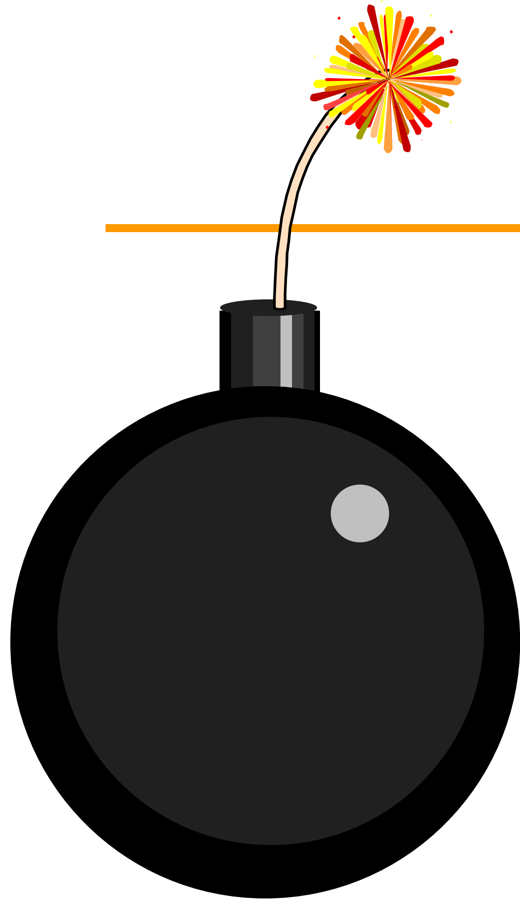
30 Years of Toxic Shock Syndrome: Evolution of an Emerging Disease



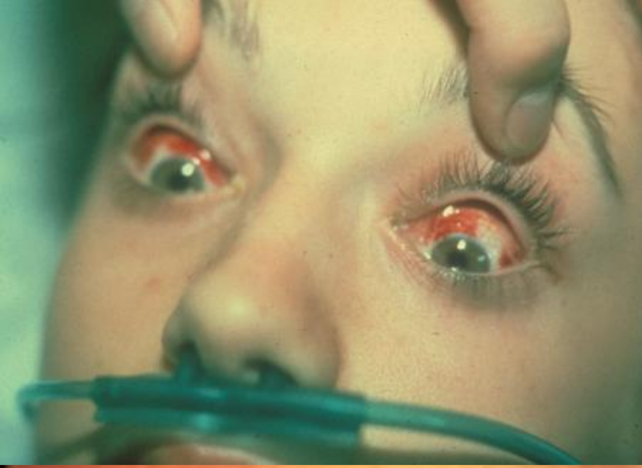
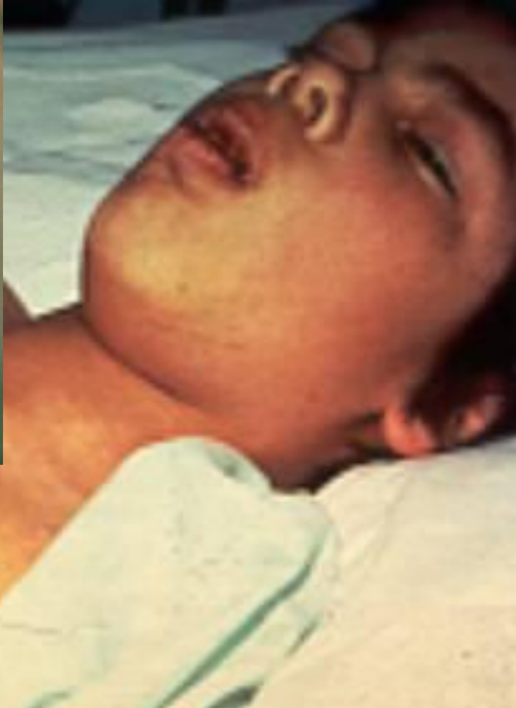
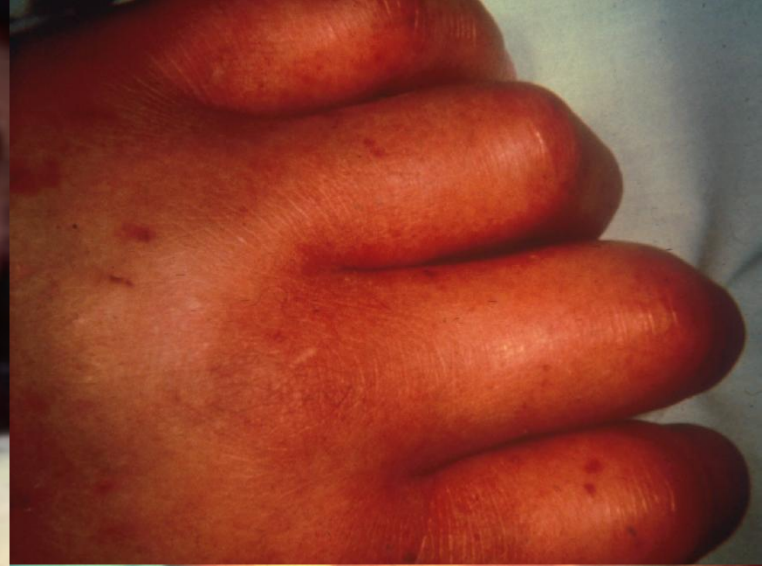
James K. Todd, MD

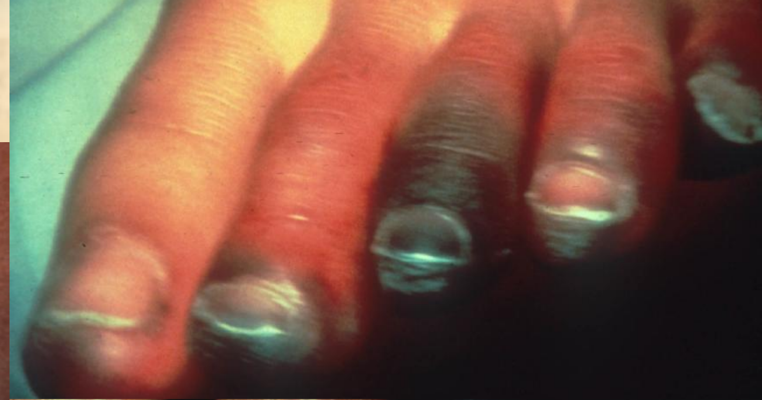
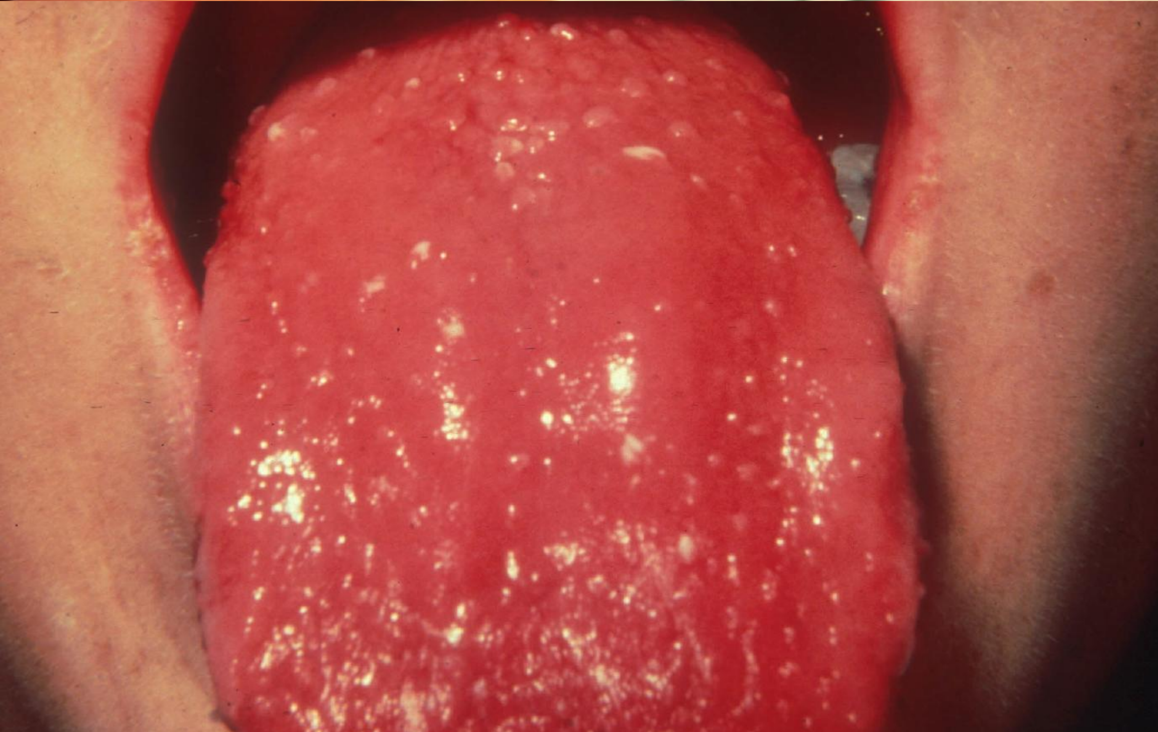
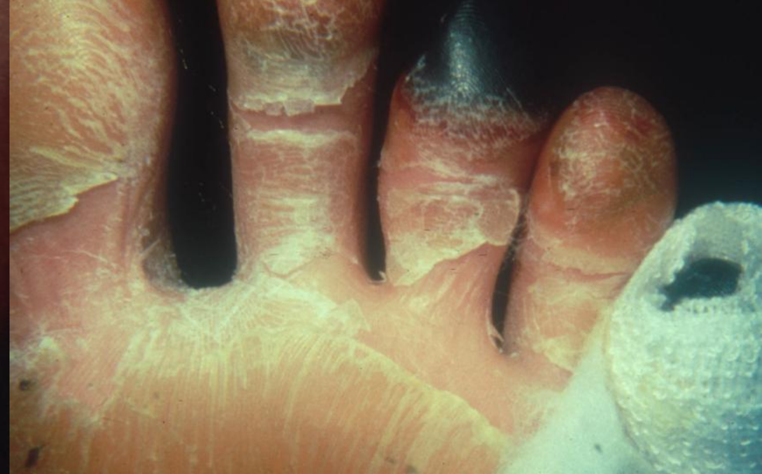
TSS Appears to be Very Rare in Africa

Seeras, R (1989). "A case of post-partum toxic shock syndrome presenting in an African patient." The Journal of tropical medicine and hygiene **92(4): 288-9.**

- A classic case of post-partum toxic shock syndrome with a possible mother-infant pair involvement is presented. Its low incidence in Africa as well as a probable source of infection is discussed.

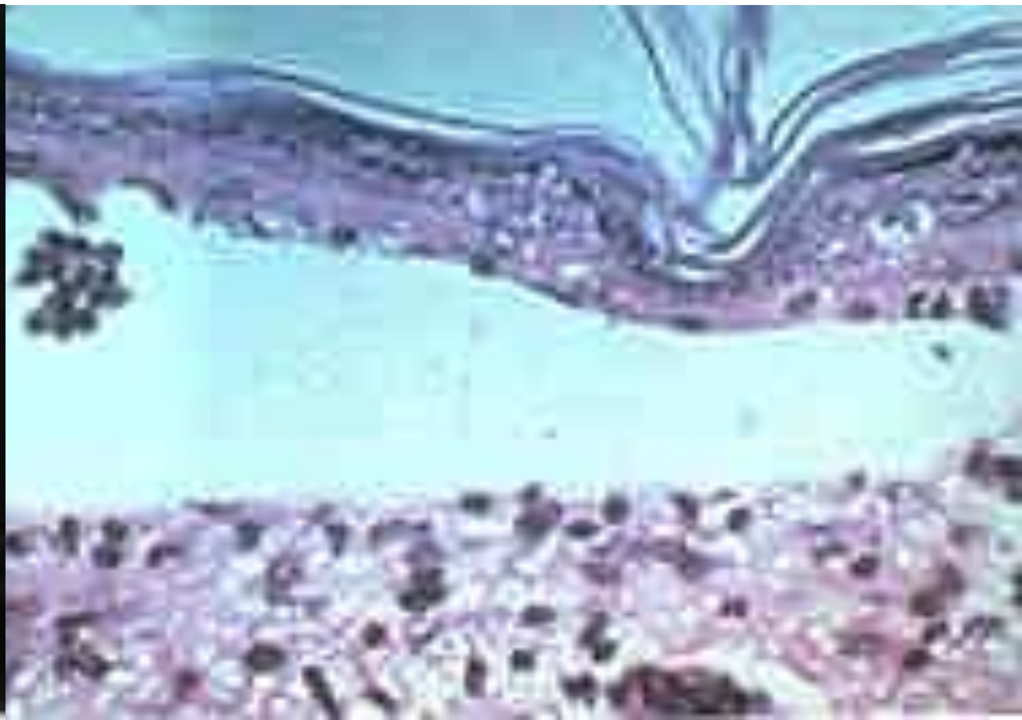
- Is it rare or just under-recognized??

TSS associated with phage group I staphylococci

- 7 Patients
  - 4 females, 3 males
  - 5 with *S. aureus*
    - *Phage group I*
    - *New epidermal toxin*



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The Lancet, Volume 312, Issue 8100, Pages 1116 - 1118, 25 November 1978
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TOXIC-SHOCK SYNDROME ASSOCIATED WITH PHAGE-GROUP-I STAPHYLOCOCCI

James Todd [a], Mark Fishaut [a], Frank Kapral [b], Thomas Welch [c]

Abstract

Seven children (aged 8-17 years) presented with a high fever, headache, confusion, conjunctival hyperæmia, a scarlatiniform rash, subcutaneous œdema, vomiting, watery diarrhœa, oliguria, and a propensity to acute renal failure, hepatic abnormalities, disseminated intravascular coagulation, and severe prolonged shock. One patient died, one had gangrene of the toes, and all have had fine desquamation of affected skin and peeling of palms and soles during convalescence. Five patients were studied prospectively. *Staphylococcus aureus* related to phage-group I was isolated from mucosal (nasopharyngeal, vaginal, tracheal), or sequestered (empyema, abscess) sites, but not from blood. This organism produces an exotoxin which causes a positive Nikolsky sign in the newborn mouse and which is biochemically, pathologically, and immunologically distinct from phage-group-II stapphylococcal exfoliatin.

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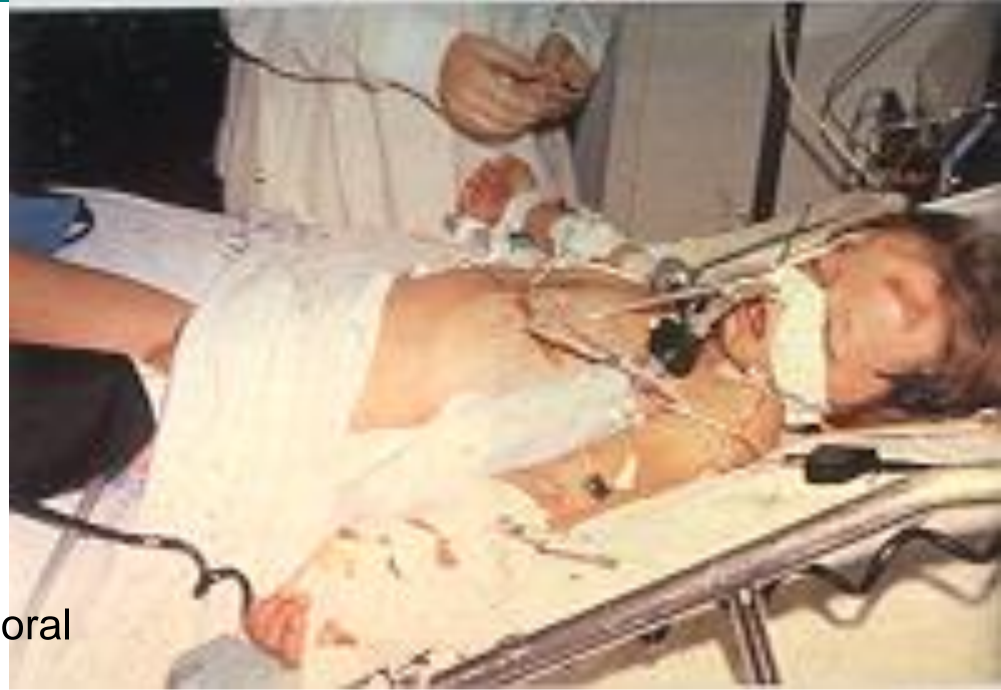
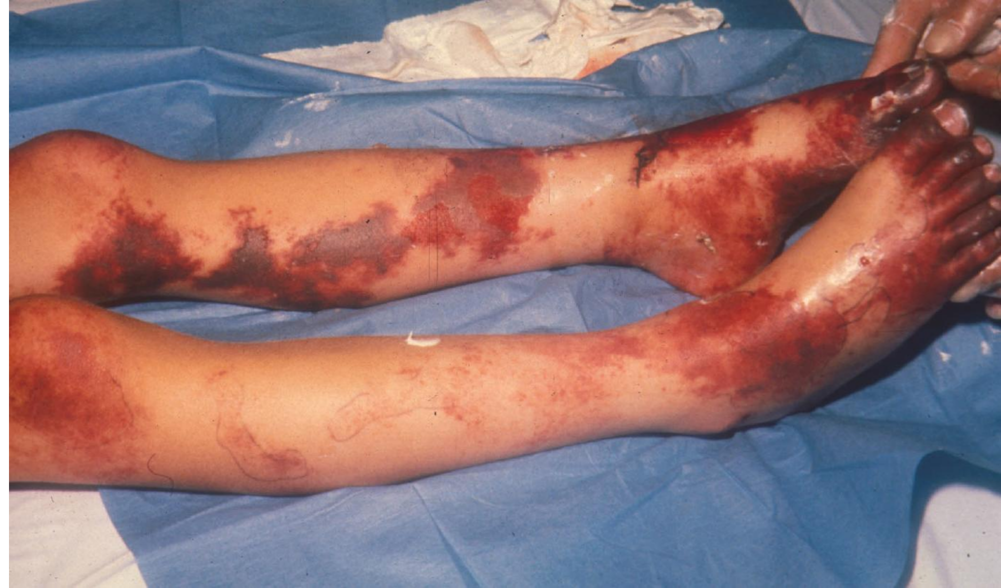
Toxic Shock Syndrome: Definition

- Acute Fever
- Erythroderma (Desquamation - usually late)
- Hypotension
- Multi-organ system involvement (at least 3):
  - Mucus membranes - conjunctiva, oral
  - Renal
  - Hepatic
  - Gastrointestinal
  - Hematologic (inc. platelets)
  - CNS
  - Muscular
- Exclusion of other diseases





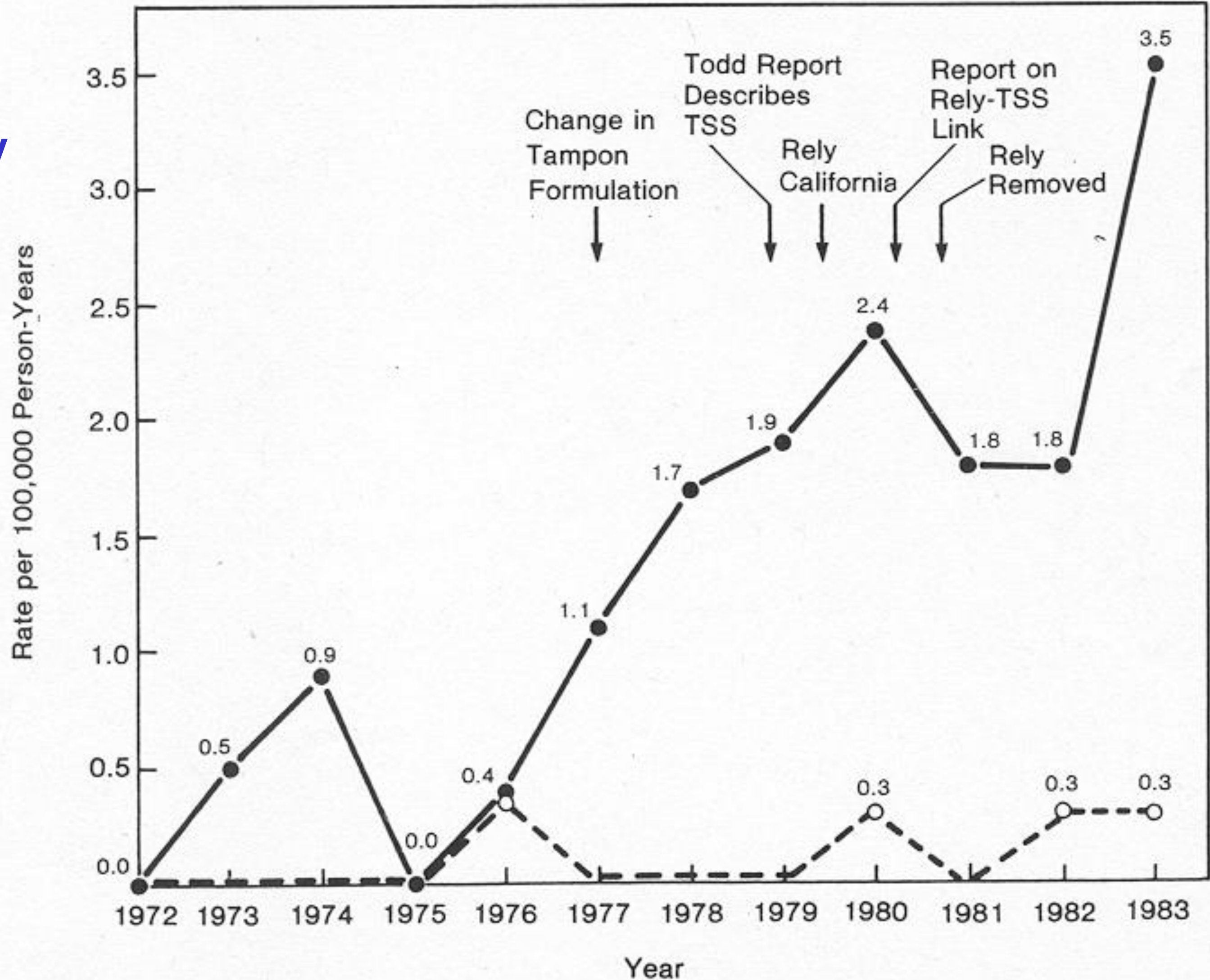
Epidemiology of TSS vs Scalded Skin Syndrome

	TSS	SSSS	p
Number	21	21	
Female/Male	16/5	8/13	0.028
Age (yrs)	12.9	2.3	0.0001
S. aureus site:			0.0001
NP	2	19	
Vagina	13	1	
Focus	6	1	

Todd JK, Todd BH, Franco-Buff A, Smith C, Lawellin DW. Influence of focal infection conditions on the pathogenesis of toxic shock syndrome. J Infect Dis 1987;155:673-81.

TSS in California

- On rise before Rely
- No change on removal of Rely in 1980
- Peak year 1983



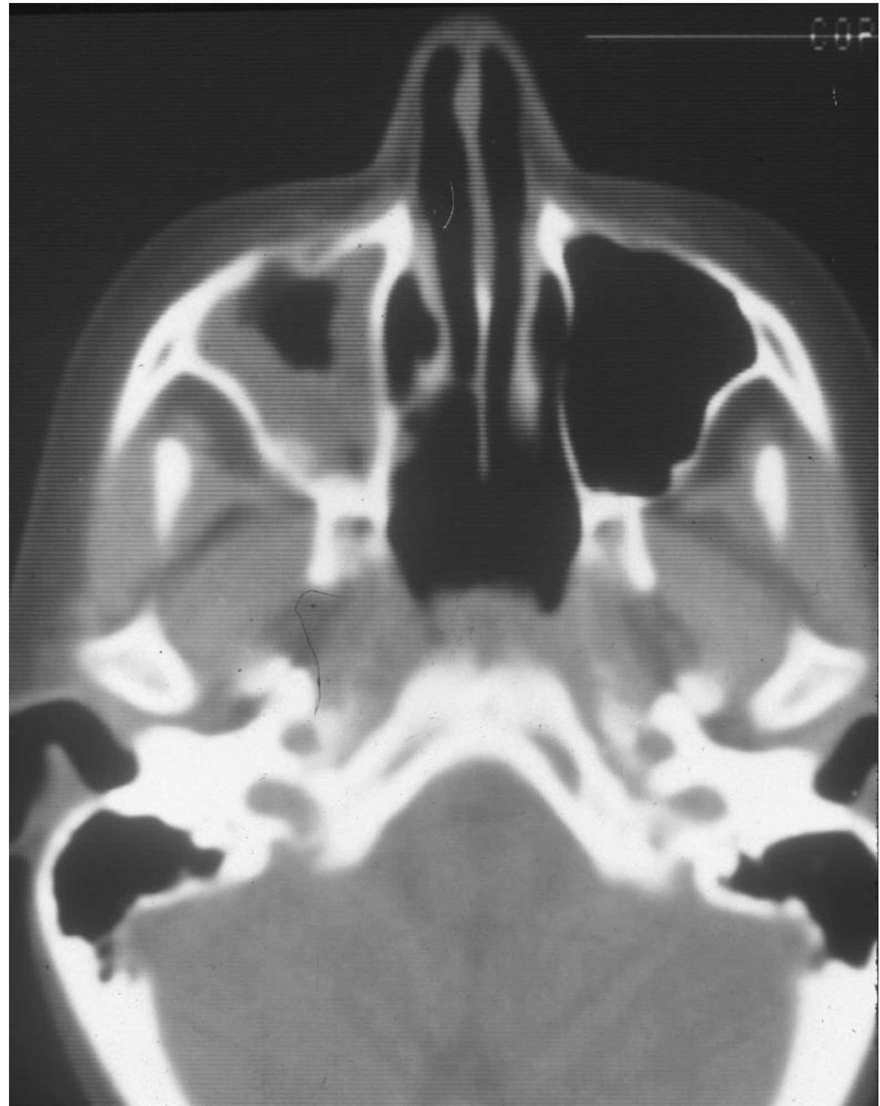
Incidence of hospitalized toxic shock syndrome (TSS) in males (dashed line) and females (solid line), aged 15 through 34 years, Northern California Kaiser-Permanente Medical Care Program, 1972 through 1983.

TSS and Sinusitis – Look for the focus!

- *Ferguson MA, Todd JK. Toxic Shock Syndrome Associated with Staphylococcus aureus Rhinosinusitis in Children. J Infect Dis 1990 May;161(5):953-5.*

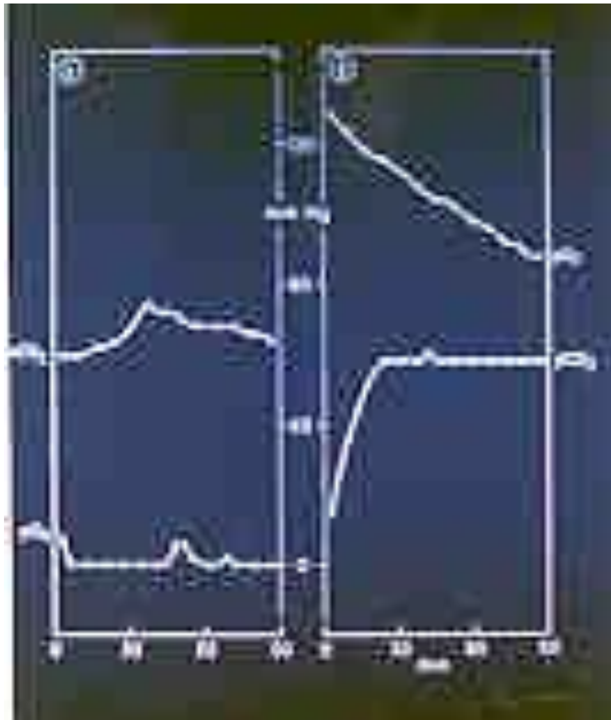
- *Abram, A. C., K. T. Bellian, et al. (1994). "Toxic shock syndrome after functional endonasal sinus surgery: an all or none phenomenon?" Laryngoscope* ***104****(8 Pt 1): 927-31.*

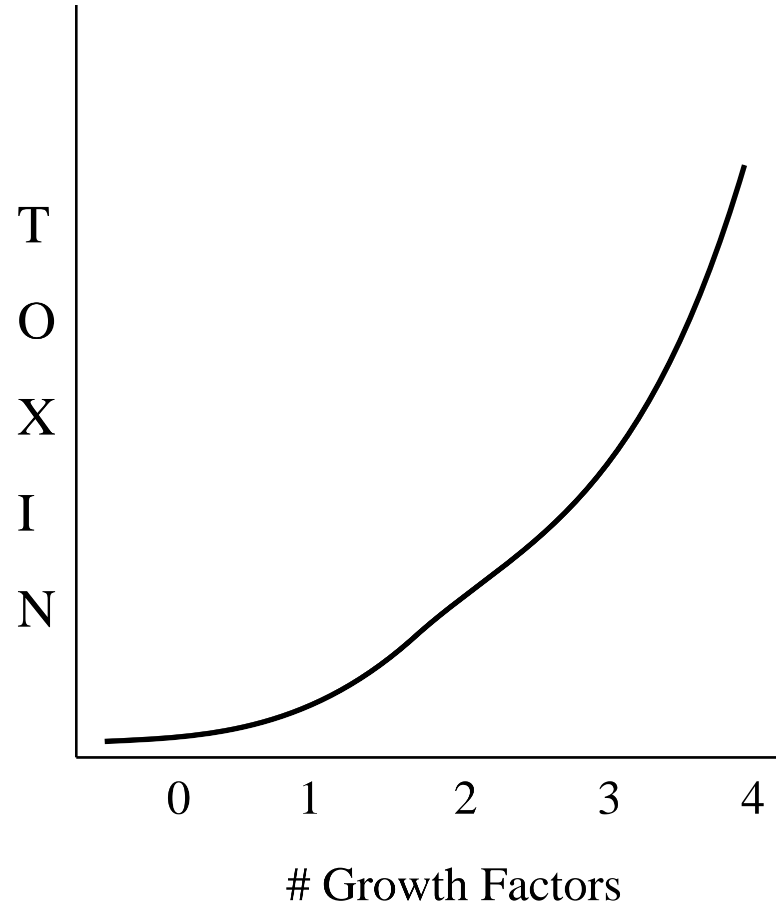
TSS cases following nasal surgery have been associated with nasal packing, mucosal barrier violation, prior S aureus phage I colonization, as well as low antitoxin antibody levels. Of the 1700 FESS procedures performed at our institution, 3 cases were complicated by classic TSS, with 2 additional patients having a postsurgical course compromised by a milder degree of TSS.



Characteristics of Staphylococcal Wound Infections & Effect on Toxin Production

- pH 7.0-7.2
- High protein
- High pO_2
- High pCO_2





Todd JK, Todd BH, Franco-Buff A, Smith C, Lawellin DW. Influence of focal infection conditions on the pathogenesis of toxic shock syndrome. J Infect Dis 1987;155:673-81.

TSS: First Superantigen Disease

- *In vitro* studies have demonstrated that TSST-1 is a powerful but selective stimulator of human T cells -- the majority of activated cells express the TCR V beta 2 gene segment

- *In vivo* confirmation:

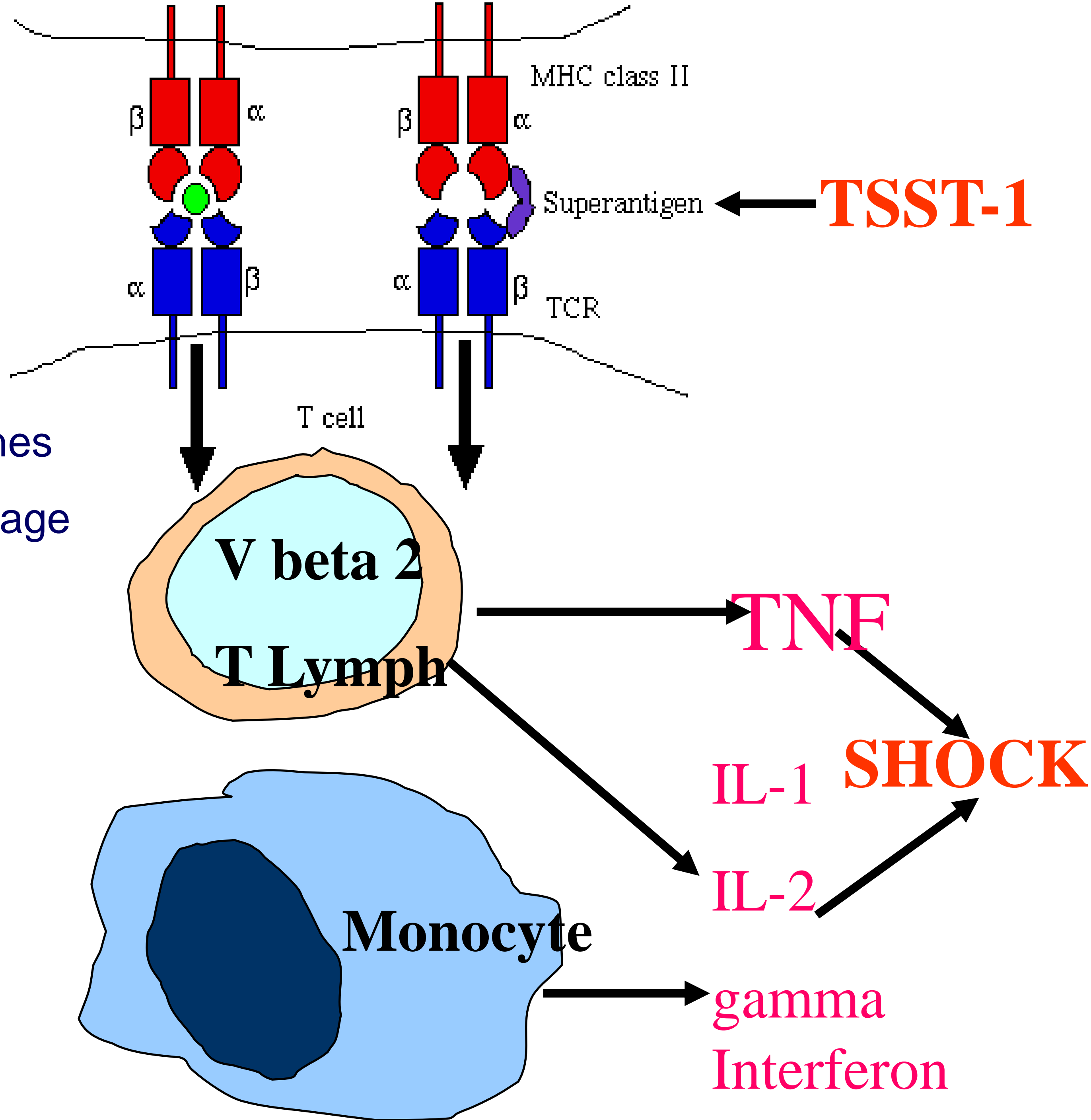
Lymphocyte Stimulation	V beta 2	V beta other
TSS Patients	5/8	0/8

- The results suggest that toxin-mediated T cell activation, which involves a large fraction of the human T cell repertoire, may be critical in the pathogenesis of TSS

Choi Y, Lafferty JA, Clements JR, Todd JK, Gelfand EW, Kappler J, Marrack P, Kotzin BL. Selective expansion of T cells expressing V beta 2 in toxic shock syndrome. J Exp Med 1990;172:981-4.

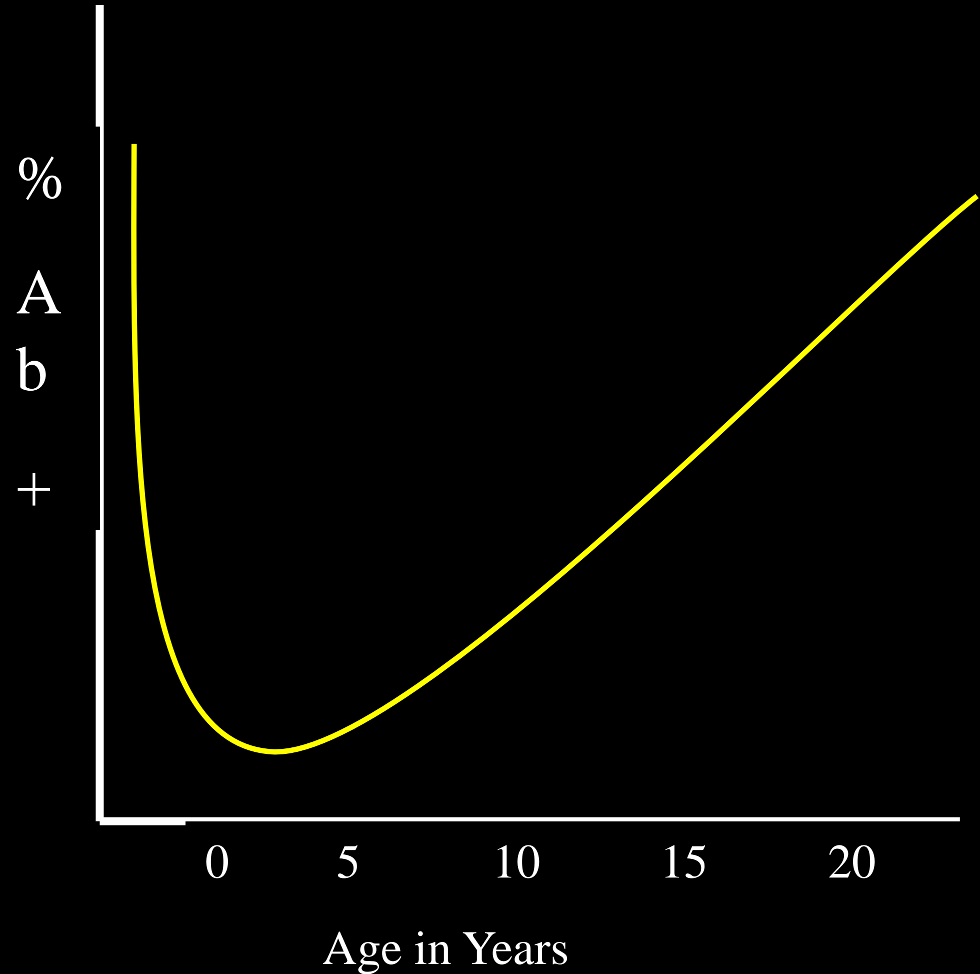
TSST-1: Mechanism of Action

- Superantigen stimulates cytokines
- Endothelial leakage



Seroepidemiology of TSS

- 30% of adults (NP) are colonized with *Staph aureus* (Vaginal 5%): 10-30% TSST-1+
- 95% of adults have antibody but the great majority have no history of symptoms of TSS
- Most antibody is due to subclinical colonization with toxin-mimicking strains
- TSS occurs in individuals with no antibody and presence of a focal Staph infection



Pathogenesis/Risk Factor-based Models Suggest Unknown Risk Factor

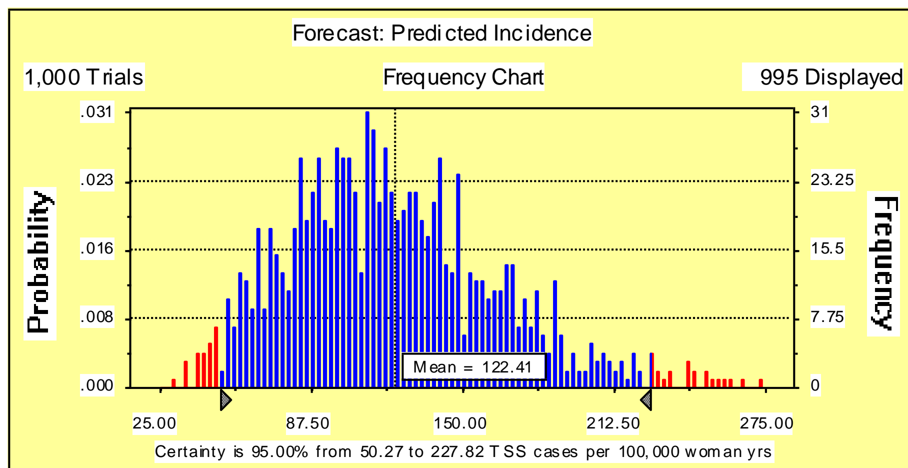
Predicting TSS Incidence in Menstruating Women

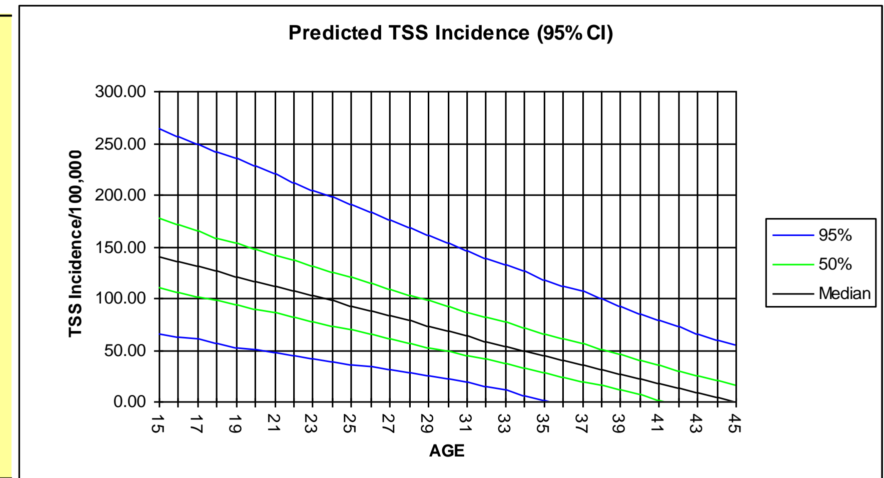
Risk Factors	%	Variation
TSST-1 S.aureus Acquisition Rate	3	.5 sd
% strains with high TSST-1 Production Rate	50	10 sd
% women with Immunity to TSS at age 15	70	5 sd
% women using tampons exclusively	33	5 sd
Age	20	"15-45"

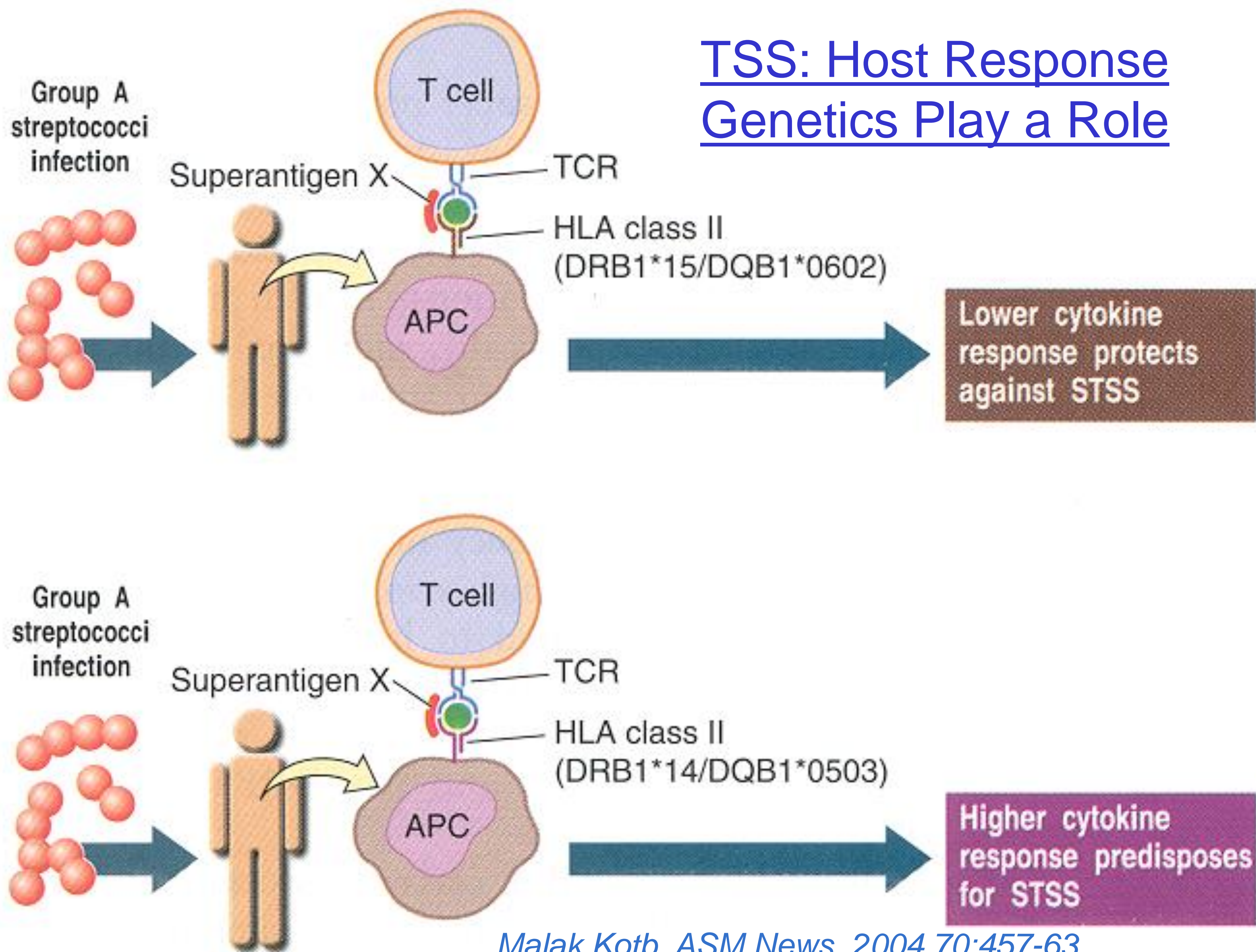
Equation:

Yearly Incidence in females 10-45=

Acq rate*High*((100-immune)-(Age-15))*Exclusive/10^8*10^5 — **123.75**



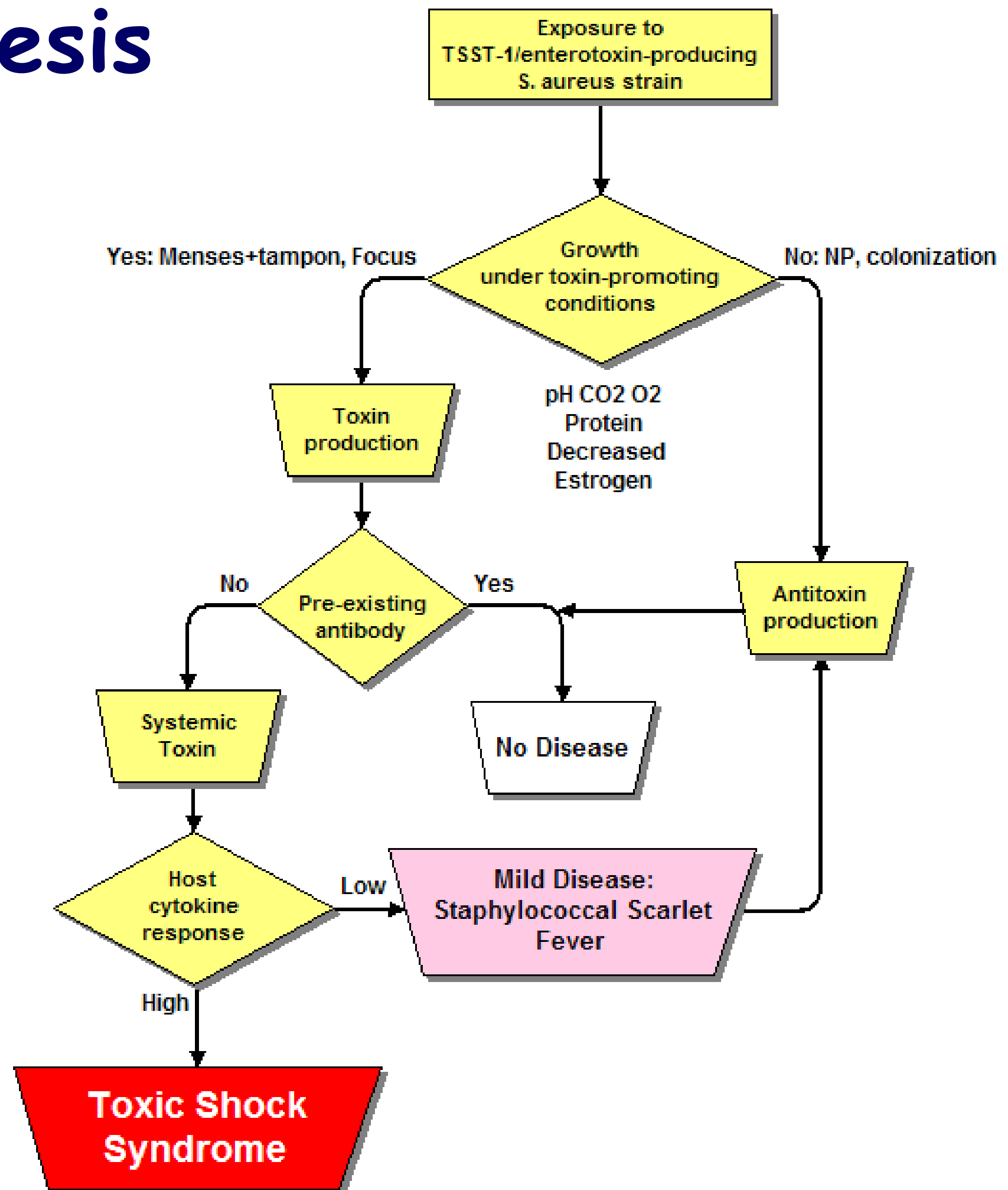



TSS: Host Response
Genetics Play a Role
Group A streptococci infection
Superantigen X
T cell
TCR
HLA class II
(DRB1*15/DQB1*0602)
APC
Lower cytokine response protects against STSS
Group A streptococci infection
Superantigen X
T cell
TCR
HLA class II
(DRB1*14/DQB1*0503)
APC
Higher cytokine response predisposes for STSS
Malak Kotb. ASM News. 2004 70:457-63

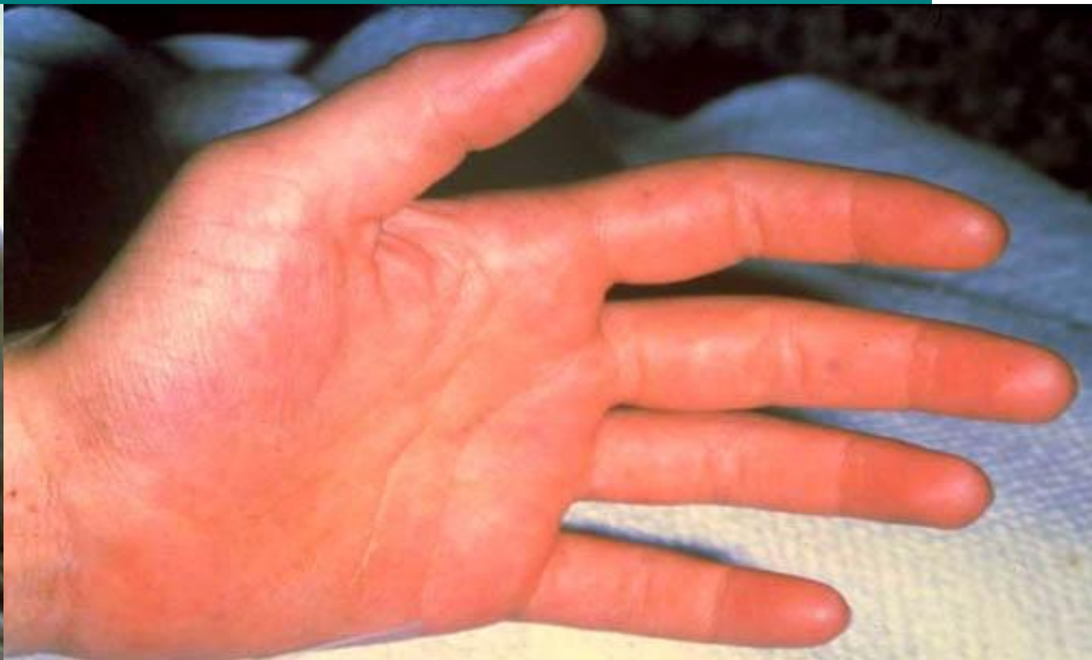
TSS Pathogenesis (Revised)

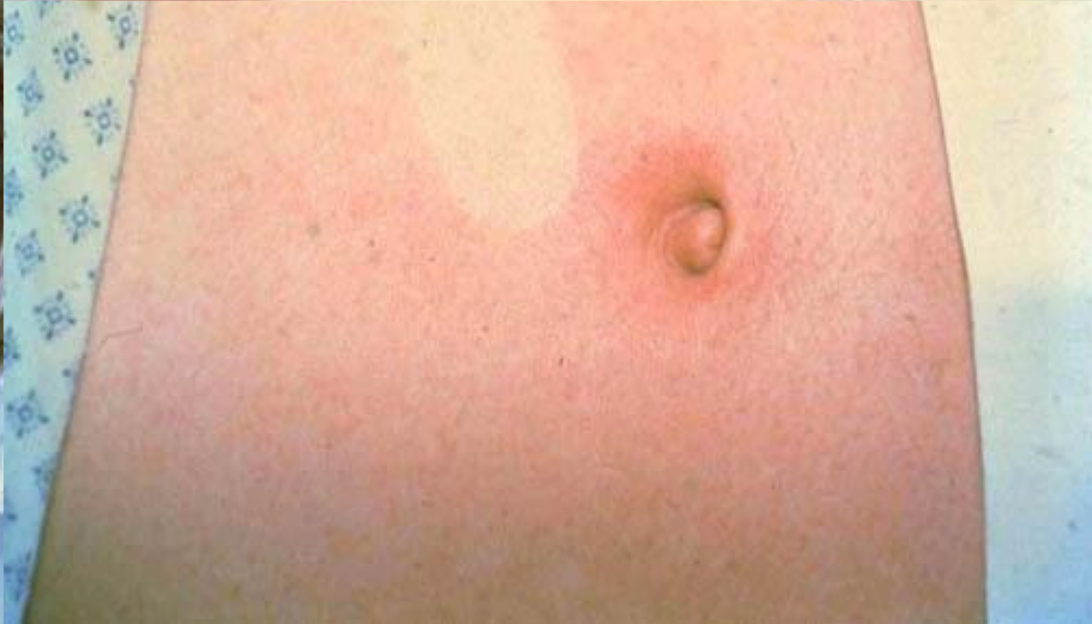
Risk Factors for TSS

- Exposure to TSST-1 (+/- enterotoxin) *S. aureus* strain.
- Growth of organism under conditions that promote toxin production.
- No pre-existing antibody to toxin(s).
- Genetically predisposed



Streptococcal Toxic Shock Syndrome





Severe Invasive Streptococcus Syndrome (SISS)

- Toxic Shock Syndrome
- Septicemia (with or without focal infection)
- Scarlet Fever
- Necrotizing cellulitis / fasciitis
- Puerperal Sepsis

JAMA 1993; 269; 390-1

Streptococcal Toxic Shock Syndrome

Hypotension or Shock plus two or more of:

- Renal Impairment
- DIC
- Liver Impairment
- ARDS
- Scarlet Fever Rash
- Soft Tissue Necrosis

- Definite Case:
  - Clinical Criteria
  - *S. pyogenes* from normally sterile site
- Probable Case:
  - Clinical Criteria
  - *S. pyogenes* from non-sterile site

JAMA 1993; 269; 390-1

The "Eagle" Effect

Beta-lactams

- "Bacteriocidal"
- Fail to kill large inoculum or stationary phase organisms - "Eagle Effect"
- May stimulate toxin production and release

Clindamycin

- Bacteriostatic
- Kills (with WBCs) all phases
- Decreases toxin and enzyme production
- Increases opsonization
- Better in animal model
- Improved clinical efficacy

Outcome of type of initial antibiotic therapy regardless of surgical intervention

	Favorable Outcome	
	Local Inf	Deep Inf
Cell-wall Inhibitor	12/25 (48%)	1/7 (14%)
Protein Synthesis Inhibitors (+/- CWI)	10/12 (83%)	10/12 (83%)
Probability	0.04	0.14

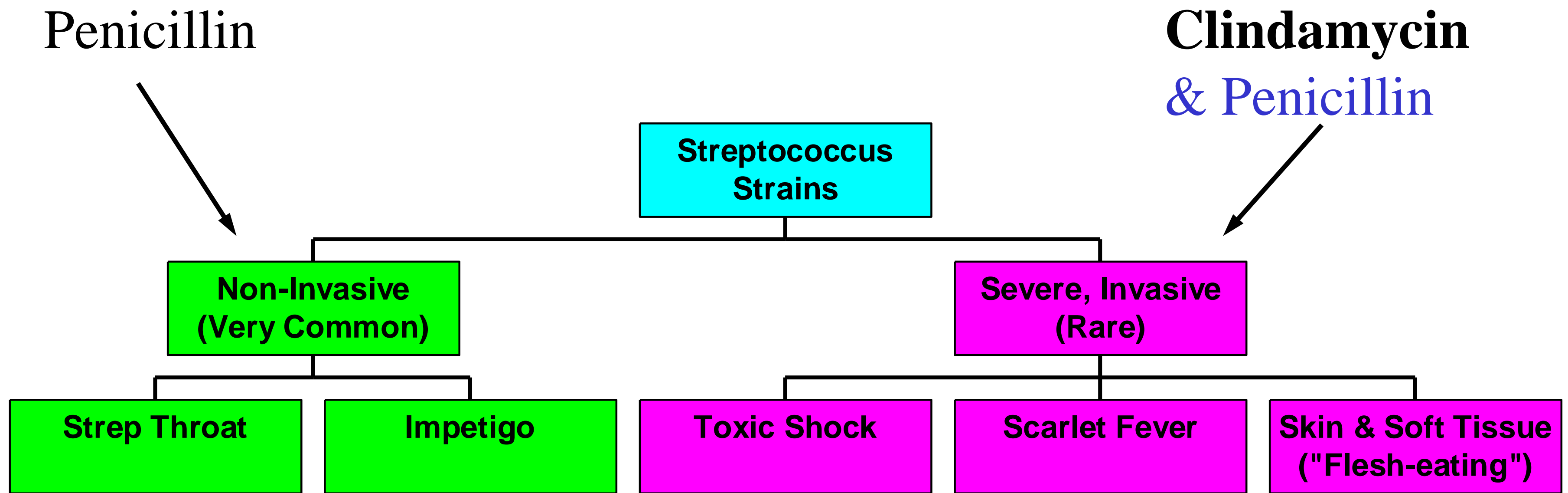
Zimbelman J, Palmer A, Todd JK. Improved outcome of clindamycin compared with beta-lactam antibiotics treatment of invasive Streptococcus pyogenes infection. Pediatr Infect Dis J 1999; 18:1096-100.

Outcome of Cell Wall Inhibiting antibiotics in the initial treatment of invasive S. pyogenes infection with or without surgical intervention

	Favorable Outcome	
	Local Inf	Deep Inf
Surgical Intervention	3/3	1/1
No Surgery	9/22 (41%)	0/6
Probability	0.04	0.14

Zimbelman J, Palmer A, Todd JK. Improved outcome of clindamycin compared with beta-lactam antibiotics treatment of invasive Streptococcus pyogenes infection. Pediatr Infect Dis J 1999; 18:1096-100.

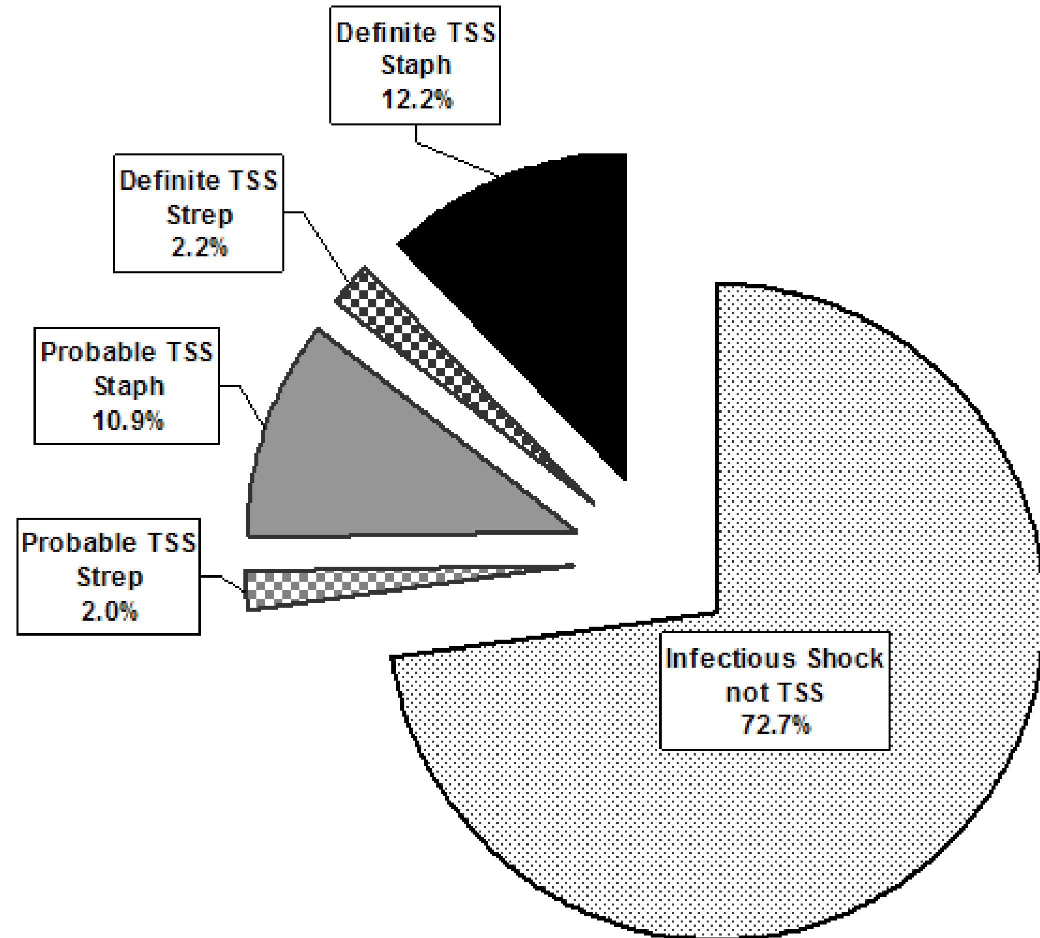
Treatment of Infection Caused by Group A Streptococcus



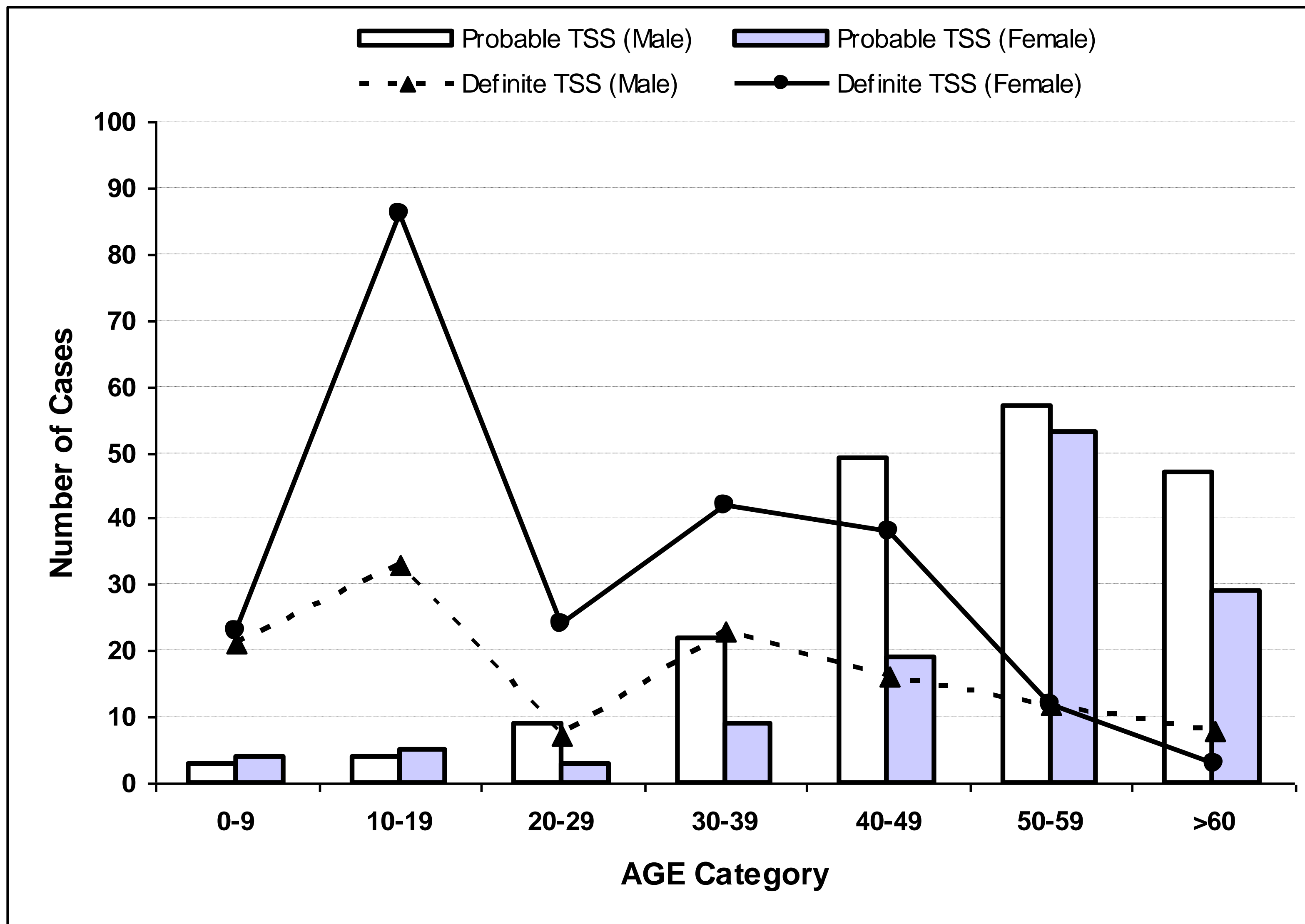
Gram-positive shock is common

Implications

- Different presentation
  - Erythroderma
  - Strawberry tongue
  - Less DIC
  - Focus
    - Abscess, Menses (Staph)
    - Fasciitis (Strep)
- Different treatment
  - Antibiotics
    - Clindamycin
    - ? Vancomycin
  - IVIG
  - ? Steroids
- Better Prognosis (If recognized)



TSS may not be recognized in males or older individuals



Gram+ shock has a better potential outcome

	Discharge Status Population (N)	Mean Fatality Rate (%)	Survivor Population (N)	Mean Length of Stay (Days)
Infectious Shock not TSS	2079	29.3%	1470	12.4
Probable TSS Strep	58	15.5%	49	14.7
Probable TSS Staph	313	27.5%	227	18.5
Definite TSS Strep	63	6.3%	59	15.5
Definite TSS Staph	348	5.5%	329	7.9
Total	2861	25.4%	2134	12.5

Signs of Gm-positiveToxemia

- Hypotension
  - Shock
  - Orthostatic hypotension
  - Orthostatic dizziness, fainting
- Scarlet Fever Rash
- Strawberry (raspberry) tongue
- Necrotizing cellulitis
- Typical Staphylococcal focus

Minimizing Toxic Effects of TSS

- Early diagnosis and treatment
- Etiologic diagnosis (aspirate) = Correct antibiotic
- Stop toxin production (Eagle effect):
  - Stop organism replication
  - Stop toxin production
- Remove reservoir of toxin (and necrosis) = Surgery
- Neutralize existing toxin = IVIG
- Support system failure (shock) - fluids, steroids?

TSST-1 Staphylococcus is in Africa

- Adesiyun AA, Lenz W, Schaal KP. Production of toxic shock syndrome toxin-1 (TSST-1) by Staphylococcus aureus strains isolated from humans, animals and foods in Nigeria. Microbiologica 1992;15:125-33.
  - Thirty one (16.0%) of 194 strains from human diarrhoea and wounds were positive for TSST-1
  - It was concluded that TSST-1 producing strains of S. aureus are widespread in humans, animals and foods in Nigeria and such distribution may play some role in the epidemiology of toxic shock syndrome, the prevalence of which is currently unknown

- Olusanya O, Naidu AS. Occurrence of toxic shock syndrome toxin-1 producing Staphylococcus aureus and the anti TSST-1 serostatus of hospital personnel in Nigeria. East Afr Med J 1991;68:507-14.
  - 8.9% TSST-1 positive
  - 48.1% of hospital personnel with anti-TSST-1

- El-Ghodban A, Ghenghesh KS, Marialigeti K, Esahli H, Tawil A. PCR detection of toxic shock syndrome toxin of Staphylococcus aureus from Tripoli, Libya. J Med Microbiol 2006;55:179-82.
  - 3/40 strains (all from clinical sources) were positive for the TSST-1 gene (tst)

Possible Explanations

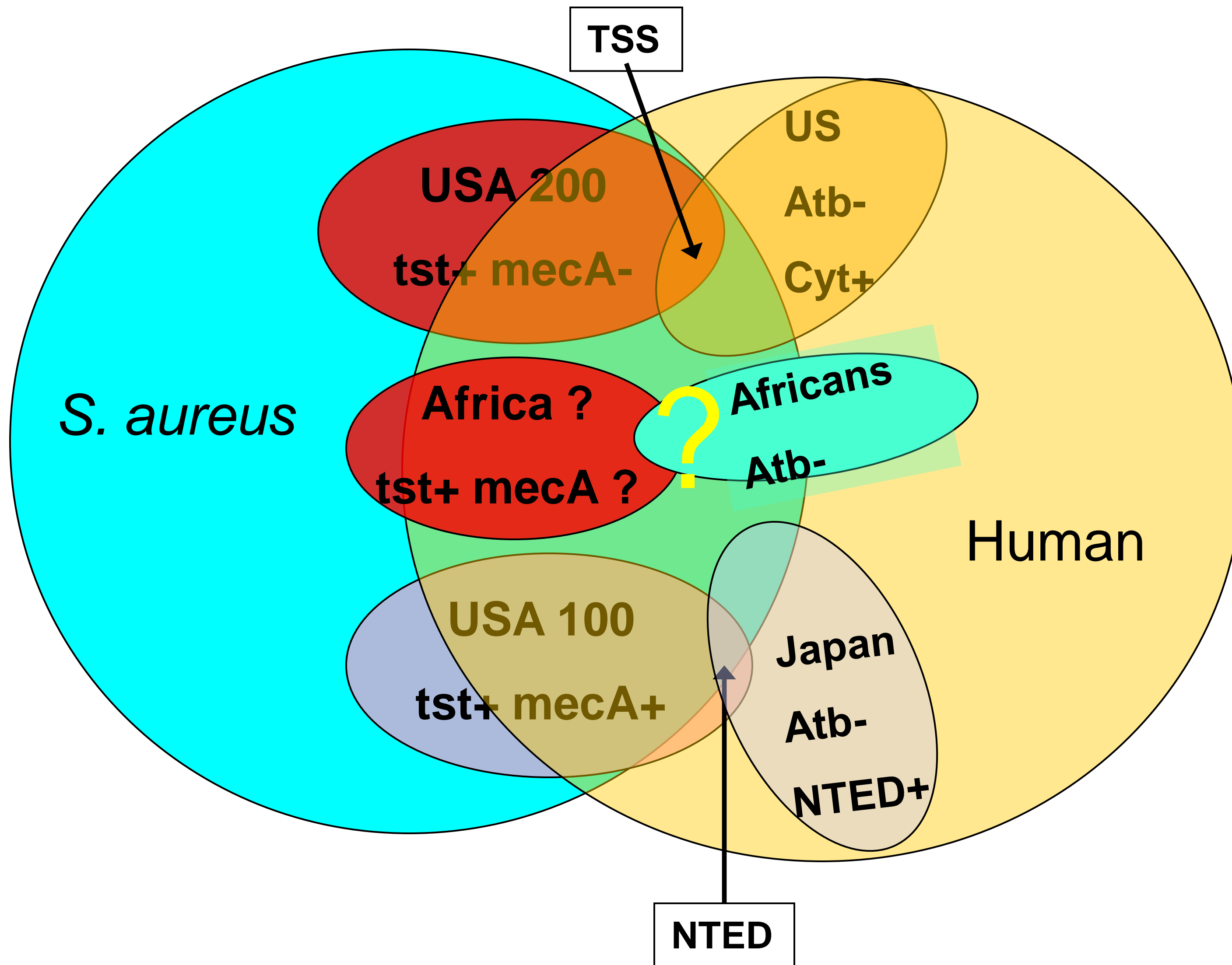
- Lower prevelance of TSST-1-producing strains in Africa (at present)
- Earlier exposure to nasopharyngeal colonization leads to protective antibody
  - Not supported by relatively low seroprevalence in adults
- Rash not recognised in dark skinned individuals
- Tampons not widely used in Africa
- Over-shadowed by more prevalent serious disorders (e.g. HIV/AIDS, TB)
- Host genotype less likely to over-respond.

Is TSS Under-recognised?

Perovic, O, H Koornhof, et al. (2006). "Staphylococcus aureus bacteraemia at two academic hospitals in Johannesburg." South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 96(8): 714-7.

- MSSA bacteremia is common
- Thirty-five (33.3%) of the 105 patients with MRSA bacteraemia died within 14 days, compared with 69 (20.1%) of 344 MSSA patients (p = 0.0048).
  - Increased MRSA fatality rate possibly explainable because of treatment choices
  - Could fatal MSSA subset be due in part to TSS?
- Fatality not related to HIV status
  - 117 (52.7%) were HIV positive, and of these 32 died (27.4%), a rate not significantly higher than that among HIV-seronegative patients (18 of 105 patients, p = 0.69).

What are the unique human and microbial subpopulations in Africa



TSS: Evolution of an Emerging Disease