Heparin induced thrombocytopenia (HIT)

Condition for which Ig use is in exceptional circumstances only

Specific Conditions	• Heparin Induced Thrombocytopenia (HIT)
Indication for Ig Use	• Spontaneous aHIT • Persistent aHIT • Treatment refractory HIT • Immediate need to correct thrombocytopenia in HIT • Prevention of rapid-onset HIT
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	HIT is a rare syndrome of thrombocytopenia and thrombosis driven by the development of anti-platelet factor 4 (PF4)/polyanion antibodies that mediate platelet activation as well as leucocyte activation, NETosis, and endothelial activation leading to thrombosis and rapid platelet consumption (Arepally and Cines, 2020). It is canonically described after exposure to heparins (unfractionated heparin or low molecular weight heparin), but can occur after exposure to other highly sulfated polyanion substances (e.g. pentosan), or spontaneously without any prior heparin exposure. Once the diagnosis is suspected based on clinical criteria (such as intermediate to high risk: 4T score >3), immediate action is undertaken to ameliorate the potential for further deleterious activation (discontinuation of heparin and commencement of non-heparin anticoagulant) while awaiting screening and eventually confirmatory testing. Early suspicion and action is key, and the majority of patients improve with the above measures (Cuker et al, 2018; Joseph et al, 2019). The diagnostic algorithm for HIT includes: 1. intermediate-high 4T score; 2. positive screening assay – demonstration of anti-PF4/polyanion antibodies using technologies such as ELISA, chemiluminescence, and rapid latex agglutination kits; 3. positive functional assay – demonstration of plasma/serum ability activate platelets at *therapeutic heparin concentrations, but abrogated by incubation with high dose heparin, IVIg, or IV.3 (a monoclonal antibody to FcgammaRIIa). Typical functional laboratory tests include: serotonin release assay (SRA), platelet aggregometry (multiple electrode or light transmission), and flow cytometry (P-selectin expression assays). *or “autoimmune” HIT if serum/plasma is able to activate platelets in the absence of heparin but still abrogated by high dose heparin Autoimmune HIT (aHIT) has emerged as an under-diagnosed entity of a HIT-like syndrome with serological evidence of platelet activation in the absence of heparin (at therapeutic doses), but abrogation of this activation with high dose heparin, IVIg, or IV.3. It is proposed that the culprit antibodies in these cases are anti-PF4 antibodies able to bridge PF4 tetramers without the need for polysulfated chains (such as heparin) (Greinacher, Selleng and Warkentin, 2017). Clinically important subtypes of aHIT include: 1. spontaneous aHIT (no antecedent heparin exposure) 2. persistent aHIT (ongoing thrombocytopenia >1 week after heparin discontinuation) Other rare subtypes have also been described such as delayed-onset HIT, fondaparinux-associated HIT, flush heparin HIT and HIT-associated DIC (Warkentin, 2019). More recently, COVID-19 vaccine induced thrombotic thrombocytopenia (VITT) was seen as analogous to aHIT (Warkentin and Greinacher, 2021; Bourguignon et al, 2021). In addition to aHIT, Warketin and Greinacher recommend IVIg as an adjunctive therapy for HIT cases with cerebral venous thrombosis, severe limb ischemia, and/or persisting thrombocytopenia. Another documented role is in the prevention of rapid-onset HIT with planned heparin re-exposure (Warkentin 2019). Diagnosis is seldom confirmed before decisive clinical action is required, and initial steps are made empirically on clinical judgement while awaiting laboratory testing. In Australia, screening tests are often batched by laboratories during business hours, with regional centralisation of most functional testing within weeks but not days. For these reasons, access to limb and/or life saving therapies must not be delayed until diagnosis is confirmed.

Indications for IVIg access in HIT:

1. spontaneous aHIT – no antecedent heparin exposure (Greinacher, Selleng and Warkentin, 2017; Mohanty et al, 2019)
2. #persistent aHIT – failure to recover platelets within 1 week of heparin discontinuation (Warkentin, 2019)
3. #treatment refractory HIT – progression of thrombocytopenia and/or thrombosis despite heparin discontinuation and commencement of non-heparin anticoagulant (including fondaparinux-associated HIT) (Padmanabhan et al, 2017; Manji, Warkentin, Sheppard and Lee, 2020)
4. immediate need to correct thrombocytopenia in HIT – either for active bleeding or in preparation for life/limb saving surgery (Abu Kar, Kaur, Khan and Bloomfield, 2022)
5. prevention of rapid-onset HIT – unavoidable heparin re-exposure (where non-heparin alternatives are not locally available e.g. cardiac bypass) (Warkentin, 2019)

The distinction between persistent aHIT and refractory HIT will be difficult to make until functional assay results are available. However, refractory disease can be established at any time after heparin cessation, non-heparin anticoagulation, and deterioration of thrombocytopenia or progressive thrombosis. In contrast, persistent aHIT is established by the failure of platelet recovery within 1 week of heparin cessation. Many cases of refractory HIT may be subsequently reclassified as persistent aHIT, or vice versa, but this information will only be available with functional assay results and will not affect the immediate treatment decisions.

