Future management of septic arthritis

Catherine J Mathews, Vivienne C Weston, Gabrielle H Kingsley & Gerald Coakley†

†Author for correspondence
Queen Elizabeth Hospital, Department of Rheumatology, Woolwich, London, SE18 4QH, UK
Tel.: +44 208 836 5025; Fax: +44 208 836 4958; gerald.coakley@nhs.net

Septic arthritis is a disease with a high morbidity and mortality. Antimicrobial therapy is not always sufficient to prevent joint damage and overwhelming sepsis. This review examines the progress that has been made in understanding the molecular mechanisms underlying joint sepsis. The results of this work suggest the basis for potential targets for adjunctive immunotherapy. Changing patterns in microbial etiology and sensitivities are also reviewed, and predictions made surrounding emerging causative organisms.

The presentation of a patient with one or more hot swollen joint(s) is a common medical emergency, which presents to a wide range of medical practitioners. It has a broad differential diagnosis, the most serious of which is bacterial septic arthritis. This is defined as inoculation of the joint with pathogenic microorganisms, either directly or, more commonly, by hematogenous spread. If left untreated, septic arthritis can cause rapid and irreversible joint destruction and subsequent disability [1]. In addition, the diagnosis carries a mortality of up to 11% [2].

Septic arthritis poses many clinical challenges. First, definitive diagnosis currently depends on the level of clinical suspicion of an experienced physician [3]. Although necessary to make an informed evaluation, neither laboratory investigations nor radiological imaging are sufficient to clinch the diagnosis beyond reasonable doubt. In addition, the sensitivities of causative microorganisms vary hugely, depending on demographic and clinical risk factors, creating difficulty when choosing appropriate antimicrobial therapy. The most common causative organism, *Staphylococcus aureus*, may be antibiotic resistant in certain situations. In addition, antibiotic therapy alone is not always sufficient to control the progression of joint damage and, in some cases, overwhelming sepsis.

In recent years, there have been significant developments in the understanding of the pathogenic mechanisms underlying septic arthritis. These studies have been performed exclusively in animal models, but the results have suggested directions in which human research could evolve. In this review, advances in the understanding of pathogenic mechanisms and management of septic arthritis will be discussed, as well as changing trends in the microbiological etiology of bacterial joint disease.

Pathogenic mechanisms in septic arthritis: mouse models

Bacterial septic arthritis continues to cause significant morbidity and mortality despite timely and appropriate antibiotic therapy. This implies that antimicrobial therapy alone is not always sufficient as a management approach. Efforts to develop improved therapeutic strategies rely principally on the use of animal models to elucidate the pathogenic mechanisms that underlie disease progression [4]. There are inherent difficulties in translating results from animal findings into human disease, as animal and human immune mechanisms are not precisely comparable. However, research on this subject in patients is made difficult by the ambiguity surrounding the timing of an immunological response following a septic insult, as well as ethical issues surrounding host or bacterial manipulation.

The use of experimental mouse models has several advantages in this area of study. First, the immune system in mice is well characterized and bears many similarities to its human counterpart. Mouse strains are available in which gene expression can be either attenuated or exaggerated to evaluate the contribution made by specific components of the immune system to disease pathogenesis. In addition, novel pharmaceutical and genetic therapies can be evaluated on the basis of the information derived from the results of these studies. Two mouse models have been extensively developed and studied.

Experimental Staphylococcus aureus*-mediated septic arthritis*

Tarkowski and colleagues developed an experimental mouse model of septic arthritis mediated by *S. aureus* [4]. *S. aureus* is the most common pathogen in human septic arthritis, accounting for over 80% of cases [2]. In humans, it is

