### 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** |
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| **Condition Name** | | **Kawasaki disease (mucocutaneous lymph node syndrome)** | **Kawasaki disease (mucocutaneous lymph node syndrome)** | | |  |
| **Specialty** | |  | Immunology | | |  |
| **Chapter** | | 5 | 5 | | |  |
| **Specific Conditions** | |  |  | | |  |
| **Level of Evidence** | | Clear evidence of benefit ([Category 1](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-1)). | Clear evidence of benefit ([Category 1](http://www.blood.gov.au/pubs/ivig/development-and-maintenance-of-the-criteria.html#el-1)). | | |  |
| **Justification for Evidence Category** | | One high-quality systematic review of 16 RCTs that showed that IVIg is of benefit in treating Kawasaki disease (Biotext 2004). | One high-quality systematic review of 16 randomised controlled trials (RCTs) that showed that IVIg is of benefit in treating Kawasaki disease (Biotext 2004). | | | Unchanged |
| **Description and Diagnostic Criteria** | | Kawasaki disease is an acute, febrile, multi-system disease of children and young infants often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage.  The cause of the condition is unknown but there is evidence that the characteristic vasculitis results from an immune reaction characterised by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals, one or more uncharacterised common infectious agents, possibly with super-antigen activity, may trigger the disease.  **Diagnosis**  A diagnosis of Kawasaki disease is generally made if fever of four or more days’ duration is associated with at least four of the following changes, which often appear sequentially:   * bilateral (non-purulent) conjunctival injection; * changes of the mucous membranes of the upper respiratory tract and oropharynx, including diffuse redness of pharyngeal mucosa, dry fissured lips, red fissured lips, and/or ‘strawberry tongue’; * changes of the extremities, including peripheral erythema, peripheral oedema, and subsequent periungual or more generalised desquamation; * polymorphous rash; * cervical lymphadenopathy.   A diagnosis of Kawasaki disease may be made if fever and fewer than four of the changes listed above are present where there is strong clinical suspicion of Kawasaki disease (refer to Newburger 2004). Between 10% and 20% of cases, particularly in younger infants, present with fever and fewer than four of the listed criteria. Expert advice should be sought.  Data support the use of IVIg while there is ongoing inflammation (usually taken as ongoing fever or raised acute inflammatory markers). Prognosis is worse if IVIg is used 10 days post-onset, but should be used at any time if there is evidence of inflammation. Up to 15% of patients do not respond to initial IVIg therapy. Consensus is for re-treatment with 2 g/kg of IVIg before considering steroids. | Kawasaki disease is an acute, febrile, multi-system disease of children and young infants, often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage.  The cause of the condition is unknown, but there is evidence that the characteristic vasculitis results from an immune reaction characterised by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals, one or more uncharacterised common infectious agents, possibly with super-antigen activity, may trigger the disease.  **Diagnosis**  A diagnosis of Kawasaki disease is generally made if fever of four or more days’ duration is associated with at least four of the following changes, which often appear sequentially, or three if coronary abnormalities are evident on echocardiogram:   * bilateral (non-purulent) conjunctival injection * changes of the mucous membranes of the upper respiratory tract and oropharynx, including diffuse redness of pharyngeal mucosa, dry fissured lips, red fissured lips, and/or ‘strawberry tongue’ * changes of the extremities, including peripheral erythema, peripheral oedema, and subsequent periungual or more generalised desquamation * polymorphous rash * cervical lymphadenopathy.   A diagnosis of Kawasaki disease may be made if fever and fewer than four of the changes listed above are present where there is strong clinical suspicion of Kawasaki disease (refer to Newburger 2004). Between 10% and 20% of cases, particularly in younger infants, present with fever and fewer than four of the listed criteria. Expert advice should be sought.  Data support the use of intravenous immunoglobulin (IVIg) while there is ongoing inflammation (usually taken as ongoing fever or raised acute inflammatory markers). Prognosis is worse if IVIg is used 10 days post-onset, but should be used at any time if there is evidence of inflammation. Up to 15% of patients do not respond to initial IVIg therapy. Consensus is for re-treatment with 2 g/kg of IVIg before considering steroids. | | | Updated to address revised diagnostic criteria when there is cardiac involvement. (A) |
