

Drug Class Review on Macrolides

Update #1: Preliminary Scan Report

May 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the reader with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with reader consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and recent systematic reviews conducted by the Agency for Healthcare Research and Quality (AHRQ) and the Canadian Agency for Drugs and Technologies in Health (CADTH), and information on black box warnings issued by the FDA and serious alerts issued by Health Canada. Other important studies could exist.

Date of original report:

August 2006 (searches through 1st Quarter 2006)

Date of Last Preliminary Update Scan:

January 2009

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different macrolide antibiotics used for treatment of specific infectious diseases. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of the Washington state Medicaid agency, with input from the public. These representatives are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. Representatives of the Washington state Medicaid agency approved the following key questions to guide this review:

1. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and Mycobacterium Avium Complex, do macrolide antibiotics differ in efficacy?
2. For adults and children with community-acquired pneumonia, acute bacterial sinusitis, acute exacerbations of chronic bronchitis, otitis media, pharyngitis, and Mycobacterium Avium Complex, do macrolide antibiotics differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy for which one macrolide is more efficacious or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Community-acquired pneumonia
- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Otitis Media
- Pharyngitis
- Mycobacterium Avium Complex

Interventions

Generic Name	Trade Name	Forms
Azithromycin	Zithromax, ZMAX	Oral tablets and suspension
Erythromycin	Ery-tab	Oral tablets and suspension
Clarithromycin	Biaxin, Biaxin XL	Oral tablets and suspension

Efficacy Outcomes

Population	Outcomes
Community-acquired pneumonia Acute bacterial sinusitis Acute exacerbations of chronic bronchitis Otitis Media Pharyngitis Mycobacterium Avium Complex	<ol style="list-style-type: none"> 1. Clinical cure rate (to be further specified) 2. Bacteriological cure rate 3. Percent switch to different antibiotic 4. Hospitalization rates 5. Mortality

Harms

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (nausea, vomiting, diarrhea, prolongation of QT interval, torsades de pointes, ventricular arrhythmias)

Study Designs

1. For efficacy, controlled clinical trials and good-quality systematic reviews
2. For safety, controlled clinical trials, good-quality systematic reviews and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (October 2008 to April Week 4, 2010). We used terms for included drugs and limits for humans, English and controlled clinical trials. All citations were imported into an electronic database (Endnote X1). We also searched for

relevant systematic reviews produced by AHRQ and CADTH since the original report was prepared. We searched FDA and Health Canada websites for identification of new drugs, indications, and black box warnings.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

No new oral macrolides were approved since the original report was published.

New Indications

None noted

New Black Box warnings

None

New studies

Searches resulted in 144 citations. Of those, there are only 2 new potentially relevant trials (Table 1). Appendix A lists the abstracts for these publications. Taken together with the new publications identified in the previous preliminary update scan (Appendix B), now there are a total of 15 new trials that would likely be added in a full update of this review.

Table 1. New Trials

Study	Population	Comparison
Jorgensen, 2009	Adults and adolescents with streptococcal pharyngitis/tonsillitis	Azithromycin IR vs ER
Morris	Aboriginal children with acute otitis media	Azithromycin vs Amoxicillin

Systematic reviews

Searches for systematic reviews produced by AHRQ and CADTH found no systematic review comparing one macrolide to the other for the treatment of community acquired pneumonia, acute bacterial sinusitis, bronchitis, otitis media, pharyngitis and mycobacterium avium complex that was published since the original report was prepared.

Appendix A

Pharyngitis/tonsillitis

Head to head trial

Jorgensen, D. M. (2009). "Single-dose extended-release oral azithromycin vs. 3-day azithromycin for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents: a double-blind, double-dummy study." Clinical Microbiology & Infection **15**(12): 1103-10.

