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The high prevalence of infections and allergic symptoms in patients with ankylosing spondylitis is associated with clinical symptoms

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Abstract Ankylosing spondylitis (AS) is strongly associated with the major histocompatibility complex (MHC) class I antigen HLA-B27. This may have influence on the physiologic immune response. Whether it leads to an increased prevalence of infections and/or allergy in AS patients is unclear. This study aims to determine the prevalence of infections and allergic symptoms in patients with AS and to detect a possible association with clinical symptoms. Data on 1,080 AS patients and on 102 disc prolapse patients were collected by questionnaire. The proportion of patients with a symptomatic infection in the last year was 65.5% in AS patients in comparison with 25.5% in disc prolapse patients ($p=0.0001$). AS patients reported more gastrointestinal (GI) [odds ratio (OR) 5.07, 95% confidence interval (CI) 2.20–11.71], urinary tract (OR 2.81, 95%CI 1.41–5.72), and respiratory (OR 5.83, 95%CI 3.38–10.08) infections than did disc prolapse patients. Multiple infections were more common in AS patients across all infection types. Allergic symptoms were reported by AS patients more frequently than by disc prolapse patients (OR 5.13, 95%CI 3.49–8.80). Patients reporting concurrent inflammatory bowel disease were more likely to report GI (OR 3.0, 95%CI 1.9–4.8) and urinary tract (OR 1.7, 95%CI 1–2.8) infection than primary AS patients. In AS patients, infection was independently

associated with female gender (OR 1.96, 95%CI 1.47–2.56), a history of significant peripheral joint inflammation (OR 1.55, 95%CI 1.18–2.05), and increasing pain duration ($p=0.05$). A high prevalence of common infections and allergic symptoms is seen in patients with AS, most of which are HLA-B27-positive. This may have implications both for underlying mechanisms of disease and for therapeutic options.

Keywords Allergy · Ankylosing spondylitis · Infection

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by inflammatory back pain due to sacroiliitis and spondylitis and by the formation of syndesmophytes leading to ankylosis. The prevalence of AS differs between populations [1, 2]. Northern European Caucasian populations are estimated to have an AS prevalence of 0.9% [3]. There is a strong association between AS and HLA-B27, with up to 90% of AS patients being B27-positive [4, 5]. The prevalence depends to a large part on the differing HLA-B27 frequencies in the populations. HLA-B27 is a member of the major histocompatibility complex (MHC) class I group of molecules, which have a physiologic role in the presentation of bacterial and self peptides to T lymphocytes and the induction of protective immune responses. There has been much debate on the functional role of HLA-B27 in the pathogenesis and immune system in AS [6, 7]. HLA-B27 positivity has been associated with altered bacterial invasion and survival in vitro [8–10] and with impairment of the Th1 cytokine response in peripheral blood [11]. However, a definitive mechanism for impaired Th1 responses in the SpA has not been described, and the functional consequences of the described phenomena are unclear [12]. It also needs to be taken into account that signs and symptoms of SpA are frequently associated with rather established 'Th1 diseases' such as Crohn's disease [13] and psoriasis [14, 15].

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Twin studies have shown that AS is associated with hyporesponsiveness to common bacterial antigens independent of HLA-B27 status [16]. Recognizing the association of both AS and HLA-B27 positivity with abnormal T cell responses, it is possible that AS might also be associated with an increased risk of common community-acquired infections. In a blood donor study, we have reported for the first time an increased incidence of infections in patients with AS [3]. It has also been suggested that atopy is increased in AS patients by means of an impaired Th1 cytokine pattern [17], although the population was not statistically different to healthy controls. This large population-based study aims to describe the incidence of common bacterial infections in AS.

Patients and methods

A questionnaire containing 30 diverse questions was published in the newsletters of the German Ankylosing Spondylitis Society (Deutsche Vereinigung Morbus Bechterew, DVMB) and the Austrian Ankylosing Spondylitis Society (Österreichische Vereinigung Morbus Bechterew, ÖVMB) in 2000. It was distributed to all of the 14,127 and 1,077 patient members of these societies, respectively. The primary aim of this retrospective survey was to gather information about potential disease triggers and the use of nonsteroidal antiinflammatory drugs (NSAIDs) in AS, but it has also provided the opportunity to investigate the incidence of common infections in AS patients. Information on diagnosis, disease onset, HLA-B27 status, and recent history of gastrointestinal (GI), respiratory, or urinary tract infections and of allergic symptoms was collected. Patients were also questioned on the current use of NSAIDs, the incidence of infections, physical trauma, and psychological stresses prior to disease onset, masking any specific study objective to reduce responder bias. The questionnaire was pretested by asking participants of a large DVMB meeting to fill it in. All misunderstandings or missing options detectable from the collected answers were corrected for the final version of the questionnaire. Self-report of respiratory infections has been previously shown as a valid method of data collection [18], although similar studies in other infective diseases are lacking. Baseline characteristics of the cohort and the wording of parts of the questionnaire have been published previously [19]; the complete questionnaire is given in the [Appendix](#) (translated from German).

