

In December of 2022, the World Health Organization (WHO) released an alert on the increase in cases of invasive group A streptococcal (iGAS) infection in Europe, especially in children under 10 years of age. During the same period, the Pan-American Health Organization (PAHO) issued an information note following cases of invasive GAS disease reported by Uruguay. In November of 2023, Argentina reported a significant increase in the notification of cases and deaths from this agent, and recent reports highlighted the presence of M1UK clones and a sublineage of M1 with the SpeC toxin in that country, which has been associated with this increase. In view of this situation, PAHO/WHO recommends that Member States conduct clinical and genomic surveillance, as well as ensure early diagnosis and timely treatment of cases of invasive group A streptococcal disease.

Summary of the situation

Streptococcus pyogenes, or group A streptococci (GAS), are gram-positive bacteria that cause a broad spectrum of infections. More frequently, GAS cause mild illnesses such as tonsillitis and pharyngitis, which are common in school outbreaks, and are generally not associated with invasive infections. Less frequently, GAS can cause severe invasive infections, such as necrotizing fasciitis, bacteremia, septic arthritis, puerperal endometritis or respiratory tract infections. Approximately one-third of these invasive infections are complicated by streptococcal toxic shock syndrome. Other serious consequences of GASs include immune-mediated diseases such as post-streptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease. In conclusion, GASs can lead to life-threatening complications and immune-mediated diseases with chronic sequelae. It is estimated that GASs are responsible for more than 500,000 deaths per year worldwide (1).

On 15 December 2022, the World Health Organization (WHO) shared information about an increase in cases of invasive GAS and scarlet fever in at least five Member States of the European Region, which had resulted in some deaths, especially in children under 10 years of age (1).

Additionally, on 19 December 2022, the Pan-American Health Organization / World Health Organization (PAHO/WHO) published an information note regarding cases of invasive disease caused by GAS in Uruguay. It mentions that on 11 December 2022, the Ministry of Public Health of the Oriental Republic of Uruguay informed PAHO/WHO about the occurrence of cases of a disease caused by *Streptococcus pyogenes* bacteria. As a result of intensified surveillance that included an active and retrospective search for cases, as of 19 December 2022, 21 hospitalized cases were identified in health centers in eight departments of that country for complications due to the invasive form of the infection (2).

In **Argentina**, in December 2022, the Ministry of Health issued an alert due to the increase in cases of invasive GAS disease in the European region and the detection of cases in Uruguay, as well as in different municipalities in Argentina. While *Streptococcus pyogenes* was included as a notifiable event in the National Surveillance System (SNVS 2.0) in 2018, in response to this situation, a strategy to strengthen surveillance of the event was implemented nationwide throughout the country (3).

On 7 November 2023, the Ministry of Health of the Republic of Argentina published an epidemiological update regarding GAS. During 2023 and up to 6 November 2023, SNVS 2.0 recorded 487 cases of invasive GAS infection nationwide, of which 78 resulted in deaths. Of the GAS cases, 49.5% (241) involved individuals under 16 years of age. Of the fatal cases, 38.5% occurred in children under 16 years of age (4). In the latest epidemiological bulletin published by Argentina, the confirmed cases of invasive *Streptococcus pyogenes* infection in this country rose to 643 cases, of which 93 (14.4%) correspond to deaths (5).

Previous reports of the National Epidemiological Bulletin of Argentina had alerted about the presence of the M1UK clone and the finding of a hypervirulent M1 sublineage that is being characterized. Based on these findings, the National Reference Laboratory, the Epidemiology Directorate and its municipalities are currently implementing an intensified surveillance protocol for non-invasive *Streptococcus pyogenes* disease, including the study of mild cases in selected centers, to characterize the frequency and distribution of the disease and the different genomic lineages (6).

Recommendations

The following is a summary of the main recommendations for surveillance, clinical management, prophylaxis and risk communication (1).

Clinical and genomic surveillance

- Strengthen activities for detection, characterization and trend monitoring of invasive GAS infection cases.
- Report to the surveillance system any unusual and unexpected form of infections by this agent (invasive forms, outbreaks).
- Notify the International Health Regulations Focal Point (IHR) of any unexpected spike in the national or regional incidence of this type of invasive infection.
- Ensure that all strains isolated from patients with invasive forms are sent to the National Public Health Laboratory for further characterization and genomic surveillance of lineages (clones) and sub-lineages.

Clinical management, infection prevention and control and prophylaxis

- Health care professionals should maintain a high clinical suspicion for GAS infection, especially when evaluating patients with previous viral infection, direct contact with scarlet fever cases, or invasive GAS infection.
- Encourage the consultation of all suspected symptomatic cases of GAS, as well as the diagnosis, isolation and adequate and timely treatment.
- In case of hospital admission due to invasive infection, precautions should be taken to avoid transmission by respiratory droplets and standard precautions should always be

observed. In case of tissue involvement (necrotizing fasciitis, infected wounds, skin lesions) contact precautions are required. Respiratory droplet and contact precautions can be discontinued after 24 hours of antimicrobial treatment.

