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Original

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Invasive group A *Streptococcus* infection (*Streptococcus pyogenes*): Current situation in Spain

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ABSTRACT

Group A ß-hemolytic *Streptococcus* (*S. pyogenes*), also known as GAS, is a Gram-positive bacterium. It can be easily identified in the microbiology laboratory by its ability to hemolyse blood in culture media. This bacterium is highly virulent due to its production of enzymes and toxins, and its ability to cause immunologically mediated diseases such as rheumatic fever and post-streptococcal glomerulonephritis.

GAS is the primary cause of bacterial pharyngotonsillitis, although it is typically a benign and non-invasive disease. However, it also has the potential to cause severe skin and soft tissue infections, necrotising fasciitis, bacteraemia and endocarditis, pneumonia and empyema, and streptococcal toxic shock syndrome, without any age or predisposition limits. The term invasive GAS disease (iGAS) is used to refer to this group of conditions.

In more developed countries, iGAS disease has declined thanks to improved hygiene and the availability of antibiotics. For example, rheumatic fever has practically disappeared in

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countries such as Spain. However, recent data suggests a potential increase in some iGAS diseases, although the accuracy of this data is not consistent.

Because of this, the COVID and Emerging Pathogens Committee of the Illustrious Official College of Physicians of Madrid (ICOMEM) has posed several questions about invasive GAS infection, especially its current situation in Spain. The committee has enlisted the help of several experts in the field to answer these questions. The following lines contain the answers that we have collaboratively produced, aiming to assist not only the members of ICOMEM but also anyone interested in this topic.

Keywords: *Streptococcus pyogenes*, **group A *streptococcus*, pharyngotonsillitis, bacteraemia, endocarditis, skin and soft tissue infection, necrotising fasciitis, pneumonia, explosive pleuritis, empyema, streptococcal toxic shock syndrome, SSTS, rheumatic fever. glomerulonephritis.**

Infección invasora por estreptococo del grupo A (*Streptococcus pyogenes*): situación actual en España

RESUMEN

Streptococcus ß-hemolítico del grupo A (*S. pyogenes*) (SGA) es una bacteria Gram positiva fácil de identificar en el laboratorio de microbiología por muchos procedimientos, pero particularmente por su capacidad de hemolizar la sangre en los medios de cultivo. Su virulencia está bien acreditada por la producción de enzimas y toxinas, pero también por la capacidad de inducir enfermedades inmunológicamente mediadas tales como la fiebre reumática o la glomerulonefritis postestreptocócica.

Es el agente causal de la mayoría de las faringoamigdalitis bacterianas que en general se comportan como enfermedades benignas y no invasoras. Al mismo tiempo, ha demostrado su capacidad de producir infecciones graves en piel y tejidos blandos, fascitis necrotizantes, bacteriemia y endocarditis, neumonías y empiemas, síndrome del shock tóxico estreptocócico y otras muchas sin respetar límites de edad ni de predisposición. Para este último conjunto de cuadros utilizamos el término de enfermedad invasora por SGA (iSGA).

La iSGA había disminuido en los países más desarrollados al amparo de la mejor calidad de la higiene y de la disponibilidad de antibióticos al punto de una práctica desaparición de la fiebre reumática en países como España. Sin embargo, datos recientes, aunque no siempre precisos, hablan de un aumento de algunas enfermedades iSGA.

Por este motivo, el Comité de COVID y patógenos emergentes, del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) se ha formulado una serie de preguntas sobre la infección iSGA y particularmente su situación en España. El Comité ha convocado a algunos expertos en el tema recabando su ayuda para responder a dichas preguntas. Las líneas que siguen son las respuestas que hemos producido entre todos, tratando de ser útiles no solo a los colegiados de Madrid si no a todos los interesados en el tema.

Palabras clave: *Streptococcus pyogenes*, ***Streptococcus* grupo A, faringoamigdalitis, bacteriemia, endocarditis, infección de piel y partes blandas, fascitis necrotizante, neumonía, pleuritis explosiva, empiema, síndrome del shock tóxico estreptocócico, SSTS, fiebre reumática, glomerulonefritis**

INTRODUCTION

The disease caused by Lancefield's group A *Streptococcus* (*Streptococcus pyogenes*) has a long history as a cause of infection in humans. Unlike less severe forms of the disease, such as pharyngitis, invasive Group A *Streptococcus* infections (iGAS) can lead to systemic and often fatal manifestations. Additionally, Group A *Streptococcus* can trigger immune responses that result in tissue damage, such as rheumatic fever and post-streptococcal glomerulonephritis. The pathogen's ability to produce toxins with multiple targets makes it one of the most feared infectious diseases in history. The availability of antimicrobials, particularly penicillin and its derivatives, has helped alleviate some of the fear associated with this pathogen.

During the pandemic years, there was a documented decrease in iGAS infections. However, there have been warnings of an increase in iGAS diseases in the aftermath, particularly in the last two years and especially in children [1]. Since the pathogen is not notifiable in most nations, records may not always be accurate, but many data point to a resurgence of iGAS as a cause of disease in all age groups.

Given these uncertainties and a desire to understand the situation in Spain, the COVID-19 and Emerging Pathogens Committee of the Official College of Physicians of Madrid (ICOMEM) has posed a series of questions on this issue and sought answers from experts. The following are the answers to these questions, discussed and agreed upon by the working group.

WHAT DEFINES A GROUP A *STREPTOCOCCUS* (*S. PYOGENES*) AS A MICROORGANISM, AND HOW CAN ITS TOXIC CAPACITY AND MECHANISMS BE DESCRIBED?

S. pyogenes, also known as group A ß-hemolytic *Streptococcus* (GAS), is a highly virulent bacterium that can cause a wide range of infections with varying severity. These infections can range from mild, such as acute pharyngitis or erysipelas, to very aggressive forms like necrotising skin and soft tissue infections or streptococcal toxic shock syndrome (SSTS). These severe cases are referred to as invasive GAS infections (iGAS). Additionally, GAS can lead to autoimmune or post-infectious diseases such as rheumatic fever (RF) and acute glomerulonephritis.

GAS is a human-exclusive pathogen, and the skin and mucous membranes of colonised individuals (healthy carriers) serve as the natural reservoir.

In terms of its essential microbiological characteristics, it is a Gram-positive bacterium that appears as cocci in chains when viewed under Gram staining.

GAS is an aerobic and facultative anaerobic, non-motile, non-spore-forming bacterium. It thrives well on standard culture media at 37°C, preferably in a 10% CO_2 environment. It produces complete hemolysis in blood-enriched culture media (Figure 1). Identification in the laboratory is straightforward.

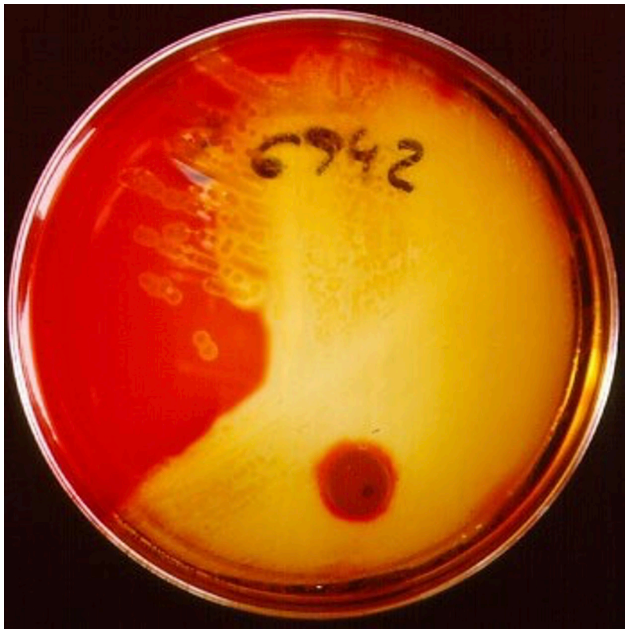


Figure 1 | **Complete haemolysis in a culture medium enriched with blood from *S. pyogenes***

Like other streptococci, it is catalase negative, which sets it apart from the *Staphylococcus* genus, and belongs to group A according to the Lancefield classification. It can ferment some carbohydrates, producing lactic acid, and can be readily identified by MALDI-TOF (matrix-assisted laser desorption/ionisation time-of-flight) and other procedures.