The azithromycin immediate-release formulation (AZ-IR) provides effective treatment for group A beta-haemolytic streptococcal pharyngitis in adults. Single-dose therapy with a novel azithromycin extended-release (AZ-ER) formulation could reduce treatment failure and eliminate non-compliance contributing to antimicrobial resistance. A randomized, double-blind, double-dummy, multicentre trial was conducted comparing AZ-ER (single oral 2-g dose) with AZ-IR (3 days, 500 mg once daily) for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents (n = 598). The primary endpoint was bacteriological eradication at test -of-cure (TOC; day 24-28) in the bacteriological per-protocol population (n = 420). Bacteriological eradication was achieved in 85.4% (175/205) and 81.4% (175/215) of subjects in the AZ-ER and AZ-IR groups, respectively (95% CI -3.1-11.1). Clinical cure at TOC occurred in 99.0% of subjects in the AZ-ER group and in 96.7% in the AZ-IR group. At long-term follow-up, bacteriological recurrence was observed in 5.5% (9/163) and 7.7% (12/156), respectively. Both treatments were well tolerated; and most adverse events (AEs) were mild to moderate in intensity. The most frequent treatment-related AE was diarrhoea, or loose stools, in 11% of both treatment groups. AZ-ER-treated and AZ-IR-treated subjects had AE burdens (AE days/patient-year) of 7.6 days and 9.2 days, respectively. A similar trend in favour of AZ-ER was noted for treatment-related diarrhoea burden (1.9 days vs. 2.5 days). A single 2-g dose of AZ-ER is as effective and well tolerated as 3 days of AZ-IR (500 mg once daily) for treating group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents.

Otitis Media

Active control trial

Morris, P. S., G. Gadil, et al. "Single-dose azithromycin versus seven days of amoxicillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial." Medical Journal of Australia **192**(1): 24-9.

OBJECTIVE: To compare the clinical effectiveness of single-dose azithromycin treatment with 7 days of amoxicillin treatment among Aboriginal children with acute otitis media (AOM) in rural and remote communities in the Northern Territory. **DESIGN, SETTING AND PARTICIPANTS:** Aboriginal children aged 6 months to 6 years living in 16 rural and remote communities were screened for AOM. Those diagnosed with AOM were randomly allocated to receive either azithromycin (30 mg/kg as a single dose) or amoxicillin (50mg/kg/day in two divided doses for a minimum of 7 days). We used a double-dummy method to ensure blinding. Our study was conducted from 24 March

2003 to 20 July 2005. MAIN OUTCOME MEASURES: Failure to cure AOM by the end of therapy; nasal carriage of *Streptococcus pneumoniae* and non-capsular *Haemophilus influenzae* (NCHi). RESULTS: We followed 306 of 320 children (96%) allocated to the treatment groups. Single-dose azithromycin did not reduce (or increase) the risk of clinical failure (50% failure rate [82/165]) compared with amoxicillin (54% failure rate [83/155]) (risk difference [RD], - 4% [95% CI, - 15% to 7%]; $P = 0.504$). Compared with amoxicillin, azithromycin significantly reduced the proportion of children with nasal carriage of *S. pneumoniae* (27% v 63%; RD, - 36% [95% CI, - 47% to - 26%]; $P < 0.001$) and NCHi (55% v 85%; RD, - 30% [95% CI, - 40% to - 21%]; $P < 0.001$). Nasal carriage of *S. pneumoniae* with intermediate or full resistance to penicillin was lower (but not significantly so) in the azithromycin group (10% v 16%), but this group had significantly increased carriage of azithromycin-resistant *S. pneumoniae* (10% v 3%; RD, 7% [95% CI, 0.1% to 12%]; $P = 0.001$). Carriage of beta-lactamase-producing NCHi was about 5% in both groups. CONCLUSION: Although azithromycin reduced nasal carriage of *S. pneumoniae* and NCHi, clinical failure was high in both treatment groups. The possibility of weekly azithromycin treatment in children with persistent AOM should be evaluated. TRIAL REGISTRATION: Australian Clinical Trials Registry ACTRN 12609000691246.

