Diagnosis and Management of Invasive Group A Streptococcal Infections

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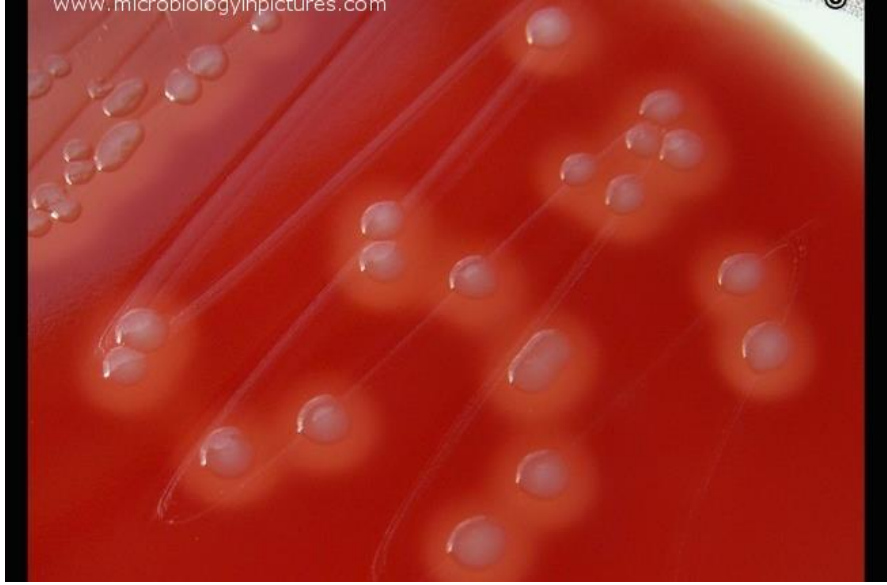
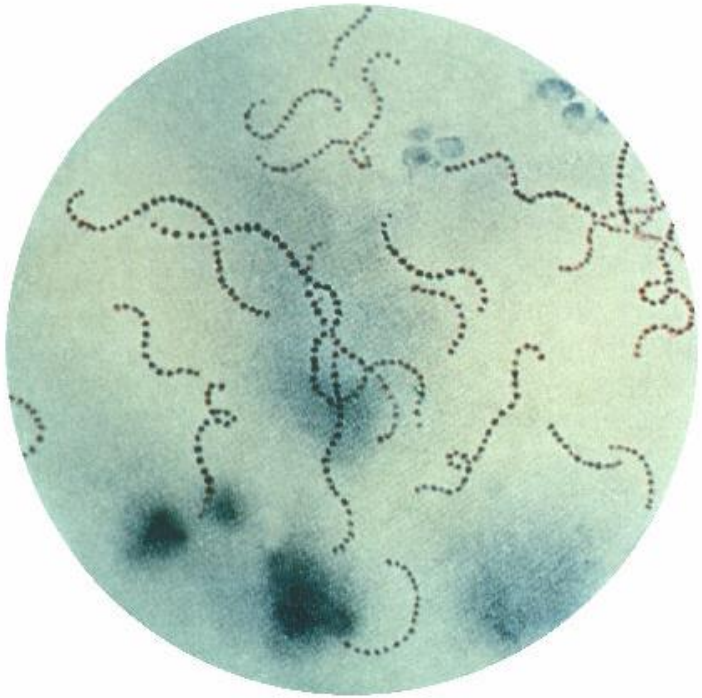
Microbiology

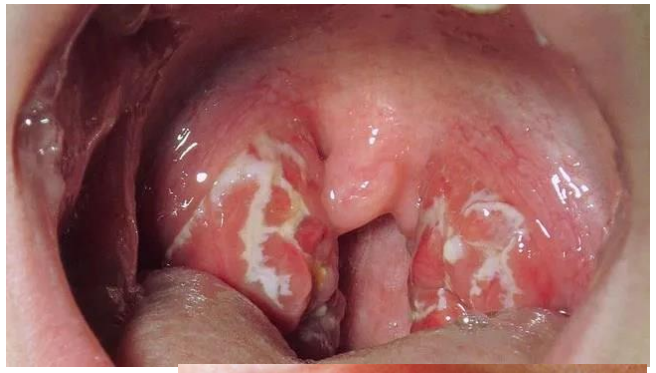


- *Streptococcus pyogenes*, or Group A streptococcus (GAS), is a facultative, Gram-positive coccus which grows in chains
- It grows best in an environment of 10% carbon dioxide and produces colonies on blood agar plates surrounded by a zone of complete (beta) hemolysis.
- Colonies are typically 0.5 to 1.0 mm in diameter, although some strains grow as larger, translucent-appearing or "mucoid" colonies due to abundant production of the hyaluronic acid capsular polysaccharide.
- GAS has also been subdivided based upon serotyping of surface-expressed M and T antigens. M-typing using specific antisera has been largely supplanted by *emm*-typing, that is, sequencing the variable region of the *emm* gene.

