Identification and treatment of comorbidity in patients with rheumatoid arthritis

Life expectancy has been notably reduced in patients with rheumatoid arthritis (RA) since the disease was first characterized, but the causes of death and disability are changing and survival appears to be improving. This review article discusses the evolving pattern of morbidity and mortality in RA and reviews the evidence base for the identification and treatment of each of the major categories of system involvement. We also address the increasing burden of sepsis in RA, and discuss the relationship of RA to both malignant disease and osteoporosis. We conclude with the assessment of fatigue – an often neglected aspect of RA. We evaluate the contribution of drug therapy both in contributing to and treating comorbidity in RA, and offer clinical guidance on how to maximize patient benefit from early identification and intervention.

KEYWORDS: morbidity ■ mortality ■ pulmonary ■ rheumatoid arthritis ■ sepsis ■ systemic disease

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Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze infections associated with RA
- Assess the relationship between RA and interstitial lung disease
- Distinguish malignancies specifically associated with RA
- Evaluate the effect of RA treatment on concomitant disease

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Causes of death in rheumatoid arthritis

The mortality rate associated with rheumatoid arthritis (RA) has been extensively studied throughout the last 50 years, with most sources finding an increased risk of death due to cardiovascular disease, sepsis, respiratory disease and certain malignancies [1], although the magnitude of this measured risk is dependent on study design and patient characteristics [2,3]. Towards the end of the century it became evident that more aggressive management strategies appeared to have reduced deaths from complications traditionally directly related to RA, such as vasculitis, scleritis and cervical myelopathy [4], while the remaining excess deaths appeared to relate to an increase in cardiovascular disease, pulmonary disease, infections and some malignancies [4,5]. Within the last decade some units have reported reductions in mortality rates equivalent to that of the general population [6].

Adverse prognostic factors have been reported to include male sex, low socioeconomic status, increasing age, high disease activity, increased markers of inflammation and associated comorbidity [7]. Comorbidity is known to be common in RA and is associated with multiple pharmacotherapy. Importantly, the presence of a positive rheumatoid factor is also associated with worse prognosis, largely from increased cardiovascular events [8]. Although deaths from extra-articular complications were generally reported less frequently by the end of the 20th century, the prevalence of interstitial lung disease (ILD) was noted to be rising [9]. Death relating to therapy remained an issue, but the causes were changing with fewer deaths from NSAID-induced renal failure and bowel perforation but an increase in deaths related to drug-induced infections. All these observations have of course necessarily been dependent on the availability of accurate death certification.

Recently, data on death in patients with RA from a single center have shown that sepsis accounted for more deaths in the last 10 years than either vascular disease or malignancy (**Figure 1**) [10]. This may relate to the effects of earlier and more aggressive therapeutic intervention in patients with RA, which might reduce deaths from malignancy, cardiac and pulmonary disease, at the risk of increasing drug-related sepsis.

Infection

Patients with RA are at greater risk of infection, and this carries an increased risk of death in RA. The risk of infection is increased in a variety of circumstances (**Box 1**) and a 10-year prevalence of as high as 45% has been reported [11,12]. Important risk factors include age, disease activity, pulmonary and cardiac comorbidity and the absence of adequate immunity [13,14]. In addition to the immunosuppressive effect of RA itself, drug therapy can contribute to the increased susceptibility for infection. Oral corticosteroids are known to increase this risk with higher dose and longer duration of therapy [15]. Disease-modifying antirheumatic drugs (DMARDs) provide protection in general, providing they do not induce neutropenia. Anti-TNF therapies are associated with an increase in certain infections, with soft tissue infections being more common, particularly in the first

6 months of therapy and chest infections in the first 8 months [16].

In addition, the use of rituximab has also been linked to an increased risk of infection, especially in patients with low IgG levels [17]. Tuberculosis is also increased in all patients on anti-TNF and other immunosuppressives, and is especially linked to the use of infliximab. Up to half of all such cases may occur at extrapulmonary locations.

Prevention of sepsis-related death relies on identification of risk factors and appropriate use of immunization. Better control of active articular disease using early aggressive therapy might reduce later infection, despite the propensity of anti-TNF therapy to increase infections [16,17]. The evidence base now supports minimizing the use of long-term oral corticosteroids [15].

Early identification of signs of sepsis in immunosuppressed patients and intervention with appropriate treatment remains essential. Guidelines on surviving sepsis should be followed in all cases [18]. The commonest sites of infection in RA patients are addressed in the next sections.

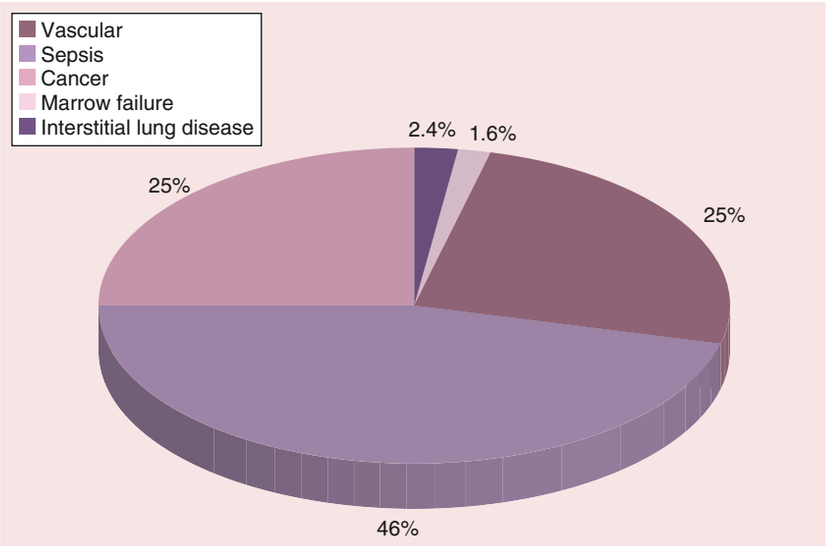

Figure 1. Distribution of causes of death in rheumatoid arthritis patients.

Respiratory

The lungs are the most common site for infection in RA, and may account for up to 70% of all acute infections in such patients. A large multicenter study showed no increase in hospitalization for pneumonia in patients with RA as a direct consequence of taking DMARDs [18]. However, the study did demonstrate an increased risk of hospitalization for pneumonia in patients taking oral corticosteroids, and found that this risk increased with increasing doses [18]. This reinforced other findings that long-term corticosteroid therapy may be a major contributory factor in the development of lower respiratory tract infection.

One study showed that both the incidence of lower respiratory tract infection and the associated mortality were doubled in RA, and suggested a number of initiatives to try and reduce this [19]. They included the immunization of all patients against pneumococcus and influenza, the avoidance of long-term oral corticosteroids and the temporary cessation of DMARDs during any intercurrent infection requiring antibiotics. When these guidelines were applied, the incidence of pneumonia among the RA population fell fourfold, with a similar reduction in case fatality. These findings were independent of age, sex and smoking status. Oral corticosteroid consumption fell by 50%, while immunization rates of the RA population against influenza had improved to 86% and against pneumococcus to 65% [19].

Concern had been raised that methotrexate (MTX) might reduce the efficacy of immunization. This was examined in over 150 RA patients on MTX. Levels of pneumococcal antibody were significantly higher in those who had been vaccinated. Patients taking oral prednisone and those who had not been vaccinated were more likely to have had pneumonia in the previous 10 years.

The relative risk for developing pneumonia among nonvaccinated patients was 9.7 and was 6.5 among corticosteroid-treated patients, after adjusting for age, sex, disease duration and comorbidity. The study concluded that a single administration of pneumovax early in RA offered up to 10 years protection against the development of pneumococcal pneumonia in RA patients on MTX [20]. The association of chronic lung infection in the form of bronchiectasis with RA has long been recognized and is dealt with under the section on airways disease.

Urinary

Urinary tract infections (UTIs) are also increased among patients with RA, and are most common in older female patients. One study of 2200 RA patients showed an overall annual incidence of hospitalization with UTIs of 2.09%, compared with 0.97% for controls. The use of long-term oral corticosteroids was associated with a relative risk of 4.46 for admission with UTIs and this rose to 9.07 in those on corticosteroids without DMARDs. Other risk factors identified included diabetes, the presence of long-term catheters and poor hand hygiene, itself associated with long-standing or severe articular disease. *Escherichia coli* accounted for

Box 1. Factors associated with increased risk of infection in patients with rheumatoid arthritis.

- Smoking
- Increasing age
- Long-term oral steroid therapy (dose-related)
- Immunosuppression and neutropenia
- Active articular disease
- Systemic involvement (cardiac or pulmonary)
- Diabetes
- Alcoholism
- Biologic therapies (anti-TNF and rituximab)

over half of all infections. Low-dose prophylactic antibiotics were recommended in RA patients with recurrent severe UTI [21].

Pulmonary disease

Interstitial lung disease

Initial studies identified a high post-mortem incidence of ILD in RA, while studies using high-resolution computed tomography (HRCT) later confirmed that up to 25% of RA patients had ILD [22,23]. Patients are less likely to be limited by joint disease as earlier effective treatment for the articular manifestations of RA has become available, while respiratory involvement in the form of ILD has become well recognized as a major factor in determining morbidity and mortality in RA [24,25]. The prognosis of patients with RA-ILD has been studied in the last two decades with several papers concluding that the mean survival from diagnosis is 3 years [24,26,27], although this is critically dependant on the stage of the disease at diagnosis, as many patients have mild disease that may remain stable for years. The failure to appreciate the effect of subtype on prognosis may also contribute to this mortality estimate as described below. Overall, patients with RA and ILD are two- to three-times more likely to die prematurely than RA patients without lung disease. Conflicting results have been reported on whether RA patients with ILD fare differently to those without RA [28,29]. However, the value of these data have been limited by the fact that most studies have been small and from single centers. ILD is the only complication of RA reported to be increasing in prevalence and it has been shown to account for around 6% of all RA deaths [30].

Symptoms of ILD include exertional dyspnea, often with a dry cough. Increasing fatigue is common and becomes almost invariable once hypoxia develops. Physicial signs include bilateral lung crackles, initially fine and heard in late inspiration, progressing to louder coarser crepitations throughout inspiration as the disease progresses. Plain chest radiography may be normal in the early stages of RA-ILD and can prove falsely reassuring. Established disease will often be visible as reticular shadows accompanied by nodular opacification of the lower lung, which is usually broadly symmetric. Lung cancer is an occasional complication of established ILD and is more likely in smokers.

The pattern of ILD must be determined by HRCT, and is a major determinant of prognosis, with usual interstitial pneumonia (UIP) carrying the worst outlook [31–34]. Nonspecific interstitial pneumonia is found in around 25% of patients, while cryptogenic organizing pneumonia is seen in less than 10% of patients [35]. This subgroup generally carries a more favorable prognosis and appears more responsive to therapy [36]. Overlapping features may be found in some patients.

Recent data suggest that disease extent, as assessed by HRCT, is a major determinant of survival in RA-ILD [37]. The extent of disease is categorized as limited if less than 20% of the lung parenchyma is affected, and as extensive otherwise. This definition was initially shown to match with prognosis in scleroderma lung disease [38], and has recently been shown to also apply to RA-ILD [37]. HRCT, importantly, also allows exclusion of other pathology that might mimic ILD or coexist with it.

The use of HRCT allows differentiation of patients with bronchiectasis from those with ILD – a distinction that cannot be made on clinical grounds or plain chest radiography alone. HRCT will also often demonstrate air trapping due to small airways disease, a feature that is increasingly recognised in RA [39–41] and discussed in the next section. Pulmonary function tests (PFTs) are sensitive but nonspecific. They are unhelpful in making a diagnosis of ILD, although sequential PFTs are invaluable in assessing the progress of the condition and response to treatment. Baseline measurement of at least vital capacity (VC) and gas transfer are recommended, as these are the most consistent comparators. Repeat measurement at annual intervals allows the clinician to plot rate of decline and to assess the effect of intervention.

Airways disease

The association between RA and chronic lung infection in the form of bronchiectasis is well recognized. A literature review revealed 289 reports of bronchiectasis with respiratory symptoms preceding articular in 90% [42]. Walker

observed a tenfold increased prevalence of bronchiectasis in patients with RA compared with the general population [43]. Subsequent studies have reinforced these findings and have shown that symptoms of bronchiectasis in the majority of cases precede the development of RA [44–47]. With the advent of HRCT of the lung, more contemporary studies have reported a prevalence of 25–29% of bronchiectasis with RA [39,48–52], although there have been exceptions [24].

Most of these studies have investigated nonsmoking RA patients. A recent large series of nearly 600 patients with RA has confirmed the association of RA with increased obstructive lung disease [53]. Almost 10% of RA patients had evidence of airways involvement and associated factors included male sex, smoking and poor disease control.

Drug-related lung disease

Anti-TNF therapy

There is now increasing evidence that all anti-TNF agents used in RA may accelerate progression of underlying ILD. There have been several reports of patients with mild ILD at baseline commenced on etanercept [54], infliximab [55] and adalimumab [56] who have developed rapidly progressive and sometimes fatal pulmonary fibrosis. It is unclear as to how many of these cases were due to MTX, which is usually coprescribed. However, the British Society for Rheumatology's Biological Register (BSRBR) has revealed that the proportion of deaths from ILD was increased threefold in those patients receiving anti-TNF therapy when compared with control patients on MTX alone, although bias cannot be fully excluded as a factor [57], either as a consequence of channeling of more severe cases to anti-TNF therapy or as a result of case clustering. With these findings it has been suggested that patients with prior RA-ILD should not receive anti-TNF treatment and a strategy to actively exclude such patients has been discussed and developed [58,59].

MTX & leflunomide

It is difficult to predict with confidence who will get MTX pneumonitis, although patients with baseline abnormalities in lung function due to ILD are at greater risk because such patients have reduced pulmonary reserve and are likely to do less well [60]. Patients are most likely to develop pneumonitis within 6 months of commencing MTX therapy and prognosis tends to be worse here with a mortality of 20% [61]. Overall, the incidence of MTX pneumonitis appears to have reduced recently from about one case in every 100 patient-years to approximately 0.5 cases. However, MTX cannot be recommended as the first-line DMARD in patients with established RA-ILD and we have recommended a strategy to screen for this with baseline pulmonary function testing in all RA patients in whom MTX is considered [58].

Leflunomide has also been noted to cause pneumonitis, although this appears to happen much more frequently in Japanese and Korean patients [62], suggesting a possible genetic link with causality. The frequency with which pneumonitis complicates leflunomide therapy in Caucasians is under 0.1 in every 100 patient-years, but patients with a history of MTX pneumonitis are at increased risk of pneumonitis with leflunomide.

Circulatory disorders

Cardiovascular

The standardized mortality ratio for myocardial infarction in RA is elevated at between 1.8 and 2.1 with increased frequency of death as a complication [63]. In addition, the standardized mortality ratio for congestive cardiac failure is as also elevated, and is linked to seropositivity and persistent disease activity as evidenced by high levels of C-reactive protein. Other factors associated with an increased cardiac event rate are diabetes, smoking, hypertension, peripheral vascular disease and the presence of an adverse lipid profile [64]. The increased risk for coronary artery disease in these patients is a consequence of accelerated atherosclerosis [65,66]. The atherogenic lipid profile and elevated carotid artery intimal thickness in rheumatoid patients improve with early treatment of RA [67]. It has been proposed that the data support evidence-based management recommendations for the further reduction of cardiovascular disease in patients with RA [68].

The influence of drug therapy on these figures in very important to understand. The use of long-term oral corticosteroids and NSAIDs are associated with an increase in cardiac events, while the use of DMARDs, especially MTX and hydroxychloroquine, appears to be protective [69]. Recent evidence also suggests that the use of anti-TNF therapy also reduces cardiovascular morbidity and mortality [69].

Cerebrovascular

The prevalence of cerebrovascular disease has been reportedly increased in RA with an excess of strokes, mainly as a result of emboli from

underlying atrial fibrillation, which is the usual cause. However, recent data suggest that may be less of an issue now. In a large review of all-cause mortality in RA patients over a decade, vascular deaths had declined overall [70]. Data from this study showing the common vascular causes of death are shown in Table 1. Box 2 shows how to reduce death in RA from the three most common causes – sepsis, pulmonary disease and vascular disease.

Malignancy

RA is associated with higher incidence of certain malignancies and there is also some conflicting evidence about the effect of certain antirheumatic drugs. Recent work has confirmed a twofold increase in both the prevalence and incidence of lymphoma in RA [71]. The risk of leukemia was similarly doubled but no association of myeloma was found. This appears to be a consequence of the chronic inflammatory nature of RA and associated immunosuppression, rather than the effect of treatment [71]. The risk of lymphoma in patients treated with anti-TNF was also similar when corrected for disease duration. Similar data from the BSRBR have also been recently reported [72].

The standardized incidence ratio (SIR) of cancers at certain other sites are also influenced by the presence of RA. Colon and rectal cancer is reduced (SIR: 0.77), probably as a result of NSAID use, while lung cancer is increased (SIR: 1.63), perhaps due to smoking and the increased prevalence of ILD [73]. Skin and prostate cancers are also reportedly more common in RA [74].

Age-adjusted mortality from cancer has been shown to be increased in patients with RA [75], perhaps as a result of later detection, with patients hospitalized as a result of RA having a hazard ratio for overall survival of 1.31 [76].

Table 1. Vascular causes of death among 52 patients with rheumatoid arthritis.

Vascular causes of death	n (%)
Myocardial infarction/acute coronary syndrome	21 (40)
Ventricular failure	9 (16)
Cerebrovascular accident	6 (12)
Abdominal aortic aneurysm	6 (12)
Bowel ischemia	4 (8)
Peripheral vascular disease	2 (4)
Hypertension	2 (4)
Thromboembolism (site unspecified)	2 (4)

Table 2 summarizes the SIRs of some of the more common cancers occurring in RA.

Anemia

Anemia has long been recognized as an association of RA. Several factors contribute to this. The anemia of chronic disease is associated with suboptimal control, while macrocytic anemia may reflect hypothyroidism, vitamin B12 deficiency or excessive consumption of alcohol. However, iron deficiency anemia is also common and has been linked with the long-term use of corticosteroids and NSAIDs. The contribution of infection with *Helicobacter pylorii* in RA has been highlighted [77] and a recent paper reported that up to 10% of patients with RA may be anemic, with iron deficiency remaining the most common cause. The need for definition of the type and investigation of the cause of the anemia was underlined by the finding that 10% of cases related to malignancy [78].

Renal disease

A range of renal disorders have been described in renal disease several decades ago [79] but these conditions have generally become less common with time. Analgesic nephropathy and interstitial nephritis were largely related to the use of large amounts of analgesia and NSAIDs, which are now rarely required. Amyloidosis has become rare as the earlier interventional approach has prevented long-term uncontrolled amyloid.

Osteoporosis

RA is associated with both juxta-articular peripheral [80] and generalized osteoporosis [81], leading to an increased risk of wrist, vertebral and hip fractures. Increasing age and female gender are invariably associated with higher fracture rates in RA, while increasing disease duration, disease severity and activity of RA may all adversely influence the degree of bone loss.

It has been established that long-term oral corticosteroid use is also predictive of bone loss in RA [82]. The association of RA with osteoporosis is strong enough for the presence of RA to be included as one of the risk factors in the fracture risk assessment tool (FRAX®; WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK) calculation [101].

A recent study assessed factors associated with risk of fractures at different sites [83]. Females were at higher risk than males of having osteoporosis at all locations, but the presence of positive anticitrullinated protein antibodies predicted

osteoporosis at the spine, while disease activity and age were both predictors of osteoporosis at the hip. Absence of therapy with DMARDs was an important factor in predicting osteoporosis, and again, use of oral corticosteroids was another factor independently associated with osteoporosis in RA. This appears to be true of axial as well as cortical bone. There are now convincing data to suggest that DMARDs and anti-TNF drugs improve bone density in RA [84].

Fatigue

Fatigue is prevalent in RA and contributes significantly to the morbidity associated with the disease. It is a symptom that is both poorly defined and difficult to measure, and yet has a marked impact on a patient's quality of life [85]. Such is the perceived importance of fatigue in RA that one of the recommendations to come out of the OMERACT 8 workshop was that fatigue should be measured in all clinical RA trials.

The predictors of fatigue in RA remain poorly understood, but both physical and psychological causes can contribute [86]. Physical causes need early exclusion and can include anemia, hypothyroidism, vitamin D deficiency and hypoadrenalism [87]. Absolute deficiency of vitamin D is a relatively good predictor of fatigue in RA – a relationship that may be explained by both the immunomodulatory effects of vitamin D and its effect on subjective experience of pain. Similarly, those with the highest reported levels of fatigue have the lowest vitamin D levels, and subjective measures of disease activity in RA correlate with vitamin D deficiency [88]. This suggests that vitamin D levels are worth checking in RA patients experiencing fatigue, although further research is needed to ascertain if vitamin D replacement improves fatigue in RA. In patients with no comorbidity to explain fatigue, it has been shown that the degree of pain rather than disease activity is the major determinant [89,90].

Future perspective

Our understanding of the nature of RA has improved, and with this has come a wide range of new therapies, with many more in advanced stages of development. Genetic studies to assess the potential response to drug intervention are ongoing and offer great promise.

The NICE guidelines for RA emphasize the need for annual review in secondary care to help tackle the high prevalence of associated comorbid condition and in primary care, the new quality and outcomes framework payments include incentives to identify and treat cardiac and bone disease in RA. Prevention of RA complications is now recognized as a major challenge for clinicians, and the establishment of multicenter networks and national databases are already showing evidence that this can be achieved. It may not be too long before each

Box 2. How to reduce mortality in rheumatoid arthritis.

Prevention of sepsis-related death

- Early assessment/admission
- Awareness that RA patients may not be pyrexial
- Regular vaccination against influenza and pnemococcus
- Minimize use of long-term oral steroids (boost infections)
- Early effective disease control with DMARDs
- Careful use of anti-TNF with prior tuberculosis screening
- Suspend DMARDs and biologics during infection
- High index of suspicion for opportunistic infection
- Guidelines on surviving sepsis should be followed

Prevention of CVD deaths in RA

- Early use of DMARD therapy
- Minimize exposure to glucocorticoids
- Avoid dependence on NSAIDs
- Achieve disease remission (if possible)
- Assessment and intervention of comorbidity contributing to CVD risk profile
- Risk stratification
- Smoking cessation advice
- Cautious use of biologics in NYHA class I/II CCF
- Avoid use of biologics in NYHA class III/IV CCF

Prevention of pulmonary deaths in RA

- Baseline pulmonary function tests
- Imaging as indicated by PFTs
- Avoid methotrexate and biologics in patients with ILD
- Evidence confirms more deaths with anti-TNF in ILD†
- Regular influenza and pneumonococcal vaccination
- Avoid use of anti-TNF in patients with recurrent infection
- Guidelines on surviving sepsis and management of pneumonia have proven to reduce mortality in this setting

†British Society for Rheumatology Rheumatoid Arthritis Register data.
CCF: Congestive cardiac failure; CVD: Cardiovascular disease; DMARD: Disease-modifying antirheumatic drug; ILD: Interstitial lung disease; NYHA: New York Heart Association; PFT: Pulmonary function test; RA: Rheumatoid arthritis.
Data taken from [18,91].

Table 2. Range of malignancy in rheumatoid arthritis with standardized incidence ratios.

Type of cancer	Standardized incidence ratio (95% CI)
Non-Hodgkin lymphoma	2.1 (1.8–2.4)
Leukemia	2.0 (1.6–2.6)
Lung cancer	1.63 (1.2–2.3)
Colorectal	0.77 (0.65–0.90)

RA patient might have their individual prognosis predicted and therapy selected on the basis of a combination of genetic, serological and environmental factors.

Our ability to achieve remission from articular disease, while minimizing the development of disease- and drug-related comorbidities, is likely to continue to improve.

Executive summary

- The pattern of morbidity and mortality in rheumatoid arthritis (RA) is changing. Patients are living longer and better, with measurable improvements in articular outcome.
- As they become more active, significant comorbidity has surfaced. Factors driving this are no longer always a consequence of severe or undertreated disease.
- The prevalence of vasculitis, scleritis, cervical myelopathy and nodular disease has fallen, but other organ-related issues have arisen.
- Cardiopulmonary disease remains a major cause for concern in our increasingly elderly RA population.
- Sepsis has become more prevalent, especially in the lungs and urinary tract.
- Malignancy accounts for a significant number of deaths and differs in its distribution from the non-RA population.
- Anemia, renal disease, osteoporosis and fatigue are all common complaints among RA patients and require clinicians to have a good working knowledge of their causes and management.

References

Papers of special note have been highlighted as:
- of interest

1 Thomas E, Symmons DP, Brewster DH, Black RJ. National study of a cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis and other rheumatic conditions: a 20 year follow up study. *J. Rheumatology* 30, 958–965 (2003).

2 Wolfe F, Mitchell DM, Sibley JT *et al.* The mortality of rheumatoid arthritis. *Arthritis Rheum.* 37, 481–494 (1994).

3 Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology* 38, 668–674 (1999).

4 Choi HK, Hernan MA, Seeger JD *et al.* Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 359, 1173–1177 (2002).

5 Gonzalez A, Icen M, Kremers HM *et al.* Mortality trends in rheumatoid arthritis: the role of rheumatoid factor. *J. Rheumatol.* 35, 1005–1014 (2008).

6 Peltomaa R, Paimela L, Kautiainem H *et al.* Mortality in patients with rheumatoid arthritis treated actively from time of diagnosis. *Ann. Rheum. Dis.* 61, 189–194 (2002).

- **Demonstrates how early active treatment of rheumatoid arthritis (RA) reduces mortality towards that of the normal population.**

7 Hamilton J, Kelly CA. What kills patients with rheumatoid arthritis? *Rheumatology* 46, 183–184 (2007).

8 Gonzalez A, Maradit Kremers H, Crowson CS *et al.* The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum.* 56, 3583–3587 (2007).

9 Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. *Curr. Opin. Rheumatol.* 20, 340–346 (2008).

10 Malik S, Kelly C, Hamilton J, Heycock C, Saravanan V, Rynne M. Has the cause of death in rheumatoid arthritis changed recently? *Rheumatology* 52(Suppl. 1), i73 (2013).

11 Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. *Ann. Rheum. Dis.* 66, 308–312 (2007).

12 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum.* 46, 2287–2293 (2002).

13 Smitten AL, Choi HK, Hochberg MC *et al.* The risk of hospitalized infection in patients with rheumatoid arthritis. *J. Rheumatol.* 35, 387–393 (2008).

14 Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. *Q J Med.* 79, 461–476 (1991).

15 Wolfe W, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalisation for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs and anti-tumour necrosis factor therapy. *Arthritis Rheum.* 54, 628–634 (2006).

- **Large database showing how the risks of sepsis in RA relate to anti-TNF therapy and increasing doses of steroids.**

16 Lane MA, McDonald JR, Zerinque AL *et al.* TNF-α antagonist use and risk of hospitalization for infection in a national cohort of veterans with rheumatoid arthritis. *Medicine (Baltimore)* 90, 139–145 (2011).

17 Gottenberg JE, Ravaud P, Bardin T *et al.* Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. *Arthritis Rheum.* 62, 2625–2632 (2010).

18 Dellinger RF, Carlet JM, Masur H *et al.* Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit. Care Med.* 32, 858–873 (2004).

19 Housden M, Bell G, Heycock C, Hamilton J, Saravanan S, Kelly CA. How to reduce morbidity and mortality from chest infections in patients with rheumatoid arthritis. *Clin. Med.* 4, 326–329 (2010).

20 Coulson E, Saravanan V, Hamilton J *et al.* Pneumococcal antibody levels after pneumovax in patients with rheumatoid arthritis on methotrexate. *Ann. Rheum. Dis.* 70, 1289–1291 (2011).

21 Puntis D, Malik S, Saravanan V, Rynne M, Hamilton J, Kelly CA. Urinary tract infections in patients with rheumatoid arthritis. *Clin. Rheumatol.* 32, 355–360 (2013).

22 McDonagh J, Greaves M, Wright AR, Heycock C, Owen JP, Kelly CA. High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease. *Br. J. Rheumatol.* 33, 118–122 (1994).

23 Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography and pulmonary function tests. *Thorax* 56, 622–627 (2001).

24 Bongartz T, Nannini C, Medina-Velasquez YF *et al.* Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 62, 1583–1591 (2010).

25 Koduri G, Norton S, Young Y *et al.* Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort study. *Rheumatology* 49, 1483–1489 (2010).

26 Gabbay E, Tarala R, Will R *et al.* Interstitial lung disease in recent onset rheumatoid arthritis. *Am. J. Respir. Crit. Care Med.* 156, 528–535 (1997).

27 Park JH, Kim DS, Park IN *et al.* Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am. J. Respir. Crit. Care Med.* 175, 705–711 (2007).

28 Rajasekaran A, Shovlin D, Saravanan V, Lord P, Kelly CA. Interstitial lung disease in patients with rheumatoid arthritis: comparison with cryptogenic fibrosing alveolitis over five years. *J. Rheumatol.* 7, 1250–1254 (2006).

29 Hubbard R, Venn A. The impact of coexisting connective tissue disease on survival in patients with fibrosing alveolitis. *Rheumatology* 41, 676–679 (2002).

30 Young A, Koduri G, Batley M *et al.* Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford)* 46, 350–357 (2007).

31 Lee HK, Lim DS, Yoo B *et al.* Histologic pattern and clinical features of rheumatoid arthritis associated interstitial lung disease. *Chest* 127, 2019–2027 (2005).

32 Hyun-Kyung L, Dong-Soon K, Bin Y *et al.* Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest* 6, 2019–2027 (2005).

33 Kim EJ, Elicker BM, Maldonado F *et al.* Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur. Respir. J.* 35, 1322–1328 (2010).

34 Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: relevance of histopathologic and radiographic pattern. *Chest* 136, 1397–1405 (2009).

35 Flaherty KR, Colby RV, Travis WD *et al.* Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. *Am. J. Respir. Crit. Care Med.* 167, 1410–1415 (2003).

36 Yoo J-W, Song JW, Jang SJ *et al.* Comparison between cryptogenic organising pneumonia and connective tissue disease related organising pneumonia. *Rheumatology* 50, 932–938 (2011).

37 Sathi N, Urwin T, Desmond S, Dawson J. Patients with limited rheumatoid arthritis-related interstitial lung disease have a better prognosis than those with extensive disease. *Rheumatology* 50, 620 (2011).

38 Goh NS, Desai SR, Veeraraghavan S *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am. J. Respir. Crit. Care Med.* 177, 1248–1254 (2008).

39 Hassan WU, Keaney NP, Holland CD, Kelly CA. High resolution computed tomography of the lung in lifelong non-smoking patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 54, 308–310 (1995).

40 Hayakawa H, Sato A, Imokawa S *et al.* bronchiolar disease in rheumatoid arthritis. *Am. J. Respir. Crit. Care Med.* 154, 1531–1536 (1996).

41 Vergnenegre A, Pugnere N, Antonimi NT *et al.* Airways obstruction and rheumatoid arthritis. *Eur. Respir. J.* 10, 1072–1078 (1997).

42 Despaux J, Toussirot E, Wending D. Bronchiectasis and rheumatoid arthritis. Incidence and etiopathogenic aspects. Review of the literature. *Rev. Med. Interne* 18, 144–152 (1997).

43 Walker WC. Pulmonary infections and rheumatoid arthritis. *Q J Med.* 36, 239–251 (1967).

44 Bamji A, Cooke N. Rheumatoid arthritis and chronic bronchial suppuration. *Scand. J. Rheumatol.* 14, 15–21 (1998).

45 Shadick NA, Fanta CH, Weinblatt ME, O'Donnell W, Coblyn JS. Bronchiectasis. A late feature of severe rheumatoid arthritis. *Medicine (Baltimore)* 73, 161–170 (1994).

46 Anaya JM, Diethelm L, Ortiz LA *et al.* Pulmonary involvement in rheumatoid arthritis. *Semin. Arthritis Rheum.* 24, 242–254 (1995).

47 Banks J, Banks C, Cheong B *et al.* An epidemiological and clinical investigation of pulmonary function and respiratory symptoms in patients with rheumatoid arthritis. *Q J Med.* 85, 795–806 (1992).

48 Hassan WU, Keaney NP, Holland CD, Kelly CA. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. *Ann. Rheum. Dis.* 53(8), 511–514 (1994).

49 Fewins HE, McGowan I, Whitehouse GH, Williams J, Mallya R. High definition computed tomography in rheumatoid arthritis associated pulmonary disease. *Br. J. Rheumatol.* 30, 214–216 (1991).

50 Mcmahon MJ, Swinson DR, Shettar S *et al.* Bronchiectasis and rheumatoid arthritis: a clinical study. *Ann. Rheum. Dis.* 52, 776–779 (1993).

51 Cortet B, Flipo RM, Rémy-Jardin M *et al.* Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 54, 815–819 (1995).

52 Mohd Noor N, Mohd Sharir MS, Shahid MS, Abdul Manap R, Shahizon Azura AM, Azhar Shah S. Clinical and high resolution computer tomography characteristics of patients with rheumatoid and lung disease. *Int. J. Rheum. Dis.* 12, 136–144 (2009).

53 Nannini C, Medina-Velasquez Y, Achenbach SJ *et al.* Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study. *Arthritis Care Res. (Hoboken)* 65, 1243–1250 (2013).

54 Hagiwara K, Sato T, Takagi-Kobayashi S *et al.* Acute exacerbation of pre-existing interstitial lung disease after administration of etanercept for rheumatoid arthritis. *J. Rheumatol.* 34, 1151–1154 (2007).

55 Ostor AJK, Crisp AJ, Somerville MF, Scott DGI. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 27, 1266–1267 (2004).

56 Collins K, Todd A, Rynne M, Hamilton J, Saravanan V, Kelly CA. Adalimumab-associated pulmonary fibrosis. *Rheumatology* 8, 1379–1380 (2007).

57 Dixon W, Hyrich KL, Watson KD, Lunt M. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the BSR Biologics Register *Ann. Rheum. Dis.* 69, 1086–1091 (2010).

58 Saravanan V, Kelly CA. Drug related pulmonary problems in patients with rheumatoid arthritis. *Rheumatology* 45, 787–790 (2006).

59 Kelly C, Saravanan V. Treatment strategies for a rheumatoid arthritis patient with interstitial lung disease. *Expert Opin. Pharmacother.* 9, 3221–3230 (2008).

60 Howes M, Tose J, White C, Kumar N, Heycock C, Kelly C. Can baseline pulmonary function tests predict pulmonary toxicity in patients receiving methotrexate for rheumatoid arthritis. *Intern. Med.* 7, 51–54 (1999).

61 Chikura B, Sathi N, Lane S, Dawson J. Variation of immunological response in methotrexate-induced pneumonitis. *Rheumatology* 47, 1647–1650 (2008).

62 Kamata Y, Nara H, Kamimura T *et al.* Rheumatoid arthritis complicated with acute interstitial pneumonia induced by leflunomide as an adverse reaction. *Intern. Med.* 43, 1201–1204 (2004).

63 Van Doornum S, Brand C, King B, Sundararajan V. Increased case fatality rates following a first acute cardiovascular event in patients with rheumatoid arthritis. *Arthritis Rheum.* 54, 2061–2068 (2006).

64 John H, Kitas G, Toms T, Goodson N. Cardiovascular comorbidity in early rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* 23, 71–82 (2009).

65 Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin. Arthritis Rheum.* 35, 8–17 (2005).

66 Del Rincon I, O'Leary DH, Freeman GL, Escalante A. Acceleration of atherosclerosis during the course of rheumatoid arthritis. *Atherosclerosis* 195, 354–360 (2007).

67 Georgiadis A, Voulgari P, Argyropoulou M *et al.* Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients. *Semin. Arthritis Rheum.* 38, 13–19 (2008).

68 Solomon DH, Peters M, Nurmohamed MT, Dixon W. Motion for debate: the data support evidence-based management recommendations for cardiovascular disease in rheumatoid arthritis. *Arthritis Rheum.* 63, 1675–1683 (2013).

69 Greenberg JD, Kremer JM, Curtis JR *et al.* TNF antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 70, 576–582 (2011).

▪ **Demonstrates how the use of anti-TNF therapy reduces the later risk of acute cardiac events.**

70 Askling J, Fared CM, Baecklund E *et al.* Haematopoetic malignancy in rheumatoid arthritis: lymphoma risk and characteristics after exposure to TNF antagonists. *Ann. Rheum. Dis.* 64, 1414–1420 (2005).

71 Baecklund E, Iliadou A, Askling J *et al.* Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum.* 54, 692–701 (2006).

72 Mercer LK, Dixon WG. Looking beyond incidence in the relationship between anti-tumor necrosis factor therapy and malignancy. *Arthritis Rheum.* 63, 1773–1775 (2011).

▪ **Data from the British Society for Rheumatology's Biological Register discussing the relationship between RA, lymphoma and drug therapy.**

73 Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res. Ther.* 10, R45 (2008).

74 Hemminki K, Li X, Sundquist K, Sundquist J. Cancer risk in hospitalised rheumatoid arthritis patients. *Rheumatology* 47, 698–701 (2008).

75 Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Influence of inflammatory polyarthritis on cancer incidence and survival: results from a community based prospective survey. *Arthritis Rheum.* 56, 790–798 (2007).

76 Ji J, Liu X, Sundquist K, Sundquist J. Survival of cancer in patients with rheumatoid arthritis: a follow up study in Sweden of patients hopsitalised with rheumatoid arthritis 1 year before diagnosis of cancer. *Rheumatology* 50, 1513–1518 (2011).

77 Grigoriadou S, Quraishi A, Saravanna S, Saravanan V, Heycock C, Kelly CA. What effect does *Helicobacter pylori* have on the risk of peptic ulceration on patients receiving NSAIDs for rheumatoid arthritis? *Eur. J. Intern. Med.* 13, 269–273 (2002).

78 Bloxham E, Vagadia V, Hamilton J, Heycock C, Saravanan V, Kelly CA. Anaemia in rheumatoid arthritis: can we afford to ignore it? *Postgrad. Med. J.* 87, 596–600 (2011).

▪ **Demonstrates the high frequency with which significant pathology was associated with anemia in RA patients.**

79 Kelly C, Mooney P, Horden L, Griffiths ID. Haematuria in RA: a follow up study. *Ann. Rheum. Dis.* 47, 993–994 (1988).

80 Franck H, Gottwalt J. Peripheral bone density in patients with rheumatoid arthritis. *Clin. Rheumatol.* 10, 1141–1145 (2009).

81 Sambrook PN, Eisman JA, Yeates MG *et al.* Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum.* 30, 721–728 (1986).

82 Kelly C, Bartholomew P, Lapworth A *et al.* Peripheral bone density in patients with rheumatoid arthritis and factors which influence it. *Eur. J. Intern. Med.* 13, 423–427 (2002).

83 Barnes J, Donnison C, Scott M *et al.* What are the predictors for osteoporosis at different sites in rheumatoid arthritis? *Rheumatology* 50(3), 93–94 (2011).

84 Barnabe C, Hanley D. Effect of tumor necrosis factor alpha inhibition on bone density and turnover markers in patients with rheumatoid arthritis and spondyloarthropathy. *Semin. Arthritis Rheum*. 39, 116–122 (2009).

85 Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis Rheum.* 51, 578–585 (2004).

86 Repping-Wuts H, van Riel P, van Achterberg T. Fatigue in patients with rheumatoid arthritis: what is known and what is needed. *Rheumatology* 48, 207–209 (2009).

▪ **Useful synopsis of the causes and assessment of fatigue in patients with RA.**

87 Methiniti D, Coulson E, Kelly CA. Fatigue in rheumatoid arthritis. *Rheumatology* 48(8), 1166 (2009).

88 Higgins M, Thalayasingam N, Mackie S, Bingham S, Hamilton J, Kelly CA. Do Vitamin D levels correlate with disease activity in rheumatoid arthritis? *Clin. Rheum.* 32, 863–867 (2013).

89 Pollard L, Choy E, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* 45, 885–889 (2006).

90 Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra articular manifestations in rheumatoid arthritis, and their impact on outcome. *Rheumatology* 52, 99–110 (2013).

91 Hoare Z, Lim WS. Pneumonia: update on diagnosis and management. *BMJ* 332, 1077–1079 (2006).

Website

101 WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. FRAX: WHO Fracture Risk Assessment Tool. www.shef.ac.uk/FRAX/tool.jsp?locationValue=1

Medscape EDUCATION Identification & treatment of comorbidity in patients with rheumatoid arthritis

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	**1**	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing a 63-year-old woman with a history of rheumatoid arthritis (RA) and a 7-day history of cough and fever. What should you consider regarding how RA affects the risk of infection?

- ☐ **A** Anti-tumor necrosis factor (TNF) therapies generally reduce the risk of infection
- ☐ **B** Patients who are at increased risk of tuberculosis should receive disease-modifying anti rheumatic drug (DMARD) therapy with infliximab
- ☐ **C** The lung is the most common site of infection among patients with RA
- ☐ **D** The pneumococcal vaccine is ineffective among patients taking methotrexate

2. The patient is hospitalized for pneumonia. During the admission, she is diagnosed with interstitial lung disease (ILD). What should you consider regarding lung disease among patients with RA?

- ☐ **A** Up to 25% of patients with RA have evidence of ILD
- ☐ **B** The mean survival duration among patients with RA and ILD is 10 years
- ☐ **C** The prevalence of ILD related to RA has declined precipitously during the past 2 decades
- ☐ **D** A cryptogenic organizing pneumonia pattern of ILD carries the worst prognosis

3	The patient is concerned regarding her risk of malignancy. RA is most associated with a higher risk of which of the following forms of cancer?
	☐ **A** Myeloma
	☐ **B** Lymphoma
	☐ **C** Colorectal
	☐ **D** Renal

4	As the patient is being prepared for discharge, what should you consider regarding the effects of her RA treatment on her risk of concurrent disease?
	☐ **A** Anti-TNF agents can reduce the progression of ILD
	☐ **B** The incidence of methotrexate-induced pneumonitis is increasing
	☐ **C** Methotrexate promotes a higher risk of cardiac events
	☐ **D** Anti-TNF agents improve bone density