Appendix B. Abstracts of trials identified in prior preliminary update scan #1

Community Acquired Pneumonia Head to Head

Drehobl, M.A., et al., Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest*, 2005. 128(4): p. 2230-7.

BACKGROUND: Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide. The inability or failure of many subjects to adhere to standard antibiotic regimens, which may last up to 10 days, results in suboptimal antibiotic treatment. Treatment with a single-dose antibiotic regimen may improve compliance with prescribed therapy. A novel microsphere formulation of azithromycin provides a single-dose regimen while maintaining tolerability. **STUDY OBJECTIVE:** To compare the efficacy and safety of a single 2.0-g dose of azithromycin microspheres to that of an extended-release formulation of clarithromycin (1.0 g/d for 7 days) for the treatment of adults with mild-to-moderate CAP. **DESIGN:** A phase III, multinational, multicenter, randomized, double-blind, double-dummy study, comparing single-dose azithromycin microspheres to extended-release clarithromycin, both administered orally. **METHODS:** Subjects with mild-to-moderate CAP (Fine class I and II) were included. The primary end point was clinical response at the test-of-cure (TOC) visit (days 14 to 21) in the clinical per protocol (CPP) population. The bacteriologic response at the TOC visit was assessed in subjects with a baseline pathogen. **RESULTS:** A total of 501 subjects were randomized, and 499 were treated. Clinical cure rates at the TOC visit in the CPP population were 92.6% (187 of 202 subjects) for azithromycin microspheres and 94.7% (198 of 209 subjects) for extended-release clarithromycin. Overall pathogen eradication rates were 91.8% (123 of 134 subjects) for azithromycin microspheres and 90.5% (153 of 169 subjects) for extended-release clarithromycin. Both agents were well tolerated. The incidence of treatment-related adverse events was 26.3% with azithromycin microspheres and 24.6% with extended-release clarithromycin. Most adverse events were mild to moderate in severity. **CONCLUSION:** A single 2.0-g dose of azithromycin microspheres was as effective and well tolerated as a 7-day course of extended-release clarithromycin in the treatment of adults with mild-to-moderate CAP.

Lee, P.-I., et al., An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. *Journal of Microbiology, Immunology & Infection*, 2008. 41(1): p. 54-61.

BACKGROUND AND PURPOSE: This study aimed to evaluate the efficacy and safety of clarithromycin and erythromycin in the treatment of community-acquired pneumonia in children. **METHODS:** Children with community-acquired pneumonia were randomly assigned to receive 10-day regimens of either clarithromycin 15 mg/kg/day, twice a day, or erythromycin 30-50 mg/kg/day, four times daily. **RESULTS:** A total of 97 children entered this study, including 26 with *Mycoplasma pneumoniae* infection, 15 with *Chlamydia pneumoniae* infection, and 6 with mixed mycoplasma and chlamydia infections. Fifty and 47 children received clarithromycin and erythromycin treatment, respectively. Three children withdrew from the study because the

identified pathogens were resistant to the study drugs. All 47 children with mycoplasma or chlamydia infection were cured clinically. Delayed defervescence, defined as a fever lasting for more than 72 h after treatment, was observed in 4 of 22 clarithromycin-treated children (18%) and in 3 of 15 erythromycin-treated children (20%) [$p>0.05$]. Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 3 of 50 children (6%) receiving clarithromycin and in 11 of 49 children (22%) receiving erythromycin ($p=0.039$). Excluding children with abnormal pretreatment liver function, abnormal liver function after treatment was observed in only one child, treated with erythromycin. Post-treatment eosinophil and platelet counts were significantly elevated after treatment in both groups. **CONCLUSIONS:** Clarithromycin showed efficacy equivalent to erythromycin for the treatment of mycoplasma or chlamydia pneumonia in children. However, the tolerability of clarithromycin was superior to that of erythromycin.

Active-control

Dean, N.C., et al., Comparing gatifloxacin and clarithromycin in pneumonia symptom resolution and process of care. *Antimicrobial Agents & Chemotherapy*, 2006. 50(4): p. 1164-9.

