

## 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 disease of the newborn (HDN)  |   |
|--|---|
| v3.0 CONDITION NAME: Haemolytic disease of the fetus (HDF)   |   |
| <p>HDF was endorsed by NIGAC and JBC in 2015 to retain in line with the recommendations of the Patient Blood Management guidelines (PBM) Module 6 published in 2015, as a condition for which Ig has a therapeutic role in exceptional circumstances only. At the time, the need for further review was acknowledged by the SWG and this review has now been completed as part of the current SWG work program.</p> <p><b>PROPOSED APPROACH:</b></p> <p><b>To retain Haemolytic disease of the fetus as a condition for which Ig has a role in <i>Exceptional circumstances only</i> with the changes as outlined.</b></p> | <p><b>SUMMARY OF RATIONALE:</b></p> <p>The recommended changes are supported by factors including that:</p> <ul style="list-style-type: none"> <li>- Intensive phototherapy is now regarded as the most effective therapy to reduce the need for exchange transfusion in neonates.</li> <li>- The level of evidence for this condition has been downgraded from 4a to 2c. A systematic review (Louis et al, 2014) of the literature found that Ig therapy did not reduce the incidence of exchange transfusion in preterm or term infants nor mortality in neonates and therefore the routine use in infants with haemolytic disease is no longer supported. This is consistent with recommendations of the Patient Blood Management guidelines (PBM), Module 6 (2016).</li> <li>- In line with the literature, a course of weekly Ig therapy should be considered in maternity patients with a fetus affected by HDF who is at high risk of early fetal hydrops or death (Louis et al, 2014), as recommended in PBM Module 6, Expert opinion point 4 (2016).</li> <li>- Given that treatment for this condition is now recommended to be only for the fetus (i.e. maternal treatment), the condition name has been revised.</li> <li>- Ig use has been reducing since 2014-15 in line with publication of the PBM guidelines and this trend is expected to continue with the recommended changes to the criteria.</li> <li>- This condition is listed as a 'red' condition (high priority in times of shortage, not requiring approval by the local trust) in the UK NHS immunoglobulin Guidelines (UK Department of Health, 2011), and is also listed in the national Canadian IVIg Utilisation Management Guidelines (Ontario Regional Blood Coordinating Network, 2016) as recommended for funded use.</li> </ul> |

**v2.1 CONDITION CATEGORY:** Conditions for which Ig is used in Exceptional circumstances only (Chapter 7)

**v3.0 CONDITION CATEGORY:** Conditions for which Ig is used in Exceptional Circumstances only (Chapter 7)

**Role of Ig therapy:** Recent, high-quality trials (Chitty et al, 2013; Liley, Lipriore & Smits-Wintjens, 2015 and Louis et al, 2014) specify the use of intensive phototherapy as the most effective neonatal treatment to reduce the need for exchange transfusions. The role of Ig therapy has changed significantly in recent years with increasing evidence that Ig does not provide the originally reported clinical benefits of either reducing the incidence of exchange transfusions in pre-term and term infants (and therefore reducing the associated risks) or mortality in neonates. Ig use in the routine treatment of neonates is therefore recommended to no longer be supported.

However, for high risk pregnancies with a fetus affected by HDF and at high risk of early fetal hydrops or death, a course of weekly Ig therapy should be considered, as recommended in PBM Module 6 (2016). The mechanism of action is understood to be due to IVIg competing with alloantibodies for Fc receptors on cells that mediate RBC breakdown, and thereby reducing the level of haemolysis.

| ITEM                       | 2015 JBC APPROVED WORDING                          | REVISIONS POST 2015 JBC APPROVED WORDING      | SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS  |
|----------------------------|--|---|--|
| <b>Condition Name</b>      | Haemolytic disease of the fetus and newborn (HDFN) | Haemolytic disease of the fetus (HDF)         | Name revised to reflect that treatment of this condition with Ig is now limited to the fetus (maternal treatment). |
| <b>Specialty</b>           | Haematology  | Haematology                                   |  |
| <b>Category</b>            | <i>Exceptional circumstances only</i>              | <i>Exceptional circumstances only</i>         |  |
| <b>Specific Conditions</b> |  |   |  |
| <b>Level of Evidence</b>   | Insufficient data (Category 4a)                    | Conflicting evidence of benefit (Category 2c) | The level of evidence is changed in line with the literature and Module 6 of the PBM                               |