The microorganism has various virulence factors involved in the adhesion and colonisation process (lipoteichoic acid), in evading the immune system (hyaluronic acid capsule, C5a peptidase, M protein, streptolysin O, streptococcal pyrogenic exotoxin B), and in facilitating the spread of the bacterium in the host's soft tissues (streptokinase, hyaluronidase, streptolysin S) [2-9]. Some of their toxins and their effects are presented in Table 1.

HOW IS THE HUMAN DISEASE CAUSED BY GAS CLASSIFIED? WHAT ARE THE LEADING CAUSES? WHAT ARE THE PRIMARY FORMS OF INVASIVE DISEASE?

GAS can cause a wide range of symptoms, from no symptoms to severe and life-threatening illnesses [10]. Diseases caused by GAS can be categorised based on how they are produced: through direct invasion of tissues by the bacteria or by toxins, immunological mechanisms, or inflammation (Table 2).

GAS can directly invade specific tissues, leading to localised infections, or enter the bloodstream and spread to other organs. The most common localised infections associated with GAS are throat and tonsil infections and skin and soft tissue infections, which significantly impact global health [11,12]. Throat and tonsil infections can lead to local suppurative infections like suppurative adenitis, cellulitis, and abscesses or spread to nearby sinuses and the central nervous system. Skin

Table 1 | **Main virulence factors of *S. pyogenes* and their effects**

Virulence factor	Effects
Lipoteichoic acid	It forms a complex with the M-protein and contributes to the adherence to epithelial cells.
Hyaluronic acid capsule	It confers antiphagocytic properties by preventing the opsonisation of the bacteria [5].
Peptidase C5a	An enzyme that degrades the C5a component of complement (essential in chemotaxis), reducing the attraction of complement to the phagocytes.
M protein	Antigen that inhibits phagocytosis by polymorphonuclear cells and prevents intracellular killing of the bacteria. The increased prevalence of M1 and M3 types has been associated with increased invasive infections by this microorganism [6].
Haemolysins or streptolysins O and S	Streptolysin O is an antigenic cytotoxin that forms transmembrane pores in leukocytes, tissue cells and platelets, leading to their lysis [7]. Streptolysin S is non-antigenic but also produces pores in various cells, especially toxic to leukocytes that phagocytose streptococci [8]. Both are responsible for the erythrocyte lysis that can be observed in the blood agar cultures mentioned above.
Streptokinase	Transformation of plasminogen into plasmin that destroys fibrin and contributes to the dissemination of the infection.
Hyaluronidase	Hydrolyses the hyaluronic acid in connective tissue, conferring the ability to disseminate it in tissues.
Streptodornases or deoxyribonucleases	They promote dissemination by depolymerising tissue DNA.
Streptococcal pyrogenic or erythrogenic toxin (Spe)	There are four types: A, B, C, and D. They behave as superantigens, causing fever, rash (scarlet fever), T-lymphocyte proliferation, B-lymphocyte suppression, and increased susceptibility to endotoxins [9] The production of types A and C depends on the presence of an early gene carried by a bacteriophage. A chromosomal gene produces B.
Protein F and LT	Surface proteins that bind to fibronectin and interfere with opsonisation.

Table 2 Diseases caused by *S. pyogenes* according to location and mechanism of production

Through direct invasion by GAS
Focal infections
Tonsillopharyngitis
Skin and soft tissue infections
Impetigo
Erysipelas
Cellulitis
Necrotising fasciitis (myonecrosis, streptococcal gangrene)
Scarlet fever*
Puerperal sepsis
Others (pneumonia, empyema, endocarditis, meningitis, arthritis, osteomyelitis)
Bacteraemia
By other mechanisms
Inflammatory: Streptococcal toxic shock syndrome
Immunological:
Glomerulonephritis
Rheumatic fever

* Produced by toxin

Table 3 Diseases caused by *S. pyogenes* according to their degree of invasion

Superficial infections
Tonsillopharyngitis
Impetigo
Scarlet fever
Invasive infections
Erysipelas
Cellulitis
Necrotising fasciitis
Bacteraemia
Streptococcal toxic shock syndrome
Puerperal sepsis
Others (pneumonia, empyema, endocarditis, meningitis, arthritis, osteomyelitis)
Non-suppurative sequelae
Glomerulonephritis
Rheumatic fever

and soft tissue infections can affect all layers, from the surface to the muscle, and can lead to severe necrotising fasciitis (NF) [13]. Additionally, GAS can affect the skin through the pyrogenic (erythrogenic) toxin, causing scarlet fever and resulting in recent outbreaks in multiple countries following its near disappearance at the end of the 20th century [14]. GAS can also lead to rare conditions such as puerperal sepsis.

Any localised infection can lead to GAS entering the bloodstream, causing bacteraemia and potentially leading to distant metastasis. Although rare, GAS can also cause other localised infections through the bloodstream (such as pneumonia, endocarditis, meningitis, and osteoarticular infections). Streptococcal toxic shock syndrome (STSS) can occur in association with any streptococcal infection, with or without bacteraemia, and is also triggered by pyogenic toxins.

In addition to direct invasion or toxin-based diseases, some GAS infections can result in non-suppurative complications through immunological mechanisms, such as developing autoantibodies and immune complexes. Post-streptococcal glomerulonephritis can develop after skin and throat infections. In contrast, rheumatic fever (RF), which typically follows a throat infection, can lead to secondary valvular heart disease and remains a common cause of early cardiovascular morbidity and mortality in young people worldwide [15] (Table 2).

Another way to classify diseases caused by GAS is by considering the level of invasion they cause (Table 3).

Based on the information above, it can be inferred that GAS infections can be divided into superficial, relatively mild cases (such as pharyngotonsillitis, superficial foot infections, and scarlet fever) and invasive, often severe infections (such as deep skin infections, bacteraemia, distant organ metastases, SSTS), which are increasingly being observed even in high-income countries [16].

WHAT IS THE CURRENT STATUS OF RHEUMATIC FEVER, BOTH GLOBALLY AND IN SPAIN?

Rheumatic fever (RF) is an inflammatory disease caused by an autoimmune response to a GAS infection. The autoimmune response is due to a similarity between the components of the *Streptococcus* and those of the affected tissues. Both humoral antibody-mediated and cellular T-cell-specific responses are involved in tissue damage. The characteristic Aschoff nodules found in RF histology account for this cellular response. Reactive arthritis, although clinically different, is considered to be part of the spectrum of RF.

The autoimmune response to GAS also contributes to post-streptococcal glomerulonephritis, which has a different immune pathogenesis from RF.

In addition to chorea, a cardinal symptom of rheumatic fever, other neurological disorders such as certain behavioral issues and stuttering have been epidemiologically linked to streptococcal infection.