In looking for outcome differences beyond rates of cure, we prospectively compared the symptom resolution, side effects, and processes of care between the use of clarithromycin and gatifloxacin for the treatment of radiographically confirmed community-acquired pneumonia. We conducted a multicenter, randomized, open-label study comparing gatifloxacin monotherapy to clarithromycin alone or combined with ceftriaxone for patients with multiple risk factors. We measured the return to usual activities and symptoms over seven interviews ending 42 days after randomization. Admission and hospital discharge decision support were provided to treating physicians. We enrolled 266 patients over the age of 18 years between September 2000 and June 2003. The groups were similar in age and gender, with a mean age of 53.5 \pm 19.4 years, and were 54% female. Patient severity as determined by the number of risk factors and the Pneumonia Severity Index was similar between groups; 95% of the patients were low risk. A total of 91% of patients completed at least five of seven symptom interviews. In the clarithromycin study arm, 64% received concomitant therapy with ceftriaxone. We found no significant difference in return to usual activities, pneumonia-specific symptom scores, and 12-item short-form health survey scores. Individual symptom scores were similar except for bad taste and injection site soreness, which were higher in clarithromycin patients. The rates of hospital admission and length of stay were similar. The cost of antibiotic was higher in the clarithromycin group: \$257 versus \$110 for gatifloxacin. We found that gatifloxacin monotherapy is similar to clarithromycin given with or without ceftriaxone for the treatment of community-acquired pneumonia, except that antibiotic cost, bad taste, and injection site soreness favor the use of gatifloxacin.

D'Ignazio, J., et al., Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired Pneumonia in adults. *Antimicrobial Agents & Chemotherapy*, 2005. 49(10): p. 4035-41.

This randomized, double-blind, noninferiority study was designed to demonstrate that a single 2.0-g oral dose of a novel microsphere formulation of azithromycin was at least as effective as 7 days of levofloxacin, 500 mg/day, in the treatment of adult patients with mild to moderate community-acquired pneumonia (Fine classes I, II, and III). In total, 427 subjects were randomly assigned to receive either a single 2.0-g dose of azithromycin microspheres ($n = 213$) or a 7-day

regimen of levofloxacin (n = 214). At baseline, 219 of 423 (51.8%) treated subjects had at least one pathogen identified by culture, PCR, or serology. The primary end point was the clinical response (cure or failure) in the "clinical per protocol" population at test of cure (days 13 to 24). Clinical cure rates were 89.7% (156 of 174) for azithromycin microspheres and 93.7% (177 of 189) for levofloxacin (treatment difference, -4.0%; 95% confidence interval, -9.7%, 1.7%). Bacteriologic success at test of cure in the "bacteriologic per protocol" population was 90.7% (97 of 107) for azithromycin microspheres and 92.3% (120 of 130) for levofloxacin (treatment difference, -1.7%; 95% confidence interval, -8.8%, 5.5%). Both treatment regimens were well tolerated; the incidence of treatment-related adverse events was 19.9% and 12.3% for azithromycin and levofloxacin, respectively. A single 2.0-g dose of azithromycin microspheres was at least as effective as a 7-day course of levofloxacin in the treatment of mild to moderate community-acquired pneumonia in adult outpatients.

Paris, R., et al., Efficacy and safety of azithromycin 1 g once daily for 3 days in the treatment of community-acquired pneumonia: an open-label randomised comparison with amoxicillin-clavulanate 875/125 mg twice daily for 7 days. *Journal of Chemotherapy*, 2008. 20(1): p. 77-86. This randomised, open-label, non-inferiority study was designed to demonstrate that a 3-day course of oral azithromycin 1 g once daily was at least as effective as a standard 7-day course of oral amoxicillin-clavulanate 875/125 mg twice daily in the treatment of outpatients with community-acquired pneumonia (Fine class I and II). In total, 267 patients with clinically and radiologically confirmed community-acquired pneumonia were randomly assigned to receive either the azithromycin (n=136) or the amoxicillin-clavulanate (n=131) regimen. At screening, 60/136 (58.8%) and 61/131 (62.9%) respectively had at least one pathogen identified by sputum culture, PCR, or serology. The primary endpoint was the clinical response in the intent-to-treat population at the end of therapy (day 8 to 12). Clinical success rates were 126/136 (92.6%) for azithromycin and 122/131 (93.1%) for amoxicillin-clavulanate (treatment difference: - 0.48%; 95% confidence interval: - 5.66%; 4.69%). Clinical and radiological success rates at follow-up (day 22-26) were consistent with the end of therapy results, no patient reporting clinical relapse. Bacteriological success rates at the end of therapy were 32/35 (91.4%) for azithromycin and 30/33 (90.9%) for amoxicillin-clavulanate (treatment difference: 0.52%; 95% confidence interval - 10.81%; 11.85%). Both treatment regimens were well tolerated: the overall incidence of adverse events was 34/136 (25.0%) for azithromycin and 22/132 (16.7%) for amoxicillin-clavulanate. In both treatment groups, the most commonly reported events were gastrointestinal symptoms. Azithromycin 1g once daily for 3 days is at least as effective as amoxicillin-clavulanate 875/125 mg twice daily for 7 days in the treatment of adult patients with community-acquired pneumonia.

Otitis Media

Active control

Biner, B., et al., The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media. *Turkish Journal of Pediatrics*, 2007. 49(4): p. 390-6.

The aim of the study was to evaluate the efficacy of short-course antimicrobial therapies [single intramuscular dose of ceftriaxone (50 mg/kg, not exceeding 1 g), 5 days of azithromycin (10 mg/kg on day 1, then 5 mg/kg daily on days 2-5) and the traditional 10-day course of amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 doses)] in children with acute otitis media

(AOM). The study was conducted as a prospective, comparative, open randomized trial between February 2001 and April 2003, and 104 children were enrolled, with a mean age of 3.8 (2.3) years. The clinical and otoscopic assessments of the children were made on days 0, 3, 11 and 30 after admission, and tympanometry was performed on day 30. The patients were diagnosed and followed with a scoring system. Clinical success was achieved in 29/34 patients (85.3%) in the ceftriaxone group, 27/31 patients (87.1%) in the azithromycin group and 34/39 children (87.2%) in the amoxicillin/clavulanate group. The rate of persistence of middle-ear fluid did not differ between the three groups ($p>0.05$). During the one-month period, no recurrent case was observed. The most common drug-related adverse effects were associated with the gastrointestinal system. In conclusion, for the treatment of children with AOM, the clinical success of single-dose intramuscular ceftriaxone and of five-day azithromycin treatments was comparable to that of the traditional 10-day therapy with high-dose amoxicillin/clavulanate.

Block, S.L., et al., A comparison of 5 days of therapy with cefdinir or azithromycin in children with acute otitis media: a multicenter, prospective, single-blind study. *Clinical Therapeutics*, 2005. 27(6): p. 786-94.

