

The Burden of Ankylosing Spondylitis

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ABSTRACT. The acute as well as chronic clinical features of ankylosing spondylitis (AS) are a burden to the patient and society. Apart from the axial and articular manifestations, extraarticular AS-related comorbidities such as uveitis, inflammatory bowel disease, and psoriasis contribute to the burden of the disease. In addition, a large proportion of patients have osteoporosis or osteopenia, which may be associated with fractures and contribute to kyphosis. All these features result in decreased quality of life. Moreover, patients with AS have an increased mortality rate. The impact of this disease also can be seen in various aspects of workforce participation, from requiring more assistance at paid work to withdrawal from the workforce. Further, patients with AS and, subsequently, society are affected by substantial healthcare costs related to medications and healthcare provider expenses. Early diagnosis and management of patients will likely prevent functional disability and improve patient outcomes. (J Rheumatol 2006;33 Suppl 78:4-11)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS

MORBIDITY

MORTALITY

COST OF ILLNESS

INTRODUCTION

Chronic diseases can adversely affect patients not only in terms of physical suffering, impaired function, and diminished quality of life, but can also have an impact on employment perspectives and out-of-pocket costs. In addition to the burden on the patient, a condition with a high prevalence can be a significant burden on society by increasing overall healthcare costs, non-healthcare costs, and disability payments due to withdrawal from the labor force.

Ankylosing spondylitis (AS) is a chronic condition that, depending on the geographical region studied, affects about 0.1% to 1.4% of the population¹⁻¹⁰. It is characterized by chronic inflammation of the axial skeleton, particularly the sacroiliac joint^{11,12}. Peripheral joints and extraarticular sites are also frequently involved^{11,13}. Because the onset of AS can occur at a relatively young age, usually during early adulthood, patients have to adjust to their disease for most of their lives. Similarly to other chronic diseases, AS can affect quality of life, morbidity, mortality, participation in paid and unpaid work, and healthcare costs. We review the various domains that contribute to the burden of AS on the patient and society.

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PHYSICAL FUNCTIONING AND QUALITY OF LIFE

A major clinical feature of AS is diminished physical functioning. The Bath Ankylosing Spondylitis Functional Index (BASFI) has shown that patients with AS have the greatest difficulty with activities requiring bending forward at the waist and being able to complete a full day of regular activity¹⁴. Cross-sectional and longitudinal studies have indicated that longer disease duration, increasing age, and smoking are associated with decreased functioning^{15,16}, whereas performing back exercises and having a greater degree of social support improves functioning¹⁵. Although it has been suggested that most of the loss in function occurs within the first 10 years of the onset of the disease¹⁷, further longitudinal studies are required to fully elucidate the rate of progression of disability. The loss in function with AS contributes to self-reported feelings of lower vitality^{18,19}. In addition, poorer function is also related to fatigue¹⁹.

When applying a patient-reported disability measure in patients with rheumatoid arthritis (RA) and AS, their disease had a similar influence on overall function, although older RA patients (≥ 51 yrs) tended to report somewhat worse physical functioning than their age-matched counterparts with AS. However, when function was assessed using the Steinbrocker index, men with AS incurred a greater physical disability than men with RA²⁰. As expected, with increasing age, both male and female patients with AS experienced reduced function, but the decline with increasing age was greater than in patients with RA. This difference can be partially explained by disease duration. The onset of AS is typically earlier than RA; therefore, in older age-matched patients, those with AS will have a longer disease duration than those with RA.

Not only is physical functioning diminished in patients with AS, but also their quality of life. With generic qual-

ity of life instruments, significant differences have been observed between AS patients and the general population, including all physical and psychosocial domains²¹. In addition, in an international longitudinal, observational study, a greater proportion of patients with AS reported moderate to severe limitations in mobility, self-care, daily activity, pain, and anxiety (the 5 EuroQoL domains) than reported in the general population (A. Boonen, unpublished data). In a study that included AS patients with high disease activity who were refractory to conventional treatment, patients with AS had lower scores in all domains of quality of life (Medical Outcome Survey Short Form-36) when compared with patients with hypertension, diabetes, or arthritis, and scores comparable to patients with chronic heart failure²¹. Further, the diminished social functioning experienced by patients with AS is similar to that seen in patients who have lost a limb. These results are not reflective of differences in age or sex ratios between conditions since the data were adjusted for these variables.

