

ing the conversion of homocysteine to cysteine in the liver or enhancing the urinary excretion of the amino acid.

No potential conflict of interest relevant to this article was reported.

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Treating Acute Asthma with Antibiotics — Not Quite Yet

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Although the root cause of asthma is not known, treatments have been developed that target facets of the underlying pathologic abnormalities of asthma: airway inflammation, hypersecretion of mucus, and airway hyperresponsiveness. These treatments not only have improved the site of drug delivery (e.g., inhaled corticosteroids) but have directly targeted the relevant pathways that contribute to symptoms (e.g., leukotriene modifiers and anti-IgE). Although these treatments have proved to be effective, practitioners are often humbled as the condition progresses despite their best efforts to control it; therapeutic strategies that target unexplored disease associations are needed.

Viral infection is strongly associated with both

wheezing in children and exacerbations of asthma in adults, and there is evidence that acute infection with the atypical pathogens *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* is associated with acute asthma episodes.¹ Despite the recommendations of clinical practice guidelines against the empirical use of antibiotics in acute exacerbations of asthma,² the presence of clinically purulent sputum and cough occasionally leads the clinician to "play it safe" and start treatment, especially in the setting of severe disease or exacerbation.

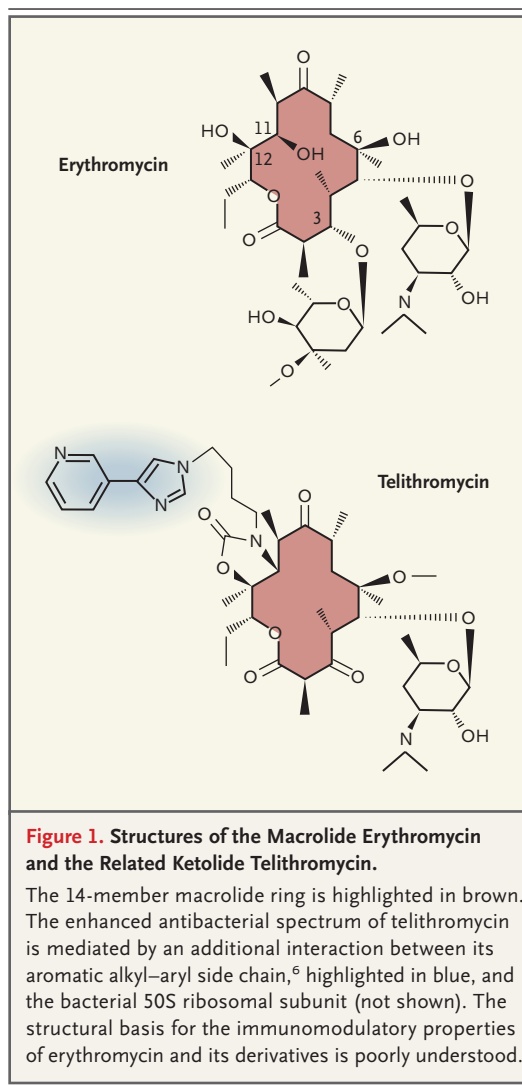
The results of the Telithromycin, Chlamydia, and Asthma (TELICAST) study, reported by Johnston et al. in this issue of the *Journal*,³ address this issue directly. In the study, patients who

presented for unscheduled care because of an acute exacerbation of asthma received either the semisynthetic macrolide derivative telithromycin or placebo. The improvement in asthma symptom scores throughout the 10-day treatment period, one of the predetermined primary efficacy end points, was significantly greater in the telithromycin group than in the placebo group, as was improvement in symptom scores between baseline and the end of treatment. Although there was no difference between groups in morning peak expiratory flow, the other primary outcome measure, there was a significant improvement over placebo in the forced expiratory volume in one second (FEV₁) at the end of the treatment period with telithromycin.

The rate of adverse effects in the telithromycin group was low and similar to that in the placebo group, with the exception of nausea, which was more common in the telithromycin group. The recent report⁴ of rapidly aggressive hepatotoxicity characterized by substantial necrosis associated with immediately antecedent telithromycin therapy is noteworthy for the resultant complications, which led to either death or liver transplantation in two of three cases. Despite extensive preapproval data, in which hepatotoxic effects were no more common with telithromycin than with several other oral antibiotics,⁵ this report should prompt clinicians to assess carefully the role of telithromycin in the management of acute asthma.

Telithromycin has been used in Europe and Japan for more than five years and has been approved since April 2004 in the United States for outpatient treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute bacterial sinusitis in adults. A ketolide whose core structure is closely related to that of the macrolides (Fig. 1), telithromycin is active against multidrug-resistant isolates of *Streptococcus pneumoniae*, including those resistant to erythromycin and penicillin.⁷ This efficacy is probably due to a specific interaction with a region of the bacterial 50S ribosomal subunit, not found in other macrolides, that also mediates enhanced inhibition of protein synthesis.⁶ The activity of the drug against atypical pulmonary pathogens, specifically *M. pneumoniae* and *C. pneumoniae*, is of direct relevance to a central issue addressed by the TELICAST study: the role of atypical infection in acute exacerbations of asthma.

A provocative finding of the TELICAST study



relates to the mechanism of benefit in symptoms and in FEV₁ among patients with asthma who were treated with telithromycin. As part of the study design, the status of each patient with respect to infection with *M. pneumoniae* and *C. pneumoniae* was determined on the basis of the serum antibody titer or bacterial DNA amplified by polymerase chain reaction in samples obtained by nasopharyngeal swab or from sputum. It is striking that nearly two thirds of patients in the study met the criteria for infection, primarily on the basis of their antibody status. This finding allowed for a robust comparison of the effect of telithromycin treatment among patients with and without signs of acute infection with atypical pathogens. The improvement in FEV₁ during the treatment period in the telithromycin group was

the same whether patients met the criteria for infection or not. The study design did not incorporate an analysis of the mechanism by which telithromycin was associated with improvement, but the data clearly show a benefit that was not attributable solely to an antibiotic effect, at least with respect to atypical pathogens. Although patients could have been infected with pathogens that were not assessed in this study, including viruses, and the pattern of infection could have differed from that of the atypical pathogens that were assessed, it seems more likely that a non-antibiotic effect was at play.

There are other issues of concern. For example, even though the increase in the FEV₁ of patients in the telithromycin group was twice that of patients in the placebo group, it is difficult to apply this finding to clinical practice. Spirometry is not routinely performed in uncomplicated exacerbations of asthma, unlike the home measurement of peak expiratory flow, which was similar in both groups. A benefit in certain but not all efficacy end points is not uncommon in clinical studies of the efficacy of asthma drugs,^{8,9} but such inconsistency does limit the conclusiveness of the study findings. I agree with the authors' statement that the results fall short of providing a basis for definitive clinical directives on the use of antibiotics in acute exacerbations of asthma.

Nevertheless, the TELICAST study is informative because of its sample size; its implications are provocative but not directive. The immunomodulatory effects of macrolides and their derivatives have been well described *in vitro*, and applications of these observations *in vivo* have markedly enhanced clinical care in certain airway disorders.¹⁰ It is well accepted that the greatly improved survival of Japanese patients with diffuse panbronchiolitis since the institution of long-term treatment with low-dose erythromycin is not due to an antibacterial effect.¹¹ Clinical studies in other airway disorders, such as cystic fibrosis, have been encouraging but less definitive.¹² Early studies assessing an antiinflammatory effect of macrolides in the treatment of asthma have demonstrated a salutary effect on airway hyperresponsiveness, as well as on certain inflamma-

tory markers in sputum.^{13,14} It is tempting to speculate that the results of the large, prospective, placebo-controlled TELICAST study mirror these findings; it clearly establishes the foundation for additional direct examination of this therapeutic opportunity in asthma. It is time for further study, not for treatment.

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