

Chronic *Chlamydia pneumoniae* lung infection: a neglected explanation for macrolide effects in wheezing and asthma?

We read with interest the recent article by Jakob Stokholm and colleagues¹ who reported that azithromycin significantly reduced the duration of acute asthma-like episodes in young children, and that earlier treatment (within 3 days of episode onset) was more effective than delayed treatment. These results complement those of Bacharier and colleagues,² who reported that early administration of azithromycin significantly reduced the risk of progression of apparent respiratory tract illness to severe lower respiratory tract illness (that often included wheezing), compared with placebo. Both articles speculated that underlying mechanisms could include anti-inflammatory or antimicrobial effects of azithromycin. However, neither article mentioned a third possibility that deserves exploration: pre-existing chronic *Chlamydia pneumoniae* lung infections.

C pneumoniae is an established cause for acute lower respiratory tract infections in all age groups and is associated with a range of chronic lung diseases including asthma, chronic bronchitis, and COPD.³ The biological plausibility for *C pneumoniae* to dysregulate the lung immune system to produce acute and chronic asthma is supported by a large body of in-vitro and in-vivo laboratory data.⁴ In a study in which lower airways of children ranging in age from 3 months to 18 years were sampled directly, *C pneumoniae* was detected in between half and three-quarters of cases.⁵ Positive detection was equally prevalent in cases of severe, refractory asthma, and in other forms of paediatric chronic lower

respiratory tract illnesses for which bronchoscopies were indicated. This provides evidence that *C pneumoniae* plays a role in protean manifestations of severe chronic lower respiratory tract infections in children.

We therefore advocate strongly for the inclusion of chlamydial diagnostics in future studies of lower respiratory tract infections in children. We recommend that both direct and indirect organism detection methods are used for several reasons. Direct methods (eg, DNA and mRNA detection, immunostaining, and culture) can establish the presence of the pathogen and perhaps its viability, but sensitivity is substantially limited because of deep tissue residence in the lung that precludes adequate sampling in many studies. Indirect methods (seroreactivity) can be valuable in differentiating acute from possible chronic infection, and newer more sensitive and specific serological assays can overcome the limitations of previous methods to provide more insight into host immune responses to *C pneumoniae* that are thought to have a major role in disease pathogenesis.

We also advocate for closer collaboration between asthma researchers and microbiologists specialising in chlamydial pathogenesis. One of the major barriers to inclusion of *C pneumoniae* as a potential cause for asthma and other chronic lung diseases could be the substantial technical difficulties in detecting the bacterium that have led either to its non-detection or to its exclusion from consideration. *C pneumoniae* has been called an atypical respiratory pathogen for a good reason. Additionally, since understandable concern exists about widespread use of antibiotics in young children with lower respiratory tract infection-associated wheezing, *C pneumoniae* could be among the biomarkers used to identify those at greatest risk and who would benefit the most from intervention aimed at halting progression to severe lower respiratory tract infection.

We declare no competing interests.

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- 1 Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016; **4**: 19–26.
- 2 Bacharier LB, Guilbert TW, Mauger DT, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. *JAMA* 2015; **314**: 2034–44.
- 3 Hahn DL, Azenabor AA, Beatty WL, Byrne GI. *Chlamydia pneumoniae* as a respiratory pathogen. *Front Biosci* 2002; **7**: e66–76.
- 4 Horvat JC, Starkey MR, Kim RY, et al. Early-life chlamydial lung infection enhances allergic airways disease through age-dependent differences in immunopathology. *J Allergy Clin Immunol* 2010; **125**: 617–25.
- 5 Webley WC, Salva PS, Andrzejewski C, et al. The bronchial lavage of pediatric patients with asthma contains infectious *Chlamydia*. *Am J Respir Crit Care Med* 2005; **171**: 1083–88.

Authors' reply

We recently reported that azithromycin significantly reduced the duration of acute asthma-like episodes in children aged 1–3 years experiencing recurrent episodes of such symptoms.¹ Apart from the main treatment effect of azithromycin, we also studied potential modifying factors that either improve or worsen the effect of the treatment. These included the episode day on which the treatment was initiated, clinical objective measures (fever, raised C-reactive protein concentrations, and objective wheeze), concurrent treatment with inhaled steroids or montelukast, and infection with common bacterial and viral airway pathogens. We noted an additional improvement of the treatment if azithromycin was initiated early in the acute episode, and also in children infected with *Haemophilus influenzae*. However, this pathogen was only cultured in 32 (24%) of the 148 asthma-like episodes, and other factors such as fever, raised C-reactive protein concentrations, and infection

with other bacteria and viruses did not lead to an improved effect of the azithromycin treatment. Therefore, we could not conclude whether the reported results were attributable to the antibacterial or anti-inflammatory effects of the macrolide.

