# Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia

**Quentin A. Hill,[1] Robert Stamps,[2] Edwin Massey,[3] John D. Grainger,[4] Drew Provan,[5] Anita Hill[1] and on behalf of the British Society for Haematology Guidelines**

*[1]Department of Haematology, Leeds Teaching Hospitals, Leeds, [2]NHSBT, Sheffield, [3]NHSBT, Bristol, [4]Royal Manchester Children's Hospital, University of Manchester, Manchester, and [5]Barts and The London School of Medicine and Dentistry, London, UK*

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## Scope

The objective of this guideline is to provide healthcare professionals with guidance on the management of patients with secondary autoimmune haemolytic anaemia (AIHA). The guidance may not be appropriate to every patient and in all cases, individual patient circumstances may dictate an alternative approach.

### *Methodology*

*Literature review details.* Recommendations are based on the systematic review of published English language literature from January 1960 to October 2015 (see Appendix S1 for further details). Although recommendations are unchanged, an expanded version of this guideline is available as Appendix S2.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guidance pack (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and the GRADE working group website (http://www.gradeworkinggroup.org.

*Working group membership.* The guideline group was selected to be representative of UK-based experts in the diagnosis and management of AIHA.

Correspondence: BSH Secretary, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK.
E-mail: bshguidelines@b-s-h.org.uk

*Review.* Review of the manuscript was performed by the BCSH General Haematology Task Force, BCSH Executive Committee and then a sounding board of the British Society for Haematology (BSH). This compromises 50 or more members of the BSH who have reviewed this Guidance and commented on its content and applicability in the UK setting.

## Background

Autoimmune haemolytic anaemia is a decompensated acquired haemolysis caused by the host's immune system acting against its own red cell antigens. The incidence is 1 per 100 000/year and approximately half of the cases are secondary to an associated disorder. Serologically, cases are divided into warm, cold (cold haemagglutinin disease and paroxysmal cold haemoglobinuria) or mixed AIHA (Table I). Cases of drug-induced immune haemolytic anaemia (DIIHA) make up about 10% of the total when included in series of patients with AIHA (Petz & Garratty, 1980; Liesveld *et al*, 1987; Sokol *et al*, 1992).

The presenting features, investigations and diagnostic approach to AIHA are covered in a recent BSH guideline on primary AIHA (Hill *et al*, 2017). This also reviews the role of transfusion and specific treatment regimens in more detail. AIHA can be diagnosed when there is laboratory evidence of haemolysis, a positive direct antiglobulin test (DAT) and clinical evaluation has excluded an alternative cause (e.g. DIIHA, haemolytic transfusion reaction or post-transplantation alloimmune haemolysis).

Some general strategies taken in primary AIHA are also applicable. Hence if DIIHA is suspected, relevant medication should be stopped. Patients should receive folic acid. Haemolysis is a risk factor for venous thrombosis and patients should be risk assessed for thromboprophylaxis. Patients receiving steroids should also be risk assessed for treatment to prevent glucocorticoid-induced osteoporosis and gastrointestinal bleeding. Patients in whom anaemia is life threatening should be transfused with red cells matched for ABO, Rh and Kell rather than waiting for full compatibility testing. An underlying disorder or its treatment may, however, influence

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**Table I.** Classification of autoimmune haemolytic anaemia.

| |
|---|
| Warm AIHA |
| Primary |
| Secondary |
| Neoplasia (CLL, lymphoma, solid organ) |
| Infection (e.g. hepatitis C, HIV, CMV, VZV, pneumococcal infection, leishmaniasis, tuberculosis) |
| Immune dysregulation |
| Connective tissue disorders (e.g. SLE, Sjögren syndrome, scleroderma) |
| Ulcerative colitis, PBC, sarcoidosis |
| Post transplantation |
| Immune deficiency syndromes (e.g. CVID) |
| Cold AIHA |
| Cold haemagglutinin disease |
| Primary |
| Secondary |
| Malignancy (e.g. CLL, NHL, solid organ) |
| Infection (e.g. mycoplasma, viral infections including IM) |
| Autoimmune disease |
| Post-allogeneic HSCT |
| Paroxysmal cold haemoglobinuria |
| Primary |
| Secondary |
| Infection (e.g. adenovirus, influenza A, syphilis, CMV, IM, VZV, measles, mumps, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*) |
| Mixed type AIHA |
| Primary |
| Secondary |
| Lymphoma, SLE, infection |

AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; IM, infectious mononucleosis; NHL, non-Hodgkin lymphoma; PBC, primary biliary cirrhosis; SLE, systemic lupus erythematosus; VZV, varicella zoster virus.

other requirements, for example, the need for an irradiated product following treatment with fludarabine.