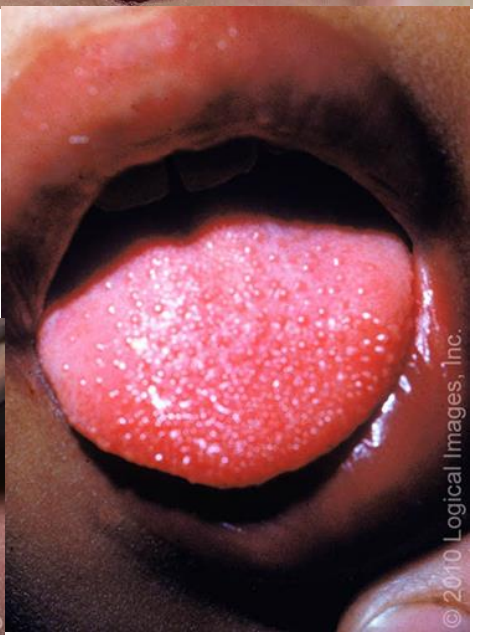


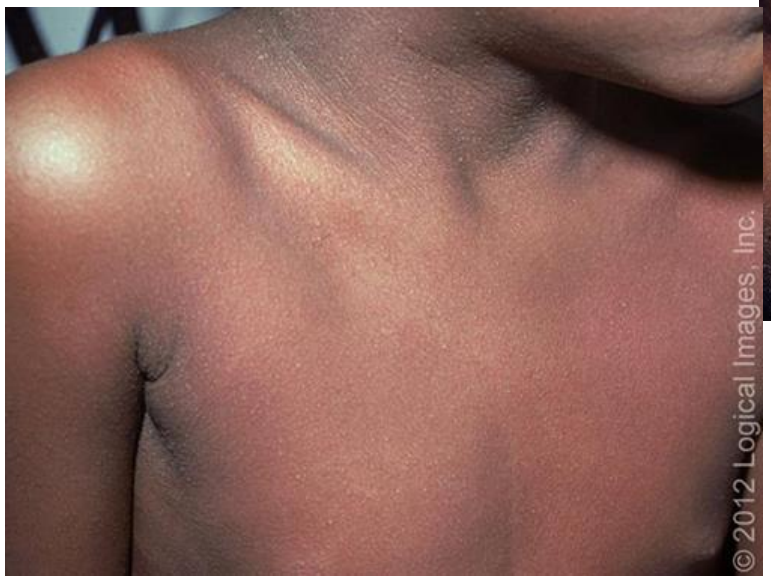
Clinical manifestations

- **Non-invasive**
  - Acute pharyngitis
  - Scarlet fever
  - Skin and soft tissue infection



- **Invasive** (isolation of GAS from a normally sterile body site) – case fatality rate 30-60%
  - Necrotising soft tissue infection
  - Puerperal sepsis
  - Bacteraemia
  - Respiratory infections (pneumonia / empyema)
  - Septic arthritis, osteomyelitis
  - Meningitis, cerebral empyema
  - Endocarditis
  - Retroperitoneal/pelvic infections





- **Autoimmune**
  - Post-streptococcal glomerulonephritis
  - Acute rheumatic fever
  - Chronic rheumatic heart disease

Invasive GAS infection (iGAS)

- Cellulitis 32%
- Bacteraemia with no focal symptoms 19%
- Septic arthritis 9%
- Necrotising fasciitis 8%
- Puerperal sepsis 3%
- Meningitis 2%

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Epidemiology of Severe *Streptococcus pyogenes* Disease in Europe▽

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- Overall 13% developed STSS (50% among cases of NF)
- Overall 19% of patients died within 7 days of diagnosis (highest fatality rate was among patients with NF – 32%)

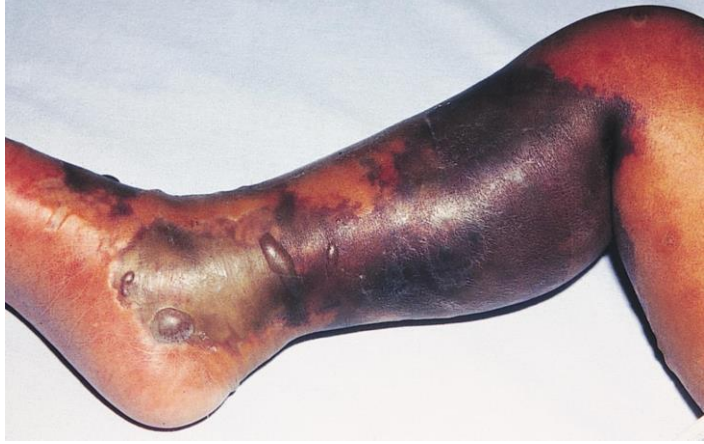
iGAS: Bacteraemia

- GAS bacteremia usually occurs in association with infection at a primary site
- The most common source of GAS bacteremia is **skin and soft tissue infection** (cellulitis/erysipelas), surgical wound infection, varicella virus infection, and burns

- In some cases, GAS bacteremia occurs in the absence of a clear localizing source. Symptoms may be nonspecific and include fever, chills, and fatigue.

- Among older patients, diabetes and peripheral vascular disease may serve as predisposing factors for isolated GAS bacteremia.
- Additional risk factors (among children and older adults) include malignancy and immunosuppression

iGAS: Necrotising fasciitis – “flesh-eating disease”



- Necrotizing soft tissue infection may include involvement of the epidermis, dermis, subcutaneous tissue, fascia, and muscle.