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|  |   |  | guidelines.   |
| <b>Justification for Evidence Category</b> | <p>Although prophylaxis programs have reduced the frequency of Rhesus (Rh) D HDN, antibodies to RhD remain the most common cause in Australia. Antibodies to other antigens in the Rh system (e.g. Rhc, E), ABO and other antigens (e.g. K) may also cause disease ranging from mild to life-threatening.</p> <p>In infants with HDFN, the routine use of IVIg is not recommended in national Australian clinical guidelines.</p> | <p>Since IVIg can compete with alloantibodies for Fc receptors on cells that mediate RBC breakdown (Hammerman et al, 1996), it has been proposed that it can reduce the incidence of exchange transfusion. One good quality systematic review in 2014 by Louis et al, (including 12 RCTs) reported that while combined results of all trials suggested that IVIg can reduce the incidence of exchange transfusion (ET) in infants with HDFN, the earlier trials were generally of low quality. When only the trials at low risk of bias were considered, there was no effect of IVIg on reducing incidence of ET or any other outcome of importance (e.g. peak bilirubin, duration of phototherapy or need for top-up transfusion). None of the trials was powered to assess rare (but potentially life-threatening) adverse effects such as TRALI, the risk of which is likely to increase with transfusion of plasma products. The recent, high-quality trials specified the use of intensive phototherapy, which is the most effective neonatal treatment to reduce the need for ET.</p> <p>Although the review suggested a benefit of IVIg in reducing ET for jaundice due to ABO incompatibility, the studies were also of low quality. It seems unlikely that IVIg would be of benefit in ABO haemolysis (which is typically milder) if there is no benefit in RhD HDFN.</p> <p>For preterm and term infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on exchange transfusion incidence is uncertain. In infants with alloimmune haemolytic disease, the effect of IVIg compared</p> | <p>The significant formal systematic review undertaken for the PBM guidelines Module 6 (2016) has supported the redrafting of this section.</p> |

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|  |   | with no IVIg on mortality is also uncertain.  |   |
| <b>Indications</b>                         |   | <b>Haemolytic disease of the fetus with high risk of early fetal hydrops or death</b>   | Developed to align with the recommendations of PBM guidelines - Module 6.                               |
| <b>Description and Diagnostic Criteria</b> | HDN arises from fetomaternal antigen incompatibility and can result in clinically significant foetal/neonatal haemolysis, severe anaemia and hyperbilirubinaemia. | <p>Haemolytic disease of the fetus and newborn (HDFN) is characterised by a breakdown of RBCs by maternal antibodies. During pregnancy, some of the mother's antibodies are transported across the placenta and enter the fetal circulation. Antibodies to the RhD, Rhc and Kell antigen are the most common causes of severe HDFN in Australia. Anaemia is the most significant problem in utero because excess fetal bilirubin crosses the placenta and is eliminated by the mother. However, bilirubin levels can rise rapidly after birth, leading to the need for intensive phototherapy and exchange transfusion. Exchange transfusions are associated with an increased risk of neonatal morbidity and mortality.</p> <p>In newborns with haemolytic disease, the routine use of IVIg is not recommended (Recommendation 7, Patient Blood Management Guidelines (PBM) Module 6 - Paediatric and neonatal). Infants at risk of haemolytic disease should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. (Practice point 43, PBM, Module 6, 2016).</p> <p>In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. (Expert opinion point 4, PBM Module 6, 2016).</p> | A more detailed description is provided to improve clarity and reference the PBM guidelines - Module 6. |

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|----------------------------|---|--|--------------------|--|---|
| Diagnosis is required      |   | Yes  | By which specialty | Haematologist<br>General Physician<br>Obstetrician | This condition requires specialist care.  |
| Diagnosis must be verified |   | No   | By which specialty |  |   |
| Exclusion Criteria         |   | Haemolytic disease of the newborn  |                    |  | In accordance with PBM guidelines: Module 6, newborns should be treated with intensive phototherapy and not IVIg. |
| Qualifying Criteria        | <p><b>IVIg may be used in selected cases in consultation with experts in fetomaternal medicine and transfusion medicine.</b></p> <p>In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. (Expert opinion point 4, Patient Blood Management Guidelines – Module 6 – Paediatric and neonatal, Section 3.5.2.)</p> | <ul style="list-style-type: none"> <li>Fetus affected by severe Haemolytic disease</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>High risk of early fetal hydrops or death</li> </ul> |                    |  | Qualifying criteria reflect the guidance provided in the PBM Guidelines Module 6.                                 |

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| <b>Review Criteria</b>  |  | <p>Review is not mandated for this condition.</p> <p>Clinical effectiveness of Ig therapy can be demonstrated by:</p> <ul style="list-style-type: none"> <li>• Live birth</li> </ul>  | Review is not mandated for this condition as treatment continues for the length of the pregnancy. An outcome has been defined to support assessment of the effectiveness of Ig therapy. |
| <b>Dose</b>   | <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><b>Dose during pregnancy: 1 g/kg (up to a maximum weight of 100 kg) weekly throughout pregnancy.</b></p> <p>The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.</p> <p><b>Refer to the current product information sheet for further information on dose, administration and contraindications.</b></p> | Dose controls have been defined.  |
| <p style="text-align: center;"><b>References</b></p> <p style="text-align: center;"><b>(Most recent update: May 2016)</b></p>   |  |   |   |
| <p>Chitty HE, Ziegler N, Savoia H, Doyle LW and Fox LM (2013) Neonatal exchange transfusions in the 21st century: a single hospital study. <i>Journal of Paediatric Child Health</i>, 49(10):825-832.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pubmed/23834341">https://www.ncbi.nlm.nih.gov/pubmed/23834341</a></p> <p>Gottstein R and Cooke RW (2003) Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. <i>Archives of Disease in Childhood — Fetal Neonatal Edition</i>, 88(1):F6–10.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1755998/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1755998/</a></p> <p>Hammerman C, Vreman HJ, Kaplan M and Stevenson DK (1996) Intravenous immune globulin in neonatal immune hemolytic disease: does it reduce hemolysis? <i>Acta Paediatrica</i>, 85(11):1351-1353.</p> <p><a href="https://www.ncbi.nlm.nih.gov/pubmed/8955465">https://www.ncbi.nlm.nih.gov/pubmed/8955465</a></p> |  |   |   |