Justification for Evidence Category

The scientific rationale: IgG inhibit platelet activation by anti-PF4 HIT antibodies via FcgammaRIIa receptors (Greinacher et al, 1994).

The clinical benefit for this indication has been described in a book, case series, case reports, and speculative by international key opinion leaders.

Diagnosis Requirements

A diagnosis must be made by a Haematologist.

Qualifying Criteria for Ig Therapy

Spontaneous aHIT

Spontaneous aHIT is a HIT-like syndrome with serological evidence of platelet activation in the absence of heparin (at therapeutic doses), but abrogation of this activation with high dose heparin, IVIg, or IV.3.

- Demonstration of anti-PF4 antibodies

  AND

- No recent heparin exposure

  AND

- Current platelet count is less than 150 x 10^9/L

Persistent aHIT

Persistent aHIT is defined by ongoing thrombocytopenia more than one week after heparin discontinuation.

- Please confirm the demonstration of anti-PF4 antibodies

  AND

- Failure of platelet recovery despite cessation of heparin

  AND

- Current platelet count is less than 150 x 10^9/L

Treatment refractory HIT

Refractory HIT is defined by the progression of thrombocytopenia and/or thrombosis despite heparin discontinuation and commencement of a non-heparin anticoagulant.

- Demonstration of anti-PF4 antibodies

  AND

- Heparin cessation and commencement of non-heparin anticoagulant

AND

- Current platelet count is less than 150 x 10^9/L

  OR

- Evidence of progressive thrombosis

Immediate need to correct thrombocytopenia in HIT

This indication is to assist in the management of active bleeding or preparation for life/limb saving surgery.

- Demonstration of anti-PF4 antibodies

  AND

- Current platelet count is less than 100 x 10^9/L

  AND

- Life/limb threatening bleeding or surgical intervention required

Prevention of rapid-onset HIT

This indication is for cases where heparin re-exposure is unavoidable (e.g. non-heparin alternatives are not locally available for an urgent procedure such as cardiac bypass).

- Demonstration of anti-PF4 antibodies

  AND

- Prior history of HIT

  AND

- Need for prevention of rapid-onset HIT due to unavoidable heparin re-exposure (where non-heparin alternatives are not available)

Review Criteria for Assessing the Effectiveness of Ig Use

Spontaneous aHIT

Review is not mandated for this indication however the information provided will support future analysis of the condition and effectiveness of treatment.

- Clinical response to Ig therapy

Persistent aHIT

Review is not mandated for this indication however the information provided will support future analysis of the condition and effectiveness of treatment.

- Clinical response to Ig therapy

Treatment refractory HIT

Review is not mandated for this indication however the information provided will support future analysis of the condition and effectiveness of treatment.

- Clinical response to Ig therapy

Immediate need to correct thrombocytopenia in HIT

Review is not mandated for this indication however the information provided will support future analysis of the condition and effectiveness of treatment.

- Clinical response to Ig therapy

Prevention of rapid-onset HIT

Review is not mandated for this indication however the information provided will support future analysis of the condition and effectiveness of treatment.

- Clinical response to Ig therapy

Dose

Spontaneous aHIT

- **Initial dose (IVIg)** - 1 - 2 g/kg in 2 divisions is recommended but may be given in up to 5 divisions.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Persistent aHIT

- **Initial Dose (IVIg)** - 1 - 2 g/kg in 2 divisions is recommended, but may be given in up to 5 divisions.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Treatment refractory HIT

- **Initial Dose (IVIg)** - 1 - 2 g/kg in 2 divisions is recommended, but may be given in up to 5 divisions

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Immediate need to correct thrombocytopenia in HIT

- **Initial dose (IVIg)** - 1 - 2 g/kg in 2 divisions is recommended, but may be given in up to 5 divisions.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Prevention of rapid-onset HIT

- **Initial dose (IVIg)** - 1 - 2 g/kg in 2 divisions is recommended, but may be given in up to 5 divisions.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Bibliography

Abu Kar, S., A. Kaur, A. M. Khan and D. Bloomfield (2022). "Early Utilization of Intravenous Immunoglobulin in Heparin-Induced Thrombocytopenia for Limb Salvaging Purposes." Cureus **14**(3): e23202.