Included in the survey sample were all patients who gave their primary diagnosis as AS, with or without any other associated conditions. Patients who did not indicate that their diagnosis was arrived at or confirmed by a physician were excluded from the survey.

A control group of 102 consecutive patients presenting to a rehabilitation outpatients' clinic with chronic back pain secondary to intervertebral disc prolapse (DP) was recruited. All patients had the diagnosis of DP confirmed by

a physician and by radiological investigation. The control patients were given the same questionnaire used in the AS mail-out to fill out without assistance.

The significance of percentage differences was determined by the χ^2 test for two-by-two tables. Where average values or standard deviations of age indications were compared, the significance was tested by the *t* test, or, where appropriate, the *F* test. Logistic regression analysis was carried out using a backwards method, controlling for all variables significantly related to outcomes in univariate analyses. Statistical analyses were performed using SPSS for Windows version 11.0.

Results

Patient characteristics

There were 1,044 respondents to our publication in Germany and 67 in Austria. Of these, 1,089 (98%) indicated that they have been diagnosed as having AS. Among these 1,089 patients, 9 were excluded because they did not state that their diagnosis was arrived at or confirmed by a physician. The remaining 1,080 patients were included in the study. The mean age of the cohort was 49.8 years, range 21–82 years, 64% of respondents were men and 74% reported primary AS [without concurrent psoriasis, inflammatory bowel disease (IBD), or reactive arthritis (ReA)]. These parameters were not significantly different to those of a previous DVMB membership survey [20–22], conducted by personal mail-out to a 20% sample of the DVMB membership population, with a response rate of 54% after one reminder.

The DP control group were significantly younger than the AS cohort (40.9 ± 12.1 years compared with 49.8 ± 10.2 years, mean difference 8.9 years, $p < 0.0001$) and were less likely to know their HLA-B27 status ($p < 0.0001$). There was a similar proportion of men in both groups (62.7% men in the DP group compared with 63.4% men in the AS cohort, $p > 0.05$). Controls were older at disease onset (33.7 ± 9.6 years compared with 25.4 ± 8.6 years in AS patients, $p < 0.0001$). Seventy-nine percent ($n=853$) of AS patients knew they were HLA-B27-positive, and a further 12.5% ($n=135$) were unaware of their HLA-B27 status.

The reported use of NSAIDs was not significantly different between AS and DP patients, with 843 (78.1%) of AS patients reporting NSAID use in the year leading up to administration of the questionnaire compared with 75 (73.5%) of the DP group ($\chi^2=1.10$, $p=0.18$).

Cumulative prevalence of infections and allergies in ankylosing spondylitis

Patients with AS reported more recent infections and allergies than did control subjects (Table 1) across all infection types reported and for both allergic rhinitis and

Table 1 Cumulative prevalence of self-reported infections and allergic symptoms (N,%) in the previous 12 months^a

	Ankylosing spondylitis	Disc prolapse	P value	Odds ratio (95% CI)
N	1,080	102		
Any recent infection	707 (65.5%)	26 (25.5%)	<0.0001*	5.54 (3.49–8.80)*
GI (diarrhea) ^a	213 (21.7%)	5 (5.0%)	<0.0001*	5.32 (2.14–13.24)*
Urinary (dysuria or discharge)	233 (21.6%)	9 (8.8%)	0.002*	2.84 (1.41–5.72)*
Respiratory (upper or lower tract)	562 (52.0%)	16 (15.7%)	<0.0001*	5.83 (3.38–10.08)*
Any recent allergic symptoms	409 (37.9%)	11 (10.8%)	<0.0001*	5.13 (2.71–9.70)*
Allergic rhinitis	223 (20.6%)	8 (7.8%)	0.002*	3.06 (1.46–6.39)*
Asthma	61 (5.6%)	1 (1.0%)	0.043	6.05 (0.83–44.07)
Skin rash	220 (27.5%)	4 (3.9%)	<0.0001*	6.27 (2.28–17.22)*

*Statistically significant, $p < 0.01$

^aGI infection in the previous 4 weeks; patients with IBD excluded

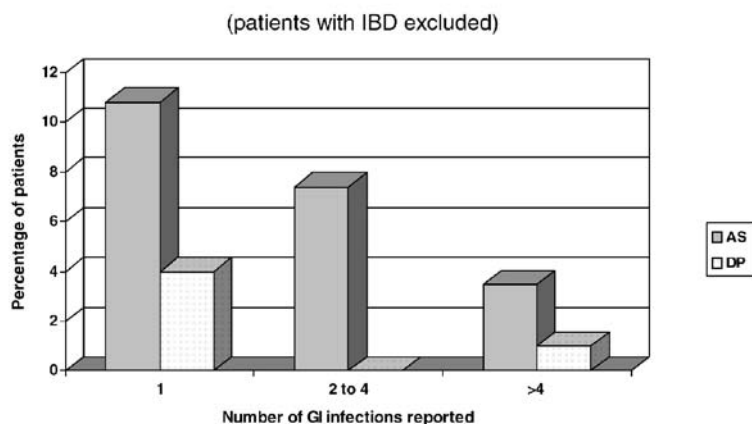
allergic skin rash. Patients reporting concomitant IBD (98 with AS and 1 with DP) were not included in the analysis of GI infection due to the difficulty separating infective from inflammatory diarrhea. Respiratory allergies, described as asthma on the questionnaire, were not con-

sidered to reach statistical significance when a Bonferroni correction for multiple testing was used.