Secondary AIHA broadly encompasses conditions that appear to occur in association with AIHA. The strength and significance of the association varies and conditions may represent two parts of a complex immune-mediated disorder (Sokol & Hewitt, 1985). Often, the associated condition should be treated in its own right following current best practice guidelines and successful treatment may (but does not always) improve the AIHA. When the associated condition appears inactive or would not otherwise require treatment, management of AIHA can usually proceed along similar lines to primary AIHA, although cases must be individualised.

The distribution of secondary AIHA varies according to the population studied but approximately half are associated with haematological malignancy, a third with infection and a sixth with collagen vascular disorders (Dacie & Worlledge, 1969; Pirofsky & Bardana, 1974; Sokol *et al*, 1992; Vaglio *et al*, 2007). Most cases are warm but secondary cold haemagglutinin disease (CHAD) is also reported. Some common or important associations are considered below. Associations are dealt with in the following order: haematological malignancy [chronic lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)], benign (ovarian teratoma, thymoma) and malignant neoplasms, infection [mycoplasma, infectious mononucleosis (IM), hepatitis C], immune dysregulation [systemic lupus erythematosus (SLE), common variable immunodeficiency, ulcerative colitis, haematopoietic stem cell transplantation (HSCT), solid organ transplantation], Evans syndrome, childhood AIHA associated with giant cell hepatitis (GCH) and DIIHA.

## Neoplasms

### *Haematological malignancy*

Autoimmune haemolytic anaemia is reported in patients with a wide range of haematological malignancies, most frequently in CLL and NHL. Patients with AIHA are also at an increased risk of subsequently developing NHL, myeloma, CLL or myeloid malignancies. A positive DAT without haemolysis is more frequent than AIHA in CLL (Dearden *et al*, 2008) and the myelodysplastic syndromes (Sokol *et al*, 1989). Diagnosis of secondary AIHA can be complex because the anaemia may be multifactorial, the lactate dehydrogenase affected by disease progression or liver dysfunction and a reticulocyte response prevented by marrow infiltration (Dearden, 2008). A bone marrow biopsy may therefore be required as part of the assessment. Cytomegalovirus (CMV) reactivation and parvovirus B19 infection should be excluded.

Of 73 patients receiving intravenous immunoglobulins (IVIg) for warm AIHA, 40% responded and secondary associations (28 had lymphoma or CLL) did not predict outcome (Flores *et al*, 1993). IVIg may therefore be considered as a rescue option in patients with a haematological malignancy and poorly controlled warm AIHA.

*Chronic lymphocytic leukaemia.* Autoimmune haemolytic anaemia occurs in 5-10% of patients with CLL (Mauro *et al*, 2000; Dearden *et al*, 2008) and its management is addressed in recent BCSH guidelines (Oscier *et al*, 2012).

*Non-Hodgkin lymphoma.* Autoimmune haemolytic anaemia may precede NHL but is usually reported at or following diagnosis. Overall, AIHA occurs in 2-3% of NHL patients but rates of 13–19% are reported in angioimmunoblastic T-cell lymphoma (Lachenal *et al*, 2007). In a literature review, complete remission was achieved in 39/56 patients with anti-lymphoma therapy but only 8/34 with steroids or immunoglobulins (Hauswirth *et al*, 2007). For B-cell NHL, treatment with rituximab as a single agent or combined with chemotherapy was often a successful approach (Hauswirth

*et al*, 2007), as was splenectomy for splenic marginal zone lymphoma. Small patient numbers and heterogeneous regimens make *detailed* treatment recommendations difficult and NHL type and remission status will influence treatment selection. NHL in complete remission and low grade NHL not otherwise requiring treatment favour an initial AIHA- rather than lymphoma-directed approach.

In recent BCSH guidelines on Waldenström macroglobulinaemia, rituximab-based therapy was recommended for symptomatic secondary CHAD, with the addition of fludarabine to be considered for those with adequate performance status and renal function (Owen *et al*, 2014).

### *Non-Hodgkin lymphoma: Recommendation*

- **The treating physician should consider lymphoma type and remission status when deciding whether treatment should be anti-lymphoma or autoimmune haemolytic anaemia (AIHA) directed (2C).**

*Hodgkin lymphoma.* Autoimmune haemolytic anaemia occurs in 0·2% of patients with HL (Xiros *et al*, 1988; Varoczy *et al*, 2002). A systematic review (Lechner & Chen, 2010) identified 34 cases, 29 of which were at an advanced stage. Eight presented with AIHA 5 months to 21 years prior to HL, 18 concurrently and 8 at time of relapse. Two IgA AIHA cases presented during complete remission of HL and were steroid responsive. Although some of the remaining patients responded to steroids or splenectomy, all treated with anti-lymphoma therapy responded, usually completely.

### *Hodgkin lymphoma: Recommendations*

- **First line therapy for AIHA associated with Hodgkin lymphoma (HL) is anti-lymphoma therapy (1C).**
- **Patients presenting with AIHA during remission of HL should be assessed carefully for relapse (1A). If the patient is in confirmed complete remission, treatment should be as for primary AIHA (2C).**

### *Solid organ neoplasia*

*Benign conditions.* The most frequently reported associations are ovarian teratoma and thymoma. Rarely, other non-malignant ovarian tumours and non-ovarian teratomas have also been reported (Payne *et al*, 1981; Buonanno *et al*, 1984; Goyal *et al*, 2010).

