Small intestinal bacterial overgrowth in patients with rheumatoid arthritis

I read with interest the paper by Henriksson et al, in which the authors demonstrated an altered character in the small bowel's bacterial flora in patients with rheumatoid arthritis. However, the authors did not demonstrate the presence of bacterial overgrowth. The syndrome of bacterial overgrowth is characterised by diarrhoea, with malabsorption. The mechanism by which the bacterial overgrowth causes symptoms is not known. These symptoms are related to an increase in the luminal bacterial flora and the presence of obligate anaerobes (colonial luminal flora) as judged by jejunal fluid culture or breath tests. The patients in the study did not have any evidence of malabsorption or diarrhoea.

The investigations used, apart from the bile acid deconjugation test, had not been previously validated in patients with bacterial overgrowth. Quantitative bacterial culture was not done; the bacterial flora was of oral type, not colonic. The presence of enterobacteriaceae (a facultative anaerobe), tryptic activity, gas production (both not specific to obligate anaerobes) and the use of jejunal biopsy culture (biopsies culture produces different flora than fluid culture) are not proven features of bacterial overgrowth of the small bowel. The controls used did not have the syndrome of bacterial overgrowth as they were not given antibiotics, which associated with an altered and increased bacterial flora, does not necessarily cause symptomatic bacterial overgrowth. Thus only the three patients with positive bile acid deconjugation test could be considered to have investigational evidence of bacterial overgrowth. In view of previously reported changes seen in the small bowel's bacterial flora of elderly and infirm people, perhaps the findings were not surprising considering the multi-system involvement of rheumatoid arthritis. To confirm their hypothesis that disease activity is due to and not causing the bacterial flora changes, the authors could have studied the influence of either proton pump inhibitors or antibiotics on disease activity.

We feel that two concepts bacterial overgrowth and bacterial overgrowth syndrome are sometimes confused. We used the concept bacterial overgrowth to designate an altered microflora in the upper small intestine in patients with RA, and the criteria were clearly stated in the article. The bacterial overgrowth syndrome, also known as blind loop or stagnant infection, is characterised by steatorrhoea and other signs of malabsorption. We agree that our patients with RA did not have the bacterial overgrowth syndrome.

Dr Lewis, however, seems to presume that only an altered small intestinal microflora complicated by the bacterial overgrowth syndrome is of interest in patients with RA. This view has to be questioned as we still do not know what types or quantities of microbes demonstrated in the upper small intestine are of interest in these patients.

The aim of our study was not to describe a bacterial overgrowth syndrome in patients with RA, but rather to denote an altered small intestinal microflora. A combination of techniques was preferred to get a comprehensive picture of small intestinal microflora, as it has been shown that different tests may be necessary to detect bacterial overgrowth in the upper small intestine. It has been suggested that a qualitative change may be more important than a quantitative change. We used the growth of Enterobacteriaceae (Escherichia coli or Klebsiella) without counting the microorganisms as one of the criteria of bacterial overgrowth. These species originate from the colon and not from the oral microflora. The clinical significance of our findings is still uncertain. The RA patients with signs of bacterial overgrowth had significantly higher rheumatic disease activity, as well as rheumatoid factor titre. Dr Lewis's suggestion that the changes in the small bowel bacterial flora may be secondary to multi-system involvement of RA certainly cannot be excluded. As for his comments that treatment with proton pump inhibitors or antibiotics would confirm our hypothesis, it should be noted that the small intestinal bacterial overgrowth in these patients was not only related to lack of gastric acid and that we know very little about the types of microorganisms involved; severe flare ups after treatment with antibiotics have been observed in patients with RA, possibly by changing the intestinal microflora in the 'wrong' direction.

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AUTHORS' REPLY: We appreciate the remarks made by Dr S J Lewis about the small bowel microflora in patients with rheumatoid arthritis (RA) and would like to give the following comments.

Relapsing polychondritis as a secondary phenomenon of primary systemic vasculitis

Papo et al recently reported that in 33 patients with relapsing polychondritis (RP) (three women, four men). The diagnosis of RP was either made histologically or according to the diagnostic criteria established by McAdam et al. In six patients, RP presented as a secondary phenomenon during an acute phase of a primary vasculitic entity. Autoantibody screening revealed cANCA (PR3 ANCA +) in two patients, pANCA in one patient and autoantibodies to native collagen type II in four. According to classification-criteria of ANCA-associated vasculitides, 26,849 and 649-56. Thus we conclude that the presence of ANCA in RP, may instead indicate, that polychondritis occurs in the context of a primary systemic vasculitis (PSV), for example, WG.