RF manifests in the second to third week after GAS infection with rapidly migrating polyarthritis (60-80% of cases) -monoarthritis may occur- and is highly responsive to anti-inflammatory drugs; pancarditis (50-80%); chorea (10-30%), a markedly later symptom; skin involvement in the form of ery-

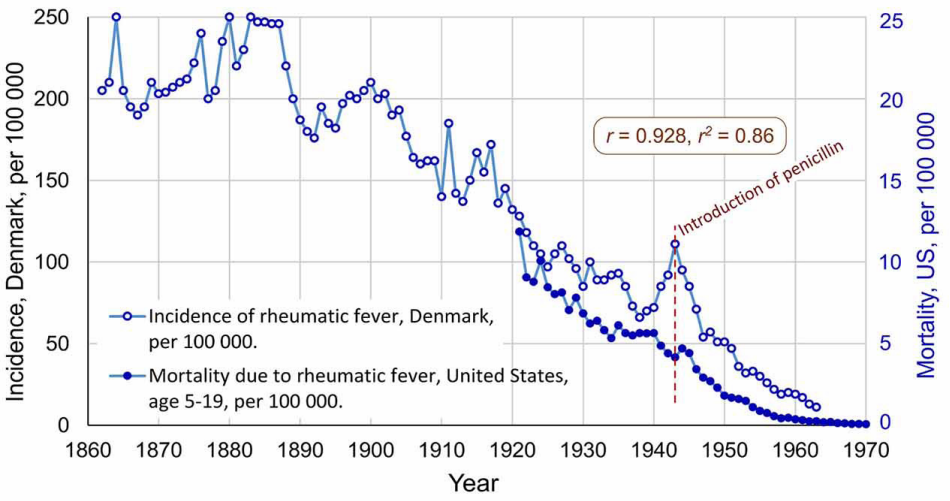


Figure 2 | **Incidence of rheumatic fever in Denmark and mortality of rheumatic fever in the United States. Taken from Alm PA [24] CC-BY license, version 4.0**

thema marginatum, a rare but characteristic lesion (less than 6%) and nodules in the subcutaneous tissue (0-10%). These symptoms and signs, notably defining the entity, are accompanied by other more frequent but non-specific symptoms and signs: fever, increase in acute phase reactants (ESR and RHDP), and prolongation of the PR interval of the electrocardiogram.

Diagnosis is primarily clinical, considering the history of pharyngitis, if present. The diagnostic criteria established by Thomas Ducktt Jones in 1944 [17] are universally accepted; they have undergone revisions considering the sensitivity and specificity of the symptoms in the different compilation series, the epidemiological risk of the population where it occurs, and the influence of the diagnostic techniques incorporated in the confirmation of previous GAS infection and the diagnosis of carditis. The latest globally accepted update was established by the American Heart Association in 2015 [18].

The disease primarily but not exclusively affects children aged 5-14 and can and often does recur. RF is a self-limiting disease, although chorea can last for months. Endocardial injury and the resulting valvulitis are responsible for the chronicity and severity and are enhanced by recurrences. Mortality in acute attacks is very low, and if it occurs, it is always due to carditis.

So important is it that in geographic areas where it is still prevalent, rheumatic heart disease (RHD) remains the most common cause of death in the 5-18 age group [19], as it was in Western countries and our environment well into the 20th century [20] and the leading cause of cardiovascular death in those under 50 years of age [21].

GAS transmission is a determinant for endemic maintenance and RF and RHD epidemic outbreaks, with overcrowding being the main risk factor [22,23].

It was previously believed that certain types of throat infections and specific strains of *Streptococcus* posed a higher risk of causing rheumatic fever (referred to as "rheumatogenic strains"). However, the current understanding of rheumatic fever epidemiology challenges this concept, as a wide range of strains are now implicated in the disease. In areas where rheumatic fever is common, skin infections such as impetigo are considered another possible initial trigger for the body's sensitisation to the disease.

Genetic susceptibility, similar to other autoimmune processes, also plays a role in rheumatic fever, although specific genetic markers have not been identified. There is a higher incidence of rheumatic fever in identical twins.

The improvement in living conditions in Europe, the United States of America, and other high-income Western countries over the last century has been a significant factor in the decline of rheumatic fever. This decline accelerated from the mid-20th century with the availability of antibiotics effective against GAS. The graph depicting this decline in Denmark applies to all the mentioned regions [24] (Figure 2).

The global incidence of rheumatic fever (RF) is estimated at 470,000 new cases annually, with 282,000 of those cases leading to rheumatic heart disease (RHD). It affects more than 33 million people in areas where it is still prevalent, and 220,000 people in the Western world. Seventy-three percent of cases are concentrated in the world's most populous countries. South Asia, Oceania, and sub-Saharan Africa bear the highest burden of the disease [25,26]. The incidence varies widely, ranging from 150-380 cases per 100,000 school-aged children among Indigenous people in Australia and New Zealand (this has been consistent since the 1980s) [27] to less than 2 per 10^5 in the same age group and less than 1 per 10^5 in the gener-

al population in the Western world. This results in 230,000 to 320,000 annual deaths from RHD worldwide.

Globally, there is a downward trend in the incidence of the disease, although occasional resurgences are reported in various regions, including the USA, Utah [28], Italy [29], Slovenia [30], South Asia, Central Africa, and Sub-Saharan Africa. The burden of the disease is higher in areas with poor epidemiological data collection, so the figures used are estimates.

In Spain, reporting of the disease ceased to be mandatory at the national level in 1996, although some regions continued to require it. The incidence declined in most countries, with a slight delay lasting until the 1970s. However, its cardiac consequences and the need for surgery remained significant until the 1980s. The most recent data in the literature is an update by Cortina et al., which covers up to the mid-1980s [31].

Today, the disease is practically non-existent in Spain, but it should always be considered [32,33], especially given the immigrant population from areas with active rheumatic fever. It's important to remember that early treatment can positively impact the course of heart disease.

WHAT IS THE TREND IN GAS BACTERAEMIA EVOLUTION IN RECENT YEARS IN SPAIN AND AROUND THE WORLD?

The occurrence of GAS bacteraemia can occur with or without focal pictures as its portal of entry. The current understanding of the incidence of GAS bacteraemia and its recent evolution is still not fully clarified. Not all data indicates a recent increase in episodes, let alone bacteraemic episodes.

It is estimated that there are between 10,649 and 13,434 cases of iGAS infections annually in the US, causing between 1,136 and 1,607 deaths [34]. In 2016, the US Centers for Disease Control and Prevention (CDC) published surveillance results for iGAS infections between 2005 and 2012 in 10 US areas with a population of 32.8 million. A total of 9,557 cases (3.8 cases per 100,000 persons per year) with 1,116 deaths (case fatality rate, 11.7%) were identified, with isolation of the organism from blood in 7,837 cases (82%). The study did not show an increase in invasive infection rates during the study period [34].

In contrast, in subsequent years, several publications have emerged warning of a recent increase in iGAS infection [35,36]. Incidence increased from 1.04 to 4.76 cases per 100,000 persons from 2008 to 2019 in Idaho [35], with SSTS numbers evolving from 0 to 6.4% of cases. In the USA, recent outbreaks associated with an increase in GAS bacteraemia in drug-addicted patients [37] have been reported in association with the presence of xylazine. Xylazine, often referred to as "tranq," is an adulterant in an increasing number of illicit drug mixtures. Among other effects, it produces vasoconstriction and necrosis, and users experience effects similar to those of opioids.

In Alberta, Canada, out of 3,551 cases, there has been an increase in the incidence of iGAS infections from 4.24 per 100,000 population in 2003 to 10.24 in 2017, with half of the cases being bacteraemic [36].

In Europe, the incidence of iGAS infections in Finland has shown a fluctuating but increasing trend. The incidence of bacteraemic cases has been estimated at 3.52 episodes/100,000 population per year, reaching 7.93 episodes/100,000 in 2018 [38]. In England, there has been an apparent increase in the incidence of GAS infections, especially respiratory tract infections in children [39], but not clearly in bacteraemic episodes.

In the Netherlands, a study involving seven hospitals showed that the incidence of GAS infections doubled after the pandemic compared to pre-pandemic data in paediatric patients [40].

In France, GAS infections requiring intensive care unit (ICU) admission have increased more than 4-fold in equivalent periods before and after the pandemic [41], as have paediatric episodes in patients with previous viral infections [42]. Data from Belgium show an increase in bacteraemia, including in adults [43].

Among the Danish population of 1,152,000 children and adolescents aged 0-17, a significant increase in iGAS infection episodes greater than 9-fold was demonstrated. The incidence of iGAS infection increased in 2022-23 compared to the three pre-COVID-19 seasons of 2016-17, 2017-18, and 2018-19 without increasing severity [44].

Other papers suggesting an increased incidence of iGAS infections in paediatrics come from Australia [45], Portugal [46], and British Columbia, Canada [47].

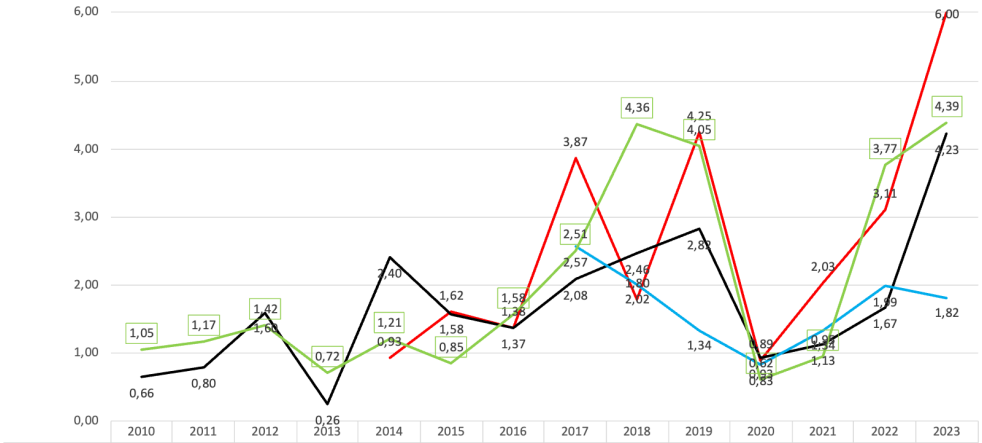
In Spain, the Gregorio Marañón Hospital published a prospective series of 100 episodes of GAS bacteraemia in 1997. At that time, 62% of the cases occurred in patients addicted to injecting drugs and had an origin in skin infections in most cases [48].

In a 2006 publication covering practically the previous decade, the Hospital La Fe in Valencia, Spain, published 42 cases of GAS bacteraemia, amounting to 1.01 cases per 100,000 inhabitants. The origin of the bacteraemia was determined in 38 patients (90.5%), with skin and soft tissue infection being the main foci [49].

Recently, a retrospective study on GAS bacteraemia in 16 hospitals in Madrid in children under 16 years of age included 109 cases, with an incidence rate of 4.3 episodes/100,000 children/year. The incidence was compared between two periods (June 2005 to June 2011 versus July 2011 to July 2017), and a non-significant increase in cases was observed over the study period. Twenty-two percent of cases required admission to the paediatric ICU (PICU) and two of the children died [50].

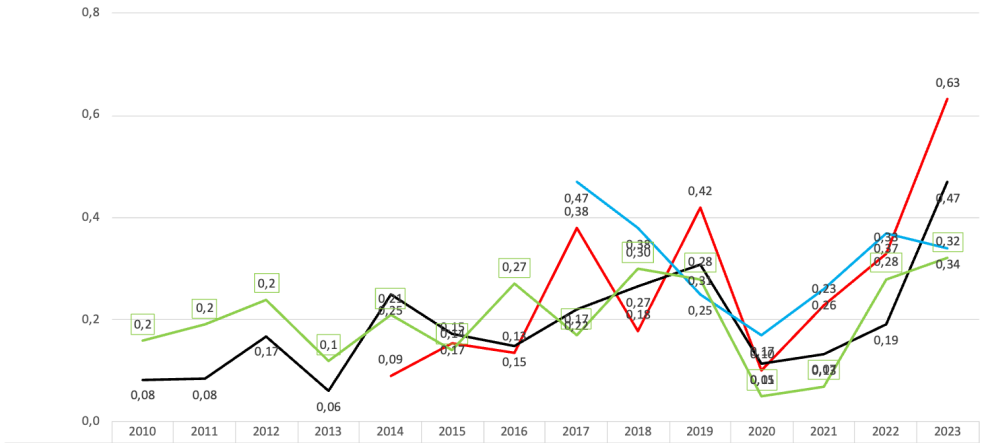
Ramírez de Arellano et al. have described the clinical, microbiological, and molecular characteristics of iGAS infections in children between September 2022 and March 2023 [51] in Spain. Ninety-three cases were included, of which 46 (49.5%) required admission to the PICU. These findings suggest but do not confirm an increase in the incidence of episodes shown in another Spanish study [52].

A high proportion of patients with GAS bacteraemia have some prior underlying disease [53], including malignant



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Doce Octubre					0,93	1,62	1,38	3,87	1,80	4,25	0,89	2,03	3,11	6,00
La Paz	0,66	0,80	1,60	0,26	2,40	1,58	1,37	2,08	2,46	2,82	0,93	1,13	1,67	4,23
Ramón Cajal								2,57	2,02	1,34	0,83	1,34	1,99	1,82
G. Marañón	1,05	1,17	1,42	0,72	1,21	0,85	1,58	2,51	4,36	4,05	0,62	0,95	3,77	4,39

Figure 3 Evolution of bacteraemia episodes per 100,000 inhabitants of GAS in four large hospitals in Madrid



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Doce Octubre					0,09	0,15	0,13	0,38	0,18	0,42	0,10	0,23	0,33	0,63
La Paz	0,08	0,08	0,17	0,06	0,25	0,17	0,15	0,22	0,27	0,31	0,11	0,13	0,19	0,47
Ramón Cajal								0,47	0,38	0,25	0,17	0,26	0,37	0,34
G. Marañón	0,2	0,2	0,2	0,1	0,21	0,14	0,27	0,17	0,30	0,28	0,05	0,07	0,28	0,32

Figure 4 Evolution of episodes of GAS bacteraemia per 1000 hospital admissions in 4 large hospitals in Madrid

diseases, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, respiratory viral infections, drug addiction, and immunosuppression from various causes [54,55].

Skin and soft tissue infections are common entry points for GAS bacteraemia, with factors such as advanced age, residence in a nursing home, recent surgery, septic shock, meningitis, pneumonia, and underlying chronic diseases being associated with poor outcomes. GAS bacteraemia has a mortality rate ranging from 5.6% to 32% [56,57].

WHAT DATA ON GAS BACTERAEMIA HAVE BEEN AVAILABLE IN FOUR LARGE HOSPITALS IN MADRID SINCE 2010?

To obtain a clear understanding of the evolution of GAS bacteraemia, four large hospitals in Madrid were asked to provide the number of episodes per 100,000 population and 1,000 hospital admissions in recent years.

Figures 3 and 4 in the accompanying report illustrate the evolution of GAS bacteraemia in these four centres using data

collected from their annual reports. The impact of the COVID-19 pandemic is evident in the data, with a significant reduction in cases across all centres in 2020 and 2021. The incidence of GAS bacteraemia episodes has ranged from 0.7 to 6 episodes per 100,000 population and from 0.08 to 0.63 cases per 1,000 hospital admissions, in those centers.

WHAT METHODS ARE AVAILABLE FOR RAPIDLY DIAGNOSING INVASIVE GAS DISEASE?

The gold standard for diagnosing GAS infection is microbiological culture, particularly in cases of invasive disease. This involves culturing blood and affected tissue samples such as deep tissue for cellulitis, necrotising fasciitis, bone samples for osteomyelitis, joint fluid for arthritis, respiratory samples for pneumonia, pleural fluid for empyema, and cerebrospinal fluid for meningitis. Culturing these samples usually yields high results and is recommended for suspected invasive infections. Blood cultures should be taken regardless of the location of the infection.