The distribution of the number of reported GI and urinary tract infections is shown in Fig. 1. A similar distribution was seen for respiratory infection, with 28.2%

Fig. 1 Distribution of infections in AS and DP patients. **a** GI (AS $N=982$, DP $N=101$) in the preceding 4 weeks (patients with IBD excluded). **b** Urinary tract (AS $N=1,080$, DP $N=102$) in the preceding 12 months

a Gastrointestinal (AS, $N=982$ and DP, $N=101$) in the preceding 4 weeks



b Urinary tract (AS, $N=1080$ and DP, $N=102$) in the preceding 12 months

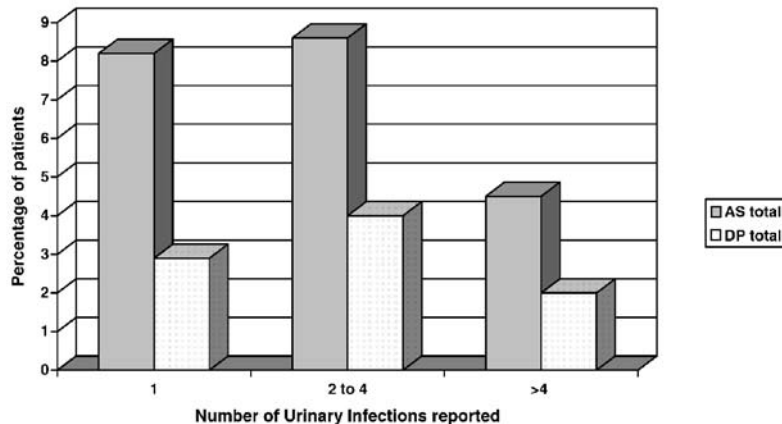
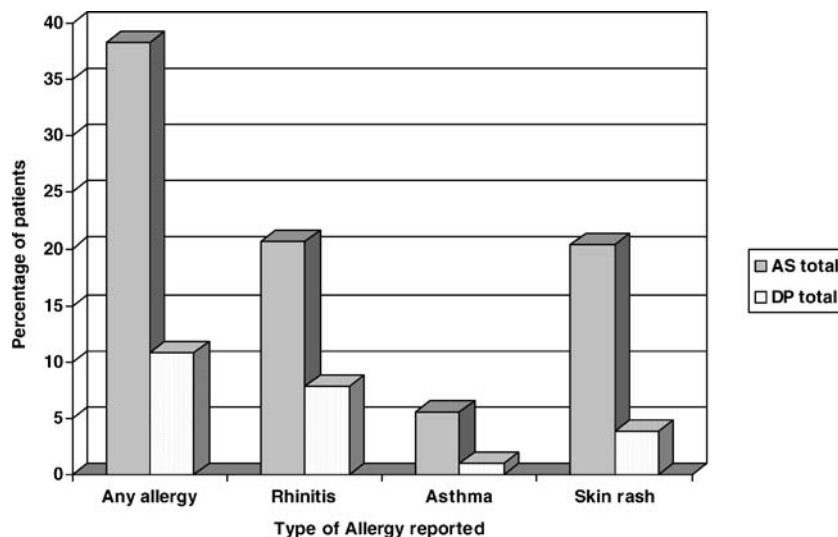


Fig. 2 Percentage of *AS* ($N=1,080$) and *DP* ($N=102$) patients reporting allergic symptoms in the preceding 12 months



of AS respondents reporting two to four events and 8.2% reporting more than four, compared with 5.9 and 2.0% of DP patients, respectively. Multiple infections over the specified period of time were not uncommon, and AS patients were more likely to report multiple infections than controls for all subgroups of infection [GI in the previous 4 weeks, odds ratio (OR) 7.63, 95%confidence interval (CI) 1.86–31.27; more than one urinary tract infection in the previous 12 months, or 2.40, 95%CI 1.03–5.59; and more than one respiratory infection in the previous 12 months, or 6.7, 95%CI 3.23–13.98]. Figure 2 shows the distribution of reported allergies in AS and DP patients.