*Ovarian teratoma* AIHA is a rare association and was not reported in a series of 517 teratomas (Comerci *et al*, 1994). Case reports show that patients respond poorly to steroids or splenectomy but AIHA consistently resolves with resection of the tumour.

### *Ovarian teratoma: Recommendations*

- **First line therapy is surgical resection (1C).**
- **When resecting the tumour, concomitant splenectomy is not indicated (1C).**

*Thymoma* warm AIHA is a rare association and in the majority, occurs at presentation with, or after diagnosis of, thymoma. Although most cases are steroid responsive, the majority of patients proceed to thymectomy, which usually leads to prompt resolution of AIHA.

### *Thymoma: Recommendations*

- **If acute treatment is required, first line therapy is prednisolone 1 mg/kg/day (2C).**
- **In all cases, consider surgical resection (2C).**

*Malignant conditions.* Only 1-2% of secondary AIHA is associated with solid organ malignancy (Spira & Lynch, 1979) and the primary tumour site and histology varies. AIHA coinciding with presentation of a malignant tumour is less frequently steroid responsive than idiopathic AIHA (Spira & Lynch, 1979; Puthenparambil *et al*, 2010). Sustained resolution of AIHA has been reported with resection of isolated ovarian, renal cell and colonic carcinomas (Spira & Lynch, 1979; Lands & Foust, 1996) and with chemotherapy ± splenectomy for seminoma (Canale *et al*, 1975; Lundberg & Mitchell, 1977; Herve *et al*, 2007). In metastatic disease, AIHA can respond to disease control or to corticosteroids.

### *Malignant conditions: Recommendation*

- **AIHA-directed therapy may be needed in addition to treatment of the underlying malignancy and a multidisciplinary approach is required (2C).**

## Infection

### *Mycoplasma and viral pneumonia*

Although secondary CHAD is a rare complication of mycoplasma infection, atypical or mycoplasma pneumonia accounted for 33% (23/70) of all CHAD patients in one series (Dacie & Worlledge, 1969). Influenza A has also been associated (Dacie, 1962; Schoindre *et al*, 2011) but a pathogen is not always identified. CHAD typically occurs 2-3 weeks after onset of the illness. Acrocyanosis, haemoglobinuria or gangrene are uncommon and haemolysis typically resolves after a further 2-3 weeks (Petz & Garratty, 1980). Most patients can be managed supportively with antibiotics (if unresolved pneumonia), warmth and transfusion for symptomatic anaemia. Some patients have also received

 

corticosteroids or immunoglobulins, although whether they influence the acute course of haemolysis is unknown.

### *CHAD secondary to atypical and mycoplasma pneumonia: Recommendations*

- **Treat supportively with appropriate antimicrobials, a warm environment and transfusion for symptomatic anaemia (1C).**
- **If haemolysis is severe and persistent, consider emergency treatment e.g. steroids or immunoglobulins (2C).**

### *Infectious mononucleosis*

Autoimmune haemolytic anaemia occurs in up to 3% of patients with IM, typically within 1–2 weeks of onset. Patients present with sore throat, fever and malaise, followed by weakness and jaundice. Lymphadenopathy and hepatosplenomegaly are common (Petz & Garratty, 1980). IM is classically associated with an anti-i cold agglutinin with high thermal amplitude (Wilkinson *et al*, 1973). Most cases are self-limiting within 4-8 weeks. Some benefit has been reported in patients treated with steroids (Keyloun & Grace, 1966; Tonkin *et al*, 1973; Bowman *et al*, 1974) and with plasma exchange in a steroid-refractory case (Geurs *et al*, 1992).

### *Infectious mononucleosis: Recommendations*

- **Patients with mild haemolysis can be monitored for resolution (1C).**
- **If haemolysis is more severe, consider prednisolone 1 mg/kg/day (2C).**
- **If AIHA due to a cold antibody, the patient should avoid cold exposure (2C).**

### *Hepatitis C*

In cases where AIHA is thought to be secondary to interferon, this should be discontinued, but in severe interferon-associated cases, steroids have also been employed prior to resolution of haemolysis. In eradication treatment naive cases, 15/16 patients had a complete response to first line prednisolone 0·5-2 mg/kg/day (two additionally received cyclophosphamide or azathioprine) (Ramos-Casals *et al*, 2003) and two steroid-refractory patients responded to rituximab 375 mg/m$^2$ weekly for 4 weeks (Etienne *et al*, 2004; Annicchiarico *et al*, 2009). However viral load can increase in patients receiving steroids and the main reported cause of death is liver failure. Hepatitis C eradication should therefore also be considered.

