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Amoxicillin did not reduce Modic change oedema in patients with chronic low back pain - subgroup analyses of a randomised trial (the AIM study)

Running head: Amoxicillin and Modic change oedema.

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ABSTRACT

Study Design: Exploratory subgroup analyses of a randomised trial (Antibiotics In Modic changes (AIM) study).

Objective: To assess the effect of amoxicillin versus placebo in reducing Modic change (MC) oedema in patients with chronic low back pain (LBP).

Summary of Background Data: The AIM study showed a small, clinically insignificant effect of amoxicillin on pain-related disability in patients with chronic LBP and MC type 1 (oedema type) on magnetic resonance imaging (MRI).

Methods: A total of 180 patients were randomised to receive 100 days of amoxicillin or placebo. MC oedema was assessed on MRI at baseline and one-year follow-up. Per-protocol analyses were conducted in subgroups with MC oedema on short tau inversion recovery (STIR) or T1/T2-weighted MRI at baseline. MC oedema reductions (yes/no) in STIR and T1/T2-series were analysed separately. The effect of amoxicillin in reducing MC oedema was analysed using logistic regression adjusted for prior disc surgery. To assess the effect of amoxicillin versus placebo within the group with the most abundant MC oedema on STIR at baseline (‘STIR3’ group), we added age, STIR3 (yes/no), and STIR3×treatment group

(interaction term) as independent variables and compared the marginal means (probabilities of oedema reduction).

Results: Compared to placebo, amoxicillin did not reduce MC oedema on STIR (volume/intensity) in the total sample with oedema on STIR at baseline (odds ratio 1.0, 95% confidence interval (95%CI) [0.5, 2.0]; n=141) or within the STIR3 group (probability of oedema reduction 0.69, 95%CI [0.47, 0.92] with amoxicillin and 0.61, 95%CI [0.43, 0.80] with placebo; n=41). Compared with placebo, amoxicillin did not reduce MC oedema in T1/T2-series (volume of the type 1 part of MCs) (odds ratio 1.0, 95%CI [0.5, 2.3], n=104). Oedema declined in >50% of patients in both treatment groups.

Conclusions: From baseline to one-year follow-up, amoxicillin did not reduce MC oedema compared with placebo.

Level of evidence: Level 2.

Key points

- Previously, the AIM study showed a small, clinically insignificant effect of amoxicillin on pain-related disability in patients with chronic LBP and MC type 1 (oedema type).
- In the present analyses of AIM-data, amoxicillin did not reduce MC oedema on STIR or T1/T2-series compared to placebo from baseline to one-year follow-up.
- MC oedema declined in >50% of patients in both treatment groups.

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Keywords: Magnetic Resonance Imaging, Spine, Low Back Pain, Amoxicillin, Prospective Studies, Modic Changes, Infection, Oedema, Randomised Controlled Trial, STIR

Abbreviations

AIM=Antibiotics In Modic changes, 95%CI=95% confidence interval, LBP=low back pain, MC=Modic change, MC1=Modic change type 1, MC2=Modic change type 2, MRI=magnetic resonance imaging, OR=odds ratio, RMDQ=Roland-Morris Disability Questionnaire, STIR=short tau inversion recovery, T1/T2=T1- and T2-weighted fast spin echo images.

INTRODUCTION

Modic changes (MCs) are magnetic resonance imaging (MRI) findings of signal changes in the vertebral bone marrow extending from the endplate. They are defined as type 1 (oedema type, MC1), type 2 (fatty type, MC2), and type 3 (sclerotic type) based on T1- and T2-weighted MRI[1,2]. Evidence for a relationship between MCs and low back pain (LBP) is diverging[3-7]. It has been proposed that MCs may be caused by endplate damage and a persistent inflammatory stimulus from an autoimmune response against intervertebral disc material and/or an occult infectious discitis[8]. One theory is that MCs may develop from a low-grade infection in a previously disrupted neo-vascularized lumbar disc[9,10]. Cutibacterium acnes is stated to be the most likely agent and the main target for treatment[10-13]. However, this theory is disputed[14-16].

