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Toxic Shock Syndrome

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Introduction

Background

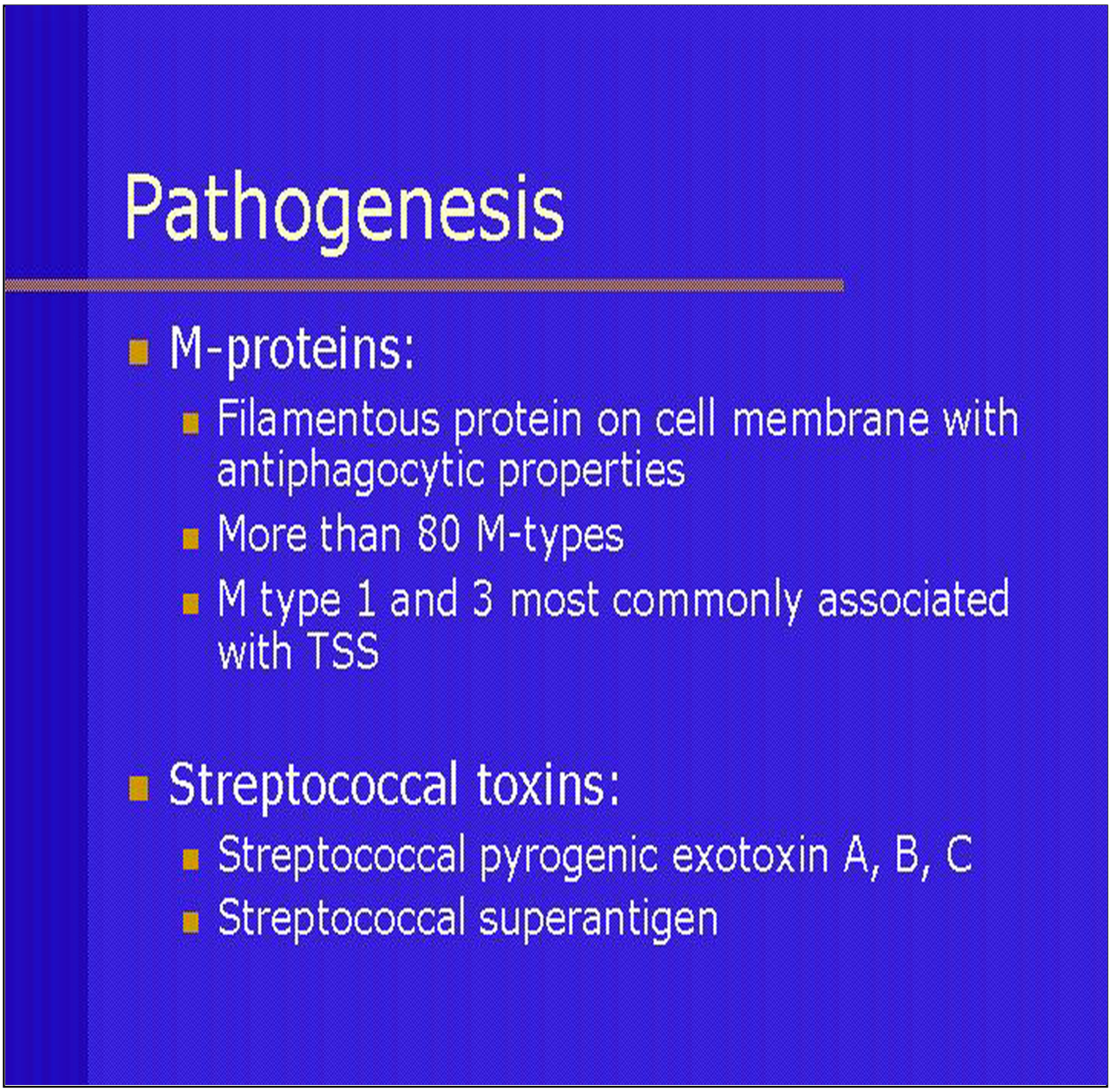
Toxic shock syndrome (TSS) is a toxin-mediated acute life-threatening illness, usually precipitated by infection with either *Staphylococcus aureus* or group A *Streptococcus* (GAS), also called *Streptococcus pyogenes.* It is characterized by high fever, rash, hypotension, multiorgan failure (involving at least 3 or more organ systems), and desquamation, typically of the palms and soles, 1-2 weeks after the onset of acute illness. The clinical syndrome can also include severe myalgia, vomiting, diarrhea, headache, and nonfocal neurologic abnormalities.

TSS was first described in children in 1978.[1] Subsequent reports identified an association with tampon use by menstruating women.[2,3,4] Menstrual TSS is more likely in women using highly absorbent tampons, using tampons for more days of their cycle, and keeping a single tampon in place for a longer period of time. Over the past two decades, the number of cases of menstrual TSS (1 case per 100,000) has steadily declined; this is thought to be due to the withdrawal of highly absorbent tampons from the market.

Notably, 50% of cases of TSS are not associated with menstruation. Nonmenstrual cases of TSS usually complicate the use of barrier contraceptives, surgical and postpartum wound infections, burns, cutaneous lesions, osteomyelitis, and arthritis. Although most cases of TSS occur in women, about 25% of nonmenstrual cases occur in men.

In the 1980s, Cone initially reported and Stevens subsequently characterized GAS as a pathogen responsible for invasive soft tissue infection ushered by toxic shock–like syndrome.[5,6] The streptococcal TSS is identical to staphylococcal TSS (STSS), except that the blood cultures usually are positive for staphylococci in STSS. Toxin-producing strains of *S aureus* infect or colonize people who have risk factors for the development of the syndrome. Most cases are related to the staphylococcal toxin, now called TSS toxin-1 (TSST-1).

GAS is an aerobic gram-positive organism that forms chains and is an important cause of soft tissue infections. Diabetes, alcoholism, varicella infections, and surgical procedures all increase the risk of severe GAS infections and hence may potentially increase the risk of GAS TSS. Severe, invasive GAS infections can cause necrotizing fasciitis and spontaneous gangrenous myositis. An increasing number of severe GAS infections associated with shock and organ failure have been reported. These infections are termed streptococcal TSS.[7]



Description of M proteins and streptococcal toxins.

Pathophysiology

Bacteriology

Toxic shock syndrome (TSS) is caused from intoxication by one of several related *Staphylococcus aureus* exotoxins. The most commonly implicated toxins include TSS toxin type-1 (TSST-1) and Staphylococcal enterotoxin B.

Almost all cases of menstrual TSS and half of all the nonmenstrual cases are caused by TSST-1. Staphylococcal enterotoxin B is the second leading cause of TSS. Other exotoxins such as enterotoxins A, C, D, E, and H contribute to a small number of cases. Seventy to 80% of individuals develop antibody to TSST-1 by adolescence, and 90-95% have such antibody by adulthood. Apart from host immunity status, host-pathogen interaction, local factors (pH, glucose level, magnesium level), and age all have a direct impact on the clinical expression of this toxin-mediated illness.

M protein is an important virulent determinant of GAS; strains lacking M protein are less virulent. M protein is a filamentous protein anchored to the cell membrane, which has antiphagocyte properties. M types 1, 3, 12, and 28 are the most common isolates found in patients with shock and multiorgan failure; furthermore, 3 distinct streptococcal pyrogenic exotoxins (ie, A, B, C) also have been identified. These toxins induce cytotoxicity and pyrogenicity and enhance the lethal effects of endotoxins. Recently, the streptococcal super antigen, a pyrogenic exotoxin, has been isolated from an M-3 strain. In some studies, strains producing exotoxins B and C have been implicated in this syndrome, to a lesser extent.

Mechanism of shock and tissue destruction

Colonization or infection with certain strains of *S aureus* and GAS is followed by the production of 1 or more toxins. These toxins are absorbed systemically and produce the systemic manifestations of TSS in people who lack a protective antitoxin antibody. Possible mediators of the effects of the toxins are cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor (TNF). Pyrogenic exotoxins induce human mononuclear cells to synthesize TNF-alpha, IL-1-beta, and interleukin 6 (IL-6).

TSS likely relates to the ability of pyrogenic exotoxins of GAS and enterotoxins of *S aureus* to act as super antigens. Superantigens are molecules that interact with the T-cell receptor in a domain outside of the antigen recognition site and hence are able to activate large numbers of T cells resulting in massive cytokine production. Normally, an antigen has to be taken up, processed by an antigen-presenting cell and expressed at the cell-surface along with class II major histocompatibility complex (MHC). By contrast, superantigens do not require processing by antigen-presenting cells but instead interact directly with the class II MHC molecule. The superantigen-MHC complex then interacts with the T-cell receptor and stimulates large numbers of T cells to cause an exaggerated, dysregulated cytokine response.

In the case of TSS, the implicated exotoxins and several staphylococcal toxins (eg, TSST-1) can stimulate T-cell responses through their ability to bind to both the class II major histocompatibility complex of antigen-presenting cells and T-cell receptors. These toxins simultaneously bind to the beta chain variable region (V-beta) elements on T-cell receptors and the class II major histocompatability antigen-processing cells. This mechanism bypasses the classical antigen-processing procedures and results in excessive T-cell proliferation.

The conventional antigens activate only about 0.01% to 0.1% of the T-cell population, whereas, the superantigens set in motion 5-30% of the entire T-cell population. The net effect is massive production of cytokines that are capable of mediating shock and tissue injury. As part of this T cell response, interferon–gamma is also produced, which subsequently inhibits polyclonal immunoglobulin production. This failure to develop antibodies may explain why some patients are predisposed to relapse after a first episode of TSS.

Frequency

United States

Estimates from population-based studies have documented an incidence of invasive GAS infection of 1.5-5.2 cases per 100,000 people annually.[8] Approximately 8-14% of these patients also will develop TSS.[9] A history of recent varicella infection markedly increases the risk of infection with GAS to 62.7 cases per 100,000 people per year. Severe soft tissue infections, including necrotizing fasciitis, myositis, or cellulitis, were present in approximately half of the patients.

STSS is much more common, although data on prevalence do not exist. In the United States, from 1979-1996, 5296 cases of STSS were reported. The number of cases of menstrual STSS is estimated at 1 per 100,000. The incidence of nonmenstrual STSS now exceeds menstrual STSS after the hyperabsorbable tampons were removed from the market.

Mortality/Morbidity

Mortality rates for streptococcal TSS are 30-70%.[10,11] Morbidity also is high; in one series, 13 of 20 patients underwent major surgical procedures, such as fasciotomy, surgical debridement, laparotomy, amputation, or hysterectomy.[6,10]

The case fatality rates for menstrual-related STSS have declined from 5.5% in 1980 to 1.8% in 1996.

Race

TSS has occurred in all races, although most cases have been reported from North America and Europe.

Sex

STSS most commonly occurs in women, usually those who are using tampons.

Age

Some studies have shown no predilection for any particular age for either the streptococcal TSS or STSS. However, other studies have reported STSS to be more common in older individuals with underlying medical problems. In a Canadian survey, STSS accounted for 6% of cases in individuals younger than 10 years compared with 21% in people older than 60 years.[8] Furthermore, menstruation-associated STSS occurred in younger women who were using tampons.

Clinical

History

Although the clinical manifestations of TSS can be diverse, the possibility of toxic shock should be considered in any individual who presents with sudden onset of fever, rash, hypotension, renal or respiratory failure, and changes in mental status.[12]

- STSS most commonly occurs in women, usually those who are using tampons, TSS develops within 5 days after the onset of menstruation. The other clinical settings where STSS has been reported include the following:
  - Surgical wound infections
  - Postpartum infections
  - Focal cutaneous and subcutaneous lesions
  - Deep abscesses
  - Empyema
  - Peritonsillar abscess
  - Sinusitis
  - Osteomyelitis
- Soft tissue infections from GAS include necrotizing fasciitis, myositis, or cellulitis. The most common initial symptom of patients with streptococcal TSS is diffuse or localized pain that is abrupt and severe. Other manifestations include the following:
  - Influenzalike syndrome
  - Fever
  - Confusion
  - Signs of soft tissue infection
- Approximately 20% of patients with STSS have an influenzalike syndrome characterized by the following:
- Fever
- Chills
- Myalgia
- Nausea
- Vomiting
- Diarrhea
- The other reported types of infection are pneumonia, unidentified bacteremia, surgical site infection, septic arthritis, thrombophlebitis, meningitis, pelvic infection, and endophthalmitis.
- Common presenting symptoms and frequency of STTS are as follows[10]:
  - Pain (44-85%)
  - Vomiting (25-26%)
  - Nausea (20%)
  - Diarrhea (14-30%)
  - Influenzalike symptoms (14-20%)
  - Headache (10%)
  - Dyspnea (8%)
- The following risk factors have been reported to be associated with STSS:
  - Patients with HIV, diabetes, cancer, ethanol abuse, and other chronic diseases
  - Patients with a recent history of varicella infection (chicken pox)
  - Patients who used nonsteroidal anti-inflammatory drugs (NSAIDs)

Physical

Fever is the most common presenting sign, although patients in shock may present with hypothermia. Shock is apparent at the time of hospitalization or within 4-8 hours for all patients. Patients become severely hypotensive and do not respond to intravenous fluid administration. Renal dysfunction progresses or persists in all patients, precedes shock in many patients, and is apparent early. Acute respiratory distress syndrome occurs in 55% of patients and requires mechanical ventilation.

A thorough search for possible sites of streptococcal and staphylococcal infection is a must. The surgical wounds should be carefully examined even if no signs of infection are apparent. Vaginal examination and removal of tampon or other foreign body should be done diligently.

- Confusion is present in 55% of patients, and coma or agitation may occur. Alteration in mental status disproportionate to the degree of hypotension can occur with or without seizures. Persistent neuropsychiatric sequelae manifested by memory loss, and poor concentration have been reported.
- Nearly 50% of patients are normotensive on presentation but become hypotensive within 4 hours.
- Approximately 80% of patients have clinical signs of soft tissue infection (eg, localized swelling, erythema), which usually progresses to necrotizing fasciitis or myositis.
- Approximately 20% of patients have various clinical presentations, including the following:
    - Endophthalmitis
    - Myositis
    - Perihepatitis
    - Peritonitis
    - Myocarditis
- Diffuse scarlatinalike erythema occurs in 10% of patients.
- Skin manifestations of streptococcal infection include the following:
- Bullae
- Scarlet fever–like rash
- Petechiae or maculopapular rashes
- Desquamation
- Mucosal involvement includes conjunctival/scleral hemorrhage and hyperemia of the vaginal and oropharyngeal mucosa. Petechial hemorrhages (“strawberry tongue”) and ulcerations of mucosal membranes can occur in severe cases.
- The possibility of STSS should be entertained in any patient who presents with a sudden onset of fever, rash, hypotension, and systemic evidence of toxicity. Five categories of clinical features are needed for the diagnosis, as follows (Centers for Disease Control and Prevention, 1990):
- Fever
- Rash - A diffuse macular erythroderma
- Desquamation - Occurs 1-2 weeks after onset of illness, involving palms and soles
- Hypotension (systolic blood pressure <90 mm Hg, orthostatic drop in diastolic blood pressure <15 mm Hg, orthostatic syncope, and dizziness)
- Evidence of multisystem involvement in 3 or more of the following systems:
    - Gastrointestinal - Vomiting or diarrhea at the onset of illness
    - Muscular - Severe myalgia or creatine kinase (CK) elevation (>2 times normal upper limit)
    - Mucous membrane - Vaginal, oropharyngeal, or conjunctival erythema
    - Renal - BUN or serum creatinine greater than 2 times the upper limit of normal
    - Hepatic - Bilirubin or transaminases greater than 2 times the upper limit of normal
    - Hematological - Platelets less than 100,000
    - Central nervous system - Disorientation or alteration in consciousness without focal signs
- Common presenting symptoms and frequency of STTS are as follows[6]:
    - Tachycardia (80%)
    - Fever (70-81%)
    - Hypotension (44-65%)
    - Confusion (55%)
    - Localized erythema (44-65%)
    - Localized swelling and erythema (30-75%)
    - Scarlatiniform rash (0-4%)

- Case definition of streptococcal TSS (Working group definition, JAMA 1993)
  - Isolation of GAS (*S pyogenes*) from a normally sterile site, eg, blood, cerebrospinal fluid, pleural fluid (definite case), or nonsterile site (probable case) and hypotension (systolic pressure £90 mm Hg in adults or less than fifth percentile for children)
  - Multiorgan involvement, as evidenced by at least 2 of the following:
    - Renal impairment - Creatinine level more than 177 µmol/L for adults or twice upper normal limit for age or more than twice the baseline level for patients with renal disease
    - Coagulopathy - Platelet count less than 100 X 10^6/L or disseminated intravascular coagulation
    - Liver involvement - Alanine aminotransferase, aspartate aminotransferase, or total bilirubin level more than twice normal limit for age or more than twice baseline in patients with chronic liver disease
    - Pulmonary involvement - Adult respiratory distress syndrome or evidence of diffuse capillary leak syndrome
    - Generalized erythematous macular rash
    - Soft tissue necrosis (necrotizing infection, necrotizing myositis, or gangrene)

Causes

- Acquisition of infection
  - Risk factors for the development of STSS are tampon use, vaginal colonization with toxin-producing *S aureus,* and lack of serum antibody to the staphylococcal toxin.[13] STSS also has occurred following use of nasal tampons for procedures of the ears, nose, and throat.
  - The portal of entry for streptococci is unknown in almost one half of the cases. Procedures such as suction lipectomy, hysterectomy, vaginal delivery, and bone pinning have been identified as the portal of entry in many cases. Most commonly, infection begins at a site of minor local trauma, which may be nonpenetrating. Viral infections, such as varicella and influenza, also have provided a portal of entry.

Differential Diagnoses

Cellulitis
Clostridial Gas Gangrene
Erythema Multiforme (Stevens-Johnson Syndrome)
Fever of Unknown Origin
Gas Gangrene
Infectious Mononucleosis
Infective Endocarditis
Kawasaki Disease
Listeria Monocytogenes
Meningococcal Infections
Meningococcemia
Pharyngitis, Bacterial
Pneumonia, Bacterial
Sepsis, Bacterial
Septic Shock
Shock, Distributive
Shock, Hemorrhagic
Staphylococcal Infections
Streptococcus Group A Infections

Other Problems to Be Considered

The differential diagnosis includes the following:

Heat stroke
Leptospirosis
Rubeola
Rocky Mountain spotted fever (RMSF): Severe headache and rash are present in most patients with this disorder. The rash is petechial in patients with RMSF, whereas it is diffusely erythematous in patients with TSS.
Rash-associated viral infections
Meningococcemia
Streptococcal or staphylococcal scarlet fever
Drug reactions
Kawasaki syndrome
Toxic epidermal necrolysis
Gram-negative sepsis: This condition may mimic TSS but is uncommon in healthy patients outside the hospital setting.
Typhoid fever: This is a food-borne illness that also should be distinguished from TSS.

Workup

Laboratory Studies

- CBC count with differential
  - Leukocytosis with a polymorphonuclear shift to the left
  - Mild leukocytosis with significant immature neutrophils on peripheral smear
- Urinalysis
  - Myoglobinuria and hemoglobinuria present
  - Sterile pyuria
- Prolonged prothrombin and activated partial thromboplastin times
- Serum biochemistry
  - Serum creatinine - Frequently elevated and precedes the development of hypotension in 50% of cases
  - Hypoglycemia
  - Low serum protein and albumin concentrations
  - Elevated blood urea nitrogen
  - Elevated transaminases
  - Elevated bilirubin and creatine phosphokinase levels
  - In myositis or necrotizing fascitis, elevated serum creatinine kinase concentration
- Blood cultures
  - Blood cultures positive for bacteria - Present in approximately 60% of the cases of disease associated with GAS
  - Compared with STSS, blood cultures rarely positive for staphylococci
- Gram stain and cultures
  - *S aureus* - Identified easily by Gram stain and culture from a well-defined focus of infection (eg, abscess, wound infection)
  - In cases associated with menstruation, as many as 90% of patients demonstrate the organism in cultures from the cervix or vagina, in the absence of clinical infection.
  - *S aureus* bacteriemia - Uncommon in patients with TSS
- Common laboratory abnormalities in patients with streptococcal TSS[10]:
- Hypoalbuminemia (85%)
- Hypocalcemia (79%)
- Elevated liver transaminase levels (63%)
- Prolonged prothrombin time and/or activated partial thromboplastin time (60-71%)
- Elevated creatinine level (40-89%)

Imaging Studies

- Chest radiographs: Patients who develop multiorgan dysfunction will have bilateral airspace infiltrates consistent with acute respiratory distress syndrome.

Staging

Case definition of streptococcal TSS

- Isolation of GAS
  1. From a sterile site
  2. From a nonsterile body site
- Clinical signs of severity
  1. Hypotension

2. Clinical and laboratory abnormalities (requires 2 or more of the following): (1) renal impairment; (2) coagulopathy; (3) liver abnormalities; (4) acute respiratory distress syndrome; (5) extensive tissue necrosis, ie, necrotizing fasciitis; and (6) erythematous rash.

- Definite case - Isolation of GAS from a sterile site and hypotension and 2 or more of the clinical and laboratory abnormalities
- Probable case - Isolation of GAS from a nonsterile body site and hypotension and 2 or more of the clinical and laboratory abnormalities

Treatment

Medical Care

TSS has a rapid, dramatic, and fulminant onset. Quick recognition of the syndrome is important for enabling appropriate and prompt treatment. *S pyogenes* continues to be susceptible to beta-lactam antibiotics. Although very effective in treating pharyngitis and other superficial infections, aggressive GAS infections do not respond well to penicillin and continue to be associated with high mortality rates and extensive morbidity.

The principles in the management of septic shock in general must be instituted as soon as possible (see Septic Shock). These include the following components:

1. Early recognition
2. Early and adequate antibiotic therapy
3. Source control and early debridement of infected/necrotic wounds
4. Early hemodynamic resuscitation and continued support
5. Corticosteroids (refractory vasopressor-dependent shock)
6. Drotrecogin alpha (Severely ill if APACHE II > 25) within 24 hours of onset of first organ dysfunction
7. Tight glycemic control (Glucose target of <180 mg/dL are considered to be adequate based on present data.)
8. Proper ventilator management with low tidal volume in patients with acute respiratory distress syndrome (ARDS) with maintenance of plateau pressures of less than 30 cm of water.

- In experimental models of *S pyogenes* infection, penicillin proved to be inferior to clindamycin. The physiologic state of the organism attributed to the inoculum effects is suggested as the mechanism of failure.
    - Penicillin and other beta-lactam antibiotics are most efficacious against rapidly growing bacteria; therefore, these antibiotics have the greatest efficacy when organisms are growing rapidly during the early stages of infection or in mild infections. When higher concentrations of GAS accumulate (eg, deep-seeded infections), the effectiveness of beta-lactam antibiotics decreases because the bacterial growth slows (stationary phase).
    - Penicillin mediates its antibacterial action against GAS by interacting with penicillin-binding proteins (PBPs). Experimentally, the binding of penicillin has been shown to decrease in stationary cells, related to cells in the logarithmic growth phase; thus, the loss of certain PBPs during the stationary growth phase may be secondary to the inoculum effect and may account for penicillin failure.
- Clindamycin
    - This drug has multiple effects against GAS infection.
    - The efficacy of clindamycin is not affected by inoculum size or growth stage; furthermore, this agent is a potent suppressor of bacterial toxin synthesis.
    - Clindamycin facilitates phagocytosis of *S pyogenes* by inhibiting M protein synthesis.
    - Clindamycin suppresses synthesis of PBPs, which also are enzymes involved in cell wall synthesis.
    - Clindamycin has a longer postantibiotic effect than penicillin.
    - Clindamycin causes suppression of lipopolysaccharide-induced monocyte synthesis of TNF.[14]
- Recommended antibiotic therapy
    - For patients with GAS infection, the administration of clindamycin (600 mg -900 mg IV q8h) is recommended. Other clinicians recommend combined therapy, in which penicillin G (4 million U IV q4h) is combined with clindamycin.
    - Because differentiating between STSS and streptococcal TSS on clinical grounds alone is difficult, intravenous penicillin also should be administered in addition to a beta-lactamase resistant antibiotic until a bacteriologic diagnosis is confirmed by culture. Alternatively, a first-generation cephalosporin or vancomycin can be used.
- Staphylococcal toxic shock syndrome
    - Large doses of a beta-lactamase–resistant, antistaphylococcal, antimicrobial agent should be administered

intravenously to patients with staphylococcal infections. The usually prescribed antibiotics are nafcillin, oxacillin, and first generation cephalosporin. Nafcillin or oxacillin (2 g q4h) is generally recommended. Vancomycin can be used in penicillin-allergic patients.

- These agents have been known to increase TSST-1 in culture possibly by cell lysis. Therefore, clindamycin may be used in combination for the first few days to reduce synthesis of TSST-1.
- The antibiotic treatment is continued for 10 to 14 days in absence of a complication.

- Intravenous fluids
  - TSS causes intractable hypotension and diffuse capillary leak; therefore, massive amounts of intravenous fluids (10-15 L/d) often are necessary. Patients in shock may require central venous monitoring or right heart catheterization to guide fluid management.
  - The patient's blood pressure may improve with administration of fluids alone; otherwise, vasopressors (eg, dopamine) or even more potent vasoconstrictors (eg, norepinephrine) are required. Norepinephrine with or without dobutamine may be more effective than high-dose dopamine or epinephrine to preserve splanchnic perfusion.
  - Patients with TSS will require supportive measures, including intubation and mechanical ventilation, dialysis in patients who have developed renal failure, and adequate nutritional support.