Factors associated with infection and allergy in ankylosing spondylitis

Women were almost twice as likely to report infection than men (OR 2.09, 95%CI 1.56–5.05), and women were more

likely to report allergic symptoms than men (OR 1.63, 95% CI 1.26–2.10). This gender difference in reporting was not seen in DP patients (for infection $\chi^2=2.43$, $p=0.2$, and for allergic symptoms $\chi^2=0.004$, $p=0.95$). Patients reporting any infection preceding the study were 1.6 years (95%CI 0.04–3.1 years) younger than those without infection ($p=0.04$). Those AS patients reporting GI infection in the past 4 weeks were 2.2 years younger than those who did not (95%CI 0.5–3.9, $p=0.01$), but other infection types and reporting of multiple infections were not significantly related to age ($p>0.06$). There was no significant difference in disease duration between those with infection and those without ($p=0.63$) or between AS patients reporting multiple infections and those who did not (all $p>0.2$). Allergic symptoms were not associated with age ($p=0.39$) or disease duration ($p=0.15$) in AS patients.

AS patients reporting infections also reported having significantly more hours of pain each day than those not reporting infection ($\chi^2=21.62$, $p=0.001$; shown in Fig. 3).

Fig. 3 Hours of pain experienced over the past 4 weeks in *AS* patients with recent infection, compared to those without infection

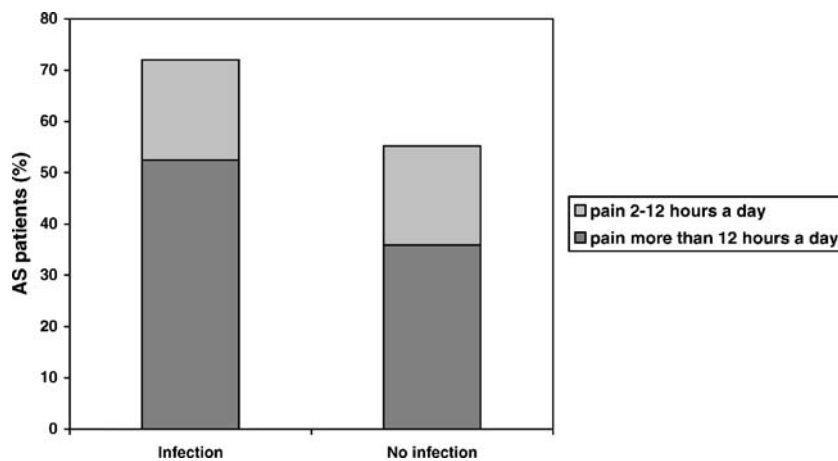


Table 2 Odds ratios for infections and allergies in primary ($N=810$) and secondary ($N=243$) ankylosing spondylitis patients compared to disc prolapse patients ($N=98$)

		<i>N</i> (%)	OR (95%CI)	<i>P</i>
Any infection	Disc prolapse	23 (23.5%)	–	–
	AS (primary)	529 (65.3%)	6.1 (3.8–10.0)	<0.0001
	AS with psoriasis	74 (62.2%)	5.4 (3.0–9.7)	<0.0001
	AS with ReA	30 (71.4%)	8.2 (3.6–18.4)	<0.0001
	AS with IBD	55 (67.1%)	6.6 (3.4–12.8)	<0.0001
GI infection	Disc prolapse	4 (4.1%)	–	–
	AS (primary)	168 (20.7%)	6.2 (2.2–17.0)	<0.0001
	AS with psoriasis	28 (23.5%)	7.2 (2.4–21.4)	<0.0001
	AS with ReA	13 (31.0%)	10.5 (3.2–34.8)	<0.0001
	AS with IBD	36 (43.9%)	18.4 (6.2–54.8)	<0.0001
Urinary tract infection	Disc prolapse	8 (8.2%)	–	–
	AS (primary)	165 (20.4%)	2.9 (1.4–6.1)	0.004
	AS with psoriasis	21 (17.6%)	2.4 (1.0–5.7)	0.04
	AS with ReA	13 (31.0%)	5.0 (1.9–13.4)	0.0005
	AS with IBD	25 (30.5%)	4.9 (2.1–11.7)	0.0001
Respiratory infection	Disc prolapse	16 (16.3%)	–	–
	AS (primary)	417 (51.5%)	5.4 (3.1–9.5)	<0.0001
	AS with psoriasis	66 (55.5%)	6.4 (3.3–12.2)	<0.0001
	AS with ReA	21 (50.0%)	5.1 (2.3–11.5)	<0.0001
	AS with IBD	42 (51.2%)	5.4 (2.7–10.7)	<0.0001
Any allergic symptoms	Disc prolapse	10 (10.2%)	–	–
	AS (primary)	288 (35.6%)	4.9 (2.5–9.6)	<0.0001
	AS with psoriasis	53 (44.5%)	7.2 (3.4–15.2)	<0.0001
	AS with ReA	21 (50.0%)	8.8 (3.6–21.4)	<0.0001
	AS with IBD	31 (37.8%)	5.6 (2.5–12.3)	<0.0001

ReA reactive arthritis, *IBD* inflammatory bowel disease, *AS* ankylosing spondylitis, *OR* odds ratio

A similar relationship is seen in patients reporting allergic symptoms ($\chi^2=19.15$, $p=0.002$). Both groups also reported more days of pain each year (in patients with infection $\chi^2=14.64$, $p=0.006$, and in patients with allergic symptoms $\chi^2=14.93$, $p=0.005$). The same relationship was seen in AS patients reporting multiple infections compared with those reporting one or no infections. Patients with DP did not show this association, with no significant effect of infection or allergic symptoms on pain reporting (all $p>0.1$).

