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Modic Antbiotic Spinal Therapy (MAST). Early experience in the use of antibiotics in Modic-related back pain (MRBP). A case report and prospective, open-label, observational study.

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Abstract.

Introduction.

Modic change is common in the back pain population. Recent reports of successful antibiotic therapy in post disc surgical cases of progressive Modic change and back pain raise the possibility of improvement for difficult to treat patients. I here report successful antibiotic treatment in a post disc surgical patient with progressive painful Modic change and the result of the treatment of 33 further cases of mixed aetiologies.

CaseReport.

The case of a 35 yr old patent who had undergone successful discectomy for sciatica and who subsequently developed progressive Modic Type 1 change and disabling back pain is presented. The patient showed and excellent response to MAST treatment adapted for penicillin allergy.

Methods.

Open label, prospective collection of MAST standardised data in daily clinical practice by one practitioner in two settings (independent NHS and Private Practice) of 36 sequential cases. Other than the case reported, these patients were usual chronic spinal pain patients, not specifically post disc surgery.

Results.

33 patients are available for evaluation to date. Of these: 3 were non-compliant and one withdrew consent. Of those who commenced treatment 22.3% failed to complete the 100 day course due of adverse effects. Of 22 patient completing treatment: 40.9% were rated as Excellent (>75% patient global improvement) and 27.3% were rated as good (>50%) while 22.7% failed. No major adverse events occurred. Reductions in RMDQ, back pain, leg pain, number of days with pain and hours per day with pain were all seen, with varying statistical significance.

Discussion.

Retention of patients was less and overall success was less in clinical practice than in clinical trial, probably due to less stringent selection criteria but overall, sufficient levels of treatment success was achieved with acceptable side effects for the author to conclude that further exploration of MAST treatment appears justified.

Introduction

Modic change is associated with low back pain occurring in about 6% of the general population and 46% of the low back pain population[1]. Types 1 to 3 are identified with Type 1 representing end plate oedema, degeneration and regeneration, Type 2 fatty bone marrow replacement and type 3 sclerosis [2,3].

There have been many reports of the possibility that lumbar disc disease is associated with infection. After screening with serological tests, Stirling et al reported positive results on prolonged culture in 53% of 36 surgical disc specimens, 84% of which were *Propionobacterium acnes* or *Corynebacterium propinquum*.[4] To differentiate from skin contamination, Stirling studied disc material from a further 207 cases of surgery for lumbar disc herniation and disc surgery cases and compared with disc material with 26 other surgical procedures (scoliosis)[5]. 37% of the disc herniation specimens and none of the others showed infection suggesting this was not surgical contamination. Corsia [6] and Agarwal [7] found infection in extruded lumbar disc material in between 19 and 70% of cases, once again mainly with P acnes or related species in findings reported in abstract. It is thought that these anaerobic mouth and skin commensal organisms gain access to the disc during normal

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bacteremias as a result of the neovascularisation associated with disc degeneration or herniation. [8-15]
Albert et al [16] studied the association of disc infection and the evolution of Modic change prospectively over 2 years post disc surgery. Of 61 cases aspirated at the time of disc protrusion surgery, 46% showed positive cultures, 86% of which were *P acnes*.
Furthermore, 20 of the 25 (80 %) with anaerobic cultures developed new Modic changes in the vertebrae adjacent to the previous disc herniation, compared to 16 of the 36 (44 %) with no identified infection or aerobic bacterial infection and these were statistically different.
The possibility that these infections could have a causative association was tested with an open label study of antibiotic therapy [17]. 32 patients who developed low back pain and Modic type 1 change (bone oedema) 1-2 years post disc protrusion surgery were treated with Amoxicillin-Clavulanic Acid (Co-Amoxiclav) 625mg TID for 90 days. The choice of treatment was on microbiologist advice. Twenty-nine patients (90.6 %) completed the treatment and three patients dropped out due to GI side effects. At the end of treatment and at long-term follow-up (mean10.8 months) there was both a clinically important and statistically significant ($p< 0.001$) improvement in all outcome measures.
Most recently, Albert and Colleagues undertook a prospective, randomised, placebo-controlled trial of Co-Amoxiclav versus placebo in post surgical cases of Modic associated back pain [18]. A total of 162 patients with low back pain and Modic Type-1 change of at least 6 months duration after disc protrusion surgery were treated with Co-Amoxiclav in one of two doses or placebo (half in each group). At the late behest of the Danish authorities, the treatment group was given a dose ranging treatment with half of the treated patients receiving Co-Amoxiclav 625mg one tablet tid and half receiving 625mg, two tablets tid for 100days (Modic Antibiotic Spinal Treatment: MAST). The dose ranging was exploratory and the study was not powered to discriminate between the two doses. There were no statistical differences between the two treatment doses of Co-Amoxiclav, though there were numerical trends in favour of the higher treatment dose in all measured response parameters. There were clear statistical differences between active and placebo-treated patients suggesting the possibility that this regime may be an effective treatment for patients with MRBP.
I therefore here report a case of typical post-surgical progressive MRBP and the results of treatment in a cohort of 33 further cases of MRBP including non-surgical instances.

