A lady with fever

Speaker: Dr. CK Leung

Chairman: Dr. KB Tai

Triage Station of AED 20.10.2012

- Forty two years old lady HKC
- Complained of dizziness and fever
- GCS 15/15
- BP 80 / 46 mmHg , PR 79/min
- Temperature 36 C
- Just discharged from hospital in mainland
- Right breast operation on 18.10.2012
- Was informed that the excised tissue was benign

Medical Officer

- P/E : normal skin , no rash
- Chest : clear
- Abd : soft, nontender,
- Calf : soft
- Wound : no haematoma, no collection, clean
- Normal saline 500ml full rate,
- investigation …….

Investigation in AED

- Hstix 6.7
- Hb 11.9
- Urine : yellow, RBC large, WBC trace, protein negative
- Temperature rechecked : 36.5 C
- CXR : clear
- CBP, RFT, LFT, amylase sent
- BP rechecked 83 /53 , admitted to medical ward

Medical ward

- Married, mother of three children
- Cosmetic work (nail polish)
- Nonsmoker, nondrinker
- History of right breast lump, workup showed low suspicion microcalcification of breast, FU Surgery NDH before
- Excisional biopsy of right breast lump under local anaesthesia on 18.10.2012

- Put on NSAID and two unknown medication after operation
- Right breast tissue: benign
- Discharged on 20.10.2012 afternoon
- Developed dizziness and vomited once when returned to HK
- No wound pain, no wound discharge, no diarrhoea/ chest symptom

- Hb 12.5 WBC 12.1 , neutrophilic , platelet count normal
- Normal Ca, CPK and amylase
- Albumin 32 TB 23 ALP 99 ALT 299
- Started on IV augmentin, keep fluid challenge,
- After a total of 2.5L of IVF challenge, BP remained low 4 hours after medical ward admission
- Temp 37.5, BP 67/45, urine output 280ml since admission
- Transferred into ICU

- BP 94 / 60 in medical ward
- Old AED record traced, SBP was 100 – 120 mmHg during previous AED visit
- SaO2 98% on room air
- Right breast wound : 2cm, mild erythema, mild tenderness, no discharge,
- Na 132 mmol/L K 2.9 mmol/l urea 3.5 crea 85 mmol / L

In ICU

- Mild sore throat
- Mild tenderness over epigastrium
- GCS 15 /15
- Urinalysis : WBC trace, Blood large, protein +++
- Temperature 37.7C
- ABG : pH 7.43 pCO2 4 pO2 12.6
- HCO3 19.6
- Put on noradrenaline infusion
- Put on iv tazocin
- RFT remained normal, urine output > 50ml/hour

Day 2 ICU

- Temperature 39.6 C
- Urine output 50 to 200ml/hour
- ABG : mild Type I respiratory failure
- HCO3 17.8
- Normal hstix
- Blood pressure maintained with IVF and noradrenaline infusion
- Fully concious
- Right breast wound : total of six stitches, no discharge, on dressing daily

Day 3 ICU

- Sore throat +
- Faint maculopapular rash
- Plt 138 WBC 15, netrophilic
- Total bilirubin 45, ALT 158
- Soft abdomen
- US abdomen : small amount of ascitic fluid, no hepatobiliary lesion
- Reviewed in evening : generalized maculopapular rashes

- ? Streptococal URTI with toxic shock syndrome
- General condition improved, able to cut down dose of inotrope, no major organ failure, not for IVIG at the moment

Day 4

- Sore throat relieved,
- Rash : subsiding
- Platelet count 162 WBC 7.6
- Wean off inotrope
- Fever subsided
- No positive culture yet

Day 5

- Off stitches over right breast wound as planned by surgeon
- Significant amount pus coming out of the wound!!
- Reviewed by surgeon : 2cm cavity, no abscess, mild slough, no implant mentioned
- Wound swab sent

Subsequent course

- Transferred to medical ward
- Wound swab: Staphylococcus aureus , sensitive to cloxacillin
- ASOT titre : no elevation
- Blood culture : sterile
- Discharge home with cloxacillin on Day 8
- FU blood test : not diabetic
- Surgical clinic: no palpable breast lump, yearly FU

Toxic Shock Syndrome(TSS)

Toxic Shock Syndrome (TSS)

- Acute, multi-system, toxin-mediated illness
- Staphylococcus aureus/streptococcus pyogenes(group A strept)
- Bacterial toxin acts as superantigens(SAgs)
- Stimulating the immune-cell expansion
- Enhancing the cytokine released and tissue damage

Staphylococcus TSS

- Staphylococcus TSS
  - First reported in 1978
  - Associated with the use of highly aborbent tampons
  - Peak incidence in early 1080s, ~6-12 cases per 100,000 per year
  - 1-5% healthy women have vaginal colonization with toxin-producing strain of S.aureus

Staphylococcus TSS

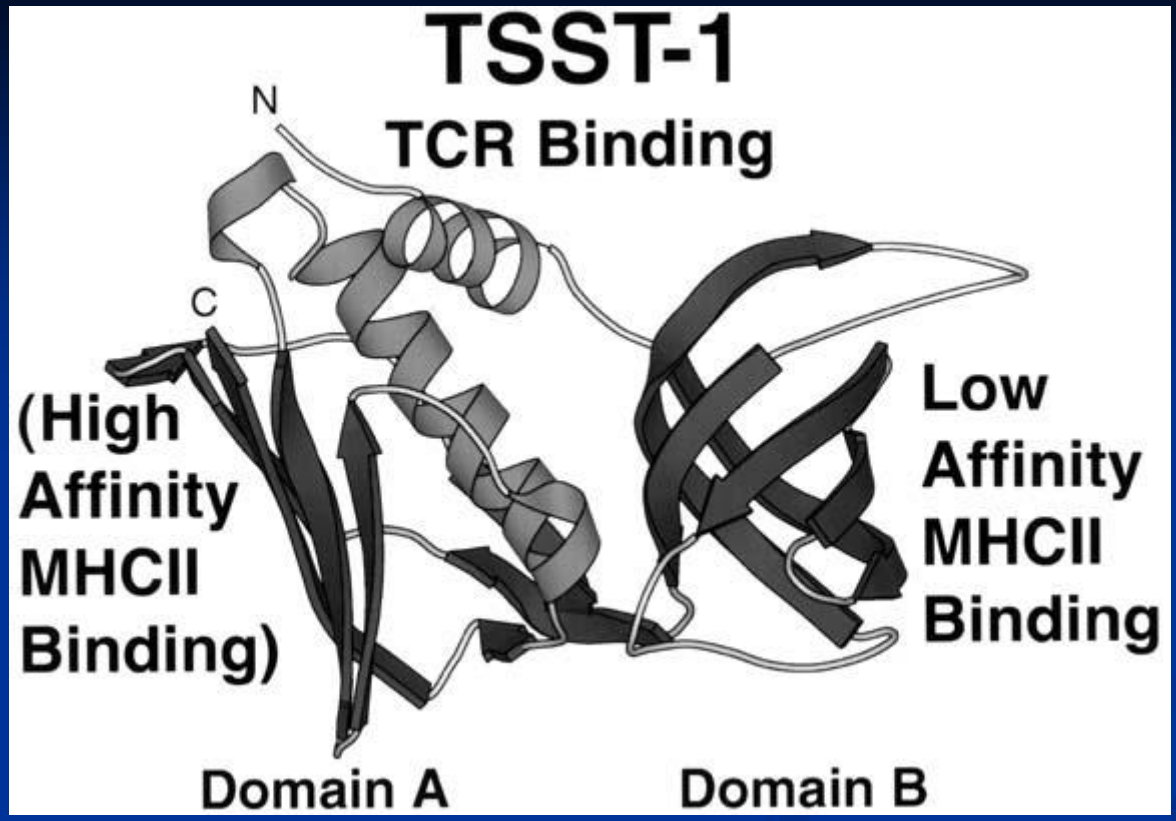
- Menstrual STSS
  - During or within 2 days of menstrual period
  - Associated with tampon used
  - Tampon-introduced oxygen -> TSST-1 production
- Non-menstrual STSS
  - Disruption of skin or mucus membrane
  - Abscess/burns/surgical or post-partum wound infection
  - Bone/joint, e.g. arthritis/osteomyelitis

Streptococcus TSS

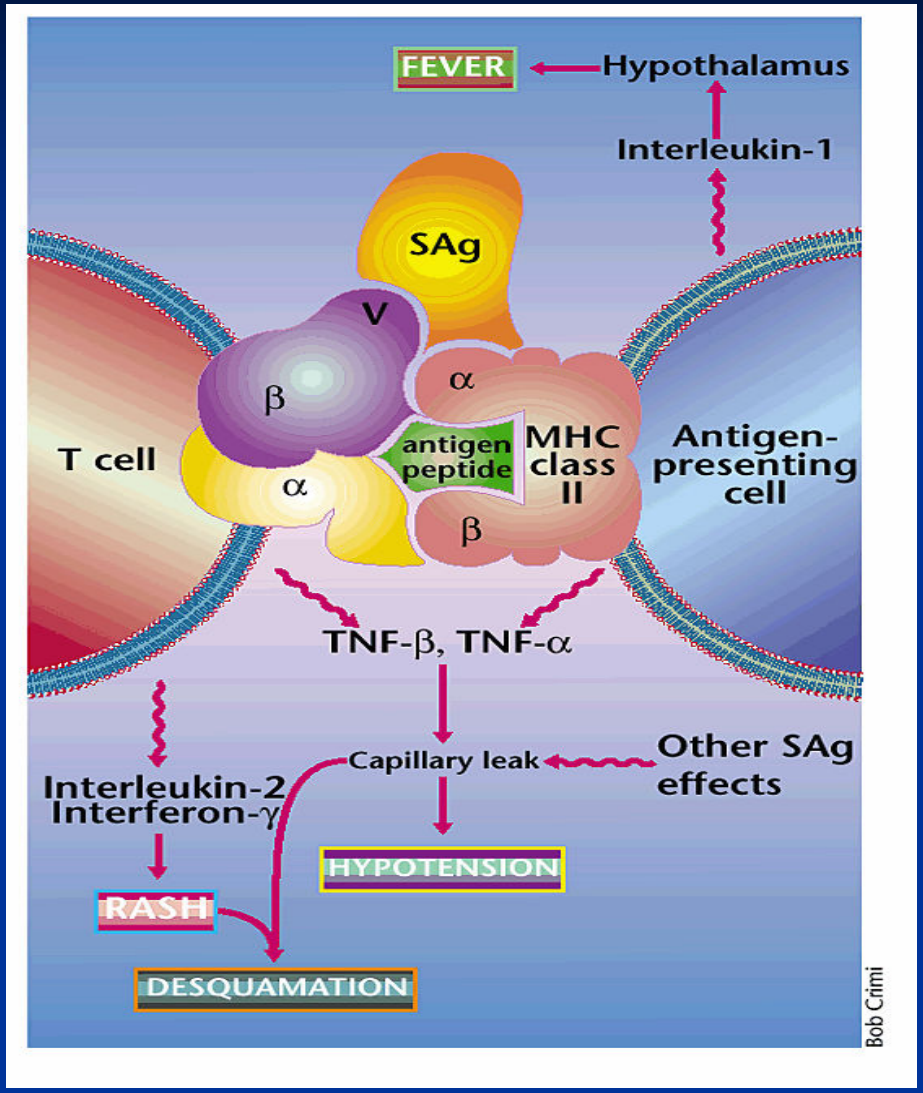
- First reported in 1987
- Usually arise from soft tissue infection
- 1.5-5.2 cases per 100,000 per year
- Mortality up to 30%
- Account for ~13% in strept infection from any source
- Up to 50% in pts with necrotizing fascilitis

Pathophysiology

- Bacterial toxin act as superantigens
- Single chain proteins bypass conventional MHC antigen processing
- trigger excessive T-cell activation -> cytokine/chemokine release



- simple, non-glycosylated protein
- resistant to heat, proteolysis (causing food poisoning)
- two-domain molecule
- domain A: beta grasp fold
- domain B: oligosaccharide binding (OB) fold



- Interact with MHC class II molecules (antigen-presenting cell) and the V β subunit (T-cell receptor)

- Unlike typical antigens activate 0.1% of host T-cell population, SAgs can activate up to 20-50%

TABLE I. Staphylococcal and streptococcal superantigens

Superantigen	Serological types
Toxic shock syndrome toxin-1 (TSST-1)	Human, ovine
Staphylococcal enterotoxins (SEs)	A, B, Cn, D, E, G-P
Streptococcal pyrogenic exotoxins (SPEs)	A, B*, C, F, G-J
Streptococcal superantigen	
Streptococcal mitogenic exotoxin	Zn
Exfoliative toxins	A*, B*

Table 2. Superantigen-associated illnesses.

Human illness	SAg association
Staphylococcal menstrual TSS	TSST-1
Staphylococcal non-menstrual TSS	TSST-1, SEB, SEC, occasionally others
1. Soft tissue infection	
2. Purpura fulminans	
3. Pneumonia	
4. Recalcitrant erythematous desquamating syndrome of AIDS	
5. Anaphylactic	
6. Kawasaki-like	
7. Scleroderma-like	
8. Rheumatoid arthritis like	
Staphylococcal extreme pyrexia syndrome	TSST-1, any SE or SE-like SAg
Staphylococcal food poisoning	Any SE
Atopic dermatitis	TSST-1, any SE or SE-like SAg
Pseudomembranous enterocolitis	TSST-1, any SE or SE-like SAg
Severe nasal polyposis	TSST-1, any SE or SE-like SAg
Perineal erythema	TSST-1, any SE or SE-like SAg
Sudden infant death syndrome	Any SAg
Streptococcal TSS	Any streptococcal SAg
PANDAS	SPE C, L and M
Acute rheumatic fever	SPE C, L and M
Guttate psoriasis	Any SPE, SMEZ or SSA

- For critical ill pt, may also expose to gram –ve organism
  - Endotoxin
- Superantigen act synergistically with endotoxin
  - Further enhance the inflammatory cascade

Host-pathogen interaction

- Colonization v.s. infection
- 1-5% healthy women have colonization of toxin-producing strain of S.aureus
- Interaction between host immune system and pathogen play a major role

Factors predispose to TSS

1. The absence of Ab to superantigens seems to be a major risk factor for development of TSS

Herman A, Kappler JW, Marrack P, Pullen AM.
Superantigens: mechanisms of T-cell stimulation and role in immune responses.
Annu Rev Immunol **1991; 9: 745–72.**

Basma H, Norrby-Teglund A, Guedez Y, et al M.
Risk factors in the pathogenesis of invasive group A streptococcal infections:
role of protective humoral immunity.
Infect Immun **1999; 67: 1871–77**

- 90.5% of patients with menstrual TSS had low or -ve concentration of Ab
- Failed to seroconvert with 2 months after acute illness

Stolz SJ, Davis JP, Vergeront JM, et al.
Development of serum antibody to toxic shock toxin
among individuals with toxic shock syndrome in Wisconsin.
J Infect Dis **1985; 151: 883–89**.

2. Sex-dependent response to sepsis and superantigen shock
   - More female cases in non-menstrual TSS

Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA.
Toxic shock syndrome in the United States: surveillance update, 1979–1996.
Emerg Infect Dis **1999; 5: 807–10**

- More pronounced TNF response to superantigen
- Deficient TNF removal
- Greater degree of TNF-induced hepatic apoptosis

Faulkner L, Altmann DM, Ellmerich S, Huhtaniemi I, Stamp G, Sriskandan S.
Sexual dimorphism in superantigen shock involves elevated TNF-alpha and TNF-alpha induced hepatic apoptosis.
***Am J Respir Crit Care Med* 2007; 176: 473–82**

Clinical features and diagnosis

- Staphylococcus TSS
  - Abruptly with influenza-like prodromal illness
    - Vomiting, diarrhoea
  - Followed by confusion/lethargy
  - Focus of infection
    - Superficial, e.g. burns/surgical wound
  - Desquamation is characteristic
    - Erythematous rash, peeling of skin on recovery (10-21 days after onset)
  - Any 3 of a multi-organ component
  - <5% have positive blood culture

Panel 1: Staphylococcal toxic shock syndrome clinical case definition

1. Fever ≥38·9°C
2. Rash—diffuse macular erythroderma
3. Desquamation—1–2 weeks after onset of illness, especially of palms and soles
4. Hypotension—systolic blood pressure ≤90 mm Hg for adults
5. Multi-system involvement—3 or more of the following:
   - a Gastrointestinal—vomiting or diarrhoea at the onset of illness
   - b Muscular—severe myalgia or elevated creatine phosphokinase
   - c Mucous membranes—vaginal, oropharyngeal, conjunctival hyperaemia
   - d Renal—blood urea nitrogen or creatinine twice-upper limit of normal
   - e Hepatic—total bilirubin twice-upper limit of normal
   - f Haematological—platelets ≤100x10³/L
   - g CNS—disorientation or alterations in consciousness without focal neurological signs
6. Negative results on the following tests:
   - a Blood, throat, or cerebrospinal fluid culture (blood culture may be positive for *S aureus*)
   - b Rise in titre to Rocky Mountain spotted fever, leptospirosis, or measles

Case classification

Probable: case with five of the six clinical findings described

Confirmed: case with all six of the clinical findings described

Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case defi nitions for public health surveillance. ***MMWR Recomm Rep* 1990; 39: 1–43.**

- Methicillin-resistant s-aureus (MRSA)
- HA-MRSA
  - Do not make large amount of SAgs
- CA-MRSA
  - High levels of SAgs
  - Greater ability to cause TSS-like illness

Streptococcal TSS

- Deep-seated invasive soft-tissue infections
  - Necrotizing fascilitis/myositis
- Influenza-like illness at early stage
- Began with trivial injury, e.g. muscle strain
- Most (60%) with positive blood culture
- Mortality much higher than staphy TSS
  - Up to 80% in association with myositis

McCormick JK, Yarwood JM, Schlievert PM.
Toxic shock syndrome and bacterial superantigens: an update.
Annu Rev Microbiol **2001; 55: 77–104**

Panel 2: Streptococcal toxic shock syndrome clinical case definition

1 Isolation of group A β-haemolytic streptococci:
   - a From a normally sterile site—blood, CSF, peritoneal fluid, tissue biopsy
   - b From a non-sterile site—throat, vagina, sputum

2 Clinical signs of severity:
   - a Hypotension—systolic blood pressure ≤90 mm Hg in adults
   - b Two or more of the following signs:
     - i Renal impairment—creatinine >2 mg/dL (>177 μmol/L)
     - ii Coagulopathy—platelets ≤100×10³/L or disseminated intravascular coagulation
     - iii Hepatic involvement—alanine aminotransferase, aspartate aminotransferase, or total bilirubin twice the upper limit of normal
     - iv Adult respiratory distress syndrome
     - v Generalised, erythematous, macular rash that may desquamate
     - vi Soft-tissue necrosis, including necrotising fasciitis, myositis, or gangrene

Case classification

Probable: case fulfils 1b and 2 (a and b) if no other cause for the illness is found

Definite: case fulfils 1a and 2 (a and b)

Working Group on Severe Streptococcal Infections.
Defi ning the group A streptococcal toxic shock syndrome.
Rationale and consensus defi nition.
***JAMA* 1993; 269: 390–91.**

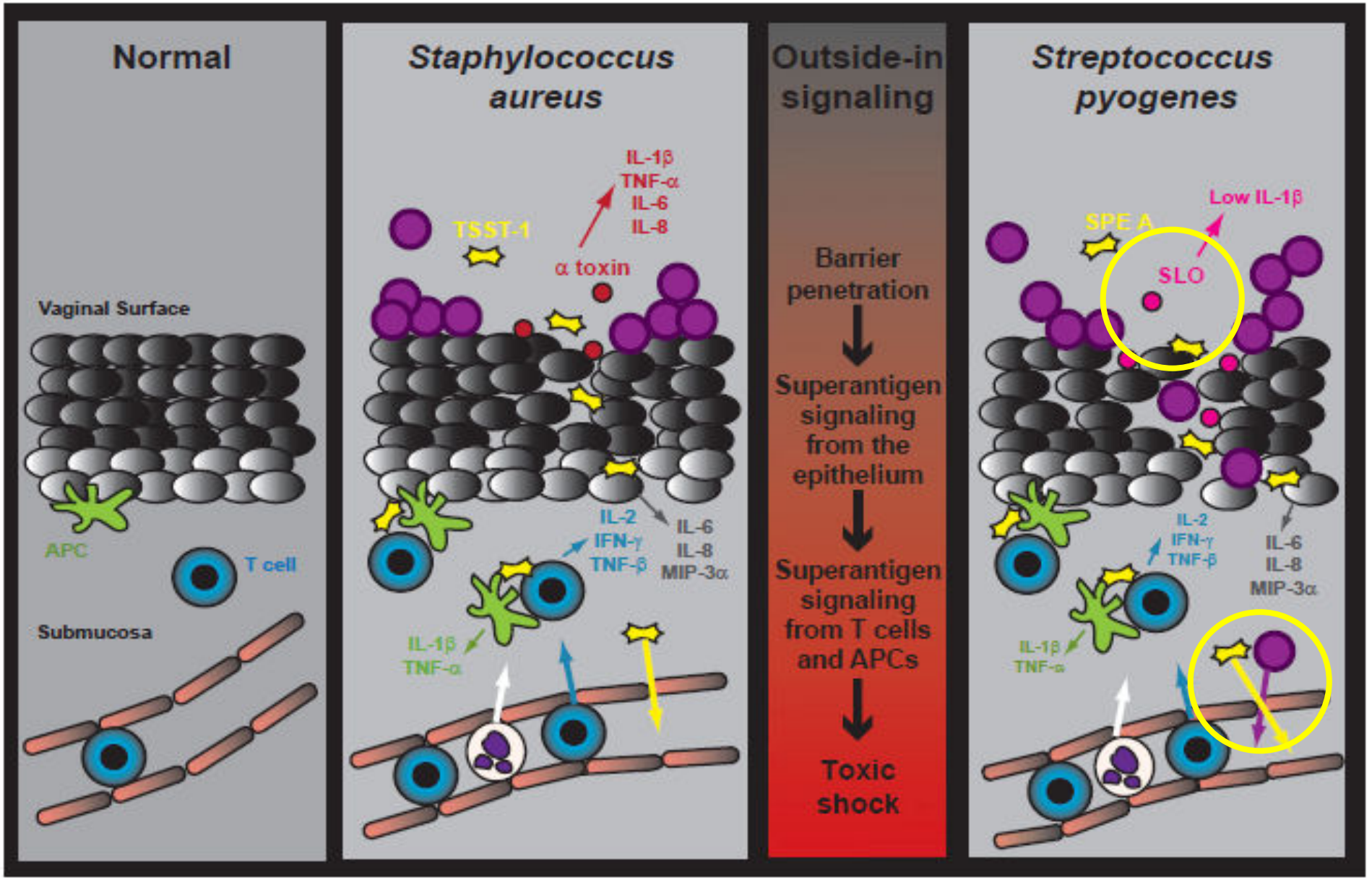
Comparison between staph/strep TSS

Staph. TSS

- Seldom with bloodstream invasion
- Localized on mucosal/body surface
- Skin rash as one of the defining clinical features

Strep. TSS

- more association with bloodstream invasion
- Often with presence of necrotizing fascilitis/myositis
- May lack of the skin rash


Normal
Vaginal Surface
APC
T cell
Submucosa
Staphylococcus aureus
IL-1β
TNF-α
IL-6
IL-8
TSST-1
α toxin
IL-2
IFN-γ
TNF-β
IL-6
IL-8
MIP-3α
IL-1β
TNF-α
Outside-in signaling
Barrier penetration
Superantigen signaling from the epithelium
Superantigen signaling from T cells and APCs
Toxic shock
Streptococcus pyogenes
Low IL-1β
SPE A
SLO
IL-2
IFN-γ
TNF-β
IL-6
IL-8
MIP-3α
IL-1β
TNF-α

New method for early dx for staph. TSS

1. PCR-based detection of staph. Superantigen genes

Granger K, Rundell MS, Pingle MR, et al.

Multiplex PCRligation detection reaction assay for simultaneous detection of drug resistance and toxin genes from Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium

J Clin Microbiol, 2010, 48:277–280

New method for early dx for staph. TSS

2. Anti-TSST-1 Ab assays
   - Antibody deficiency as maker of susceptibility

Javid Khojasteh V, Rogan MT, Edwards-Jones V, et al.

Detection of antibodies to Staphylococcus aureus toxic shock syndrome toxin-1 using a competitive agglutination inhibition assay

Lett Appl Microbiol 2003, 36:372–376

New method for early dx for staph. TSS

3. Flow cytometric analysis of T-cell population
   - massive expansion of a V β 2-positive T-cell subset

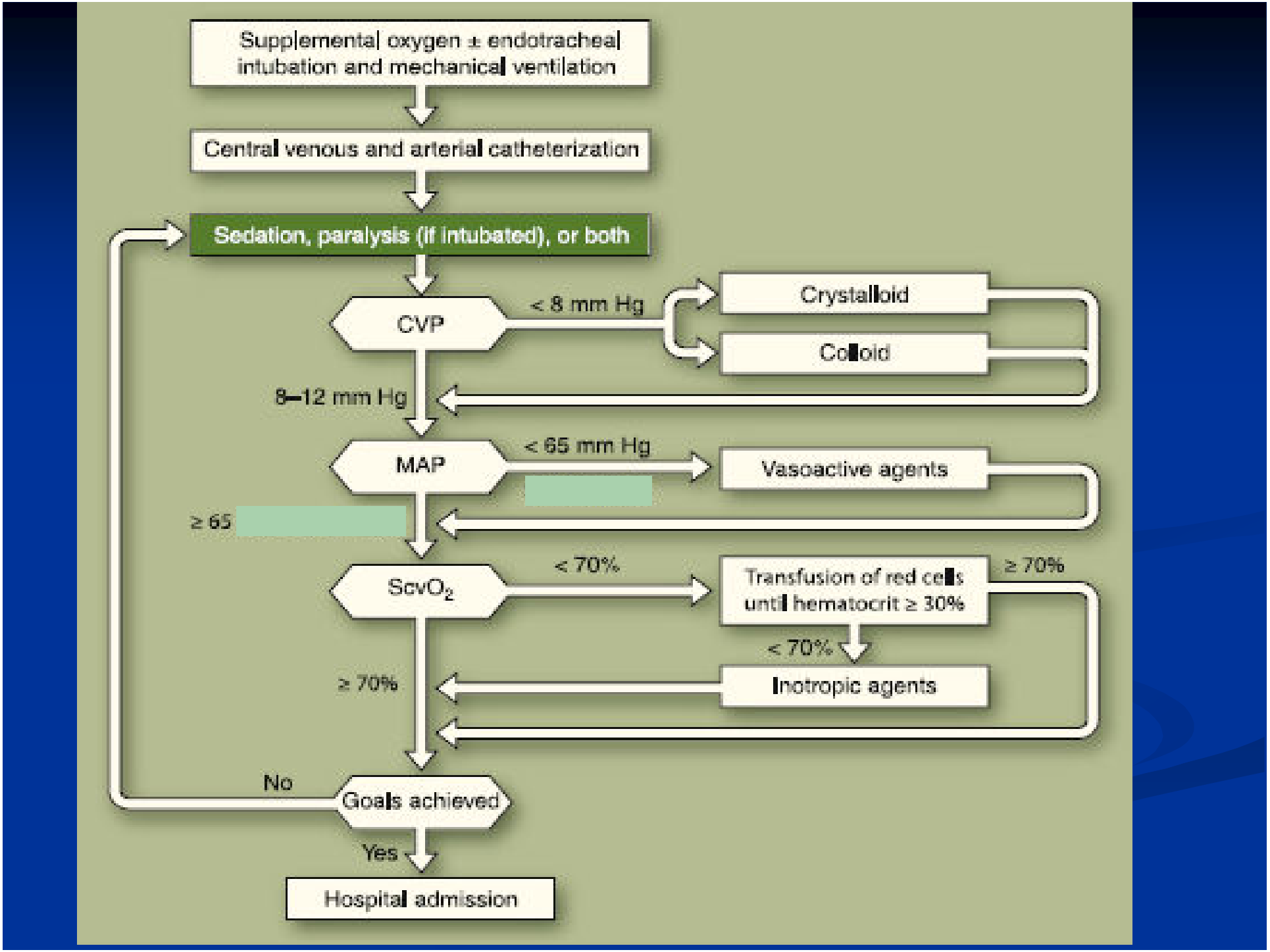
Ferry T, Thomas D, Perpoint T, et al

Analysis of superantigenic toxin Vb T-cell signatures produced during cases of staphylococcal toxic shock syndrome and septic shock

Clin Microbiol Infect, 2008, 14: 546–554

Treatment of TSS

- Required ICU care
  - Aggressive shock management
    - Early goal-directed therapy
    - Ventilatory management if ARDS develops
- Complete sepsis workup
- Removal of foreign bodies, i.e. tampon or nasal packing
- Start IV antibiotics promptly after culture taken
- Surgical debridement in case suspecting necrotizing fascilitis


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
< 8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
< 65 mm Hg
Vasoactive agents
≥ 65
ScvO2
< 70%
Transfusion of red cells until hematocrit ≥ 30%
≥ 70%
< 70%
Inotropic agents
≥ 70%
No
Goals achieved
Yes
Hospital admission

Antibiotics

- Aim to reduce both organism load and toxin production
- Usually include B-lactam agents (e.g. penicillin G)
  - Bactericidal
  - Covering both S. aureus/S. pyogenes
- Iincosamide (e.g. clindamycin)
  - Inhibitory actions on protein synthesis
  - Inhibit toxin production

Table 2 Antimicrobial options in staphylococcal toxic shock syndrome

Organism	Option A	Option B (β-lactam intolerant)	Option C
Methicillin-sensitive *Staphylococcus aureus*	Nafcillin or cloxacillin or flucloxacillin, and clindamycin	Clarithromycin +/− gentamicin, and clindamycin	Linezolid or daptomycin or tigecycline, +/− rifampicin
Methicillin-resistant *S. aureus*	Vancomycin or teicoplanin, and clindamycin	N/A	Linezolid or daptomycin or tigecycline, +/− rifampicin
Glycopeptide-resistant or glycopeptide-intermediate sensitivity *S. aureus*	Linezolid +/− clindamycin, or daptomycin	N/A	Tigecycline

Jonathan A. Silversides & Emma Lappin &, Andrew J. Ferguson
Staphylococcal Toxic Shock Syndrome: Mechanisms and Management
Curr Infect Dis Rep (2010) 12:392–400

	Option 1	Option 2 (β-lactam intolerant)	Option 3	Comments
Group A streptococcus	Penicillin G and clindamycin	Macrolide or fluoroquinolone, and clindamycin	Linezolid or daptomycin or tigecycline	Macrolide and fluoroquinolone resistance increasing
MLS-resistant group A streptococcus	Penicillin G, and vancomycin or teicoplanin	Vancomycin or teicoplanin	Linezolid or daptomycin or tigecycline	Macrolide resistance associated with clindamycin resistance

Emma Lappin, Andrew J Ferguson
Gram-positive toxic shock syndromes
***Lancet Infect Dis* 2009; 9: 286**

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Necrotizing fasciitis [171]				Immediate surgical intervention essential. Urgent consult clinical microbiologist.
1. Following exposure to freshwater; seawater or seafood	*Aeromonas hydrophilia, A. caviae; Vibrio vulnificus*	I.V. fluoroquinolone + I.V. amoxicillin-clavulanate		
2. Following cuts and abrasion; recent chickenpox; IVDU; healthy adults	Group A streptococci	I.V. penicillin G + I.V. linezolid [172]		Add high dose IVIG (1–2 g/kg for 1 dose) for streptococcal toxic shock syndrome [173] [a]. In HK, Group A streptococci : more often resistant to clindamycin (50-80%) [170].
3. Following intra-abdominal; gynaecological or perineal surgery [174]	Polymicrobial: *Enterobacteriaceae*, streptococci, anaerobes	I.V. imipenem or meropenem	I.V. amoxicillin-clavulanate + levofloxacin	

IMPACT Guideline
Hong Kong
Fourth Edition 2012

Intravenous Immunoglobulin (IVIG)

- Pt with deficient Ab response at risk of primary and recurrent TSS
- Pt with invasive GAS infection with lower concentration of superantigen-neutralizing Ab

Basma H, Norrby-Teglund A, Guedez Y, et al M. Risk factors in the pathogenesis of invasive group A streptococcal infections: role of protective humoral immunity. *Infect Immun* 1999; **67:** 1871–77

Mechanism of IVIG

- Commercially available IVIG with antibodies capable of neutralizing the toxins (superantigens)
- Suppressive effect of whole IVIG on T-cell proliferation/cytokine production

Kato K, Sakamoto T, Ito K.
Gamma-globulin inhibits superantigen-induced lymphocyte proliferation and cytokine production
Allergol Int 2007; **56:** 439–44

IVIG use in staphylococcus TSS

- Little data exist/no case-control studies to determine the effectiveness
- Some anecdotal examples showing its effectiveness
  - Esp in community/hospital-associated MRSA
    - Higher level of superantigens

IVIG in Streptococcal TSS

Lamothe F, D'Amico P, Ghosn P, Tremblay C, Braidy J, Patenaude JV.
Clinical usefulness of intravenous human immunoglobulins in invasive group A streptococcal infections:case report and review.
***Clin Infect Dis* 1995; 21: 1469**

Perez CM, Kubak BM, Cryer HG, Salehmugodam S, Vespa P, Farmer D.
Adjunctive treatment of streptococcal toxic shock syndrome using intravenous immunoglobulin: case report and review.
***Am J Med* 1997; 102: 111–13.**

- Case reports published in 1990s suggested improved outcomes using IVIG in streptococcal TSS

Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome a comparative observational study

Kaul R, McGeer A, Norrby-Teglund A, et al.

Clin Infect Dis 1999; 28: 800–07

- Comparative observational study
- 21 STSS patients given IVIG v.s. 32 control cases
- No different in duration of ventilation or hospital stay
- Higher 30-day survival in IVIG group
  - 67% v.s. 34%

Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: A European randomized, double-blind, placebo-controlled trial

Darenberg J, Ihendyane N, Sjolin J, et al.

Clin Infect Dis 2003; 37: 333–40.

- Randomized, placebo-controrlled trial
- 21 patients enrolled
  - 10 received IVIG (1g/kg at day 1, 0.5g/kg at day 2,3)
  - 11 received placebo (1% albumin)
- Primary endpoint was 28-day mortality
  - 3.6 times higher in placebo (36% v.s. 10%)
    - Statistically significance not reached
  - Greater improvement in sepsis-related organ failure (SOFA score) at day 2 (P=0.02) and 3 (P=0.03)

- Current UK department of Health IVIG in infectious diseases recommends:
  - *IVIG may be added to adequate toxin-neutralising antimibrobials, source control and sepsis management when these approaches have failed to elicit a response*
  - *May be use for TSS resulting from an infection refractory to several hrs of aggressive therapy, in presence of undrainable focus or persistent oliguria with pul edema*

IVIg Guideline Development Group of the IVIg expert Working Group. Clinical Guidelines for Immunoglobulin Use. Department of Health Clinical guidelines for Immunoglobulin use, United Kingdom (DHUK), 2nd ed. May 30;2008

Table 1: United Kingdom department of health guidelines for immunoglobulin use in infectious diseases[5]

Condition	Short term	Long term	Recommendation/evidence grade	Alternatives
Severe invasive GAS	Selected	No	B, Ib	APC, antibiotics
Staphylococcal toxic shock	Selected	No	C, III	Antibiotics
Necrotizing (PVL-associated staph. sepsis)	Selected	No	C, III	APC, antibiotics
Severe or recurrent clostridium difficile colitis	Selected	No	C, III	Antibiotics, colectomy

GAS = Group A streptococcus; APC = Activated protein C

Streptococcal Toxic-Shock Syndrome (STSS), 2010 Case Definition.
CSTE Position Statement Number: 09-ID-60.
Centers for Disease Control and Prevention

Conclusion

1. TSS is uncommon but can be a life threatening condition
2. Clinical diagnostic difficulty
   - There is often no definite infective foci identified
   - high index of clinical suspicion
3. Severe complication can occur in a well looking wound
   - Reassessment is important
4. Treatment
   - Intensive care for haemodynamic/organ support
   - Early surgical intervention
   - Choice of antibiotics
5. IVIG
   - No strong evidence of its effectiveness
   - Positive result from previous case studies
6. Future development
   - New technology aim for early diagnosis