Invasive group A streptococcal infection (iGAS) is the most common cause of monomicrobial necrotising fasciitis. Necrotising infections of the extremities may present directly to orthopaedic surgeons or by reference from another admitting specialty. Recent epidemiological data from the Health Protection Agency suggest an increasing incidence of iGAS infection in England. Almost 40% of those affected had no predisposing illnesses or risk factors, and the proportion of children presenting with infections has risen. These observations have prompted the Chief Medical Officer for the Central Alerting System in England to write to general practitioners and hospitals, highlighting the need for clinical vigilance, early diagnosis and rapid initiation of treatment in suspected cases.

The purpose of this annotation is to summarise the recent epidemiological trends, describe the presenting features and outline the current investigations and treatment of this rare but life-threatening condition.

Overview of group A streptococcal infection

Group A streptococcus (GAS, Streptococcus pyogenes) is a human-specific facultative anaerobic bacterium which causes high morbidity, characterised by infections in the skin and upper respiratory tract.1 The prevalence of asymptomatic carriage of the bacterium is 15% to 20% in children, but much lower in the general adult population (1% to 2%), although the rates vary with age and ethnicity.1,2 The most common presentation of GAS infection is with pharyngitis, which accounts for 5% to 40% of cases seen by general practitioners in the United Kingdom.3 Skin and soft-tissue infections such as impetigo, erysipelas and localised cellulitis are also common.1,4 Less commonly GAS infection may become invasive, leading to bacteraemia, necrotising skin and soft-tissue infections, including necrotising fasciitis, myositis, pneumonia and puerperal sepsis.4-7 In up to 50% of cases invasive infections may be complicated by toxic shock syndrome.5,8,9 Scarlet fever and puerperal sepsis have historically been the leading causes of morbidity and mortality due to GAS, with death rates of 25% to 30% toward the end of the 19th century.7 The sequelae of streptococcal infection include acute rheumatic fever, glomerulonephritis and reactive arthritis. These are associated with significant morbidity and mortality worldwide.10

Definition of invasive GAS infection

Invasive group A streptococcal (iGAS) infection is defined as the culture of group A streptococci from a normally sterile site.11 It may occur following a direct penetrating injury or a surgical incision, but in up to 45% of cases there is no direct injury.12,13 These infections develop spontaneously, or secondarily to minor blunt trauma or muscle strain, with haematogenous or lymphatic spread responsible for the translocation of GAS from the colonised pharynx to the site of muscle injury.14 The majority of patients do not have preceding symptoms of pharyngitis or tonsillitis.15 Severe pain, swelling and erythema may be the initial features, with subsequent rapid development of a compartment syndrome15,16 and the classic blistered, necrotic sloughing of the skin typical of necrotising fasciitis. Most cases of myositis involve a single muscle group, but because patients are frequently bacteraemic, many additional sites might become involved.16,17 Severe pain out of proportion to the clinical signs at early presentation should raise concern of possible iGAS infection rather than simple cellulitis.12

iGAS bacteremia occurs most commonly in the very young and the elderly.18 Predisposing factors in children include burns, varicella infection, malignancy, immunosuppression and age less than two years.18 In the elderly, the source of iGAS infection is normally the skin,
associated with conditions such as cellulitis or erysipelas. Diabetes, peripheral vascular disease, malignancy and corticosteroid use are also risk factors. Mortality rates of 35% to 80% have been described in these groups.28

Mechanisms of pathogenicity
The mechanisms of Group A streptococcal virulence have been extensively studied but this has historically been hampered by the lack of a suitable animal model that replicates the manifestations of GAS in humans.19 The recent acquisition of an appropriate animal model of human-like pharyngitis has facilitated our understanding of intracellular bacterial invasion and the ways the streptococci avoid the immune system.20

Adherence to epithelial cells
GAS is a Gram-positive organism with the primary surface antigen proteins M and T. Pili-like structures on its surface are important for adherence of epithelial cells and biofilm formation.19,21 The major subunit of the pilus corresponds to the T antigen, which forms the basis of one scheme of classifying GAS (Lancefield T serotypes).22,23 GAS fibronectin-binding proteins (FnBPs) are also important for adherence and in addition inhibit the deposition of C3 (complement protein) on the cell surface, thereby conferring resistance to phagocytosis.19,24

Intracellular invasion
GAS is predominantly an extracellular pathogen, but it may invade and survive within epithelial cells. This ability is conferred through FnBPs and M proteins,19 and is associated with resistance to treatment with penicillin.25

Immune system avoidance
The hyaluronic acid capsule and surface M proteins of the organism are important mechanisms which allow GAS to escape the host’s immune response.19 M proteins prevent phagocytosis and inhibit neutrophil chemotaxis.26

In addition to the virulence factors identified above, the ability of GAS to cause invasive disease is dependent on a number of additional characteristics.

Tissue necrosis. Extracellular proteases and pore-forming cytoxins, such as streptolysin O,27 secreted by iGAS cause widespread tissue destruction, creating an environment favourable to bacterial invasion.19

Direct actions against host immune-defence molecules. The secreted Mac1, protein homologue of human leucocyte β2-integrin,19 inhibits the function of neutrophils by binding CD1628 and also cleaves IgG, thereby enhancing pathogen survival.19 SpeB, a broad-spectrum cysteine protease, activates host matrix metalloproteinases, and this results in the autodegradation of important barriers to bacterial invasion in a mechanism analogous to tumour cell invasion.19 M proteins have also been demonstrated to bind host organism plasminogen, which is converted into plasmin by GAS streptokinase. This increases bacterial virulence and may be one reason why coagulopathy is a well-recognized feature of the more severe diseases caused by GAS.19

Pyrogenic exotoxins. Streptococcal pyrogenic exotoxins A and B induce human mononuclear cells to produce tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6, and thereby mediate the fever, shock and organ failure present in patients with streptococcal toxic shock.7 Streptococcal pyrogenic exotoxins A, B and C act as superantigens and stimulate T-cell proliferation by binding to both antigen-presenting cells and T cells. This leads to further production of inflammatory cytokines that are important in the development of toxic shock.7

Host factors: environment, comorbidity and genetics. Individuals infected with the same strain can develop variable manifestations of disease according to the interactions between the host environment, comorbidities and genetics.19 Blunt trauma may encourage invasion of GAS because of the upregulation of vimentin expression in injured and regenerating soft tissue, as this molecule acts as a GAS-binding protein.19 In children, preceding varicella-zoster infection, use of non-steroidal anti-inflammatory drugs (NSAIDs) and age of first exposure are associated with iGAS infection.19,29,30 In adults, any condition that leads to immunosuppression or a weakness in anatomical or physiological defences will predispose to iGAS disease. Examples include intravenous drug abuse, malignancy, diabetes, alcoholism and the use of NSAIDs.19

Certain human leucocyte antigen (HLA) class I haplotypes appear to confer protection from more severe infection, but others may predispose to it.31 This may be explained by differential binding to GAS superantigens,32 polymorphisms in TNF haplotypes31 and the level of cytokine response.33 There may therefore be a role for immunomodulatory agents in the management of iGAS infection.19

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An epidemiological update

The number of spontaneous community-based cases of necrotising fasciitis caused by iGAS has increased over the last six years. The generalised increase in iGAS disease has continued during 2008 and 2009, prompting a period of enhanced surveillance by the Health Protection Agency, and Communication from the Chief Medical Officer for England’s Central Alerting System to general practitioners and hospitals. The latest report of the Health Protection Agency in July 2009 preliminarily identified 1012 cases of iGAS between week 37, 2008 and week 20, 2009, compared to between 712 and 887 cases for the same period in the previous four years. These cases are identified through routine national laboratory surveillance and isolate referral to the National Reference Laboratory, with reports issued by the Health Protection Agency. A further iGAS situation report, issued by the Health Protection agency on 15 January 2010, indicates a > 50% increase in iGAS isolates for the summer months in 2009, compared to 2008 (Fig. 1). The clinical and demographic data for 2009 are presented in Figure 2. This report is not yet in the public domain and is therefore not formally citable at the time of writing.

The increases seen in 2009 are specific to certain regions. Provisional data up to July 2009 for the East Midlands, London, North East, North West, South East and South West demonstrated higher than expected case loads, but Wales and Northern Ireland have not observed such increases. At present it remains unclear why this recent increase in incidence, which is beyond the normal seasonal variation or the natural cycle, has occurred.

The latest provisional analysis of data for 2009 has not demonstrated a disproportionate increase in any single at-risk group, although the proportion of children presenting is higher than in 2003-2004, the previous period of enhanced surveillance. The proportion of younger adults and those with no pre-existing comorbidities has increased in recent years. Environmental, host behaviour and bacterial factors are implicated. As the majority of cases occur spontaneously, the possibilities for preventative public health campaigns are limited. There are concerns that a swine influenza A (H1N1v) pandemic will lead to a higher number of patients vulnerable to secondary bacterial infections, including iGAS.

The increased incidence of iGAS over the past two decades is due mainly to the emergence of new virulent strains. Enhanced pathogenicity may partly explain these trends. Although analyses of isolates submitted to the National Reference Laboratory has not identified any unusual serotypes to be currently circulating; a significant increase in M3 subtypes was seen during 2009. The M protein is the primary factor responsible for resistance to phagocytosis, thereby
determining the degree of virulence of the organism.\textsuperscript{39} This protein reduces the activation of complement by the alternate pathway and so inhibits deposition of C3 complement on the bacterial cell, thereby increasing resistance to complement and phagocytosis. The modern invasive streptococcal strains that are encapsulated and rich in M protein, have enhanced virulence\textsuperscript{39} and are more likely to result in rapid and wider tissue destruction,\textsuperscript{16} which is associated with a very high mortality rate (80\% to 100\%).\textsuperscript{5} The M1 and M3 serotypes are associated with severe clinical presentations\textsuperscript{9,13,40} and are currently the focus of intensive molecular studies.\textsuperscript{11}

In 2009, 20 confirmed iGAS cases presented to our hospital. Of these, eight involved the extremities and were managed by the Combined Orthopaedic and Medical Microbiology Service. Five of the 20 cases developed severe toxic shock syndrome. There were five fatalities, three of whom had toxic shock syndrome. The M3 serotype was the most common, seen in eight cases.

### Laboratory and radiological aids to diagnosis

Although investigations may aid the diagnosis, it is important that these should not delay surgical debridement.

By definition, the diagnosis of iGAS infection requires isolation of the organisms from normally sterile sites such as blood and joint fluid, and from debridement specimens. Blood cultures should be obtained prior to commencing antibiotic therapy. All tissue samples should be microbiologically cultured and epidemiologically investigated with M and T typing. Fascial biopsy, whereby the specimen is sent for Gram stain, frozen section and culture, may be helpful to confirm necrotising fasciitis but should be reserved for stable patients in whom the diagnosis is unclear.\textsuperscript{12}

Scoring systems based on laboratory results have been described to aid in the diagnosis of necrotising fasciitis and its differentiation from less severe infections, including cellulitis.\textsuperscript{41} Wong et al's\textsuperscript{42} Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) score is calculated from the serum CRP, white cell count and measurements of haemoglobin, sodium, creatinine and glucose (Table I). A score of \( \geq 6 \) is reported to have a positive predictive value of 92\%, and a score < 6 a negative predictive value of 96\% for necrotising streptococcal infections.\textsuperscript{42} The serum lactate is also a useful indicator of severity and a predictor of mortality.\textsuperscript{43}

