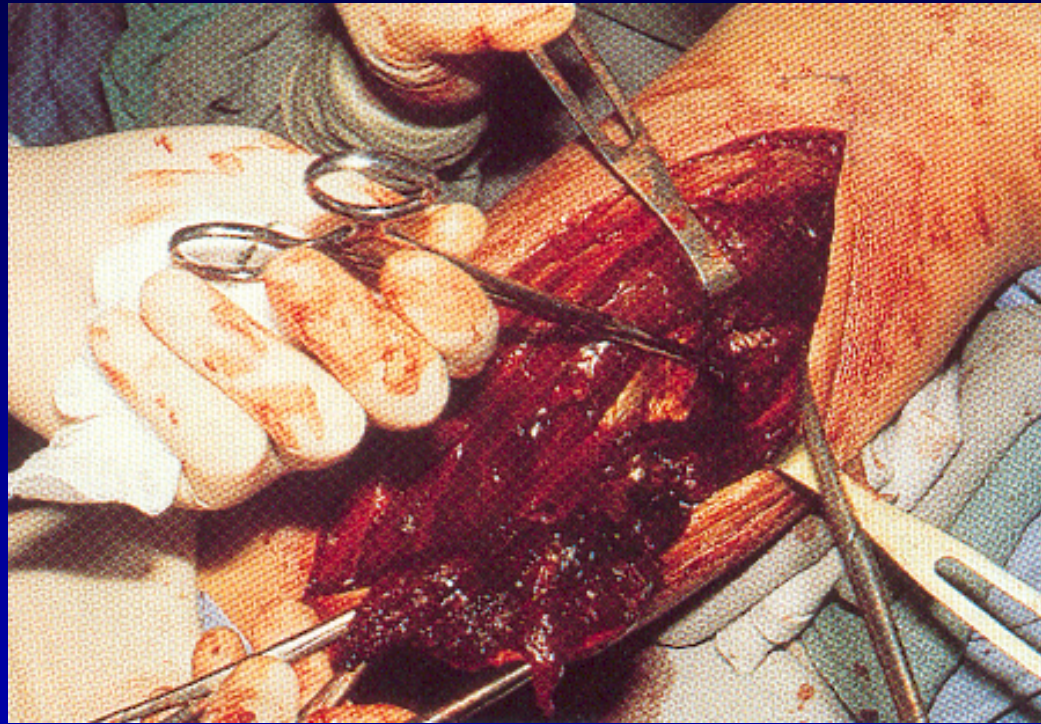


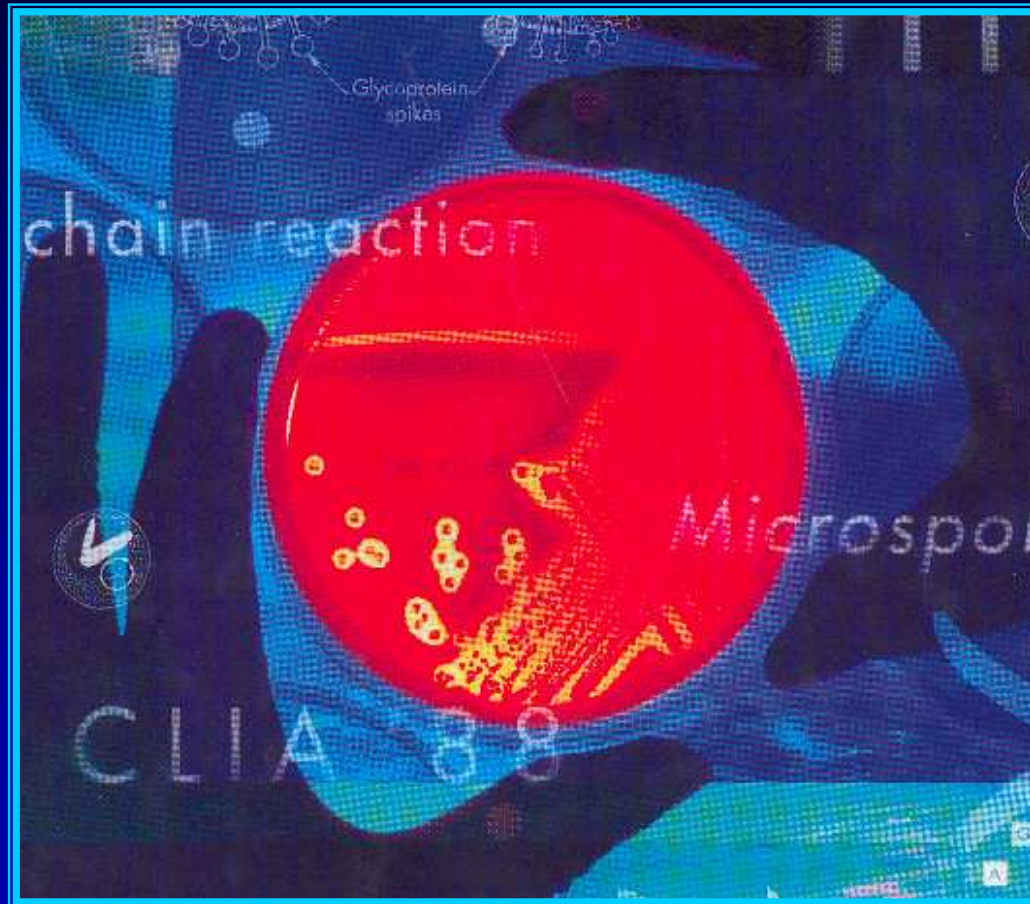
The Flesh-Eating Bacterium



Pierrette MELIN

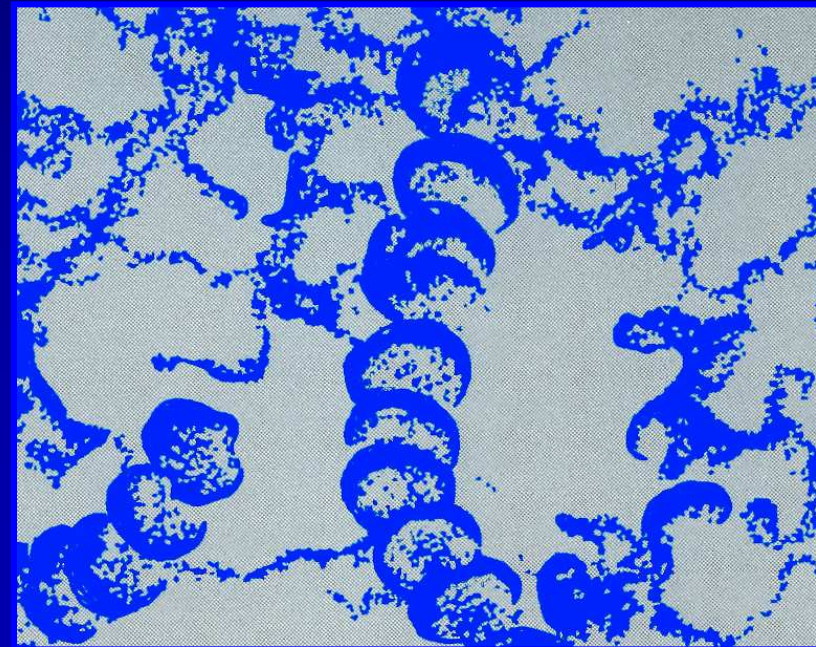
Medical Microbiology, University hospital of Liege, Belgium

Streptococcus pyogenes



also named Group A Streptococci (GAS)

- ◆ Introduction
- ◆ Microbiological characteristics
- ◆ Virulence factors
- ◆ Epidemiology
- ◆ Clinical types of infection
- ◆ Strep TSS
- ◆ Conclusion



Introduction

- ◆ Since the mid-1980s, marked increase number of highly invasive group A streptococcal infections:
 - ◆ *With shock and organ failure*
 - ◆ *With or without necrotizing fasciitis*
- ◆ ***"Streptococcal toxic shock syndrome (STSS)"***
- ◆ *1-5 cases (up to 25 cases)/100,000 population annually*
- ◆ 30 % mortality despite appropriate treatment
- ◆ If survival : major tissue loss, amputation of extremities

True increase in both number and severity of cases

"Will these types of GAS infections decline, stay the same, or increase?"

- ◆ Before the advent of antibiotics

- ◆ Many epidemics of GAS infections :

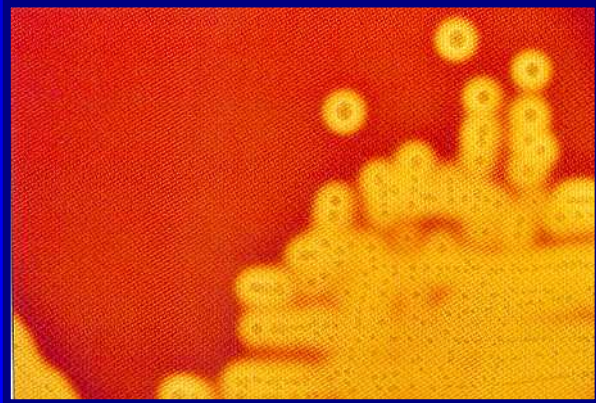
waxed and waned

- ◆ Changes in socioeconomic conditions ?
 - ◆ Variations in expression of virulence factors ?
 - ◆ Acquisition of herd immunity to virulence factors ?

GAS epidemiology is complex

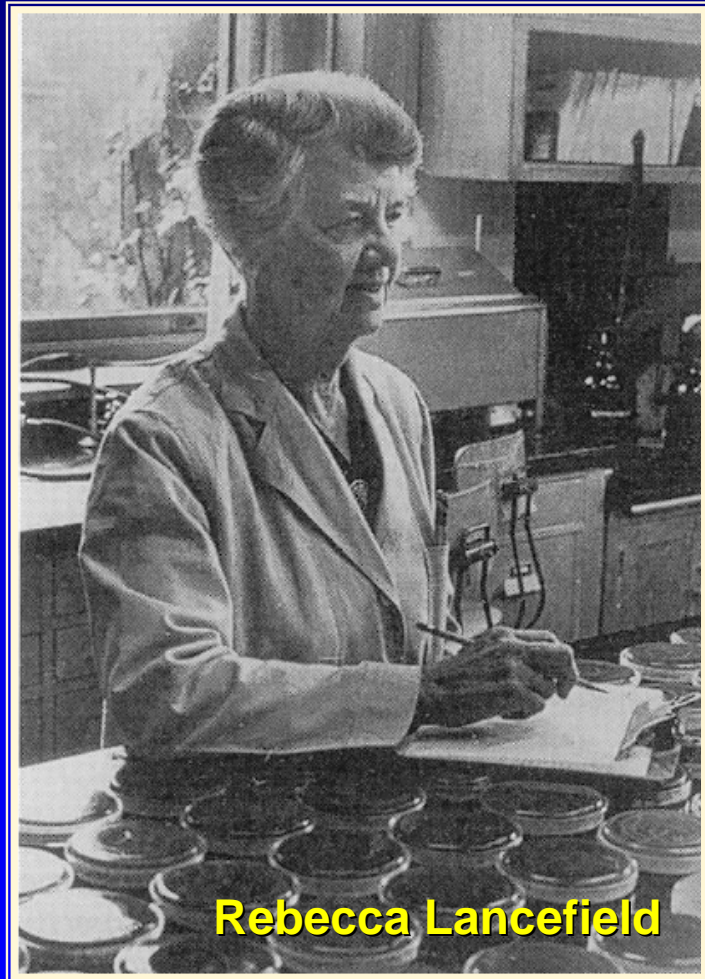
Streptococcus pyogenes

Microbiological Characteristics



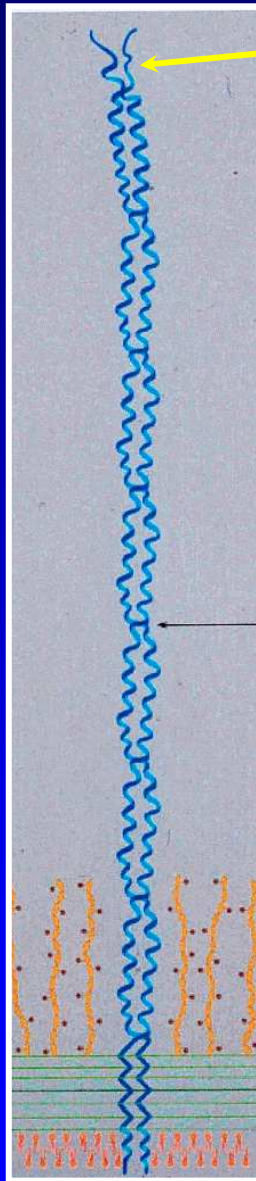
- ◆ Gram positive cocci
 - ◆ In chains or pairs
- ◆ Growth on blood agar media
- ◆ Facultative anaerobe
- ◆ Growth best with 10 % CO₂
- ◆ β-Hemolytic
- ◆ Catalase negative
- ◆ Capsule
- ◆ Bacitracin susceptibility

Streptococcus pyogenes

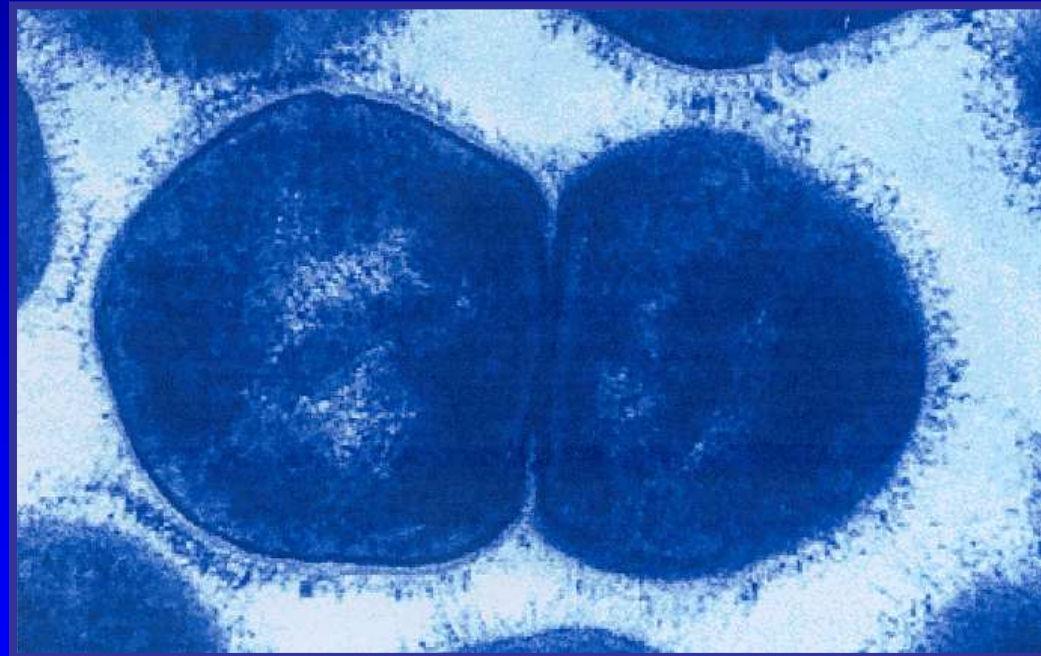


- ◆ Group A antigen
- ◆ Type-specific antigen
 - ◆ M protein
 - ◆ > 80 M serotypes
 - ◆ Fimbriae
 - ◆ Major virulence factor
 - ◆ Elicits protective Ab
 - ◆ T protein
 - ◆ Useful epidemiologic marker
 - ◆ Function unknown
- ◆ Sequencing of *emm* gene encoding M protein

Streptococcal M Protein

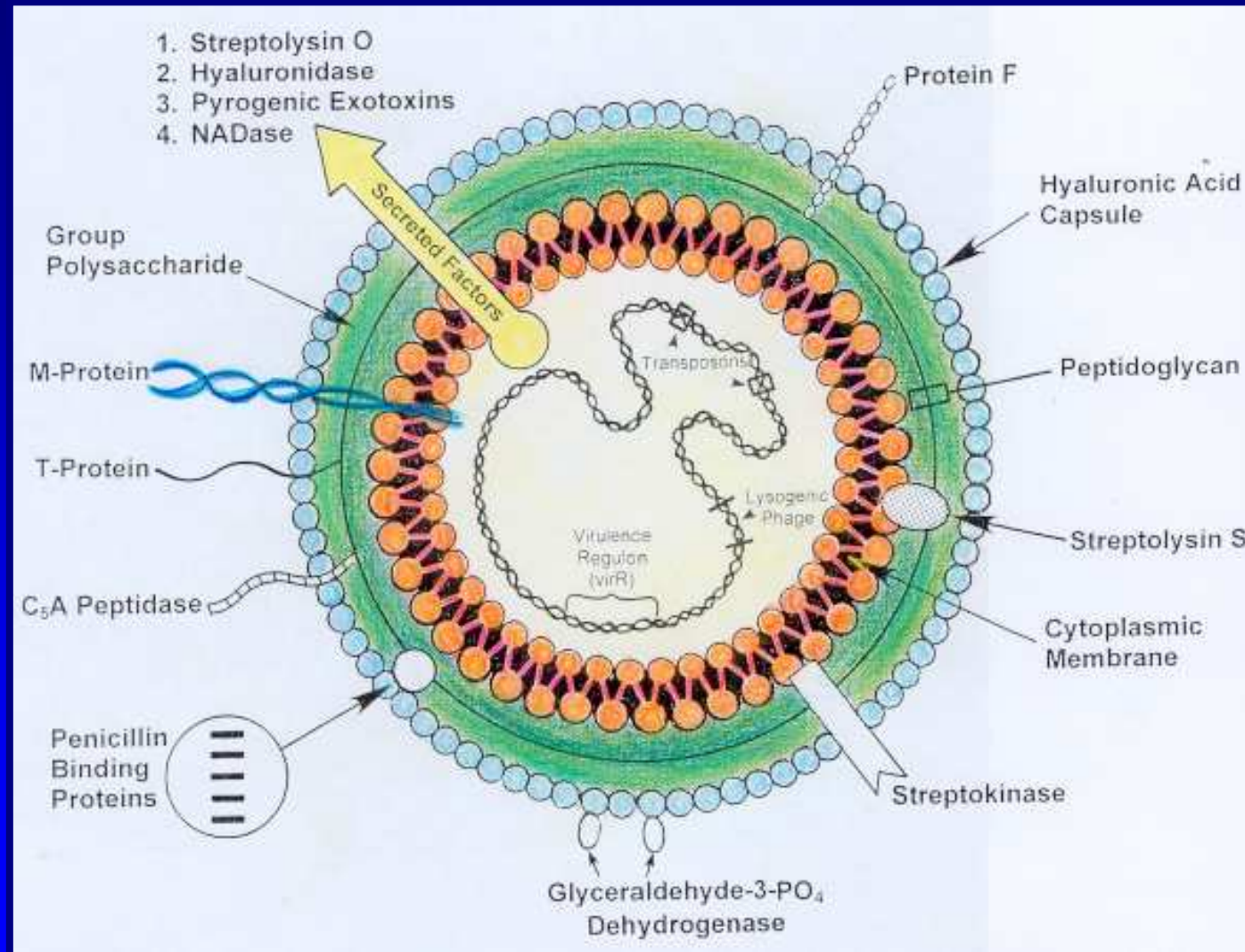


N-terminus



C-terminus

Schematic location of intracellular, cellular and extracellular virulence factors



Virulence factor -Biologic effect

Capsule

-Antiphagocytic

M proteins

-Adhesin; **antiphagocytic**; degrades complement component C3b

M-like proteins

-Binds IgM, IgG and α 2-macroglobulin

Protein F

-Fibronectin-binding protein. Mediates adherence to epithelial cells

Streptolysine S

-Lyses leucocytes, platelets and erythrocytes; stimulates release of lysosomal enzymes; nonimmunogenic

Streptolysine O

-Lyses leucocytes, platelets and erythrocytes; stimulates release of lysosomal enzymes; immunogenic

Virulence factor -Biologic effect

Hyaluronidase

-Hydrolyzes hyaluronic acid in deeper tissue; facilitates spread of infection along fascial planes

Streptokinase

-Lyses blood clots, facilitates spread of infection in tissue

C5a peptidase

-Degrades complement component C5a

Pyrogenic exotoxins

-SPE type A, B and C = *erythrogenic* or *scarlatina toxins*. Cause rash seen in scarlet fever, induce lymphocytes blastogenesis, **potentiate endotoxin-induced shock**, induce fever, suppress antibody synthesis and act as super antigen (⤵ massive release IL, TNF)

Streptococcal Pyrogenic Exotoxins - SPE

◆ SPEA

- ◆ Carried by lysogenic phage (not all strains)
- ◆ Variation in quantity produced / decade
- ◆ Mutation, variation in potency

◆ SPEB

- ◆ Mediated by chromosome gene
- ◆ Variably expressed
- ◆ Severe cases of scarlet F and STSS

◆ SPEC

- ◆ Carried by lysogenic phage (not all strains)

Epidemiology

- ◆ Natural reservoir
 - ◆ Purely a human pathogen, skin and mucous mb.
- ◆ Relationship to humans
 - ◆ Asymptomatic colonization
 - ◆ Age : 15-20 % in children; <5 % in adults
 - ◆ Infections
 - ◆ Age :
 - most I.: incidence higher in younger (< 10 years)
 - Bacteremia : neonates and elderly
 - **1986-1988: prevalence bacteremia √√ 800-1000 % in adolescents and adults**
 - ◆ Climate :
 - *Pharyngitis, scarlet fever*
 - *Impetigo*

Epidemiology

- ◆ Pharyngeal or cutaneous acquisition, person-to-person spread via
 - ◆ Aerosolized microdroplets
 - ◆ Direct contact
- ◆ In most cases of GAS infection
 - ◆ Transmission and portal of entry ascertained
- ◆ Patients with STSS
 - ◆ Portal of entry obvious only in 50 % of cases

Clinical Types of Infection

- ◆ Pharyngitis and asymptomatic carriage (1-70%)
- ◆ Scarlet fever
- ◆ Erysipelas
- ◆ Streptococcal pyoderma (Impetigo Contagiosa)
- ◆ Lymphangitis
- ◆ Cellulitis
- ◆ **Necrotizing fasciitis**
 - ◆ Myositis, pneumonia
- ◆ **STSS**
- ◆ Puerperal sepsis
- ◆ Endocarditis
- ◆ Postinfectious sequelae
 - ◆ Rheumatic fever, poststreptococcal glomerulonephritis

Strep TSS - Demographic Features

- ◆ Increasing incidence of sporadic cases !
 - ◆ North America and Europe
- ◆ In any age group
- ◆ Sometimes when underlying diseases
- ◆ Mostly in non immuno-compromised patients
- ◆ With Severe complications
 - ◆ Bacteremia with aggressive soft tissue infection
 - ◆ Shock
 - ◆ Acute respiratory distress syndrome (ARDS)
 - ◆ Renal failure
- ◆ **Course of infection is rapid**

Sharp contrasts with previous GAS bacteremia

Strep TSS - Demographic Features

Severe complications of GAS soft tissue infections	% of patients
Shock	95
Acute respiratory distress syndrome-ARDS	55
Renal impairment	80
Irreversible	10
Reversible	70
Bacteremia	60
Mortality	30 (70)
Morbidity (major surgical debridement, amputation, ...)	> 65

Strep TSS - Acquisition

Portal of entry	Cases (%)
◆ Skin	35
◆ Minor trauma	
◆ Surgical procedures	
◆ IV drug abuse	
◆ Mucous membrane	20
◆ Pharynx	
◆ Vagina	
◆ Unknown	45

Risk of secondary cases = very low, despite a high prevalence of « virulent strains of GAS » in population

Strep TSS - The Clinical Picture

◆ PAIN

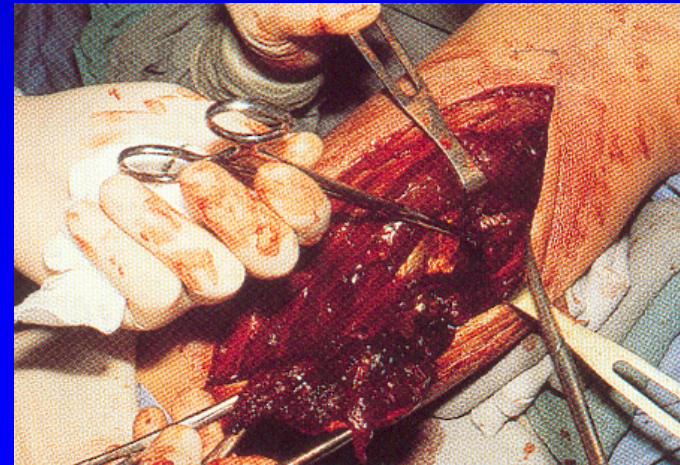
- ◆ Most common initial symptom
- ◆ Abrupt in onset
- ◆ Severe
- ◆ Usually precedes tenderness or physical findings
- ◆ Pain usually involves an extremity
 - ◆ But may mimic peritonitis, pelvic inflammatory disease, pneumonia, acute myocardial infarction or pericarditis
- ◆ **Fever** : most common presenting sign

Strep TSS

Other symptoms and signs	% of patients
Influenza like syndrome	20
Mental confusion	55
Hypotension, systolic	
Soft tissue swelling (necrotizing fasciitis, myositis)	80 (70)
Endophalmitis, peritonitis, perihepatitis myocarditis, overwhelming sepsis	20
Diffuse scarlatina like erythema	10
<i>Positive blood culture</i>	<i>69-97</i>
<i>Positive site of infection culture</i>	<i>95</i>

GAS Necrotizing Fasciitis (NF)

- ◆ Deep-seated infection of subcutaneous tissue
- ◆ Progressive destruction of fascia and fat
- ◆ May spare skin and muscle
- ◆ « Streptococcal gangrene »
- ◆ Severe pain out of proportion to superficial appearance of skin



GAS Necrotizing Fasciitis

- ◆ + Severe manifestation of systemic illness
- ◆ + High morbidity
 - ◆ Despite antibiotics, dialysis, ventilators, IV fluids and improved surgical techniques
- ◆ Skin signs
 - ◆ Diffuse swelling and tenderness
 - ◆ Erythema, and later, bullae
 - ◆ Colour change from red to purple or black

GAS Myositis

- ◆ First, severe pain, chills and fever
- ◆ Later, swelling and erythema
 - ◆ May be apparent after development of muscle compartment syndrome
- ◆ Differentiation with gas gangrene difficult
- ◆ Case fatality rate
 - ◆ GAS NF : 20-50 %
 - ◆ GAS myositis : 80-100 %

GAS Bacteremia

- ◆ In the past, in very young or elderly
 - ◆ Among children, predisposing factors
 - ◆ Burns, varicella, immunosuppression, neoplasy, age < 2
 - ◆ In older adults + elderly
 - ◆ Source = skin infection, cellulitis or erysipelas
 - ◆ Diabetes, malignancy, corticosteroid use
 - ◆ Rare in 14-40 years of age
 - ◆ Puerperal sepsis
- ◆ Recently
 - ◆ IV drug addicts, highest prevalence of GAS Bacteremia
- ◆ In the late 1980s, 600-800% increase in adolescent and young adults
- ◆ Mortality: 24-26 %

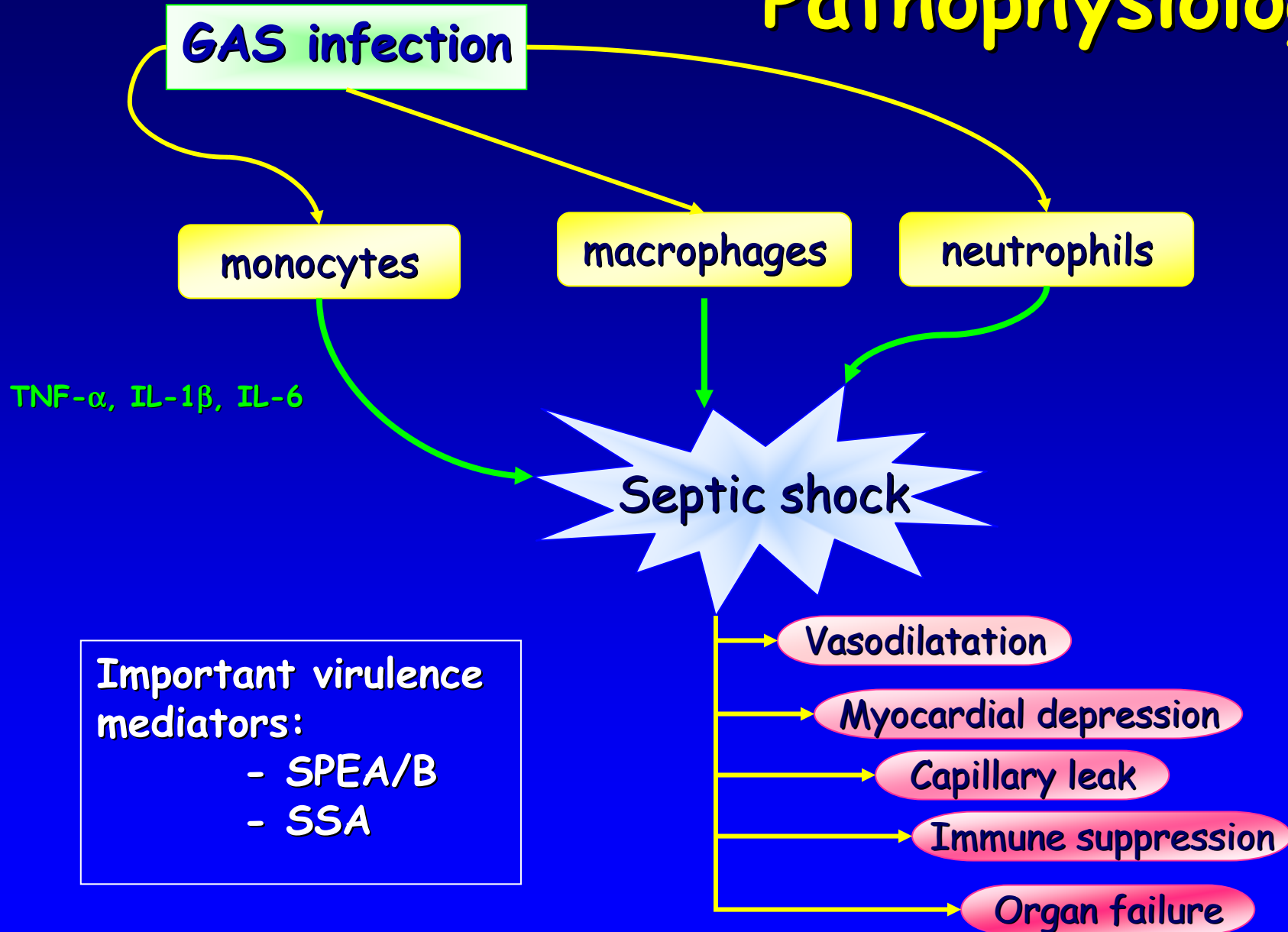
Strep TSS - The Clinical Course

- ◆ Impressive rapidity
 - ◆ Progression of shock and multi-organ failure
 - ◆ Many patients may die within 24-48 h of hospitalization
 - ◆ Shock at time of admission or within 4-8 h
 - ◆ Renal impairment often present at time of admission, progression or persistence; dialysis
 - ◆ If ARDS, intubation, ventilation in 90% cases

Strep TSS, Characteristic of Clinical Isolates

- ◆ **M types 1, 3, 6, 12 and 28** : majority of isolates
 - ◆ Sweden, 80 % M-type 1 strains
- ◆ **Streptococcal exotoxin type A (SPEA) and/or type B (SPEB)**
 - ◆ SPEA in 15 % of all clinical isolates / in > 80 % of strains causing STSS.
 - ◆ SPEA most frequently in USA / SPEB most common in Europe
- ◆ **Streptococcal superantigen (SSA)**, a novel pyrogenic exotoxin, isolated in M-3 strains

Pathophysiology



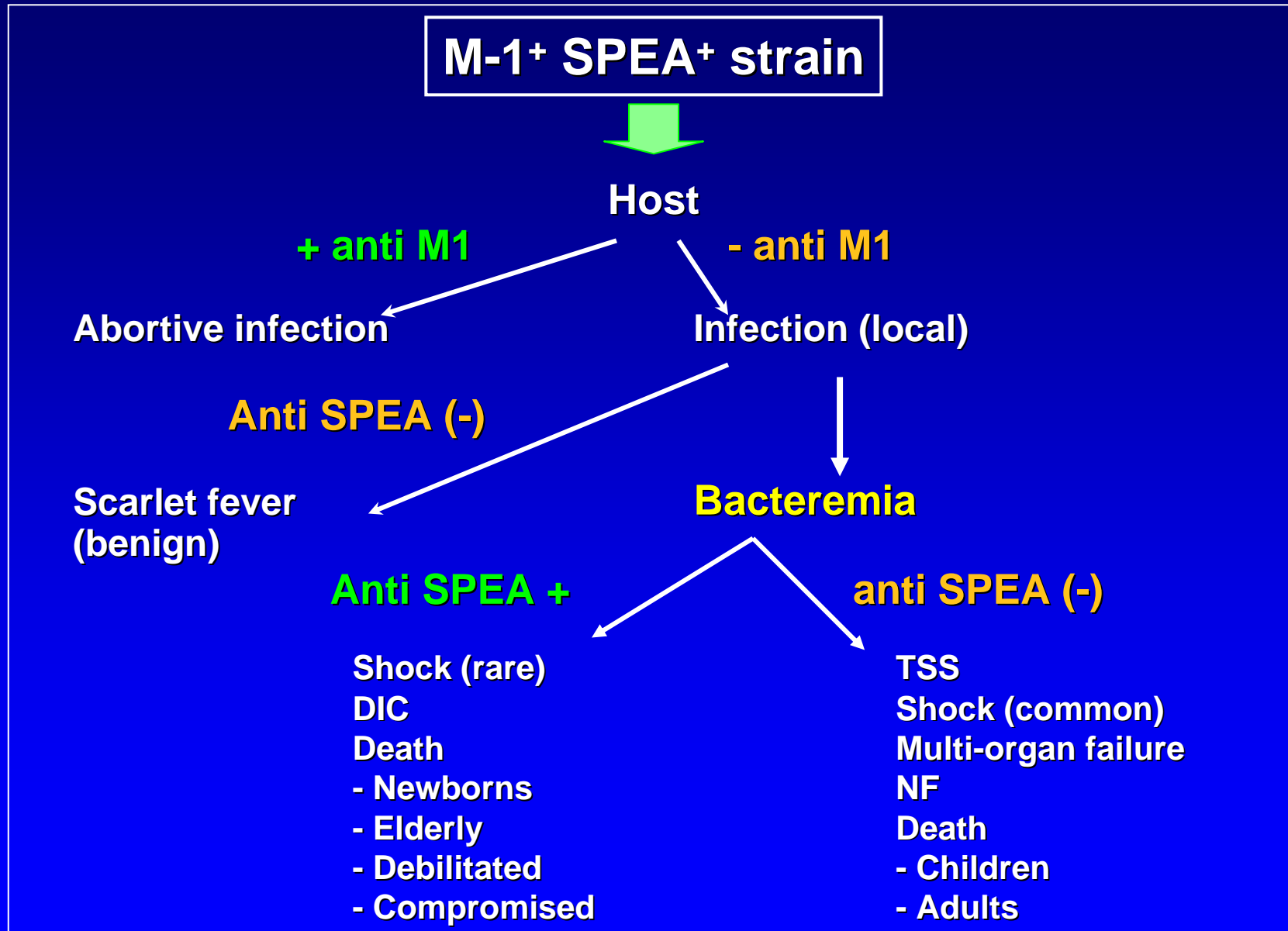
Strep TSS - Pathophysiology

- ◆ Why worldwide increase of severe GAS infections ?
- ◆ Why no epidemics ?

UNCLEAR !

- ◆ Host factors, immunity
 - ◆ Same strain may cause severe invasive disease / mild uncomplicated disease / carrier state
 - ◆ Level of Ab -M, and - SPEA
- ◆ Bacterial factors
 - ◆ Change in prevalence of strains with specific virulence factors

Pathogenesis of Scarlet Fever, Bacteremia and S-TSS



Strep TSS, Management

Surgical emergency is mandatory

- ◆ Diagnosis should be made by surgical exploration
- ◆ IMMEDIATE aggressive surgical debridement of all necrotic tissue
 - ◆ May include amputation
 - ◆ Repeated often daily
- ◆ Lesion often much more extensive / examination of skin surface
- ◆ Spread of infection >> rate of surgery

Strep TSS, Management

- ◆ *GAS* remain Sensitive to penicillin
- ◆ But reduced efficacy in severe *GAS* infection
 - ◆ High inoculum
 - ◆ Decrease in expression of Penicillin Binding Protein (PBP) by *GAS* in stationary phase
- ◆ Clindamycin more effective
 - ◆ Not affected by inoculum or stationary phase
 - ◆ Inhibits synthesis of bacterial toxins
 - ◆ Facilitates phagocytosis of *GAS* by inhibiting synthesis of M protein
 - ◆ Suppresses PBP Synthesis & degradation
 - ◆ Longer post-antibiotic effect /penicillin

Strep TSS, Management

Supportive management

- ◆ Early admission to intensive care unit
- ◆ Management for septic shock
- ◆ Dialysis
- ◆ Tracheal intubation, mechanical ventilation
- ◆ Massive amounts of IV fluids

Prophylaxis

- ◆ Risk of household's contact :
 - ◆ 200 times higher/general population
 - ◆ CDC : no definitive recommendations
 - ◆ ? Cephalosporin or macrolide : 10-day ?
- ◆ Nosocomial transmission and transmission to health care workers
 - ◆ Appropriate precautions
 - ◆ Gown, mask, gloves and **meticulous handwashing**

Where do we go from here

- ◆ A wild « flesh-eating strain » has recently emerged
- ◆ A major epidemic would be expected
- ◆ Other GAS epidemics (pharyngitis, scarlet fever, rheumatic fever) occurred in the past
- ◆ Last decade: incidence of GAS TSS has remained low
- ◆ Large outbreaks of STSS did not occur, WHY ?

Where do we go from here

Large outbreaks of STSS did not occur, WHY ?

- ◆ Vast majority of population
 - ◆ Probably immunity to 1 or more virulence factors
- ◆ Predisposing conditions required in a given patient
 - ◆ Varicella, use of non-steroidal anti-inflammatory drugs
- ◆ Small % of population with some other immunological predisposing factors
 - ◆ HLA class II ag type, B cell alloantigens, or ...

What should be done ?

- ◆ Pathogenesis : more information needed
- ◆ Continued epidemiological and microbiological surveillance
- ◆ Improvement of therapeutic
- ◆ Prevention strategy
 - ◆ Development of M-vaccine