The impact of AS on quality of life is consistently shown not only in generic quality of life instruments^{14,21-23}, but also in studies that assess specific factors contributing to quality of life in AS. When asked to identify those areas that influence their quality of life, patients with AS are most concerned with factors such as stiffness, pain, fatigue, and poor sleep²³. The Ankylosing Spondylitis Quality of Life (ASQoL) is a disease-specific quality of life instrument developed from interviews with AS patients. The items most often reported by patients were related to pain, fatigue, mood, sleep disturbance, and decreased functioning, especially related to household tasks, family activities, dressing, and personal

hygiene²⁴. As discussed below, having paid employment contributes to better physical and mental quality of life^{25,26}.

COMORBIDITIES AND EXTRAARTICULAR MANIFESTATIONS

Ankylosing spondylitis is associated with a variety of extraarticular manifestations that can result in a number of comorbid conditions (Table 1). Osteoporosis, one of the more common comorbid conditions, can ultimately result in vertebral fractures²⁷. Studies indicate that 46% to 56% of patients with AS have a bone mineral density T-score ≤ -1.0 (measured at lumbar spine) and can be classified as osteoporotic or osteopenic^{27,28}. Bone loss is higher in AS patients who are older and have longer disease duration²⁷.

Patients with AS are at heightened risk for sustaining a vertebral fracture. This is a result of decreased mechanical strength (as a consequence of osteoporosis), spinal rigidity, and kyphotic deformities²⁹. In a population-based inception cohort in Minnesota, USA, the risk for thoracolumbar compression fractures was 7.6 (95% confidence interval 4.3–12.6) when compared with the population rates³⁰. In another report, about 6% of patients with AS had sustained at least one vertebral fracture³¹. However, this value increases to 14% in patients with AS for 42 years or more. Forty-seven percent of patients with AS who experience a clinical cervical vertebral fracture experience some form of neurological complication, ranging from transient paresthesia to chronic loss of strength in the arms or legs³². Notably, 65% of patients with AS who experience a vertebral fracture do not recover completely from subsequent neurological complications.

Table 1. Clinical conditions contributing to the burden of ankylosing spondylitis.

	Prevalence*,%	Hazard Ratio†	Identified Risk Factors*
Morbidity as consequence of AS			
Low BMD ^{27,28}	46–56		Advancing age Disease duration
Kyphosis ³⁴	45 ^{††}		Radiographic evidence of spinal damage Disease activity (BASDAI)
Vertebral fracture ^{30,31}	6	7.6 (95% CI 4.2-12.6)	
Myocardial infarction ³⁸		1.44 (95% CI 1.15-1.81)	
AS-related comorbid conditions			
Uveitis ⁴¹	20–30		
Psoriasis ⁴⁷	9		
IBD ^{46,47}	1–6		

*Among patients with ankylosing spondylitis. †Compared with the normal population. ††Defined as occiput–wall distance > 0. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMD: bone mineral density; IBD: inflammatory bowel disease.

Later in the course of the disease, patients may lose their normal spinal posture and develop thoracic kyphosis¹². The degree of kyphosis is related to spinal deformity resulting from vertebral fractures and due to wedging of the intervertebral discs³³. In a cross-sectional study, patients with kyphosis were older and had lower physical functioning³⁴. In addition, kyphosis was seen in a greater percentage of men than women. Factors that independently contributed to the degree of kyphosis (measured by mean vertebral wedging) included radiographic evidence of spinal damage and disease activity³⁴.

These changes that occur in the spine predispose patients to spinal cord injuries. In a study of the Finnish population, patients with AS sustained spinal cord injuries at a rate 11 times greater than the general population²⁹. Slipping was cited as the cause of the trauma in over half the patients with AS who sustained a spinal cord injury versus 7% in the whole population of patients with traumatic spinal cord injuries.

The additional risk of cardiovascular disease noted in patients with AS³⁵ is now receiving further attention. Aortic insufficiency, conduction disturbances, diastolic disturbances, cardiomyopathy, and pericarditis are significantly associated with AS^{36,37}. Men with AS also have a higher rate of first-time myocardial infarctions than men without AS³⁸. A study in Norway reported that patients with AS or related spondyloarthropathies (SpA) underwent their first coronary artery bypass graft at a significantly earlier age than those without SpA. Moreover, AS/SpA is a stronger predictor of aortocoronary bypass at a young age than the traditional cardiovascular risk factors³⁹.

Uveitis, psoriasis, and inflammatory bowel disease (IBD) are well recognized disease-related manifestations⁴⁰. There is a 20% to 40% likelihood of the occurrence of one or more attacks of acute anterior uveitis in patients with AS^{41,42}. In some patients it may become chronic or result in visual impairment⁴³. Uveitis can also influence physical functioning. In a longitudinal study (duration up to 6 yrs), patients with AS who had uveitis had a significant decline in BASFI scores compared with patients without uveitis⁴⁴. Patients with eye involvement also have greater radiologic changes of the axial skeleton than AS patients without uveitis⁴⁵. An estimated 1% to 6% of patients with AS will also have IBD^{46,47}, and about 9% will have psoriasis⁴⁷. Patients with AS who also have psoriasis and/or IBD have a higher degree of disease activity and lower physical functioning compared with those patients who do not have these comorbid conditions⁴⁵.

MORTALITY

Population studies that include patients with varying degrees of disease activity have shown no increase in

mortality rate between AS patients and the general population^{48,49}; however, other reports describe decreased survival in AS patients. Although it is no longer considered a viable treatment option, some older patients with AS have undergone radiotherapy, which may affect their longterm survival. Therefore, it may not be surprising that those who received radiotherapy have a mortality rate higher than the general population or the nonirradiated AS population⁴⁹⁻⁵¹. When nonirradiated patients from hospitals or rheumatology clinics were evaluated, those with AS had a higher mortality rate than expected from the general population^{35,52,53}. The discrepancy between the results in population studies versus those that selected patients from clinics and hospitals may be due to differences in disease activity. Patients in clinics and hospitals may have a higher degree of disease activity; whereas in the population studies, there is a greater inclusion of patients with mild disease⁵⁴⁻⁵⁶.

There may be many underlying causes for the increase in mortality rate seen in patients with AS, especially those with more severe disease. For instance, severe spinal conditions associated with AS (e.g., bamboo deformity, kyphoscoliosis, and cervical flexion) can lead to respiratory difficulties and contribute to death⁵⁷. Although amyloidosis is now a rare complication of AS, it was cited as the cause of AS-related death in 70% of cases reported in a Finnish study⁵². Cardiovascular disease is often listed as the cause of death in many patients with AS³⁶. In addition, a study indicated that patients with AS are more likely to die of an accident or violence than those in the healthy Finnish population⁵⁷.

LOSS OF PRODUCTIVITY

Patients with AS have lower employment rates, incur more official work disability, and experience more absences from work than the general population^{58,59}. Figures 1 and 2 summarize the findings of 14 studies (13 cross-sectional and 1 cohort) that included either employment or work disability among work-related outcomes and at the same time provided the disease duration of the studied sample. Reported employment of patients with AS ranges from 55% (in The Netherlands) to 89% (in Finland)^{20,60-63}. In a study conducted in the US, 13% of patients with a median disease duration of 21 years had left the labor force⁶², compared with 36% in France⁵⁴ and 31% in The Netherlands⁶⁴. In The Netherlands, patients with AS were 3 times more likely to withdraw from the labor force than expected in the general population⁶⁴, and this was more pronounced in patients with a manual job⁶⁵. Differences in the economic environment⁵⁹ or social security system⁶³ have been identified as factors that may explain some differences seen in the employment of patients with AS in different countries.

The employment status of patients can influence their

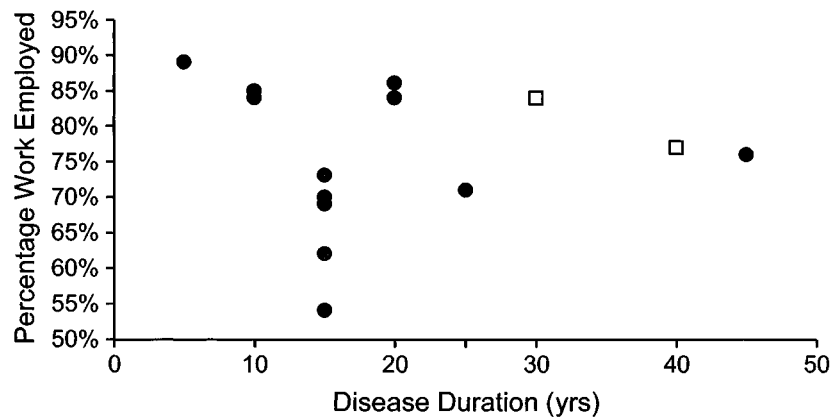


Figure 1. Proportion of patients employed as a function of disease duration. Summary of data reported in 14 cross-sectional studies. Squares represent data from 1 study that reported 2 followup points with different disease durations.

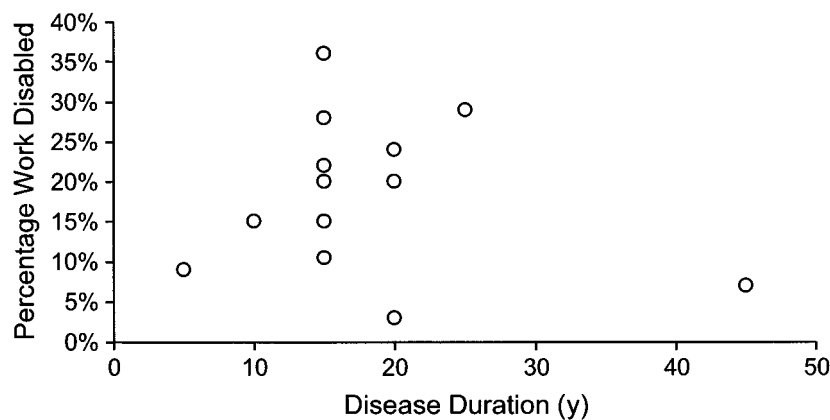


Figure 2. Proportion of patients work disabled as a function of disease duration. Summary of data reported in 13 cross-sectional studies and 1 cohort study.

Table 2. Risk factors associated with diminished work status.

	Reduced Hours ^{62*}	Requiring Assistance ^{62*}	Episodes of Sick Leave ^{63*}	Duration of Sick Leave ^{25,54,62*,63*}	Changing Job ^{62*}	Work Disability ^{62*}	Withdrawal ^{25,54,58,64-66}
Manual labor		•	•	•	•	•	•
Other job characteristics							•
Disability	•	•	•	•			
Sex	• (F)				• (F)		• ††
Pain	•	•		•	•		
Comorbid condition				• †		•	
Socioeconomic environment			•			•	
Disease activity				•			
Older age of disease onset						•	•
Education						•	
Passive coping strategies							•

*Outcomes were prospectively assessed. †Specific for inflammatory bowel disease. F: female; ††inconsistent for sex.

quality of life. Studies have consistently demonstrated that patients who are no longer employed have a lower quality of life^{22,26,64}.

Factors associated with various aspects of employment are summarized in Table 2. Consistently, manual labor (Figure 3)^{25,62,65,66}, age at onset of disease^{62,64}, and passive avoidance coping strategies independently influence employment⁶⁴. In addition, women and those with comorbid conditions have a greater likelihood of receiving disability compensation⁶². Although gender may influence employment, it does not appear to be an independent factor in all studies that examine the influence of gender^{58,64,65}. With increasing disease duration, more patients become work disabled. However, the risk of becoming work disabled when compared with the general population is especially increased in younger patients⁶⁴. Anecdotal evidence indicates that fatigue is the major concern of patients in terms of maintaining full employment⁶¹. Other concerns cited included pain, limited mobility, and the unpredictability of symptoms. However, many patients could continue their employment if technical or ergonomic adjustments were available^{25,54}.

Even when patients continue in a salaried position, AS adversely affects their workplace performance. In Europe, about half of patients with AS report having to take sick leave (at least 1 day in duration) related to their disease⁶³. In the US, 15% had long periods of sick leave over a period of 4 years⁶². Having a position requiring manual labor or having a greater degree of disability independently predicts the occurrence of sick leave⁶³. On the other hand, the length of each sick leave episode is longer for those patients with higher disease activity (Bath Ankylosing Spondylitis Disease Activity Index)⁶³, greater functional disability⁶², IBD⁶³, and higher levels of pain⁶². With increasing functional disability, pain, or

physically demanding activities there is a 2 to 5 times greater need for assistance⁶². Women are more likely to switch to a less physically demanding position or decrease their hours than men⁶². In addition, patients who report a higher degree of pain and have a more physically demanding position are at greater risk of switching jobs.

In addition to loss of productivity in paid employment, many patients with AS need to spend time resting, exercising, or attending a healthcare clinic. These activities can reduce the time available for other activities by an average of 1.25 hours per day⁶⁷. With increasing disease activity and worsening function, the amount of work time lost to these activities increases.

In summary, AS clearly diminishes all domains of work status for patients (Table 2). The economic environment and social security system in which the patients live have an important influence on the absolute figures on work participation. Independent of the socioeconomic environment, patients who are employed in a position requiring manual labor or who have greater physical limitations or pain are at greater risk of experiencing some loss in productivity than those in professional positions or those in whom the disease has not progressed to the point of limitation in physical functioning.

HEALTHCARE COSTS

Costs associated with a disease include direct and indirect (productivity) costs. Direct costs include expenses incurred obtaining medical services or treatment for the disease (including visits to healthcare providers, hospitalizations, treatments, assistive devices, and paid or unpaid household help). Indirect costs encompass the expenses incurred with loss of productivity, which were described in the previous section. It is often difficult to compare direct costs between countries, mainly due to price differences for healthcare resources. Further, studies vary in

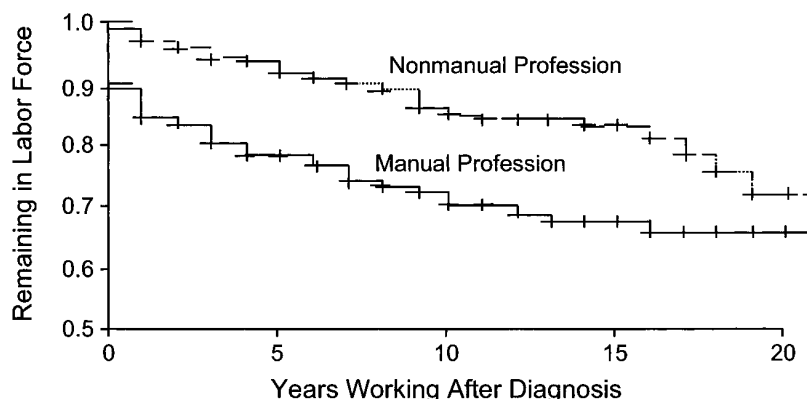


Figure 3. Influence of type of profession on unemployment in patients with AS. The probability of remaining in the work force is represented by Kaplan-Meier curves for those employed in manual versus nonmanual positions. From Boonen A, *et al.* *Ann Rheum Dis* 2001;60:1033-9, with permission.

Table 3. Average annual costs associated with AS (2003 US dollars)*. Adapted from Boonen and van der Heijde. Expert Rev Pharmacoeconomics Outcomes Res 2005;5:163-81, with permission.

	United States ⁶⁹	United Kingdom ¹⁶	European Tri-nation ^{†70}
Direct costs	1913	4478	3307
Indirect costs	5287	6143	8535
Total costs ^{††}	7243	10,620	11,843

*As adjusted for differences in timing of consumer price indices and purchasing power parities.

†Nations studied: France, Belgium, The Netherlands.

††Studied using the human capital method.

design, type of patients included, and data collection. Even with these limitations, it is clear that there is a substantial societal cost related to the medical treatment of AS. After converting to US dollars (2003) and adjusting for differences in timing of consumer price indices and purchasing power parities, direct costs ranged from \$1913 in the US to \$4478 in the United Kingdom. Total indirect costs associated with AS account for 73% and 58% of the total costs and range from \$5287 in the US to \$8535 in Europe (Table 3)⁶⁸. In the US, medications account for 42% of the direct costs associated with AS; ambulatory and hospital care account for 15% and 16%, respectively⁶². Costs associated with ambulatory and hospital care (21%–31% and 2%–27%, respectively) account for a greater percentage of direct costs in studies performed in European nations⁶⁸. The costs associated with medications contributed only 6% to 12.5% to the direct costs associated with AS in these studies.

In the US, women and patients with greater functional disability have higher annual direct costs associated with their disease⁶⁹. In European studies, higher costs are incurred by patients who have longer duration of disease, higher disease activity, lower physical functioning, and a lower level of formal education^{16,70}. Also, patients who have extraspinal disease manifestations incur higher direct costs⁷⁰.

In terms of costs to the patient, a study of 3 European nations indicated that the greatest percentage of costs came from loss of income⁶⁷. Further, non-healthcare costs, such as private household help, transportation, and exercise, accounted for 64% of out-of-pocket (non-healthcare) expenses. Significant differences were seen between countries, which are most likely due to differences in national healthcare policy.

It is important to note that these studies were performed before the approval of biologic agents for the treatment of AS. Further studies are needed to determine the effects of biologic therapy on overall disease costs. Studies modeling the cost-effectiveness of the biologic agents are addressed in the following section.

COST-EFFECTIVE TREATMENT

A limited number of studies have evaluated the cost-utility of treatments in patients with AS. In these studies, the additional costs incurred by the new treatment are weighted against the extra gain in utility, resulting in a cost-utility ratio. Comparing the added benefits of 3 weeks of spa therapy in Austria or The Netherlands with standard care (weekly group exercise), the spa therapy had favorable cost-benefit and cost-utility ratios⁷¹. The additional costs of spa therapy were partly offset by lower costs associated with healthcare providers, physiotherapy, and medications as compared with standard treatment and resulted in a substantial gain in utility.

Another study evaluated the cost-effectiveness of inhibiting tumor necrosis factor- α . Data on effectiveness were based on a German infliximab trial and data on costs and utilities were derived from a cross-sectional observation of patients in the United Kingdom. The longterm (30 yr) treatment with infliximab was projected to result in a cost of less than £10,000 per quality-adjusted life-year (QALY) gained¹⁶ if both direct and indirect costs were considered. However, in the model that included direct costs only or that applied a short-term time horizon, the cost per QALY was substantially higher. Whether these ratios are acceptable will depend upon regional thresholds that are applied by decision makers to judge an intervention as cost-effective.

The issue of cost-utility of treatment of AS with biologics is also addressed in a recent Markov study⁷². It needs to be stressed that modeling of data to estimate costs per QALY of treatment with biologics in AS has limitations. It can be expected that early diagnosis and recognition of patients at risk for severe disease course will enable selection of patients who will derive longterm benefits from early aggressive treatment, leading to savings in future healthcare and productivity costs. Further, clinical trials with biological therapies included patients with AS with long disease duration who had adapted to their disease, and the possible gain in utility has been underestimated. These points should be taken into account when modeling the cost-utility and considering reimbursement, otherwise, the estimated costs per QALY will be inflated. Future research should concentrate on studying factors that predict severe disease course and the correct assessment of the longterm loss of utility. The better we are able to predict prognosis, the more cost-effective our treatments will be.

CONCLUSION

Ankylosing spondylitis is a chronic disease that lowers the physical function of patients, thereby reducing their quality of life. Patients with AS may also have an increased mortality rate compared with the general population and an increased risk of comorbid conditions.

The clinical burden of disease results in significant direct and indirect costs to the patient and the healthcare system. As discussed elsewhere in this supplement series, effective treatments to reduce the symptoms of AS are available. In order to offer effective treatment, however, patients with AS must be diagnosed early, and patients with poor prognosis must be identified. Because functional disability is the main contributor to the burden associated with AS, it is important that patients at risk for a severe course of disease are recognized and treated in a timely manner.

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