BACKGROUND: Short-course therapy for acute otitis media (AOM) improves adherence and may reduce secondary bacterial resistance. **METHODS:** In this multicenter, prospective, investigator-blinded study, patients between the ages of 6 months and 6 years with a clinical diagnosis of AOM were randomized to receive cefdinir oral suspension 7 mg/kg q12h for 5 days or azithromycin oral suspension 10 mg/kg once daily on day 1 and 5 mg/kg once daily on days 2 through 5. Clinical response was assessed at the end-of-therapy (EOT) visit (days 7-9) and the follow-up visit (days 20-25). **RESULTS:** Three hundred fifty-seven patients were enrolled in the study. The treatment groups were similar at baseline with respect to demographic characteristics (mean [SD] age, 3.0 [1.7] years; 55% male), incidence of bilateral AOM (45%), and presenting signs and symptoms. The majority of evaluable children (77%) had previously received conjugated heptavalent pneumococcal vaccine (PCV7) against *Streptococcus pneumoniae*. At the EOT visit, clinical cure rates were comparable for cefdinir and azithromycin (87% [151/174] and 85% [149/176], respectively; 95% CI, -5.5 to 9.8). In addition, clinical cure rates at the EOT visit in the children who had been vaccinated with PCV7 were comparable between cefdinir and azithromycin (86% vs 83%; 95% CI, -6.5 to 11.8). No significant difference in clinical cure rates was observed at the follow-up visit (76% and 86%; 95% CI, -18.9 to 0.0). Parental satisfaction was similar between treatment groups with regard to ease of use, taste, compliance, health care resource utilization, and missed days of work and day-care. Both antibiotics were well tolerated; diarrhea and abnormal stools were the most common antibiotic-related adverse events (< or = 7% each). **CONCLUSIONS:** Short courses (5 days) of therapy with cefdinir or azithromycin were comparable in these children with AOM based on clinical end points, parental preferences, and health care utilization.

Güven, M., et al., Bacterial etiology of acute otitis media and clinical efficacy of amoxicillin-clavulanate versus azithromycin. *International Journal of Pediatric Otorhinolaryngology*, 2006. 70(5): p. 915-23.

BACKGROUNDS: Acute otitis media (AOM) is one of the most common acute bacterial infection in childhood and also the most frequent reason for outpatient antibiotic therapy. Little recent information about susceptibility patterns of AOM bacterial pathogens in Turkish children has been reported. **OBJECTIVE:** To determine the bacterial etiology of acute otitis media in children and to compare the efficiency of 3 days course of azithromycin with a 10 days course of

amoxicillin-clavulanate. **METHODS:** This prospective, single blind, randomised comparative study was carried out in 180 children with AOM. Paracentesis was performed for middle ear fluid culture before the first dose antibiotic therapy. Children with acute otitis media were randomised to receive either low dose amoxicillin-clavulanate (45/6.4 mg/kg/day in two divided doses for 10 days) or low dose azithromycin (10mg/kg/day for 3 days). Clinical response was assessed on days 2-4, 11-13, 26-28. **RESULTS:** Bacterial pathogens were isolated from 108 (60%) of 180 children. *Streptococcus pneumoniae* was the most common isolated pathogen (39.7%), followed by *Haemophilus influenzae* (20.7%), *Moraxella catarrhalis* (15.5%), *Staphylococcus aureus* (13.8%), Group A beta-hemolytic streptococcus (5.1%), *Escherichia coli* (3.4%) and *Enterococcus faecalis* (1.7%). This study demonstrated low resistance rates compared to studies of different countries. Although clinical response rates were better in patients treated with amoxicillin-clavulanate, this was not statistically significant [86.6% (78 of 90)] versus [95.2% (80 of 84)]. Success rates of amoxicillin-clavulanate were high for both *S. pneumoniae* and *H. influenzae*. Difference between success rates was not statistically significant ($P=0.144$ and 0.352). **CONCLUSIONS:** Bacteria were isolated in 60% of AOM cases. The clinical efficiency of amoxicillin-clavulanate was found to be equal compared to azithromycin in children with acute otitis media.

Bronchitis

Active Control

Fogarty, C., et al., Five-day telithromycin once daily is as effective as 10-day clarithromycin twice daily for the treatment of acute exacerbations of chronic bronchitis and is associated with reduced health-care resource utilization. *Chest*, 2005. 128(4): p. 1980-8.