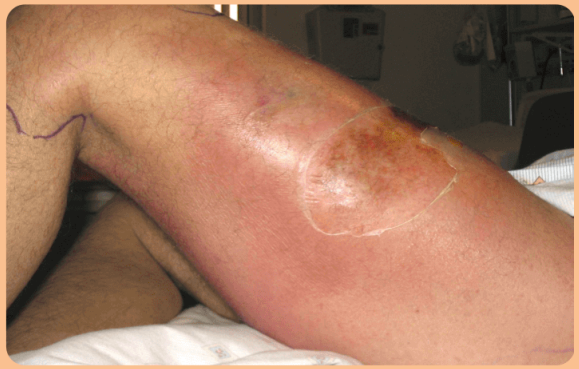
- Most commonly involves the extremities (lower extremity more commonly than upper extremity), particularly in patients with diabetes and/or peripheral vascular disease.

- **Necrotizing fasciitis** is an infection of the deep soft tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat

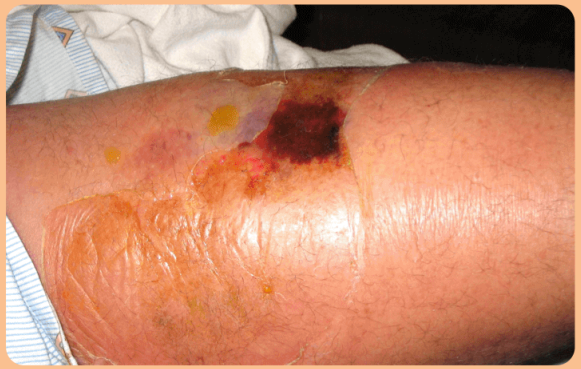
LOOK

CLINICAL FEATURES are progressive… **mortality doubles after 24 hours of presentation!**

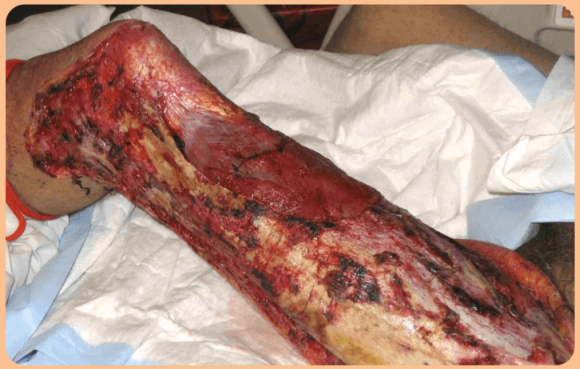
STAGE 1 Erythema, swelling, warmth, **TENDERNESS** beyond area of affected skin.



STAGE 2 Blisters, bullae formation, serous fluid, fluctuance and induration of the skin.



STAGE 3 Numb, crepitus, bleeding, discolouration, necrosis progressing to gangrene.

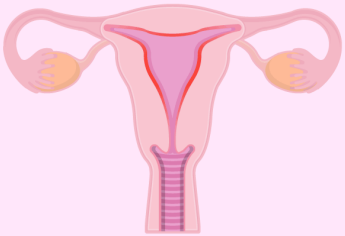


REMEMBER… the initial skin lesion / injury may be <u>small</u> with disproportionate pain

Source: East Midlands Emergency Medicine Educational Media
Em3.org.uk
@EM3FOAMed

- Development of anesthesia may precede the appearance of skin necrosis
- Usually presents acutely (over hours)
- Rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death.

iGAS: Puerperal sepsis



Puerperal endometritis

- A **rare** but important cause of maternal and infant mortality
- Tropism of GAS for placenta / uterus, disruption of tissue barriers, pregnancy-related immune suppression
- Most occur during the first 48 to 72 hours after delivery
- **Endomyometritis** (typical symptoms: fever, uterine pain, purulent uterine discharge) and **necrotizing soft tissue infection** are the two most common types of infection.
- Physical examination findings:
  - signs of sepsis (eg, fever, tachycardia, tachypnea, hypotension), abdominal and bimanual examination may reveal abdominal and/or uterine tenderness or wound infection.
  - Vulvovaginal examination may reveal vaginal or cervical purulent discharge or inflammation at the site of a laceration.
  - Rarely, cellulitis elsewhere (eg, of an extremity) or a diffuse erythematous rash may be present.
- The diagnosis should be suspected in pregnant or recently postpartum patients who develop fever, chills, and abdominal or postpartum wound pain, especially if fever is greater than 38.5°C (>101.3°F) or pain is out of proportion to findings on physical examination

iGAS: Others / Respiratory infections

- GAS pneumonia / multilobar pneumonia / pleural effusion / empyema
- suppurative complications of pharyngitis such as peritonsillar abscess and with extension of infection into the sinuses, middle ear, and mastoids
- Other (relatively uncommon) manifestations of invasive GAS infection include septic arthritis, osteomyelitis, peritonitis, and meningitis

Streptococcal Toxic Shock Syndrome (STSS)

- a complication of invasive GAS disease characterized by shock and multiorgan failure
- occurs as a result of capillary leak and tissue damage due to release of inflammatory cytokines induced by streptococcal toxins
- Develops in up to **1/3** of patients with invasive GAS disease
- Despite aggressive treatment, the reported mortality rate for STSS ranges 30-60%.
- Blood culture is positive in about 60% of patients with STSS

- Clinical features: iGAS infection + early onset (eg, within hours) of shock and organ failure
  - Fever is common; hypothermia may be present.
  - Altered mental status (about half of case).
  - An influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea occurs in about 20% of patients.
  - A diffuse, scarlatina-like erythema occurs in about 10% of cases

Risk factors for invasive disease

- Minor trauma, including injuries resulting in hematoma, bruising, or muscle strain
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Recent surgery
- HIV infection
- Other viral infection (eg, influenza, varicella)
- Intravenous drug use
- Homelessness
- Postpartum state
- Burns
- Obesity
- Peripheral vascular disease
- Malignancy
- Corticosteroid use
- Diabetes mellitus and other forms of immunosuppression
- Cardiac disease