Microbiological culture is also crucial for non-invasive infections like streptococcal pharyngitis, with pharyngeal exudate being the most common culture. However, rapid point-of-care techniques have become more common for ruling out GAS pharyngitis and avoiding unnecessary antibiotic use [58-60]. Molecular techniques, such as rapid tests based on the detection of genetic material, have increased the sensitivity of detection. While rapid antigen detection testing (RADT) is licensed for detecting GAS in pharyngeal samples, its off-label use has had varying success in samples from patients with invasive infections. Studies have compared the performance of RADTs, culture, GAS PCR, and 16S rRNA gene PCR assays with a composite gold standard (GAS-PCR assay or culture) for diagnosing severe GAS infection. A total of 192 specimens from deep-tissue sites enriched for 75 GAS-positive samples were enrolled in the study. The three evaluated RADTs showed sensitivities ranging from 88.0% to 94.7% versus 98.7% for GAS PCR, 84% for 16S rRNA gene PCR, and 77.3% for culture. Antigen detection has even been used in surgical procedures to assess the extent of soft tissue necrotising lesions and debridement decision-making [61]. Point-of-care systems based on molecular diagnostic techniques have also been evaluated in non-invasive skin and soft tissue infections with 100% sensitivity and 99.5% specificity compared to culture [62].

Syndromic molecular panels are a new addition to microbiological diagnostics. These panels detect microorganisms associated with a specific type of infection and identify genes linked to resistance mechanisms. Some approved panels target bacteraemia (performed on a positive blood culture) and lower respiratory tract infections, such as community-acquired pneumonia, hospital-acquired pneumonia, and those linked to mechanical ventilation. Some panels even include GAS as a detection target [63]. Although they are suitable for bacteraemia and respiratory infections [64], they have shown promising results when used off-label for conditions like joint infection, empyema, or brain abscesses [65,66]. However, when used in these cases, the panels should be used under control, and the results should be discussed with the clinical decision-makers. It's important to note that a negative result does not necessarily mean the absence of GAS (false negatives). Additionally, there are no case series or multicentre evaluations to determine their sensitivity and specificity in these situations.

WHAT ARE THE MECHANISMS OF ANTIBIOTIC RESISTANCE PRESENT IN GAS?

The latest World Health Organisation (WHO) report of 2024, revising the list of priority pathogens for developing new antimicrobials, introduces GAS. It classifies it as a medium-priority pathogen, essentially because of its resistance to macrolides, especially in low- and middle-income countries [1].

GAS has traditionally been considered universally susceptible to penicillin, although isolates that lose sensitivity to penicillin have been described. Moreover, they may be associated with some therapeutic failure. Initially recognised in Japan, such isolates have been reported from different parts of the world, which, although considered sensitive to penicillin, have somewhat higher minimum inhibitory concentrations (MICs) than most isolates [67-69]. These sporadic strains have mutations in some penicillin-binding proteins (such as PBP2x and PBP1a), sites of action of ß-lactam antibiotics. They also have higher MIC values for ampicillin and cefotaxime in the antibiogram, which can be used for phenotypic recognition [70]. Exceptionally, isolates for which penicillin has a MIC value of 2 mg/L have been isolated in Japan [71]. In Spain, although there is a lack of epidemiological surveillance studies over time to ensure categorically that they are not present in our environment, the studies carried out with invasive isolates of GAS do not demonstrate their presence [51,72].

More worrying is macrolide resistance. Since the first description of erythromycin-resistant GAS in 1968 in the USA, macrolide resistance has been progressively increasing. In some countries, it reaches percentages of up to 40%, being lower in Spain in both upper respiratory tract isolates (10-15%) and invasive isolates (3%) [51,72]. Resistance of GAS to macrolides is due to different mechanisms. The most prevalent is produced by post-transcriptional modification of the target of action by the production of rRNA methylases associated with erm genes. This mechanism can be constitutive or inducible, leading to resistance to macrolides, lincosamides (clindamycin), and streptogramin B (MLSB phenotype). In Spain, it is the most important mechanism and is present in 80% of the resistant isolates. It is also produced by mutations in the 23S rRNA subunit of the ribosome or in ribosomal proteins (L4 and L22) that confer a variable phenotype and mechanisms associated with expulsion pumps (*mef* genes) that determine resistance to macrolides, but susceptibility to clindamycin (phenotype M) [73]. The latter would be present in 25-30% of isolates). Overall, clindamycin resistance would be 8% in non-invasive isolates and 3% in invasive isolates [51,72,73].

Resistance to fluoroquinolones is rare (3-5%) and is due to mutations in the quinolone resistance-determining region

(QRDR) of gyrase (*gyrA* mutations) and topoisomerase IV (*parC* mutations). More than one mutation is required for a significant increase in MICs of fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) [73]. No resistance mechanisms to fluoroquinolones associated with expulsion pumps have been described in this pathogen.

Finally, GAS resistance to tetracyclines is produced by enzymatic inactivation, ribosomal protection, or efflux mechanisms, the latter being the most prevalent worldwide. In Spain, GAS resistance to tetracycline reported is 12% [72].

WHAT ARE THE RISK FACTORS FOR INVASIVE GAS INFECTION?

Risk factors that increase the likelihood of severe iGAS infection in adults include age, comorbidities, dermatological diseases, history of trauma resulting in hematomas, surgical wounds, immunosuppression, and treatments such as corticosteroids [43,74,75].

The incidence of iGAS is higher in patients with pre-existing chronic conditions such as cancer, diabetes, chronic renal failure, chronic suppurative respiratory disease, and immunodeficiency diseases, particularly HIV infection [76,77].

Previous viral skin diseases, especially varicella and herpes zoster, may lead to impetigo and subsequent development of iGAS [43].

Even blunt trauma leading to small hematomas can result in severe and high-mortality necrotising fasciitis (NF) caused by GAS [78]. The factors contributing to the development of NF without skin breakdown or cellulitis are poorly understood. However, they appear to be related to microorganism-dependent factors, high-pathogenicity strains, and host factors such as low body mass index [78,79]. NF can also occur in connection with abscesses resulting from injections and surgical wounds [43,78]. iGAS associated with injecting drug use has been well-documented [43,80,81].

Other factors linked to an increased risk of iGAS include malnutrition with a low body mass index, NF, smoking, and alcohol consumption [43,74,75].

Additionally, older individuals in institutional care are at a higher risk of iGAS compared to those with similar characteristics in the general community [82], as well as older individuals receiving care from external caregivers [83]. This heightened risk, as reported in England due to its home care organisation, should be considered in our setting, especially as home care aids are becoming increasingly common.

WHAT IS THE CURRENT REALITY OF STREPTOCOCCAL TOXIC SHOCK SYNDROME?

SSTS is a complication of iGAS disease characterised by shock and multi-organ failure. It occurs due to capillary leakage and tissue damage caused by inflammatory cytokines released by streptococcal toxins [84].

Between 8% and 22% of patients with severe GAS infection and 40-50% of patients with NF will develop SSTS. SSTS can occur in all age groups, and most patients with SSTS are not immunosuppressed. Confirmatory diagnosis requires the presence of hypotension, multi-organ dysfunction, and isolation of GAS in usually sterile tissues. The main focus of infection is the vagina, pharyngeal mucosa, skin, and soft tissues. In 45% of patients with SSTS, no clear entry point is identified, and blood cultures are positive in 60-86% of cases.

The main superantigenic exotoxins described in GAS are the streptococcal pyrogenic exotoxins (SpE) A, B, and C, and the streptococcal superantigen A (SSA). The mortality rate of SSTS is high, estimated to be between 14% and 64%, and can exceed 25% within the first 24 hours. It is also associated with high morbidity, requiring admission to the ICU.

