

Infection and low back pain: seeking evidence or fear of exploring new indications for antibiotics?

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Infection in the spine might be the cause of symptoms in a group of patients with severe chronic low back pain (LBP). What about the large body of research recommending biopsychosocial management? Where have we heard a similar story before? Well, *Helicobacter pylori* infection as the cause of indigestion was a major challenging discovery that led to a paradigm shift in managing that condition which had hitherto been managed mainly through symptomatic and psychological approaches, and sometimes major surgery. The similarities between these stories are uncanny—not least in the challenges facing attempts to establish the clear evidence.

So what are the challenges that face proving the principle of infection theory in LBP? Following the Koch's postulates linking infection and a disease state [1], we have to demonstrate that an infectious agent is present. Intact intervertebral discs are avascular and sterile but pathogens have been identified in herniated and degenerated discs since the 1970s [2, 3]. Compared to the stomach, access to intervertebral discs is difficult and sampling carries a high risk of contamination from the skin. This is particularly relevant as the most common pathogens isolated are *Propionibacterium acnes* and coagulase negative *Staphylococci*, both common skin commensals. Two recent reviews

conclude that micro-organisms are found in about 35 % of surgically removed discs, and that *P. acnes* is the most frequently identified species [4, 5]. When samples are taken from the vertebral body rather than from the disc, no evidence of bacteria can be found [6].

In 1987, particular signs or changes seen on magnetic resonance imaging (MRI) of the spine were described for the first time [7], Michael Modic then classified them into three types with distinct radiological and histological features [8]. Type 1 Modic changes correspond to bone oedema of the vertebral endplate; type 2 fatty degeneration and type 3 end-stage sclerosis. These changes are thought to be caused by inflammatory mediators in the adjacent herniated or degenerated discs triggered by infection in these discs. In other words, these changes could be biomarkers for disc infection. An important link in this developing chain is establishing whether Modic changes are associated with symptoms of LBP. Several studies evidence such an association [4, 5, 9–12] and provide prevalence estimates in LBP patients that vary widely, from 0.5 % [13] to 62 % [14] depending on study design, setting and inclusion criteria. A consensus seems to suggest that type 1 changes in particular are associated with symptoms of LBP [9–11, 15] and their prevalence in LBP patients ranges from 12 to 24 %.

Based on this evidence, a randomised controlled trial (RCT) (162 participants) from Denmark investigated the effectiveness of antibiotics for hospital patients with severe chronic LBP with type 1 Modic changes [16]. It showed that co-amoxiclav (500/125 mg tablets, three times a day for 100 days) was better than placebo (effect size of 0.3 on RMDQ at end of 100 days of treatment and 1.0 at 12 months). The finding received much international attention. A replication RCT on 71 participants has since been published [17] and showed similar results. At least

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three other replication RCTs among hospital patients with LBP and Modic changes are underway [18–20].

Given the low virulence of the organisms identified, the question remains as to whether the organisms are truly responsible for causing symptoms. It clearly is not possible to obtain direct evidence of a causal association through the deliberate inoculation of healthy human discs with pathogens, as was done with *H. pylori*, although an animal model is feasible and probably being considered. Similarly, it is not feasible to perform repeated disc biopsies and culture on individual patients undergoing therapy. We therefore have to seek circumstantial evidence, for example by testing an alternative class of antibiotic, thereby making a non-antibiotic effect less likely, or by culturing disc material obtained from surgically treated patients either before or after antibiotic therapy or placebo. A trial designed with this objective in mind would allow either confirmation or rejection of two of Koch's postulates.

So where does all of this leave us on the path of assessing the potential for a paradigm shift in managing chronic LBP? The evidence is incomplete and even with the results of the ongoing RCTs it will remain incomplete, for the following reasons. Both of the published [16, 17] and planned trials [18–20] rely on Modic changes as *the* biomarker for response to antibiotics, and all have used the same broad spectrum antibiotic. This leaves a number of important questions unanswered: (1) what is the association between Modic changes, infection and LBP? The evidence on this is not beyond doubt, as only a small number of studies that isolated bacteria in intervertebral discs examined Modic changes [4, 5]; (2) are Modic changes *the* only marker to identify potential treatment responders?; (3) are the antibiotics used in trials on LBP unnecessarily broad spectrum? If *P. acnes* is the main pathogen, there is no theoretical advantage to be gained by using co-amoxiclav as compared to benzyl penicillin or other similarly narrow spectrum agent. With the current rising risk of antibiotic resistance caused by their inappropriate use [21, 22], it is even more important to ensure a judicious assessment of the evidence before wider implementation in clinical practice. Research is also needed that tests the role of Modic changes and other MRI findings and of simpler clinical features from patients' symptoms and signs that might identify responders to antibiotics. In particular, identifying clinical markers could provide a much more cost-effective approach, compared with MRI scans, with greater utility in primary care where most chronic LBP patients are managed.

Despite these important gaps in the evidence, investigators in several countries have found it very difficult to secure funding for research that addresses these gaps—in the UK we know of four unsuccessful applications. The lack of evidence-based patient selection and clear treatment

protocols has led to a growing tide of clinicians resorting to ad hoc use of antibiotics, encouraged by an increasingly frustrated patient population. Given the prevalence of chronic LBP, its societal impact and the limited benefit from current treatments, robust testing of this potentially revolutionary intervention is merited. We ask research funders for courage in their decision-making to help us decide whether or not this pig can fly.

Compliance with ethical standards

Conflict of interest None.

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