### *Hepatitis C: Recommendations*

- **If interferon-induced drug-induced immune haemolytic anaemia (DIIHA) is suspected, discontinue interferon (1A). Consider steroids for severe persistent haemolysis (2C).**
- **In hepatitis C eradication treatment naive patients with AIHA, first line treatment is prednisolone (2C).**
- **In cases of controlled AIHA, consider hepatitis C eradication (2C).**

## Immune Dysregulation

### *Systemic lupus erythematosus*

A positive DAT is present in 18-65% of SLE patients (Giannouli *et al*, 2006) while AIHA occurs in 5-10%. Approximately two-thirds of cases occur at SLE presentation but AIHA can also present first.

Initial steroid treatment results in a 75-96% response rate (Pirofsky & Bardana, 1974; Gomard-Mennesson *et al*, 2006) and the recurrence rate, estimated at 3-4 per 100 patient years (Kokori *et al*, 2000; Gomard-Mennesson *et al*, 2006), appears lower than primary warm AIHA. Where AIHA is the dominant feature, case reports suggest that oral immunosuppressants, such as azathioprine (Gomard-Mennesson *et al*, 2006) or mycophenolate mofetil (Alba *et al*, 2003; Gomard-Mennesson *et al*, 2006), may be useful agents. Danazol can also act as a steroid-sparing agent and the reported response rate was 60% in a series of 15 patients with secondary AIHA, 12 of whom had SLE (Ahn, 1990). Rituximab, which appears beneficial in refractory lupus (Lan *et al*, 2012), has been successfully used in a small number with AIHA, including complete remission in 4/4 paediatric patients (Kumar *et al*, 2009).

In a series of patients undergoing splenctomy, 3/3 patients responded but 2 responses were partial requiring additional medical therapy (Akpek *et al*, 1999). In other studies, only 1/4 (Gomard-Mennesson *et al*, 2006) and 0/2 (Videbaek, 1962) achieved sustained responses. In a comparison of 15 SLE patients with ITP and/or AIHA treated medically *vs.* 15 who received splenectomy, the frequency of cytopenias was the same but splenectomised patients had significantly more serious infections (18 *vs.* 2) including 2 infection-related deaths (Rivero *et al*, 1979). Splenectomy should therefore be reserved for failure of medical management.

### *SLE where AIHA is the predominant feature: Recommendations*

- **First line: steroids (1B).**
- **Second line: azathioprine, danazol, mycophenolate mofetil, rituximab (2C).**

### *Common variable immunodeficiency*

Immune dysregulation, leading to autoimmunity (especially immune cytopenias) is a common manifestation of primary

immunodeficiencies. Common variable immunodeficiency (CVID) is the most frequent clinically expressed primary immunodeficiency in adults. AIHA occurs in 4-7% of CVID patients. Fewer patients appear to develop immune cytopenias while receiving maintenance immunoglobulin therapy (Wang & Cunningham-Rundles, 2005). Therapy similar to primary warm AIHA can be considered, although lower doses and shorter treatment periods have been recommended (Cunningham-Rundles, 2008). Steroids are usually effective first line therapy and, in one series, 6/9 patients required no further treatment (Wang & Cunningham-Rundles, 2005). In another, 15/18 (83%) responded although only 4 had a sustained complete response (Seve *et al*, 2008). Of 12 patients (5 AIHA; 7 Evans syndrome) receiving rituximab (majority 375 mg/m$^2$ weekly for 4 weeks), 10/12 responded (7/12 complete responses) and 4/8 responding adults maintained their response at 17-105 months. Four had severe infections (Gobert *et al*, 2011). AIHA responded to splenectomy in 4/6 (Resnick *et al*, 2012), 3/5 (Wong *et al*, 2013) and 7/7 patients (Seve *et al*, 2008). In the latter study, 4/7 relapsed after a mean 14 years follow-up.

Post-splenectomy infection from encapsulated bacteria is a particular concern in CVID patients and in one study 5/12 developed life threatening infection with *Streptococcus pneumoniae* and/or *Neisseria meningitides* (Seve *et al*, 2008). All had discontinued prophylactic penicillin. In the largest study, 9/40 CVID patients developed bacterial meningitis or pneumococcal sepsis post-splenectomy (Wong *et al*, 2013). Seven episodes were within 3 years of splenectomy and 7/9 were not on IVIg replacement.

