

2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia

| v2.1 CONDITION NAME: Haemolytic transfusion reaction | |
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| v3.0 CONDITION NAME: Haemolytic transfusion reaction not associated with identifiable red cell antibodies | |
| <p>PROPOSED APPROACH:</p> <p>Retain Haemolytic transfusion reaction (not associated with identifiable red cell antibodies) as a condition for which Ig should be used in <i>Exceptional circumstances only</i></p> | <p>SUMMARY OF RATIONALE:</p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> - Insufficient evidence was found to support Ig therapy in the context of a haemolytic transfusion reaction with alloimmune red cell antibodies. - There is a growing awareness of a rare complication of hyper-haemolysis arising as a result of red cell transfusion where no red cell antibodies can be identified, with increased reports over recent years, including in Australia (Stokes et al, 2010). In the UK, hyperhaemolysis has been reportable to Serious Hazards Of Transfusion (SHOT) since 2012. It is listed under 'Autoimmune haemolytic anaemia including post transfusion hyper-haemolysis' (medium priority in times of shortage but recommended for use) in the UK NHS immunoglobulin Guidelines (UK Department of Health, 2011). - While very rare, this is a potentially fatal condition and Ig therapy in combination with steroids is regarded as life-saving. - The name has been amended to better reflect when Ig therapy will derive demonstrable clinical benefit, and a further condition, 'Alloimmune haemolysis' added to <i>Condition for which Ig use is not supported</i>, indicating when Ig treatment is inappropriate. - Characteristically the condition is reported in children with Sickle cell disease and for this reason, it is recommended that 'Sickle cell disease' be removed from the category 'Conditions not supported for funding', as it may cause confusion because Ig treatment would be appropriate in the setting of a hyper-haemolysis syndrome (with no identifiable red cell antibodies) in a transfused patient with Sickle cell disease. - Ig use has been very low with fewer than five patients being treated nationally over the last five years. However, given that it is increasingly reported in the literature, and Sickle cell disease is more commonly seen in Australia, the SWG recommends access to Ig treatment be retained given that appropriate qualifying criteria are now proposed and Ig would be life-saving in combination with steroid therapy in this context. - The Canadian IVIg Utilisation Management Guidelines (indications recommended for government funding) include Hemolytic transfusion reaction in sickle cell disease (Ontario Regional Blood Coordinating Network, 2016). |

v2.1 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)

v3.0 CONDITION CATEGORY: Condition for which Ig use is in exceptional circumstances only (Chapter 7)

Role of Ig therapy: This condition is exceedingly rare but potentially fatal and increasingly recognised in the literature, including reports in Australia (Stokes et al, 2010). It constitutes a hyper-haemolysis syndrome - essentially an unusual delayed transfusion reaction associated with red cell transfusions but no red cell antibodies are identifiable. Haemolysis of both donor and recipient red cells occurs and the haemoglobin invariably drops to pre-transfusion levels. The pathogenesis is poorly understood and recommended treatment includes the avoidance of further transfusion where possible and immune modulation with high dose steroids in combination with Ig therapy. Although it is characteristically seen in sickle cell disease (Stokes et al, 2010 and Talano et al, 2003) in childhood, there have been reports in thalassaemia, myelofibrosis and lymphoma (Win et al, 2005).

The Specialist Working Group recommendation to exclude alloimmune delayed HTR from access to Ig therapy is following a detailed review of the literature. There have only been six cases ever reported in the literature across two publications. Four of the six cases had autoantibodies accounting for the incompatibility. In the remaining two reported cases where only alloantibodies were reported, both were Kpb. Both were given high dose corticosteroids. IVIg doses were single dose (0.4g/kg and 25g (weight not stated)) daily for three days. One patient had evidence of haemolysis, and the other did not and transfusion of Kpb positive cells to an antibody positive recipient without haemolysis has been reported on at least one other occasion. This is very weak evidence indicating that there is no role for Ig therapy in the treatment of a delayed alloimmune haemolytic transfusion reaction.