Treatment is based on early diagnosis, adequate resuscitation of shock, combined antibiotic treatment with clindamycin and ß-lactams, drainage of the focus of infection, and support of organ dysfunction. Intravenous immunoglobulins (IVIG) may reduce mortality [85]. In a recent meta-analysis, the factors associated with prognosis in SSTS were clindamycin treatment and, within this subgroup, IVIG treatment, albeit with a low level of evidence [86].

Different series in Spain have been published showing an increase in incidence [87]. One of the most significant case series is that of Vall D'Hebron Hospital in Barcelona, which includes 13 patients with iGAS infection and sepsis code criteria admitted to the ICU from November 2022 to March 2023. The study identified three distinct phenotypic profiles: hyperinflammatory with high levels of cytokines and endotoxemia; with low perfusion, the presence of cardiomyopathy (54%), and need for extracorporeal venous, arterial support techniques (38.4%); and hypogammaglobulinemia, which could guide personalised therapeutic approaches [88]. In the paediatric setting, an increase in incidence has also been observed without correlation with an increase in antibiotic resistance or a shift in M-protein types (emm) [51].

In the ISTRE (Infections invasives à Streptocoque du groupe A en Réanimation) study in 37 French ICUs, considering the pre- and post-pandemic period for COVID-19, the case rate and frequency of SSTS was higher in the post-pandemic period (205 vs 949/100,000 ICU admissions and 61% vs 45%), with no increase in ICU mortality (14% vs 22%). Mechanical ventilation was required in 61%, and vasoactive support in 74%. The causes of this increase in incidence are proposed to be more virulent strains, their relationship with respiratory viral infections such as influenza, favouring co-infection and superinfection, or the loss of immunity following the restrictive measures of the pandemic [41].

WHAT IS THE EXTENT OF NECROTISING SKIN AND SOFT TISSUE INFECTION CAUSED BY GAS?

It's important to remember that iGAS infection can cause a condition called necrotising fasciitis (NF). NF is characterised by

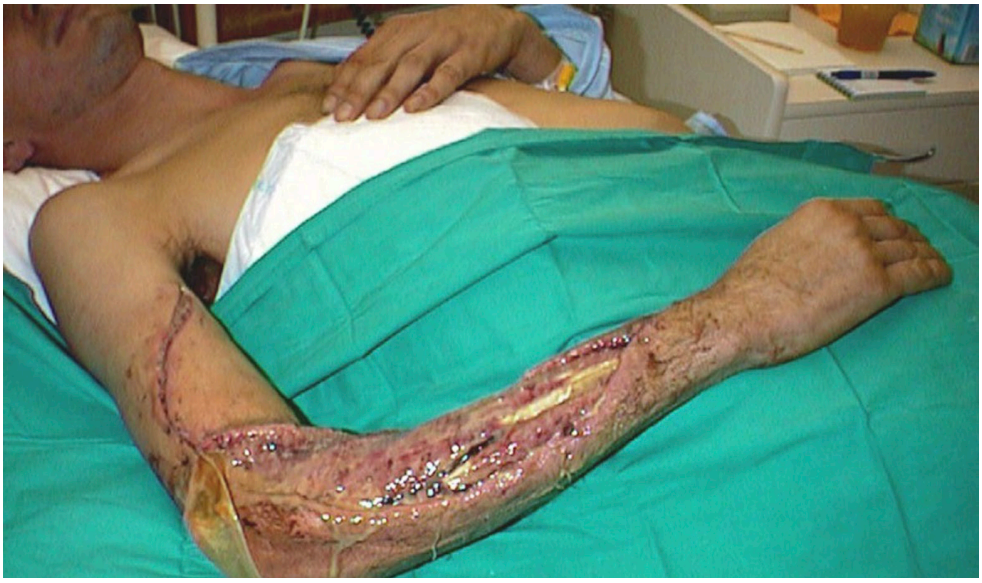


Figure 5 | ***S. pyogenes* necrotising fasciitis**

rapidly progressing soft tissue damage and can lead to sepsis, systemic toxicity, multiple organ failure, and potentially fatal outcomes. The infection rapidly spreads along tissue planes, causing blockages in small blood vessels, tissue necrosis, and affecting multiple tissue layers. Initially, the skin may look normal, but it can become hot, red, and tender after a few days. Early detection is crucial because only prompt surgical removal of affected tissue can reduce the risk of death. However, accurate diagnosis at the time of presentation is only achieved in 15% to 34% of cases. The most commonly affected areas are the extremities (58%), followed by the trunk (26%) and perineum (40%). This also includes specific subgroups like Fournier gangrene, as well as the head and neck, periorbital region, and hands (Figure 5).

The most common clinical signs of necrotising fasciitis (NF) include local inflammation, pain, fever, and symptoms of systemic toxicity, often disproportionate to the original lesion [89-92].

In established NF, the affected fascia is usually not attached to adjacent layers, allowing the surgeon to quickly dissect with the finger along the fascial plane (finger test). If there is a high suspicion of NF, and the imaging results are negative or the necessary means are not available, the finger test can confirm the diagnosis. Local scanning also allows examination of the underlying fat and muscle [90,92]. Although the loss of tissue adherence is a sensitive sign for NF, it may not be present early. It does not apply to all entities within the classification of necrotising soft tissue infections. It is essential to follow the evolution until the symptoms improve, as even if initially no NF is present, there may be an evolution towards NF in the following hours/days.

In 2004, Wong et al. introduced the concept of the LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score based on six analytical parameters as a tool to distinguish NF from other soft tissue infections [93]. In 2021 [94], this scale (m-LRINEC) was modified to include renal disease and diabetes, suggesting a high sensitivity for early diagnosis of NF, but validation in more extensive studies is needed.

WHEN AND WHY SHOULD SURGERY BE PERFORMED?

If necrotizing fasciitis (severe infection, rapid deterioration, crepitus, necrosis, blistering) is present or highly suspected, early surgical debridement is essential. This helps stop the infection from getting worse, reduces tissue loss, lowers the likelihood of amputation, and decreases the risk of death. The initial debridement should be thorough, and samples need to be taken from the edge of the wound for microbiological and histological examination. Even tissue that looks normal can have extensive blood clotting when examined under a microscope. That's why it's important to remove tissue down to where it's well-vascularized and bleeding [95-96].

A second necessary surgical procedure should be scheduled within 24 hours of the initial debridement unless the patient's condition worsens quickly. In that case, the surgical revision should happen sooner. It may be necessary to perform multiple operations, with an average of 3 to 4 debridements.

After removing the dead tissue, the exposed area needs to be treated with negative pressure wound therapy, also known as vacuum-assisted wound closure (VAC). This therapy involves applying continuous or intermittent sub-atmospheric pressure

to a filler substance (such as foam or gauze) on the surface of the wound. VAC therapy helps prepare the exposed tissue for subsequent reconstruction by maintaining a moist and closed environment, controlling excess exudate, reducing the need for frequent dressings, minimizing pain, and promoting the early formation of granulation tissue [97].

Once the tissue is healed, the infection is under control, and no further surgical debridement is needed, reconstruction and coverage of the exposed tissues should be carried out.

HOW IMPORTANT IS GAS AS A CAUSE OF INFECTION IN PAEDIATRICS?

On December 2, 2022, a UK alert reported an unusual increase in the incidence of GAS infections, mainly tonsillitis and scarlet fever, along with a significant number of deaths of children under ten years of age in a short period [98]. Several European countries quickly reported a similar rise in streptococcal infections [99-101], and cases of pneumonia may have been the clinical condition that increased the most during this epidemic outbreak [102].

This increase in incidence had already been observed in the years before the pandemic, as described by other authors [40,102], and also observed in Spain [52].