STUDY OBJECTIVES: To demonstrate equivalence in the clinical efficacy of telithromycin vs clarithromycin treatment of outpatients with acute exacerbations of chronic bronchitis (AECB), and to compare the tolerability and respiratory-related health-care resource utilization associated with these treatment regimens. **DESIGN AND PATIENTS:** A randomized, double-blind, multicenter, clinical study was conducted at 105 centers in 14 countries. Adult outpatients (age $>$ or $=$ 30 years) received oral telithromycin, 800 mg qd for 5 days ($n = 270$), or oral clarithromycin, 500 mg bid for 10 days ($n = 282$), for the treatment of AECB. Clinical and bacteriologic outcomes were assessed at the posttherapy/test-of-cure (TOC) visit (days 17 to 24; per-protocol population). Health-care resource utilization data were collected for each patient by investigators blinded to study medication up to the late posttherapy visit (days 31 to 36).

RESULTS: Clinical cure rates at the posttherapy/TOC visit were comparable between the groups (telithromycin, 193 of 225 patients [85.8%]; clarithromycin, 206 of 231 patients [89.2%]); bacteriologic outcome was satisfactory for 59 of 72 telithromycin-treated patients (81.9%) vs 63 of 76 clarithromycin-treated patients (82.9%). Health-care resource utilization assessed up to the late posttherapy visit was lower in the telithromycin treatment group than the clarithromycin treatment group, with significantly fewer hospitalizations for respiratory-related causes (one hospitalization vs eight hospitalizations for a total of 4 inpatient days vs 39 inpatient days, respectively), significantly fewer AECB-related emergency department visits (0 vs 8), and fewer unscheduled outpatient visits (11 vs 18). Fewer telithromycin-treated patients reported days lost from work (21 of 91 patients [23.1%]; 133 days) compared with those receiving clarithromycin (30 of 98 patients [30.6%]; 141 days). Telithromycin was well tolerated; adverse events considered possibly related to study medication were reported by 61 of 269 patients (22.7%) and 100 of 280 patients (35.7%) receiving telithromycin and clarithromycin, respectively.

CONCLUSIONS: In this study, 5-day telithromycin treatment was as effective and well tolerated as 10-day clarithromycin treatment for patients with AECEB, and was associated with a reduced utilization of health-care resources.

Martinez, F.J., et al., Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750 mg. *European Respiratory Journal*, 2005. 25(6): p. 1001-10.

This is the first prospective clinical trial in which patients with acute bacterial exacerbation of chronic bronchitis have been stratified by degree of underlying illness. Uncomplicated patients were randomised to levofloxacin 750 mg once daily (q.d.) for 3 days or azithromycin q.d. for 5 days. Complicated patients were randomised to levofloxacin 750 mg q.d. for 5 days or amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days. Regardless of therapy, complicated patients demonstrated lower clinical and microbiological success than uncomplicated patients. Clinical success for clinically evaluable patients was similar for levofloxacin and azithromycin (93.0 versus 90.1%, respectively), and levofloxacin and amoxicillin/clavulanate (79.2 versus 81.7%, respectively). For microbiologically evaluable patients, clinical response to levofloxacin for 3 days was superior to azithromycin for 5 days (96.3 versus 87.4%, respectively), and levofloxacin for 5 days was similar to amoxicillin/clavulanate for 10 days (81.4 versus 80.9%, respectively). Microbiological eradication was superior for levofloxacin for 3 days compared with azithromycin for 5 days (93.8 versus 82.8%, respectively), and similar for levofloxacin and amoxicillin/clavulanate for 10 days (81.4 versus 79.8%, respectively). In conclusion, levofloxacin 750 mg for 3 days was comparable to azithromycin for 5 days for uncomplicated patients with acute bacterial exacerbation of chronic bronchitis, while 5 days of 750 mg levofloxacin was comparable to 10 days of amoxicillin/clavulanate for complicated acute bacterial exacerbation of chronic bronchitis.

Zervos, M., et al., Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. *International Journal of Antimicrobial Agents*, 2007. 29(1): p. 56-61.