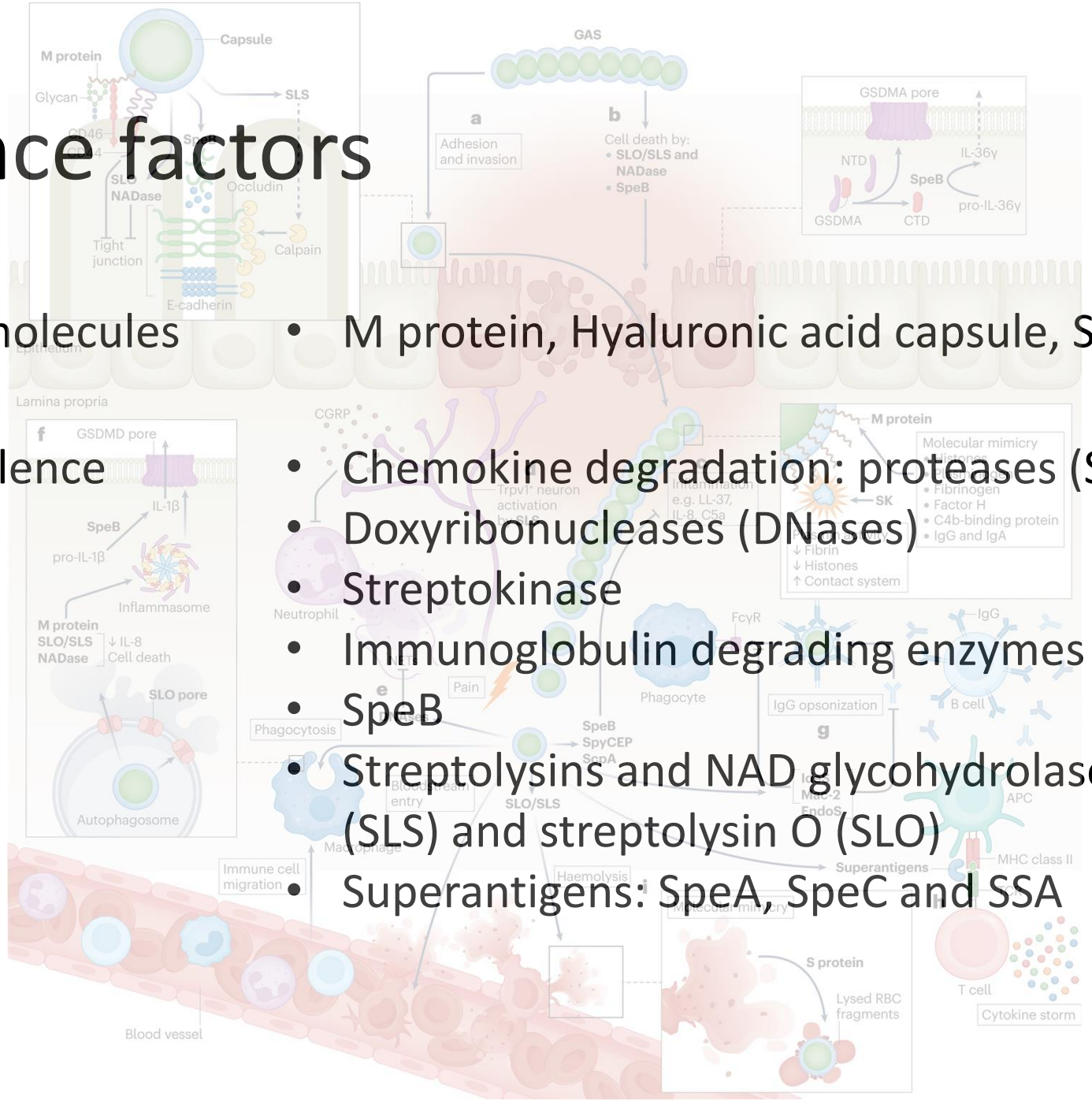
Virulence factors

Cell-surface molecules

- M protein, Hyaluronic acid capsule, S protein

Secreted Virulence factors

- Chemokine degradation: proteases (SpyCEP, ScpA)
- Doxyribonucleases (DNases)
- Streptokinase
- Immunoglobulin degrading enzymes
- SpeB
- Streptolysins and NAD glycohydrolase: streptolysin S (SLS) and streptolysin O (SLO)
- Superantigens: SpeA, SpeC and SSA



M protein

- More than 220 *emm* genotypes have been identified
- M-1 and M-3 strains - the most frequent isolates from cases of streptococcal toxic shock syndrome (TSS), although many other M types have also been recovered from such cases, including some nontypeable strains.
- M types 1 and 3 - also commonly isolated from asymptomatic carriers and patients with pharyngitis or mild scarlet fever

Table 1 | Diseases caused by GAS infection

Disease	Signature clinical symptoms	Associated M types	Treatment
Invasive			
Bacteraemia	High fever, nausea, vomiting	1, 3, 6, 12, 28[a], 53, 68, 81, 89[a]	Intravenous antibiotics, IVIG
Cellulitis	Erythema, oedema, warmth and tenderness	Unknown	Oral or systemic antibiotics depending on disease severity
Puerperal sepsis	Fever, chills, pain, purulent vaginal discharge in pregnant or recent postpartum women	1, 4[a], 11, 12, 13, 28[a]	Intravenous antibiotics, surgical intervention if required
Necrotizing fasciitis	Fever, malaise, local erythema, swelling, myalgias, abdominal pain	1, 3, 28[a]	Intravenous antibiotics and surgical debridement and/or amputations
Streptococcal toxic shock syndrome (STSS)	Fever, rash, hypotension, end organ failure	1, 3	Intravenous fluids and antibiotics, IVIG

GAS, Group A *Streptococcus*; IVIG, intravenous immunoglobulin. [a]Capsule-negative *emm* types[51].