During the COVID-19 pandemic, viral and bacterial infections were significantly reduced. However, in the winter of 2022-23, a resurgence of infections in children was observed, leading to the concept of "immune debt" [103]. In Spain, cases of GAS infection, including the invasive forms, are not officially reported, so accurate data is not available. Nonetheless, the paediatric network "PedGAS-net," supported by the Spanish Society of Paediatric Infectious Diseases, has been collecting data on invasive infections since 2019 from a network of 51 national public hospitals. Initially, some national publications suggested a return to pre-pandemic normality. However, a group from Madrid later calculated the incidence of paediatric GAS infections seen in the emergency department (ED). In the first half of 2023, the incidence was 22.85 per 1000 ED visits, which is double the rates found in 2022 (10.2 per 1000 visits) and 2019 (12.38 per 1000 visits). Similarly, the rate of invasive infections also increased during this period, nearly doubling from 0.2 per 1000 visits in 2022 and 0.38 per 1000 ED visits in 2019 to 0.58 per 1000 visits in 2023. Analysis by PedGAS-Net showed a significant increase in invasive GAS infections in late 2022 and early 2023, surpassing the frequency and severity observed in the pre-pandemic years [104-105]. This surge in cases, which are often associated with a significant number of pneumonias, has coincided with an increase in cases of respiratory infections caused by RSV and influenza in both the United Kingdom and Spain, often involving virus-bacteria co-infections.

In terms of circulating strains, the same pre-pandemic strains appear to be detected, particularly in invasive infections [106], with a predominance of serotype M1 and a variant M1UK, especially in pneumonia. However, a study conducted in Spain in collaboration with Centro Nacional de Microbiología (CNM), PedGAS-net, and the CIBER de Enfermedades Infecciosas (CIBERINFEC) did not find any evidence of new strains or significant microbiological differences between mild and severe cases that could explain the recent epidemic. It also seems that resistance to GAS to different antibiotics was not the cause of the severe cases. No resistance to penicillin or clindamycin has been identified, which could explain more severe cases of invasive infections, often treated with these antibiotics as an adjuvant [51].

It is also believed that the recognized virus-bacteria co-infection could have been the perfect breeding ground for the emergence of this significant outbreak, which, although it may still be too early to tell, does not seem to be recurring with the same intensity in the current season.

IS GAS A DREADED PATHOGEN IN PREGNANCY AND THE POSTPARTUM PERIOD?

The significance of GAS infection during pregnancy, childbirth, and the postpartum period is primarily due to its potential role in causing puerperal infection, leading to early endometritis shortly after childbirth or cellulitis in the surgical wound. In rare cases, it can progress to sepsis or even more rarely, invasive diseases such as necrotizing fasciitis or streptococcal toxic shock syndrome. Among cases of puerperal sepsis, invasive GAS infection still contributes to at least 45-50% of deaths. Prepartum GAS infection is uncommon, accounting for 7-15% of all pregnancy-related GAS infections, and may also occur in the context of septic abortion. A systematic review of 9 studies in high- and middle-income countries reported that the incidence of invasive GAS infection during pregnancy and the postpartum period was 0.12 per 1000 live births (95% CI 0.11 to 0.14) [107-112].

During childbirth or a caesarean section, GAS can cross the vaginal-skin mucosal barrier, increasing the risk of infection in the postpartum period. Other suggested risk factors for infection include immunosuppression during pregnancy, genetic susceptibility, virulence of the bacterial strains, or the presence of superantigens. GAS colonization in the vagina can occur through contact with carriers of GAS from the throat or skin, respiratory secretions, or contact with skin exudates and infected wounds. Although vaginal GAS identification is rare in the general population (0.03% to 0.37%), hospital isolates of GAS are associated with infections related to pregnancy or the postpartum period. The rupture of membranes can alter vaginal pH and facilitate the growth and ascension of microorganisms. Given the low vaginal colonization by GAS in the general population, it is suggested that the oropharynx is a possible route of entry, and symptomatic maternal pharyngitis is considered a risk factor for pregnancy-related GAS infection.

Maternal infection usually occurs in the first two days after childbirth (0-5 days). However, a significant percentage of women with puerperal sepsis acquire the infection from their other children at home or from other contacts. Symptoms

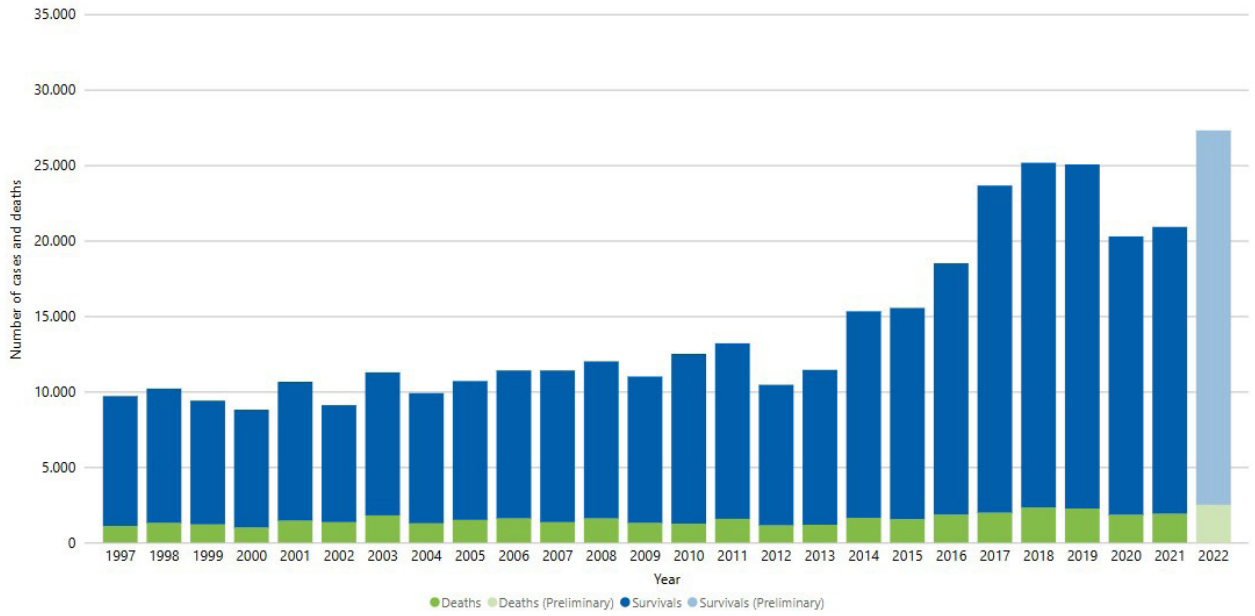


Figure 6 | **Estimated number of cases and deaths due to invasive GAS disease in USA [117,118].**

typically include high fever, abdominal pain, purulent vaginal discharge, uterine tenderness, chills, and gastrointestinal symptoms. Uncommon symptoms such as leukocytosis, tachycardia, and hypotension may indicate a more severe course of infection. Upon examination, inflammation and infection may be found at the episiotomy, perineal tear, or caesarean section wound, and in severe cases, this can progress to necrotizing forms.

To prevent a potentially deadly iGAS infection in pregnant or postpartum women, it's crucial to consider this condition in a patient with suspicious symptoms or disproportionate pain during physical examination. Early diagnosis, antibiotic treatment, and timely surgical debridement if necessary are essential [113].

There are national and international protocols for managing and preventing puerperal sepsis [114]. Prevention measures include proper hygiene practices for the patient, her family, and healthcare workers (such as handwashing and avoiding contact with contaminated items), cleaning and disinfecting wounds, and using appropriate dressings. Standard precautions should be followed in healthcare settings.

WHAT ARE THE MOST RECENT OUTBREAKS OF GAS DISEASE DESCRIBED?