- Other treatment measures
  - Intravenous immunoglobulin: Several anecdotal reports, 1 large series of 21 patients and a case control study, reported lower mortality rates for patients with Streptococcal TSS treated with intravenous immunoglobulins.[11,15,16] Intravenous immunoglobulins also have been reported to be beneficial in severe cases of Staphylococcal TSS. A single dose of IVIG (400 mg/kg), generates protective levels of antibody to TSST-1 that persist for week. The recommended initial dosage is 2 g/kg, followed by 0.4 g/kg for as long as 5 days. The mechanism responsible for the efficacy of gamma-globulin therapy may be neutralization of the circulating toxins, inhabitation of TNF-alpha production via nonspecific inhabitation of monocyte or T-cell activation, or inhibition of other streptococcal virulence factors. The contraindications include a history of anaphylaxis from immune globulin in past, immunoglobulin A (IgA) deficiency, and circulating anti-IgA antibodies.A recent case series described 7 patients with severe soft tissue infection caused by GAS and toxic shock syndrome. All were treated with effective antimicrobials and high-dose intravenous immune serum globulin (IVIG). Surgery was either not performed or only limited exploration was carried out. Six of the patients had toxic shock syndrome. The study suggests that the use of a medical regimen including IVIG in patients with severe GAS soft tissue infections may allow a minimally invasive approach. This can limit the need to perform immediate wide debridements and amputations in unstable patients.[17] Another prospective, randomized, controlled study included patients with severe sepsis and septic shock of intra-abdominal origin admitted to the ICU. Polyvalent IgM-enriched immunoglobulin (Ig) (Pentaglobin; IVIG group) at a dosage of 7 mL/kg/day for 5 days or an equal amount of 5% human albumin (control group) was randomized. Fifty-six patients were enrolled. The overall mortality rate was 37.5%. In the intent-to-treat analysis, the mortality rate was reduced from 48.1% in patients treated with antibiotic plus albumin to 27.5% for patients with antibiotic plus IVIG. IVIG administration in combination with adequate antibiotics improved the survival of surgical ICU patients with intra-abdominal sepsis.[18]
  - Hyperbaric oxygen has been used anecdotally in few patients, but whether this treatment is useful is not clear.
  - High-dose corticosteroid therapy has not been shown to be beneficial; Stress dose steroids (hydrocortisone 50 mg IV every 6 hours) should be considered in patients with refractory shock despite adequate antimicrobial theory and source control.
  - In recent years, research is continuing to develop either monoclonal antibodies against TSST-1 or other peptides to block the ability of bacterial toxins to activate T cells, therefore blocking the toxicity cascade. Most of this research presently is focused on in vitro and animal models of toxic shock.

Surgical Care

Prompt, aggressive exploration and debridement of patients thought to have deep-seeded pyogenic infection constitutes a surgical emergency. Surgical exploration through a small incision with visualization of the muscle and fascia may provide an early and definitive diagnosis of necrotizing fasciitis. Infection often is more extensive than is apparent from external examination. Surgical debridement of infected tissue is extremely important and often requires re-exploration to ensure adequacy of resection.

Consultations

- Consultation with a surgeon should occur early.
- A consultation with an infectious diseases specialist is mandatory, and a consultation with an intensivist also is required for management of these patients in an intensive care unit.

Medication

The goals of pharmacotherapy are to reduce morbidity, prevent complications, and eradicate the infection.

Antibiotics

Antimicrobial therapy must cover all likely pathogens in the context of the clinical setting.

Clindamycin (Cleocin)

Lincosamide for treatment of serious skin and soft tissue staphylococcal infections. Also effective against aerobic and anaerobic streptococci (except enterococci). As much as 20% of group B streptococci may be resistant. Inhibits bacterial growth, possibly by blocking dissociation of peptidyl tRNA from ribosomes causing RNA-dependent protein synthesis to arrest.

Dosing

Adult

600 mg IV q8h

Pediatric

25-40 mg/kg/d IV divided tid/qid

Interactions

Increases duration of neuromuscular blockage induced by tubocurarine and pancuronium; erythromycin may antagonize effects; antidiarrheals may delay absorption

Contraindications

Documented hypersensitivity; regional enteritis; ulcerative colitis; antibiotic-associated colitis; hepatic impairment

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Adjust dose in severe hepatic dysfunction; no adjustment necessary in renal insufficiency; associated with severe and possibly fatal colitis

Aqueous penicillin G (Pfizerpen)

Interferes with synthesis of cell wall mucopeptide during active multiplication, resulting in bactericidal activity against susceptible microorganisms.

Dosing

Adult

2-4 million U IV q4h; for streptococcal TSS, not STSS

Pediatric

150,000 U/kg/d IV divided q4h

Interactions

Probenecid can increase effects of penicillin; coadministration of tetracyclines can decrease effects of penicillin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Caution in impaired renal function; traditional drug for the treatment of lung abscess, but its spectrum of activity is narrow

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Nafcillin (Nafcil, Unipen, Nallpen)

Initial therapy for suspected penicillin G–resistant staphylococcal infections. Use parenteral therapy initially in severe infections. Due to thrombophlebitis, particularly in elderly patients, administer parenterally only for short term (1-2 d); change to oral route as clinically indicated.

Dosing

Adult

2 g IV q4h

Pediatric

0-4 kilograms (neonates): 10 mg/kg IM bid
4-40 kilograms: 25 mg/kg IM bid
Alternatively, 100-200 mg/kg/d IV/IM in 4-6 divided doses

Interactions

Associated with warfarin resistance when administered concurrently; effects may decrease with bacteriostatic action of tetracycline derivatives

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

To optimize therapy, determine causative organisms and susceptibility; >10 d treatment to eliminate infection and prevent sequelae (eg, endocarditis, rheumatic fever); obtain cultures after treatment to confirm that infection is eradicated

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Vancomycin (Lyphocin, Vancocin, Vancoled)

Potent antibiotic directed against gram-positive organisms and active against *Enterococcus* species. Useful in treatment of patients with septicemia and skin structure infections. Indicated for patients who cannot receive or have failed to respond to penicillins and cephalosporins or who have infections with resistant staphylococci (eg, MRSA). For abdominal penetrating injuries, combine with an agent active against enteric flora and/or anaerobes.
Use creatinine clearance to adjust dose in patients with renal impairment.

Dosing

Adult

1 g IV q12h

Pediatric

40 mg/kg IV divided tid/qid for 7-10 d

Interactions

Erythema, histaminelike flushing, and anaphylactic reactions may occur when administered with anesthetic agents; when taken concurrently with aminoglycosides, risk of nephrotoxicity may increase above that with aminoglycoside monotherapy; effects in neuromuscular blockade may be enhanced when coadministered with nondepolarizing muscle relaxants

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in renal failure, neutropenia; red man syndrome is caused by too rapid IV infusion (dose administered over a few min) but rarely happens when dose is administered as a 2-h administration or as PO or IP administration; red man syndrome is not an allergic reaction

Oxacillin (Bactocill, Prostaphlin)

Bactericidal antibiotic that inhibits cell wall synthesis. Used in the treatment of infections caused by penicillinase-producing staphylococci. May be used to initiate therapy when staphylococcal infection is suspected.

Dosing

Adult

2 g IV q4h

Pediatric

Not established

Interactions

Decreases effects of oral contraceptives and tetracycline; when administered concomitantly with disulfiram and probenecid, may increase oxacillin levels; effect of anticoagulants increase when large IV doses of oxacillin are administered

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Caution in renal impairment

Follow-up

Transfer

Most patients who develop TSS are critically ill and should be transferred to an intensive care unit of an institution capable of caring for these patients.

Deterrence/Prevention

- Patients who recover from TSS are at risk of recurrent episodes of STSS. Consider or recommend preventive therapy (eg, discontinuation of tampon usage, administration of antistaphylococcal antibiotics) before and during each menstrual period for several months.
- Chemoprophylaxis of household contacts of STSS patients: Household contacts of people with STSS have a higher risk of invasive GAS infection compared to the general population. The Centers for Disease Control and Prevention have not made definite recommendations; some authors have recommended a 10-day course of cephalosporin.

Complications

- Severe complications from STTS include the following:[6]
  - Prolonged and refractory hypovolemic shock (95%)
  - Adult respiratory distress syndrome (55%)
  - Acute renal failure (reversible in 70%, irreversible 10%)
  - Bacteremia (60%)
  - Electrolyte and acid-base imbalance

    - Cardiac dysrhythmia
    - Disseminated intravascular coagulation with thrombocytopenia

- STSS carries a mortality rate of 3%, and streptococcal TSS has a mortality rate of 30%.
- TSS may recur in patients who are not treated with beta-lactamase–resistant antimicrobial drugs.
- Some patients with streptococcal TSS have respiratory symptoms and develop lobar consolidation and empyema. This condition may need to be distinguished from overwhelming *Streptococcus pneumoniae* sepsis.

Patient Education

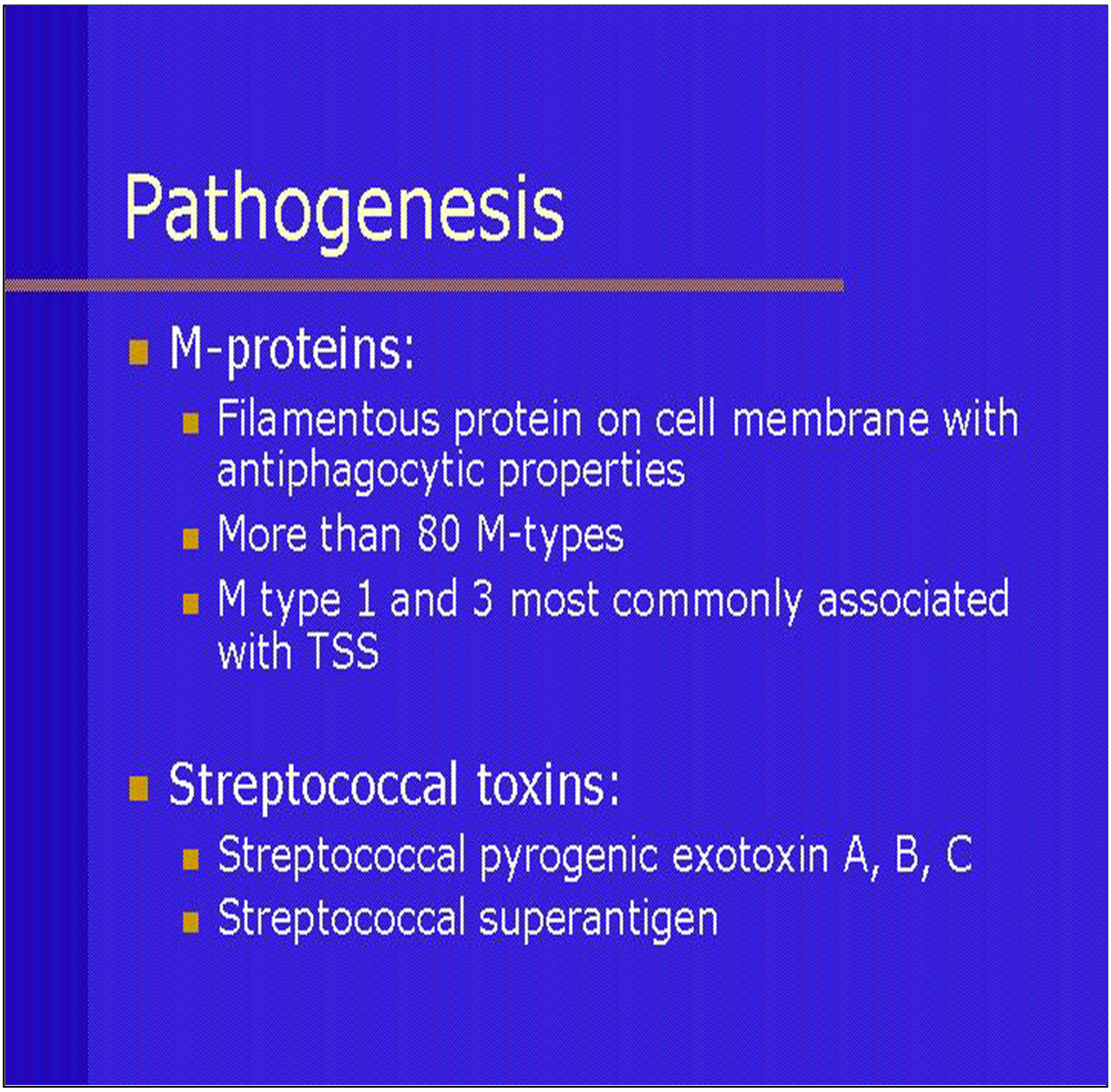
- Patient education about early signs and symptoms, risk factors and avoidance of tampon use may help prevent relapses.
- For excellent patient education resources, visit eMedicine's Women's Health Center. Also, see eMedicine's patient education article Toxic Shock Syndrome.