Kaplan M, Vreman HJ, Hammerman C and Stevenson DK (1996) Intravenous immune globulin in neonatal ABO isoimmunisation: factors associated with clinical efficacy. *Biology of the Neonate*, 70:69–72.

<https://www.ncbi.nlm.nih.gov/pubmed/8864425>

Liley HG, Gardener G, Lopriore E and Smits-Wintjens V (2015) Immune Hemolytic Disease. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood, 8th Edition*, Elsevier.

Louis D, More K, Oberoi S and Shah PS (2014) Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: An updated systematic review and meta-analysis. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, Elsevier.

<https://www.ncbi.nlm.nih.gov/pubmed/24514437>

Miqdad AM, Abdelbasit OB, Shaheed MM, Seidahmed MZ, Abomelha AM and Arcala OP (2004) Intravenous immunoglobulin G therapy for significant hyperbilirubinaemia in ABO haemolytic disease of the newborn. *Journal of Maternal-Fetal and Neonatal Medicine*, 16(3):163–6.

<https://www.ncbi.nlm.nih.gov/pubmed/15590442>

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/>.

Patient Blood Management Guidelines, Module 6 – Paediatric and neonatal (2016). National Blood Authority, Section 3.5.2.:113-4.

UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at:

[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/216671/dh\\_131107.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf)

UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at:

[https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster\\_v4\\_February2016.pdf](https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster_v4_February2016.pdf)

**POTENTIAL OPERATIONAL IMPACT**

Given that Ig therapy is no longer supported for routine use in neonates and Ig use will be limited to very high risk pre-term infants, the operational impact will be a reduction in the number of Ig infusions being given to newborns, with all future infusions being limited to those pregnant women with very high risk pregnancies. This trend may have already commenced with the publication of PBM Module 6 in 2015 and launch of BloodSTAR v2.1 in 2016. Given that the current criteria are very vague, leaving decision making up to the clinician as to the circumstances and time to commence treatment, (including supporting the treatment of neonates), the PBM module 6 practice points have been included into BloodSTAR v2.1 supporting the Authoriser to question requests for routine use. A communication strategy is planned to ensure that all prescribers are aware of the changed criteria in v3.0.

**POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE**

|   |  |                |                |                |                |   |
|---|--|----------------|----------------|----------------|----------------|---|
| <b>Description of impact on patients:</b> | The publication of revised treatment guidelines for managing this condition in new born babies confirms that the best clinical outcomes for treatment after birth are achieved with phototherapy (light therapy) and therefore, Ig therapy no longer has a role in the routine care of the new born. Specific communications will be provided to doctors to make sure that they are aware of these findings. However, it is also recognised that Ig therapy still plays an important role in treatment during pregnancy and access will continue for those pre-term infants identified to be at risk. Transition planning will ensure that any existing patients receiving Ig therapy will continue treatment as required during implementation of v3.0. |                |                |                |                |   |
| <b>Impact on demand:</b>                  | It can be seen that there is a trend of a reducing number of patients treated with Ig in this condition since 2014-15 and, the revised criteria are expected to continue this trend. Analysis of current use has indicated that over the past 2 years, 75 to 80 newborns have been treated, albeit the doses used on each occasion would have been low.  |                |                |                |                |   |
|   | <b>2011-12</b>   | <b>2012-13</b> | <b>2013-14</b> | <b>2014-15</b> | <b>2015-16</b> | The Specialist Working Group estimated magnitude of effect:<br>Marginal: <\$500K reduction against projected demand |
| <b>Patient number</b>                     | <b>105</b>   | <b>108</b>     | <b>101</b>     | <b>82</b>      | <b>86</b>      |   |
| <b>Total Grams issued</b>                 | <b>4,364</b>   | <b>6,146</b>   | <b>6,661</b>   | <b>2,013</b>   | <b>5,636</b>   |   |
| <b>% Total Grams issued</b>               | <b>0.13%</b>   | <b>0.17%</b>   | <b>0.17%</b>   | <b>0.05%</b>   | <b>0.11%</b>   |   |

**Specialist Working Group knowledge development opportunities and recommendations**

Inform paediatricians about the superiority of phototherapy compared to Ig therapy in the treatment of HDF. In neonates with HDF, the use of IVIg is not



recommended (Patient Blood Management Guidelines, Module 6, 2016).

**END OF PUBLIC CONSULTATION DOCUMENT**

**Next review: Twelve to eighteen months after BloodSTAR v3.0 implemented**