A history of joint inflammation lasting at least a month was significantly associated with an increased risk of infection (OR 1.71, 95%CI 1.31–2.21) and of allergic symptoms (OR 1.58, 95%CI 1.20–2.05, $p<0.0001$). A history of iritis was slightly less common in patients reporting recent infection (28% vs 32%), but this did not reach statistical significance (OR 0.83, 95%CI 0.63–1.08, $p=0.19$). Iritis was not associated with allergic symptoms (OR 0.99, 95%CI 0.77–1.28, $p=0.95$).

Two hundred and forty-three AS patients also reported common conditions that can be associated with secondary AS. There were 119 patients reporting psoriasis, 42 reporting ReA, and 82 reporting IBD. An additional 27 patients

reported more than one coexistent condition; these individuals were not included in the subgroup analyses. The higher incidence of infection and allergic symptoms in AS patients was seen across all subgroups of AS, independent of whether the disease was ‘primary’ or ‘secondary’, as shown in Table 2. Patients reporting concomitant IBD were more likely to report GI infection than primary AS patients (OR 3.0, 95%CI 1.9–4.8), over 50% more likely to report urinary tract infection than primary AS patients (OR 1.7, 95%CI 1–2.8), and four times as likely to report more than one episode of diarrhea in the previous 4 weeks, but other secondary AS subgroups were not statistically different from primary AS (all $p>0.1$). The cumulative prevalence of allergic symptoms was not statistically different between primary and secondary AS (all $p>0.06$).

Independent predictors of infections and allergic symptoms in AS are shown in Table 3 and include being female, peripheral joint inflammation, and a higher amount of reported daily pain. Diarrhea and urethritis were independently associated with secondary AS. Gender and amount of daily pain were also independently associated with multiple GI or urinary tract infections.

Table 3 Independent predictors of infection and allergic symptoms in patients with ankylosing spondylitis

		β	SE	Wald	<i>p</i>	OR (95%CI)
Any infection ($R^2=0.07$)	Constant	1.26	0.15	71.60	<0.0001	
	Gender (male)	-0.67	0.15	21.36	<0.0001	0.51 (0.39–0.68)
	Pain			10.89	0.054	
	Joint inflammation	0.44	0.14	9.61	0.002	1.55 (1.18–2.05)
GI infection ($R^2=0.11$)	Constant	0.76	0.43	3.15	0.076	
	Age	-0.02	0.01	10.56	0.001	0.98 (0.97–0.99)
	Comorbidity			25.28	<0.0001	
	Pain			22.96	<0.0001	
More than one GI infection ($R^2=0.11$)	Joint inflammation	0.57	0.18	10.51	0.001	1.77 (1.25–2.50)
	Constant	0.01	0.29	0.04	0.85	
	Gender (male)	-0.49	0.20	5.87	0.02	0.61 (0.41–0.91)
	Comorbidity			30.97	<0.0001	
Urinary tract infection ($R^2=0.10$)	Pain			17.92	0.003	
	Constant	-0.09	0.28	0.11	0.74	
	Gender (male)	-0.74	0.16	22.58	<0.0001	0.48 (0.35–0.65)
	Comorbidity			8.31	0.04	
More than one urinary tract infection ($R^2=0.13$)	Pain			24.73	<0.0001	
	Constant	-1.02	0.17	37.16	<0.0001	
	Gender (male)	-1.09	0.19	32.01	<0.0001	0.34 (0.23–0.49)
	Pain			15.52	0.008	
Respiratory infection ($R^2=0.04$)	Joint inflammation	0.54	0.23	5.41	0.02	1.72 (1.09–2.70)
	Constant	0.22	0.14	2.44	0.12	
	Gender (male)	-0.58	0.13	19.64	<0.0001	0.56 (0.43–0.72)
	Joint inflammation	0.35	0.13	7.22	0.007	1.42 (1.10–1.84)
More than one respiratory infection ($R^2=0.03$)	Constant	-0.57	0.14	15.72	<0.0001	
	Gender (male)	-0.47	0.13	12.31	<0.0001	0.63 (0.483–0.81)
	Joint inflammation	0.44	0.14	9.73	0.002	1.55 (1.17–2.03)
	Constant	-0.46	0.18	6.22	0.013	
Any allergic symptoms ($R^2=0.06$)	Gender (male)	-0.41	0.14	8.25	0.004	0.66 (0.52–0.88)
	B27	0.45	0.24	3.59	0.058	1.57 (0.98–2.50)
	Pain			18.44	0.001	
	Joint inflammation	0.41	0.15	7.02	0.008	1.50 (1.11–2.03)

Variables included in initial models: age, gender, pain (number of hours of pain in the last week), comorbidity (secondary AS), HLA-B27 status, disease duration, joint inflammation

Discussion

The immune response of patients with AS is of central interest for the pathogenesis of the disease. This is the first large study to show an increased incidence of infection and allergic symptoms in AS patients. As discussed below, several smaller studies have already pointed in the same direction.