| **Diagnosis is required** | | Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist. | Yes | Which Speciality | General paediatrician or immunologist or rheumatologist | Rheumatologist added as can be the treating specialist (A) |
| **Diagnosis must be verified** | |  | No | Which Specialty |  |  |
| **Exclusion Criteria** | |  |  | | |  |
| **Indications** | | Early Kawasaki Disease to prevent coronary artery pathology | **Early Kawasaki disease to prevent coronary artery pathology.**  **Continued inflammation more than 36 hours after the initial dose of Ig therapy in early Kawasaki disease.** | | | Second indication added to provide controlled access to a second dose. (A) |
| **Qualifying Criteria** | | Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist. | **Early Kawasaki disease to prevent coronary artery pathology.**   * A clinical diagnosis of Kawasaki disease has been made.   Therapy should be initiated within 10 days of fever onset if possible; however, children who present after 10 days of fever still should be treated if fever or other signs of persistent inflammation are present.  **Continued inflammation more than 36 hours after the initial Ig dose in early Kawasaki disease.**   * A clinical diagnosis of Kawasaki disease has been made and treated with an initial dose of Ig therapy   AND   * There is evidence of ongoing inflammation at least 36 hours after the initial dose of Ig therapy, with persistent fever and/or ongoing elevated inflammatory markers. | | | Qualifying criteria have been defined including evidence items for second dose. (A)  Script added to educate prescribers and ensure patients are treated early, however, when late presentation, treatment should be given where fever or other signs of inflammation have persisted. (A) |
| **Review Criteria** |  | Review is not mandated for this condition. | | | No useful outcome data was seen to be of value given that the condition already has level 1 evidence. |
| **Dose** | 2 g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only.  Re-treatment with 2 g/kg in a single dose may be given when there is ongoing inflammation.  **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.** | **Induction** - 2 g/kg in a single dose over 10–12 hours.  **Induction dose with impaired cardiac function –** 2 g/kg in a divided dose.  Dose Postscript  Given over 10–12 hours, unless impaired cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only.  Re-treatment with 2 g/kg in a single dose may be given when there is ongoing inflammation.  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.** | | | Dosing unchanged but reformatted with slight rewording regarding cardiac impairment (A) |

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| **BIBLIOGRAPHY** |
| Biotext 2004, ‘Summary data on conditions and papers’, in *A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks*, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 255–6. Available from: www.nba.gov.au/pubs.htm [cited 7 Dec 2007]  Burns, JC & Glode, MP 2004, ‘Kawasaki syndrome’, *Lancet*, vol. 364, no. 9433, pp. 533–44.  De Zorzi, A, Colan, SD, Gauvreau, K, et al 1998, ‘Coronary artery dimensions may be misclassified as normal in Kawasaki disease’, *Journal of Pediatrics*, vol. 133, no. 2, pp. 254–8.  Durongpisitkul, K, Soongswang, J, Laohaprasitiporn, D, et al 2003, ‘Immunoglobulin failure and retreatment in Kawasaki disease’, *Paediatric Cardiology*, vol. 24, no. 2, pp. 145–8.  Feigin, RD, Cecchin, F & Wissman, SD 2006, ‘Kawasaki disease’, in JA McMillan (ed.), *Oski’s paediatrics: principles and practice*, 4th edn, Lippincott Williams & Wilkins, Philadelphia, pp. 1015–20.  Newburger, JW, Takahashi, M, Gerber, MA, et al 2004, ‘Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association’, *Paediatrics*, vol. 114, no. 6, pp. 1708–33.  Oates-Whitehead, RM, Baumer, JH, Haines, L, et al 2003, ‘Intravenous immunoglobulin for the treatment of Kawasaki disease in children (Cochrane Review)’, in *The Cochrane Library*, Issue 4, John Wiley & Sons, Ltd, Chichester, UK.  Rosenfeld, EA, Shulman, ST, Corydon, KE, et al 1995, ‘Comparative safety and efficacy of two immune globulin products in Kawasaki disease’, *Journal of Paediatrics*, vol. 126, no. 6, pp. 1000–3.  Stiehm, ER 2006, ‘Lessons from Kawasaki disease: all brands of IVIg are not equal’, *Journal of Paediatrics*, vol. 148, pp. 6–8.  Tsai, MH, Huang, YC, Yen, MH, et al 2006, ‘Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin’, *Journal of Paediatrics*, vol. 148, no. 1, pp. 38–43.  Wang, CL, Wu, YT, Liu, CA, et al 2005, ‘Kawasaki disease: infection, immunity and genetics’, *The Pediatric Infectious Disease Journal*, vol. 24, no. 11, pp. 998–1004. |
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