Reactive arthritis, a missing link: comment on the recent article from Sepriano *et al*

The recent paper from Sepriano *et al* provides an extremely important new insight on the concept of axial spondyloarthritis (axSpA).[1] Clearly, the *Gestalt* of axSpA is heterogeneous, with three recognisable clinical entities labelled as: 'pure axial SpA', 'axial SpA with peripheral signs' and 'axial SpA at risk'. The finding given in the paper suggests a larger overlap between axSpA and pSpA than anticipated at the time when the Assessment of SpondyloArthritis international Society (ASAS) criteria were developed. Thus, the question arises as to how accurately the three recognisable clinical entities of the ASAS classification criteria represent the diseases entities originally lumped together in the historical concept of SpA.

The unifying historical concept of SpA lumps together an interrelated yet heterogeneous group of disorders which includes ankylosing spondylitis (AS), psoriatic arthritis, arthropathy of inflammatory bowel diseases (ulcerative colitis and Crohn's disease), reactive arthritis (ReA), undifferentiated SpA and juvenile SpA.[2] ReA is characterised by preceding infections of the urogenital, gastrointestinal and respiratory tract, and these are best explored for *Chlamydia trachomatis* and *Chlamydia pneumoniae* infections for the joint and spine manifestations.[3] Preceding infection of urethritis/cervicitis or diarrhoea within 1 month prior to the onset of arthritis/enthesitis/dactylitis is included in the ASAS criteria for peripheral SpA but not in those for axial SpA. Baseline patient characteristics and the final latent class analysis models in the SPondyloArthritis Caught Early (SPACE) and DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR) cohorts do not mention preceding infections.[1] Thus, the latent class and transition analyses neglect infections, although ReA typically manifests with peripheral arthritis as well as enthesitis, tendinitis, bursitis and inflammatory low back pain.[4] Moreover, remitting and chronic ReA may evolve into sacroiliitis in 14%–49%, and into AS in 12%–26% of patients, depending on the triggering infection; a minority of patients even manifest radiological sacroiliitis during the first known attack or arthritis (compare ref 5). Importantly, the causative infections are often asymptomatic or mild, or they may precede the arthritis by several years. Therefore, these silent infections may not appear in medical history and are only discovered by targeted investigation, such as has been demonstrated, for example, for *C. trachomatis* and *C. pneumoniae* (compare ref 6).

Diseases are defined and categorised in a variety of ways: by the symptoms with which they present (syndromic), their underlying causes (aetiological), the biological mechanisms involved (pathogenic), available treatments, historical precedent and through diagnostic exclusion.[7] Understanding gut microbiota–host genetic relationships may contribute to clarification of the pathogenesis of postinfectious SpA and pave the way from symptomatic to aetiological classification.[8] Of note, in the study from a geographic region with a high prevalence of ReA (Guatemala), prospectively included adult subjects with preceding infections developing arthritis classified as pSpA, and control subjects not developing arthritis, both had radiographic sacroiliitis in 56% and 50% of individuals, respectively; thus the postinfectious pSpA would presumably meet the *Gestalt* of 'axial SpA with peripheral signs'.[8]

In conclusion, in recent years the ASAS classification criteria for axial SpA have provided an important contribution to education, research and clinical trials addressing earlier diagnosis, outcome measurements and new treatments for axial SpA. Nonetheless, future classification sets which specify relevant infectious triggers should be useful in advancing classification and related treatment studies, thus giving increased validity also for geographic regions outside Europe which display a higher prevalence of ReA.

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Contributors HZ wrote the first draft of the manuscript. HZ and APH reviewed the draft version and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Zeidler H, Hudson AP. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-217326

Received 12 March 2020
Accepted 14 March 2020

Ann Rheum Dis 2020;**0**:1. doi:10.1136/annrheumdis-2020-217326

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