Antibiotic therapy is of clinical benefit in certain patients with acute exacerbations of chronic bronchitis (AECEB). In this randomised, investigator-blinded, multicentre trial, azithromycin (500mg once a day (qd) for 3 days) was compared with moxifloxacin (400mg qd for 5 days) for the treatment of outpatients with AECEB (forced expiratory volume in 1s (FEV₁) >35%). Of 342 patients randomised to either treatment, 169 received azithromycin and 173 received moxifloxacin. The mean age in the azithromycin and moxifloxacin groups was 56.4 years and 55.5 years, respectively. In the intent-to-treat analysis, clinical success rates for azithromycin and moxifloxacin were comparable at Days 10-12 (90% versus 90%, respectively) and Days 22-26 (81% versus 82%, respectively). Among patients who were culture-positive at baseline for *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* or *Haemophilus parainfluenzae*, clinical efficacy for azithromycin versus moxifloxacin at Days 10-12 was 93% versus 84%, respectively, and at Days 22-26 it was 89% versus 73%, respectively. The incidence of at least one treatment-related adverse event (AE) in the azithromycin and moxifloxacin groups was 18.3% and 19.1%, respectively. The most common AEs were diarrhoea, nausea, abdominal pain and vaginitis. Most treatment-related AEs were of mild or moderate severity, with no serious treatment-related AEs. One subject in the moxifloxacin group discontinued treatment

owing to a treatment-related AE (precordial pain and dry throat). Compliance with both regimens was >90%. Three-day azithromycin and 5-day moxifloxacin demonstrate comparable efficacy and safety for the treatment of AECB in outpatients.

Pharyngitis and/or Sinusitis

Active control or other

Block, S.L., Comparative tolerability, safety and efficacy of tablet formulations of twice-daily clarithromycin 250 mg versus once-daily extended-release clarithromycin 500 mg in pediatric and adolescent patients. *Clinical Pediatrics*, 2006. 45(7): p. 641-8.

Clarithromycin is widely used to treat respiratory tract and superficial skin infections in pediatric and adult populations. Using clinical endpoints and 7-day therapy, we compared the efficacy of clarithromycin 250 mg tablets given twice daily versus clarithromycin 500 mg extended-release tablets given once daily in ambulatory children and adolescents 6 to 16 years old. Of the 199 evaluable patients, 124 were infected with group A streptococcal pharyngitis, 39 with sinusitis, 21 with ambulatory pneumonia, and 15 with superficial skin infections. The overall cure rate exceeded 90% for each treatment group. Discontinuation rates and adverse events were 4.5% and 24.6%, respectively.

Murray, J.J., et al., Efficacy and safety of a novel, single-dose azithromycin microsphere formulation versus 10 days of levofloxacin for the treatment of acute bacterial sinusitis in adults.[see comment]. *Otolaryngology - Head & Neck Surgery*, 2005. 133(2): p. 194-200.

OBJECTIVE: To compare the efficacy and safety of a single 2.0-g dose of a novel azithromycin microsphere formulation with that of 10 days of levofloxacin, 500 mg/d, when used to treat adults with uncomplicated acute bacterial maxillary sinusitis (ABS). **STUDY DESIGN AND SETTING:** An international, multicenter, randomized, double-blind, double-dummy trial. Eligible outpatients > or =18 years of age with clinical and radiographic evidence of ABS underwent maxillary sinus aspiration before randomization. Primary endpoint was clinical efficacy at the test-of-cure visit (day 17-24). **RESULTS:** Clinical success rates were 94.5% (242/256) in azithromycin-microspheres-treated patients and 92.8% (233/251) in the levofloxacin group. In patients with documented *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*, clinical cure rates were 97.3% (36/37), 96.3% (26/27), and 100% (8/8), respectively, for the azithromycin group and 92.3% (36/39), 100% (30/30), and 90.9% (10/11), respectively, for the levofloxacin group. **CONCLUSIONS:** Single-dose azithromycin microspheres provided clinical and bacteriologic efficacy and safety comparable to 10 days of levofloxacin. **SIGNIFICANCE:** A novel microsphere formulation of azithromycin given as a single dose was safe and effective for the treatment of ABS.