*Brouwer, S., et al. Nat Rev Microbiol **21**, 431–447 (2023*

M-protein: immunomodulatory effects

- Can directly bind to and recruit numerous host components, including plasmin(ogen) and fibrinogen, to the streptococcal surface → confer resistance against innate and adaptive immune responses
- Can trigger programmed cell death in macrophages, leading to the processing and secretion of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18
- Contributes to host colonization through adhesive interaction with epithelial cell receptors, such as the membrane cofactor protein (MCP; also known as CD46) and cell-surface glycans

$M1_{UK}$

- A sublineage of M1
- large seasonal upsurges in scarlet fever were documented annually in England between 2014-2018, coinciding with the expansion and recognition of a new lineage of *emm*1 termed $M1_{UK}$ among *S. pyogenes* isolates.
- $M1_{UK}$ differed from other globally circulating *emm1* strains ($M1_{global}$) by 27 signature SNPs, was characterised by increased expression of the scarlet fever toxin, streptococcal pyrogenic exotoxin A (*speA*)
- $M1_{UK}$ has recently been linked to the rise in numbers of severe infections in Europe, Australia, North America, and Japan seen after pandemic restrictions were lifted
- Upsurge of STSS in Japan 2024:
  - 656 STSS cases caused by GAS were reported by 19/6/2024
  - 221/377 GAS isolates (58.6%) were M1 serotype, of which 194 (87.8%) were $M1_{UK}$ sublineages

Superantigens

- commonly referred to as Spes
- Streptococcal superantigens have been implicated in a range of human diseases, most notably toxic shock syndrome and scarlet fever.
- To date, 13 distinct superantigens have been identified in GAS
  - chromosome-encoded: *speG*, *speJ*, *speQ*, *speR* and *smeZ*
  - prophage-encoded: *speA*, *speC*, *speH*, *speI*, *speK–M* and *ssa*
- SpeA, SpeC and SSA have been linked with increased fitness and virulence of contemporary GAS strains causing scarlet fever and invasive disease.