David Hahn and Wilmore Webley suggest an alternative explanation for the observed results through treatment of the atypical pathogenic bacteria *Chlamydia pneumoniae*. Indeed, azithromycin is effective against this pathogen, but it is very unlikely that treatment of *C pneumoniae* mediates a substantial part of the treatment effects that we recorded. We deliberately chose not to include the atypical bacteria *C pneumoniae* and *Mycoplasma pneumoniae* in our study analyses because of a very low prevalence in the Danish paediatric population. In our analogous COPSAC₂₀₀₀ cohort study,² we reported that atypical bacteria detected by PCR were identified in less than 2% of airway samples from young Danish children with asthma-like episodes, and only in 1% of children with clinical pneumonia. In other countries, both *C pneumoniae* and *M pneumoniae* might have a larger role in chronic asthma and during acute exacerbations in young children.³

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- 1 Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016; **4**: 19–26.
- 2 Bisgaard H, Hermansen MN, Bønnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ* 2010; **341**: c4978.
- 3 Johnston SL, Martin RJ. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*: a role in asthma pathogenesis? *Am J Respir Crit Care Med* 2005; **172**: 1078–89.

Cardiovascular and neuropsychiatric risks of varenicline

On Oct 29, 2015, our Twitter-based journal club (@respandsleepjc, #rsjc) had the pleasure of discussing the study by Daniel Kotz and colleagues.¹ This retrospective cohort study used the National Health Service QResearch database to assess whether varenicline is associated with increased cardiovascular and neuropsychiatric events compared with nicotine replacement therapy. Our discussion generated several questions, mainly centred on possible confounders.

A key distinguishing feature of the study is that it directly compares varenicline to other pharmacotherapy, whereas previous studies suggesting adverse effects of varenicline compared it against placebo.² This distinction leads us to wonder whether emotional and physical stresses of the acute smoking cessation period itself, rather than the pharmacotherapy used, might confer a small short-term risk of cardiovascular and neuropsychiatric events before the much more substantial long-term risk reductions conferred by smoking cessation, thereby representing a risk trade-off analogous to many surgical procedures.³ We therefore found it interesting that the hazards of several outcomes were not proportional over time in the present study. We asked Kotz whether results collected in the study during the first few weeks after the prescription date suggested increased cardiovascular and neuropsychiatric events around the expected quit date; in reply, he said that no such trends were recorded.⁴ The effect of timing and success of quitting on adverse events associated with cessation interventions should be assessed in future studies.

Although a reduced risk of ischaemic heart disease and depression was seen with varenicline compared with

nicotine replacement therapy, we support the authors' conservative interpretation of this, noting that data were not available on drug adherence. We also asked Kotz whether propensity matching succeeded in balancing baseline covariates across groups, which was not shown in the Article; he replied that others have posed this question and he is examining this.⁵

For varenicline to be associated with increased cardiovascular and neuropsychiatric events, the authors estimated that an unmeasured confounder with a hazard ratio (HR) of more than 3 and differential distribution between groups was required. Previous studies have reported HRs of more than 4 for cardiovascular disease in current smokers with substantial cigarette exposure (37 pack-years).⁶ The differences in baseline comorbidities between the varenicline and nicotine replacement therapy groups—such as older age, lower socioeconomic status, and more cardiovascular and psychiatric comorbid disorders in the nicotine replacement therapy group—could also be attributable to a disparity in the cumulative cigarette exposure between treatment groups. If available, data on pack-years of smoking history would provide a valuable comparison across groups and could be incorporated into the analyses.

Overall, the participants of our journal club reached consensus that this study provides reassurance that varenicline does not increase the risk of cardiovascular and neuropsychiatric events compared with nicotine replacement therapy over 6 months. We commend the authors for coordinating a study of this magnitude and believe that confirming the safety of the most effective drug shown to assist with smoking cessation is crucial.

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