The control group is composed of patients with chronic back pain due to DP, a mechanical problem which is not expected to be associated with a high risk of infection but might confer an increased risk due to decreased mobility, chronic pain, and disability or hospitalization. The 2.5-fold higher likelihood of AS patients having one or more recent infections compared with the DP group suggests it is the underlying disease that is conferring a higher risk and not the disability it brings with it. The DP control group was

similar to our AS cohort in gender and perceived disease severity (as seen by similar pain rates and NSAID usage), but the groups were dissimilar in age and disease duration. It is difficult to find a control group with a similar age distribution as AS patients; subgroup analysis of patients of different ages did not alter our results, suggesting that age has not contributed to the differences between AS and DP patients.

A recent Mexican study of 95 nonselected spondyloarthritis patients, including 52 with AS, has described the prevalence of infection in this group (assessed by clinical examination) to be over 50% and associated with active disease [23]. This is consistent with our self-report rate of 65% in AS patients (not significantly different from the Mexican cohort, $p=0.08$), lending validity to our results despite it not being possible to formally examine for signs of infection. Although our study design did not include the assessment of disease activity, it is interesting that patients

reporting infectious events had more severe pain than those without infection, this is also consistent with the findings of Martinez et al. This may be a reflection of responder bias in our larger cohort, with those patients who perceive their disease to be worse reporting more infections, pain, and other complications, but the consistency with the previous study would argue that this effect is small.

Breustedt et al. [24] have described more urogenital symptoms in HLA-B27-positive rheumatology patients compared with HLA-B27-negative controls, which could not be explained by different rates of antichlamydial antibodies in the groups. Work from our group on the prevalence of spondyloarthritis in HLA-B27-positive and HLA-B27-negative blood donors [3] showed that HLA-B27-positive individuals were more likely to report more than one episode of urethritis in the previous 12 months than HLA-B27-negative individuals. However, this was not related to clinical symptoms. In the present study, we did not analyze this association, as assessment of the HLA-B27 status was based solely on patients' report, and the prevalence of 79% HLA-B27 positivity in our AS cohort is somewhat less than reported elsewhere, and 12.5% of the patients were unaware of their HLA-B27 status. The number of HLA-B27-negative patients is mostly too small to detect significant differences in AS studies.

GI infections as a trigger for the development of AS have raised much interest. Immunological studies of the T cell response to *Klebsiella* antigens have shown abnormal cellular immune responses in AS patients independent of their HLA-B27 status [25, 26]. Both IgG and IgA antibodies to common GI bacteria, including *Klebsiella* and *Escherichia coli*, have been shown to be significantly increased in patients with AS [27–32], but results are inconsistent in HLA-B27-positive individuals [33, 34]. AS patients reportedly have an increased small bowel permeability [35], and over 50% have been found to have inflammatory bowel lesions on ileocolonoscopy [36]. Our questionnaire asked only about episodes of GI diarrhea, which might have elicited positive responses from those patients who have underlying IBD or subclinical lesions not related to infection. In our study, patients with IBD-related AS were three times as likely to report GI infection (diarrhea) than patients with primary AS or other secondary variants of AS. In addition to real infections, this finding is in part likely to be explained by IBD-related GI inflammation. Interestingly, patients with AS related to IBD also reported an increased incidence of urinary tract infections. Reports of GI infections over the previous 4 weeks had not been statistically different between groups in the previously cited study [3].

GI infection in patients with AS was found to be associated with younger age, independent of disease duration or symptoms in the present study. This is in contrast to a higher incidence of infection in other adult hospital and community groups with increasing age [37–41]. It is possible that younger AS patients are more likely to be exposed to enteropathic bacteria than their older counterparts, and the difference we see is a reflection of differential exposure, not differential susceptibility. However,

a similar relationship to age is not seen with genitourinary or respiratory infections, suggesting an infection-specific mechanism. Thus, this finding may be rather explained by HLA-B27 or another disease-related mechanism.

The presence of peripheral joint inflammation in AS conferred a higher risk of all infections and allergies in this group. This may be a measure of disease severity but is independent of AS-associated pain and disease duration which argues against this. It is possible that AS with peripheral joint involvement is a different disease entity to isolated spinal disease, with different immunological deficits or alterations, and we are seeing peripheral joint disease and infection as common endpoints of the immunological profile. Iritis was not related to infection in any of the groups examined, suggesting a different underlying mechanism for some extra-articular manifestations of AS.