- Although there is no general recommendation on the administration of prophylaxis, this measure could be considered depending on the degree of exposure and the immune status of the contacts. For example, prophylaxis could be considered in close family members who have shared a bed or who have had close contact, as well as in caregivers who have spent many hours with an infected person. It could also be evaluated in immunocompromised contacts, pregnant women, those who have had recent surgery or injury, or those with a family history of rheumatic fever. It could also be considered during outbreaks of pharyngitis, acute rheumatic fever or post-streptococcal glomerulonephritis in closed communities.
 - The regimen consists of penicillin (adults, 250 mg vo q6h for 10 d; children, 25mg/kg - maximum 250 mg per dose - po q6h for 10 d). If penicillin allergy is present, clindamycin or azithromycin may be chosen, after confirming the susceptibility of the index patient's isolate to these antimicrobials (7).

Antibiotic treatment (7,8)

Antibiotic treatment is indicated in group A streptococcal infections; the choice of drug, dose and route of administration depends on the clinical manifestations, location of the infection and patient characteristics.

In cases of **invasive infection** (e.g. bacteremia, necrotizing fasciitis) or **toxic shock**, the support of a clinical team with infectious disease experts, surgeons, and intensivists is required, as treatment includes immediate administration of intravenous antimicrobials, fluid management and hemodynamic support, surgical evaluation if needed for resection of necrotic tissue and other supportive measures, such as possible administration of immunoglobulin G. In the initial presentation of invasive infection or toxic shock due to group A *Streptococcus*, it cannot be distinguished from sepsis due to other pathogens, so empirical treatment should also cover *Staphylococcus aureus* (including methicillin-resistant), as well as gram-negative bacilli. The duration of antimicrobial treatment should be adjusted to the patient's characteristics, including the origin of the infection and the clinical course. Patients with bacteremia should be treated for at least 14 days.

Table 1. Antimicrobial Treatment for Invasive Group A Streptococcus (GAS) Infections

Infection	Treatment
Necrotizing fasciitis/myositis	Early and extensive surgical debridement, plus: Empirical treatment -Adults: piperacillin/tazobactam 4.5 g/iv q8h + clindamycin 600 mg/iv q8h + vancomycin 1 g/iv q12h or linezolid 600 mg/iv q12h

	<p>-Children: penicillin G crystalline 200,000 U/kg/iv/d divided in four doses (q6 h) + clindamycin 40 mg/kg/iv/d divided in three doses (q8 h) + third generation cephalosporin in usual doses¹.</p> <p>If GAS confirmed, de-escalate to:</p> <p>-Penicillin G (adults 4 million units q4h iv, children, 200,000 units/kg iv daily, divided q4-6h, maximum daily dose 24 million units) + clindamycin (adults, 900 mg iv q8h, children 40 mg iv divided in 3 doses (q8h), maximum daily dose 2.7 g)</p>
Streptococcal toxic shock	<p>Patients with community-acquired sepsis, empirical treatment:</p> <p><u>-Adults</u>: piperacillin/tazobactam 4.5 g/iv q6-8h or ertapenem 1 g/iv w/24 h; consider adding vancomycin 1 g q12 h, according to local epidemiology</p> <p><u>-Children (> 1 month of age)</u>: ceftriaxone 100 mg/kg/iv/d in one daily dose or cefotaxime 200 mg/kg/iv/d divided in four doses (q6 h) + ampicillin 200 mg/kg/iv/d divided in four doses (q6 h)</p> <p>Patient with sepsis/toxic syndrome, confirmed GAS, de-escalate to:</p> <p>-Penicillin G (adults 4 million units q4h iv, children, 200,000 units/kg iv daily, divided q4-6h, maximum daily dose 24 million units) + clindamycin (adults, 900 mg iv q8h, children 40 mg iv divided in 3 doses (q8h), maximum daily dose 2.7 g).</p> <p>-Consider adding adjuvant treatment with immunoglobulin G (dose in adults and children: 1 g/kg iv on day 1, followed by 0.5 g/kg iv on days 2 and 3)</p>
Bacteremia (in the absence of shock, organ failure or necrotizing infection)	<p>Confirmed GAS:</p> <p>-Penicillin G (adults 4 million units q4h iv, children, 200 000 - 400 000 units /kg iv daily, divided q4-6h, maximum daily dose 24 million units) + clindamycin (adults, 900 mg iv q8h, children, 40 mg iv divided in 3 doses (q8 h), maximum daily dose 2.7 g)</p>

Disclaimer: the antimicrobial recommendations are provided for informational purposes only and does not replace in any case the advice, diagnosis, treatment or recommendations of health professionals.

Risk communication

- Promote the dissemination of public health messages to physicians and the general population to improve early recognition, reporting and prompt initiation of treatment of these cases.
- Inform and educate about the risk of invasive disease among household contacts of scarlet fever cases, emphasize proper hand hygiene, and adequate indoor ventilation as additional protective measures.

¹ In case of suspicion of methicillin-resistant *S. aureus*, add vancomycin 60mg/kg/iv/d divided in 3 doses (c/8 h).

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