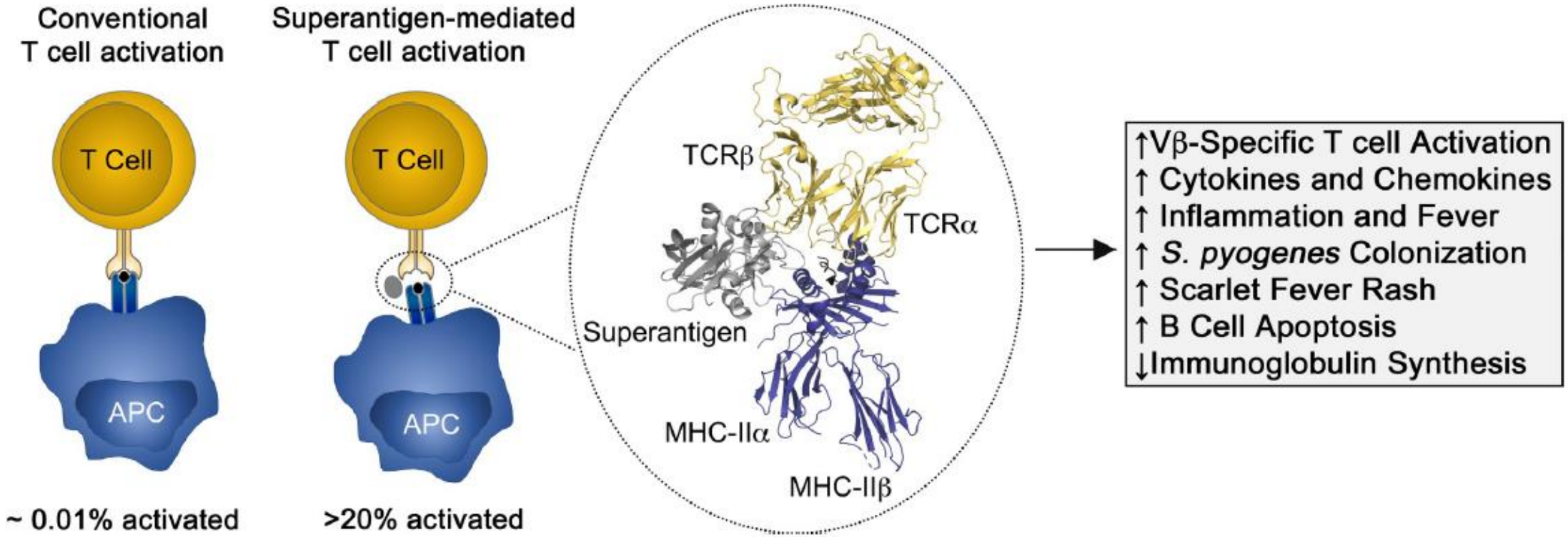


Fig 1. Overview of T cell activation by streptococcal superantigens and functional outcomes. Displayed are cartoons showing a comparison of conventional versus superantigen-mediated T cell activation, and a ribbon diagram of the SpeA superantigen (gray) in complex with the TCR expressed on a T cell (yellow) and MHC-II expressed on an APC (blue). Compared with convention T cell activation, note how the superantigen engages the β-chain of the TCR and displaces the TCR away from the MHC-II presented antigenic peptide (black) leading to the Vβ-specific activation of T cells. The structural model was generated using the co-crystal structure of SpeA in complex with mouse Vβ8 (PDB code 1L0Y) and superimposing a human αβ TCR (PDB code 1FYT) and human MHC-II from the staphylococcal enterotoxin C3 superantigen in complex with HLA-DR1 (PDB code 1JWM). The ribbon diagram was generated using PyMOL Molecular Graphics System (https://pymol.org). APC, antigen presenting cell; MHC-II, MHC class II molecule; TCR, T cell receptor.

Hurst, Jacklyn & Brouwer, et al. (2021). PLOS Pathogens. 17. e1010097. 10.1371/journal.ppat.1010097.

Diagnosis - iGAS

- The diagnosis of invasive GAS infection is established via positive culture for GAS from a normally sterile site (most commonly blood; less commonly pleural, pericardial, joint, or cerebrospinal fluid)
- For patients with suspected invasive GAS infection, blood cultures (at least two sets) should be obtained (ideally prior to antibiotic administration).
- cultures should be collected from clinically relevant sites
  - skin or soft tissue infection - wound culture
  - Patients who undergo debridement should have debrided material sent for culture
  - Postpartum women - endometrial aspirate
  - pneumonia - throat and sputum culture
  - patients who undergo thoracentesis should have pleural fluid sent for culture and pleural fluid chemistries.

- *The diagnosis of necrotizing infection is established via surgical exploration of the soft tissues in the operating room, with physical examination of the skin, subcutaneous tissue, fascial planes, and muscle
- Imaging studies

Clinical criteria for streptococcal TSS:

- Hypotension (systolic blood pressure ≤90 mmHg in adults or <5th percentile for age in children <16 years)
- Multiorgan involvement characterized by ≥2 of the following:
  - Renal impairment – In adults, creatinine ≥2 mg/dL (177 micromol/L); in children, ≥2 times the upper limit of normal for age; in patients with pre-existing renal disease, ≥2 times elevation over baseline
  - Coagulopathy – Platelets ≤100,000/mm^3 (100 x 10^6/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
  - Liver involvement – Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥2 times the upper limit of normal for the patient's age; in patients with pre-existing liver disease, ≥2 times elevation over baseline
  - Acute respiratory distress syndrome
  - Erythematous macular rash, may desquamate
  - Soft tissue necrosis (eg, necrotizing fasciitis, myositis, or gangrene)

- A probable diagnosis of TSS: clinical criteria (in the absence of another identified etiology for the illness) with isolation of GAS from a nonsterile site (eg, throat, vagina, skin lesion).
- A confirmed diagnosis of TSS: clinical criteria, with isolation of GAS from a normally sterile site (eg, blood, cerebrospinal fluid, joint fluid, pleural fluid, pericardial fluid, peritoneal fluid, tissue biopsy, or surgical wound).

Centers for Disease Control and Prevention. Streptococcal Toxic Shock Syndrome (STSS) (Streptococcus pyogenes) https://ndc.services.cdc.gov/conditions/streptococcal-toxic-shock-syndrome/

Important Differential Diagnoses:

- Staphylococcal toxic shock syndrome
- Gram negative sepsis
- Meningococcemia
- Typhoid fever
- Kawasaki Disease

Table 1. Diagnostic criteria for staphylococcal and streptococcal TSS according to the CDC recommendations [1,17].

Staphylococcal TSS	Streptococcal TSS
Clinical criteria	
1. Fever ≥ 38.9 °C. 2. Rash—diffuse macular erythroderma. 3. Desquamation—1–2 weeks after onset of the illness, particularly on palms and soles. 4. Hypotension—systolic blood pressure ≤ 90 mm Hg for adults or <5th percentile for children <16 years. 5. Multisystem involvement—at least 3 of the following: a. Gastrointestinal—vomiting or diarrhea; b. Muscular—severe myalgia or elevated creatine phosphokinase twice the upper limit of normal; c. Mucous membranes—hyperhaemia of any mucosal surface; d. Renal—blood urea nitrogen or creatinine twice-upper limit of normal; e. Hepatic—total bilirubin twice-upper limit of normal; f. Hematological—platelets ≤ 100,000/mm^3; g. Central nervous system-disorientation, combativeness, or alterations in consciousness without focal neurological signs.	1. Hypotension—systolic blood pressure ≤90 mm Hg in adults or <the fifth percentile by age for children <16 years. 2. Two or more of the following signs: a. Renal impairment: Creatinine greater than or equal to 2 mg/dL (>177 µmol/L) for adults or greater than or equal to twice of the upper limit to normal age. If preexisting renal disease, greater than twofold elevation over the baseline level; b. Coagulopathy—platelets ≤ 100,000/mm^3 or disseminated intravascular coagulation; c. Hepatic involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin twice the upper limit of normal. If preexisting liver disease, greater than twofold increase over the baseline level; d. ARDS; e. Generalized, erythematous, macular rash that may desquamate; f. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.
Laboratory criteria	
Negative results on the following tests: a. Blood, throat or CSF (blood culture may be positive for *S. aureus*); b. Rise in titer to Rocky Mountain spotted fever, leptospirosis, or measles.	Isolation of group A β-hemolytic streptococci: a. From a normally sterile site (blood, CSF, joint, pericardial, pleural, peritoneal fluid, tissue biopsy); b. From a nonsterile site (throat, vagina, sputum).
Case classification Probable TSS: a case which meets 4 of the 5 clinical criteria and the laboratory criteria. Confirmed TSS: a case which meets all 5 clinical criteria (including desquamation) and laboratory criteria.	**Case classification** Probable TTS: a case which fulfils clinical case definition and isolation of group A β-hemolytic streptococci from a normally nonsterile site in the absence of other etiology for the illness. Definite TSS: a case which fulfils clinical case definition and isolation of group A β-hemolytic streptococci from a normally sterile site.

TSS: toxic shock syndrome; CSF: cerebrospinal fluid; ARDS: adult respiratory distress syndrome.

Atchade, E., et al. Antibiotics 2024 , 13 (1), 96

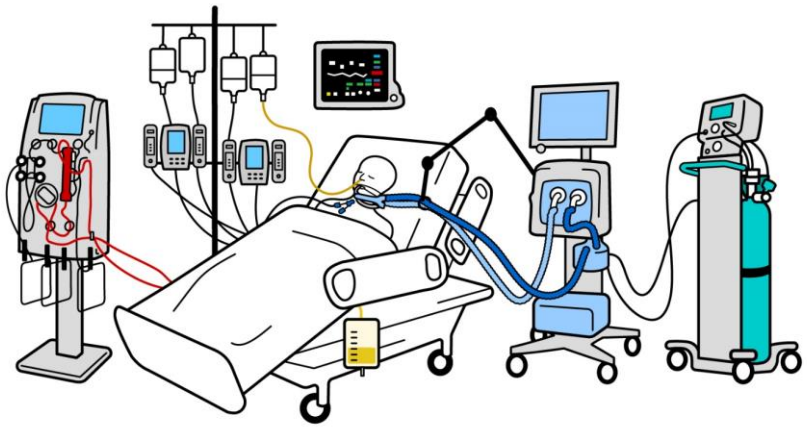
Management

- Given the rapid clinical progression, effective management of invasive group A streptococcal infections hinges on early recognition of the disease and prompt initiation of supportive care (often intensive care) together with antibacterial therapy.

- aggressive supportive care and early targeted antibacterial therapy are the most important aspects of management, particularly of STSS.
- Other important considerations:
  - removal of infected tissue
  - use of intravenous immunoglobulin (IVIG);
  - use of clindamycin as an adjunct antibacterial
  - avoidance of non-steroidal anti-inflammatory drugs (NSAIDs).

Supportive care

- Toxic shock syndrome is characterized by profound hypotension caused by toxin-mediated capillary leak, also associated with hypoalbuminemia, and third spacing
- Large quantities of **intravenous (IV) fluids** (up to 10 to 20 L/day) and vasopressors may be required early to maintain perfusion.
- Because TSS can cause sepsis-associated cardiomyopathy, echocardiography can be helpful, particularly since patients with cardiomyopathy may be particularly susceptible to vasopressor-associated symmetrical gangrene of the extremities
- Renal support may be required early
- Patients frequently require endotracheal intubation and ventilation, particularly when ARDS develops



Surgical Debridement (esp for NF)

- Surgical exploration is required to establish the diagnosis of necrotising fasciitis, evaluate the scope of involvement
- Surgical exploration should **not** be delayed when there is clinical suspicion for a necrotising infection while awaiting results of radiographic imaging, culture results, or other diagnostic information.
- Intraoperative specimens should be sent for Gram stain and culture
- The goal of operative management is to perform aggressive debridement of all necrotic tissue until healthy, viable (bleeding) tissue is reached
- Inspection and debridement should be continued every one to two days until necrotic tissue is no longer present
- For severe necrotizing infection involving the extremities, amputation may be needed to control the infection

Antimicrobial

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Dennis L. Stevens,[1] Alan L. Bisno,[2] Henry F. Chambers,[3] E. Patchen Dellinger,[4] Ellie J. C. Goldstein,[5] Sherwood L. Gorbach,[6] Jan V. Hirschmann,[7] Sheldon L. Kaplan,[8] Jose G. Montoya,[9] and James C. Wade[10]

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Beta-lactam

(Inhibits cell wall synthesis)

+

Clindamycin (inhibits protein synthesis)

- Necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci should be treated with both clindamycin and penicillin – IDSA Guideline 2014
  e.g.: IV penicillin G 4MU Q4H + IV Clindamycin 600mg-900mg Q8H

- no naturally occurring penicillin-resistant GAS strain has been found, and GAS remains susceptible to β-lactam antibiotics
- the resistance rate of GAS to macrolides and clindamycin have been rising

Penicillin

- No naturally occurring penicillin-resistant GAS strain has been found, and GAS remains susceptible to β-lactam antibiotics
  - Some subclinical penicillin resistant strains have been identified

- Studies have noted an association between penicillin monotherapy and treatment failure in the setting of high inoculum
  - beta-lactam antibiotics are most effective against rapidly growing bacteria. in the setting of high inoculum, the available numbers of penicillin-binding proteins (PBPs) on the organism surface during stationary-phase growth is reduced → the efficacy may be diminished as organism concentrations increase and the rate of bacterial growth slows.
  - In the setting of deep-seated infection, the concentration of organisms may be sufficiently high to reduce the effectiveness of beta-lactam antibiotics.

Clindamycin

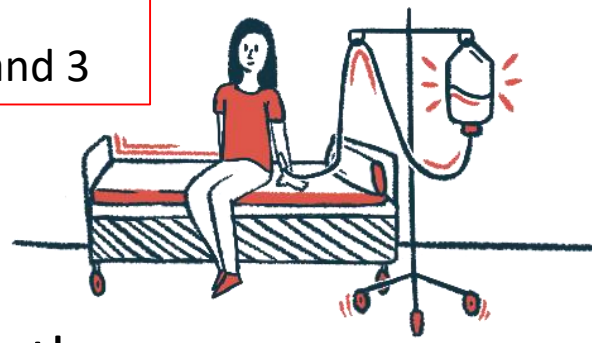
- A lincosamide inhibiting protein synthesis via 50S ribosome
- More effective than penicillin in high inoculum of GAS
- Clindamycin **suppresses streptococcal toxin** (streptolysin S, M protein, streptococcal pyrogenic exotoxins) and cytokine production.
- May increase GAS opsonisation and phagocytosis via complement
- Studies suggest iGAS treated with clindamycin is associated with reduced mortality
- Clindamycin resistance is increasing among GAS

Combination therapy with penicillin and clindamycin should be continued until patients are clinically and hemodynamically stable (ie, 48 to 72 hours); thereafter, clindamycin therapy should be discontinued and the patient should be maintained on penicillin monotherapy.

Linezolid

- An alternative adjunctive antitoxin antibiotic for iGAS
- Susceptibility of GAS to linezolid remains high
- Attenuates GAS virulence - one study showed penicillin and linezolid combination had similar rapid reduction of streptococcal exotoxin to clindamycin combination
- Reduces production of streptolysin O and DNase while increasing susceptibility to phagocytosis
- Also has activity against MRSA
- Clindamycin has higher risk for *clostridioides difficile* infection (CDI)

IVIg 1g/kg day 1,
Then 0.5g.kg on days 2 and 3



Adjunctive therapy: IVIg

- Main mediator for inflammatory response and systemic toxicity are the streptococcal superantigens and surface M protein
- Previous studies have shown that protective humoral immunity to both cell-associated and soluble GAS virulence factors are important in preventing invasive disease.
- Studies showed patients with invasive GAS disease had significantly lower serum levels of protective antibodies against M-protein and superantigens, compared with serum samples from noninvasive cases.
- IVIg is a **potentially beneficial** adjunctive therapy
- Human polyspecific intravenous IgG (IVIG) was suggested as a potential adjunctive therapy for invasive GAS diseases mainly because of its ability to neutralize a wide variety of superantigens and to facilitate opsonization of streptococci.

IVIg

- **Conflicting** results from clinical trials
- An observational cohort study of iGAS + STSS reported decreased 30-day mortality rates in patients treated with IVIG compared with controls (34% vs 67%, p = .02)[1]
- Cochrane review: IVIG reduced mortality among adults with sepsis, this benefit was not seen in trials with low risk of bias[2]
- placebo-controlled trial (prematurely terminated due to slow recruitment) reported decreased mortality rates in patients treated with IVIG (10 recipient vs 11 placebo; 3.6 fold higher mortality rate in placebo group)[3]
- Comparative observational study: 23 patients received IVIG therapy compared with 44 who did not. Adjusted analysis revealed that factors influencing 28-day survival in STSS were SAPS II (odds ratio [OR], 1.1; P = .007), clindamycin (OR, 8.6; P = .007), and IVIG (OR, 5.6; P = .030).[4]

- *1. Kaul R, et al. Clin Infect Dis 1999;28:800–7.*
- *2. Alejandria MM, et al. Co-chrane Database Syst Rev 2013; 9:CD001090.*
- *3. Darenberg J, et alClin Infect Dis 2003; 37:333–40.*
- *4. Linnér A, et al. Clin Infect Dis. 2014 Sep 15;59(6):851-7.*

Other therapies

- High-dose corticosteroid therapy has not been shown to be beneficial; stress dose steroid may be considered for refractory shock
- The use of hyperbaric oxygen has been reported in a small number of patients with streptococcal TSS. There are no controlled trials, and the efficacy of this treatment is not known.
  - Possible mechanisms:
    - Counteract the relative hypoxic environment of NF, improving bacterial killing mediated by neutrophil free radical production and phagocytosis
    - Suppresses production of cytokines / other inflammatory mediators
    - Increases bactericidal activity of certain antibiotics
- Use of anti-TNF antibody has been studied in an animal model of streptococcal TSS with promising results; further study is needed.

Prevention

- it is important to maintain good personal, hand, and environmental hygiene.
- Symptomatic patients should wear a surgical mask, refrain from work or attending classes at school, avoid going to crowded places, and seek medical advice promptly.
- No commercial GAS vaccine is available at the moment, research on GAS vaccine development is ongoing

Conclusion

- Group A streptococcus remains an important pathogen, and invasive diseases are associated with high mortality rates
- STSS: early recognition and a high index of suspicion is important in compatible clinical syndromes
- Early surgical intervention for source control and aggressive resuscitation may be required
- Antibiotic therapy: beta-lactam antibiotic + clindamycin / linezolid
- IVIg may be considered as adjunctive treatment