Treatment of bronchiectasis exacerbations in children: Which antibiotic?

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Bronchiectasis in children that is unrelated to cystic fibrosis is a relatively neglected disease. However, it is an important cause of respiratory morbidity in low-income and middle-income countries (occurring as a sequela of lower respiratory tract infection) as well as in specific populations in high-income countries such as Aboriginal or Maori and Pacific Islander populations.[1] Most adult bronchiectasis has its roots in childhood disease, with up to 80% of adult patients reporting chronic symptoms from childhood.[2]

Intercurrent respiratory exacerbations of bronchiectasis, characterised by increasing cough, sputum volume, or purulence, are associated with reductions in quality of life, parental stress, and economic costs, and severe events can lead to reduced lung function.[3,4] However, there are few data on the best treatment for exacerbations; empirical antibiotic therapy is often used.[5,6] In *The Lancet,* Vikas Goyal and colleagues[7] report a randomised controlled trial comparing amoxicillin–clavulanate with azithromycin for 21 days for treatment of a non-severe exacerbation in 179 New Zealand or Australian children with bronchiectasis unrelated to cystic fibrosis. The results for the primary outcome, exacerbation resolution at 21 days, were similar in both groups, with 84% of children achieving resolution. However, the duration of an exacerbation was shorter in the amoxicillin–clavulanate group than in the azithromycin group (10 *vs* 14 days). There were no significant differences in adverse events, time to next exacerbation, quality-of-life scores, or lung function between groups at the end of treatment. A potential advantage of azithromycin treatment is improved adherence associated with single daily dosing; however, in this study, the differences in adherence between groups were not significant

Goyal and colleagues found an increase in the proportion of children carrying macrolide-resistant nasal bacteria in the azithromycin group (from 22% to 80%) but not in the amoxicillin–clavulanate group; however, the increase in actual number of macrolide-resistant organisms was small (from six to eight isolates in the azithromycin group). The effect of multiple courses of azithromycin treatment for repeated exacerbations on macrolide resistance, and treatment efficacy requires careful study. Macrolide resistance was also present in a quarter of bacteria cultured at baseline, whereas penicillin resistance was uncommon among pneumococci (one of 13 isolates). The results of this study may not be generalisable to settings with different background prevalences of antibiotic resistance among respiratory pathogens.

Optimum antibiotic treatment depends on the underlying aetiology of an exacerbation, but establishing causality can be challenging. Children with bronchiectasis are chronically colonised with bacteria, mainly *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*, and *Staphylococcus aureus.*[8] Although pulmonary exacerbations are often characterised by an increased bacterial density of colonising organisms, viruses have been commonly reported[9] and indeed in this study were found in 48% of episodes. However, detection of viruses from an upper respiratory tract sample and absence of a control population without an exacerbation make it difficult to infer pathogenicity, especially as most viruses (76%) were rhinoviruses, which are common in healthy children.[10] Increasing data suggest that lower respiratory tract infection in children results from the interaction of several organisms, which is likely to be particularly important in chronic infectious conditions such as bronchiectasis. Further work on the role of viruses and their interaction with potential bacterial or other pathogens is needed. Additionally, children were not tested for fungal or mycobacterial pathogens throughout the study, although those with mycobacterial infection were excluded at enrolment. The role of non-tuberculous mycobacteria in cystic fibrosis is increasingly being appreciated and this requires further research in children with bronchiectasis not related to cystic fibrosis.

The duration of treatment, 21 days, was chosen on the basis of the investigators' prior data of symptom resolution. However, European guidelines for adults recommend 2 weeks of treatment, and this is common in clinical practice. In this study, resolution of symptoms occurred in a median of 10 days (IQR 6–15) in children treated with amoxicillin-clavulanate; therefore, 3 weeks

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Published **Online**
September 18, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32004-X

See **Online/Articles**
http://dx.doi.org/10.1016/S0140-6736(18)31723-9

of therapy might not be needed. Further research on the optimum duration of antibiotic therapy is needed to minimise prolonged unnecessary use, which is a key driver of antimicrobial resistance.

Although better defining the optimal treatment for exacerbations is important, prevention of exacerbations should be a priority in children. No data were provided on the immunisation status of children, but the effect of pneumococcal conjugate or *H influenzae b* vaccination on colonisation and on exacerbation frequency, aetiology, and severity is worth studying in other settings where vaccination is not routine. Prophylactic azithromycin therapy or inhaled antibiotic therapy could also be used to reduce the frequency or severity of exacerbations, but further studies are needed in bronchiectasis unrelated to cystic fibrosis.[11] A trial[12] of 2 years of oral weekly azithromycin for children with non-cystic fibrosis bronchiectasis found a substantial reduction in exacerbations but an increase in carriage of azithromycin-resistant bacteria. Until further evidence for other strategies to treat exacerbations is available, this study indicates that amoxicillin–clavulanate should be used empirically for treatment of exacerbations, rather than azithromycin.

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HJZ reports grants from the Bill & Melinda Gates Foundation, National Institutes of Health, MRC South Africa, South African National Research Foundation, and the European & Developing Countries Clinical Trials Partnership. MPN reports grants from Pfizer.

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