We have seen such an association of PSV with polychondritis in six of seven patients with RP (three women, four men). The diagnosis of RP was either made histologically or according to the diagnostic criteria established by McAdam et al. In six patients, RP presented as a secondary phenomenon during an acute phase of a primary vasculitic entity. Autoantibody screening revealed cANCA (PR3 ANCA +) in two patients, pANCA in one patient and autoantibodies to native collagen type II in four. According to classification-criteria of ANCA-associated vasculitides, 26,849 and 649-56. Thus we conclude that the presence of ANCA in RP, may instead indicate, that polychondritis occurs in the context of a primary systemic vasculitis (PSV), for example, WG.

We think that polychondritis can be diagnosed more often as a secondary phenomenon in PSV than has previously been recognised. The diagnosis of PSV has been considerably improved by the detection of ANCA and the establishment of ACR-Classification-Criteria for Polymyalgia Rheumatica and Giant Cell Arteritis, 26,849 and 649-56. Thus we conclude that the presence of ANCA in RP, may instead indicate, that polychondritis occurs in the context of a primary systemic vasculitis (PSV), for example, WG.

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4 Henriksson A E K. Unpublished observations.

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Table

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Extended ELK-Classification (Nölle et al. 1989): B = constitutional symptoms, E = ENT, Ey = eye, H = heart, (K) = kidney (non dialysis dependent), N = nervous system, W = Wegener’s granulomatosis, mPA = microscopic polyangiitis, cPAN = classic panarteritis nodosa, RP = relapsing polychondritis


Authors’ Reply: In their series of seven patients with relapsing polychondritis (RP), Handrock and Gross could detect ANCA in six patients, two with Wegener’s granulomatosis (WG), three with microscopic polyangiitis and one with classical polyarteritis nodosa. They conclude that the presence of ANCA in RP indicates that polychondritis occurs as a secondary event of a primary systemic vasculitis.

Our experience is very different. Among our eight ANCA-positive RP patients, we have only had vasculitis. Among these three, Wegener’s granulomatosis (WG), three with microscopic polyangiitis and one with classical polyarteritis nodosa. They conclude that the presence of ANCA in RP indicates that polychondritis occurs as a secondary event of a primary systemic vasculitis.

Nevertheless, we agree with these authors that chondritis can probably occur as an epiphenomenon on the background of definite inflammatory disorders. This is true not only for primary systemic vasculitides, but also for systemic lupus erythematosus, but possibly for rheumatic diseases, and even for Wegener’s granulomatosis.1,7,4,5 In definite circumstances, cartilage involvement frequently differs from the particular features of RP, regarding the usual sparing of the respiratory tree and the lack of a relapsing/remitting course of disease. But histo-pathological and immunological data on auricular chondritis is rare.

A clear-cut categorisation of patients with vasculitis manifestations and chondritis seems impossible. Definitions of RP, WG and microscopic polyangiitis and episcleritis, can remain purely descriptive of clinical symptoms and pathological data that sometimes overlap, in the absence of a comprehensive view of their pathophysiology and aetiology. Recent studies on ANCA have provided new and promising insights into the processes involved, but their application to diagnosis is mainly restricted to the close association of WG with ANCA-positive anti-proteinase 3, which were constantly negative in our patients with RP.1 Computer-derived criteria for the classification of vasculitides, such as those developed by the American College of Rheumatology, are the result of large studies but not particularly relevant for individual patients, especially in the discussion of overlaps between diseases sharing many manifestations. For example, a patient with a typical history of WG, including arthritis and episcleritis, can be classified as RP if auricular chondritis occurs, according to the empirical criteria used by Michet.1

Finally, some practical conclusions can be drawn. In most cases RP is a primary disease, even in the presence of vascular manifestations. It should not be considered or treated as a vasculitis on the sole basis of ANCA positivity. Moreover, some rare cases patients share manifestations of RP and WG. Due to the poor response of WG to steroids alone, first-line regimes used in such patients with RP/WG overlap should probably include additional cyclophosphamide.1

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Ann Rheum Dis 1993 52: 895-897
doi: 10.1136/ard.52.12.895-c

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