| ITEM | CRITERIAv2.1 | PROPOSED REVISIONS TO THE CRITERIA | SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS |
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| Condition Name | Haemolytic transfusion reaction | Haemolytic transfusion reaction not associated with identifiable red cell antibodies | The name has been refined to better reflect the intent of the use of funded Ig. The original reference (Win et al, 2005) supporting Ig use describes a 'hyper-haemolysis syndrome' however, the previous condition name inadequately describes appropriate Ig use for this rare condition. In addition, the Specialist Working Group have recommended that the condition 'Sickle cell disease' should be removed for which Ig use is not supported (Chapter 8) as this could be confusing because 'hyper-haemolysis syndrome' can occur in |

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| | | | Sickle cell disease. |
| Specialty | Haematology | Haematology | |
| Category | <i>Exceptional circumstances only</i> | <i>Exceptional circumstances only</i> | |
| Specific Conditions | Haemolytic transfusion reaction | | |
| Level of Evidence | Insufficient data (Category 4a) | Insufficient data (Category 4a) | |
| Justification for Evidence Category | | There is a growing awareness of this uncommon complication of transfusions through the number of case reports over the last few years including in Australia. In the UK, hyperhaemolysis has been reportable to serious hazards of transfusion (SHOT) as a defined event since 2012. | A summary of the literature has been added. |
| Indications | | Haemolytic transfusion reaction not due to alloantibodies when haemolysis of both donor and recipient red cells is suspected (hyperhaemolysis syndrome). | The literature supports the use of Ig in conjunction with corticosteroids in patients with hyper-haemolysis syndrome unrelated to red cell Abs. The Specialist Working Group noted that this is a very rare event. |

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| Description and Diagnostic Criteria | <p>Intravenous immunoglobulin (IVIg) may be considered in the management or prevention of severe haemolytic transfusion reaction not responding to other interventions (e.g. corticosteroids).</p> <p>Reference: Win N, Madan B, Gale R and Matthew F (2005). Intravenous immunoglobulin given to lymphoma patients with recurrent haemolytic transfusion reactions after transfusion of compatible blood. <i>Hematology</i>, 10(5):375–8.</p> | <p>Hyperhaemolysis is an uncommon but potentially fatal type of delayed haemolytic transfusion reaction characterised by a drop in haemoglobin to below the pretransfusion levels due to haemolysis of both donor and recipient red cells, reticulocytopenia and an absence of allo red cell antibodies. Although it is characteristically seen in sickle cell disease in childhood, there are reports in thalassaemia, myelofibrosis and lymphoma. The pathogenesis is poorly understood.</p> <p>Recommended treatment includes avoidance of transfusion where possible and immune modulation with high dose steroids and IVIg concurrently.</p> | | | Revised information provides greater detail of the relevant diagnostic criteria based on the literature and an expanded bibliography has been added. |
| Diagnosis is required | | Yes | By which specialty | Haematologist | Diagnosis confined to Haematologists who are expected to be involved in the |

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| Diagnosis must be verified | | No | By which specialty | | management of this severe acute and rare condition. |
| Exclusion Criteria | | <p>Autoimmune haemolytic anaemia (AIHA)</p> <p>Alloimmune delayed haemolytic transfusion reaction with a positive direct agglutination test where haemolysis of only transfused red cells is suspected.</p> | | | <p>Exclusion criteria have been defined to support evidence based prescribing practice. AIHA is excluded because it is a standalone condition in the Emerging role category (the system will link users to the correct condition).</p> <p>There is insufficient evidence of benefit for the use of Ig therapy in delayed allo-immune reaction. There have been only six cases reported in the literature across two papers with the evidence being very weak with four of the six cases being auto-antibodies.</p> |
| Qualifying Criteria | | <ul style="list-style-type: none"> Severe haemolytic transfusion reactions where there is suspected haemolysis of both donor and recipient red cells as evidenced by a fall in haemoglobin below pre-transfusion levels <p>AND</p> <ul style="list-style-type: none"> Ig therapy is given in conjunction with high dose corticosteroids | | | <p>Qualifying criteria have now been developed to align with the literature. The supporting evidence items will confirm that the drop in haemoglobin is related to the transfusion, compare the significance of drop in haemoglobin compared with the transfusion volume, and that ensure intravenous steroids are being given in combination with Ig therapy.</p> |
| Review Criteria | | <p>Review is not mandated for this condition however the following criteria may be useful in assessing the effectiveness of therapy.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> | | | <p>Review is not mandated for this condition because treatment is by one-off dose.</p> |

