Back pain & Antibiotics

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Low Back Pain

- Chronic non-specific LBP leading cause of disability in Global Burden of Disease reports 1990 and 2010
- Rarely attributable to a specific cause
- MRI scans in some patients with LBP have identified characteristic changes in the vertebral bodies adjacent to the disc spaces
- These were classified by Modic, an American radiologist
Dr Michael Modic

- Professor Neuroradiology
- Cleveland Clinic, Ohio, USA
- Publication: Radiology 1988
- Reviewed lumbar MRIs of 474 consecutive patients referred for MRI
- Classified into type 1 and 2 to reflect vertebral body marrow changes associated with DDD
Type 1

- Decreased intensity $T_1$
- Increased intensity $T_2$
- Represent bone marrow oedema and inflammation
Type 2

- Increased intensity on T1
- Isointense or slightly increased on T2
- Represent conversion normal marrow to fatty as result of ischaemia
Modic change

- Modic change is not in itself the causal process for back pain, but a response of the bone marrow to a pathologic process

- Modic changes common adjacent to DDD or herniated discs

- Modic changes uncommon in asymptomatic individuals without DDD
Back Pain Theory

• DDD on its own is asymptomatic, but with Modic change is associated with clinical symptoms
• Type 1 changes are bone oedema and are commonly observed in, and closely correlate with back pain:
• A recent systemic review showed a 46% prevalence for any type of Modic change in patients with non-specific low back pain as opposed to 6% in the general population.
Infection theory

- **Sterling et al:** Proprionibacterium acnes and Corynebacterium propinquum in 53% of the patients in nuclear material during lumbar disc hernia surgery

- **Corsia et al:** Staphylococcus (36%) and P. Acnes (18%)

- **Agarwal et al:** P. Acnes
What Causes Cavities?

Susceptible Tooth

Time

Cavities

Sugar

Bacteria

ORAL ANSWERS
Infection theory chronic LBP

- Low Virulence
- Bacteraemia
- Insult/injury to disc
- Susceptible disc lower lumbar
- Mobile lumbar

LBP
Study 1

- Prospective cohort 67 patients, 61 at follow-up
- All primary discectomy, MRI at baseline and 1-2 years
- Intra-op biopsy 5 nuclear material samples per patient
- Positive bacterial culture 46%, anaerobic growth 43%
- Out of the 46% positive, 86% were P. Acnes, 80% had developed new Modic 1 changes

Study 2

- Double blind randomised clinical trial
- 162 patients with chronic LBP over 6 months
- Known previous disc herniation and type 1 Modic
- Randomised to 100 days antibiotics Bioclavid-Amoxicillin/Clavulanic Acid (500mg/125mg) TDS or placebo (Calcium carbonate)
- Reviewed at 1 year follow-up

Outcome measures

- **Primary**: disease specific disability, lumbar pain

- **Secondary**: leg pain, number of hours with pain last 4 weeks, global perceived health, EQ-5D thermometer, days with sick leave, bothersomeness, constant pain, magnetic resonance image (MRI)
<table>
<thead>
<tr>
<th><strong>Table 1</strong> Outcome measures</th>
<th><strong>Questionnaire characteristics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reported questionnaires</strong></td>
<td><strong>Questionnaire characteristics</strong></td>
</tr>
<tr>
<td>Global perceived effect</td>
<td>The patients compare their baseline status with their status at follow-up, measured on a 7-point Likert scale</td>
</tr>
<tr>
<td>Roland Morris Disability Questionnaire (RMDQ)</td>
<td>A disease-specific disability questionnaire in which the patient answers 23 yes/no questions. The scale width is 0–23, where high scores are worst [27]</td>
</tr>
<tr>
<td>LBP pain rating scale</td>
<td>Three 11-point box scales measuring current pain, the worst within the last 2 weeks and usual pain within the last 2 weeks. These three scores are measured and averaged for both leg and lumbar pain independently [28]</td>
</tr>
<tr>
<td>Hours with LBP during the last 4 weeks</td>
<td>Number of days during the last 28 days (4 weeks) the participant had experienced LBP (0–28 days), and, on an typical day, how many of the hours awake they experienced LBP (0–16 h). The number of days and hours are multiplied (a 0–448 scale)</td>
</tr>
<tr>
<td>EQ-5D: Thermometer</td>
<td>Quality-adjusted health status EQ-5D [40] on a vertical Thermometer (1–100), 100 is best</td>
</tr>
<tr>
<td>Days with sick leave</td>
<td>The number of days within the last year the participant was on sick-leave support from the government</td>
</tr>
<tr>
<td>Bothersomeness</td>
<td>Measured on a 11-point box scale, where 0 = none, 10 = my life is worthless due to my back pain [41]</td>
</tr>
<tr>
<td>Constant pain</td>
<td>Pain that can vary during the day but is always present</td>
</tr>
<tr>
<td>MRI</td>
<td>Volume of the vertebrae with Modic type 1 change, (1–4)</td>
</tr>
<tr>
<td>Serum analysis</td>
<td>Leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, P/S creatinine, lactate dehydrogenase, alkaline phosphatase, C-reactive protein</td>
</tr>
</tbody>
</table>
Study flow chart

347 patients with a 6-24 months old MRI confirming a lumbar disc herniation and pain in the lumbar region

178 were excluded, because the new MRI revealed no new Modic changes or Modic type 2 changes only.
7 = refused participation, 3 wished to become pregnant and were advised against participation, 4 did not like the idea of long-term antibiotics

162 patients were randomised

45 took single dose antibiotics
45 took double dose antibiotics
36 took single dose placebo
36 took double dose placebo

Drop outs = 13
4 – side effects
3 – new disc herniation
1 – no show at follow-up
2 – > 65 year of age
1 – Modic 2
2 – new cancer

77 (85.6%) participated in 1 year follow-up

Drop outs = 5
3 – new disc herniation
2 – no show at follow-up

67 (93.1%) participated in 1 year follow-up
Assumption of study

- Colonisation of the disc herniations with PA is underlying pathology
- Also assumed that colonisation was the pathology for CLBP and Modic change in the participants of study
- And that they were successfully treated with antibiotics
- But no formal microbiological testing performed to corroborate the link
Results

- 90% completed study
- ABx group showed statistically significant improvement on all primary outcome measures at 100 days and further improved at 1 year
- Subjects reported clinical improvement from 6-8 weeks post treatment onwards
- Significant difference noted on Modic volume changes in antibiotic group
- Positive trend towards dose/response relationship (not statistically significant)
- Higher side effects in antibiotic group (GI)
<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Antibiotic Baseline ( n = 90 )</th>
<th>Antibiotic 1-Year Follow-Up ( n = 77 )</th>
<th>Placebo Baseline ( n = 72 )</th>
<th>Placebo 1-Year Follow-Up ( n = 67 )</th>
<th>( P ) Value for Difference between Placebo and Antibiotic Groups at 1-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had low back pain</td>
<td>100 %</td>
<td>67.5 %</td>
<td>100 %</td>
<td>94.0 %</td>
<td>0.00001</td>
</tr>
<tr>
<td>Had constant pain</td>
<td>75.3 %</td>
<td>19.5 %</td>
<td>73.1 %</td>
<td>67.2 %</td>
<td>0.00001</td>
</tr>
<tr>
<td>Had disturbed sleep at night due to pain</td>
<td>74.0 %</td>
<td>29.9 %</td>
<td>76.1 %</td>
<td>61.2 %</td>
<td>0.001</td>
</tr>
<tr>
<td>Had pain during the Valsalva maneuver</td>
<td>75.3 %</td>
<td>41.6 %</td>
<td>71.6 %</td>
<td>56.7 %</td>
<td>0.05</td>
</tr>
<tr>
<td>Had pain during active flexion of the lumbar spine</td>
<td>96.1 %</td>
<td>49.4 %</td>
<td>100 %</td>
<td>83.6 %</td>
<td>0.00001</td>
</tr>
<tr>
<td>Had pain during active extension of the lumbar spine</td>
<td>87.0 %</td>
<td>51.9 %</td>
<td>86.6 %</td>
<td>74.6 %</td>
<td>0.005</td>
</tr>
<tr>
<td>Positive cranial compression test</td>
<td>36.4 %</td>
<td>19.5 %</td>
<td>35.8 %</td>
<td>34.3 %</td>
<td>0.044</td>
</tr>
<tr>
<td>Had pain during springing test</td>
<td>92.2 %</td>
<td>55.8 %</td>
<td>94.0 %</td>
<td>77.6 %</td>
<td>0.006</td>
</tr>
<tr>
<td>Consulted a doctor the follow-up year due to back pain</td>
<td>23.4 %</td>
<td>41.8 %</td>
<td>41.8 %</td>
<td>41.8 %</td>
<td>0.002</td>
</tr>
<tr>
<td>Compliance consuming 95–100 % of all tablets</td>
<td>94.8 %</td>
<td>94.0 %</td>
<td>94.0 %</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Observed volume volume 1, minute size</td>
<td>16</td>
<td>29</td>
<td>31</td>
<td>24</td>
<td>0.05</td>
</tr>
<tr>
<td>Observed volume volume 2–4, moderate/large size</td>
<td>126</td>
<td>113</td>
<td>99</td>
<td>96</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Concerns regarding study

- Control group showed no improvement - unusual for a back pain study
- Rapid recruitment in a single centre study
- Both groups advised not to exercise
- First study had no cross contamination controls, when such controls are used they reveal high levels of P.Acnes in skin, drapes and air
- No formal microbiology tests in study 2 to corroborate the link
- Side effect profile of antibiotics
- Antibiotic amoxycillin has a weak anti-inflammatory effect
Side effect profile of amoxicillin/clavulanic acid

- Very common: >10% Diarrhoea
- Common: >1% GI effects: nausea, vomiting, nails and mucous membranes infection
- Uncommon: >0.1% abnormal lab results, feeling dizzy, headaches, indigestion, skin reactions such as skin rashes, urticaria, and itching
- Rare: >.01% blood and bone marrow problems, erythema multiforme
- Other problems: clostridium difficile, cadidiasis, allergic anaphylaxis
• BASS actively promotes study of spinal disorders and welcomes any research aimed at improving the understanding and treatment of spinal conditions.

• Recently media coverage of a study published in the European Spine Journal suggesting that some patients with severe low back pain may benefit from treatment with abx.

• BASS considers this to be a well conducted trial which provides evidence that a small number of patients could gain some moderate improvement in their condition with a course of antibiotics.
A patient who may be appropriate for consideration of this treatment needs to fulfil specific criteria. They need to have:

- Low back pain of more than six months duration
- Pain which occurs after a previous disc herniation (whether or not it was treated with surgery)
- Inflammatory Changes in the bone either side of the herniated disc identified by an MRI scan referred to as Modic type I changes

If your general practitioner considers that you might fulfil these criteria then it would be sensible to seek the opinion of a local spinal specialist.
Future

- Study must not be rejected because it is high quality and challenges beliefs

- Other study groups repeating the study and further evidence needed before change in practice