Albert HB, Sorensen JS, et al. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J 2013;22:697-707.

Population/sample size/setting:

- 162 patients (93 women, 69 men, mean age 45) treated for chronic low back pain in a university setting in Denmark
- Eligible if they were between 18 and 65 with MRI confirmed disc herniation L3/L4 or L4/L5 orL5/S1 in the preceding 6-24 months, LBP more than 6 months duration, with or without sciatica or neuropathic pain
    - Both surgically and nonoperatively treated patients were eligible
    - Numerical Pain Rating Score, calculated from averaging the current LBP, the mean LBP in the previous 2 weeks and worst LBP during the previous weeks, had to be at least 6
- Exclusion criteria were allergy to antibiotics, pregnancy, kidney disease, and pending litigation
- All eligible patients had a repeat MRI, and were eligible to continue only if they had Modic type 1 changes adjacent to the previously herniated disc

Main outcome measures:

- Randomized to treatment with amoxicillin-clavulanate (n=90) or identical appearing placebo (n=72), each to be taken 3 times per day for 100 days
    - There were 4 dosage groups to test dose-response relationships: 1 antibiotic tablet (n=45), 1 placebo tablet (n=36), 2 antibiotic tablets (n=45), and 2 placebo tablets (n=36)
- Clinical evaluations were done at baseline and one year later
    - These consisted of a physical examination, MRI, blood samples, and self-reported questionnaires
        - Questionnaires were Roland-Morris Disability Questionnaire (RMDQ) and the lumbar pain rating scale as primary outcomes
    - Completion of the questionnaires was checked by an administrator before the patient left the examination center to ensure complete collection of data
    - Examinations and MRI were blinded to treatment group
- In addition to the baseline and 1 year examinations, the patients also received a mailed questionnaire at the end of the 100 days of treatment
- Follow-up was good, with questionnaire completion at 100 days being received from 147 patients (90.7%), and 1-year examinations completed by 144 (88.9%)

- The antibiotic group and the placebo group had equal scores on the RMDQ at baseline (15.0); the respective scores at 100 days were 11.5 and 14.0; the respective scores at 1 year were 7.0 and 14.0, showing a significant difference in disability scores in favor of the antibiotic group
- The other main outcome, LBP pain, decreased in the antibiotic group from 6.7 at baseline, 5.0 at 100 days, and 3.7 at 1 year; the placebo group had LBP pain scores of 6.3 at all three measurements
    - There was a trend towards a positive dose-response relationship with the double dose antibiotic appearing to be more efficacious, but the study was underpowered to detect the difference between dose levels
- Onset of pain relief was gradual, becoming apparent to patients at the end of 6 to 8 weeks, continuing to improve at the end of 100 days of treatment, and continuing to improve after 100 days until the 1 year follow-up
- At the 1 year repeat MRI, reduction in volume of the Modic changes was seen in the antibiotic group but not the placebo group
- Adverse effects were more common in the antibiotic group, primarily gastrointestinal complaints such as loose bowel movements lasting more than 3 weeks (27% of antibiotic group and 11% of placebo group); the adverse effects were not apparently dose-related

Authors' conclusions:

- For patients with Modic type 1 changes, antibiotic treatment demonstrates statistically and clinically significant benefits over placebo treatment, reducing disability and lumbar pain and reducing the size of the Modic lesions
- *Propionibacterium acnes* bacteria secrete propionic acid, which may dissolve fatty bone marrow and bone; this may be the mechanism of Modic changes in patients harboring *P. acnes*
- Chronic low back pain with Modic changes is difficult to treat with conservative methods, and the placebo group showed virtually no improvement over the course of the year of observation
- Amoxicillin-clavulanate has no appreciable anti-inflammatory effects through TNF alfa which is present in Modic changes; an anti-inflammatory effect is not a likely explanation of the treatment effect
- Additional interventions by physicians is not a likely explanation of the antibiotic effect; 23.4% of the antibiotic group consulted a doctor for back pain during the trial, but 41.8% of the placebo group consulted a doctor for back pain
- The gradual onset of pain effect, mainly in a slow reduction in the waking hours with back pain, is consistent with an antibiotic effect on an infection with low virulence
- High-dose long-term antibiotics should not be prescribed for most cases of chronic LBP; the criteria for this study were LBP more than 6 months duration, with Modic

Type 1 changes at a vertebral level adjacent to a previous disc herniation, where they may be an option after other treatment options have failed
- The MRI did change over the course of the year of observation; often, as with osteomyelitis, the imaging may not change even if symptoms resolve

Comments:

- The study methods are well planned and executed; the common GI side effects may threaten to unblind the study, but bias was controlled as carefully as can be expected
- The authors are appropriately cautious about the circumstances for antibiotic therapy of chronic LBP, restricting the study population to a narrow spectrum of back pain patients
- The organism was not identified, but P. acnes can be difficult to culture; it is not certain that it was growing in the affected discs or endplates
- The results do not apply to Type 2 Modic changes (fatty degeneration of the vertebral body marrow with increased T1 signal on MRI) but *only* to Type 1 changes (marrow edema with decreased T1 signal on MRI)

Assessment: High quality study supporting evidence that a 100-day course of amoxicillin-clavulanate may reduce pain and disability in patients with chronic low back pain associated with Modic Type 1 changes adjacent to a previous disc herniation

Reference:
Modic MT, Steinberg PM, et al. Degenerative Disc Disease: Assessment of Changes in Vertebral Body Marrow With MR Imaging. Radiology 1988;166:193-99.