MRI has a sensitivity of 90\% to 100\% with a specificity of only 50\% to 85\% for detecting necrotising infections.\textsuperscript{44} Findings that are relatively specific to these infections include a hyperintense signal on T2-weighted images in the deep fascia and within the muscles, and peripheral enhancement on contrast enhanced T1-weighted images.\textsuperscript{45} Plain radiographs may demonstrate subcutaneous emphysema which, albeit pathognomonic for necrotising infection, is often not present until the advanced stages of the condition.\textsuperscript{5}

### Treatment

**Surgical.** Early complete surgical debridement is the only intervention shown to alter the rate of mortality of necrotising fasciitis.\textsuperscript{46} The incision should be placed directly over the infected tissue, with debridement to pink, bleeding viable tissue. On occasion amputation may be the only way to ensure an adequate debridement. Surviving patients will require further wound inspections and ultimately soft-tissue reconstruction as appropriate, in liaison with plastic surgeons. Vacuum-assisted closure dressings may be used as an adjunct to promote an environment for wound healing.\textsuperscript{47}

**Medical.** The management of iGAS infection requires aggressive antibiotic treatment. Empirical antibiotics should be commenced when necrotising fasciitis is suspected. A Gram-stain followed by the results of culture should then guide more focused antibiotic prescription. Despite universal sensitivity to penicillin,\textsuperscript{7} penicillin monotherapy is associated with higher failure rates and poor outcomes in cases of severe streptococcal infection.\textsuperscript{7,48} This may be explained by its relative ineffectiveness when large numbers of organisms are present (the Eagle effect),\textsuperscript{7,49} and the evolving ability of GAS to invade cells where penicillin cannot reach sufficiently high concentrations.\textsuperscript{25,30} Clindamycin has several advantages in the management of iGAS infection (Table II). For empirical therapy, high doses should be administered (1.2 g six-hourly).

| Table II. Important factors contributing to the efficacy of clindamycin in the treatment of iGAS infection\textsuperscript{7} |  |
| --- | --- | --- |
| Factor | Mechanism | Effect |
| Efficacy is unaffected by the inoculum size or stage of growth of bacterium | Bacteria in stationary phase do not synthesise penicillin-binding proteins (penicillin target) but continue to synthesise proteins (clindamycin target) | Effective even if treatment delayed (compared with penicillin) |
| Inhibits bacterial ribosome function | Suppresses synthesis of exotoxins (superantigens) | Limits unregulated immunological response |
| | Suppresses synthesis of M proteins | Facilitates phagocytosis |
| | Suppresses synthesis of penicillin-binding proteins | Inhibits cell wall synthesis |
| Long post-antibiotic effect | Observed in antibiotics that suppress nucleic acid or protein synthesis | Superior efficacy over penicillin |
| Suppresses tumour necrosis factor and other cytokines | Suppresses synthesis of superantigens | Modulates immune response to iGAS and toxic shock |
The phenomenon of dissociated cross-resistance is clinically important and a potential concern with clindamycin. Erythromycin, a macrolide, has been widely prescribed to treat GAS, particularly in patients allergic to penicillin. However, GAS resistance to erythromycin is widespread, with rates of up to 10%.\textsuperscript{51,52} Dissociated cross-resistance occurs when an iGAS strain showing an \textit{in vitro} resistance to erythromycin and sensitivity to clindamycin, exhibits an \textit{in vivo} resistance to clindamycin on treatment. Cross-resistance is detected with a simple disc approximate test, commonly referred to as the ‘D test’. Resistance may be due to methylation of the ribosomal drug-binding site, which mediates resistance to macrolides, lincosamides and streptogramin group B (MLS\textsubscript{B}).\textsuperscript{52} Methylases are encoded by the \textit{erm} genes, particularly \textit{ermB}.\textsuperscript{52} Although cross-resistance is uncommon, occurring in less than 5%,\textsuperscript{52} and clindamycin remains the most effective antibiotic therapy, most authorities would recommend the addition of another agent, such as a \textit{β}-lactam or linezolid, until the results of sensitivity tests are known.\textsuperscript{12} Linezolid also inhibits bacterial ribosome function, reducing M protein and the production of exotoxin.\textsuperscript{12} The combined effect of clindamycin and linezolid is to facilitate phagocytosis of bacteria and suppress the synthesis of TNF-\textit{α}, thereby limiting excessive immune response.\textsuperscript{12,48} Clindamycin combined with a \textit{β}-lactam (e.g. meropenem) or linezolid is recommended as the first-line treatment for iGAS.\textsuperscript{12}

