Toxic shock syndrome (TSS)

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• Streptococcal TSS • Staphylococcal TSS
Indication for IVIg Use	• Early use in streptococcal TSS • Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Toxic shock syndrome (TSS) is an acute multi-system, toxin mediated illness typically resulting in shock and multi organ failure early in its clinical course. Particular toxins produced by S aureus and group A *streptococcus* (GAS) can act as 'superantigens' that bypass the normal antigen presenting processes of the immune system and instead bind directly to T cell antigen receptors, resulting in polyclonal T-cell stimulation and massive cytokine release. Key clinical features of TSS are hypotension often accompanied by fever or rash with rapid progression to shock and multi organ failure. Early recognition (and thus assessment for these criteria) followed by appropriate surgical intervention, antibiotics (including anti toxin agents such as clindamycin) and consideration of IVIg, are a corner stone of management. **Streptococcal TSS** is defined by: I. Group A streptococci (*S. pyogenes*) isolated from: • (IA) a normally sterile site (e.g. blood cerebrospinal fluid, pleural or peritoneal fluid, tissue biopsy, surgical wound); or • (1B) a non sterile site (e.g. throat, sputum, vagina, superficial skin lesion). IIA. Hypotension: systolic blood pressure $\leq$ 90 mmHg in adults or 5th percentile for age in children; and IIB. Two or more of the following: 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 two; 2. Coagulopathy: platelet count ≤100 x 10^{9}/L or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level and the presence of fibrin degradation products; 3. Liver involvement: alanine aminotransferase, 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 two; 4. 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 hypoalbuminaemia; 5. Generalised erythematous macular rash that may desquamate; 6. Soft tissue necrosis, including necrotising fasciitis or myositis; or gangrene. A *definite* case is an illness fulfilling criteria IA and II (A and B). A *probable* case is an illness fulfilling criteria IB and II (A and B) where no other aetiology is identified.

	(Working Group on Severe Streptococcal Infections 1993).
	
	Staphylococcal TSS (issued by the United States Centers for Disease Control and Prevention) is defined by:
	
	1. Fever: temperature ≥38.9°C
	2. Hypotension: systolic blood pressure ≤90 mmHg for adults or less than fifth percentile by age for children less than16 years of age
	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 ≤100 x 10^9/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 percent in adults and 5–10 percent 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	Intravenous immunoglobulin (IVIg) has been reported to facilitate bacterial opsonisation, neutralise super antigens and toxins, stimulate leukocytes and exert a generalised anti-inflammatory effect through its effects on Fc receptor expression, complement, cytokines and B and T cells. There are a number of clinical studies supporting the use of IVIg, particularly for streptococcal TSS and less so for staphylococcal TSS. Observational cohort studies of patients treated with IVIg suggested increased the 30-day survival rates compared to untreated controls (Kaul et al, 1999 and Linner et al, 2014). In the absence of randomised controlled clinical trials, particularly in specific patient cohorts such as children, it is difficult to reliably quantify the benefit of IVIg therapy. However, given the severity of disease that can result from TSS and the relatively good safety profile of IVIg, coupled with the evidence suggesting potential benefit of IVIg, it is regarded as adjunctive therapy in cases of TSS.
Diagnosis Requirements	A diagnosis must be made by a General Medicine Physician, Intensivist or an Infectious Diseases Specialist.
Qualifying Criteria for IVIg Therapy	Early use in streptococcal TSS • Probable or confirmed diagnosis of streptococcal TSS AND • Supportive measures are planned to be used in conjunction with Ig therapy

	Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures • Probable or confirmed diagnosis of staphylococcal TSS AND • Failure to achieve rapid improvement with fluid resuscitation, inotropes, antibiotic therapy and other supportive measures
Review Criteria for Assessing the Effectiveness of IVIg Use	Early use in streptococcal TSS **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Patient survival Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Patient survival
Dose	Early use in streptococcal TSS • **Induction Dose** - 2 g/kg as a single dose. Refer to the current product information sheet for further information on dose, administration and contraindications. Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures • **Induction Dose** - 2 g/kg as a single dose. Refer to the current product information sheet for further information on dose, administration and contraindications.

Bibliography

Carapetis, JR, Jacoby, P, Carville, K, et al 2014, 'Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive Group A streptococcal infections', *Clinical Infectious Diseases*, vol. 59, pp. 358–65. http://cid.oxfordjournals.org/content/early/2014/04/29/cid.ciu304

Darenberg, J, Ihendyane, N, Sjolin, J, et al 2003, 'Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized double-blind placebo- controlled trial', *Clinical Infectious Diseases*, vol. 37, no. 3, pp.

333–40. https://www.ncbi.nlm.nih.gov/pubmed/12884156

Kaul, R, McGeer, A, Norrby-Teglund, A, et al 1999, 'Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study', The Canadian Streptococcal Study Group, *Clinical Infectious Diseases,* vol. 28, no. 4, pp. 800–7. https://www.ncbi.nlm.nih.gov/pubmed/10825042

Lappin, E & Ferguson, AJ 2009, 'Gram-positive toxic shock syndromes', *Lancet Infectious Diseases*, vol. 9, no. 5, pp. 281–90. https://www.ncbi.nlm.nih.gov/pubmed/19393958

Linner, A, Darenberg, J, Sjolin, J, et al 2014, 'Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study', *Clinical Infectious Diseases*, vol. 59, no.6, pp. 851–7. https://www.ncbi.nlm.nih.gov/pubmed/24928291

Shah, SS, Hall, M, Srivastava, R, et al 2009, 'Intravenous immunoglobulin in children with streptococcal toxic shock syndrome', *Clinical Infectious Diseases*, vol. 49, no. 9, pp. 1369–76. https://www.ncbi.nlm.nih.gov/pubmed/19788359

Waddington, CS, Snelling & TL, Carapetis, JR 2014, 'Management of invasive group A streptococcal infections*', Journal of Infection*, vol. 69, Suppl 1, pp. S63–9. https://www.ncbi.nlm.nih.gov/pubmed/25307276

Wharton, M, Chorba, TL, Vogt, RL, et al 1990, 'Case definitions for public health surveillance', *Morbidity Mortality Weekly Report*, vol. 39, no. RR-13, pp. 1-43. https://www.cdc.gov/mmwr/preview/mmwrhtml/00025629.htm

Working Group on Severe Streptococcal Infections, 1993, 'Defining the Group A streptococcal toxic shock syndrome: rationale and consensus definition', *Journal of the American Medical Association*, vol. 269, no. 3, pp. 390–1. https://www.ncbi.nlm.nih.gov/pubmed/8418347

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