
In the name of
GOD

Invasive group A streptococcal infections in children

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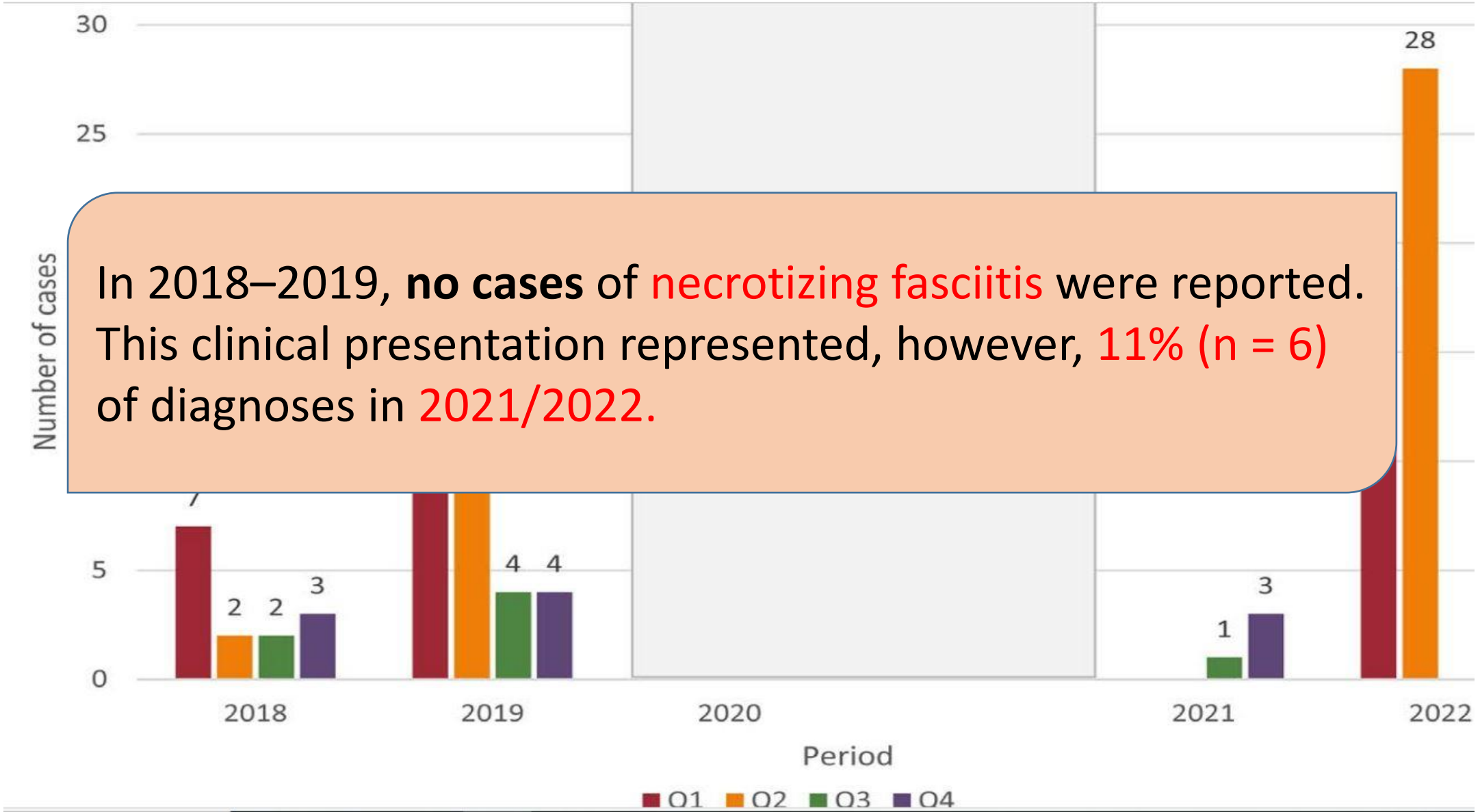
WHO (12 December 2022)

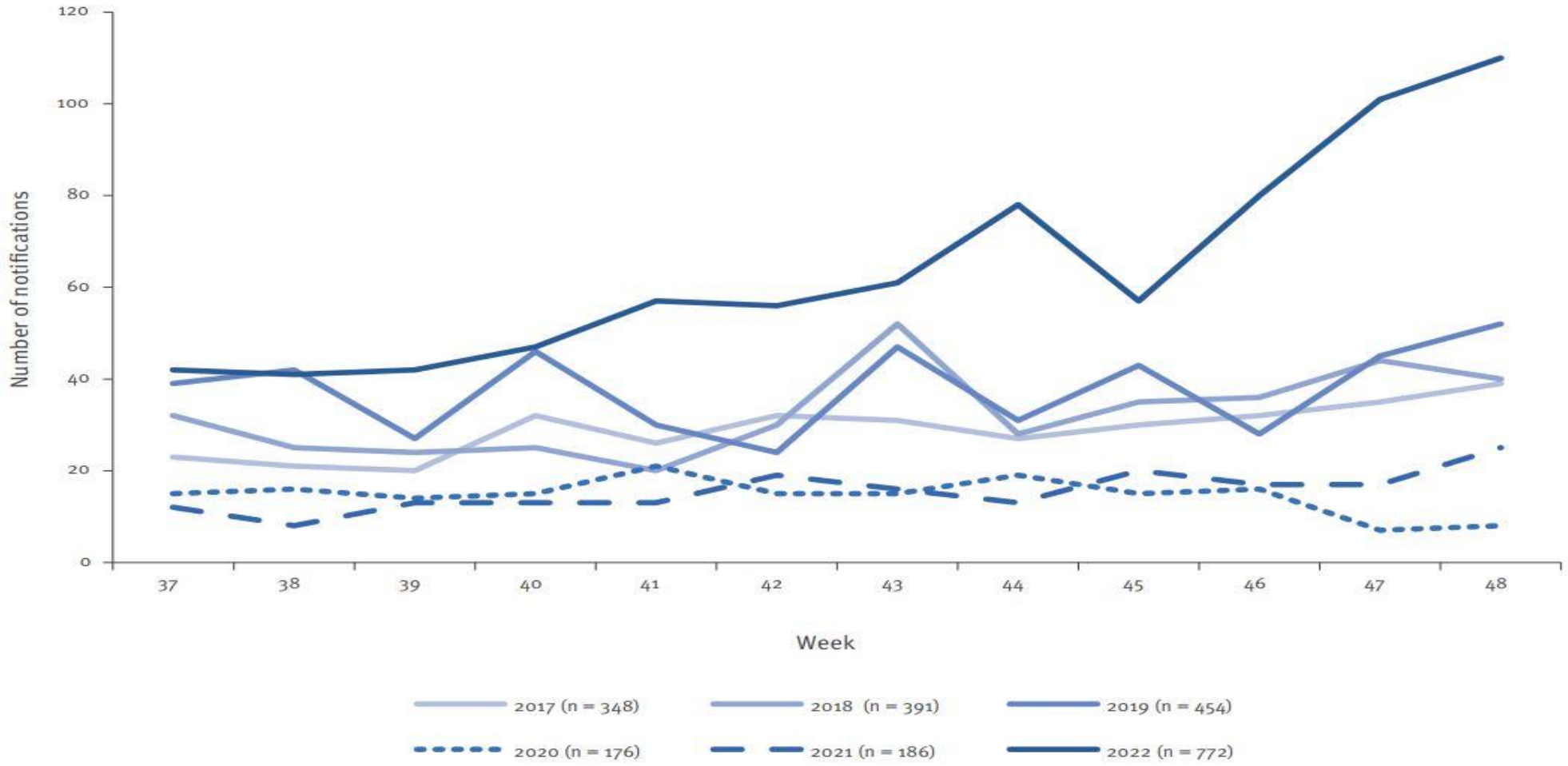
- A number of European countries (France, Ireland, the Netherlands, Sweden and the United Kingdom) have indicated an increase in 2022, particularly since September, in the number of cases of iGAS disease among children under 10 years of age.
- It is likely that the increase in cases of iGAS disease in children is also associated with the **recent increased circulation of respiratory viruses**, including seasonal influenza and respiratory syncytial virus, as coinfection of viruses with GAS may increase the risk of iGAS disease.
- Although investigations are ongoing, early typing data suggests that the surge of cases is not related to a specific or new strain, nor an increase in antibiotic resistance of GAS.

Number of cases by year-quarter



In 2018–2019, **no cases** of necrotizing fasciitis were reported. This clinical presentation represented, however, 11% (n = 6) of diagnoses in 2021/2022.

Weekly laboratory notifications of invasive group A streptococcal infections, England, weeks 37–48, 2017–2022a (n = 2,327)



Respiratory virus coinfections

Respiratory viral co-infections within +/− 1 day of invasive group A streptococcal infection, by age group, in children younger than 15 years, England, November 2022 (n = 97)

	Age group				Total
	<1 year	1–4 years	5–9 years	10–14 years	
Number of children with iGAS	10	50	30	7	97
Number of children with co-infections	3	15	6	1	25
Co-infections[a]	5	32	11	1	49
Adenovirus	0	2	1	0	3
Severe acute respiratory syndrome coronavirus 2	1	3	1	0	5
Enterovirus	0	3	0	0	3
Human metapneumovirus	1	8	2	0	11
Influenza A	1	0	1	1	3
Influenza B	0	1	0	0	1
Parainfluenza	0	3	1	0	4
Respiratory syncytial virus	2	8	2	0	12
Rhinovirus	0	4	3	0	7

Increased reports of iGAS cases in children younger than 15 years with respiratory virus co-infections (+/−1 day of the iGAS specimen) were noted in October and November 2022

Of the 10 deaths in children younger than 15 years diagnosed with iGAS infection in November 2022, **five** were identified as having a **respiratory virus co-infection**.

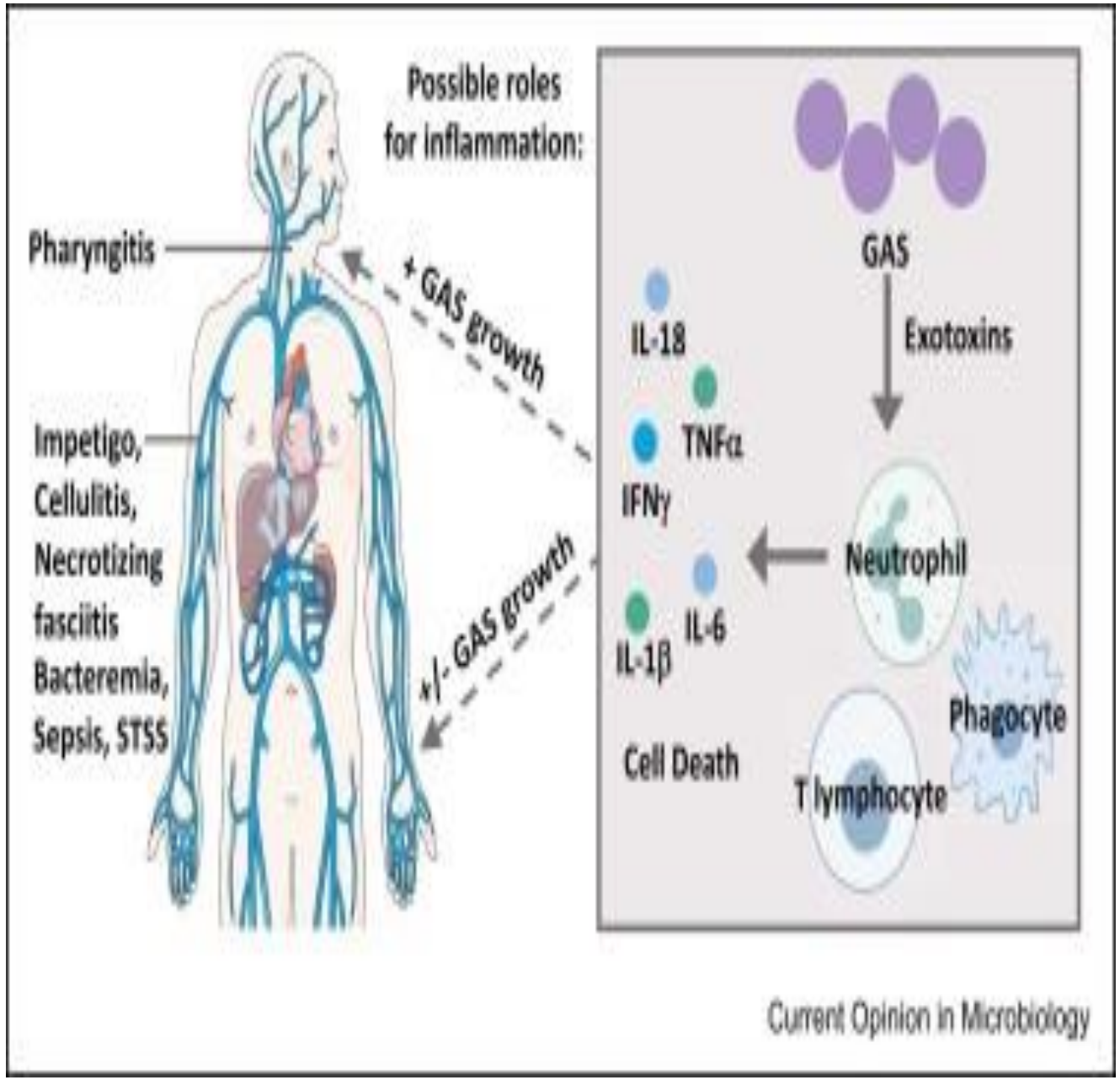
Group A streptococcal

- Group A streptococcus (GAS, *Streptococcus pyogenes*) is an aerobic gram-positive coccus that is a common cause of acute bacterial pharyngitis and other cutaneous and invasive infections in children.

- More than 240 distinct serotypes or genotypes of group A streptococci (strep. Pyogenes) have been identified based on M-protein serotype or M-protein gene sequence (emm types).

Invasive GAS infection

- The factor responsible for the increase in incidence of iGAS are not fully understood.
- Alterations in the distribution of GAS strain M types, together with an increasing prevalence of toxin-producing strains, may be responsible.
- About half of iGAS are caused by a limited number of GAS types (1, 3, 4, 6, 28); the remaining half are caused by a variety of strains, including nontypeable strains.



- GAS infects the skin and upper respiratory tract, secreting exotoxins that trigger a host inflammation.
- GAS superantigens activate T lymphocytes, resulting in IFNγ, IL-6, and TNFα production.

Invasive GAS infection

- Invasive GAS infection is defined by isolation of GAS from a normally sterile body site.

- **Forms of invasive GAS infection include:**
  - Necrotizing soft tissue infection
  - Pregnancy-associated infection
  - Focal and systemic infections

    bacteremia, meningitis, pneumonia, septic arthritis

    osteomyelitis, surgical wound infection

Necrotizing soft tissue infection(NSTI)

- Include necrotizing forms of **fasciitis, myositis, and cellulitis**.
- NSTI can include involvement of the epidermis, dermis, subcutaneous tissue, fascia, and muscle.
- Fulminant tissue destruction, systemic signs of toxicity, and high mortality.
- Accurate diagnosis and appropriate treatment (early surgical intervention and antibiotic therapy).

Necrotizing fasciitis

- Necrotizing fasciitis is an infection of the deep soft tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat.
- Infection typically spreads along the muscle fascia due to its relatively poor blood supply; muscle tissue is frequently spared because of its generous blood supply.

Necrotizing myositis

- **Necrotizing myositis**

Necrotizing myositis is an infection of skeletal muscle typically caused by GAS (and other beta-hemolytic streptococci).

It may be preceded by skin abrasions, blunt trauma, or heavy exercise.

Necrotizing cellulitis

- Necrotizing cellulitis is typically caused by *anaerobic pathogens* and may be divided into two types:

  clostridial (usually caused by *Clostridium perfringens*

  nonclostridial (caused by polymicrobial infection).
- In both types, crepitus is observed in the skin
- But there is **sparing of fascia and deep muscles**.
- Pain, swelling, and systemic toxicity are not prominent features.

RISK FACTORS

Necrotizing infection can occur among healthy individuals with no past medical history or clear portal of entry in any age group.

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

RISK FACTORS

- **VZV lesions** act as a portal of entry to the dermal and fascial layers, or that varicella infection itself causes immunosuppression, particularly a decrease in humoral immunity

Fever on or beyond the fourth day of the exanthem in children with VZV should prompt consideration of GAS bacteremia.

NSAID/iGAS

- An association has been noted among varicella, ibuprofen, and iGAS (controversy).
- NSAIDs may inhibit neutrophil function, suppress fever, and augment cytokine release.
- Regardless of their role in pathogenesis, NSAIDs may mask signs and symptoms of inflammation in patients with NSTI, which may be associated with a delay in diagnosis.

Necrotizing fasciitis

- Necrotizing fasciitis may be divided into two microbiologic categories: polymicrobial (type I) and monomicrobial infection (type II)
- Polymicrobial (type I) necrotizing infection is caused by aerobic and anaerobic bacteria.
- Monomicrobial (type II) necrotizing infection is usually caused by GAS or other beta-hemolytic streptococci.
- Infection may also occur as a result of *Staphylococcus aureus*.

Necrotizing fasciitis

- Nearly 50% of patients with NF caused by S.pyogenes have no portal of entery.

- In such circumstances, the pathogenesis of infection likely consists of hematogenous translocation of GAS from the throat (asymptomatic or symptomatic pharyngitis) to a site of blunt trauma or muscle strain.

CLINICAL MANIFESTATIONS

- Most commonly involves the extremities
  (lower extremity >upper extremity)
- Particularly in patients with diabetes and/or peripheral vascular disease.
- Necrotizing infection usually presents acutely (over hours); rarely, it may present subacutely (over days).
- Rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death .
- Therefore, early recognition of necrotizing infection is critical

Necrotizing soft tissue infection(NSTI)

- Erythema (without sharp margins)
- Edema that extends beyond the visible erythema
- Severe pain (out of proportion to exam findings)
- Fever
- Crepitus
- Skin bullae, necrosis, or ecchymosis
- Other symptoms include malaise, myalgias, diarrhea, and anorexia

Necrotizing fascitis

- Swelling of soft tissue usually is noted
- But the erythema may be subtle.
- **The hallmark tip- off on examination** :
  - pain out of proportion to the swelling and erythema
  - tenderness extending beyond the apparent involved area
  - indistinct margins
  - rapid progression (typically over hours)

Skin changes that occur during the subsequent **24 to 48** hours include blistering with belb formation, and a dusky appearance.

Compartment syndrome

- Tight edema
- Pain on motion
- Loss of distal sensation and pulses

Surgical emergency

Laboratory findings

- **Laboratory findings are generally nonspecific**
- leukocytosis with left shift, acidosis, coagulopathy, hyponatremia, elevated inflammatory markers (CRP,ESR).
- Elevations in serum creatinine, lactate, creatine kinase (CK), AST
- Elevations in serum CK or AST concentrations suggest deep infection involving muscle or fascia (as opposed to cellulitis)

Laboratory findings

- NSTI cannot be predicted reliably using laboratory parameters, particularly in the setting of early infection.
- Positive Blood cultures

  60 percent of patients with monomicrobial (type II) necrotizing fasciitis

  Blood cultures (two sets) should be obtained prior to administration of antimicrobial therapy

DIAGNOSIS

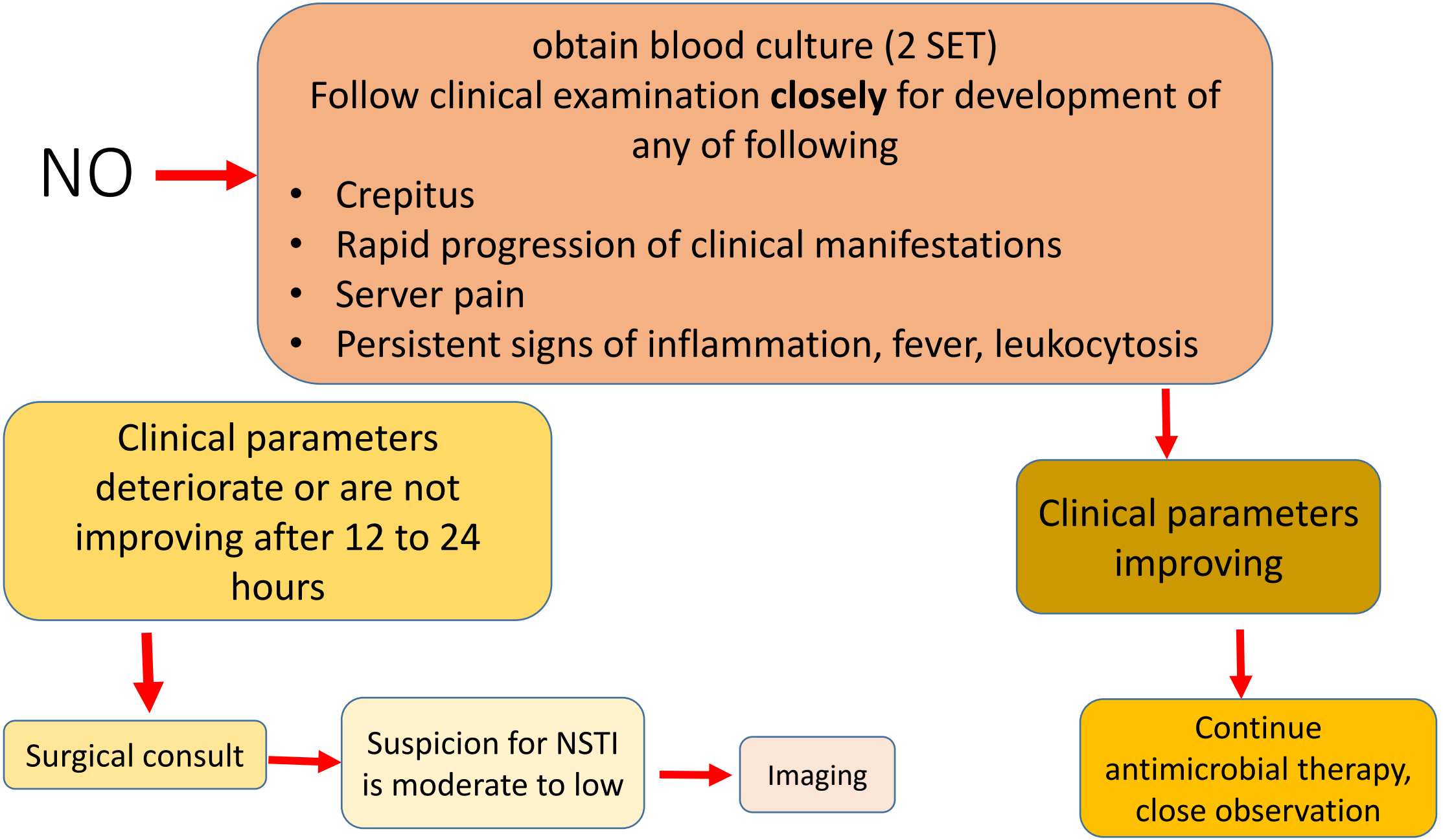
Presence of soft tissue infection
(erythema, edema, warmth)
And
Signs of systemic illness(fever, hemodynamic instability)

Are there clear signs and symptoms concerning for NSTI
(**any of the following**)

- Crepitus, skin discoloration or necrosis
- foul –smelling wound discharge
- Rapid progression of clinical manifestations
- Server pain (out of proportion to skin finding in some cases

yes →

- ❖ Obtain blood cultures then begin antimicrobial therapy
- ❖ Urgent surgical exploration to evaluate fascia and obtain material for gram stain, culture (aerobic and anaerobic) and pathologic examination
- ❖ Aggressive surgical debridement for confirmed disease


NO
obtain blood culture (2 SET)
Follow clinical examination **closely** for development of any of following
• Crepitus
• Rapid progression of clinical manifestations
• Server pain
• Persistent signs of inflammation, fever, leukocytosis
Clinical parameters deteriorate or are not improving after 12 to 24 hours
Clinical parameters improving
Surgical consult
Suspicion for NSTI is moderate to low
Imaging
Continue antimicrobial therapy, close observation

Imaging

- **The first-line imaging study depends on** :

The anatomic location, clinical condition of the patient, availability of technology, and expertise at interpretation.

imaging modalities include CT scan MRI and ultrasound.

MRI is the preferred technique.

Imaging findings of NSTI:

Gas in the soft tissues, fluid collections, absence or heterogeneity of tissue enhancement with intravenous contrast, and inflammatory changes beneath the fascia.

TREATMENT

- Early and aggressive surgical exploration and debridement of necrotic tissue,
- Broad-spectrum empiric antibiotic therapy and hemodynamic support.

Administration of antibiotic therapy **in the absence of debridement** is associated with a mortality rate approaching 100 percent.

Surgical debridement

- NSTI is a surgical emergency.
- Radiographic imaging studies should not delay surgical intervention (crepitus on examination or rapid progression of clinical manifestations).
- The goal of operative management:

  aggressive debridement of all necrotic tissue until healthy,

  viable (bleeding) tissue is reached.

  every one to two days until necrotic tissue is no longer present

Surgical debridement

- In the typical clinical scenario in which the index of suspicion for necrotizing fasciitis is high:

  surgical exploration is appropriate, even in the presence of normal MRI finding

Antibiotics

- Empiric treatment of necrotizing infection should consist of broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms
- A carbapenem(imipenem, meropenem) or Piperacillin-tazobactam

PLUS

- An agent with activity against MRSA; such as vancomycin

PLUS

- Clindamycin

Antibiotic therapy

- Group A streptococcal (GAS) or other beta-hemolytic streptococcal infection:

  Penicillin(300,000 units/kg per day)

  plus

  clindamycin (40 mg/kg per day)

Antibiotic therapy

- Antibiotics should be continued until:
  - no further debridement is needed and
  - the patient's hemodynamic status has normalized

This duration often consists of at least two weeks of treatment and must be tailored to individual patient circumstances

Hemodynamic support

Hemodynamic instability may require:

- ✓ Aggressive supportive care with **fluids and vasopressors**.
- ✓ **Albumin** replacement may be required in the setting of capillary leak syndrome associated with streptococcal toxic shock syndrome
- ✓ **IVIG** for patients with NSTI in the setting of streptococcal TSS.

  The combination of clindamycin and IVIG is likely efficacious by reducing circulating toxins produced by GAS

Infection control

- standard precautions
- droplet precautions
- contact precautions

Droplet and contact precautions may be **discontinued** after the first 24 hours of antimicrobial therapy.

OUTCOME

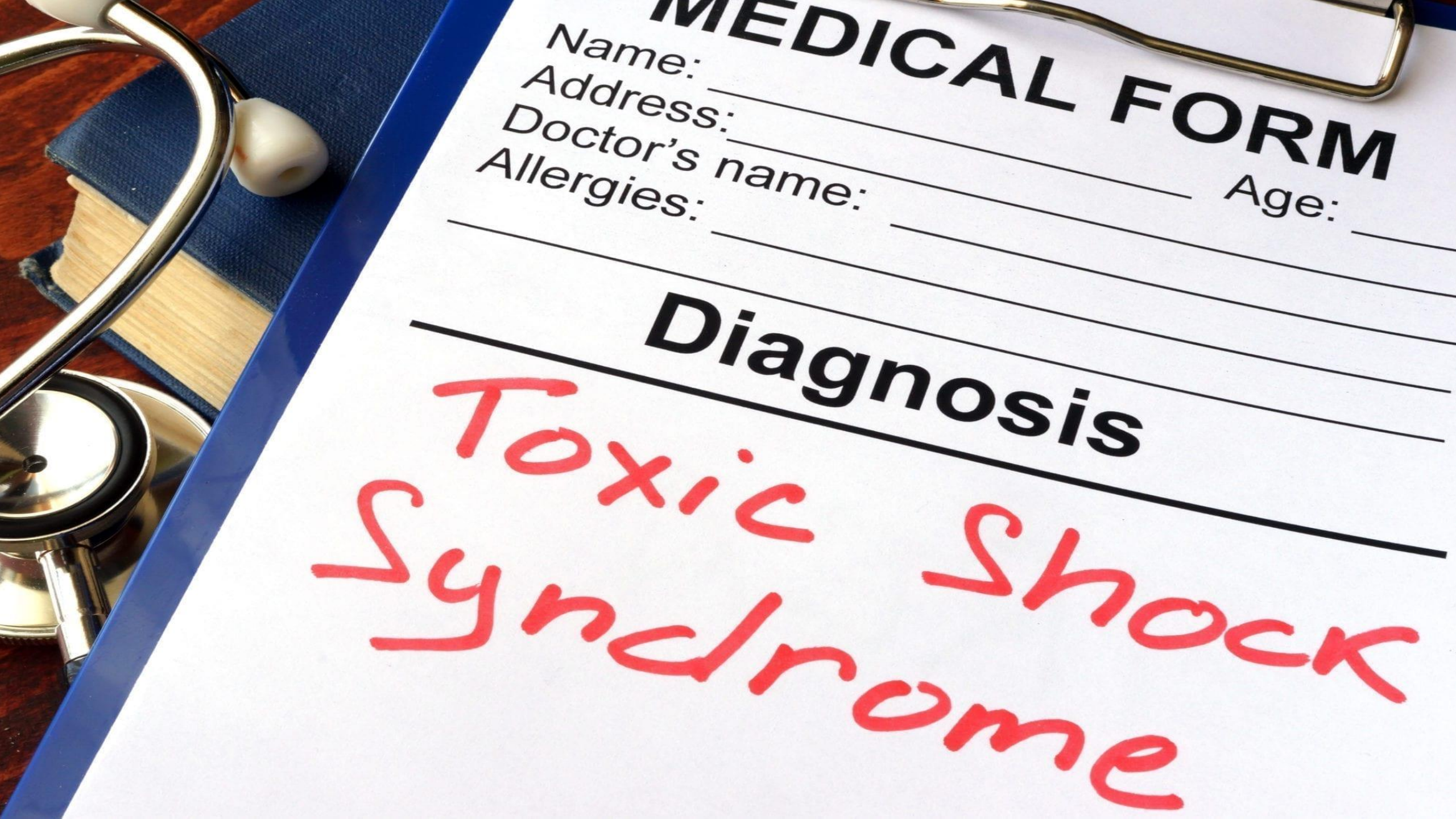
- Necrotizing infection is associated with considerable mortality, even with optimal therapy.
- Mortality rates:

  Polymicrobial (type I) necrotizing fasciitis – 21 percent

  Monomicrobial (type II) necrotizing fasciitis – 14 to 34 percent

OUTCOME

- Factors associated with increased mortality include:
  - White blood cell count >30,000/microL; band neutrophils >10 percent
  - Serum creatinine >2.0 mg/dL (177 mmol/L)
  - Age >60 years
  - Streptococcal toxic shock syndrome
  - Delay in surgery for more than 24 hours
  - Infection involving the head, neck, thorax, or abdomen


MEDICAL FORM
Name:
Address:
Doctor's name:
Age:
Allergies:
Diagnosis
Toxic Shock Syndrome

Toxic shock syndrome (TSS)

- Streptococcal TSS is a complication of invasive GAS disease characterized by shock and multiorgan failure
- It occurs as a result of **capillary leak and tissue damage** due to release of inflammatory cytokines induced by streptococcal toxins.
- TSS develops in up to **one-third** of patients with **invasive GAS** disease.
- The rate of TSS among patients with necrotizing fasciitis is approximately 50 percent.

Diagnostic criteria

- Hypotension

Multiorgan involvement characterized by two or more of the following:

- Renal impairment: creatinine ≥2 times ULN for the patient's age)
- Coagulopathy (Platelets ≤100,000/mm^3 , prolonged clotting times, low fibrinogen level)
- Liver involvement(AlT, AST, or total bilirubin levels ≥2 times ULN for the patient's age)
- Acute respiratory distress syndrome
- Erythematous macular rash, may desquamate
- Soft tissue necrosis (necrotizing fasciitis, myositis, or gangrene)

Diagnostic criteria

- **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 (throat, vagina, skin lesion).

- **A confirmed diagnosis of TSS**:

clinical criteria, with isolation of GAS from a normally sterile site (blood, CSF, joint fluid, pleural fluid, pericardial fluid, peritoneal fluid, tissue biopsy, or surgical wound).

Management (TSS without NF)

- Fluid management
- Anticipatory management of multisystem organ failure
- Parenteral antimicrobial therapy at maximum doses:
  - kill organism with bactericidal cell wall inhibitor
  - decrease enzyme, toxin, or cytokine production with protein synthesis inhibitor(clindamycin)
- IGIV (1 gr/kg on day 1, 0.5 g/kg on 1-2 subsequent days)