Since the COVID-19 pandemic, there has been a noticeable increase in iGAS disease cases in Spain, other European countries, Asia, Canada, the USA, and Latin America, especially since 2022. This increase could be related to changes in the strains of the bacteria, an overall rise in GAS infections, co-infection with respiratory viruses like influenza and respiratory syncytial virus, and improved surveillance measures. The disease can occur in outbreaks among children sharing school and leisure time or in older adults' homes.

The CNM reported an epidemic of iGAS infections starting in October 2022, which was also observed globally [52]. The initial surge was seen in the emm12 serotype, followed by an increase in the emm1 serotype. This epidemic situation continued for several months in 2023. Furthermore, resistance rates are higher, particularly for tetracycline, which is double the average from 2007 to 2019. The presence of uncommon tetracycline-resistant serotypes like emm81, emm94, emm102, emm118, emm119, and emm183, along with the low incidence of usually susceptible emm1, emm3, and emm89, could explain the increase in resistance rates [52].

In Europe, there has been a reported increase in the number of iGAS cases among children under ten in countries such as Ireland, France, the Netherlands, Sweden, and the United Kingdom since September 2022 [1,115]. Portugal [56] and Denmark [116] have also subsequently reported increased cases. Meanwhile, in the US, there were more cases and deaths from invasive disease in 2022 than during the COVID-19 pandemic [117]; however, the 2022 figures were quite similar to 2018 and 2019 (Figure 6). Preliminary results from 2023 indicate that the number of cases of invasive disease is the highest in 20 years [118].

Public health authorities recommend improved surveillance of the problem, increased vaccination coverage against viruses (influenza, syncytial virus) that cause co-infection to

reduce severity, increased hand and respiratory hygiene to reduce transmission, and early diagnosis and treatment of cases to improve prognosis [115,118].

WHAT IS THE CURRENT MEDICAL TREATMENT OF INVASIVE GAS INFECTION?

Treating iGAS infection involves collaboration between infectious disease specialists, microbiologists, intensivists, and surgeons. This usually requires a multidisciplinary approach based on the clinical condition of the patient. In this section, we will focus only on medical treatment and disregard surgical treatment and the management of septic shock, which have already been addressed.

Empirical antibiotics should be administered immediately while awaiting confirmatory results. Generally, the antimicrobial regimen includes a ß-lactam agent (which inhibits cell wall synthesis) in combination with clindamycin or other agents that inhibit protein synthesis.

It is recommended to use a combination of agents with different targets because using ß-lactam alone has been linked to higher morbidity and mortality, particularly in severe invasive infections [119-121]. Research indicates that penicillin monotherapy is ineffective when the bacterial inoculum is high and growth rates decrease [122]. In such cases, the availability of PBPs to bind ß-lactams may decrease [123]. Clindamycin, on the other hand, remains effective regardless of inoculum size or growth stage, inhibits bacterial toxin production, and has a more prolonged post-antibiotic effect compared to ß-lactams [124].

Observational studies have shown that adding clindamycin to ß-lactams is associated with lower mortality, even in patients without shock and necrotizing fasciitis [125].

The recommended dose of clindamycin for adults is 900 mg IV every eight hours. For children, the recommended dosage is 30-40 mg/kg IV per day, administered every six to eight hours.

In cases where patients have clindamycin-resistant isolates, linezolid can be used as an alternative, as resistance to oxazolidinones is very low [126-128].

For patients with hypersusceptibility to ß-lactams and a history of anaphylaxis, vancomycin or other glycolipopeptides may be used.

Combination therapy with penicillin and clindamycin should be continued until clinical and hemodynamic stability is achieved, typically for 48-72 hours. After this period, penicillin monotherapy can be considered.

Combination therapy with penicillin G and clindamycin is recommended for the initial treatment of GAS bacteraemia or pneumonia in the absence of shock, organ failure, or necrotising infection. However, in these circumstances, penicillin G monotherapy is a reasonable alternative.

For patients with bacteraemia and those with complicated deep infections, it is advisable to continue treatment for at least 14 days, and sometimes longer.

Non-antibiotic treatments for SSTS (streptococcal toxic shock syndrome) include intravenous immunoglobulin (IVIG), hyperbaric oxygen, and anti-tumor necrosis factor (TNF) antibodies.

In patients with invasive SSTS, intravenous immunoglobulins (IVIG) are recommended for treating patients at a dosage of 1 g/kg on the first day, followed by 0.5 g/kg over the next 2-3 days. A meta-analysis conducted by Parks et al. [85] in 2018, which included five studies of patients with SSTS, concluded that the use of IVIG was associated with a reduction in 30-day mortality (33.7% to 15.7%). However, subsequent studies do not confirm the efficacy of IVIG [129,130]. A Spanish study group also found no confirmation of IVIG's efficacy in patients with GAS bacteraemia requiring ICU admission. This retrospective multicenter study, conducted in nine ICUs in southern Spain, included 57 patients, and it was observed that clindamycin but not IVIG behaved as a protective factor for mortality [130].

The use of hyperbaric oxygen has been proposed for a small number of patients with SSTS [131,132], but no controlled trials have been conducted to affirm the efficacy of this treatment.

Since TNF levels are elevated in patients with SSTS [133], the use of TNF blockers has been occasionally studied in experimental animals [134,135], but no clinical data justifies their use in humans.

HOW CAN GAS INFECTION BE PREVENTED THROUGH VACCINES?

Preventing and controlling GAS infection requires a comprehensive approach [136]. This approach includes promoting hygiene, educating the community, promptly diagnosing and treating infections, and implementing specific strategies to manage outbreaks [83,137]. Health professionals, educators, and the community need to collaborate to reduce the impact of these infections and prevent serious complications. The following preventive measures are highlighted [136, 38]:

Educational campaigns should emphasize training programs, particularly for high-risk populations such as children, the elderly, and institutionalized individuals. The focus should be on promoting handwashing, especially after coughing or sneezing, before meals, or after using the toilet. Additionally, individuals should be encouraged to cover their nose and mouth with their elbow when coughing or sneezing, or to use a disposable handkerchief, while following mask recommendations for respiratory diseases.

It's important to maintain good control of indoor environments by disinfecting surfaces and ensuring proper ventilation to reduce the spread of respiratory droplets. To control outbreaks, it's important to use rapid antigen detection tests and throat cultures for early diagnosis. Infected individuals should

be temporarily isolated and should avoid close contact with others until at least 24 hours after starting antibiotic treatment. Surveillance systems should be implemented to detect and monitor cases of GAS infections. Close contacts of confirmed cases should be identified and assessed, and prophylactic treatment should be provided when necessary.

Regarding vaccination, there is currently no commercially available vaccine against GAS, but research in this area is a major focus.

The development of an effective and safe vaccine against GAS presents several challenges due to the genetic diversity of the pathogen, potential autoimmune epitopes, and issues with animal models [136]. Currently, only four candidates have progressed to early clinical trials [136,138,139]. These candidates primarily target the M protein of GAS, excluding autoepitopes and utilizing N-terminal fragments from different serotypes. For instance, StreptAnova® has demonstrated immunogenicity and good tolerance in initial trials, while MJ8CombiVax® has been reformulated to include epitopes that protect against highly virulent variants. Other vaccines are based on non-M proteins, with examples from GlaxoSmithKline® and Vaxcyte® showing efficacy in animal models.

Recent efforts led by the WHO, which have recognized GAS vaccine research and development as a global priority, are resulting in significant progress in vaccine formulation and delivery, including the potential use of microarray patches. However, greater investment is necessary in the formulation and delivery of vaccines, along with coordinated efforts to achieve comprehensive global vaccine coverage and substantially reduce the disease burden caused by GAS [140].

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Nothing to declare

CONFLICTS OF INTEREST

The authors declare the absence of conflicts of interest.

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