
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 or L5/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: