

Toxic shock syndrome (TSS)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	<ul style="list-style-type: none">• Streptococcal TSS• Staphylococcal TSS
Indication for IVIg Use	<ul style="list-style-type: none">• Early use in streptococcal TSS in conjunction with surgical intervention, antibiotic therapy and supportive measures.• Staphylococcal TSS, where rapid improvement is not obtained with fluid resuscitation and inotropes in conjunction with surgical intervention, antibiotic therapy and supportive measures.
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	<p>TSS is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by <i>Staphylococcus aureus</i> (rarely isolated) or <i>Streptococcus pyogenes</i> that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale, resulting in a massive release of inflammatory cytokines.</p> <p>Streptococcal TSS is defined by:</p> <p>I. Group A streptococci (<i>Streptococcus pyogenes</i>) isolated from:</p> <ul style="list-style-type: none">• (IA) a normally sterile site (e.g. blood, cerebrospinal fluid, pleural or peritoneal fluid, tissue biopsy, surgical wound)• (1B) a non-sterile site (e.g. throat, sputum, vagina, superficial skin lesion). <p>IIA. Hypotension: systolic blood pressure = 90 mmHg in adults or 5th percentile for age in children; and</p> <p>IIB. Two or more of the following:</p> <ol style="list-style-type: none">1. Renal impairment: serum creatinine for adults at least twice the upper limit of normal for age; in patients with existing renal disease, elevation over baseline by a factor of at least two2. Coagulopathy: platelet count $\leq 100 \times 10^9/L$ or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level and the presence of fibrin degradation products3. Liver involvement: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level at least twice the upper limit of normal for age; in patients with existing liver disease, elevation over baseline by a factor of two4. Adult respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxaemia in the absence of cardiac failure; or evidence of diffuse capillary leak manifested by acute onset or generalised oedema; or pleural or peritoneal effusions with hypoalbuminaemia5. Generalised erythematous macular rash that may desquamate6. Soft tissue necrosis, including necrotising fasciitis or myositis; or gangrene. <p>A <i>definite</i> case is an illness fulfilling criteria IA and II (A and B). A <i>probable</i> case is an illness fulfilling criteria IB and II (A and B) where no other aetiology is identified.</p>

(Working Group on Severe Streptococcal Infections 1993).

Staphylococcal TSS is defined by:

1. Fever: temperature $\geq 38.9^{\circ}\text{C}$
2. Hypotension: systolic blood pressure ≤ 90 mmHg or in the 5th percentile for age in children
3. Diffuse macular rash with subsequent desquamation one or two weeks after onset (including palms and soles)
4. Multisystem involvement (three or more of the following):
 - Hepatic: bilirubin or aminotransferase ≥ 2 times normal
 - Haematologic: platelet count $\leq 100 \times 10^9/\text{L}$
 - Renal: blood urea nitrogen or serum creatinine level ≥ 2 times normal
 - Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia
 - Gastrointestinal: vomiting or diarrhoea at illness onset
 - Muscular: severe myalgia or serum creatinine phosphokinase level ≥ 2 times upper limit
 - Central nervous system: disorientation or alteration in consciousness without focal neurological signs and in the absence of fever or hypotension.

A *confirmed* case is one with all the manifestations described above. However, in severe cases, death may occur before desquamation develops.

A *probable* case is an illness with all but one of the manifestations above (Wharton et al 1990).

Prognosis

Streptococcal TSS has a mortality of 30–80% in adults and 5–10% children, with most deaths secondary to shock and respiratory failure.

Staphylococcal TSS can also be fatal, but mostly has a better prognosis.

Justification for Evidence Category

Streptococcal TSS: A small case series (Norrby-Teglund et al 2005), a cohort study (Kaul et al 1999), and a randomised controlled trial (RCT) that was terminated prematurely (Darenberg et al 2003) suggested that intravenous immunoglobulin (IVIg) improves outcomes.

Staphylococcal TSS: In vitro and animal studies suggested that IVIg is effective in neutralising staphylococcal superantigens. Anecdotal reports refer to the clinical effectiveness of IVIg in staphylococcal TSS.

Qualifying Criteria for IVIg Therapy

Early use in streptococcal TSS in conjunction with surgical intervention, antibiotic therapy and supportive measures.

- Probable or confirmed diagnosis of streptococcal TSS.

AND

- Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.

Staphylococcal TSS, where rapid improvement is not obtained with fluid resuscitation and inotropes in conjunction with surgical intervention, antibiotic therapy and supportive measures.

- Probable or confirmed diagnosis of staphylococcal TSS.

AND

- Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.

Review Criteria for Assessing the Effectiveness of IVIg Use

Early use in streptococcal TSS in conjunction with surgical intervention, antibiotic therapy and supportive measures.

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.

Clinical effectiveness of Ig therapy may be demonstrated by:

- One month survival.

Staphylococcal TSS, where rapid improvement is not obtained with fluid resuscitation and inotropes in conjunction with surgical intervention, antibiotic therapy and supportive measures.

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.

Clinical effectiveness of Ig therapy may be demonstrated by:

- One month survival.

Dose

Early use in streptococcal TSS in conjunction with surgical intervention, antibiotic therapy and supportive measures.

- **Dose** - 2 g/kg as a single dose.

There have been reported differences between various preparations of IVIg and their ability to neutralise streptococcal superantigens that may relate to geographical regions from which the plasma was collected, which may reflect differences in Group A streptococcal exposure (Schrage et al 2006). The clinical significance of these findings is not yet known.

Darenburg et al (2004) suggested that higher doses of IVIg might be required for staphylococcal TSS than for streptococcal TSS, based on in vitro neutralisation of superantigens.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Dosing above 1 g/kg per day is contraindicated for some IVIg products.

Refer to the current product information sheet for further information.

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