Supportive. In addition to cardiovascular, renal and nutritional support in critical care, intravenous immunoglobulins are an effective adjunctive therapy and act by neutralising superantigen.\textsuperscript{12} The benefits of hyperbaric oxygen are unproven.\textsuperscript{53} NSAIDs are best avoided as they may mask the clinical signs, and accelerate the course of infection.\textsuperscript{54} A protocol for management is shown in Figure 3.

Fig. 3
Outcomes
The rate of mortality in necrotising fasciitis generally ranges between 11% and 30%. Cases of iGAS necrotising infection have a rate of mortality of between 80% and 100%. Age less than one or more than 60 years, the development of streptococcal toxic shock syndrome and immunocompromise are independent predictors of mortality. Survivors have a high morbidity, requiring long stays in acute hospitals, and frequently have disabilities that require complex support in the community.

Illustrative case
A 50-year-old woman, previously healthy, sustained a cut on the plantar aspect of her left great toe. After three days she developed erythema on the dorsum of the foot and at six days had rigors and a fever of 40°C. She attended the A&E department on the ninth day after injury and was noted to be apyreal. A clinical diagnosis of cellulitis was made. She was discharged on a regimen of clindamycin 450 mg six-hourly. On day 11 she re-presented with purple blistering on the dorsum and sole of the foot. Her ankle was stiff and painful, the calf swollen, and she was unable to walk. Her blood pressure was 84/50 mmHg and she remained afebrile. A clinical diagnosis of necrotising fasciitis was made and she underwent emergency surgical debridement. The operative findings confirmed the suspected diagnosis, with grey sloughing of the skin and seropurulent fluid throughout the superficial soft tissues of the dorsum of the foot. Debridement, which included the superficial peroneal nerve, was carried out to healthy tissue. The empirical antibiotic regimen commenced was linezolid 600 mg 12-hourly, vancomycin 1 g 12-hourly, clindamycin 1.2 g six-hourly. All samples grew iGAS, resistant to erythromycin and sensitive to clindamycin, but later tested positive for dissociated cross-resistance to iGAS, resistant to erythromycin and sensitive to clindamycin, and higher rates of mortality. These patients frequently present as orthopaedic emergencies, as demonstrated by our illustrative example. Although the current high incidence may not be sustained, it is important that orthopaedic surgeons are aware that diagnosis primarily relies upon clinical suspicion, but may be augmented by scores such as the LIRINEC, that patients may deteriorate rapidly, and that prompt surgical debridement together with appropriate antimicrobial therapy is essential and associated with an improved outcome.

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Summary
Epidemiological data suggest that there has been a recent increase in the incidence of iGAS infection, with a higher proportion of cases affecting individuals with minimal comorbidity. Although the reasons for these trends are not clear, the bacteria isolated are more virulent and consequently associated with more widespread tissue destruction and higher rates of mortality. These patients frequently present as orthopaedic emergencies, as demonstrated by our illustrative example. Although the current high incidence may not be sustained, it is important that orthopaedic surgeons are aware that diagnosis primarily relies upon clinical suspicion, but may be augmented by scores such as the LIRINEC, that patients may deteriorate rapidly, and that prompt surgical debridement together with appropriate antimicrobial therapy is essential and associated with an improved outcome.

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