MATTERS ARISING

Staphylococcal septic arthritis in rabbits

The article by Wysenbeek *et al*¹ provides intriguing insights to the 15 day rabbit *Staphylococcus epidermidis* infectious arthritis model. However, challenge must be made to their conclusion that injection of corticosteroids into the infected joint seems to be harmless, in the setting of infectious arthritis.

Several issues render this model unacceptable for establishing safety of intra-articular corticosteroids in the setting of infectious arthritis. *Staphylococcus epidermidis* has low infectivity and pathogenicity compared with most articular pathogens.^{2,4} If you were to consider use of intra-articular corticosteroids as rendering the patient equivalent to the immunosuppressed patient, reduction of synovitis and proteoglycan depletion might be of interest. Of course, use of corticosteroids might change the use of the injected joint, assessment of which probably would require additional controls.

The real question seems to be what happens to the joint after antibiotic (and intra-articular corticosteroid) treatment. Analysis two weeks, two months, and six months post-treatment would seem important to identify clinically important effects of intra-articular corticosteroids.

One technical question seems appropriate. How were the section sites selected? The blinding does not seem to have taken place until after the slides were prepared. More detail on the selection process might provide insights as to whether "prime sites" were selected or if the same exact cuts were made in all knees.

The study by Wysenbeek *et al*¹ provides insights to effect of short-term intra-articular corticosteroids on a low pathogenicity/low infectivity form of infectious arthritis. It is unclear if their conclusion about corticosteroid safety can be extrapolated to organisms of high infectivity/pathogenicity and to clinically significant impact.

BRUCE M ROTHSCILD
Arthritis Center of Northeast Ohio,
5500 Market Street, Youngstown,
Ohio 44512, USA

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Table 1 LMP2/CfoI genotypic distribution in B27 positive controls and ankylosing spondylitis patients with and without acute anterior uveitis stratified by HLA-DR4

Subjects	LMP2/Cfo I Genotypes		
	AA	AB	BB
Total B27+ Controls	4 (7.4%)	25 (46.3%)	25 (46.3%)
Total B27+ AAU/AS	1 (1.2%)	24 (70.9%)	61 (70.9%)
B27+ DR4+ Controls	2 (8.7%)	11 (47.8%)	10 (43.5%)*
B27+ DR4+ AAU/AS	0	13 (30.2%)	30 (69.8%)*
B27+ DR4- AAU/AS	1 (23.3%)	11 (25.6%)	31 (72.1%)

*p<0.05 (LMP2 AA and AB versus LMP2 BB).

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Authors' reply

We thank Dr Rothschild for his remarks.

The importance of *Staphylococcus epidermidis* in joint infections is in infected prosthetic joints, where *S epidermidis* is more common than *S aureus*.^{1,2} We hypothesised that as a first step, it might be advisable to start the study with not the most virulent bacteria. As stated in the article, we believed that the lower virulence of *S epidermidis* might give us a better observation of corticosteroid effect. Further research should investigate additional bacterial strains.

Our study was for 15 days. We agree, and stated in our paper, that future studies should investigate long term effect of this treatment.

All joints of the various study groups were cut and prepared identically.

A J WYSENBECK
Department of Internal Medicine B, Assaf
Harofeh Medical Centre, Zerifin 70300, Israel

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LMP2 polymorphisms and spondyloarthropathies

Dr Hohler and colleagues¹ have examined LMP2 polymorphisms and extraspinous manifestations in spondyloarthropathies arriving at the conclusion that there is no independent association between LMP2 genotypes and the occurrence of uveitis in HLA-B27 positive subjects when stratified for HLA DR. In my view, this study lacks sufficient power to decide this question definitively. Careful analysis of DR4 positive subjects from the data provided in table 1 of their report shows that 81.25% of patients with acute anterior uveitis carry the LMP2 BB genotype compared with 62.5% of B27 positive controls and 61.5% of spondyloarthropathy patients with axial disease only. This suggests that LMP2 may contribute independently of DR4 to the development of uveitis, though small numbers of DR4 positive patients and controls (eight B27 positive controls, 16 spondyloarthropathy patients with acute anterior uveitis and 26 patients with axial disease only) do not permit statistically significant conclusions. Table 1 summarises our current data and includes larger numbers

permitting significant conclusions. Thirty of 43 B27 positive DR4 positive ankylosing spondylitis patients with acute anterior uveitis (69.9%) carry the LMP2 BB genotype compared with 10 of 23 B27 positive DR4 positive healthy controls (43.5%) (p<0.05). Furthermore, the prevalence of the LMP2 BB genotype is almost identical in acute anterior uveitis patients whether they carry DR4 or not. There are some other points of concern in the study by Hohler and colleagues. Only 27.3% of patients were recorded as having had an episode of uveitis, which seems rather low when compared with that noted in other much larger white populations,² suggesting that some, as yet unaffected, may later develop acute anterior uveitis. This ascertainment error will vary from study to study. It may be more realistic to compare polymorphisms in people who have already manifest a particular phenotype with an HLA matched control group, rather than with diseased people who have not yet developed that particular phenotype. The authors also cite certain references purported to support the view that DR 4 and LMP2 B are in linkage disequilibrium.^{3,4} The first was based on work in consanguineous homozygous typing cells suggesting linkage disequilibrium between alleles of HLA-DQ, TAP2 and LMP7 rather than a population-based study. No formal evidence for linkage disequilibrium between HLA-DR4 and LMP2 B was presented.³ In contrast, two population-based studies have shown no evidence for linkage disequilibrium between LMP2 alleles and HLA DR4.^{4,5} This is consistent with our own findings in a white population of 282 people where linkage disequilibrium was only noted between LMP2 A and HLA DR3 confirming previous observations.^{4,5} Finally, Hohler *et al* do not actually provide any data to support linkage disequilibrium between DR4 and LMP2 B from their own population. In contrast, our work reinforces the requirement for large population-based studies in view of the necessity for HLA stratification of implicated HLA encoded polymorphisms, particularly in the context of disease phenotypes, if important associations are not to be missed.

WALTER P MAKSYMOWYCH
Rheumatology/Clinical Immunology, 562
Heritage Medical Research Centre, University of
Alberta, Edmonton, Alberta, Canada T6G 2S2

- 1 Hohler T, Schaper T, Schneider PM, Krumme-nauer F, Rittner C, Meyer zum Buschenfelde KH, *et al*. No primary association between LMP2 polymorphisms and extraspinous manifestations in spondyloarthropathies. *Ann Rheum Dis* 1997;56:741-43.
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Author's reply

Thank you for giving me the opportunity to respond to the letter concerning our paper on LMP2 polymorphisms in patients with ankylosing spondylitis. We agree with the author of the letter that it would be desirable to compare patients that have already manifest a certain disease phenotype (for example, uveitis, peripheral arthritis), however we query the age limit they would suggest. The average age in our study was 47 years, well beyond the 41.5 years, which was the average age in the Maksymowych study.¹ The author fails to provide any epidemiological data on his study population. Acute anterior uveitis was observed only in 27.3% of our patients compared with 45.1% in the Maksymowych

study,² which may be attributable to ethnic heterogeneity (particularly in Canada), different MHC haplotypes or other still unknown genetic factors in the different populations.

The study by Van Endert was indeed based on work in homozygous typing cell lines, but the authors also cite unpublished own data showing linkage between DR4 and LMP2 in a population of 140 subjects.

Concerning the data provided in the table 1 I think that the numbers are small and the difference in the LMP2 distribution between B27+ DR4+ controls and B27+ DR4+ acute anterior uveitis/ankylosing spondylitis patients just reaches statistical significance before correction for multiple comparisons, which should be done. Unfortunately the

given data do not provide any new evidence but just reinforce, as the author states in the last sentence, the requirement for large population-based studies.

T HÖHLER

Langenbeckstr 1, D-55101 Mainz, Germany

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