar rates of clinical success.

Clarithromycin and upper respiratory infections

Clarithromycin is a new macrolide antibiotic with *in vitro* activity similar to erythromycin.[35-37] Clarithromycin is effective against a wide range of microorganisms, including Gram-positive cocci, *Haemophilus influenzae*, *Moraxella catarrhalis*, mycoplasma, chlamydia, selected mycobacteria, *Legionella* spp. and protozoan organisms.[38] Pharmacokinetic studies showed that clarithromycin, in combination with its active 14-hydroxy metabolite, has a longer half-life and higher plasma level than erythromycin, thus allowing twice-a-day dosing.[39] It is concentrated in cells and tissues, including tonsil, nasal mucosa, middle ear fluid and lung. Higher concentrations of drug are achieved in lung tissue than in concurrent samples of plasma.[38,40] Appears to be safe and generally very well tolerated. In comparative clinical trials, overall adverse event rates associated with clarithromycin were similar to those with amoxicillin, penicillin, cefaclor and cefadroxil.[38] Related gastrointestinal side effects were shown to

occur at a lower frequency than those associated with erythromycin.[41] Clinical efficacy has been demonstrated in randomized trials of children with acute otitis media, streptococcal pharyngitis, infections of skin and skin structures, and some lower respiratory infections or diseases such as bronchiolitis or pneumonia.[38,42,43]

Considering the evidence described above, the objective of this systematic review with meta-analysis was to evaluate the efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections.

METHODOLOGICAL DESIGN OF THE REVISION

Criteria used for study inclusion in this review

- **Types of studies.** We selected all of the published RCTs that compared, as some of its treatment branches, clarithromycin *vs.* another antibiotic in children with URIs who were ≤ 12 years.
- **Types of participants.** We selected for our review the articles that included children ≤ 12 years of age who had any upper respiratory tract infection (acute pharyngitis, tonsillitis, pharyngo-tonsillitis, bacterial acute rhinitis, or acute otitis media).
- **Types of interventions.** All of the RCTs that evaluated the efficacy and safety of clarithromycin compared with other antibiotics in children ≤ 12 years with URIs were included in the study (regardless of dose, route of administration, and duration of treatment).
- **Types of outcomes analyzed.** The outcomes analyzed were:
    - Bacteriological eradication.
    - Clinical cure [defined as complete resolution of clinical signs and symptoms, and documentation of a nonhyperemic, nonbulging tympanic membrane with effusion (flattened tympanogram) or without effusion (normal tympanogram)].
    - Clinical success (defined as cure plus improvement).
    - Relapsing rate (defined as the return of pretreatment signs and symptoms of infection within 4 days after completion of treatment), and
    - The presence of any related adverse events.

Search methods for the identification of studies

Two authors of this review conducted simultaneous and independent searches of the literature on this topic, both in English and Spanish. The databases used included The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 5, 2010); MEDLINE (1966-January 2010), using the highly sensitive search strategy developed by The Cochrane Collaboration for the identification of RCTs;[44] and EMBASE (1980 to May 2010), using the search strategy adapted by the Cochrane Collaboration to search for RCTs in this database.[45] Additionally, we searched for further information in Lilacs (from 1980 to 2011), Artemisa (from 1999 to 2009) and in the gray literature that was obtained through a manual search or a query via email.

Information collection and analysis

- **Selection of studies.** The evidence review was conducted blindly and independently by three of the authors of this review. These authors, after carefully analyzing each item, excluded the studies that were considered irrelevant for the purposes of this review. If there were any discrepancies between the reviewers, an agreement was reached through the Delphi panel method.
- **Information extraction.** Information extraction was performed using forms of standardized data extraction including:
    - Title of the article.
    - Test design.
    - Method of randomization.
    - Type of blinding.
    - Presence of intention to treat analysis.
    - Allocation scheme.
    - Total number of participants.
    - Detailed explanation of follow-up failures.
    - Stages of completion of the study (multicenter or single center).
    - A description of the population.
    - A detailed description of maneuvers, and
    - A detailed description of the outcomes.

When appropriate, the subgroups were also described based on:

- Duration of follow-up by subgroups, and
- Description of the presence of risk factors.

- **Classification of allocation schemes.** Allocation schemes were classified as adequate (methods of randomization that allow neither the researcher nor the participant to know or influence the allocation of patients), unclear (insufficient information to make judgments) or inadequate (description of randomization methods, such as non-opaque envelopes or the presence of information that would allow a biased assignation of the subject to a specific group).
- **Classification of the types of blinding.** These were classified according to the blinding of the investigator, the participant or the assessor in regards to the outcome and what was appropriate in terms of the objective (open, single, double or triple blinding).
- **Classification of the intention to treat analysis (ITA).** The ITA was classified as either clearly described, not described but confirmed on the study assessment or absent.

Statistical analysis

Statistical analysis was conducted using the STATA statistical package 11.0 for Mac considering the subroutines for the development of the meta-analysis. For dichotomous outcomes (e.g., bacteriological eradication *vs.* no eradication), the results were expressed as a risk ratio (RR) with confidence intervals at 95% (CI 95%). For continuous measurements, data were expressed as a weighted mean difference (WMD). In those cases for which the primary survey identified a value of heterogeneity (I^2) above 60%, the results were analyzed using a random effects model (inverse variance). Statistical heterogeneity was explored using Egger graphs, and the publication bias was evaluated using funnel plots.