Arcinas, L. A., R. A. Manji, C. Hrymak, V. Dao, J. I. Sheppard and T. E. Warkentin (2019). "Autoimmune heparin-induced thrombocytopenia and venous limb gangrene after aortic dissection repair: in vitro and in vivo effects of intravenous immunoglobulin." Transfusion **59**(6): 1924-1933.

Arepally, G. M. and D. B. Cines (2020). "Pathogenesis of heparin-induced thrombocytopenia." Transl Res **225**: 131-140.

Bourguignon, A., D. M. Arnold, T. E. Warkentin, J. W. Smith, T. Pannu, J. M. Shrum, Z. A. A. Al Maqrashi, A. Shroff, M.-C. Lessard, N. Blais, J. G. Kelton and I.

Bibliography

Nazy (2021). "Adjunct Immune Globulin for Vaccine-Induced Immune Thrombotic Thrombocytopenia." New England Journal of Medicine **385**(8): 720-728.

Chen, V. M., J. L. Curnow, H. A. Tran and P. Y.-I. Choi (2021). "Australian and New Zealand approach to diagnosis and management of vaccine-induced immune thrombosis and thrombocytopenia." Medical Journal of Australia **215**(6): 245-249.e241.

Cuker, A., G. M. Arepally, B. H. Chong, D. B. Cines, A. Greinacher, Y. Gruel, L. A. Linkins, S. B. Rodner, S. Selleng, T. E. Warkentin, A. Wex, R. A. Mustafa, R. L. Morgan and N. Santesso (2018). "American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia." Blood Advances **2**(22): 3360-3392.

Dougherty, John & Yarsley, Robyn. (2020). Intravenous Immune Globulin (IVIG) for Treatment of Autoimmune Heparin-Induced Thrombocytopenia: A Systematic Review. Annals of Pharmacotherapy. 55. 106002802094354. 10.1177/1060028020943542.

Greinacher, A., U. Liebenhoff, V. Kiefel, P. Presek and C. Mueller-Eckhardt (1994). "Heparin-associated thrombocytopenia: the effects of various intravenous IgG preparations on antibody mediated platelet activation--a possible new indication for high dose i.v. IgG." Thromb Haemost **71**(5): 641-645.

Greinacher, A., K. Selleng and T. E. Warkentin (2017). "Autoimmune heparin-induced thrombocytopenia." Journal of Thrombosis and Haemostasis **15**(11): 2099-2114.

Joseph, J., D. Rabbolini, A. K. Enjeti, E. Favaloro, M.-C. Kopp, S. McRae, L. Pasalic, C. W. Tan, C. M. Ward and B. H. Chong (2019). "Diagnosis and management of heparin-induced thrombocytopenia: a consensus statement from the Thrombosis and Haemostasis Society of Australia and New Zealand HIT Writing Group." Medical Journal of Australia **210**(11): 509-516.

Manji, F., T. E. Warkentin, J. I. Sheppard and A. Lee (2020). "Fondaparinux cross-reactivity in heparin-induced thrombocytopenia successfully treated with high-dose intravenous immunoglobulin and rivaroxaban." Platelets **31**(1): 124-127.

Mohanty, E., S. Nazir, J. I. Sheppard, D. A. Forman and T. E. Warkentin (2019). "High-dose intravenous immunoglobulin to treat spontaneous heparin-induced thrombocytopenia syndrome." J Thromb Haemost **17**(5): 841-844.

Padmanabhan, A., C. G. Jones, S. M. Pechauer, B. R. Curtis, D. W. Bougie, M. S. Irani, B. J. Bryant, J. B. Alperin, T. G. Deloughery, K. P. Mulvey, B. Dhakal, R. Wen, D. Wang and R. H. Aster (2017). "IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia." Chest **152**(3): 478-485.

Warkentin, T. E. (2019). "High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review." Expert Review of Hematology **12**(8): 685-698.

Warkentin, T. E. and A. Greinacher (2021). "Spontaneous HIT syndrome: Knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia." Thromb Res **204**: 40-51.

Generated on: 29 February 2024