### *CVID: Recommendations*

- **Therapy.**
  - **First line: steroids (1B).**
  - **Second line: rituximab (2C).**
  - **Third line: immunosuppression, splenectomy (2C).**
- **Patients receiving steroids, immunosuppression or splenectomy should also receive maintenance intravenous immunoglobulin (IVIg) (1C).**
- **Patients who require splenectomy should receive lifelong prophylactic antibiotics (1B).**

### *Ulcerative colitis*

Autoimmune haemolytic anaemia is rare in Crohn disease but occurs in 0·5-0·7% of patients with ulcerative colitis (Gumaste *et al*, 1989; Snook *et al*, 1989; Lakatos *et al*, 2003). AIHA almost always occurs in the presence of active colitis (Ramakrishna & Manoharan, 1994) and control of colitis appears central to management. CMV reactivation, common in such patients (Mowat *et al*, 2011) and associated with AIHA (Salloum & Lundberg, 1994) should be excluded. Results with steroids as a single agent are disappointing, with remission of AIHA and colitis in only 5/18 (28%) patients, rising to 7/16 (44%) if combined with immunosuppressive therapy (Ramakrishna & Manoharan, 1994). Immunosuppression is most frequently a thiopurine, with successful use of ciclosporin (Molnar *et al*, 2003) or infliximab (Leo Carnerero *et al*, 2009) reported in refractory cases. Resolution of both AIHA and colitis occurred in 10/10 patients following colectomy and 6/6 following colectomy with splenectomy (Ramakrishna & Manoharan, 1994). Isolated splenectomy achieved remission of AIHA in 4/9 patients (Hernandez *et al*, 1994; Ramakrishna & Manoharan, 1994) but does not treat colitis and the expected durability of remission is unclear.

### *Ulcerative colitis: Recommendations*

- **Patients should be managed in conjunction with a gastroenterologist (1C).**
- **Patients with warm AIHA and active colitis (mild or moderate) should receive first line: (1) oral prednisolone and (2) an immunosuppressive agent, such as azathioprine (1C).**
- **In refractory cases of warm AIHA with active colitis, aim to control the active colitis under the care of a gastroenterologist based on current British Society of Gastroenterology best practice guidelines** (www.bsg.org.uk) **(2C).**
- **Patients with colitis that is poorly controlled or refractory to medical therapy may require panproctocolectomy. This controls both colitis and AIHA such that concomitant splenectomy is not indicated (2C).**
- **If active colitis has been actively excluded, consider treatment as for primary AIHA (2C).**

### *Haematopoietic stem cell transplantation*

Two to four per cent of patients develop AIHA after a median time of 3–10 months following allogeneic HSCT. Alloimmune haemolysis can usually be distinguished by its early presentation, the presence of ABO mismatch or the antibody specificity. Less frequently, alloimmune haemolysis may present later due to mixed chimerism and blood group disparity (Sokol *et al*, 2002; Kordes *et al*, 2008). Serological investigation is aided by undertaking extended red cell typing of donor and recipient prior to transplantation. Alternatively, samples stored following human leucocyte antigen typing can be retrieved for extended red cell genotyping if auto- and panagglutinins occur and specifically ruling out allo-antibodies of donor or recipient origin would be useful. Transplant-associated thrombotic microangiopathy and DIIHA can occur with calcineurin inhibitors (O'Brien *et al*, 2004) and should be considered in the differential. AIHA may coincide with CMV reactivation, onset of graft-*versus*-host disease (GVHD) or relapsing disease (Chen *et al*, 1997).

 

*Treatment.* Autoimmune haemolytic anaemia resolves in less than half of patients treated with steroids and multiple agents are often required. Rituximab is an effective agent and in one series, 8/9 patients responded to steroids and rituximab given first line and 4/5 responded to rituximab second line (Daikeler *et al*, 2013). In other series, rituximab first or second line resulted in complete remission in 8/8 patients (Faraci *et al*, 2014), and combined with prednisolone or other immunosuppression second or third line resolved AIHA in 6/13 cases (Wang *et al*, 2015). Other immunosuppressants, such as azathioprine, mycophenolate mofetil, cyclophosphamide and alemtuzumab, as well as immunoglobulins and plasma exchange have been used but it is often unclear which treatment the patient responded to (Holbro *et al*, 2012). Response to splenectomy was reported in 5/13 (38%) patients from 4 series (Drobyski *et al*, 1996; Chen *et al*, 1997; Cwynarski *et al*, 2001; Wang *et al*, 2015). Severity of AIHA is variable and although some patients die of refractory disease, most deaths are secondary to infection, relapse or GVHD.

### *HSCT: Recommendations*

- **Consider pre-transplant storage of DNA from donor and recipient, for genotyping in the event of the development of auto- and panagglutinins (2C).**
- **At presentation of AIHA, re-evaluate chimerism and remission status. Assess for and treat infection and graft-*versus*-host disease (GVHD) (1C).**
- **Consider switching GVHD prophylaxis (2C).**
- **First line: steroids (2C).**
- **Second line: rituximab (2C).**

### *Solid organ transplantation*

Autoimmune haemolytic anaemia appears rare in adults but occurs in 5-10% of children following liver and/or intestinal transplantation (Botija *et al*, 2010; Czubkowski *et al*, 2011; Li *et al*, 2012) and 2·5% following pancreas transplantation (Elimelakh *et al*, 2007). Unlike alloimmune haemolysis, which usually presents within the first few weeks, AIHA tends to present months or even years after the transplant. Underlying causes, such as CMV infection, parvovirus B19 infection and Epstein Barr virus-associated post-transplant lymphoproliferative disorder, should be identified. The evidence base for treatment is limited. Post-transplant immune suppression (e.g. tacrolimus) is often reduced or switched, but the importance of this is debated (Li *et al*, 2012). First line therapy is usually steroids although response rates appear lower than in primary AIHA (Botija *et al*, 2010; Li *et al*, 2012). Rituximab for relapsed or refractory AIHA resulted in remission for 3/4 (Li *et al*, 2012) and 3/5 (Botija *et al*, 2010) paediatric patients.