RESULTS

We originally identified a total of 76 controlled clinical trials that were reviewed in their entirety, resulting in the rejection of 52 articles; thus, a total of 24 articles were selected for development of evidence tables and the meta-analysis[45-69] (Tables 1-2). Clarithromycin was therapeutically equivalent to other antibiotics studied with respect to clinical cure

Table 1. Characteristic of included studies.

Author, year	Type of study*	Disease**	Age	n1	n2	Clarithromycin doses	Antibiotic control doses
Still, 1993	RSBCT-Published	FAA	6 m-12 y	176	191	Clarithro 7.5 mg/kg/bid/5-10d	Penicillin V 13 mg/kg/tid/10d
Bedregal, 1995	RSBCT-Published	FAA	2 y-15 y	22	21	Clarithro 15 mg/kg/bid/5-10d	Penicillin V 13 mg/kg/tid/10d
Padilla-Raygoza, 1995	RSBCT-Published	FAA	1 y-12 y	102	99	Clarithro 15 mg/kg/bid/10d	Amoxycillin-Clavul 40 mg/kg/tid/10d
Padilla, 1996	ROBCT-Poster	FAA	1 y-16 y	102	99	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin-Clavul 13 mg/kg/tid/10d
Castaño, 1996	ROBCT-Poster	FAA	3 y-15 y	34	37	Clarithro 7.5 mg/kg/bid/5-10d	Cefadroxil 15 mg/kg/vida/10d
Kearsley, 1997	RSBCT-Published	FAA	1 y-12 y	98	91	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin 10 mg/kg/tid/5-10d
Venuta, 1998	RDBCT-Published	FAA	6 m-12 y	74	63	Clarithro 7.5 mg/kg/bid/5-10d	Azitromicin 10 mg/kg/tid/5-10d
McCarty, 2000	RDBCT-Published	FAA	6 m-12 y	268	260	Clarithro 7.5 mg/kg/bid/5-10d	Penicillin V 13 mg/kg/tid/10d
Oliveros-Lozano, 2001	RSBCT-Published	FAA	2 y-12 y	87	102	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin 50 mg/kg/bid/5-10d
Kafetziz, 2004	ROBCT-Published	FAA	3 y-13 y	86	88	Clarithro 7.5 mg/kg/bid/5-10d	Cefprozil 30 mg/kg/bid/5d
Syrogiannopoulos, 2004	ROBCT-Published	FAA	2 y-16 y	155	155	Clarithro 15 mg/kg/bid/5d	Amoxycillin-Clavul 44 mg/kg/tid/5d
Padilla-Raygoza, 2005	RSBCT-Published	FAA	1 y-17 y	91	91	Clarithro 15 mg/kg/bid/5-10d	Azitromicin 10 mg/kg/tid/5-10d
Coles, 1993	RSBCT-Published	OMA	1 y-12 y	132	127	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin 10 mg/kg/tid/5-10d
Gooch, 1993	RSBCT-Published	OMA	6 m-12 y	150	131	Clarithro 7.5 mg/kg/bid/5-10d	Cefador 20 mg/kg/bid/5-10d
Pukander, 1993	RSBCT-Published	OMA	1 y-12 y	39	40	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin 20 mg/kg/tid/5-10d
McCarty, 1993	RSBCT-Published	OMA	6 m-12 y	161	177	Clarithro 7.5 mg/kg/bid/10d	Amoxycillin-Clavul 13 mg/kg/tid/10d
Aspin, 1994	RSBCT-Published	OMA	6 m-12 y	90	90	Clarithro 15 mg/kg/bid/10d	Amoxycillin-Clavul 40 mg/kg/tid/10d
Ramet, 1994	ROBCT-Published	OMA	5 m-6 y	72	75	Clarithro 7.5 mg/kg/bid/5-10d	Azitromicin 10 mg/kg/tid/5-10d
Arguedas, 1995	ROBCT-Poster	OMA	9 m-11 y	45	48	Clarithro 7.5 mg/kg/bid/5-10d	Azitromicin 10 mg/kg/tid/5-10d
Ramet, 1996	ROBCT-Poster	OMA	5 m-7 y	102	97	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin-Clavul 7-10 mg/kg/tid/10d
Craft, 1996	RSBCT-Poster	OMA	1 y-12 y	22	24	Clarithro 7.5 mg/kg/bid/5-10d	Amoxycillin 14 mg/kg/tid/5-10d
Kafetziz, 1996	ROBCT-Poster	OMA	6 m-52 m	15	15	Clarithro 7.5 mg/kg/bid/5-10d	CefuroximeAxetil 15 mg/kg/bid/5d
Syriopoulou, 1996	ROBCT-Poster	OMA	5 m-12 y	38	31	Clarithro 7.5 mg/kg/bid/5-10d	Cefaclor 13 mg/kg/tid/10d
Gooch, 1999	RSBCT-Published	OMA	6 m-3 y	117	117	Clarithro 7.5 mg/kg/bid/10d	Loracarbef 15 mg/kg/bid/10d

*RDBCT: randomized double blind controlled trial. RSBCT: randomized single blind controlled trial. ROBCT: randomized open blinded controlled trial. **FAA: acute pharyngitis. OMA: acute otitis media.

Table 2. Characteristic of included studies (continued).