Miscellaneous

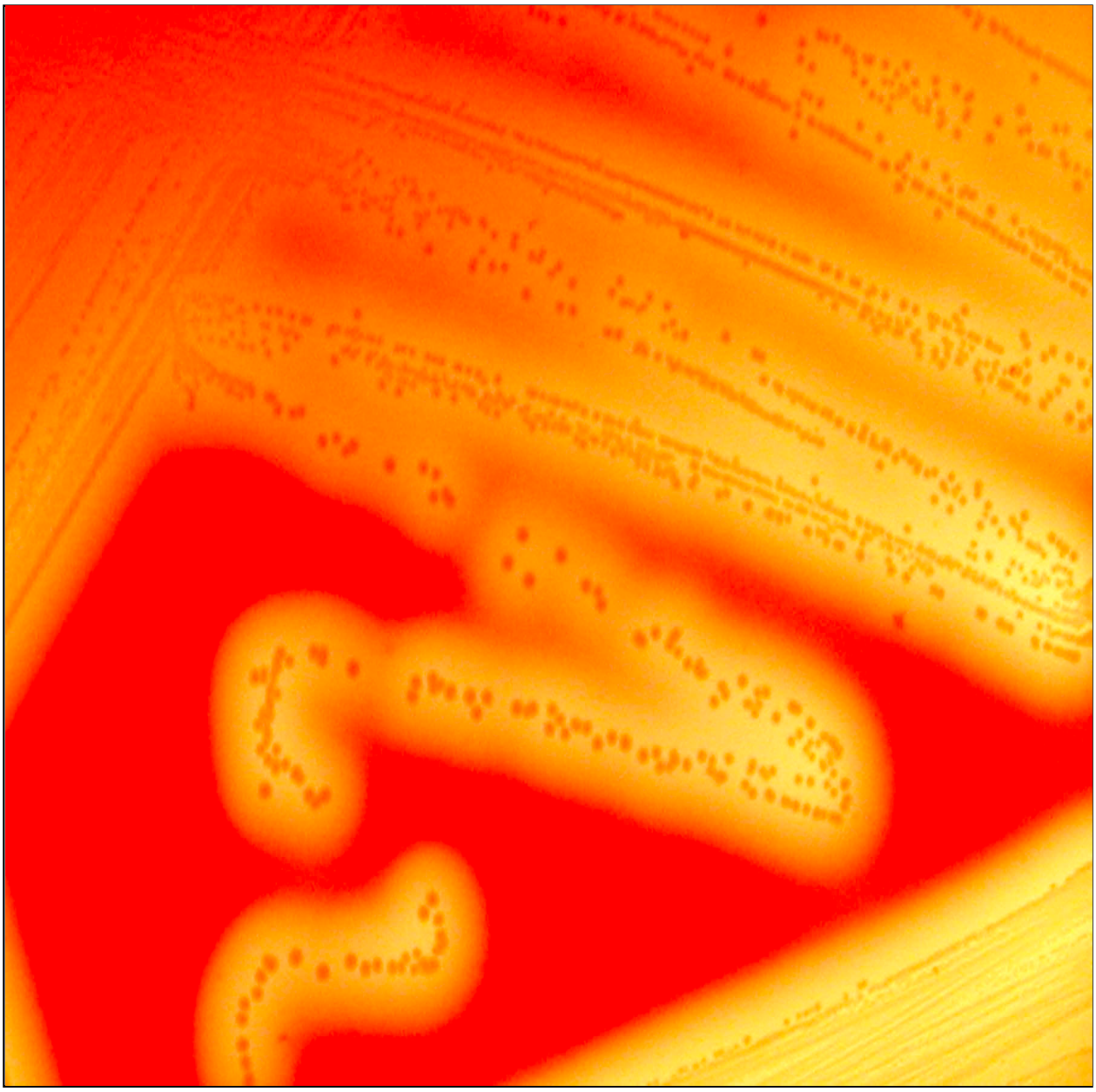
Medicolegal Pitfalls

- Streptococcal TSS emerged as a serious infectious disease in the 20th century.
- Streptococcal TSS is associated with GAS infection and shock and multiorgan failure.
- Rapid progression of what appears to be cellulitis, swelling, formation of vesicles, and bullae is an ominous sign.
- Emergent surgical exploration should be performed to distinguish GAS infection from other causes and debride the necrotic tissues.
- In a female who develops a shock state, a history and/or examination for tampon use should be performed. The STSS should be considered in the differential diagnosis.
- Streptococcal TSS should be considered in any patient who presents from the community in shock. Empirical therapy should be undertaken because culture results may not be available for 24 hours.
- Acute meningococcemia may be confused with streptococcal shock syndrome because of the petechial rash.

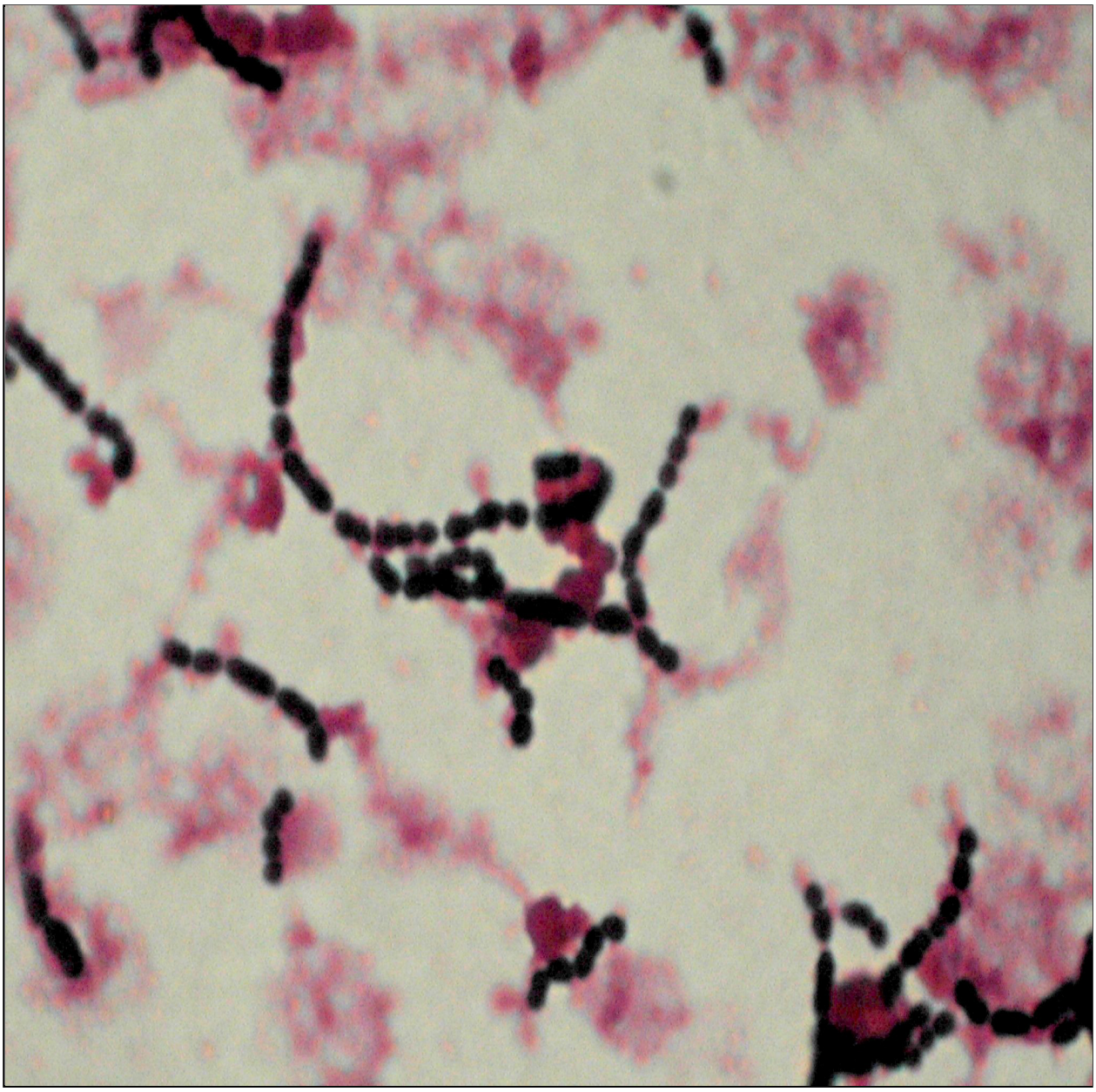
Multimedia



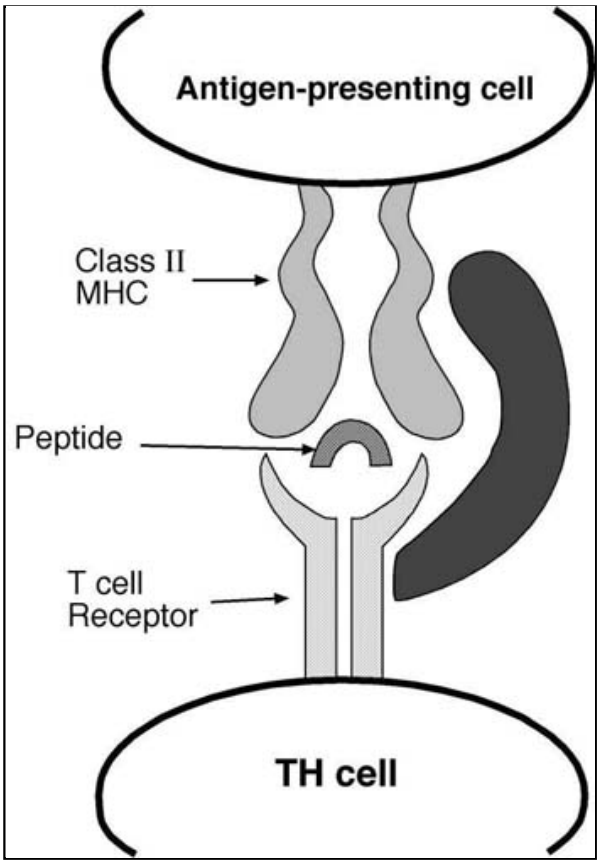
Media file 1: Description of M proteins and streptococcal toxins.



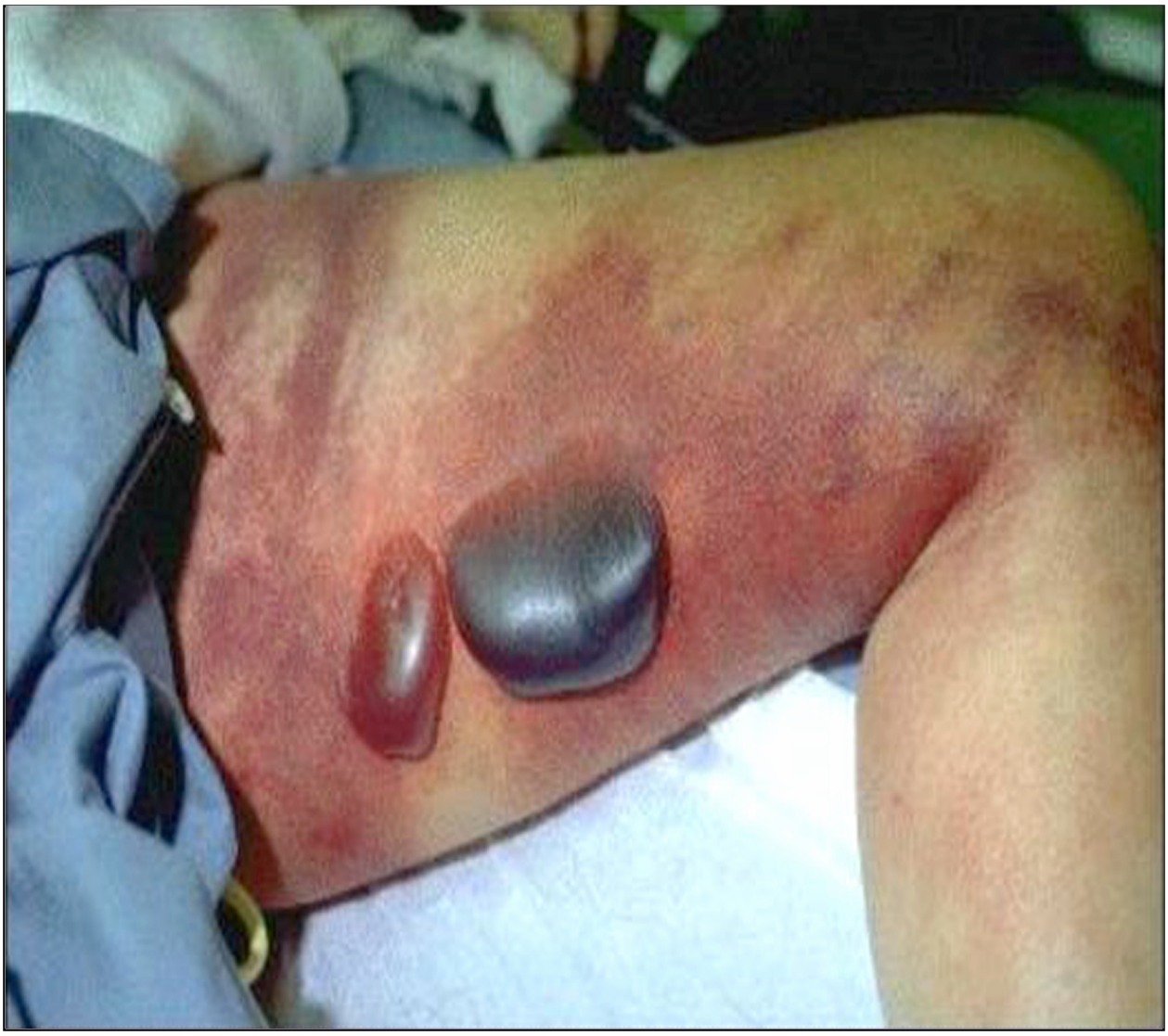
Media file 2: Group A streptococci cause beta hemolysis on blood agar.



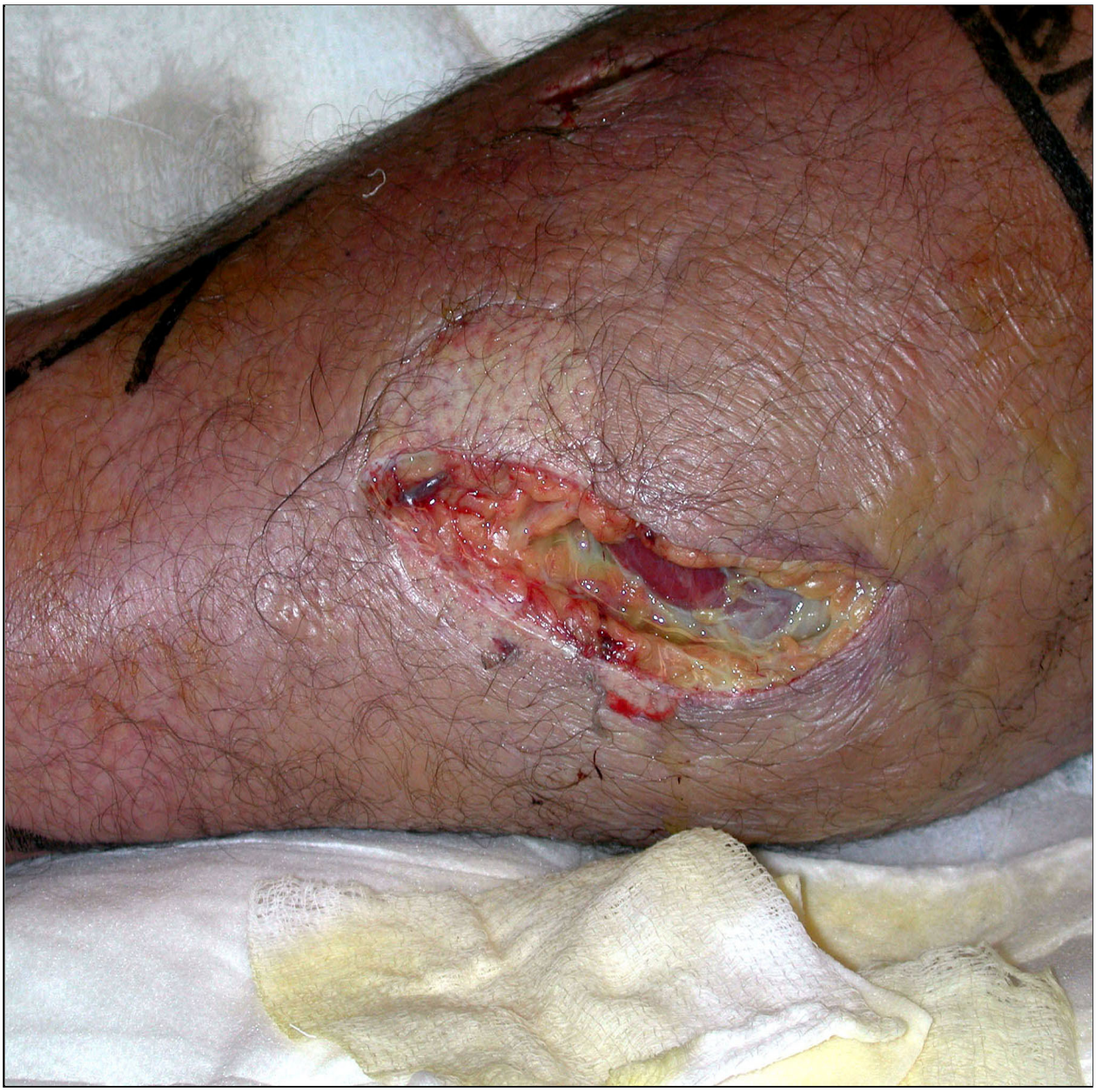
Media file 3: Group A streptococci on Gram stain of blood isolated from a patient who developed toxic shock syndrome. Courtesy of T. Matthews.



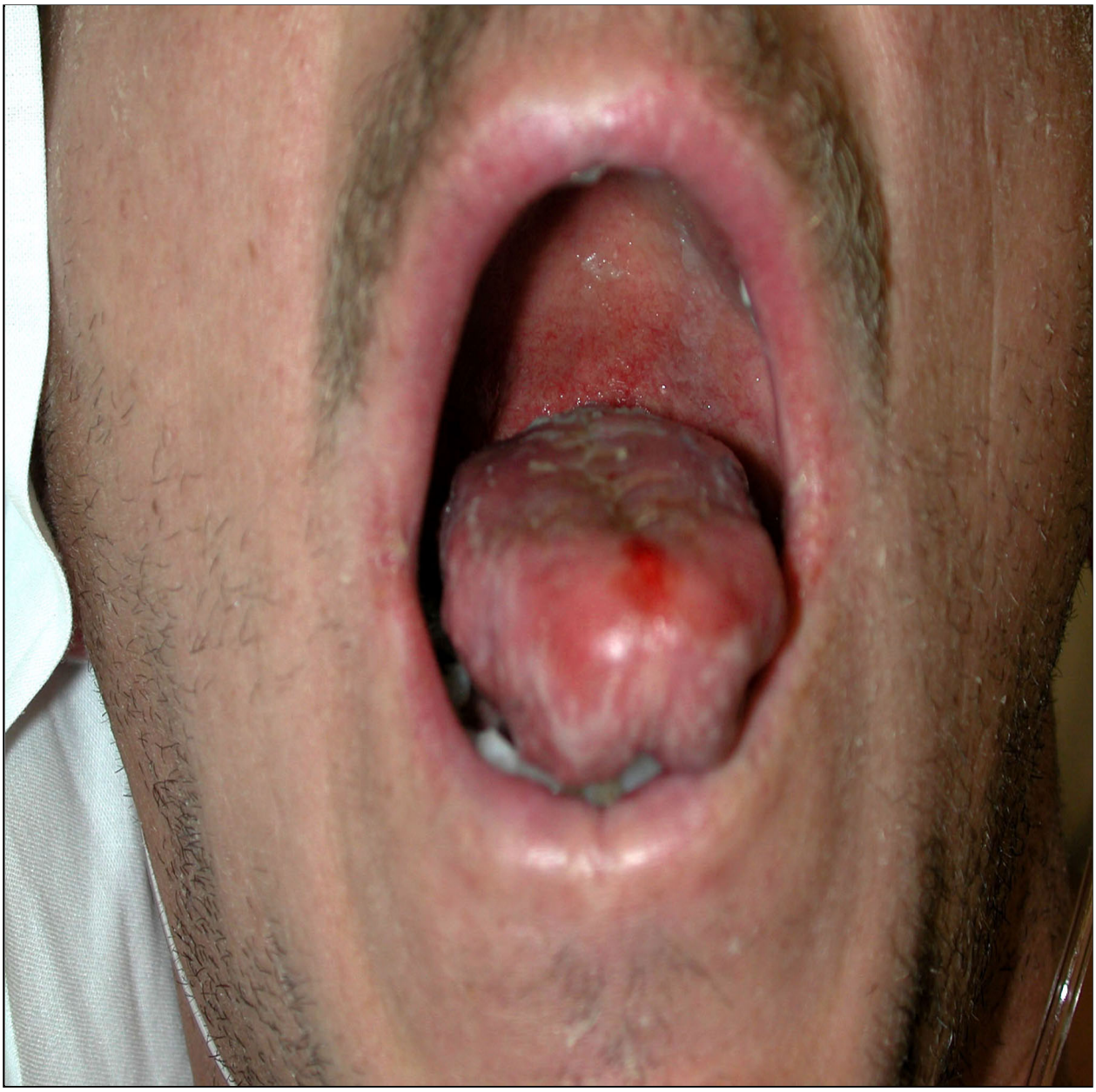
Media file 4: This schematic shows interaction among T-cell receptor, superantigen, and class II major histocompatability complex. The binding of superantigen to class II molecules and T-cell receptors is not limited by antigen specificity and lies outside the normal antigen binding sites.



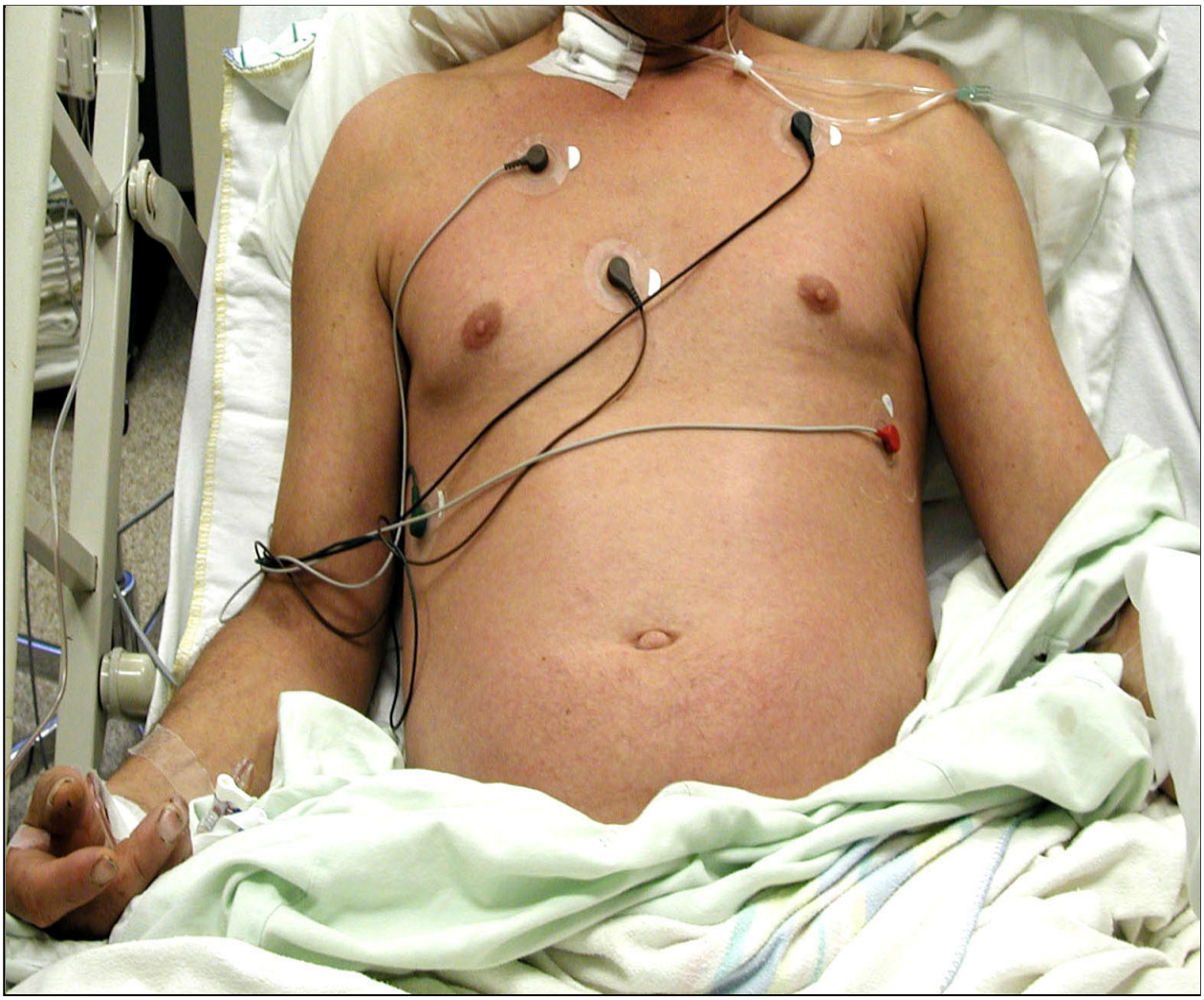
Media file 5: Progression of soft tissue swelling to vesicle or bullous formation is an ominous sign and suggests streptococcal shock syndrome. Courtesy of S. Manocha.



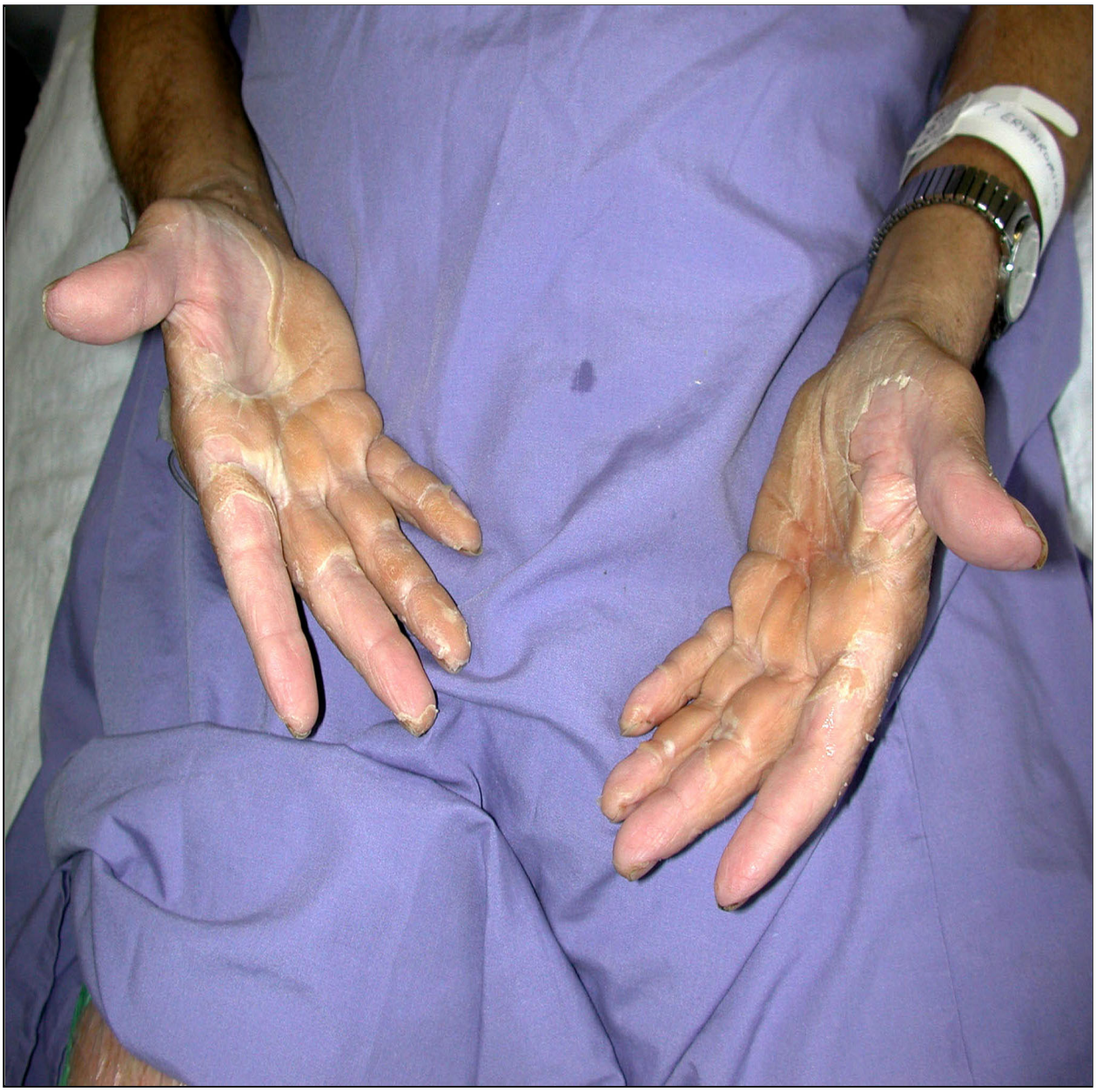
Media file 6: A 46-year-old man presented with nonnecrotizing cellulitis and streptococcal toxic shock syndrome. The leg was incised to exclude underlying necrotizing infection. Courtesy of Rob Green, MD.



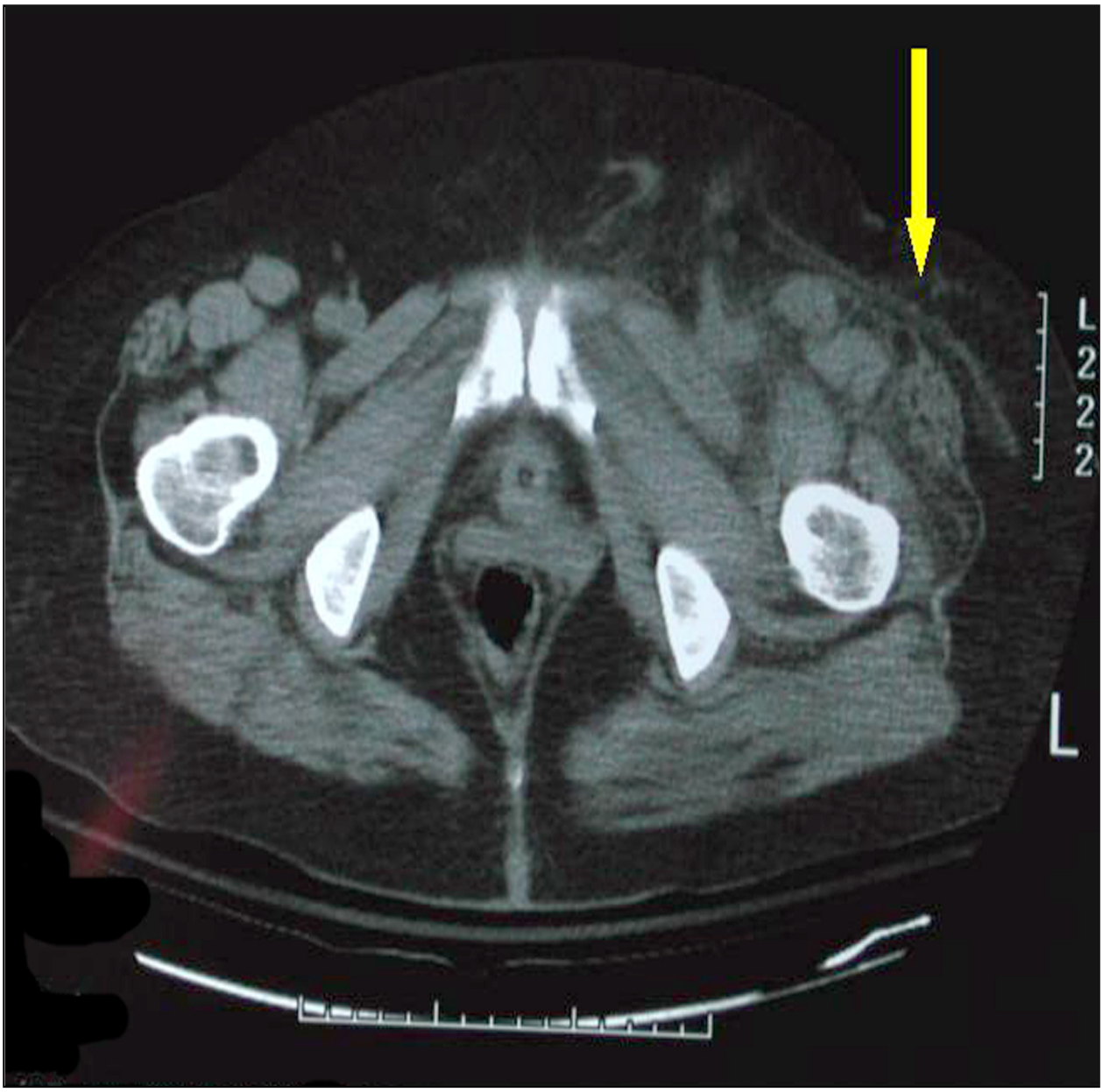
Media file 7: A 46-year-old man presented with nonnecrotizing cellulitis and streptococcal toxic shock syndrome. This patient also had streptococcal pharyngitis. Courtesy of Rob Green, MD.



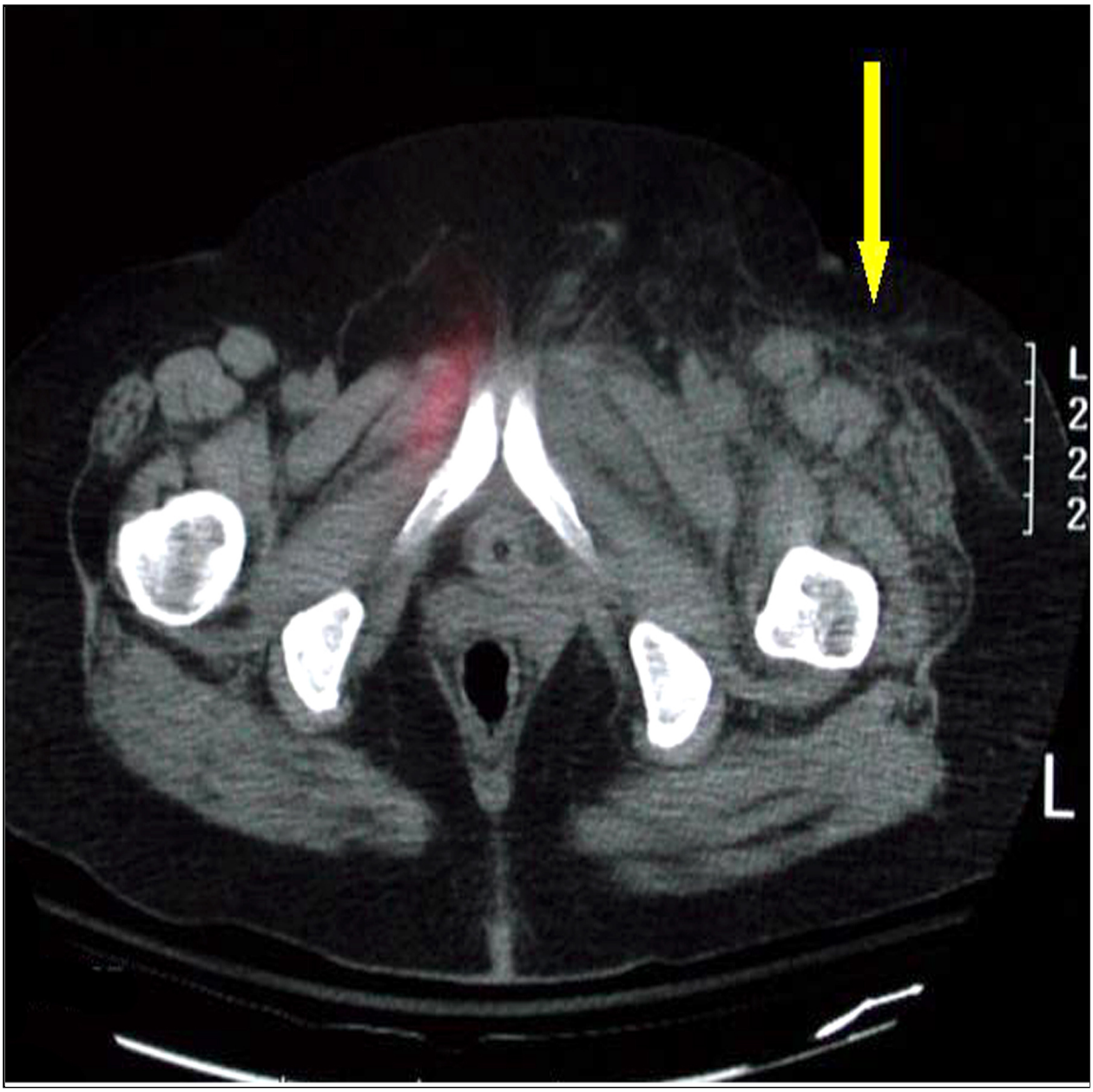
Media file 8: A 46-year-old man presented with nonnecrotizing cellulitis and streptococcal toxic shock syndrome. The patient had diffuse erythroderma, a characteristic feature of the syndrome. Courtesy of Rob Green, MD.



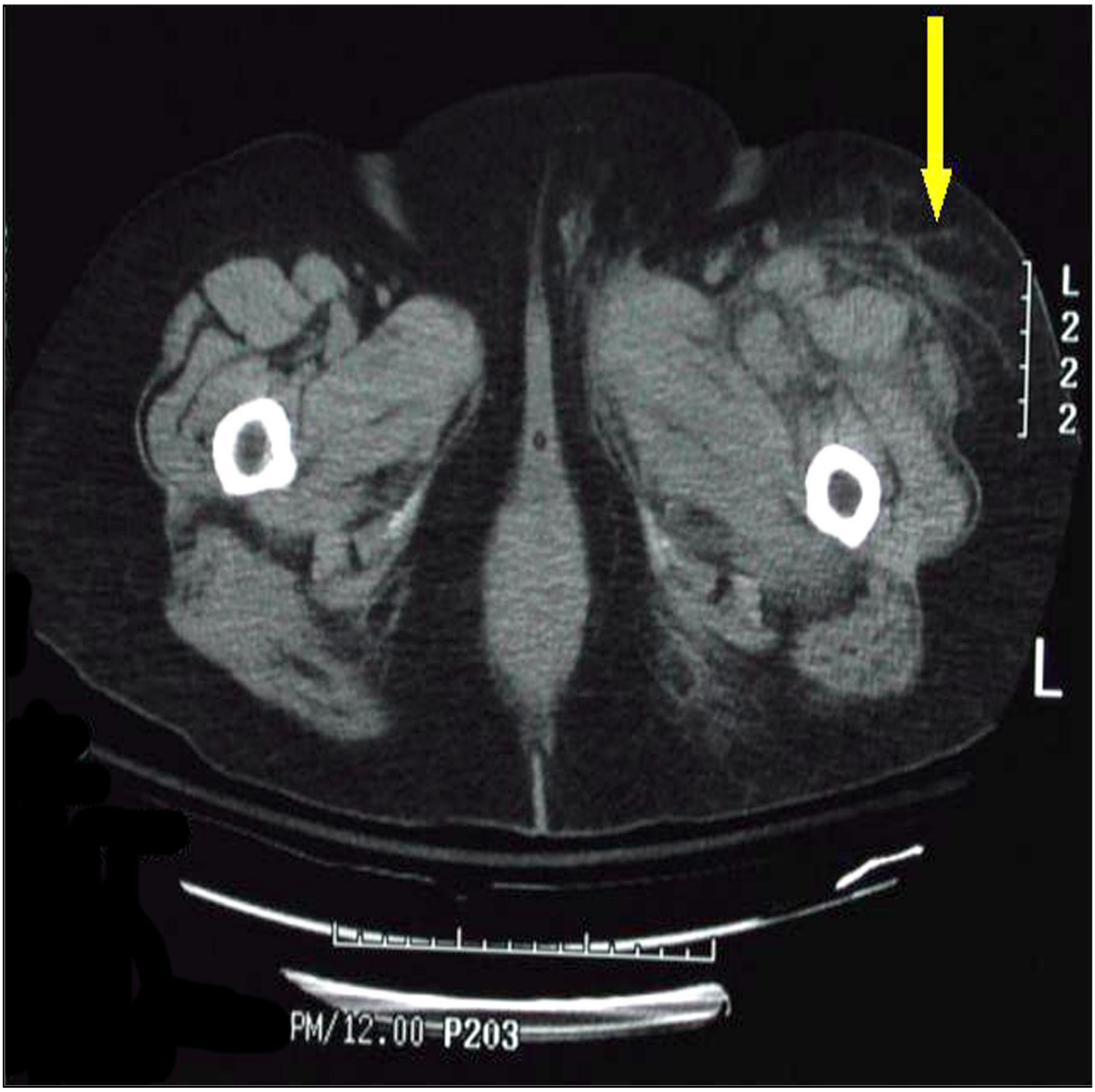
Media file 9: A 46-year-old man presented with nonnecrotizing cellulitis and streptococcal toxic shock syndrome. The patient had diffuse erythroderma, a characteristic feature of the syndrome. The patient improved with antibiotics and intravenous gammaglobulin therapy. Several days later, a characteristic desquamation of the skin occurred over palms and soles. Courtesy of Rob Green, MD.



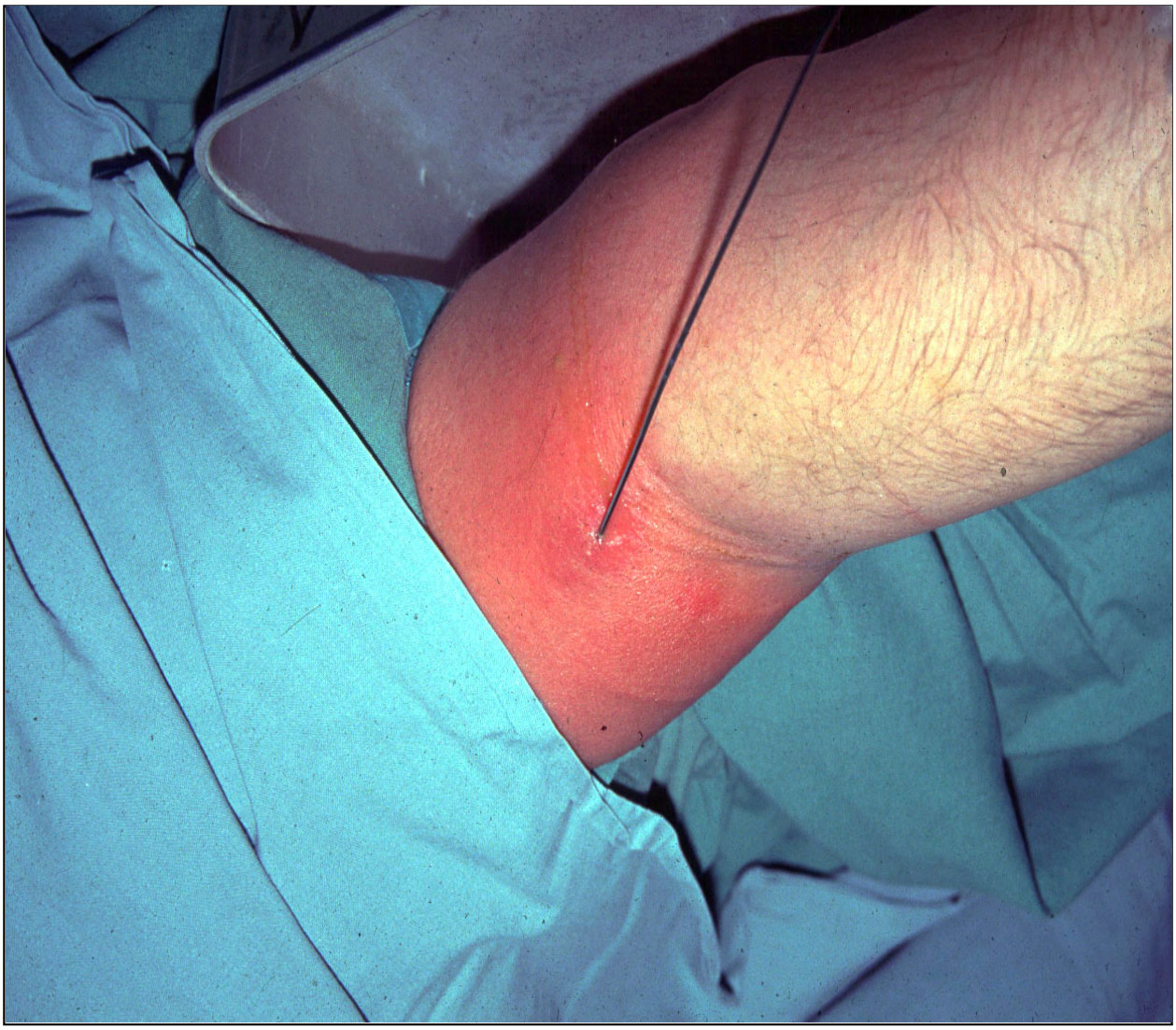
Media file 10: A 58-year-old patient presented in septic shock. On physical examination, progressive swelling of the right groin was observed. On exploration, necrotizing cellulitis, but not fasciitis, was present. The cultures grew group A streptococci. The patient developed severe shock (toxic shock syndrome). The CT scanning helped evaluate the extent of infection and exclude other pathologies, such as psoas abscess, osteomyelitis, and inguinal hernia.



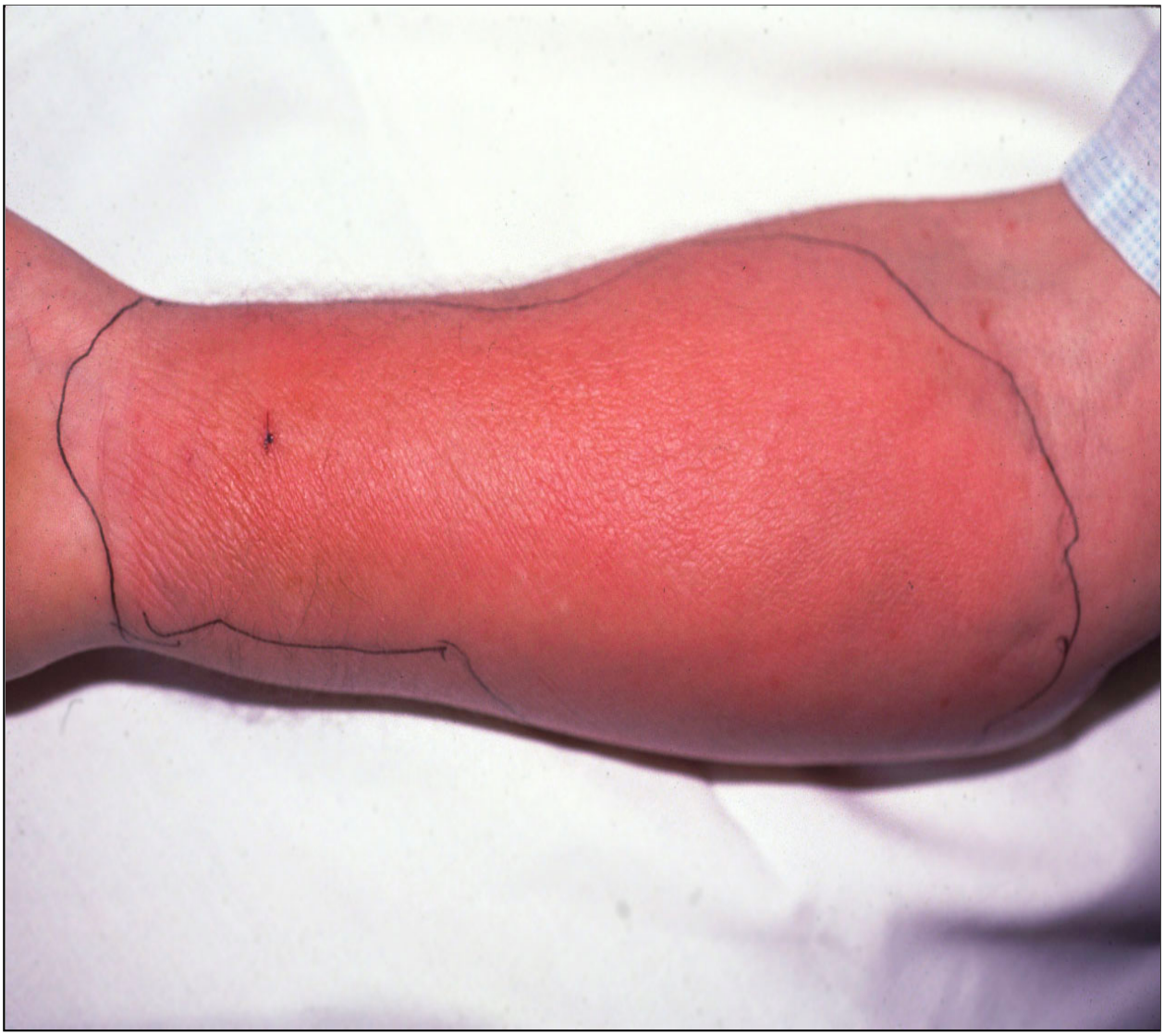
Media file 11: A 58-year-old patient presented in septic shock. On physical examination, progressive swelling of the right groin was observed. On exploration, necrotizing cellulitis, but not fasciitis, was present. The cultures grew group A streptococci. The patient developed severe shock (toxic shock syndrome). The CT scanning helped evaluate the extent of infection and exclude other pathologies, such as psoas abscess, osteomyelitis, and inguinal hernia.



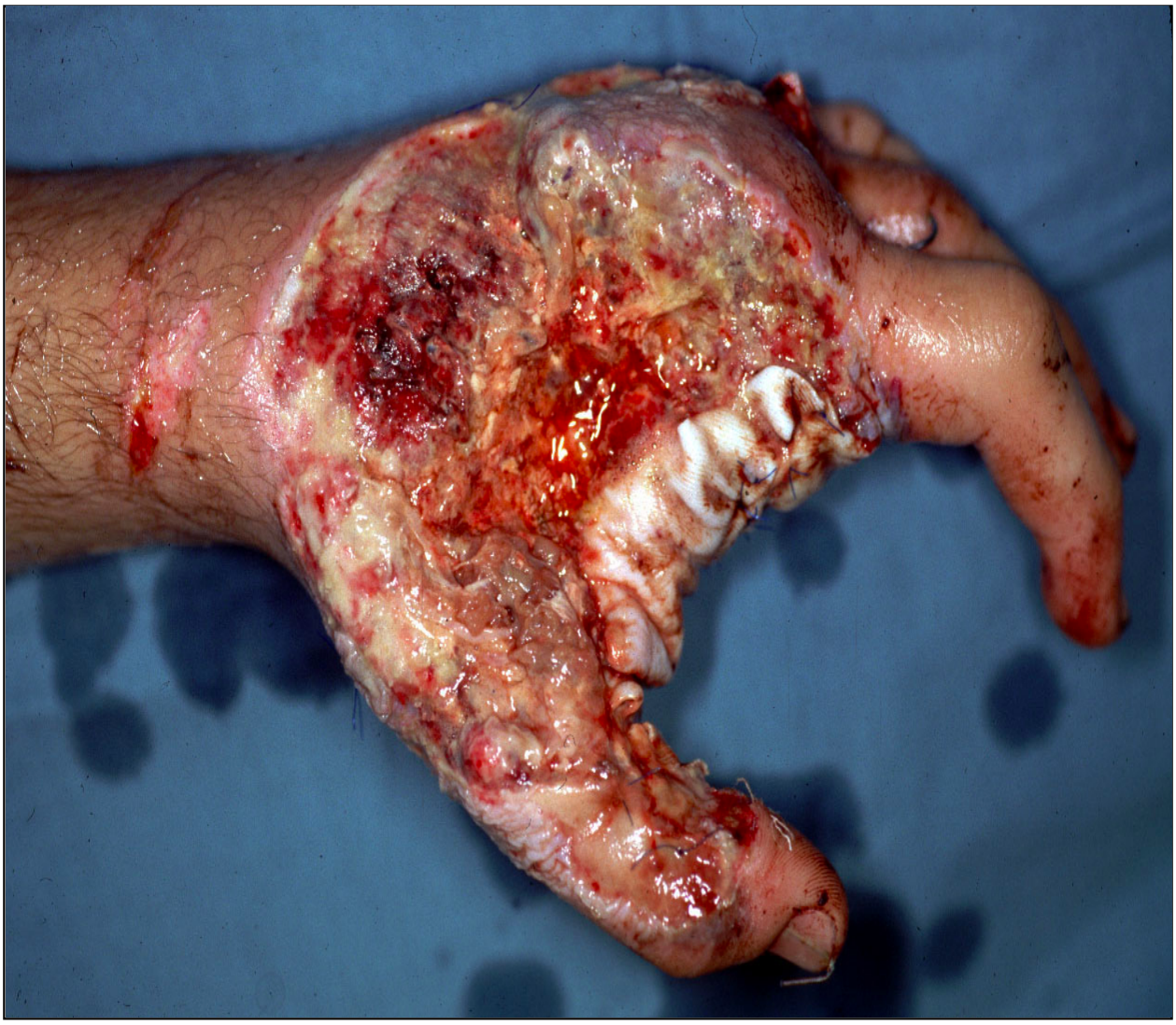
Media file 12: A 58-year-old patient presented in septic shock. On physical examination, progressive swelling of the right groin was observed. On exploration, necrotizing cellulitis, but not fasciitis, was present. The cultures grew group A streptococci. The patient developed severe shock (toxic shock syndrome). The CT scanning helped evaluate the extent of infection and exclude other pathologies, such as psoas abscess, osteomyelitis, and inguinal hernia.



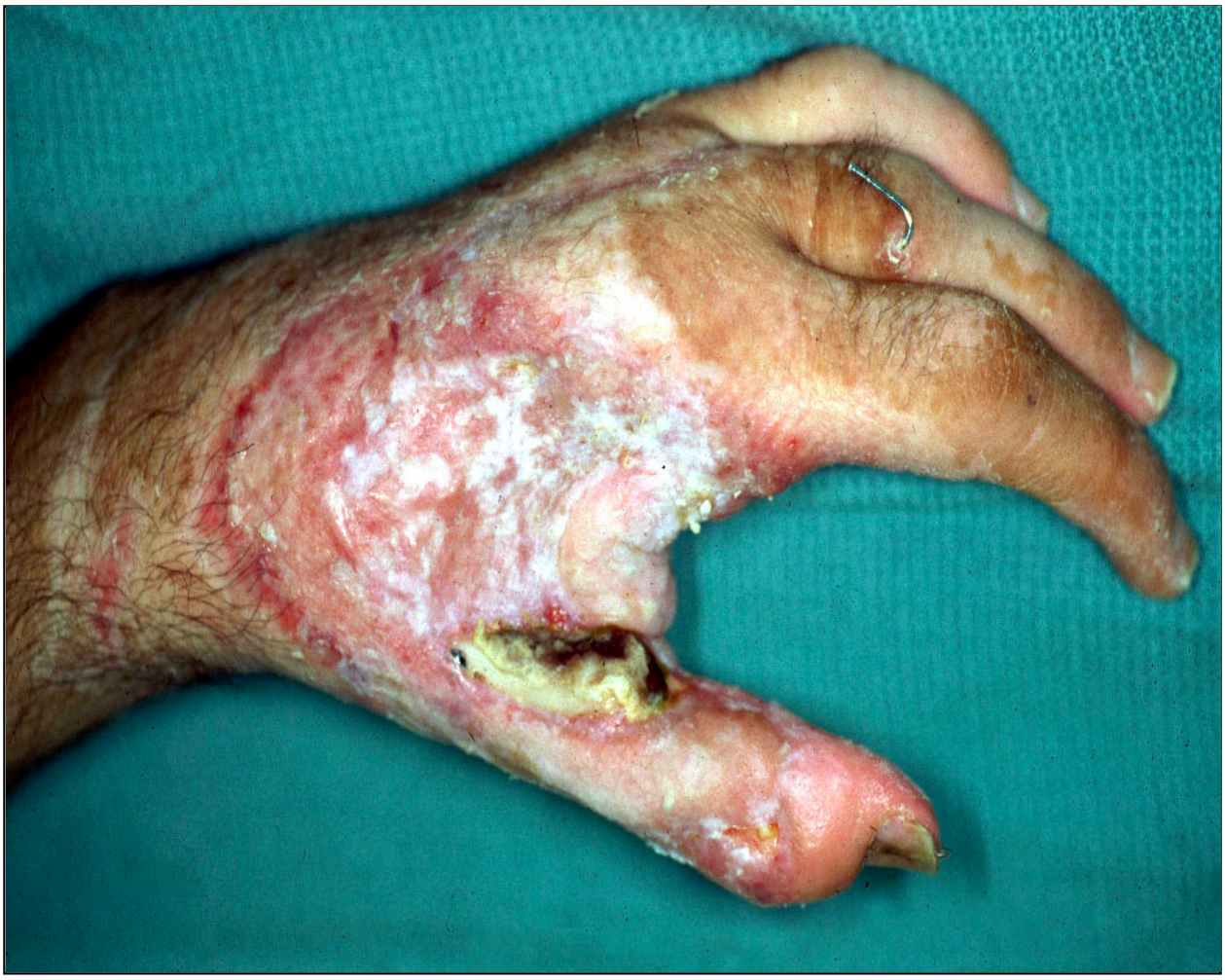
Media file 13: Necrotizing cellulitis of toxic shock syndrome.



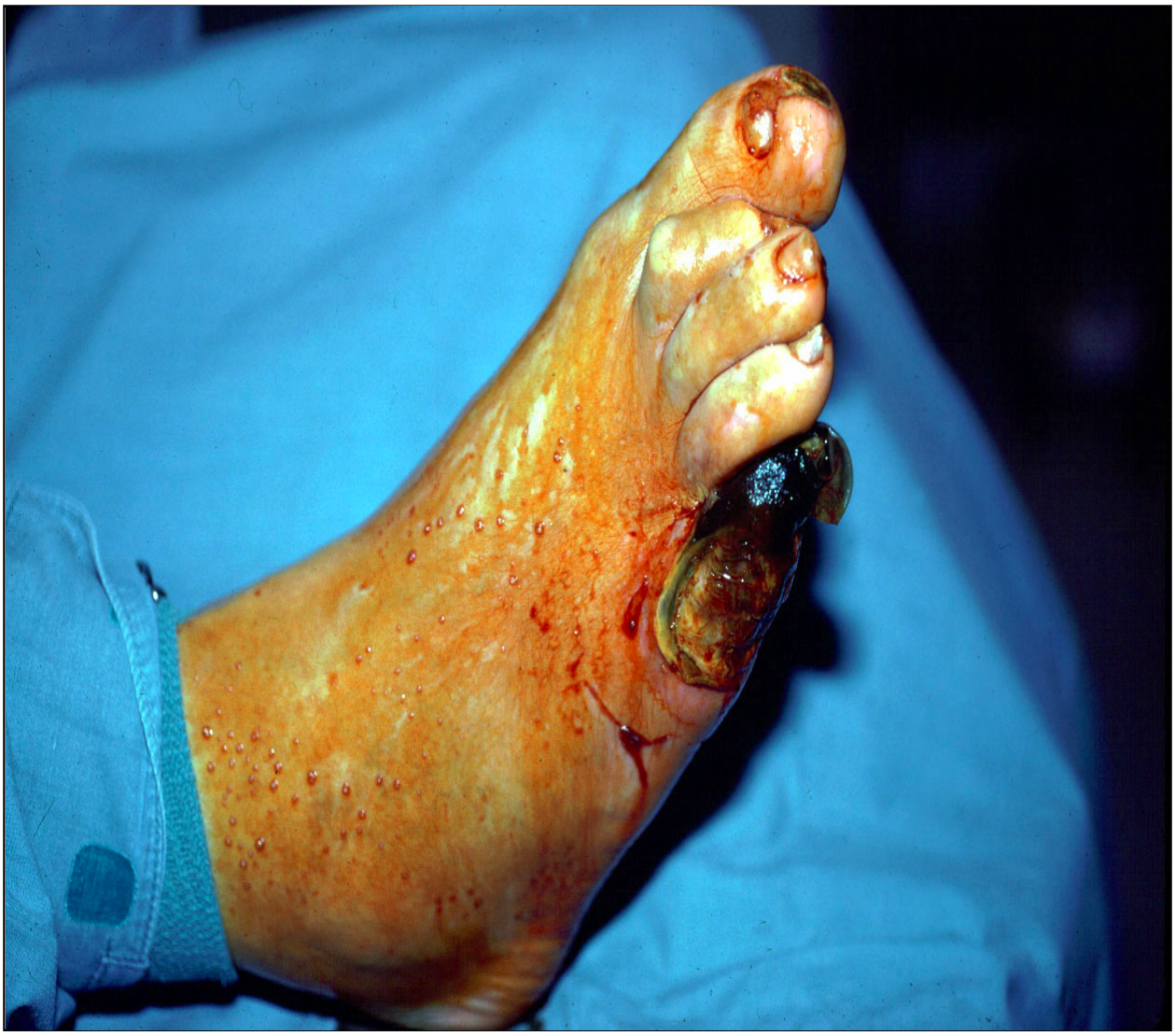
Media file 14: Soft tissue infection secondary to group A streptococci, leading to toxic shock syndrome.



Media file 15: Extensive debridement of necrotizing fasciitis of the hand.



Media file 16: The hand is healing following aggressive surgical debridement of necrotizing fasciitis of the hand (see Image 15).



Media file 17: Necrosis of the little toe of the right foot and cellulitis of the foot secondary to group A streptococci.

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Keywords

toxic shock syndrome, TSS, flesh-eating disease, toxic shock, septic shock, *Staphylococcus aureus, S aureus,* group A *Streptococcus,* GAS, *Streptococcus pyogenes, S pyogenes*

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Further Reading

Clinical guidelines

Female barrier methods.
Faculty of Sexual and Reproductive Healthcare - Professional Association. 2007 Jun. 17 pages. NGC:006305

Practice guidelines for the diagnosis and management of skin and soft-tissue infections.
Infectious Diseases Society of America - Medical Specialty Society. 2005 Nov 15. 34 pages. NGC:004581

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