AZMATICS: a pragmatic clinical trial for asthma

Dr David Hahn was the first to link bacterial infection with intractable asthma. However, barriers remain despite subsequent confirmatory findings and patient testimonies that antibiotics can quell the condition

Could you offer an introduction to your book, *A Cure for Asthma*?

The first section – Stories – contains accounts written by people with new-onset asthma, longstanding severe treatment-resistant asthma or the 'overlap' syndrome (asthma with chronic obstructive pulmonary disease), whose lives were improved after antibiotic treatment. Section two – Evidence – presents the science supporting a causal association between infection and asthma. Section three – Challenges – explores why you probably haven't heard about this topic even after more than 20 years of accumulating evidence. And section four – Solutions – presents my guidelines for antibiotic treatment and recommendations for more effective research.

***Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been associated with asthma by several authors, yet a causal link has not been fully established. Why is this the case?**

Rather, why has it taken so long to establish (or reject) a causal link? This is because most asthma studies are conducted on highly selected groups of patients who do not resemble the typical asthma patients seen in primary care. This excludes most asthmatics who are likely to be infected by these bacteria and thus respond to antibiotic treatment.

What methods did you apply in your pragmatic trial using azithromycin for bronchial asthma in adults – AZMATICS?

AZMATICS was a double-blind, controlled parallel group randomised trial of azithromycin versus placebo, with a couple of twists. These twists involved recruiting from practice-based research networks (PBRNs) and collecting patient-reported outcome measures over the internet.

The strength of PBRNs is their ability to robustly generalise. The challenge is the high cost of recruiting from geographically dispersed locations. The National Institutes of Health (NIH) rejected funding AZMATICS because the reviewers didn't approve of generalisable asthma studies. Dr Jon Temte, then the Director of the Wisconsin Research and Education Network (WREN), recommended the low-cost approach of internet data collection. Many eligible subjects with severe, treatment-resistant asthma – the most likely to respond – contacted me to be enrolled. Upon learning they had a 50 per cent chance of receiving placebo, most of these desperate folks begged to be treated. So I added an open-label (OL) arm to AZMATICS that, as I expected, revealed a huge treatment effect. Ironically, our randomised trial was affected by patient preferences rather than by *a priori* protocol exclusions.

Why is there systematic exclusion of large numbers of asthma patients from efficacy trials?

As I say in my book, we have a perfect storm: a funding system heavily tilted toward basic science and efficacy, away from applied medical research and population-based effectiveness, that is driven by financial incentives to control rather than cure diseases. Asthma experts – who are not really experts at all when it comes to the full range of asthma in communities, and who favour disease-orientated efficacy over patient-orientated effectiveness – are heavily funded by the pharmaceutical industry. It is these experts that set the national agenda for asthma research and control its funding, and who create the guidelines upon which practising physicians depend. Lastly, we have a weak primary care infrastructure that has been unable to make meaningful contributions to asthma research.

Have collaborations with PBRNs and a community-based allergist conferred benefits for your research?

This research has been a true labour of love on the part of many groups: PBRN clinicians donated their time and efforts; patients participated without compensation; and I have never been paid a penny for any of it. Funding for materials, equipment and staff time came from a broad private-public collaboration with no federal contribution. The Dean Foundation for Research and Education funded early work; the American Academy of Family Physicians (AAFP) and AAFP Foundation also funded projects; and the Wisconsin Academy of Family Ph ysicians (WAFP) chipped in. The University of Wisconsin Department of Family Medicine, WREN and the Wisconsin Network for Health Research (WiNHR) provided in-kind support. One of the largest financial contributions came from a grateful person whose asthma was successfully treated. Without these collaborations, the research would not have been possible.

What are your plans for future investigations?

I am now the Director of a university-affiliated PBRN – WREN – and this position has opened an array of unanticipated options. I am happy to report that I am now collaborating with National Heart, Lung and Blood Institute-level asthma principal investigators on pragmatic approaches to asthma management. I hope that NIH reviewers will reconsider their current attitudes and support the large randomised azithromycin trials in severe asthma that I advocate in my book. Stay tuned.

Simply curing **severe asthma**

Clinical trials at the **University of Wisconsin School of Medicine and Public Health**, USA have revealed that biomarkers of bacterial infection are linked to asthma severity and indicate that prolonged antibiotic treatment can help, and even cure, this condition

ASTHMA IS A recurrent breathing disorder, widely believed to be triggered by reaction to allergens in the air, medicines, exercise or emotional stress. The World Health Organization (WHO) defines asthma as a noncommunicable disease for which there is no cure and estimates that 235 million people worldwide suffer from the condition. According to the American Centers for Disease Control and Prevention, its annual economic and health burden in the US alone is at least $56 billion and 3,300 deaths.

Over recent decades, bacterial infection has increasingly been associated with a number of chronic diseases, either as a trigger or as an exacerbating factor in their aetiology. Examples include the discovery that the bacterium *Helicobacter pylori* causes stomach ulcers, the finding that the risk of carotid atherosclerosis is more than double for people with persistent bacterial infection, and the attribution of acute exacerbation of chronic obstructive pulmonary disease (COPD) – one of the biggest killers in the developed world – to the bacteria *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*, and to a lesser extent *Chlamydia pneumoniae*.

C. pneumoniae is a species distinct from other members of the *Chlamydia* genus. It is transmitted through respiratory secretions from person to person and infection can cause bronchitis or pneumonia, although it can also be asymptomatic. An estimated 50 per cent of adults in the US will have, at some point, contracted the infection by the time they are 20 years old. The bacterium has not only been associated with atherosclerosis, but also with Alzheimer's disease and arthritis; its link with asthma was first revealed in a paper entitled 'Association of *C. pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis and adult-onset asthma', published in the *Journal of the American Medical Association* in 1991. The paper's author was Dr David Hahn, then a physician at the Dean Medical Center in Madison, Wisconsin, who had carried out a prospective clinical and microbiological study of 365 people from four family practice clinics with support from the Dean Foundation. Hahn is currently Director of the Wisconsin Research and Education Network in the Department of Family Medicine at the University of Wisconsin School of Medicine and Public Health and retired from practice at the Dean Medical Center at the end of 2013.

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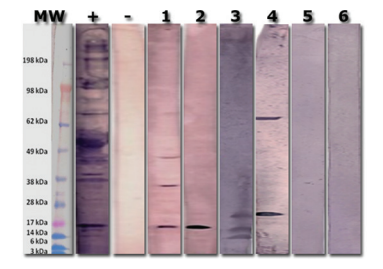
PRAGMATIC RESEARCH

Hahn followed up his 1991 finding with a number of related research projects. Over the following years, he constructed a case series of patients who had developed chronic asthma after an acute bacterial infection and carried out various case control studies. In 1995, he conducted his first trial on asthma patients using azithromycin – a member from the macrolide family of antimicrobial and anti-inflammatory drugs – which is generally used to treat sexually transmitted *C. trachomatis* infection. Hahn primarily selected azithromycin from the viewpoint of safety and practicality, as he explains: "Azithromycin, unlike other macrolides, accumulates and persists within cells and may be given once a week. Side-effects (mostly gastrointestinal) are usually mild to moderate and rarely require discontinuation". The trial showed that the treatment cured or significantly lessened asthma in about half of the 46 subjects.

A later case control study then indicated an association between biomarkers of chronic bacterial infection and new-onset asthma, chronic asthma and the development of irreversible airflow limitation. The finding prompted a further project in 2012 to establish whether previous or current *C. pneumoniae* infection is common in asthma patients: "This important study was made possible through a collaboration with Dr Wilmore Webley at the University of Massachusetts," explains Hahn.



Immunoblots demonstrating IgE against *C. pneumoniae*: + = positive control; – = negative control; patient samples 1-4 show positive bands; patients samples 5 and 6 are negative.

66 asthma patients were recruited from non-academic medical practices in the local community. Because the aim was to obtain a representative sample to increase the validity of the results, the study was specifically designed to include people who smoked and/or had COPD as well as asthma, and to reflect a broad range of asthma severity. The project comprised measurement of *C. pneumoniae*-specific immunoglobin E (IgE) alongside two case control studies of asthmatics and healthy people. 50 per cent of the asthma patients were found to have antibodies against *C. pneumoniae* and 25 per cent had *C. pneumoniae* DNA in their blood, whereas the incidences were insignificant in the blood of the healthy people. In addition, the study revealed that the severity of a patient's asthma correlated with detection of IgE.

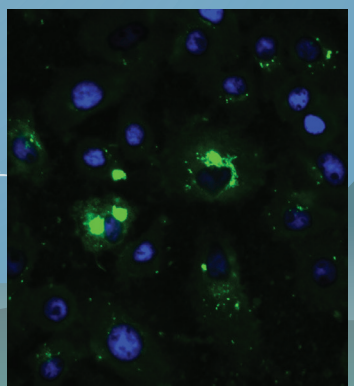
During the course of this project, some patients with refractory asthma elected to receive antibiotic treatment with azithromycin. Hahn and Webley found that these patients reported significant improvements that persisted after the completion of the treatment. This prompted a larger network of trials – named AZMATICS – of azithromycin with patients from four practice-based research networks.

GROWING EVIDENCE

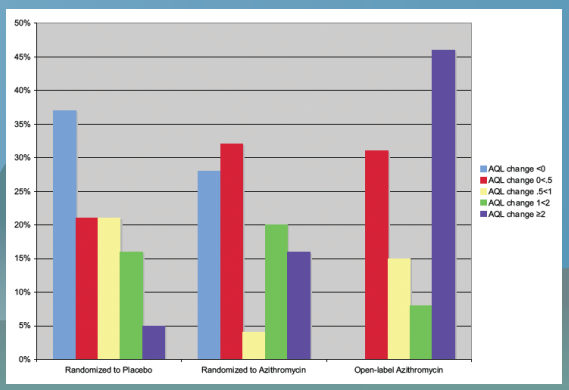
The AZMATICS trial sought to establish whether the condition of patients with persistent, steroid-resistant asthma would not only improve with azithromycin treatment for a period of 12 weeks, but whether the improvement would persist. 97 patients were recruited, 22 of whom participated on an open-label (OL) basis. The rest were equally randomised to either placebo or azithromycin. All were followed up nine months after the treatment ended. Though there was no clear result for the randomised patients, the OL patients, more of whom had severe asthma, showed a strong response: "In these patients we found very large and statistically significant improvements in symptoms, asthma control and quality of life after the treatment. Notably, these benefits largely persisted throughout the following nine months, long after the antibiotic ceased to be present," Hahn noted.

As an individual practitioner, Hahn has found it difficult to obtain government funding for research or interest from other researchers in pursuing the causal link between *C. pneumoniae* and asthma over the years: "This research programme has been grassroots from beginning to end," he states. Hahn is confident that his approach of trialling antimicrobial treatment with representative samples of community-dwelling asthma patients with real-world profiles, including health or lifestyle complications, renders his results more generalisable than the usual asthma research approach, which he describes as "exclude, exclude, exclude, until you know a lot about a little". He would like to see the asthma research community adopt the 'large simple trials' approach used for decades in heart research by the National Heart, Lung and Blood Institute: "Asthma researchers are trying to apply the principles of bench research to human populations and it is not working," he asserts. Some other investigations into antibiotic treatment for asthma have meanwhile shown promising results, but they have tended to be limited in scope or in the nature of patient samples.

Hahn has now published a book on his work, which he thinks can provide valuable information for patients: "Asthmatics who are not responding to conventional treatments can possibly benefit now". He also hopes that the book will prompt other research into the notion that treating bacterial infection is a viable way of curing asthma. The official publication date for the book is 28 November 2013 and copies can be obtained from www.peoplespharmacy.com/cure-asthma.



Immunofluorescent staining of intracellular *C. pneumoniae*: green fluorescence = intracellular cytoplasmic *C. pneumoniae* inclusions abutting the nucleus.



Persisting improvement in asthma quality of life (AQL) nine months after completing azithromycin treatment: AQL > 0.5 is the minimum clinically important improvement (yellow bars); AQL > 1.5 is a large improvement (some green and all purple bars).

INTELLIGENCE

INFECTION AS A TREATABLE CAUSE FOR ASTHMA

OBJECTIVES

To investigate a causal association between infection and asthma.

KEY COLLABORATORS

Dr John Beasley; **Dr Jon Temte**, past Directors, Wisconsin Research and Education Network (WREN), USA • **Dr Rjurik Golubjatnikov**, Wisconsin State Laboratory of Hygiene, USA • **Dr Rosanna Peeling**, Laboratory Centre for Disease Control, Health Canada, Winnipeg, Canada • **Dr Pekka Saikku**, National Public Health Institute, Oulu, Finland • **Dr Wilmore Webley**, University of Massachusetts, Amherst, USA

PARTNERS

Wisconsin Research and Education Network (WREN) • **Wisconsin Network for Health Research** (WiNHR) • **Cleveland Ambulatory Research Network** (CLAREN) • **Oklahoma Physicians Resource/Research Network** (OKPRN) • **Ambulatory Network for Scholarship and Research** (ANSR)

FUNDING

Dean Foundation for Research and Education

American Academy of Family Physicians (AAFP)

Wisconsin Academy of Family Physicians (WAFP)

Anonymous donors with asthma

CONTACT

Dr David Hahn

University of Wisconsin School of Medicine and Public Health
Department of Family Medicine
1100 Delaplaine Court
Madison, WI 53715
USA

T +1 608 265 5324
E dlhahn@wisc.edu

www.jabfm.org/content/25/4/442.long

DAVID L HAHN, MD, MS is a past Clinical Professor and current Director of the WREN in the Department of Family Medicine at the University of Wisconsin School of Medicine and Public Health. Hahn has been in community-based medical practice for over 30 years and has been performing practice-based clinical research for almost as long. He holds a Master's degree in Epidemiology and has received advanced research training in medical microbiology, immunology and clinical trial design.

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