### *Solid organ transplantation: Recommendation*

- **At presentation, assess for and treat infection or post transplant lymphoproliferative disorder (1C).**

## Evans Syndrome

Evans syndrome is an uncommon disorder in which there is autoimmune thrombocytopenia (ITP) and AIHA either occurring at the same time, or consecutively. Neutropenia is also a common feature, present in around 55% at presentation (Pui *et al*, 1980; Wang, 1988; Mathew *et al*, 1997). The disease is generally chronic and affects both children and adults (Pui *et al*, 1980).

Although Evans' original description was of an acquired haemolytic anaemia and primary ITP (Evans & Duane, 1949; Evans *et al*, 1951), this combination of immune cytopenias can also be secondary to an underlying disorder. In a review of 68 adults, 50% were secondary, mostly to immunodeficiency, collagen vascular disorders or haematological malignancy (Michel *et al*, 2009). Evans syndrome may also develop following stem cell transplantation, drugs or infection. Another important cause of secondary Evans syndrome is autoimmune lymphoproliferative syndrome (ALPS) (Teachey *et al*, 2010), especially in children.

Because of its rarity, the precise incidence and prevalence of Evans syndrome are not known. In one series of AIHA and ITP cases, only 4% had primary Evans syndrome (Pui *et al*, 1980). The features seen are those expected in ITP or AIHA and include lethargy, jaundice, shortness of breath, petechiae, bruising or mucocutaneous bleeding. Unlike ITP, clinical examination may reveal hepatosplenomegaly. Lymphadenopathy is suggestive of an associated disorder. Important differential diagnoses in suspected Evans syndrome include: paroxysmal nocturnal haemoglobinuria, disseminated intravascular coagulation, liver disease, acquired or inherited thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome and Kasabach-Merritt syndrome. The approach to investigation is similar to that for AIHA but all patients should be tested for ALPS by flow cytometry on peripheral blood for T-cell subsets. Bone marrow examination may help exclude infiltration in patients with pancytopenia.

### *The management of Evans syndrome*

Data for the management of Evans syndrome are limited to case reports and retrospective studies with small numbers of patients (Norton & Roberts, 2006). It is also not always clear for which cytopenia the treatment was initially started. Treatment for secondary Evans syndrome will depend on the underlying disorder and must be individualised.

*First line treatment. Corticosteroids*: Corticosteroids are the mainstay of first line therapy (Pui *et al*, 1980; Wang, 1988). Paediatric studies using prednisone 1-2 mg/kg/day resulted in remission in 5 of 7 children (Pui *et al*, 1980). In adults, the same dose achieved an 83% (53/64) response rate when given for AIHA and 82% for ITP (Michel *et al*, 2009). Unfortunately, the majority of patients relapse.

*Intravenous immunoglobulin*: This is useful for patients with Evans syndrome failing to respond to corticosteroids or requiring high doses of corticosteroids to remain in remission. In responders, one or more of the cytopenias may correct. Short term responses have been reported in 60-87% (Mathew *et al*, 1997; Michel *et al*, 2009). Most patients receive 2 g/kg in divided doses (Norton & Roberts, 2006) although successful treatment of AIHA has been reported with a higher dose of 1 g/kg for 5 days (Hilgartner & Bussel, 1987).

*Second line treatment.* The treatments used are similar to those for AIHA and ITP and include ciclosporin, mycophenolate mofetil, azathioprine, vincristine (for ITP), danazol, rituximab and splenectomy. Most data for immunosuppressants in Evans syndrome are anecdotal and single centre (Mathew *et al*, 1997; Kotb *et al*, 2005). For patients who fail to respond to single agent immunosuppressants, multiagent treatment has been shown to be of some value (Scaradavou & Bussel, 1995; Chemlal *et al*, 1999).

*Azathioprine and other thiopurines*: In larger series, 9-14% of patients received azathioprine (Mathew *et al*, 1997; Michel *et al*, 2009) but response rates were not reported and evidence of effectiveness remains anecdotal for azathioprine (Goebel *et al*, 1974) or mercaptopurine (Tattersall, 1967; Lyu *et al*, 1986).

