Specialist Working Group for Immunology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA (INCLUDING ADAPTATION TO THE IG SYSTEM)	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Toxic shock syndrome (TSS)**	**Toxic shock syndrome (TSS)**	
Specialty	Immunology	Intensive care ; Immunology; Infectious diseases	Relevant treating specialists have been included.
Chapter	6	6	
Specific Conditions		Streptococcal TSS Staphylococcal TSS	
Level of Evidence	Small case studies only; insufficient data (Category 4a).	Small case studies only; insufficient data (Category 4a).	
Justification for Evidence Category	**Streptococcal TSS:** A small case series (Norrby-Teglund et al 2005), a cohort study (Kaul et al 1999) and an RCT, which was terminated prematurely (Darenberg et al 2003), suggested that 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.	**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.	Unchanged

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Description and Diagnostic Criteria	TSS is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by Staphylococcus aureus (rarely isolated) or Streptococcus pyogenes that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale resulting in a massive release of inflammatory cytokines. **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 • (IB) a non-sterile site (e.g. throat, sputum, vagina, superficial skin lesion). IIA. Hypotension: systolic blood pressure = 90 mmHg in adults or in the 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	TSS is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by *Staphylococcus aureus* (rarely isolated) or *Streptococcus pyogenes* that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale, resulting in a massive release of inflammatory cytokines. **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 = 90 mmHg in adults or 5^{th} 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	Unchanged

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	a factor of at least 2; 2. Coagulopathy: platelet count of ≤100x10^9/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 (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 2; 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	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** is defined by : 1. Fever: temperature ≥38.9◦C 2. Hypotension: systolic blood pressure	

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	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** is defined by: 1. Fever: temperature ≥38.9°C; 2. Hypotension: systolic blood pressure ≤90 mmHg in adults or in the 5th percentile for age in children; 3. Diffuse macular rash with subsequent desquamation one to two weeks after onset (including palms and soles); 4. Multisystem involvement (three or more of the following): 1. Hepatic: bilirubin or aminotransferase ≥2 times normal; 2. Haematologic: platelet count ≤100x10^9/L; 3. Renal: blood urea nitrogen or serum	≤90 mmHg 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): a. Hepatic: bilirubin or aminotransferase ≥2 times normal b. Haematologic: platelet count ≤100 x 10^9/L c. Renal: blood urea nitrogen or serum creatinine level ≥2 times normal d. Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia e. Gastrointestinal: vomiting or diarrhoea at illness onset f. Muscular: severe myalgia or serum creatinine phosphokinase level ≥2 times upper limit g. 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	

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	creatinine level ≥2 times normal; 4. Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia; 5. Gastrointestinal: vomiting or diarrhoea at onset of illness; 6. Muscular: severe myalgia or serum creatine phosphokinase level ≥2 times upper limit; 7. Central nervous system: disorientation or alteration in consciousness without focal neurological signs and in the absence of fever or hypotension. A *confirmed* case is a case with all of the manifestations described above. However, in severe cases death may occur before desquamation develops. A *probable* case is an illness with all but any one of the manifestations described above (Wharton et al 1990). **Prognosis** Streptococcal TSS has a mortality rate of 30–80% in adults and 5–10% in children, with most deaths secondary to shock and respiratory	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.	

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	failure. Staphylococcal TSS can also be fatal but mostly has a better prognosis.		
Diagnosis is required	Which Speciality	Yes — Which Speciality: General Physician/ Intensive Care Physician /Infectious Diseases Physician	
Diagnosis must be verified	Which Specialty	Which Specialty	
Exclusion Criteria			
Indication for use	**Streptococcal TSS:** In view of the high mortality risk, IVIg is indicated for early use in both adults and children. **Staphylococcal TSS:** IVIg is indicated where rapid improvement is not obtained with fluid resuscitation and inotropes. In both conditions IVIg is used in addition to surgical intervention, antibiotic therapy and supportive measures.	**Early use in streptococcal TSS.** **Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes surgery, antibiotic therapy and other supportive measures.**	
Qualifying Criteria	1. Diagnosis of streptococcal or staphylococcal TSS in accordance with	**Early use in streptococcal TSS.** • Probable or confirmed diagnosis of	Qualifying criteria have been defined in line with existing criteria - requiring confirmed or

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	criteria listed above, preferably with isolation of organism; AND 2. Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.	streptococcal TSS. AND • Failure to achieve rapid improvement with supportive measures. **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 supportive measures.	suspected diagnosis and failure to achieve rapid improvement with supportive measures.
Review Criteria	N/A	**Early use in streptococcal TSS.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. **Outcome data to be measured** • One month survival • Documented clinical response to Ig therapy. **Staphylococcal TSS where rapid improvement is not obtained with fluid resuscitation, inotropes surgery, antibiotic therapy and other supportive**	Given that TSS requires one-off treatment, there is no review with automatic patient outcome data collection. Outcome measures have been developed including: • One month survival a) Patient alive, and recovered b) Patient still in ICU c) Patient rehabilitating d) Patient deceased

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		measures. Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. **Outcome data to be measured** • One month survival • Documented clinical response to Ig therapy.	
Dose	2 g/kg as a single dose. Schrage et al (2006) reported differences between various preparations of IVIg and their ability to neutralise streptococcal superantigens. They commented that 'the variations between IVIg preparations from different manufacturers are most likely caused by the different geographical regions from which the plasma samples were collected and might reflect differences in ... group A streptococcal ... exposure.' The clinical	**Induction 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	Dosing unchanged - minor revision to script**.**

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	significance of these findings is not yet known. Darenberg et al (2004) suggested that higher doses of IVIg might be required for staphylococcal TSS than streptococcal TSS, based on in vitro neutralisation of superantigens. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	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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