Some of the medications used for the treatment of AS may have an effect on the immune system, particularly corticosteroids and methotrexate. These medications are not commonly used in AS due to poor efficacy [42, 43], and it is this lack of effective therapy that has contributed to the excitement over new biologic therapies [44], but population studies on the rates of conventional disease-modifying antirheumatic drug (DMARD) use in AS are lacking. Data on concurrent steroid or DMARD use were not collected in this study cohort; hence, we can only infer a low rate from accepted clinical practice. The rate of TNF- α receptor blocker use was also not measured, although it could be assumed to be quite low (<3% in Germany), because the medication has only recently been available for use for spondyloarthritis in Germany. The incidence of severe infection with infliximab therapy is low in AS compared to rheumatoid disease [45], suggesting the effect of such immunomodulatory therapy may not have a large effect on the underlying predisposition for infection in AS.

A limitation of this study is the low response rate to our questionnaire and the subsequent risk of selection bias. The demographics of our group and the proportion of patients with associated HLA-B27, psoriasis, IBD, or ReA in the current study were similar to those seen in a previous larger study of the DVMB membership with a higher response rate, suggesting similar disease severity and supporting the validity of the current study sample. The questionnaire covered a broad range of topics, with the aim of masking the main objective of the study to reduce responder biases.

A weakness of any population-based survey is that it is not possible to distinguish causative relationships due to the basic study design. We have described an increased cumulative prevalence of infection and allergic symptoms in AS, and further studies will be important to define the underlying mechanisms of this phenomenon. There are important clinical implications of impaired host defenses in AS, particularly as the therapy of AS moves into biologics which bring their own increased risk of infection, and it will be important to consider the role of prophylactic measures in this high-risk group.

In conclusion, these data suggest that AS patients have more infections and more allergic symptoms than other individuals with mechanical causes of back pain. Whether

this relates to HLA-B27 or other factors associated with the disease is unknown. This study should clearly encourage further work in this area.

Appendix

Translated wording of questions in our questionnaire (from German):

1. Which diagnosis was given for your disease?

- Ankylosing spondylitis
- Reiter's disease or reactive arthritis

Alternative question given to control group:

1. Which diagnosis was given for your disease?

- Disc prolapse
- Degenerative back pain

2. Was the diagnosis given or confirmed by a physician?

- Yes
- No
- I don't know

3. Was the diagnosis checked by radiography, computed tomography, or magnetic resonance imaging?

- Yes
- No
- I don't know

4. In which area did your symptoms first start? (multiple answers possible)

- cervical spine
- hip joints
- buttocks/thighs
- thoracic spine
- knee joints
- lumbar spine
- ankle joints
- Achilles tendons
- in none of these
- I don't remember

5. How old were you when the first complaints occurred which you attribute to the disease?

- (... years)

6. How old were you when the diagnosis marked in item 1 was given for the first time?

- (... years)

7. What is your present age?

- (... years)

8. What is your sex?

- Male
- Female

9. Are you HLA-B27 positive?

- Yes
- No, HLA-B27 negative
- I don't know

10. Which of the following diseases has been diagnosed in addition? (Multiple answers possible)

- Psoriasis
- Crohn's disease or ulcerative colitis (inflammatory bowel diseases)
- Reactive arthritis or Reiter's disease in addition to ankylosing spondylitis
- None of these

11. Have you had a bowel infection (diarrhoea) in the past 4 weeks?

- Yes
- Once
- 2 times
- 3 times
- 4 times
- More frequently
- No

12. Have you had a urinary infection (urinary burning or discharge) in the past 12 months?

- Yes
- Once
- 2 times
- 3 times
- 4 times
- More frequently
- No

13. Have you had a respiratory infection (nose, windpipe, lungs) in the past 12 months?

- Yes
- Once
- 2 times
- 3 times
- 4 times
- More frequently
- No

14. Have you had allergic symptoms in the past 12 months? (Multiple answers possible)

- Yes, with difficulties
- In the nasal passages (hay fever)
- On the skin
- In the lungs (asthma)
- No, I had no allergies in these places

15. Have you had repeated episodes or at least one month of one of the following joint inflammations? (more than one answer possible)