Case Report.
The patient was a 35 yr old woman with no prior history of significant spinal problems who developed typical sciatica with fully consistent MRI appearances (figure 1) of L5/S1 disc protrusion. After failed conservative management, she was treated successfully by conventional surgical microdiscectomy in July 2013. Her leg pain resolved. However, she developed back pain which became progressive and ultimately severe. After 15 months she was referred by the consulting neurosurgeon for consideration of MAST therapy. At this point she was in severe pain, continuous daily graded 8/10cm average with frequent exacerbation to 10/10 cm a 10cm VAS. Her RMDQ score was 22. The pain was unrelieved by Ibuprofen 400mg QID. It was unrelieved by rest, sleep was variable, she showed intense exercise intolerance with any attempted activity or heavier ADL (vacuuming, making a bed) resulting in severe exacerbation of pain for around 2 days (pay-back). Repeat MRI showed significant progression of MRI appearance of Type 1 Modic change with also some end plate disruption (Figure 2). Full blood count and biochemistry were normal. ESR was 2.

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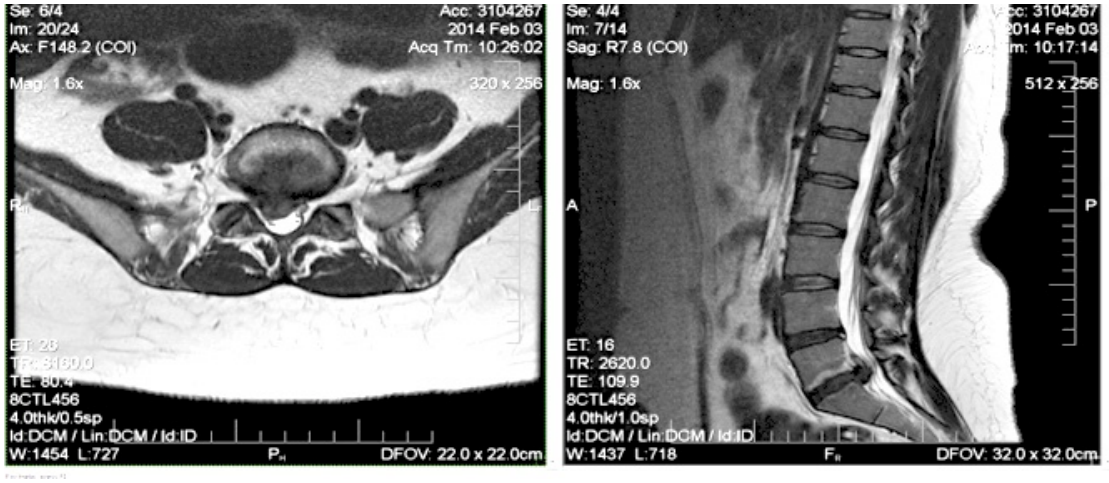

Figure 1. Pre discectomy T2 weighted MRI showing L5/S1 disc protrusion and minor L5 inferioir end plate changes.