Author, year	Clinical cure Clarithro (%)	Clinical cure Control (%)	Clinical success Clarithro (%)	Clinical success Control (%)	Bacterial cure Clarithro (%)	Bacterial cure Control (%)	Adverse events Clarithro (%)	Adverse events Control (%)
Still, 1993	NR*	NR	0.96	0.94	0.95	0.85	0.20	0.06
Bedregal, 1995	0.86	0.90	NR	NR	0.86	0.90	NR	NR
Padilla-Raygoza, 1995	NR	NR	0.93	0.87	0.87	0.81	0.02	0.12
Padilla, 1996	NR	NR	0.94	0.86	0.88	0.86	NR	NR
Castaño, 1996	0.94	0.95	NR	NR	0.91	0.92	NR	NR
Kearsley, 1997	NR	NR	0.99	0.99	NR	NR	NR	NR
Venuta, 1998	0.96	0.97	NR	NR	0.81	0.94	NR	NR
McCarty, 2000	NR	NR	0.97	0.94	0.94	0.78	NR	NR
Oliveros-Lozano, 2001	0.95	0.96	NR	NR	NR	NR	NR	NR
Kafetziz, 2004	0.98	0.99	NR	NR	0.73	0.92	0.06	0.05
Syrogiannopoulos, 2004	NR	NR	0.80	0.85	0.48	0.51	0.14	0.15
Padilla-Raygoza, 2005	NR	NR	0.90	0.89	0.95	0.79	NR	NR
Coles, 1993	0.69	0.56	0.83	0.80	NR	NR	0.03	0.06
Gooch, 1993	NR	NR	0.86	0.90	NR	NR	0.20	0.24
Pukander, 1993	0.92	0.90	NR	NR	NR	NR	0.26	0.18
McCarty, 1993	NR	NR	0.75	0.75	NR	NR	0.12	0.32
Aspin, 1994	0.89	0.91	NR	0.00	NR	NR	0.18	0.48
Ramet, 1994	NR	NR	0.99	0.99	NR	NR	0.14	0.15
Arguedas, 1995	NR	NR	0.96	0.98	NR	NR	NR	NR
Ramet, 1996	0.90	0.93	NR	NR	0.92	0.95	NR	NR
Craft, 1996	0.91	0.79	0.95	0.92	0.50	0.33	NR	NR
Kafetziz, 1996	0.87	0.87	0.87	0.87	NR	NR	NR	NR
Syriopoulou, 1996	0.84	0.84	0.89	0.87	NR	0.00	NR	NR
Gooch, 1999	0.58	0.56	NR	NR	NR	0.00	0.41	0.46

*Non reported.

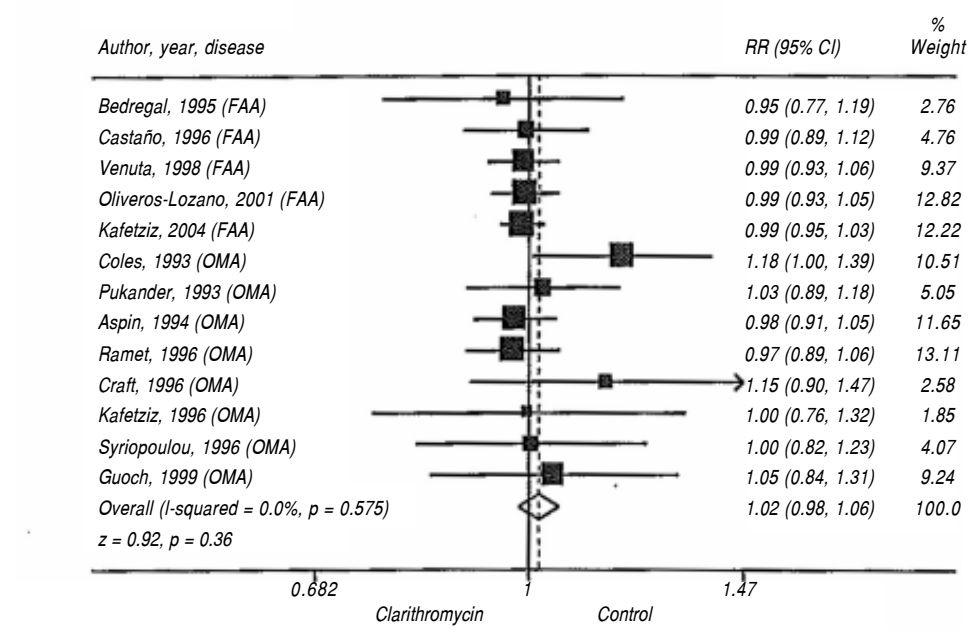
[RR 1.02 (0.98 to 1.06), p NS], clinical success [RR 1.01 (0.99 to 1.03), p NS] and relapse risk [RR 1.34 (0.81 to 2.21), p NS], but was associated with a better bacteriological eradication [RR 1.06 (1.02 to 1.09), p 0.001], and a lower risk for related adverse events [RR 0.77 (0.65 to 0.90), p = 0.001] (Figures 1-5).

DISCUSSION AND CONCLUSIONS

Since 1990, various clinical trials had been showed that clarithromycin is as effective as other antibiotics for the treatment of pediatric patients with URIs.[46-59] In 1993, Coles, *et al*., compared the safety and efficacy of clarithromycin and amoxycillin in the treatment of otitis media in pediatric patients. Two hundred and fifty-nine patients aged 1-12 were prescribed suspensions of clarithromycin (132 patients) or amoxycillin (127 patients). Both suspensions were prescribed at a dose of 125 mg for children weighing less that 25 kg or at 250 mg for children weighing more than 25 kg, but three doses of amoxycillin per day were given, while only two doses clarithromycin per day were required. Each drug was administered for approximately 5 days. Clinical evaluations were performed pre-treatment (Study day 1), at the end of treatment (Study days 6-9), and post-treatment (Study days 28-32). At the end of treatment, 91 out of 114 evaluable patients (80%) had clinical cures with clarithromycin, while 71 out of 105 evaluable patients (68%) had clinical cures with amoxycillin (p = 0.057). Clinical success rates were 96% for both treatments (110/114, clarithromycin; 101/105 amoxycillin). Adverse events related to the study medications occurred in four of 132 patients receiving clarithromycin (3%) and eight out of 127 subjects receiving amoxycillin (6%). Three patients discontinued treatment due to adverse events, all three receiving amoxycillin. At the doses administered, clarithromycin given twice-daily was as safe and effective as given three-times-daily in the treatment of acute otitis media in pediatric patients.[57]

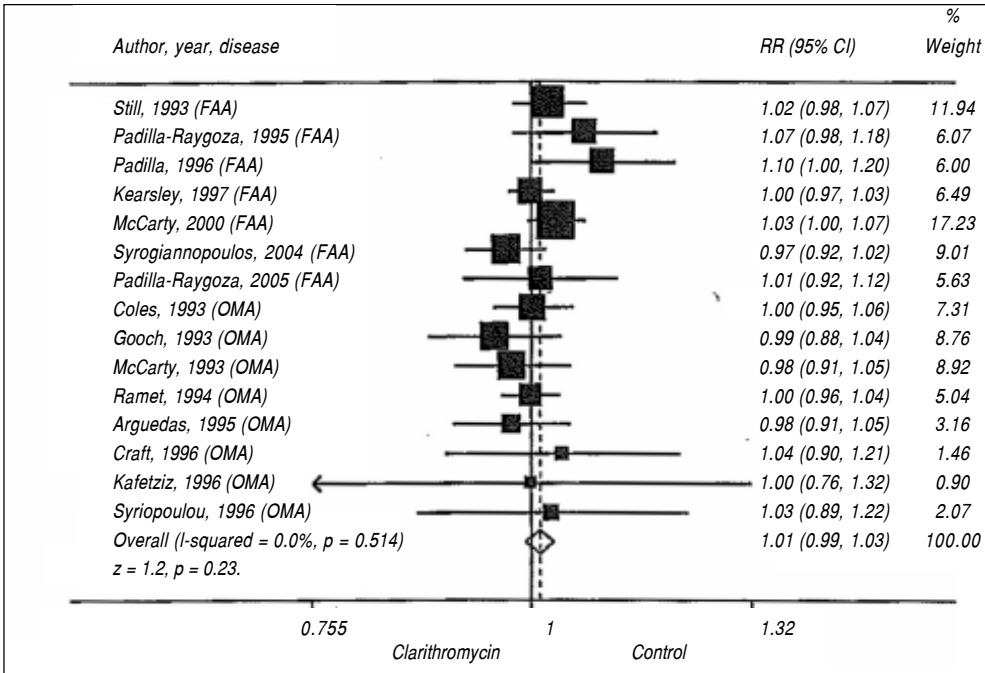
In 1995, Ramet, *et al*., evaluate safety and efficacy of short course treatment with a new oral suspension formulation of clarithromycin in 153 children aged 5 months to 6 years with signs and

symptoms of acute otitis media. Children were randomized to receive a 5-day course of clarithromycin oral suspension (7.5 mg/kg; maximum 500 mg) twice daily or azithromycin oral suspension (10 mg/kg on day 1, followed by 5 mg/kg daily for 4 days) once daily. Specific clinical response criteria were developed based on pretreatment signs and symptoms. Of the 153 patients enrolled, 147 patients (96%) were evaluable (clarithromycin, 72; azithromycin, 75). There were no demographic differences between the two groups. Clarithromycin and azithromycin suspensions were similarly effective for the treatment of acute



FAA: acute pharyngitis. OMA: acute otitis media.

Figure 1. *Efficacy of clarithromycin in pediatric patients with upper respiratory infections (clinical cure).*



FAA: acute pharyngitis. OMA: acute otitis media.

Figure 2. *Efficacy of clarithromycin in pediatric patients with upper respiratory infections (clinical success).*

otitis media. Clinical success (cure, cure with effusion, or improvement) was achieved in 99% of both clarithromycin- and azithromycin-treated patients. Both drugs were well tolerated; adverse events considered probably drug related were reported by 10 (13%) of clarithromycin recipients and 11 (14%) of azithromycin recipients. There were no significant differences between the groups in the numbers of patients reporting events that were thought to be related to study medication. A 5-day regimen of clarithromycin suspension (7.5 mg/kg twice daily) appears to be as safe and effective as a 5-day regimen

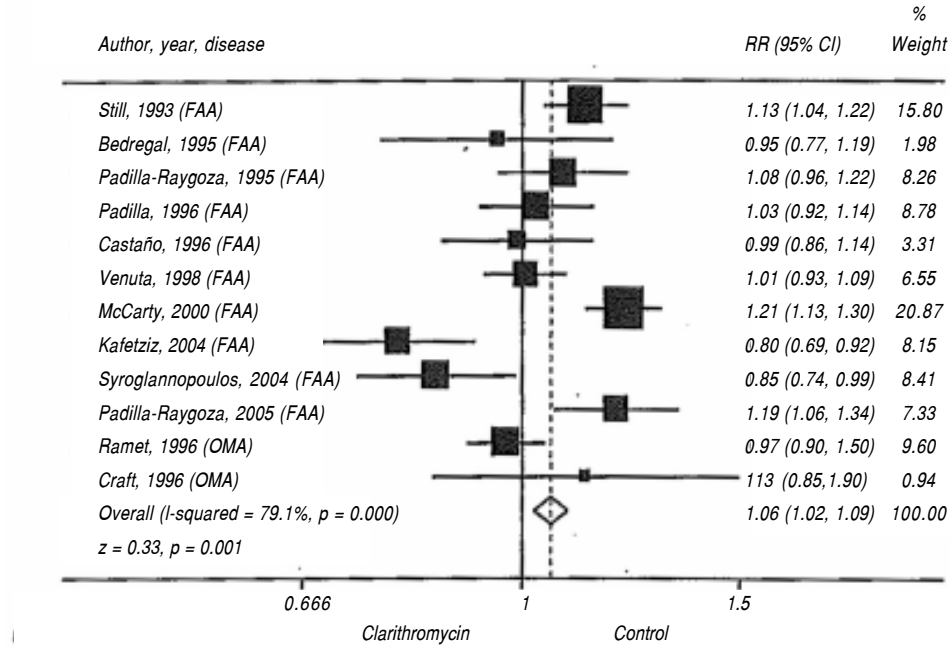


***Figure 3**. Efficacy of clarithromycin in pediatric patients with upper respiratory infections (bacteriological cure).*

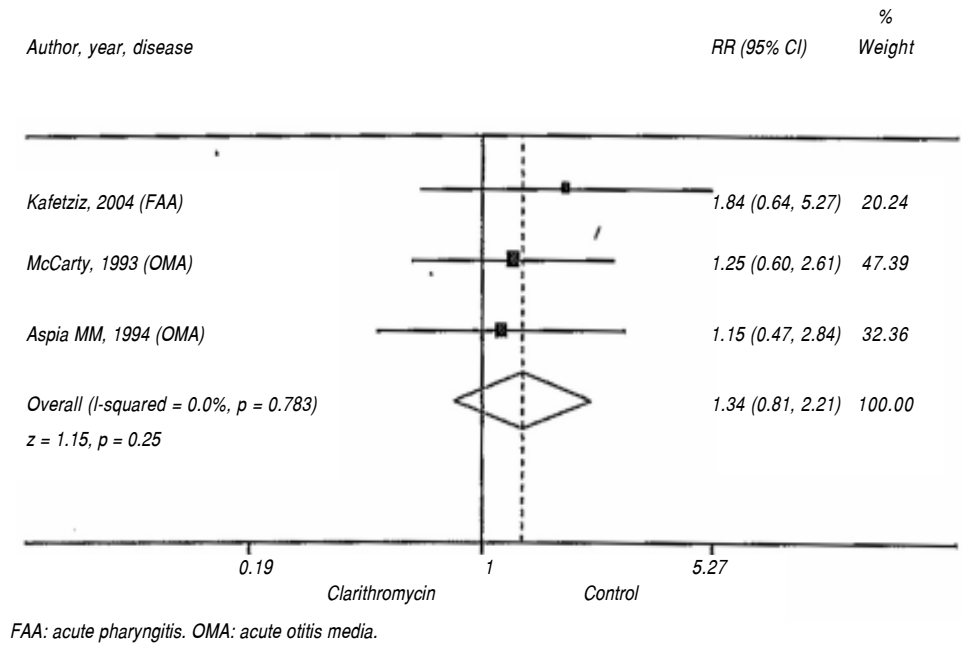
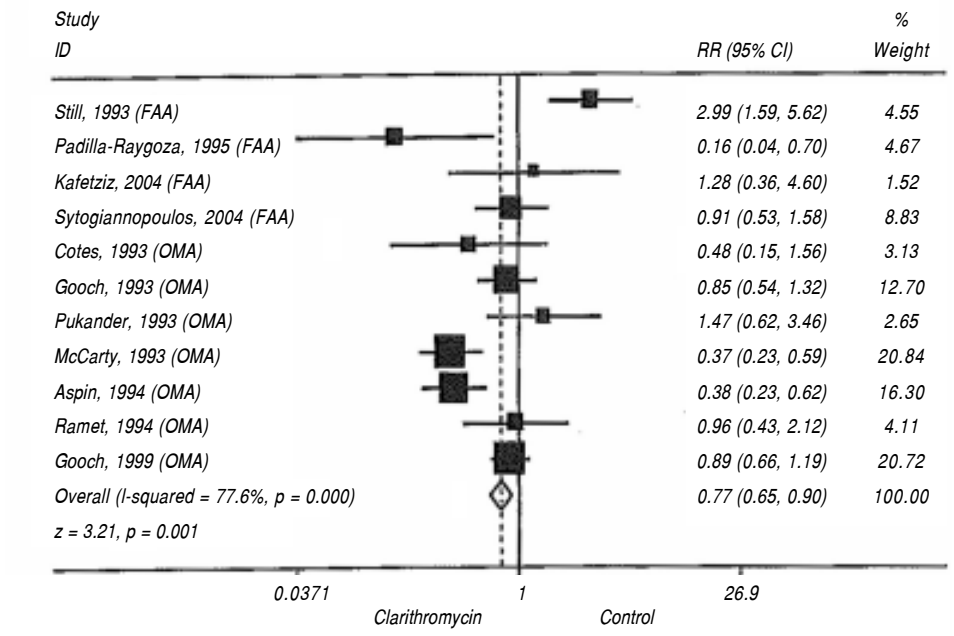


*Figure **4**. Efficacy of clarithromycin in pediatric patients with upper respiratory infections (relapse rate).*



FAA: acute pharyngitis. OMA: acute otitis media.

Figure 5. Safety of clarithromycin in pediatric patients with upper respiratory infections (adverse events risk).

of azithromycin suspension for the treatment of acute otitis media in children.[63]

In 1997, Kearsley, *et al.,* compare in 229 paediatric patients (aged 1-12 years, body weight > 8 kg) with clinical evidence suggestive of streptococcal tonsillitis and/or pharyngitis clarithromycin suspension (7.5 mg/kg twice daily) or amoxycillin syrup (125 mg/kg three times daily body weight < 25 kg, or 250 mg/kg three times daily body weight 25 kg) for 7 days and were followed up 3-8 days post treatment and 21-28 days later. Clinical and microbiological assessments were made at each visit. A total of 189 patients (98 on clarithromycin and 91 on amoxycillin) were clinically evaluable. At the post-treatment visit, clinical success rates were high and comparable: 98% on clarithromycin and 97% on amoxycillin. *Streptococcus* pyogenes was eradicated in 88% of clarithromycin patients and 86% of amoxycillin patients. Both treatments were well tolerated. In conclusion, clarithromycin suspension was as safe and at least as effective as amoxycillin syrup for the treatment of pharyngitis and/or tonsillitis in children, and would be a suitable alternative therapy.[51]

Similar to previous published evidence, results of this systematic review with meta-analysis showed that clarithromycin was therapeutically equivalent to other antibiotics studied with respect to clinical cure, clinical success and relapse risk, but associated with a better bacteriological eradication and a lower risk for related adverse events. This data let consider that clarithromycin is a safe and effective alternative for the treatment of URIs in pediatric patients, being superior to other antibiotics in relation to bacterial eradication. Its equivalence profile related to clinical cure, clinical success and relapse risk, let to consider it as an important alternative for the treatment of children with upper respiratory infections, such as acute pharyngitis or acute otitis media.

REFERENCES

1. Snow V, Mottur-Pilson C, Coope RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *Ann Intern Med* 2001; 134: 506-8.
2. Poses RM, Cebul RD, Collins M, Fager SS. The accuracy of experienced physicians' probability estimates for patients with sore throats: implications for decision making. *JAMA* 1985; 254: 925-9.
3. Komaroff AL, Pass TM, Aronson MD, Erwin CT, Cretin S, Winickoff RN, Branch Jr. WT. The prediction of streptococcal pharyngitis in adults. *J Gen Intern Med* 1986; 1: 1-7.
4. Dowell SF, Schwartz B, Phillips WR. Appropriate use of antibiotics for URIs in children: Part II. Cough, pharyngitis, and the common cold. *Am Fam Physician* 1998; 58: 1335-42, 45.
5. Bisno AL, Gerber MA, Gwaltney Jr. JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002; 35: 113-25.

6. Randolph MF, Gerber MA, DeMeo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr* 1985; 106: 870-5.
7. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis: placebo-controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA* 1985; 253: 1271-4.
8. Catanzero FJ, Stetson CA, Morris AJ. The role of streptococcus in the pathogenesis of rheumatic fever. *Am J Med* 1954; 17: 749-56.
9. Rammelkamp CH. Rheumatic heart disease-a challenge. *Circulation* 1958; 17: 842-51.
10. Committee on Infectious Diseases. Group A streptococcal infection. In: Pickering LK (ed.). Red Book. Elk Grove Village, IL.; 2001, p. 526-36.
11. McCarty J, Hedrick JA, Gooch WM. Clarithromycin suspension versus penicillin V suspension in children with streptococcal pharyngitis. *Adv Ther* 2000; 17: 14-26.
12. O'Doherty B. Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. Paediatric Azithromycin Study Group. *Eur J Clin Micro Infect Dis* 1996; 15: 718-24.
13. Mehr, S, van Moerkerke M, Welck J, Sverrisson G, Sirotiakova J, Marr C, et al. Short course therapy with cefuroxime axetil for group A streptococcal tonsillopharyngitis in children. *Pediatr Infect Dis J* 1998; 17: 452-7.
14. Boccazzi A, Tonelli P, DeAngelis M, Bellussi L, Passali D, Careddu P. Short course therapy with ceftibuten versus azithromycin in pediatric streptococcal pharyngitis. *Pediatr Infect Dis J* 2000; 19: 963-7.
15. Adam D, Hostalek U, Troster K. 5-day therapy of bacterial pharyngitis and tonsillitis with cefixime: comparison with 10-day treatment with penicillin V. Cefixime Study Group [in German]. *Klin Padiatr* 1996; 208: 310-13.
16. Pichichero ME, Gooch WM, Rodriguez W, Blumer JL, Aronoff SC, Jacobs RF, et al. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis: ten days of penicillin V vs. 5 days or 10 days of cefpodoxime therapy in children. *Arch Pediatr Adolesc Med* 1994; 148: 1053-60.
17. Tack KJ, Henry DC, Gooch WM, Brink DN, Keyserling CH. Five-day cefdinir treatment for streptococcal pharyngitis. Cefdinir Pharyngitis Study Group. *Antimicrob Agents Chemother* 1998; 42: 1073-5.
18. Lorenz J. Comparison of 5-day and 10-day cefixime in the treatment of acute exacerbation of chronic bronchitis. *Chemotherapy* 1998; 44(Suppl. 1): 15-18.
19. Reyes H, Guiscafre H, Munoz O, Perez-Cuevas R, Martinez H, Gutierrez G. Antibiotic noncompliance and waste in upper respiratory tract infections and acute diarrhea. *J Clin Epidemiol* 1997; 50: 1297-1304.
20. Daly KA, Brown JE, Lindgren BR, Meland MH, Le CT, Giebink GS. Epidemiology of otitis media onset by six months of age. *Pediatrics* 1999; 103(6, pt. 1): 1158-66.
21. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. *JAMA* 2002; 287(23): 3096-102.
22. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 1989; 160(1): 83-94.
23. Soni A. Ear infections (otitis media) in children (0-17): use and expenditures, 2006. Statistical Brief No. 228. Agency for Healthcare Research and Quality Web site. December 2008. Available from: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st228/stat228.pdf [Accessed September 20, 2010].
24. Simel DL, Rothman R, Keitz S. Update: otitis media, child. In: Simel DL, Rennie D [eds.]. The Rational Clinical Examination: Evidence-Based Clinical Diagnosis. New York, NY: McGraw-Hill; 2009. Available from: http//www jamaevidence.com/content/3484986 [Accessed September 2, 2010].
25. Spurling GK, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev* 2007; (3): CD004417.
26. Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SE, et al. Short course antibiotics for acute otitis media. *Cochrane Database Syst Rev* 2000; (2): CD001095.
27. Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SE, et al. Treatment of acute otitis media with a shortened course of antibiotics: a meta-analysis. *JAMA* 1998; 279(21): 1736-42.
28. Rosenfeld RM, Vertrees JE, Carr J, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty-three randomized trials. *J Pediatr* 1994; 124(3): 355-67.
29. Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2004; (1): CD000219.
30. Takata GS, Chan LS, Shekelle PG, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media, I: the role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics* 2001; 108(2): 239-47.
31. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics* 2004; 113(5): 1451-65.
32. Coco A, Vernacchio L, Horst M, Anderson A. Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. *Pediatrics* 2010; 125(2): 214-20.
33. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2010; 29(4): 304-09.
34. Rosenfeld RM, Kay D. Natural history of untreated otitis media. *Laryngoscope* 2003; 113(10): 1645-57.
35. Roblin PM, Montalban G, Hammerschlag MR. Susceptibilities to clarithromycin and erythromycin of isolates of Chlamydia pneumoniae from children with pneumonia. *Antimicrob Agents Chemother* 1994; 38: 1588-9.
36. Welsh L, Gaydos C, Quinn TC. In vitro activities of azithromycin, clarithromycin, erythromycin, and tetracycline against 13 strains of Chlamydia pneumoniae. *Antimicrob Agents Chemother* 1996; 40: 212-4.
37. Hardy RD, Rios AM, Chavez-Bueno S, Jafri HS, Hatfield J, Rogers BB, et al. Antimicrobial and immunologic activities of clarithromycin in a murine model of Mycoplasma pneumoniae-induced pneumonia. *Antimicrob Agents Chemother* 2003; 47: 1614-20.
38. Klein JO. Clarithromycin: where do we go from here? *Pediatr Infect Dis J* 1993; 12(12 Suppl. 3): S148-S151.
39. Hardy DJ, Swanson RN, Rode RA, Marsh K, Shipkowitz NL, Clement JJ. Enhancement of the in vitro and in vivo activities of clarithromycin against Haemophilus influenzae by 14-hydroxy-clarithromycin, its major metabolite in humans. *Antimicrob Agents Chemother* 1990; 34: 1407-13.
40. Neu HC. The development of macrolides: clarithromycin in perspective. *J Antimicrob Chemother* 1991; 27(Suppl. A): 1-9.
41. Chien SM, Pichotta P, Siepman N, Chan CK. Treatment of community-acquired pneumonia. A multicenter, double blind, randomized study comparing clarithromycin with erythromycin. Canada-Sweden Clarithromycin-Pneumonia Study Group. *Chest* 1993; 103: 697-701.
42. Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC. Mycoplasma pneumoniae and Chlamydia pneumoniae in pe-

diatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. Erythromycin ethylsuccinate. *Pediatr Infect Dis J* 1995; 14: 471-7.
43. Still JG, Hubbard WC, Poole JM, Sheaffer CI, Chartrand S, Jacobs R. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. *Pediatr Infect Dis J* 1993; 12(12 Suppl. 3): S134-S141.
44. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; 309: 1286.
45. Lefebvre C, McDonald S. Development of a sensitive search strategy for reports of randomized controlled trials in EMBASE. Fourth International Cochrane Colloquium; 1996; Adelaide (Australia).
46. Still JG, Hubbard WC, Poole JM, Sheaffer CI, Chartrand S, Jacobs R. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. *Pediatric Infect Dis J* 1993; 12(12 Suppl. 3): S134-S141.
47. Bedregal GP, Riedel KI, Casterán VJC, Berríos CX. Claritromicina versus penicilina en el tratamiento de las faringoamigdalitis por estreptococo beta hemolítico grupo A en niños. *Rev Chil Infectol* 1995; 12(2): 80-6.
48. Padilla-Raygoza N, Figueroa-Ferrari RC, Rivera-Sosa MR. Estudio comparativo del tratamiento de la faringitis streptococcica con claritromicina vs. amoxicilina-clavulanato. *Rev Mex Pediatric* 1995; 62: 13-5.
49. Padilla N, Figueroa R, Rivera R. Clarithromycin and amoxicillin clavulanate in the management of pharyngotonsyllitis. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
50. Castano E, Ortega C, Vallarino D, et al. Comparison of four antibiotics for the treatment of children with streptococcal pharyngitis. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
51. Kearsley NL, Campbell A, Sanderson AA, Weir RD, Kamdar MK, Coles SJ. Comparison of clarithromycin suspension and amoxycillin syrup for the treatment of children with pharyngitis and/or tonsillitis. *Br J Clin Pract* 1997; 51(3): 133-7.
52. Venuta A, Laudizi L, Beverelli A, Bettelli F, Milioli S, Garetti E. Azithromycin compared with clarithromycin for the treatment of streptococcal pharyngitis in children. *J Int Med Res* 1998; 26(3): 152-8.
53. McCarty J, Hedrick JA, Gooch WM. Clarithromycin suspension vs. penicillin V suspension in children with streptococcal pharyngitis. *Adv Ther* 2000; 17(1): 14-26.
54. Oliveros-Lozano F, Baltasar-López E. Eficacia clínica de la claritromicina comparada con la amoxicilina en infecciones respiratorias superiores en pacientes pediátricos. *Rev Mex Puericultura y Pediatr* 2001; 8: 150-9.
55. Syrogiannopoulos GA, Bozdogan B, Grivea IN, Ednie LM, et al.; The Hellenic Antibiotic-Resistant Respiratory Pathogens Study Group. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group a streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 2004; 23: 857-65.
56. Padilla-Raygoza N, Moreno-Pacheco M. Comparación entre claritromicina, azitroicina y penicilina en el manejo de la faringitis estreptocócica en niños. *Arch Inv Ped Mex* 2005; 8: 5-11.
57. Coles SJ, Addlestone MB, Kamdar MK, Macklin JL. A comparative study of clarithromycin and amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. *Infection* 1993; 21(4): 272-8.
58. Gooch WM 3rd, Gan VN, Corder WT, Khurana CM, Andrews WP Jr. Clarithromycin and cefaclor suspensions in the treatment of acute otitis media in children. *Pediatr Infect Dis J* 1993; 12(12 Suppl. 3): S128-S133.
59. Pukander JS, Jero JP, Kaprio EA, Sorri MJ. Clarithromycin vs. amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. *Pediatr Infect Dis J* 1993; 12(12 Suppl. 3): S118-S121.
60. McCarty JM, Phillips A, Wiisanen R. Comparative safety and efficacy of clarithromycin and amoxicillin/clavulanate in the treatment of acute otitis media in children. *Pediatr Infect Dis J* 1993; 12(12 Suppl. 3): S122-S127.
61. Aspin MM, Hoberman A, McCarty J, McLinn SE, Aronoff S, Lang DJ, Arrieta A. Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media in children. *J Pediatr* 1994; 125: 136-41.
62. Still JG, Hubbard WC, Poole JM, Sheaffer CI, Chartrand S, Jacobs R. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. *Pediatric Infect Dis J* 1993; 12(12 Suppl. 3): S134-S141.
63. Ramet J. Belgian Pediatrician Clarithromycin Working Group. Comparative safety and efficacy of Clarithromycin and Azithromycin suspensions in the short course treatment of children with acute otitis media. *Clan Drug Invest* 1994; 9(2): 61-6.
64. Arguedas AG, Louisa C, Rodriguez F, et al. Azithromycin vs. Clarithromycin in children with bacteriologically documented acute otitis media with effusion. Presented at the 19th congress on chemotherapy 1995, July 16-22, Montreal.
65. Ramet J. Belgian Pediatrician Clarithromycin Working Group. A comparative saftey and efficacy study of clarithromycin vs. Amoxicillin/clavulanate suspension in the short course treatment of children with acute otitis media. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
66. Craft JC, Siemen N, Palmer RN, et al. Treatment of acute otitis media in children comparing clarithromycin vs. amoxicillin/clavulanate. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
67. Kafetziz DA, Bairamis T, Apostolopulus N. Five days treatment of children with acute otitis media with clarithromycin. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
68. Syriopoulu V, Pavlopoulu J, Theodoridou M, et al. Clarithromycin vs. cefaclor suspension in the treatment of acute otitis media in children. Poster presented at the third International Conference on Macrolides 1996; Jan Lisbon.
69. Gooch WM 3rd, Adelglass J, Kelsey DK, Masica D, Johns D Jr, Weinberg BC. Loracarbef versus clarithromycin in children with acute otitis media with effusion. *Clin Ther* 1999; 21(4): 711-22.

Correspondence and reprint request:

Dr. José Luis Mayorga-Buitrón
Departamento de Otorrinolaringología
Instituto Nacional de Pediatría
Insurgentes sur, Núm. 3700-C
Col. Cuicuilco
04530, México, D.F.
Correo electrónico:
jose luis.mayorga@oidosnarizygarganta.com.mx

Recibido el 12 de mayo 2011.
Aceptado el 22 de septiembre 2011.