A Danish trial reported effect of 100 days' treatment with amoxicillin and clavulanic acid on clinical outcomes and MC volume in patients with chronic LBP and MC1[17]. The Antibiotics In Modic changes (AIM) study[18] found a much smaller, not clinically important effect of 100 days amoxicillin on pain-related disability (-2.3 points on the 0-24 Roland-Morris Disability Questionnaire, RMDQ) in patients with chronic LBP and MC1, and no effect in the MC2 group[19]. A subsequent subgroup analysis suggested a larger effect of amoxicillin (-5.1 RMDQ points) in a small group with abundant MC oedema at baseline ("STIR3" group, defined below), assessed using short tau inversion recovery (STIR) images, but the 95% confidence interval (95%CI) for the effect estimate was wide ([-8.2, -1.9]), and there was no effect on LBP[20].

These findings in patients with MC oedema on T1/T2 images (MC1) or on STIR make it relevant to clarify whether amoxicillin reduces MC oedema, since the effect on MC1 reported

in the Danish trial needs replication, and MC oedema affected the effect of amoxicillin on disability in the AIM study. Oedema is an essential part of inflammatory and infectious responses, and increased sensitivity to oedema can make such processes easier to identify. STIR is more sensitive to oedema than the T1/T2-series without fat suppression and can also show oedema in MC2[21,22]. The AIM-study cohort underwent lumbar spine MRI with non-fat-suppressed T1/T2 images and STIR both at baseline and at one-year follow-up. Here, we describe MRI findings at one year in each treatment group (amoxicillin or placebo). The main purpose of this exploratory analysis of AIM data was to assess the effect of amoxicillin versus placebo in reducing MC oedema in patients with chronic LBP.

MATERIALS AND METHODS

The AIM study included 180 patients from six hospital outpatient clinics in Norway from 2015 to 2017[18,19]. This report concerns MRI findings at one year for all patients with one-year MRI (n=172) and reductions in MC oedema in three subgroups (defined below) with MC oedema at baseline (n=141, n=41, and n=104). The inclusion criteria for AIM were age 18-65 years, LBP for more than six months with an intensity of at least 5 (mean score on three 0-10 numerical rating scales), lumbar disc herniation on MRI in the preceding two years, and MC1 or MC2 (with height ≥10% of the vertebral body height and diameter >5 mm) at the previously herniated disc level. A prior disc herniation was required also in the Danish trial, based on a theory that the neovascularisation associated with disc herniation allows hematogenous bacterial contamination of the disc. All eligibility criteria are listed in Table A1 in the Supplemental file, Supplemental Digital Content 1, http://links.lww.com/BRS/B937. Trial flow chart, trial methods, and baseline characteristics are published[18]. The AIM trial, this present study, and the statistical analysis plans are registered at ClinicalTrials.gov (identifier: NCT02323412). All patients provided written informed consent prior to inclusion.

Summary of trial methods

Patients were randomised to receive oral amoxicillin 750 mg or placebo (maize starch) three times daily for 100 days. Amoxicillin in this dosage was used to re-assess the findings in the Danish trial, which used 500 mg or 1000 mg amoxicillin (plus clavulanic acid) three times daily for 100 days. The tablets had identical encapsulation, containers, and labelling. A third-party statistician created randomisation lists using Stata 13 (StataCorp, Texas, USA). Allocation was stratified by prior disc surgery (yes/no) and MC type (any MC1 (n=118) or MC2 only (n=62)) at the previously herniated disc level(s), with a 1:1:1:1 allocation and random block sizes of four and six[19]. The allocation sequence was concealed and centrally administered. All care providers, research staff, statisticians, and patients were blinded to the treatment allocation during data collection.

MRI assessment

Baseline and one-year MRI of the lumbar spine were performed at six centres using identical protocols on the same type of 1.5-T scanner (Magnetom Avanto B19 or Avanto fit E11 (used for 16 one-year MRIs), Siemens Healthineers, Erlangen, Germany). All MRIs included sagittal T1- and T2-weighted fast spin-echo ('T1/T2') and sagittal STIR images. The MRI parameters were identical between centres[23]. The integrated spine array coil was used, and no surface coils. Echo time (ms)/repetition time (ms) was 11/575 for T1, 87/3700 for T2, and 70/5530 for STIR. Echo train length was 5 for T1, 17 for T2 and 20 for STIR. Matrix was 384×269 for T1/T2 and 320×224 for STIR. Inversion time for STIR was 160 ms. Slice thickness/spacing was 4 mm/0.4 mm and field of view was 300 mm × 300 mm for all three sequences.

Three radiologists blinded to clinical outcomes and treatment allocation independently evaluated MRI findings[23]. All had >10 years of experience in musculoskeletal MRI. The same three radiologists interpreted all baseline and one-year MRIs from all study centres. They scored changes in MRI findings by comparing one-year and baseline image slices from the same anatomical location side-by-side.

The present study

This study focused on MRI findings at the index level(s) only, that is, the level(s) with prior disc herniation and MC1 or MC2 at baseline, since this level was hypothesised to contain low-grade discitis that was the target for the treatment. All MRI variables were predefined and described in detail in the statistical analysis plan after the radiologists had performed a pilot study (n=8) to determine MRI evaluation criteria and align their evaluations. Pilot study patients were not included in the present study.

The following definitions were used:

- MCs on T1/T2: signal changes in the vertebral bone marrow that extend from the endplate but are not separated from the endplate, are not round-shaped and abutting the endplate with a smaller base than height (more likely focal fatty marrow or haemangiomas), and do not extend through the endplate (Schmorl's nodes).
- MC oedema on STIR: a high STIR signal compared to normal vertebral body marrow, located in or abutting a region with MC on T1/T2 and/or shaped as an MC [25].
- MC oedema on T1/T2: the type 1 part of any MC, defined by low signal on T1 and high signal on T2. Borderline type 1 vs type 2 MCs with high T2 signal but near isointense T1 signal were defined as type 2.

The following categorical variables were visually rated across all index-level endplates at the one-year follow-up.

STIR variables:

- 1ySTIRvol change: change in volume of high STIR signal (smaller, unchanged, larger)
- 1ySTIR change: change in STIR signal volume/intensity combined (decreased, unchanged, increased)
- Largest 1y STIR volume: score for largest volume of high STIR signal (0=0%, 1= <10%, 2=10%–<25%, 3=25-50%, 4= >50% of vertebral body marrow volume)

T1/T2 variables:

- 1yMC1vol change: change in the volume of the type 1 part of MCs (smaller, unchanged, larger)
- 1yMCvol change: change in total MC volume (any MC type) (smaller, unchanged, larger)
- Largest 1y MC volume: score for largest volume of MC (scored 0-4 as for STIR volume)

At each index-level endplate, a change on STIR or T1/T2 (e.g., 'smaller') was noted if it was present on ≥2 slices and on ≥2 more slices than any opposite change (e.g., 'larger'). In each patient, a variable was rated as 'unchanged' if unchanged at all index level endplates, 'smaller' if smaller at ≥1 endplate and larger at 0 endplates, and 'larger' if larger at ≥1 endplate and smaller at 0 endplates. If different endplates showed opposite changes, a change in the patient was reported if it outweighed any opposite change on ≥2 slices. Conclusive MRI findings were based on the three radiologists' majority or median rating. Fig. 1 shows MRI examples of reduced MC oedema.

Baseline data used here were previously reported[20]: largest STIR volume (largest volume of high STIR signal, scored 0-4 as above), largest MC volume (scored 1-4; 0 impossible at baseline), and STIR 1/2/3, a categorical composite variable based on oedema abundance on STIR. STIR3 was noted if the high STIR signal (MC oedema) fulfilled all the following criteria: volume ≥25% and height >50% of the vertebral body, maximum intensity increase ≥25% (0%, normal vertebral body marrow; 100%, cerebrospinal fluid), and presence on both sides of the disc. STIR1 and STIR2 implied less severe high signals. At baseline, the interrater agreement (mean Fleiss' kappa across L4-S1) was 0.88, 0.81, and 0.86, for the presence of any MC/ MC1/ high STIR signal, 0.69 for MC volume score, and 0.56 for STIR volume score[23,24].

Predefined exploratory hypotheses

Our research hypothesis was that amoxicillin is superior to placebo in reducing MC oedema from baseline to one-year follow-up on STIR (1ySTIR change) and T1/T2 (1yMC1vol change). The statistical null hypothesis was that amoxicillin does not differ from placebo in reducing MC oedema. The statistical two-sided alternative hypothesis was that amoxicillin differs (any direction) from placebo in reducing MC oedema.

Analyses

We report the frequency of one-year MRI findings in all 172 patients with a one-year MRI scan. The treatment effects of amoxicillin on MC oedema were analysed in subsamples of the per-protocol population (patients completing the trial without major protocol deviations). See the flowchart in Fig. 2 and details in the Supplemental file, Supplemental Digital Content 1, http://links.lww.com/BRS/B937.

In a sample with MC oedema on STIR at baseline (n=141), logistic regression was performed with 1ySTIR change (dichotomised into decreased or not) as dependent variable. The independent variables were treatment group (amoxicillin or placebo=reference group) and prior disc surgery (yes/no). To assess the effect of amoxicillin within the STIR3 group (n=41), we added age, STIR3 (yes/no), and STIR3×treatment group (interaction term) as independent variables and compared marginal means (probabilities of 'decreased' 1ySTIR change) between amoxicillin and placebo within the STIR3 group.

In the sample with MC oedema on T1/T2 at baseline (n=104), logistic regression was performed with 1yMC1vol change (dichotomised into smaller or not) as dependent variable. The independent variables were treatment group (amoxicillin or placebo=reference group) and prior disc surgery (yes/no).

The analyses were explorative, and the significance level was set at 0.05 (two-sided). Missing values were replaced with imputed values from a multiple-imputation model (Supplemental file, Table A2, Supplemental Digital Content 1, http://links.lww.com/BRS/B937). Inter-observer agreement was analysed using Cohen's kappa coefficient. All analyses were predefined in the statistical analysis plan (available at ClinicalTrials.gov). Analyses and imputations were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the AIM cohort (n=180) are shown in Table A3 in the Supplemental file, Supplemental Digital Content 1, http://links.lww.com/BRS/B937. One-year MRI findings were generally similar in both treatment arms (n=172) (Table 1).

Compared with placebo, amoxicillin did not reduce MC oedema on STIR in patients with MC oedema on STIR at baseline (n=141) (odds ratio (OR) 1.0, 95%CI [0.5, 2.0]) or in the STIR3 group (n=41). Based on marginal means, the probability of 'decreased' 1ySTIR change (reduced oedema) in the STIR3 group was 0.69 (95%CI [0.47, 0.92]) with amoxicillin and 0.61 (95%CI [0.43, 0.80]) with placebo (OR 1.4; p=0.50 for interaction between STIR3 and treatment group). In both treatment groups, >50% of the patients had reduced oedema at one year, both in the total STIR sample (Table 2) and in the STIR3 group (Table 3).

Compared to placebo, amoxicillin did not reduce the volume of the type 1 part of MCs on T1/T2 (1yMC1vol change) in the sample with MC1 at baseline (n=104) (OR 1.0, 95%CI [0.5, 2.3]). At one year, the type 1 part of MCs was smaller in >50% of patients in both treatment groups (Table 4).

Mean Cohens' kappa for the MRI change variables ranged from 0.68 to 0.74, Table A4 in the Supplemental file, Supplemental Digital Content 1, http://links.lww.com/BRS/B937. Including also non-index levels when assessing the effect of amoxicillin in reducing MC oedema would not have changed the results in the analysed samples. Oedema reductions (yes or no) differed between all levels and the index level(s) in only 3 of the 141 patients on STIR and none of the 104 patients on T1/T2.

DISCUSSION

From baseline to one-year follow-up, amoxicillin did not reduce MC oedema compared to placebo, neither on STIR nor on T1/T2-series. Oedema declined in >50% of patients regardless of treatment, which is in line with earlier observations that MC1 in many cases gradually transforms into MC2[25,26].

Our findings contrast with the Danish MC1 trial[17], which reported effect on MC volume at one-year follow-up (n=144): "A significant decrease in volume was observed in the antibiotic group, where changes of volume 2–4 were reduced to volume 1 (p=0.05). This reduction was not observed in the placebo group." The number of patients with volume reduction was not given. At one year, 10 patients in both treatment arms had no MCs[17]. It is not clear why the results differed between the two trials. Most patients (>80%) had MC volume 2–4 at baseline in both studies, using the same volume scoring system. It was not reported in the Danish trial whether one-year and baseline images were evaluated separately or compared to ascertain reliable assessment of changes in MRI findings[27].

It is possible that one-year of follow-up is too short to detect an effect of antibiotic treatment on MC oedema caused by a low-grade disc infection. There is a lack of trials evaluating the effects of antibiotics on bone oedema in patients with verified low-grade bacterial disc infections. Bone oedema due to infectious spondylodiscitis may persist and even increase during the first 1-4 months after treatment initiation[28-32]. The oedema may persist for years, but usually subsides within 4-9 months[33-35]. In a study by Zarrouk et al[35], oedema persisted in 75% of patients at 3 months and 15% at 6 months. Euba et al[33] found bone oedema in 70% of patients at a median of six months after the end of treatment. These studies[28-34] involved patients referred by clinicians for follow-up MRI. Those not referred (68-84% in two samples)[30,33] may have been less likely to have persistent oedema. If the MC oedema in our cohort was due to a vertebral disc infection, and amoxicillin treatment was effective, we would expect to find less oedema in the amoxicillin-treated group than in the placebo group at one-year follow-up.

Strengths and limitations

The strengths of this study include the use of identical MRI protocols in all centres at baseline and at one-year follow-up. Three experienced musculoskeletal radiologists evaluated changes in MC oedema, and their inter-rater agreement was good. Treatment allocation was stratified by MC type, strengthening the results in the MC1 group (n=104). There was little missing data. Only 4% (8/180) lacked a one-year MRI scan.

An important limitation is the use of per-protocol analyses to assess treatment effects. This increases the risk of bias compared with the use of the intention-to-treat population. However, we found it relevant to focus on the actual effect of amoxicillin, not the effect of randomisation to amoxicillin. The STIR samples were defined after all the participants were enrolled, which also implies a risk of bias. In the small STIR3 subsample (n=41), the estimates had wide 95%CIs, reflecting low statistical power. Our results were restricted to patients with prior lumbar disc herniation. We used previously unvalidated categorical MRI oedema change variables that were visually rated. We did not use measurements because measuring volume and intensity by hand-drawing regions of interest on all relevant image slices would have been very time-consuming. Automated computer-based techniques are being developed but were not available to us.

We may have missed differences in oedema reduction by classifying oedema as reduced or not, and not by degree of reduction. However, it seems unlikely to observe no difference in the frequency of oedema reduction if the degree of reduction clearly differs. If amoxicillin influences MC oedema, it is also unlikely to observe similar frequencies of increased MC oedema between the treatment groups (Tables 2-4).

Finally, since amoxicillin did not reduce MC oedema, we did not assess whether reduced MC oedema mediated any effect of amoxicillin on clinical outcomes. The relationship between reduced MC oedema and clinical outcomes, regardless of treatment group, will be reported in a separate paper.

Interpretation and implications

The present results support the previous clinical results of the AIM study, which did not show clinically important effects of amoxicillin compared to placebo[19,36]. Interestingly, our results do not suggest a biological effect of amoxicillin on MC oedema in the small subgroup with the most abundant oedema at baseline[20]. We cannot exclude the possibility that MC oedema may require a longer time to decline in response to amoxicillin treatment in low-grade infectious discitis. However, based on relevant prior research, it is unlikely to see no effect of amoxicillin on MC oedema at one-year follow-up, if the oedema is due to a disc infection and amoxicillin is an effective treatment for the infection. Previous studies have not reported any anti-inflammatory effect of amoxicillin[37,38]. The current and previous results from the AIM study do not support the use of antibiotic treatment for chronic LBP with MCs.

Conclusion

In patients with MCs and chronic LBP, amoxicillin did not reduce MC oedema compared with placebo.

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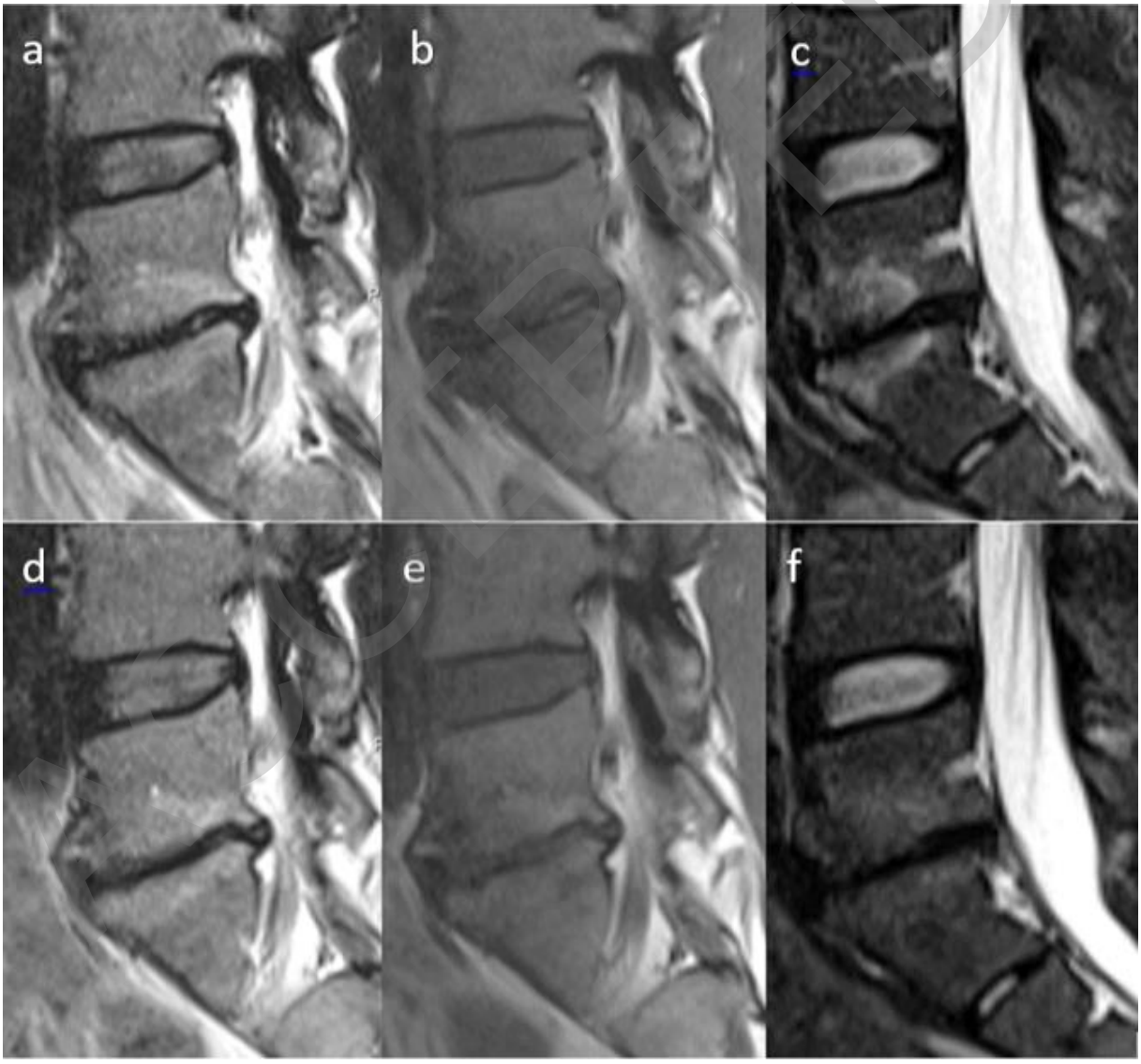
Fig. 1 – Examples of reduced MC oedema

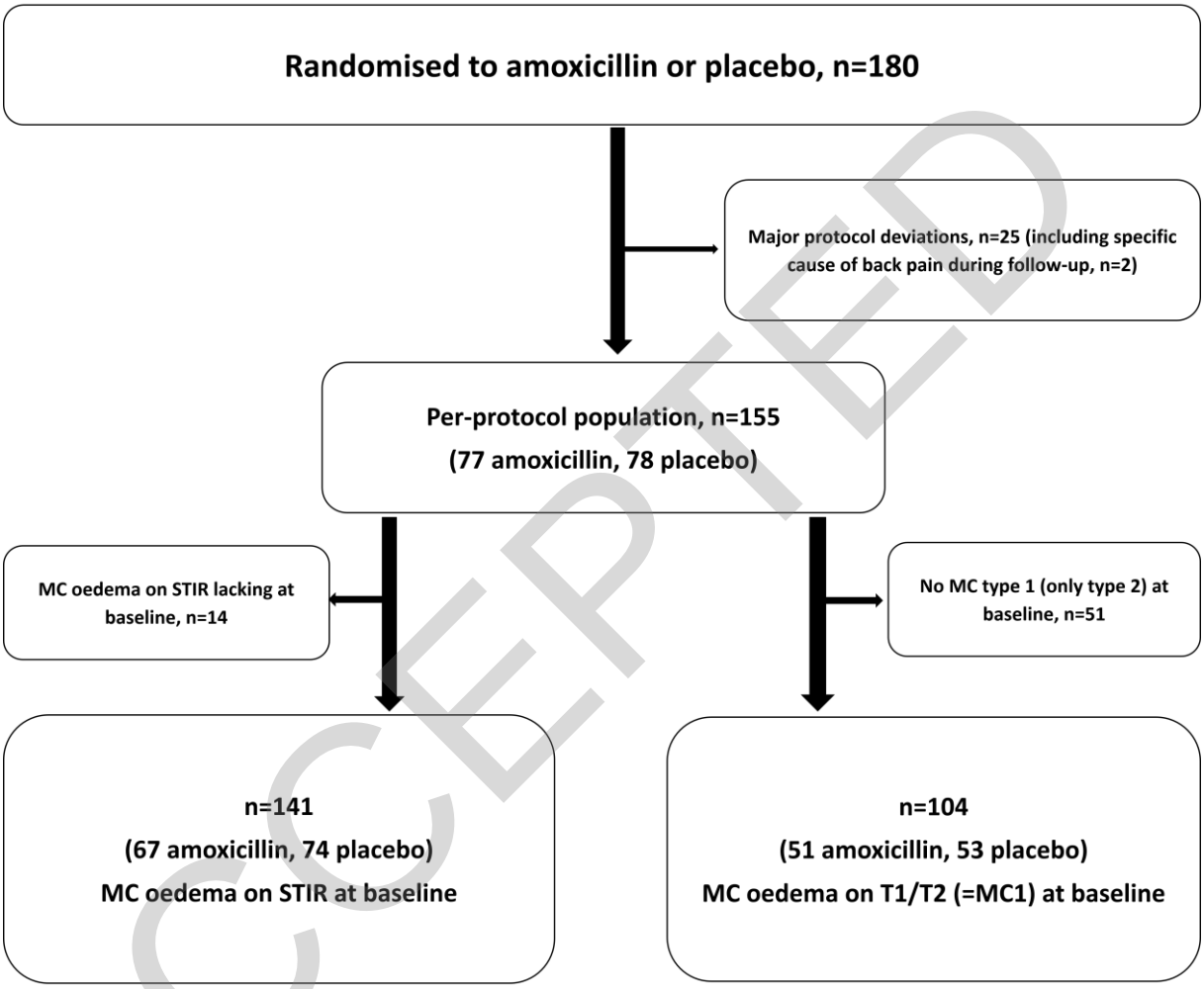
(a-f) Example of MC oedema at L5/S1. Baseline MRI shows MC oedema with high T2 signal (a), low T1 signal (b) (i.e. MC1), and high signal on STIR (c). One-year MRI shows unchanged T2 signal (d) and higher signal with some hyperintense areas on T1 (e) (i.e. smaller area of the type 1 part of the MC) and reduced area and intensity of high signal on STIR (i.e. decreased MC oedema on STIR).



MC=Modic change. STIR=short tau inversion recovery. MC1=MC type 1. T1/T2=T1- and T2-weighted fast spin-echo images.

Fig. 2 - Definition of study samples

MC=Modic change. STIR=short tau inversion recovery. MC1=MC type 1. T1/T2=T1- and T2-weighted fast spin-echo images.



Amoxicillin did not reduce Modic change oedema in patients with chronic low back pain - subgroup analyses of a randomised trial (the AIM study)

Table 1 – One-year MRI findings in the total cohort by treatment group				
	Amoxicillin group* (N = 83)		Placebo group* (N = 89)	
Variable	n	%	n	%
1ySTIR change – change in MC related STIR signal (intensity and volume combined) from baseline to one year				
decreased	37	45%	42	47%
unchanged, STIR signal at one year and baseline	19	23%	25	28%
unchanged, no STIR signal at one year or baseline	10	12%	4	4%
increased	17	20%	18	20%
1ySTIRvol change – change in volume of MC related STIR signal from baseline to one year				
smaller	32	39%	39	44%
unchanged, STIR signal at one year and baseline	23	28%	28	31%
unchanged, no STIR signal at one year or baseline	10	12%	4	4%
larger	18	22%	18	20%
Largest 1y STIR volume – highest score at an index level endplate (% of vertebral body marrow volume)				
0 (0%)	10	12%	10	11%
1 (<10%)	29	35%	41	46%
2 (<25%)	31	37%	17	19%

3 (25-50%)	11	13%	17	19%
4 (>50%)	2	2%	4	4%
Change in score for largest STIR volume from baseline to one year				
lower	24	29%	27	30%
unchanged, STIR signal at one year and baseline	43	52%	50	56%
unchanged, no STIR signal at one year or baseline	10	12%	4	4%
higher	6	7%	8	9%
1yMC1vol change – change in the volume of the type 1 part of MCs from baseline to one year				
smaller	30	36%	34	38%
unchanged, MC type 1 at one year and baseline	13	16%	15	17%
unchanged, no MC type 1 at one year or baseline	24	29%	25	28%
larger	16	19%	15	17%
1yMCvol change – change in total MC volume (any MC type) from baseline to one year				
smaller	1	1%	0	0%
unchanged	62	75%	65	73%
larger	20	24%	24	27%
Largest 1y MC volume – highest score at an index level endplate (% of vertebral body marrow volume)				
0 (0%)	0	0%	0	0%
1 (<10%)	13	16%	15	17%

2 (<25%)	34	41%	31	35%
3 (25-50%)	28	34%	29	33%
4 (>50%)	8	10%	14	16%

MRI, magnetic resonance imaging. STIR, short tau inversion recovery. MC, Modic change.

*One-year MRI is lacking for 6 of 89 patients in the amoxicillin group and 2 of 91 patients in the placebo group.

Table 2 – Change in MC oedema on STIR in sample with oedema on STIR at baseline

	Amoxicillin group, N = 65*		Placebo group, N = 74	
1ySTIR change	n	%	n	%
Decreased	34	52.3	39	52.7
Unchanged	18	27.7	19	25.7
Increased	13	20.0	16	21.6

STIR=short tau inversion recovery. MC=Modic change. 1ySTIR change=change in MC oedema on STIR from baseline to one year based on volume/intensity of high signal.

*One-year MRI is lacking for 2 of 67 patients.

Table 3 – Change in MC oedema on STIR in STIR3 sample with abundant baseline oedema

	Amoxicillin group, N = 20		Placebo group, N = 21	
1ySTIR change	n	%	n	%
Decreased	14	70.0	12	57.1
Unchanged	4	20.0	6	28.6
Increased	2	10.0	3	14.3

STIR=short tau inversion recovery. MC=Modic change. 1ySTIR change=change in MC oedema on STIR from baseline to one year based on volume/intensity of high signal.

Table 4 – Change in MC oedema on T1/T2 in sample with oedema (MC1) at baseline				
	Amoxicillin group, N = 49*		Placebo group, N = 53	
1yMC1vol change	n	%	n	%
Smaller	28	57.1	31	58.5
Unchanged	13	26.5	14	26.4
Larger	8	16.3	8	15.1

MC=Modic change. MC1=MC type 1. 1yMC1vol change=change in volume of the type 1 part of MCs on T1/T2-weighted fast spin-echo images from baseline to one year.

*One-year MRI is lacking for 2 of 51 patients.