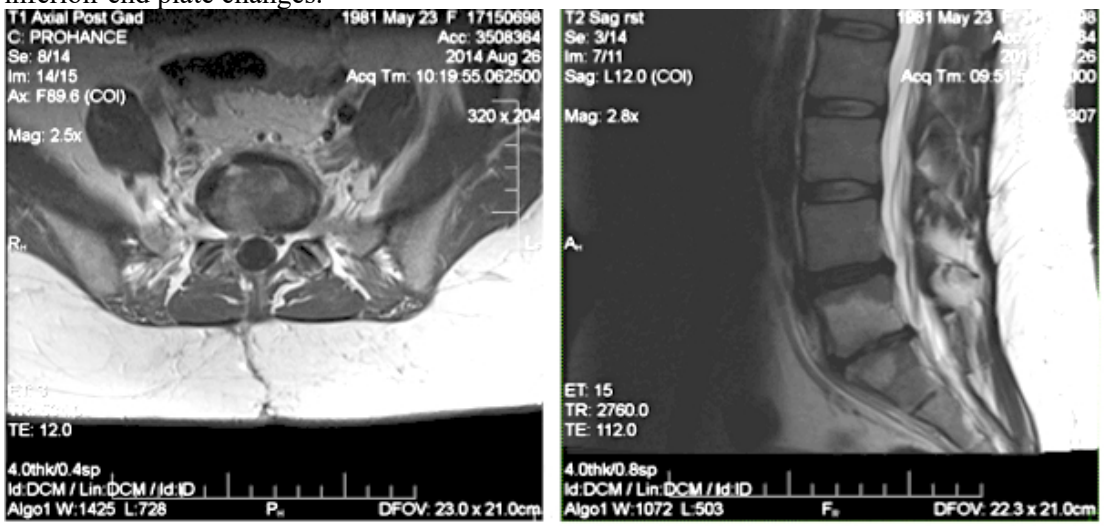

Fig 2. 15 months post surgery. T2 Gadolinium enhanced san showing dramatic extension of Modic Type 1 change (confirmed on T1) adjacent to the operated level.

In view of the clinical situation and MRI appearances, an attempt to aspirate and culture the affected disc was made. Under conscious sedation, in main theatre with full sterile technique, a 20 gauge spinal needle was passed to the centroid of the L5/S1 disc and 5 mls of normal saline injected then re-aspirated. After a patient re-aspiration, approximately 5 mls of bloody disc fluid was obtained and sent for culture in aerobic and anaerobic blood culture bottles. After 5 days, the culture was positive for *Propionobacter* Species, confirming MRBP. Unfortunately the patient was Penicillin allergic reporting significant rash on exposure. The favoured, but not evidence based alternate regime for Penicillin allergic patients is Doxycycline 100mg BD for 100 days. After discussion with Microbiology colleagues, it was decided to add Rifampacin 600mg BD as an additional tissue-penetrating bactericidal antibiotic. This regime requires monthly FBC and LFT monitoring for Rifampicin related hepatotoxicity. This was carried out successfully without event and the patient showed a prompt response, reporting symptomatic benefit at the first (30day) follow up. Measured response parameters before and after 100 days of MAST therapy are as shown below (table 1).

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MAST Rx	RMDQ	Back Pain			Leg Pain			Days with pain	Hours with pain	Sick leave	Analgesics	% Improvement
		Now	Worst	Average	Now	worst	Average					
Baseline	22	9	10	9	5	5	5	28	16	0	Ibup QID	
Post	1	2	2	1	0	0	0	2	0.5	0	0	85%

Table 1. Patient baseline and Post adapted MAST therapy (Doxycycline and Rifampacin) pain and disability scores.

MAST Treatment Series.

Including the reported patient, the author has made a total of 36 prescriptions for MAST therapy in patients with low back pain attributed by the author to the associated Modic change on MRI including both type-1, type-2 and mixed patterns. Four patients had prior surgery, including 1 disc replacement. Unlike the reported case there appeared no close temporal sequence between the surgery and the evolution of back pain. The remaining patients were referred for assessment of chronic spinal pain. These patients therefore seem to represent the population seen in pain clinics rather than spinal surgery services. In view of the small numbers no attempt was made to analyse those with previous surgical history separately.

Average age was 51yrs with 10 male and 26 female patients. The average duration of continuous pain prior to therapy was 52.7 months (6 – 240), the median value was 30 months.

Patients were seen in 2 distinct clinical settings. Eight were seen as NHS cases in the Horder Centre, Crowborough a charitable independent NHS provider unit and the remainder were seen in private practice at The Kent Institute for Medicine and Surgery, Bearsted, Maidstone, Kent. Only the global perceived benefit was collected from 7 of these 8 NHS patients due to resource difficulties. One case (non-responder) did give detailed responses and was included. The average global improvement in these NHS cases did not differ from the private cases at 50 and 58.9% (NS) respectively and they have been analysed together.

Of 36 prescriptions, 3 patients were non-compliant and did not commence treatment leaving 33 ITT cases. At this time 3 cases are in progress and so there are 30 evaluable ITT (ITT/E) cases. The disposition of cases and the treatments given is shown below in table 2. Of 30 ITT/E cases, 8 withdrew. Three because of GI side effects, 3 non-specific ill health, 1 vasculitic skin rash (on Co-Amoxiclav) which resolved on withdrawal (this patient subsequently tolerated 100 days of alternate therapy Doxycyline/Rifampacin without success). One patient withdrew consent. One patient on doxycycline alone and 2 on Doxycycline/Rifampacin combination failed due to adverse effects. 22 patients have therefore completed treatment.

ITT Population	33
Evaluable (ITT/E)	30 (90.9%)
Treatment Completers	22 (73.3%)

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Incomplete: TEAE: Rash 1, GI 3, Non-specific 3	7 (23.3%)
Incomplete W/D consent	1 (3.3%)
Co-Amoxiclav 625mg 2 tid	25
Doxycycline 100mg BD	2
Doxycycline 100mg/Rifampacin600mg BD	9

Table 2. The treatment disposition of 36 patients prescribed MAST treatment (TEAE: treatment emergent adverse events).

Results.

Data collected were equivalent to the variables recorded in previous MAST studies. Including: RMDQ (Roland-Morris Disability Questionaire), Back pain average Now, worst in the last 14 days and average voer the last 14 days. Leg pain as per back pain. The number of days ion the last 28 days with pain and the hours per day with pain, excluding sleep and assuming there are maximum 16 waking hours/day. Data on work and absence and analgesic use were requested but were not reliably reported by patients.

The results of this prospective observational study are shown below in tables 3 and 4. 10% of patients did not comply with prescription, one took a second opinion and withdrew. Of those who commenced, 23% (approximately) failed to complete due to adverse effects. Of those who completed the course of treatment (completers) 16% failed to respond and 9% show only moderate responses while 41% are graded excellent (>75% improved on patient global improvement VAS) and 20% are good (>50%). Detailed responses were available from 29 cases. Average RMDQ fell from 14.7 to 8.4 (42.8%), Back pain, now, worst and average from 5.2, 8, 5.5 to 3.1, 5.2, 3.4 (39.7%, 34.8%, 37.5%) respectively. Leg Pain Now, worst and average reduced from 1.4, 2.6, 2.1 to 0.4,1.8,0.3 respectively. Average hours with pain and hours/day with pain reduced from 27.0 and 20.9 to 13.7 and 7.9. Of these, reductions in RMDQ, worst and average back pain in last 14 days, average leg pain intensity and average hours/day with pain were statistically significant with the others non-significant in small numbers tested. A numerical trend to reduction was observed in all reported parameters (table 4).

Statistical analysis.

These data are on relatively small numbers with 17 patients for whom detailed data were available. In a small number paired data were missing so conservative assumptions have been made. For example 2 patients whose global assessment was "failed" did not have initial back pain scores and so were assigned the same original as the recorded final score. Only 6 patients recorded leg pain. 4 of these reduced under treatment (2,5,5,6 to 0,0,0,0) but results were not significant in small numbers. In each measurement, there was a tendency to numerical reduction with variable statistical significance. 2-tailed Mann-Whitney U test was used throughout with no correction for repeated testing..

Results	ITT/E (N=30)	Completers (N=22)
Incomplete	8(23.3%)	22 (72.7%)
Failed	5 (16.7%)	22.7%

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Excellent (>75%)	9 (30%)	40.9%
Good (>50%)	6(20%)	27.3%
Moderate(>25%)	2(6.7%)	9.1%

Table 3. Results expressed as response quartiles for the ITT/E (ITT/evaluable) and completer population were Excellent = >75% on the patient rated global perceived benefit scale, Good = >50%, Moderate, >25% and failed = less than 25%. 1 patient worsened under treatment and was excluded from analysis

	Baseline	Post MAST	% reduction
RMDQ	14.7	8.4	42.8% (P<0.023)
Back Pain			
Back Pain Intensity Now	5.2	3.1	39.7% (NS)
Worst Intensity in last 14 days	8.0	5.2	34.8% (P<0.012)
Average Intensity in last 14 days	5.5	3.4	37.5% (P<0.027
Leg Pain			
Leg Pain Intensity Now	1.4	0.4	73.4% (NS)
Worst Intensity in last 14 days	2.6	1.3	52.6% (NS)
Average Intensity in last 14 days	2.1	0.8	64.9% (P<0.021)
Number of Days in 28 with Pain	27.0	13.7	49.2% (NS)
Average Hours with pain in day	20.9	7.9	62.5% (P< 0.013)
Patient Perceived Global Improvement			56.5%

Table 4 Results. Baseline and post therapy response parameters collected from Privately treated patients and 1 NHS case who completed treatment (n = 17).

Discussion.

The Possibility that low grade infection with skin or oral anaerobic commensals contributes to the development of Modic change and concomitant pain is raised by the studies described and by the promising results of Albert and colleagues showing open label and controlled responses to MAST therapy with Co-Amoxiclav in extended courses of 90 or 100 days. [17,18] The case presented here is typical of the index cases described by Albert et al with post discectomy progression of type 1 Modic change, a positive culture for *Propionobacter* species and an excellent response to adapted MAST therapy. This probably represents the optimal case for selection for MAST therapy.

Only 4 of the cases reported here were post surgical and the responses seen here support the hypothesis that patients with non surgically-related MRBP could share the same potential pathological mechanisms of bacteraemic ingress during phases of disc neovascularisation after disc injury.

Albert's cases showed dominant Modic type 1 change and this is probably the optimal clinical setting. However, Modic changes are a spectrum and Dr Albert and colleagues do not exclude Type 2 from treatment. (H Albert, personal communication). The cases treated here showed mixed radiographic patterns and extent of Modic change in the context of significant persistent back pain and many appear to respond in an equivalent fashion to the index cases described by Albert and colleagues. However, response rated reported here are somewhat lower than Albert et al and this presumably reflects less stringent selection criteria. Real life retention rates are also much lower than the 93%

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trial retention reportd by Albert [18]: of 33 evaluable prescriptions there were only 22 fully completed treatments (72.7%) due to non-compliance and side effects.

The kinetics of clinical response to MAST therapy are unusual in that symptoms often do not change till approximately 80 days of treatment then rapidly reduce (Dr Albert, personal communication). Anecdotally, this was the pattern observed here with Co-Amoxiclav treatment. However, with the doxycycline/Rifampacin variant for Penicillin allergic cases, responses appear to be seen much earlier. There is no data on the minimum possible treatment duration. Variant regimens for Penicillin allergic patients are not evidence based.

In the Albert trial [18], 2 doses of Co-Amoxiclav were used. 625mg TID and 625mg 2 tabs (total 1250mg) TID. The study was not powered to show a difference and there were no statistical differences between the 2 groups. However, there was a strong trend to numerical superiority in the higher dose group and around 80 versus 60% of patients in the higher group responded. I have therefore chosen to use the higher dose regime but it would be acceptable to use the lower dose or mix the 2 doses.

There is no A-priori way of judging whether the Modic mechanism is relevant to any individual patient. However, there are certain features of the patient's history which seem recognisable. The pain is often severe, never remits, lacks mechanical features of resolution on sitting or lying and usually persists as a throbbing discomfort overnight, intruding sleep rather than simply disturbing it when the patient moves. The phenomenon of exercise intolerance with prolonged exacerbation on any over-exertion (pay back) is pronounced. When associated with "significant" degrees of Modic changes, as judged empirically on inspection of the current MRI, the author has felt it justified to consider MAST treatment as an option. Particularly, since, in the author's opinion, there is very little alternative therapy including complex or sequential interventions or surgery which would be a credible or preferable alternative.

However, the potential adverse effects of prolonged antibiotic treatment are not trivial. Diarrhoea due to altered bowel flora is to be expected in the first few weeks and can be reduced by daily dosing of live yoghurts and OTC travellers diarrhoea remedies. Ongoing non-specific GI discomforts are common. Skin rash is a common problem with Penicillins. Treatment should be withdrawn but can be restarted at very low, incremental doses. In this series one patient suffered a significant vasculitic type purpuric rash, with no systemic effects and treatment was withdrawn. She subsequently tolerated 100 days Doxycycline and Rifampacin without benefit. Thrush occurs or recurs in those prone or with previous history and responds to the usual treatments but can mandate withdrawal. The feared complication is *C. Difficile* colitis. Patients should be warned that a change in bowel habit with blood, mucous, pus, fever or pain mandates withdrawal and immediate medical attention. In this study, 22% of those who commenced antibiotics failed to complete the course because of side effects, mainly GI related but one case of a self-limiting leucocytoclastic type rash was also seen. Since this study was concluded the author has seen 2 patients with significant reactions attributed to Rifampicin with systemic reaction, palpitations, nausea and diarrhoea, bot self limiting without sequel but suggesting that a smaller dose of 600mg OD should be employed.

For these reasons and issues with antibiotic overuse, there is considerable public health concern about the indiscriminate use of antibiotics in a common condition such as back pain and of course this practice is not encouraged here. Many specialists may consider

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it too early to adopt MAST therapy till such issues have been fully resolved and this is a respected attitude. However, the considered prescription in carefully selected cases under specialist supervision, when other options have been assessed, tried or out-ruled may at this point none-the-less be justified for the individual in view of the high levels of disability, suffering and the societal costs associated with this condition.

In summary, in this open label prospective study, patients so treated reduced disability by 40%, spent approximately half as much time in pain, their pain was 40-60% (back and leg respectively) less severe, and on average considered themselves almost 60% improved. 63% of patients who could complete treatment were considered excellent or good. Less potentially toxic regimes and further research are needed.

Keywords: Modic Change, Modic antibiotic spinal therapy, MAST,

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