- Inflammation of one or both hips
- Inflammation of one or both knees

- Inflammation of one or more other joints, excluding the spine?
 - None of these joint inflammations
16. Have you had at least one episode of eye inflammation (iritis)?
- Yes, and since the beginning of my disease I have had iritis:
 - Once
 - 2–3 times
 - 4–7 times
 - 8–15 times
 - 16–30 times
 - More than 30 times
 - And in the last 12 months I have had iritis:
 - I have not had iritis in the last 12 months
 - 1–2 times
 - 3–4 times
 - More often
 - No, I have never had iritis
17. How often in the past 4 weeks have you had back or joint pain?
- Continuously
 - Generally, more than 12 hours per day
 - Generally, more than 2 hours per week
 - Less often or not at all
18. On how many days in the last 12 months have you had back or joint pain?
- Not at all, or less than 30 days
 - Between 30 and 90 days
 - Between 90 and 270 days
 - More than 270 days
19. How many days in the last 12 months were you unable to go to work *due to your spine and joint disease*?
- _____ days
 - I am/was not employed in the last 12 months/was off work for other reasons for more than 3 months
20. Were you admitted to hospital *due to your spine and joint disease* in the last 12 months?
- Yes, _____ days in an acute hospital (not rehabilitation)
 - Yes, _____ days in a rehabilitation facility
 - No
21. Have you needed to take non-steroidal anti-inflammatory drugs in the last 12 months? (Multiple answers possible)
- Yes, and (on average) daily: (Respondents were given dosage options for various NSAIDs, including:
 - Celecoxib (Celebrex) — up to 200 mg, 400 mg, 600 mg, more than 600 mg
 - Diclofenac (Voltaren) — up to 50 mg, 100 mg, 150 mg, more than 150 mg
 - Ibuprofen (Brufen, Imbun) — up to 600 mg, 1200 mg, 1800 mg, more than 1800 mg
 - Indomethacin (Amuno) — up to 50 mg, 100 mg, 150 mg, more than 150 mg
 - Meloxicam (Mobec) — up to 7.5 mg, 15 mg, 22.5 mg, more than 22.5 mg
 - Naproxen (Proxen, Naprosyn) — up to 500 mg, 1000 mg, 1500 mg, more than 1500 mg
 - Piroxicam (Felden) — up to 10 mg, 20 mg, more than 20 mg
 - Rofecoxib (Vioxx) — up to 12.5 mg, 25 mg, 50 mg, more than 50 mg
 - Another non-steroidal anti-inflammatory drug
 - No, no non-steroidal anti-inflammatory drug necessary
22. *If you have marked more than one medication, go ahead to Question 24. If you only marked one medication:* How well does the medication work for you?
- I have no more pain
 - Pain reduced to 1/4
 - Pain reduced to 1/2
 - Pain reduced to 3/4
 - The medication has no effect
23. Have you had any serious side-effects from these medications? (Multiple answers possible)
- Yes, and they were
 - nausea
 - abdominal pain
 - stomach ulcer
 - headache, dizziness
 - colon problems
 - bleeding in the GI tract
 - black-coloured faeces
 - other serious side-effects
 - No, I have not had any serious side-effects
24. How long have you been taking one of the non-steroidal anti-inflammatory drugs?
- For less than a year
 - For 1–2 years
 - For 2–4 years
 - For more than 4 years
25. Have you changed your medication during this time?
- No (*move on to Question 28*)
 - I don't know (*move on to Question 28*)
 - Yes
26. Why did you change medications? (Multiple answers possible)
- Because of serious side-effects, which were:
 - nausea
 - abdominal pain

- stomach ulcer
- headache, dizziness
- colon problems
- bleeding in the GI tract
- black-coloured faeces
- other serious side-effects
- Because the drug(s) did not work well
- For other reasons

27. The medication that was stopped was:

- Celecoxib (Celebrex)
- Diclofenac (Voltaren)
- Ibuprofen (Brufen, Imbrun)
- Indometacin (Amuno)
- Meloxicam (Mobec)
- Naproxen (Proxen, Naprosyn)
- Piroxicam (Felden)
- Rofecoxib (Vioxx)
- A different non-steroidal anti-inflammatory drug

28. Have you ever had a vertebral fracture?

- Yes, when I was ____ years old
- As the result of an accident/trauma
- It was not the result of an accident/trauma
- No, I have not had a vertebral fracture

29. Did any of the following significant events happen in the 2 years before your disease began? (Multiple answers possible) How long before your first symptoms did they occur? (*Choice between 'less than 3 months', '3–6 months', '6–9 months', '9–12 months', '12–18 months' or '18–24 months before my first symptoms' for each event option*).

- Severe accident with bone fracture
- Severe accident with joint injury
- Other severe accident
- Non-accident related orthopaedic surgery
- Other serious surgery
- Bowel infection (diarrhoea)
- Urine infection (burning or discharge)
- Respiratory infection (bronchitis, pneumonia)
- Allergic symptoms
- In the nasal passage (hay fever)
- In the lungs (asthma)
- On the skin
- Pregnancy
- Heavy physical activity
- Work-related
- Competitive sport
- Intensive recreational sport
- Death of a closely related person
- Severe family-related problems
- Severe work-related problems
- No such event occurred in the 2 years leading up to the onset of the disease

30. How exactly do you remember when the event occurred?

- To the day
- To the week
- To the month
- Not exactly to the month

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