*Ciclosporin*: Variable doses and responses have been reported from 0·5-10 mg/kg/day (Rackoff & Manno, 1994; Emilia *et al*, 1996; Ucar *et al*, 1999; Williams & Boxer, 2003). Response rates when combined with corticosteroids and danazol reached 89% (Liu *et al*, 2001).

*Danazol*: Limited published data suggest that danazol may be a useful steroid-sparing agent in Evans syndrome (Wang, 1988; Scaradavou & Bussel, 1995). In a retrospective multicentre survey, a 60% response rate was reported in 23 adult patients (Michel *et al*, 2009) but danazol may be less well tolerated in children (Norton & Roberts, 2006).

*Mycophenolate mofetil*: This immunosuppressant has been used in Evans syndrome (Howard *et al*, 2002; Hou *et al*, 2003; Kotb *et al*, 2005; Guirat-Dhouib *et al*, 2010). The number of patients treated is small and it is difficult to estimate the response rates.

*Rituximab*: This has been shown to be of value in several autoimmune diseases and has been used successfully in Evans syndrome. Doses used range from 100 mg weekly for 4 weeks to 375 mg/m$^2$ weekly for up to 4 weeks. Response rates were 13/17 (Bader-Meunier *et al*, 2007), 9/11 (Michel *et al*, 2009), 5/5 (Zecca *et al*, 2003) and 2/4 (Shanafelt *et al*, 2003).

*Splenectomy*: The response rates for splenectomy are lower than those seen in ITP, at less than 70%, but data are limited (Blanchette & Price, 2003). Responses are sometimes transient with relapses seen at 1-2 months post-splenectomy (Pui *et al*, 1980; Wang, 1988; Mathew *et al*, 1997). However in one series, 52% (10/19) maintained a response at a mean follow-up of 8 years (Michel *et al*, 2009). Splenectomy is best avoided in children under the age of 6 years (Norton & Roberts, 2006) but should be considered in older children and adults if other treatments fail.

*Vincristine*: This is useful for treating the thrombocytopenia in Evans syndrome (Wang, 1988). From available data, vincristine looks more useful when combined with other agents (Scaradavou & Bussel, 1995; Williams & Boxer, 2003).

*Treatment options for patients failing second line therapies.* Again, data are very limited but third line agents have included cyclophosphamide, alemtuzumab and stem cell transplantation. Cyclophosphamide has been used at 1-2 mg/kg orally (Oda *et al*, 1985; Wang, 1988; Gombakis *et al*, 1999). Alemtuzumab has been used successfully in a few cases (Willis *et al*, 2001). Stem cell transplantation (autologous and allogeneic) has been reported in a few patients. Although the numbers are small, in one group of patients 50% were alive and in complete remission (Raetz *et al*, 1997; Huhn *et al*, 2003; Passweg *et al*, 2004; Hough *et al*, 2005).

*Novel therapies.* The thrombopoietin receptor agonist, romiplostim, has been used successfully in a patient with Evans syndrome to elevate the platelet count (Gonzalez-Nieto *et al*, 2011). Currently the drug is not approved for use in Evans syndrome but is likely to be useful in this setting.

### *Primary Evans syndrome: Recommendations*

- **First line treatment: Corticosteroids, IVIg (1C).**
- **Second line treatment: azathioprine, ciclosporin, danazol, mycophenolate mofetil, rituximab, splenectomy, vincristine (ITP) (2C).**

## Childhood AIHA associated with giant cell hepatitis

Giant cell hepatitis is a histological finding, more commonly seen in neonates with cholestasis. When associated with AIHA, GCH usually presents between 2 months and 2 years of age with jaundice, hepatomegaly, elevated conjugated bilirubin and alanine aminotransferase. GCH typically presents simultaneously with a DAT-positive (IgG + C) warm AIHA but in a third of cases AIHA presents first (Maggiore *et al*, 2011).

Autoimmune haemolytic anaemia associated with GCH is usually severe and relapsing. Unless there is acute refractory liver failure requiring transplantation, treatment of both

GCH and AIHA is with immunosuppression. Initial treatment has usually been prednisolone and azathioprine, but sustained remission is uncommon. Hepatic injury appears to be B-cell mediated and from two series, 8/8 treatment refractory patients responded to 375 mg/m$^2$ rituximab weekly for 3–5 weeks (Bakula *et al*, 2014; Paganelli *et al*, 2014).

### *Childhood AIHA with giant cell hepatitis: Recommendations*

- **Unexplained elevated hepatic transaminases should lead to the consideration of giant cell hepatitis and liver biopsy (2C).**

## Drug-induced immune haemolytic anaemia

The incidence of DIIHA is approximately 1 per million/year (Garratty, 2010). Over 130 individual drugs have been implicated but the most commonly reported include second- and third-generation cephalosporins, diclofenac, rifampicin, oxaliplatin and fludarabine (Salama, 2009) (see also Table II and Appendix S3 for a detailed list). Therapeutic IVIg can also cause acute haemolysis related to passive transfer of antibodies e.g. to ABO or Rh antigens. Some drugs (e.g. fludarabine, cladribine, levodopa, mefenamic acid and procainamide) cause drug-independent DIIHA that can be serologically indistinguishable from warm AIHA, while others can only be detected *in vitro* in the presence of the drug or its metabolites (drug-dependent DIIHA).

Patients can present within hours of exposure to drug with severe complement-mediated intravascular haemolysis (e.g. ceftriaxone) or sub-acutely with extravascular haemolysis after several months of exposure. Fatality rates of 6-15% have been reported with cephalosporins and diclofenac (Ahrens *et al*, 2006; Garratty, 2010). Acute intravascular DIIHA can be mistaken for a haemolytic transfusion reaction or acute sepsis and the drug history should include perioperative antibiotics and over the counter analgesia (e.g. non-steroidal anti-inflammatory drugs).

**Table II.** Distribution of cases of drug induced haemolytic anaemia in 2 major series.

| | Cases reported by | |
|---|---|---|
| Drug | Garbe *et al* (2011) | Garratty (2010) |
| Anti-infectives | | |
| Ceftriaxone | 3 | 17 |
| Other cephalosporins | | 37 |
| β-lactamase inhibitors | | 6 |
| Piperacillin | 3 | 14 |
| Ciprofloxacin | 3 | |
| Doxycyclin | 2 | |
| Amoxicillin | 2 | |
| Cotrimoxazole | 2 | |
| Influenza vaccine | 2 | |
| Other | 14 | 3 |
| Antineoplastics | | |
| Fludarabine | 6 | |
| Oxaliplatin | 3 | 3 |
| Chlorambucil | 2 | |
| Other | 3 | 1 |
| Musculoskeletal | | |
| Diclofenac | 14 | 1 |
| Paracetamol | 3 | |
| Ibuprofen | 2 | |
| Other | 3 | |
| Cardiovascular | | |
| Hydrochlorothiazide | 3 | |
| Amlodipine | 3 | |
| Ramipril | 3 | |
| Enalapril | 2 | |
| Other | 10 | |
| Alimentary | | |
| Omeprazole | 2 | |
| Other | 2 | 1 |
| Miscellaneous | 12 | |
| Total | 104 | 84 |

Both studies presented 10-year data (2000–2009). In the series reported by Garratty (2010), 36 cases (43%) were due to cefotetan, an antibiotic not available in the United Kingdom.

### *Investigations*

The DAT is almost always positive for IgG and/or C3 (unless massive intravascular haemolysis has occurred or red cell transfusion has been given prior to testing) (Garratty, 2010). Warm AIHA is more common than DIIHA and further investigation is only required if there is clear evidence of haemolysis and a good temporal relationship with the suspected drug. Serological investigation is not indicated if the suspected drug is known to be associated with drug-independent haemolysis (e.g. fludarabine). Investigation should be undertaken by an experienced red cell reference laboratory. The laboratory should be consulted about appropriate samples (e.g. patient's blood, sample of suspected medication, urine from patient or volunteer taking same medication, for metabolites).

### *Management*

The suspected drug should be stopped and haematological improvement usually occurs in 1-2 weeks. In patients with acute severe DIIHA, establish intravenous access and commence fluid resuscitation. Monitor vital signs, urine output, renal function and haemoglobin. Patients may require an intensive care environment and temporary dialysis. Approximately 55% of patients with DIIHA will require blood transfusion (Garbe *et al*, 2011). The addition of steroids is of uncertain benefit and any influence is hard to distinguish from the effects of stopping the drug, however in one study

105/124 (85%) patients received corticosteroids (Garbe *et al*, 2011).

*DIIHA: Recommendations*

- **Discontinue the suspected drug (1A).**
- **When DIIHA is suspected, liaise early with the local red cell immunohaematology reference centre to determine appropriate investigations (1C).**
- **The benefit of corticosteroids is unclear. The decision whether to start corticosteroids must be individualised and will depend on the severity of haemolysis and strength of clinical suspicion that haemolysis is drug-induced (2C).**

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## Author contributions

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## Declaration of interests

All authors have made a full declaration of interests to the BCSH and Task Force Chairs, which may be reviewed on request. The following members of the writing group have no conflicts of interest to declare: QAH, RS, EM, DP, JDG and AH.

## Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website at www.bcshguidelines.com. If minor changes are required due to changes in level of evidence or significant additional evidence supporting current recommendations a new version of the current guidance will be issued on the BCSH website.

## Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Committee for Standards in Haematology (BCSH) nor the publishers accept any legal responsibility for the content of these guidelines.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Systematic review methodology for the 2016 BCSH guideline on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia.

**Appendix S2.** Expanded version of the 2016 BSH guideline on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia.

**Appendix S3.** Drugs associated with cases of immune haemolytic anaemia (IHA), positive direct antiglobulin test (DAT) or both.

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