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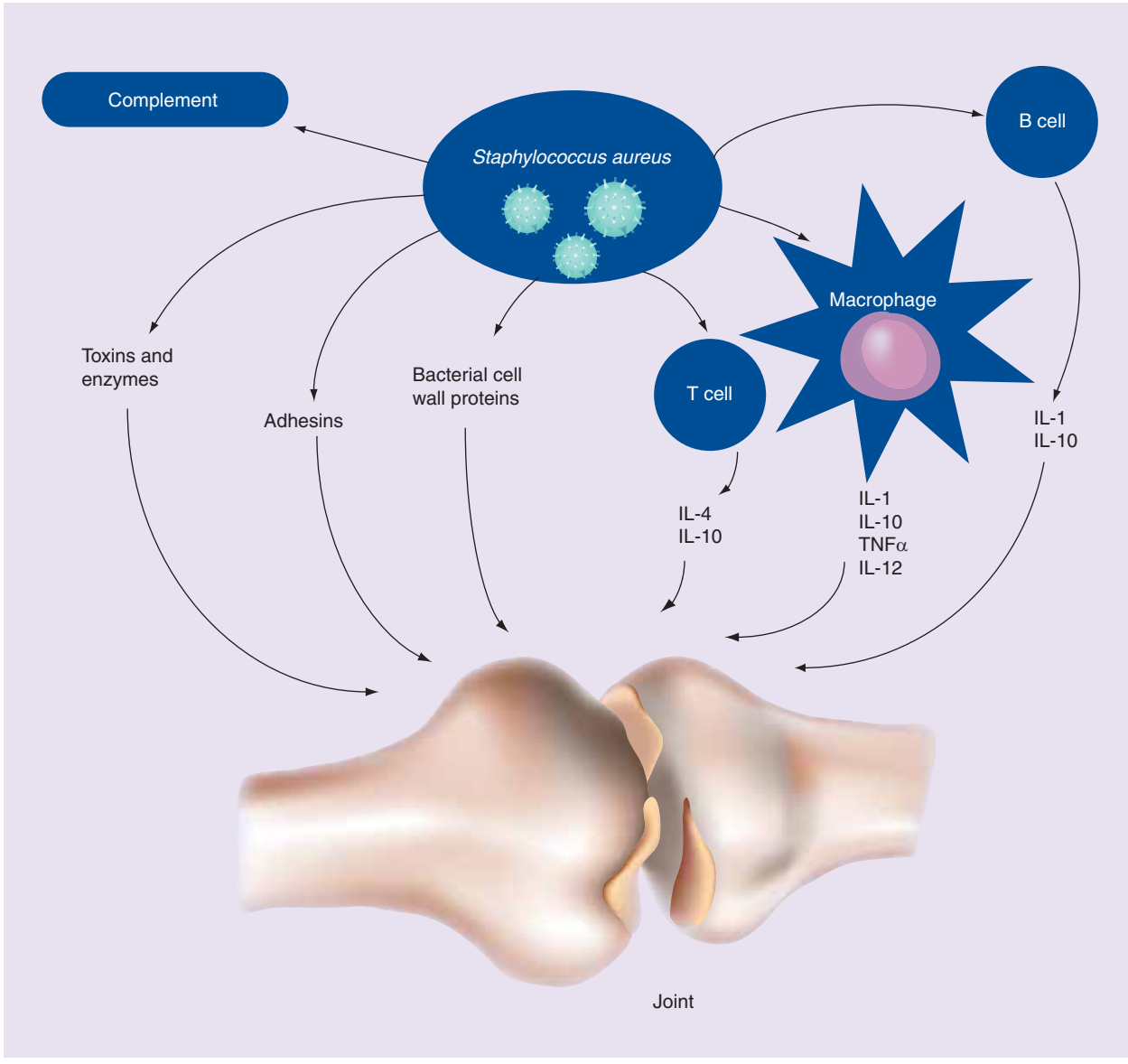
associated with a mortality of up to 11%, as well as severe morbidity due to joint destruction. This murine model parallels human disease pathogenesis closely in that the pathogen is introduced hematogenously by intravenous injection. More than 90% of the mice develop septic arthritis within 24 h of inoculation, and their joints show a severe degree of bone erosion, similar to the changes seen in the human septic joint.

The pathogenesis of staphylococcal septic arthritis is highly simplified and depicted schematically in Figure 1. Seen as a series of inter-dependent events, it is possible to visualize how targeting one or more of the steps in the pathogenic process could generate novel prophylactic or therapeutic strategies.

This model has been extensively studied to identify factors that can be manipulated to change the progression of disease. In broad terms these factors can be divided into two categories:

- Factors that determine bacterial virulence
- Factors that determine the host response to a bacterial insult

Figure 1. Simplified schematic representation of the pathogenesis of staphylococcal septic arthritis, showing potential therapeutic targets.



Bacterial virulence factors

One way in which individual components of the bacterial armamentarium can be isolated and studied is through their genetic deletion. *S. aureus* produces a large number of interacting virulence factors, which include an array of extracellular toxins, enzymes and other cell-associated components [4]. The genetic coding for these molecules, and their interactions, is also complex, and in most instances a number of genes are involved at each step. However, selective silencing of factors through genetic deletion or mutation has been performed in the *S. aureus* model. For example, a strain mutant for two gene regulators at the *agr/hld* locus, in which much lower levels of several extracellular toxins and enzymes are produced, is a much less virulent bacterial strain, with reduced erosive arthropathy in mouse recipients [5].

The virulence of bacterial molecules can also be studied by immunizing animals with purified concentrates of bacterial components. Passive immunization involves the transfer of antibodies directed against particular bacterial components into the host. Active immunization is achieved by challenging the host with antigen and the subsequent development by the host of specific antibodies. Using these approaches, the initiation of *S. aureus* arthritis through adhesion of the bacteria to tissues within the joint has been studied. Specific adhesins that facilitate *S. aureus* infection have been well characterized [6]. Inactivation of adhesins through vaccination with recombinant collagen adhesin confers a protective effect on mice subsequently challenged with intravenous *S. aureus* [7]. Mice immunized with a recombinant version of fibrinogen-binding adhesin clumping factor A, which ordinarily aids the adherence of bacteria to host tissues, also follow a less severe course of septic arthritis [8].

Constituents of the bacterial cell wall can also significantly modulate bacterial virulence. Staphylococcal protein A is one example of a protein that is expressed on the bacterial cell surface that when abrogated, in staphylococcal protein A-deficient strains, gives rise to less severe disease [9].

Certain oligonucleotide sequences within bacterial DNA have also been found to contribute to inflammatory processes in septic joints. Synthetic analogues of these sequences can themselves trigger joint inflammation and, interestingly, may also play a role in aseptic arthritis [10].

Host response factors

One of the most elegant ways of assessing the host response to staphylococcal infection is to use genetically modified knockout mice. This method has shed light on the roles of multiple components of the immune response.

The genetic deletion of macrophage-derived cytokines, including lymphotoxin-α, TNF-α and the IL-1 receptor, have been shown to reduce host protection in *S. aureus* sepsis, causing increased morbidity and mortality [11,12]. Similarly, the absence of the anti-inflammatory cytokine IL-10 in IL-10 knockout mice appears to increase the frequency and severity of staphylococcal joint disease secondary to reduced clearance of pathogens [13]. By contrast, the IL-4 knockout mouse is associated with reduced incidence and mortality. It is suggested by the authors that this may reflect the role of IL-4 in enhancing bacterial growth and/or decreasing bacterial clearance from the joint space [14]. IL-12 also appears to be critical for the survival of mice with *S. aureus*-induced arthritis [15].

The protective role of neutrophils early on in the progression of *S. aureus* infection has been shown by inoculating mice with granulocyte-depleting monoclonal antibody before being subjected to *S. aureus*. All depleted mice died of sepsis within 2–3 days whereas the control mice survived [16].

By contrast, mice administered granulocyte-macrophage colony-stimulating factor before and after inoculation with *S. aureus* follow a similar clinical course to control animals. Thus, despite the role that macrophages play in host protection, the upregulation of these cells does not appear to confer added protection.

Modulation of transcription factors also significantly influences disease progression. T-box transcription factor expression correlates with increased production of the proinflammatory cytokine IFN-γ, and in mice deficient for T-box transcription factor, the prognosis in animals with infected joints is worse [17].

Toxins can also eliminate certain components of the immune system, and in one study, cobra venom factor has been used to deplete complement, resulting in a worsening of the clinical course of septic arthritis [18].

Experimental group B streptococcus-mediated septic arthritis

An alternative murine model, developed by Tissi *et al.*, evaluates group B streptococcal (GBS) infection in adult CD-1 mice challenged

intravenously with GBS type IV microorganisms [19]. In this model, 80% of mice develop an acute exudative arthritis characterized by irreversible joint damage and ankylosis. GBS accounts for a large proportion of bone and joint infections in neonates [20], as well as contributing to the etiology of adult septic arthritis in the elderly and those patients with underlying joint disease. This model has been useful in the study of the immune mechanisms involved in disease pathogenesis and host resistance.

Treatment of mice with etoposide selectively depletes the monocyte/macrophage population, resulting in reduced production of proinflammatory cytokines. Subsequent inoculation with GBS leads to a significantly less severe arthritis than in control animals. It is suggested that a combination therapy of etoposide together with antibiotics could improve the outcome in septic arthritis [21].

Using this model, a direct correlation has been found between the severity of bacterial arthritis and the concentrations of proinflammatory cytokines, including IL-6, IL-1β and IL-18 in the joint [22,23]. In addition, the neutralization of IL-18 results in a reduction in arthritis severity, as well as downregulation of other proinflammatory cytokines presumed to be partly responsible for articular damage. Analogous to Tarkowski's model, IL-10 appears to play a protective role in GBS arthritis, and IL-10 treatment confers a better prognosis [24]. IL-12 induces the production of both IFN-γ and IL-10 and, via these cytokines, appears to ameliorate the course of septic arthritis [25].

In summary, both of these experimental mouse models have identified potential targets for therapy through elucidating the disease pathogenesis more clearly. These potential therapeutic targets are summarized in Tables 1 & 2.

Evolving adjunctive treatments

Whilst intravenous antibiotics and removal of purulent material are the gold standard for the treatment of septic arthritis, there still remains a high degree of morbidity secondary to joint destruction with resulting disability [1]. The murine models described above have demonstrated that much of the damage following the initial septic insult is due to the host's T-cell-mediated immune response. Instinctively, many physicians assume that the use of corticosteroids in the treatment of joint sepsis would be detrimental, owing to suppression of the defence mechanisms offered by the host immune system. However, there is a growing body of evidence to suggest that the immune system exacerbates, rather than ameliorates, the course of septic arthritis [26]. In fact, it might be that the concomitant use of steroids, together with appropriate antimicrobial therapy, might be a more effective treatment regimen than antibiotics alone. In one experiment using Tarkowski's murine model, mice were treated with intraperitoneal corticosteroid together with intraperitoneal cloxacillin 3 days after inoculation with intravenous *S. aureus*. The prevalence, severity and mortality associated with the subsequent arthritis were reduced compared with those mice treatment with intraperitoneal cloxacillin alone [26]. This could be due to the ability of corticosteroids to reduce the expression of adhesion molecules in T cells so that fewer T cells enter the target organ.

The use of corticosteroids is one area in which a double-blind, randomized, placebo-controlled trial has been performed in humans [27]. A total of 123 children were enrolled into a clinical trial assessing the use of dexamethasone therapy for hematogenous septic arthritis. Results showed that a short 4-day course of low-dose dexamethasone, given in conjunction with antibiotic therapy, reduced both the duration of the clinical course of disease and the extent of residual joint damage and dysfunction compared with those children given antibiotics alone.

Table 1. *Staphylococcus*-mediated septic arthritis.

Therapeutic target	Potential clinical relevance	Ref.
Bacterial virulence factors		
Collagen adhesion, ClfA, SpA	Vaccination with recombinant adhesins to improve outcome	[7–9]
Host response factors		
Lymphotoxin-α, TNF-α, IL-1	Use of anti-TNF-α as an adjunct to antibiotic treatment	[11,12]
IL-10	Use of recombinant IL-10 as an adjunct to antibiotic treatment	[13]

Table 2. Group B *Streptococcus*-mediated septic arthritis.

Therapeutic target	Potential clinical relevance	Ref.
Monocyte/macrophage population	Use of etoposide as an adjunct to antibiotic therapy	[21]
IL-18	Neutralization of IL-18 improves outcome	[23]
IL-10	Treatment with IL-10 improves outcome	[24]
IL-12	Ameliorates the course of disease	[25]

The addition of bisphosphonates to intraperitoneal corticosteroid and antibiotics adds further benefit, with an even greater reduction in the incidence and severity of arthritis. This is postulated to be due to a decrease in osteoclast activity and, therefore, reduced skeletal destruction [28].

A novel potential adjunctive therapy, in the form of free radical trap treatment, has also been shown to confer additional prognostic benefit. The addition of the compound α-phenyl-*N*-tert-butyl nitrone, which detects and traps free radicals, ameliorated the course of experimental *S. aureus* arthritis when added to antibiotic therapy, compared with treatment with antibiotics alone [29].

Nitric oxide (NO) also mediates arthritis and the reduction of NO breakdown by NO synthase aggravates the course of disease [30]. Since corticosteroids may inhibit NO synthase, this could be another mechanism by which corticosteroids exert their beneficial effect.

The role of leptin in sepsis is not clear. There are reports of leptin being an inducer of pro-inflammatory mediators, and it is perhaps surprising that leptin levels drop in mice during the course of *S. aureus* septic arthritis. Treatment of such mice with recombinant leptin significantly lowers the severity of septic arthritis, although mouse mortality is not affected [31].

Further studies would be needed in animal models before any such strategies could be contemplated in humans.

Microbiological perspective

The incidence of septic arthritis has changed over recent decades and is likely to continue to change, both as a consequence of the alteration in host risk factors and the constant evolution of organisms, which enables them to evade the host immune system or develop resistance to commonly used antibiotic treatments or vaccines.

Infection can be introduced into a joint either by direct inoculation or as a result of hematogenous spread. Infection is more likely to become established if the patient is immunosuppressed, the joint is damaged or prosthetic material is present [32]. The presence of prosthetic material enables coagulase-negative staphylococci and other skin organisms, which are traditionally uncommon causes of native joint infections, to establish a low-grade infection, that often results in failure of the prosthesis [33]. With a year-on-year increase in prosthetic joint replacements being performed, these traditionally less-pathogenic organisms will increase in importance [101]. Bacteremia is more likely to occur in immunosuppressed patients and nosocomially, particularly in those who have invasive procedures, intravascular devices or urinary catheters. A number of recent case series have demonstrated that the risk of septic arthritis increases with age, and that there is a wider range of likely causative organisms in the elderly, including Gram-negative enteric bacilli [1]. Therefore, with an aging population, more procedures being performed, more devices being inserted and the increasing use of immunosuppressive agents, the incidence of healthcare-associated infections, including septic arthritis, is likely to increase. Moreover, sepsis is more likely to be due to resistant Gram-negative and Gram-positive microorganisms such as methicillin-resistant *S. aureus* (MRSA) [2,34,35]. Immunosuppression also enables organisms that are usually unable to evade and establish infections to do so. With an increase in the use of both traditional and newer immunosuppressive agents, such as the anti-TNF-α therapies, and the increase in HIV infection, the incidence of more unusual infections of the joint, such as mycobacterial infections, will grow [36–38].

Organisms are constantly evolving and developing resistance to antibiotics. A worrying example is the emergence, in many countries, of new types of MRSA. These have been isolated from community-associated (CA) infections, including joint infections in children who do not have any of the traditional risk factors for MRSA acquisition. These CA-MRSAs have been responsible for an increase in the incidence of joint infections in some areas of

North America and are now emerging in the UK [39,40]. They have a different genetic profile and antibiotic-sensitivity pattern to the common healthcare-associated MRSA isolates and are again different from the MRSA that has been isolated from intravenous drug users in the UK and Switzerland [40,41].

Some of the traditional causative organisms are also altering their ability to produce invasive disease. For example, some of the sensitive *S. aureus* and community MRSA strains have gained the Panton–Valentine leukocidin cytotoxin, which enables them to survive in neutrophils. Panton–Valentine leukocidin cytotoxin-positive strains have been associated with fulminant infections including joint infections in previously healthy patients, and are starting to be seen in the UK [42]. In other European countries, *Kingella kingae* has emerged as a common cause of septic arthritis in young children. This may, in part, be due to better laboratory detection using molecular techniques but is still an uncommon cause in the UK. It should be considered if culture-negative cases in children increase [43–45]. By contrast, *Neisseria gonorrhoeae* is now a rare cause of septic arthritis in Western Europe, and if a *Neisseria* sp. from a septic joint is isolated it is more likely to be *Neisseria meningitidis* than *N. gonorrhoeae* [1,2,35,46].

Organisms may also decline in incidence owing to the introduction of new vaccines, as seen with the successful introduction of the *Hemophilus influenzae* type b conjugate vaccine. This vaccine was introduced to reduce the incidence of childhood meningitis but has also produced a dramatic reduction in bone and joint infections in young children [34]. The recent introduction of a conjugate pneumococcal vaccine is unlikely to have such a dramatic effect, as pneumococci are a less common cause of septic arthritis and only a limited number of serotypes can be contained within the conjugate vaccines.

In conclusion, the incidence of septic arthritis is likely to increase and the spectrum of organisms will continue to change. Therefore, it is important to take appropriate specimens for culture prior to starting empirical antibiotic treatment, and guidelines for septic arthritis should be reviewed and updated regularly. Treatment should take into account the patient's risk factors and up-to-date information on the likely pathogen, together with sensitivity data [3].

Conclusion

There is now a large body of evidence from experimental animal studies shedding light on the molecular pathogenesis of bacterial septic arthritis. The use of mouse models has increased the understanding of bacterial virulence and host response factors, providing the basis for potential adjunctive immunotherapeutic targets in the treatment of joint sepsis. Clinical studies have shown that there may be a role for steroids and bisphosphonates as useful therapies in conjunction with standard antibiotic regimes.

The increase in arthroplastic surgery is changing the frequency of causative organisms in septic arthritis. In addition, new strains of community MRSA and increasing numbers of immunosuppressed individuals are changing the patterns of microbiological involvement.

Future perspective

Much of the work from the animal studies described in this review focuses on the development of adjunctive immunotherapies, which might in the future be used in conjunction with traditional antimicrobial regimes in the treatment of septic arthritis. Apart from clinical studies on the use of corticosteroid therapy in children, these novel therapies are still a long way from human trials. The use of glucocorticoids and bisphosphonates is perhaps closer to making the transition from bench to bedside, and it may be that these therapies will emerge as viable additions to antibiotic treatment.

Changing microbial sensitivities and the emergence of newer causative organisms, such as community MRSA, mycobacteria and *K. kingae*, will also take on a much higher profile in the investigation and treatment of suspected septic arthritis in the future. Close consultation with local microbiological departments will continue to be required to ensure that antimicrobial agents with adequate sensitivities are used in the initial empiric stages of treatment.

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Executive summary

Mouse models of septic arthritis

- The use of experimental mouse models of septic arthritis has increased the understanding of bacterial virulence factors and host factors that influence disease outcome.
- These provide the basis for potential immunotherapeutic targets as adjunctive treatment in septic arthritis.
- As yet, there has been no translation of this work from the bench to the bedside.

Evolving adjunctive therapies

- Trials have suggested that both steroids and bisphosphonates may be useful therapies, in addition to the use of antibiotics, in septic arthritis.

Microbiological perspective

- The increasing use of prosthetic joints is changing the spectrum of causative organisms in septic arthritis.
- New strains of resistant organisms, such as evolving methicillin-resistant *Staphylococcus aureus* isolates, are providing challenges in the choice of effective antibiotic therapy.
- Increasing immunosuppression, both iatrogenic and pathogenic, is also changing the pattern of causative organisms.

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Affiliations

- *Catherine J Mathews*
  Queen Elizabeth Hospital, Department of Rheumatology, Woolwich, London, UK
- *VC Weston*
  Nottingham University Hospitals NHS Trust, Department of Microbiology, QMC Campus, Nottingham, UK
- *G Kingsley*
  University Hospital Lewisham, Department of Rheumatology, London, UK
  and,
  Kings College Hospital, Department of Rheumatology, London, UK
- *Gerald Coakley*
  Queen Elizabeth Hospital, Department of Rheumatology, Woolwich, London, UK
  Tel.: +44 208 836 5025
  Fax: +44 208 836 4958
  gerald.coakley@nhs.net