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| | | <ul style="list-style-type: none"> Resolution of haemolysis Stable haemoglobin Rise in haemoglobin | |
| Dose | <p>Refer to the current product information sheet for further information.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> | <p>Induction Dose – Up to 2 g/kg over 1-2 days</p> <p>Additional dose may be requested when the patient's haemoglobin has not improved.</p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p>Refer to the current product information sheet for further information on dose, administration and contraindications.</p> | <p>While a continuing treatment period of Ig therapy is not required, this condition is likely to involve prolonged haemolysis and Ig is seen as life-saving.</p> <p>The Specialist Working Group advised that uncommonly, a second dose might be required, when the patient has not improved, and may be requested up to six weeks after the first dose.</p> |
| <p style="text-align: center;">References (most recent update: July 2016)</p> | | | |
| <p>Danaee A, Howard J, Roberston B and Robinson S (2014) Hyperhaemolysis in a patient with HbH disease. <i>Transitional Medicine</i>, 24:244-5.</p> <p>http://onlinelibrary.wiley.com/doi/10.1111/tme.12131/abstract</p> <p>Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIg) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/.</p> <p>Stokes IC, Downie PA, Wood EM, Bowden DK, Monagle PT and Barnes CD (2001) Hyperhaemolysis in sickle cells disease – an unusual and potentially life-threatening complication. <i>Medical Journal of Australia</i>, 192:281-2.</p> | | | |

<https://www.ncbi.nlm.nih.gov/pubmed/20201763>

Talano JA, Hillery CA, Gottschall JL, Baylerian DM and Scott JP (2003) Delayed hemolytic transfusion reaction/hyperhemolysis syndrome in children with sickle cell disease, *Pediatrics*, 111(6 Pt 1):661-e665.

<https://www.ncbi.nlm.nih.gov/pubmed/12777582>

Win N, Madan B, Gale R and Matthey F (2005) Intravenous immunoglobulin given to lymphoma patients with recurrent haemolytic transfusion reactions after transfusion of compatible blood. *Hematology*, 10(5):375–8.

<https://www.ncbi.nlm.nih.gov/pubmed/16273724>

POTENTIAL OPERATIONAL IMPACT

The revised criteria provide significantly greater guidance for access to Ig therapy and specifically exclude patients with identifiable red cell antibodies. The criteria now require confirmation that Ig will be given in combination with steroid therapy, however, previously the criteria suggested that treatment might be used when steroids had been unsuccessful. Given that there have been very few patients treated over the last few years, any impact is considered to be minimal, however, an improved clinical outcome might be expected when steroids and Ig are used in combination rather than alone.

POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE

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| Description of impact on patients: | | This is a very rare condition. The changes aim to provide greater guidance and clarity as to where Ig therapy can provide the greatest benefit. Given that there has been very low use for this condition over the last five years, there is unlikely to be any impact on patients as a result of the proposed changes. The formal access criteria now proposed for this condition require that a haematologist makes the diagnosis and manages the ongoing patient treatment. This is because it is a very rare condition and it is important to ensure its correct diagnosis and treatment as patients are often gravely ill. It has been shown that the best clinical outcome is achieved when Ig therapy and steroids are used together. The treatment is short lived so it is unlikely that any patients will be directly impacted at the time of implementation. This rare condition can occur in patients with a variety of diseases including Sickle cell disease, and therefore, while not routinely used in patients with Sickle cell anaemia, that condition will be removed from the listed 'Not supported conditions' – to avoid any potential for confusion. | | | | |
| Impact on demand: | | No impact on demand is anticipated as a result of these changes, given that Ig use is already extremely low. | | | | |
| | 2011-12 | 2012-13 | 2013-14 | 2014-15 | 2015-16 | The Specialist Working Group estimated magnitude of effect: No impact against projected demand |
| Patient number | 0 | <5 | <5 | 0 | <5 | |
| Total Grams issued | | <500 | <500 | 0 | <500 | |
| % Total Grams issued | 0.000% | <0.01% | <0.01% | 0.000% | <0.01% | |

SWG knowledge development opportunities and recommendations

None identified at this stage.

END OF PUBLIC CONSULTATION DOCUMENT

Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation