Guidelines on the Use of Intravenous Immune Globulin for Hematologic Conditions

David Anderson, Kaiser Ali, Victor Blanchette, Melissa Brouwers, Stephen Couban, Paula Radmoor, Lothar Huebsch, Heather Hume, Anne McLeod, Ralph Meyer, Catherine Moltzan, Susan Nahirniak, Stephen Nantel, Graham Pineo, and Gail Rock

Canada's per capita use of intravenous immune globulin (IVIG) grew by approximately 115% between 1998 and 2006, making Canada one of the world's highest per capita users of IVIG. It is believed that most of this growth is attributable to off-label usage. To help ensure IVIG use is in keeping with an evidence-based approach to the practice of medicine, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services convened a panel of national experts to develop an evidence-based practice guideline on the use of IVIG for hematologic conditions. The mandate of the expert panel was to review evidence regarding use of IVIG for 18 hematologic conditions and formulate recommendations on IVIG use for each. A panel of 13 clinical experts and 1 expert in practice guideline development met to review the evidence and reach consensus on the recommendations for the use of IVIG. The primary sources used by the panel were 3 recent evidence-based reviews. Recommendations were based on interpretation of the available evidence and where evidence was lacking, consensus of expert clinical opinion. A draft of the practice guideline was circulated to hematologists in Canada for feedback. The results of this process were reviewed by the expert panel, and modifications to the draft guideline were made where appropriate. This practice guideline will provide the NAC with a basis for making recommendations to provincial and territorial health ministries regarding IVIG use management. Specific recommendations for routine use of IVIG were made for 7 conditions including acquired red cell aplasia; acquired hypogammaglobulinemia (secondary to malignancy); fetal-neonatal alloimmune thrombocytopenia; hemolytic disease of the newborn; HIV-associated thrombocytopenia; idiopathic thrombocytopenic purpura; and posttransfusion purpura. Intravenous immune globulin was not recommended for use, except under certain life-threatening circumstances, for 8 conditions including acquired hemophilia; acquired von Willebrand disease; autoimmune hemolytic anemia; autoimmune neutropenia; hemolytic transfusion reaction; hemolytic transfusion reaction associated with sickle cell disease; hemolytic uremic syndrome/thrombotic thrombocytopenic purpura; and viral-associated hemophagocytic syndrome. Intravenous immune globulin was not recommended for 2 conditions (aplastic anemia and hematopoietic stem cell transplantation) and was contraindicated for 1 condition (heparin-induced thrombocytopenia). For most hematologic conditions reviewed by the expert panel, routine use of IVIG was not recommended. Development and dissemination of evidence-based guidelines may help to facilitate appropriate use of IVIG.

DESCRIPTION OF INTRAVENOUS IMMUNE GLOBULIN

INTRAVENOUS IMMUNE GLOBULIN (IVIG) is a fractionated blood product consisting of concentrated immunoglobulin, primarily immunoglobulin G (IgG), derived from human plasma in pools of 3000 to 10,000 plus donors. Intravenous immune globulin was first introduced in the early 1980s for the treatment of primary humoral immunodeficiencies and is currently licensed by Health Canada for treatment of primary and secondary immunodeficiency diseases, allogenic bone marrow transplantation, chronic B-cell lymphocytic leukemia, pediatric human immunodeficiency virus (HIV)-infection, and idiopathic thrombocytopenic purpura.

In addition to its licensed indications, IVIG is used to treat a growing range of "off-label" indications, including a variety of immunological disorders, hematological conditions, and neurological diseases. Health Canada has not evaluated the efficacy and risk of using a licensed IVIG product in the treatment of off-label clinical indications. Nevertheless, some of these applications have a reasonably strong foundation in the medical literature, whereas others have a less conclusive or even no basis in evidence.

From the IVIG Hematology and Neurology Expert Panels.
Address reprint requests to David Anderson, MD, FRCPC, Professor of Medicine and Pathology, QEII Health Sciences Centre and Dalhousie University, Room 430, Bethune Bldg., 1172 Tower Road Halifax, Nova Scotia, Canada V3H 1V8. E-mail: david.anderson@dal.ca
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In appropriately selected patients and clinical settings, IVIG therapy can be lifesaving. However, there are risks and significant costs associated with IVIG. This provides a strong incentive to ensure that IVIG is prescribed only for appropriate clinical indications where there is a known benefit.[1-3]

RISKS ASSOCIATED WITH IVIG

The rate of systemic reactions to IVIG infusion is usually reported to be in the 3% to 15% range. These reactions are typically self-limited, of mild to moderate severity, and can often be avoided by reducing the rate of infusion during subsequent transfusions of IVIG. However, there is a paucity of published reports of prospectively collected data on the adverse event rate associated with IVIG. Moreover, each brand of IVIG may have unique tolerability and safety profiles because of propriety differences in the manufacturing methods.

A recent review by Pierce and Jain[4] found that a significant number of IVIG-associated serious adverse events affecting renal, cardiovascular, central nervous system (CNS), integumentary, and hematologic systems have been reported. In view of the seriousness of potential adverse events and current lack of data surrounding their frequency, the review concluded that clinicians should limit their prescription of IVIG to conditions for which efficacy is supported by adequate and well-controlled clinical trials.

The risk of infectious complications from IVIG is extremely low. The requirements for donor screening and transmissible disease testing of input plasma are stringent. In addition, the IVIG manufacturing process itself includes at least 1 and usually 2 steps of viral inactivation or removal to protect against infectious agents that might be present despite screening procedures. Hepatitis B virus and HIV have never been transmitted through IVIG. There has been no reported transmission of hepatitis C virus from any product used in Canada, and there is no known case of Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease transmission due to IVIG transfusion. Nevertheless, IVIG is a product made from large pools of human plasma, and it is not possible to claim with certainty that there is no risk of infectious disease transmission.

COSTS OF IVIG

In 1997 there was a worldwide IVIG shortage. The shortage was caused primarily by disruption of production and product withdrawals caused by the need for US-based plasma fractionators to comply with more stringent US Food and Drug Administration requirements. Although such a severe shortage has not recurred, the cost of IVIG has continued to rise. This has led to the adoption of various approaches to control IVIG use in several countries, in particular in Canada and Australia.

Intravenous immune globulin is an expensive therapeutic alternative in disease states where other interventions may be possible or where its efficacy is questionable. Intravenous immune globulin represents the single largest component (approximately one third) of Canadian Blood Services (CBS) plasma protein products budget, which, in turn, represents approximately half of the CBS total budget. Because Canada is not self-sufficient in plasma, IVIG used in this country is manufactured from plasma donated either voluntarily in Canada or by paid donors in the United States. The CBS ensures a supply of IVIG for Canada through multi-year agreements with manufacturers, which provide stability in pricing and purchase volumes. Funding for IVIG comes from provincial and territorial health budgets as part of their payment to CBS; thus, this charge is not directly visible to either patient or provider. Provinces and territories are charged for the actual amount of product used in their province/territory. There are also direct hospital costs, as IVIG must be administered intravenously over several hours.

Intravenous immune globulin currently costs between $51 and $64 per gram (all estimates in Canadian dollars), but in past years, with a less favorable US exchange rate, the cost has been as high as $75 to $80. The cost of one infusion of 1 g/kg of IVIG for a 70-kg adult is approximately $4000 (see Table 1).

Canada's per capita use of IVIG grew by approximately 83% between 1998 and 2004 (and another 18% between 2004 and 2006), making Canada one of the highest per capita users of IVIG in the world. It is believed that most of the growth in use is attributable to off-label usage.

IMPETUS AND MANDATE TO DEVELOP AN IVIG PRACTICE GUIDELINE

In view of the escalating costs, potential for shortages, and growing off-label usage associated with IVIG, over the past 5 years there have been several initiatives in Canada aimed at ensuring IVIG

Table 1. Examples of the Cost of IVIG

Patient	Schedule	Cost of IVIG*		
		0.5 g/kg	1.0 g/kg	2.0 g/kg
20-kg child	1 dose	$550	$1100	$2200
	1 × monthly for 1 y	$6600	$13,200	$26,400
	1 × 3 wk for 1 y	$9350	$18,700	$37,400
70-kg adult	1 dose	$2000	$4000	$8000
	1 × monthly for 1 y	$24,000	$48,000	$96,000
	1 × 3 wk for 1 y	$34,000	$68,000	$136,000

*Cost of IVIG alone does not include costs associated with administration of IVIG. All prices are in Canadian dollars.

use remains appropriate and in keeping with an evidence-based approach to the practice of medicine. Toward this end, CBS convened a national consensus conference entitled, "Prescribing Intravenous Immune Globulin: Prioritizing Use and Optimizing Practice," in Toronto in October 2000. British Columbia implemented an IVIG use management program in 2002, which involved the division of medical conditions into those requiring either "regular" or "special" approval for IVIG use based on the evidence of benefit. The Atlantic provinces implemented a similar program in 2003, and individual facilities in other provinces undertook their own use management initiatives.

To help strengthen these efforts, the National Advisory Committee on Blood and Blood Products (NAC), an advisory group to provincial and territorial Deputy Ministers of Health and Canadian Blood Services regarding blood use management issues, has been working on the development of an interprovincial collaborative framework for IVIG use management. To facilitate this objective, the NAC and CBS convened a panel of national experts to develop an evidence-based practice guideline on the use of IVIG for 18 hematologic conditions.

The mandate of the expert panel was to review evidence regarding use of IVIG for 18 hematologic conditions and formulate recommendations on IVIG use for each condition. The practice guideline developed by this process will provide the NAC with a basis for making recommendations to provincial and territorial health ministries regarding IVIG use management. The practice guideline will also be widely circulated to clinicians in Canada.

METHODS

Expert Panel

Letters of invitation were sent to a number of hematologists from across Canada regarded by their peers as experts in their field. The panel consisted of 13 clinical experts and 1 expert in practice guideline development (see Table 2).

Table 2. Members of the Expert Panel

Experts	Affiliation
Clinical experts	
Dr Kaiser Ali	Head, Division of Pediatric Hematology/Oncology, University of Saskatchewan, Saskatoon
Dr David Anderson (Chair)	Head, Division of Hematology, QE II Health Sciences Centre, Halifax
Dr Victor Blanchette	Chief, Division of Hematology/Oncology, Hospital for Sick Children, Toronto
Dr Stephen Couban	Director, Blood and Marrow Transplant Program, QE II Health Science Centre, Halifax
Dr Lothar Huebsch	President, Canadian Blood and Marrow Transplant Group and Director BMT Program, Ottawa Hospital, Ottawa
Dr Heather Hume	Executive Medical Director, Transfusion Medicine, CBS, Ottawa
Dr Anne McLeod	University Health Network, University of Toronto, Toronto
Dr Ralph Meyer	Division Director, Hematology, Juravinski Cancer Centre and McMaster University, Hamilton
Dr Catherine Moltzan	Medical Director, Hematology/Blood Bank, St. Boniface General Hospital, Winnipeg
Dr Susan Nahirniak	Medical Director, Transfusion Services, University of Alberta, Edmonton
Dr Stephen Nantel	Leukemia/BMT Program of BC, Vancouver General Hospital, Vancouver
Dr Graham Pineo	Head, Division of Hematology, Foothills Hospital, Calgary
Dr Gail Rock	Division of Hematology and Transfusion Medicine, Ottawa Hospital, Ottawa
Practice guidelines expert	
Dr Melissa Brouwers	Director, Program in Evidence-based Care, CCO. Assistant Professor, McMaster University, Hamilton

Abbreviation: BMT, bone marrow transplantation.

Table 3. Included Clinical Conditions

Clinical conditions	
Acquired hemophilia	HDN
Acquired hypogammaglobulinemia	Hemolytic transfusion reaction
Acquired red cell aplasia	Hemolytic transfusion reaction in SCD
AvWD	HUS
Aplastic anemia	HIT
AIHA	HIV-associated thrombocytopenia
Autoimmune neutropenia	Idiopathic thrombocytopenic purpura
Evans syndrome*	PTP
F/NAIT	Virus-associated hemophagocytic syndrome
HSCT	

*Evans syndrome was also reviewed by the expert panel, but specific recommendations were not made for this condition.

The panel met in Toronto on March 10 and 11, 2005. Panel members were asked to declare any potential conflicts of interest. Conflicts were declared and noted by the Chair.

Clinical Conditions

The expert panel evaluated the use of IVIG for 18 hematologic conditions (see Table 3 for further details).

Evidence-Base for Practice Guideline

The expert panel was provided with recent evidence-based reviews of IVIG use from 3 sources:

1. Systematic reviews by the Chalmers Research Institute, University of Ottawa.
   (a) Sources searched: Medline, Embase, Current Contents, PreMedline, Dissertation Abstracts, CENTRAL (Cochrane Library's controlled clinical trials registry) plus manual searching of relevant journals, reference lists, and unpublished sources.
   (b) Dates searched: 1966 to 2004
2. The Appropriateness of IVIG Evidence Review conducted by Dr Feasby and colleagues as part of Canadian Institute of Health Research (CIHR)-funded research, University of Alberta.
   (a) Sources searched: PubMed, the Cochrane Library, and reference lists of relevant publications.
   (b) Publication dates searched: Not reported
3. A systematic review of the efficacy of IVIG produced by Biotext for Australia's National Blood Authority.
   (a) Sources searched: Medline, Embase, Cinahl, BioMedCentral, the Cochrane

Table 4. Sources Used in the Development of the Practice Guideline

Clinical condition	Appropriateness of IVIG review	Chalmers Research Institute SR of IVIG	Australian SR of the efficacy of IVIG	Literature search by expert panel
Acquired hemophilia	✓			
Acquired hypogammaglobulinemia	✓	✓	✓	
Acquired red cell aplasia	✓			✓
AvWD	✓			
Aplastic anemia	✓			
AIHA	✓			
Autoimmune neutropenia	✓			
Evans syndrome	✓			
F/NAIT	✓			
HSCT	✓	✓	✓	
HDN	✓			✓
Hemolytic transfusion reaction	✓			
Hemolytic transfusion reaction in SCD	✓			
HUS	✓			
HIT				✓
HIV-associated thrombocytopenia	✓	✓	✓	
Idiopathic thrombocytopenic purpura in children		✓		✓
Idiopathic thrombocytopenic purpura in adults		✓		✓
PTP	✓			
Virus-associated hemophagocytic syndrome	✓			

Abbreviation: SR, systematic review.

Library, internet searches for policy documents, reference lists of relevant publications, and contacting key researchers.

(b) Publication dates searched: 1982 to 2004

Members of the expert panel were also encouraged to identify any additional studies relevant to the development of evidence-based recommendations (see Table 4 for further information regarding sources used for each of the conditions considered by the expert panel).

The level of evidence available to inform recommendations for each condition was assessed using a system developed by Bob Phillips, Chris Ball, David Sackett, Brian Haynes, Sharon Straus, and Finlay McAlister from the National Health Service Centre for Evidence-Based Medicine (see Table 5 for further details).[5]

Development of Recommendations for Use of IVIG

Recommendations were based on interpretation of the available evidence and where evidence was lacking, consensus of expert clinical opinion.

Table 5. Levels of Evidence

Level of evidence	Whether a treatment is efficacious/ effective/harmful
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval), including well-designed crossover trials
1c	All or none*
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low-quality RCTs)
2c	"Outcomes" research; ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Developed by B. Phillips, C. Ball, D. Sackett, B. Haynes, S. Straus, F. McAlister from the NHS Centre for Evidence-Based Medicine.

Abbreviation: RCT, randomized control trial.

*Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before treatment became available, but none now die of it.

Table 6. Contextual and Methodological Factors

Common factors considered by expert panel
• For rare conditions, small sample size and study design used will not likely improve
• The severity of the condition and the availability of alternative treatment options
• Juxtaposing the level of evidence (eg, case series) against the natural history of the disease
• The presence of clinical heterogeneity of the study sample and/or in presentation of the disorder
• The appropriateness of the comparison group (eg, placebo-controlled or appropriate "standard" therapy)
• The appropriateness of outcomes measured and whether the most important outcomes were evaluated
• The consistency of findings across different studies for the same condition
• The clinical significance of improvement versus statistical significance

Interpretation of the evidence involved recognition and discussion of factors influencing the decision-making process. The expert panel evaluated IVIG for a diverse range of hematologic conditions, and the level of evidence required to recommend IVIG varied depending upon the condition for several reasons. For example, for rare diseases that have no effective alternative treatments, the threshold was lower than for common diseases with established standard therapies (see Table 6 for a list of some of the factors considered by the expert panel in their deliberations). Although the members of the panel are cognizant of the costs associated with IVIG, the role of costs and cost utilization was not systematically factored into the discussions and the recommendations that emerged.

For several of the hematologic conditions addressed by this guideline, IVIG was not recommended for use except under certain urgent or life-threatening circumstances. The expert panel discussed this issue and agreed there may be local variability in the definition of urgent and/or life-threatening circumstances in the context of IVIG use that should be determined at the health center, district, or provincial level. However, to assist the decision-making process, it is recommended that should IVIG be used for these indications, objective outcome measures with a defined review time point be established before the initiation of IVIG therapy. It is also suggested that local blood transfusion or therapeutic review committees be involved in the development of these definitions.

External Review

Feedback on this practice guideline was obtained from hematologists in Canada. The process was informed by the Practitioner *Feedback* methodology used to create clinical practice guidelines on cancer care in Ontario.[6] A draft of this practice guideline along with an accompanying letter of explanation and feedback survey was e-mailed to members of the following associations: Canadian Blood and Marrow Transplant Group, Canadian Hematology Society, Association of Hemophilia Clinic Directors of Canada, Canadian Pediatric Thrombosis and Hemostasis Network, and the Canadian Apheresis Group. The draft guideline was also sent electronically to several hematologists in Ontario and British Columbia. Practitioners were given the option of faxing their completed survey or providing their responses online through a Web-based survey tool. Written comments on the draft guideline were encouraged.

ACQUIRED HEMOPHILIA

Clinical Description

Acquired hemophilia A is a rare bleeding disorder caused by the development of an autoantibody against factor VIII (FVIII). The reported incidence is 0.2 to 1 per million population. Soft tissue and muscle bleeds, hematuria, gastrointestinal bleeding, and postpartum or postoperative hemorrhages are typical presenting features. The bleeding may be life-threatening. Joint bleeding, which is characteristic of the congenital form of hemophilia, is uncommon in patients with acquired FVIII deficiency.

A number of clinical conditions associated with acquired FVIII inhibitors have been reported. These include autoimmune disorders (eg, rheumatoid arthritis, lupus), malignancies (eg, lymphoproliferative), inflammatory bowel disease, pemphigus, drug therapy (penicillin), and postpartum status.

The presence of bleeding manifestations, a prolonged aPTT, which does not correct in vitro with mixing with normal plasma, and a reduced FVIII level on laboratory testing are characteristic. Calculation of the strength of the inhibitor (Bethesda unit [BU] assay) is helpful in guiding therapy. It is important to exclude a nonspecific (lupus-type) inhibitor in the laboratory investigation, but clinically, it is usually not difficult to eliminate this explanation for the prolonged aPTT.

Treatment of these patients is typically 2-pronged: (1) procoagulant and (2) immunosuppressive. Procoagulant strategies include either the use of large doses of rFactor VIII (low titer inhibitors <5 BU) or the use of rFactor VIIa (inhibitor titer >5 BU). This latter product has largely replaced the use of activated factor concentrates (eg, factor VIII inhibitor bypass activator [FEIBA]) for this condition. Immunosuppressive strategies typically include the use of corticosteroids (prednisone, 1-2 mg kg^{-1} d^{-1}) and cyclophosphamide (1-1.5 g IV every 4-6 weeks or 50-150 mg PO daily).

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 2 case series, 1 case series presented data from a literature review of published case reports and a current series (level of evidence, 4). Overall, complete response rate was 22% (8/37), and partial response rate was 43% (16/37) (see Table 7). No data on prior treatment failures were provided.

Table 7. Acquired Hemophilia IVIG Studies

Studies	Design	No. of patients	Intervention	Response*	Clinical outcome
Crenier[7]	Review of published case reports	26	IVIG	Complete: 3/26 (12%) Partial: 13/26 (50%) Failure: 10/26 (38%)	Sustained remission: 4/26 Some benefit: 3/26 No or probably no benefit: 15/26 Not reported: 4/26
	Case series	4	IVIG ± steriods	Partial: 2/4 (50%) Not assessable: 2/4 (50%)	No benefit: 2/4 Uncertain: 2/4 (CR with steroid Tx)
Dykes[8]	Case series	7	IVIG + steriods	Complete: 4/7 (57%) Partial: 1/7 (14%) Failure: 2/7 (29%)	Sustained remission: 4/7 Some benefit: 1/7 No benefit: 2/7 (one pt. died)

Abbreviation: CR, complete response.

*Complete response defined as inhibitor disappeared and partial response as titer decreased ≥25% from baseline.

Interpretation and Consensus

Most patients with acquired hemophilia receive other immunosuppressive therapy, so determining the role of IVIG is difficult. However, it is agreed in the clinical community that rFactor VIIa is the preferred procoagulant therapy, and immunosuppression is achieved with prednisone and cyclophosphamide. In the opinion of the expert panel, there is no convincing evidence of clinical benefit of IVIG in this disorder, and routine use is not recommended.

Recommendation

Intravenous immune globulin is not recommended for routine use in the treatment of acquired hemophilia.

Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies, such as steroids, in urgent situations in this disorder.

ACQUIRED HYPOGAMMAGLOBULINEMIA (SECONDARY TO MALIGNANCY)

Clinical Description

Several cancers may be associated with defects in antibody production. This deficiency may be contributed to by lympholytic chemotherapy. Hypogammaglobulinemic patients with cancer are at increased risk for infection, especially bacterial infections. In addition, both the nature and treatment of the underlying malignancy may be associated with other hematologic risks for infection, including neutropenia and disorders of T-cell function.

The major populations of interest are patients with chronic lymphocytic leukemia (CLL) or multiple myeloma. The number of new cases of multiple myeloma in Canada in 2000 was 1652 (Canadian Cancer Society [CCS], 2004), and in the United States in 2003, it was 14,600 (American Cancer Society [ACS], 2004). There were 7300 new cases of CLL in the United States, suggesting that the annual Canadian incidence is approximately 800 patients. More detailed analyses would be required to determine the percentage of these patients who develop hypogammaglobulinemia.

Patients with cancer-related hypogammaglobulinemia may be treated with antimicrobials and/or growth factors for specific presentations. The rationale for prophylaxis with IVIG is to decrease the risk of infection.

Evidence Summary

Overall, 12 randomized controlled trials of IVIG for acquired hypogammaglobulinemia associated with malignancy were identified (level of evidence, 1b). The Australian systematic review of the efficacy of IVIG included 10 unique randomized trials. A systematic review by the Chalmers Research Institute on this topic included 7 randomized trials, 2 of which were not included in the Australian review. The Appropriateness of IVIG Evidence Review included 4 randomized trials, all of which were included in the other reviews. All of the trials were conducted between 1984 and 1994. A total of 10 of the studies investigated prophylactic use of IVIG, and 2 trials assessed IVIG for treatment of infection.

Seven randomized controlled trials evaluated IVIG prophylaxis in adults compared with either placebo or no therapy. In 4 trials, patients had hypogammaglobulinemia (and/or previous serious infections) associated with CLL, and in 2 trials, patients had hypogammaglobulinemia (and/or previous serious infections) secondary to multiple myeloma. The remaining trial included patients with either CLL or multiple myeloma. The incidence of serious infection, defined as requiring antibiotics, was significantly lower with IVIG compared with controls in all 5 trials that measured this outcome. Data regarding infection rates with IVIG versus controls were not reported in 2 trials (see Table 8 for further details).

Two randomized trials compared different doses of IVIG as prophylaxis for adults with CLL, and neither reported a significant difference in rate of infection.

Three randomized controlled trials evaluated IVIG in children with acute lymphoblastic leukemia. One trial assessed prophylactic use of IVIG and reported significantly fewer infections at 1 year in children given IVIG compared with those who received no therapy (P value not reported). In 2 trials, IVIG was given in addition to antibiotics as treatment for active infection. One trial reported significantly fewer febrile days ($P < .05$) and fewer febrile episodes ($P < .01$) in children who received IVIG plus antibiotics compared with antibiotics alone. The other trial also reported patients treated with IVIG and antibiotics had significantly shorter duration of fever (P value not reported) but found no

Table 8. Acquired Hypogammaglobulinemia (Secondary to Malignancy) IVIG Studies

Study	Design	Intent	No. of patients	Intervention	Outcome	*P*
Chronic lymphocytic leukemia						
Boughton[9]	RCT	Prophylaxis	42	IVIG vs Placebo	Significantly fewer infections overall in IVIG group	.04
					Significantly fewer serious infections in IVIG group	.02
CGSIGCLL[10]	RCT	Prophylaxis	84	IVIG vs Placebo	Significantly fewer serious infections in IVIG group	.026
					Significantly fewer bacterial infections with IVIG	.01
Chapel et al[11]	RCT	Prophylaxis/Dose	34	IVIG 0.5 g/kg vs IVIG 0.25 g/kg	No significant difference between $IVIG_{(0.5\ g)}$ and $IVIG_{(0.25\ g)}$ groups in rate of infection	n.s.
Gamm et al[12]	RCT	Prophylaxis/Dose	36	IVIG 0.5 g/kg vs IVIG 0.25 g/kg	No significant difference between $IVIG_{(0.5\ g)}$ and $IVIG_{(0.25\ g)}$ groups in rate of infection	n.s.
Griffiths et al[13*]	RCT crossover	Prophylaxis	12	IVIG vs Placebo	Significantly fewer serious infections during IVIG	.033
					Significantly fewer serious bacterial infections during IVIG	.001
Molica et al[14]	RCT crossover	Prophylaxis	42	IVIG vs No tx	Significantly lower incidence of both overall and serious infections during IVIG:	
					In 30 patients who completed 6 mo	.01
					In 17 patiens who completed 12 mo†	.02
Multiple myeloma						
Chapel et al[15]	RCT	Prophylaxis	83	IVIG vs Placebo	Significantly lower incidence of serious infections in IVIG group	.007
Hargreaves et al[16]‡	RCT	Prophylaxis	39	IVIG vs Placebo	Serious infection rate was 0.066 infections per patient-month (not clear if this is for IVIG or overall)	NR
Multiple myeloma or CLL						
Schedel[17]	RCT	Prophylaxis	70	IVIG vs controls§	No information provided on infection rates between IVIG and control groups in SR	N/A
Acute lymphoblastic leukemia						
Gebauer et al[18]	RCT	Treatment	48	IVIG + antibiotics vs antibiotics	Significantly fewer febrile episodes in IVIG group	.01
					Significantly fewer febrile days in IVIG group	.05
Gimesi et al[19]	RCT	Prophylaxis	60	IVIG vs no tx	Significantly lower no. of infections at 1year in IVIG group	NR in SR
					No significant difference between groups in number of days with fever	
Sumer et al[20]	RCT	Treatment	33	IVIG + antibiotics vs antibiotics	Significantly shorter duration of fever in IVIG group	NR in SR
					No significant difference between the groups in duration of neutropenia or hospitalization	

Serious infection defined as requiring antibiotics.

Abbreviations: CGSIGCLL, Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia; NR, not reported; N/A, not applicable; n.s., not significant.

*Included patients with CLL or low-grade non-Hodgkins Lymphoma.

†*P* value NR for serious infections.

‡Published as an abstract.

§No details on control group in SR.

significant difference in duration of hospitalization or neutropenia compared with patients who received only antibiotics.

Interpretation and Consensus

Adults. The panel recognized that although the trials were small and dated, their quality was generally adequate to good, and the findings were consistently positive for prophylactic use of IVIG. Evidence regarding the optimum dose and duration of therapy is uncertain. Randomized trials have typically used doses of 0.4 g/kg every 3 weeks for 1 year. There was agreement by the panel members that this dose and schedule are suitable. Although there was agreement that reevaluation of therapy every 4 to 6 months was reasonable, no consensus could be reached regarding the specific criteria to be used regarding the duration of the therapy. Some options included a trial of withdrawal to determine if infection reoccurs or decisions based on the preferences of the patient and physician.

Pediatric. Although the results from 3 small trials were generally positive, in the opinion of the expert panel, the use of IVIG for hypogammaglobulinemia associated with malignancy has not yet been properly evaluated in the pediatric population. Given other prophylactic options and treatments directed at other risks for infection (eg, growth factors and antibiotics for neutropenic-related infections), IVIG is not recommended for routine use in this patient population.

Recommendations

Adult. Intravenous immune globulin is recommended for infection prophylaxis in adults with malignant hematologic disorders associated with hypogammaglobulinemia or dysfunctional gammaglobulinemia and either of the following:

(i) a recent episode of a life-threatening infection that is reasonably thought to be caused by low levels of polyclonal immunoglobulins; or
(ii) recurrent episodes of clinically significant infections (eg, pneumonia) that are reasonably thought to be caused by low levels of polyclonal immunoglobulins.

Based on consensus by the expert panel, IVIG may be considered one option for the treatment of acute life-threatening infection in patients with malignant hematologic disorders associated with hypogammaglobulinemia or more specifically, low levels of polyclonal immunoglobulins.

The panel also recommends health care providers consider the role of other contributing risks for infection (eg, neutropenia or chemotherapy-related mucositis) in determining the likely role of hypogammaglobulinemia in the development of the infectious process.

Pediatric. Intravenous immune globulin is not recommended for routine use in children with hematologic malignancies (with or without hypogammaglobulinemia). The panel recognizes 2 possible exceptions to this general recommendation:

(i) For children with hematologic malignancies with acquired hypogammaglobulinemia and either a history of severe invasive infection or recurrent sinopulmonary infections, IVIG may be considered a treatment option according to the above recommendations for adult patients.
(ii) Some multinational protocols for the treatment of hematologic malignancies (and/or hematopoietic stem cell [HSC] transplantation) in childhood recommend routine use of IVIG for hypogammaglobulinemia, even in the absence of severe or recurrent infections. These recommendations are protocol-specific and not necessarily consistent across protocols of similar intensity. Consequently, the panel suggests that IVIG may be administered to children registered on such clinical trials to comply with protocol recommendations. However, because the benefit of this approach has not been adequately studied and there is considerable uncertainty as to the efficacy of such an approach, the panel suggests that IVIG not be routinely used for non-registered patients.

Dose and Duration

Based on consensus of the expert panel, a dose of 0.4 g/kg every 3 weeks with reevaluation every 4 to 6 months is recommended as a reasonable option for prophylaxis in adult patients.

ACQUIRED RED CELL APLASIA

Clinical Description

Acquired red cell aplasia or pure red cell aplasia (PRCA) is a rare syndrome of severe anemia,

reticulocytopenia, and a selective deficiency of erythroid progenitors in an otherwise cellular marrow. Erythropoietin levels are typically elevated.

There are 3 etiologic subtypes of PRCA: immunologic, viral, and myelodysplastic (MDS) (Abkowitz, JL, ASH Education Book, 2000). Immunologic PRCA is the most common subtype. The immunologic mechanism may be humoral (antibodies against erythroid progenitors) or cellular (T-cell or large granular lymphocyte-mediated). Immunologic PRCA may be caused by tumors (thymoma, lymphoma, CLL, large granular lymphoma) as a paraneoplastic phenomenon unrelated to the extent of tumor. The incidence of PRCA in CLL is 6% and is thought to be due to T-cell dysfunction. Other causes of immunologic PRCA include drugs (azathioprine, procainamide, isoniazid, carbamazepine, and recombinant erythropoietin), connective tissue disorders (rheumatoid arthritis, lupus, Sjogren syndrome), and ABO-incompatible bone marrow transplantation.

Viral PRCA is caused by parvovirus B19 infection. Giant pronormoblasts may be seen in the marrow, although they are not diagnostic as they may be seen in HIV-1–infected individuals without parvovirus infection. P-antigen (globoside) is the cellular receptor for parvovirus B19 infection, accounting for the tropism for erythroid progenitors. Parvovirus B19 infection in healthy individuals is usually asymptomatic because of the 120-day red cell lifespan. It may manifest as erythema infectiosum or slapped cheek syndrome (children) or as a symmetric polyarthropathy (adults). Parvovirus B19 infection in pregnancy may cause nonimmune hydrops fetalis. In immunocompromised individuals, particularly HIV-1–infected patients, and in those with chronic hemolysis, parvovirus B19 may cause PRCA and life-threatening anemia.

Pure red cell aplasia may be the only or initial manifestation of MDS. Abnormal cytogenetics and failure to respond to immunosuppressive therapy characterize this rare subtype.

Treatment of PRCA depends on the etiologic subtype. Standard first-line therapy for immunologic PRCA is prednisone followed by cyclophosphamide or cyclosporin. Other anecdotal therapies include rituximab, alemtuzumab, apheresis, antithymocyte globulin (ATG), IVIG, and bone marrow transplantation. Viral PRCA due to persistent parvovirus B19 infection has been treated with IVIG to reduce viral load. Immunocompromised patients with PRCA due to parvovirus B19 infection are uniformly responsive to IVIG. There has been one case report of a life-threatening parvovirus B19 infection transmitted by IVIG in Japan.[21] Pure red cell aplasia as a manifestation of MDS does not typically respond to immunosuppressive therapy or IVIG.

Evidence Summary

For immunologic PRCA, the Appropriateness of IVIG Evidence Review identified 26 cases treated with IVIG (level of evidence, 4). Overall, 50% (13/26) of patients showed an initial benefit with IVIG, and in 38% (10/26), this was sustained and clinically significant (ie, patients became transfusion independent with little or no toxicity). Information about the duration of remissions is lacking (see Table 9 for further details).

Table 9. Immunologic PRCA IVIG Studies

Study	No. of patients	Response to IVIG	Maintenance IVIG needed
Ballester et al[22]	2	No (one patient tx failure, one patient died of HIV complications)	N/A
Casadevall et al[23]	10	2/10 (20%) transient response after 1 cycle; 8/10 (80%) failures	N/A
Castelli et al[24]	1	Yes (sustained remission)	Yes
Clauvel et al[25]	4	2/4 (50%) responded with remission in 1 to 2 cycles	No
Cobcroft[26]	1	Yes (tx with IVIG + cylcophosphamide + prednisolone)	No
Ilan and Naparstek[27]	1	Yes (complete remission after 1 cycle)	No
Huang et al[28]	1	Yes (remission after 1 cycle)	No
Larroche et al[29]	1	Yes (complete remission after 1 cycle)	No
Mant[30]	1	Yes (sustained remission)	Yes
McGuire et al[31]	1	Yes (sustained remission)	Yes
Needleman[32]	1	Yes (complete remission after 1 cycle)	No
Ohashi et al[33]	1	Failure	N/A
Roychowdhury and Linker[34]	1	Failure	N/A

Table 10. Viral PRCA IVIG Studies

Study	No. of patients	Response to IVIG	Maintenance IVIG needed
Amiot et al[35]	1	Unclear (spontaneous remission of PRCA)	N/A
Koduri et al[36]	1	Yes (resolution with IVIG)	Yes
Koduri et al[37]	8	8/8 (100%) Responded	Yes, 6/8 (75%)
Kondo et al[38]	1	Yes (amelioration with IVIG)	No
Wong et al[39]	1	Failure	N/A

The Appropriateness of IVIG Evidence Review did not include viral PRCA studies. A literature search was conducted by a member of the expert panel. Data for use of IVIG in viral PRCA caused by parvovirus B19 also come from small case series and case reports (level of evidence, 4). Overall, 75% (9/12) of patients showed an initial benefit, and in all of these patients, the benefit was sustained and clinically significant (ie, patients became transfusion independent with little or no toxicity) (see Table 10 for additional information).

Myelodysplastic syndrome–associated PRCA is a rare condition. There are no data on the use of IVIG in this setting.

Interpretation and Consensus

The expert panel recognizes the evidence for use of IVIG for immunologic PRCA is based on anecdotal reports of benefit in which response rate is likely overestimated because of publication bias. The panel also acknowledges that it is not clear if the benefit seen was due to IVIG, as many patients received previous therapies, and IVIG was used with other agents in 1 patient. Despite these limitations, it is the consensus of the panel that IVIG is a reasonable option as a second-line therapy for this serious clinical condition.

Evidence for the use of IVIG for viral PRCA associated with parvovirus B19 is also limited and comes from a small case series and case reports. Three published expert opinions for treatment of parvovirus B19–associated PRCA were identified by the literature review. All 3 made definitive recommendations for the use of IVIG. The panel was surprised at the strength of the published opinions, given the sparse quantity and weak quality of the data. Despite these limitations, it is the consensus of the expert panel that IVIG is a reasonable option as first-line therapy for PRCA associated with parvovirus B19 occurring in an immunocompromised patient. Currently, diagnosis of viral PRCA associated with parvovirus B19 is made based on the typical clinical presentation and the finding of giant pronormoblasts in an immunocompromised patient.

Recommendations

Intravenous immune globulin is not recommended as first-line therapy for immunologic PRCA.

Based on consensus by the expert panel, IVIG is a reasonable option for patients with immunologic PRCA who have failed other therapies (eg, prednisone or cyclosporin).

Intravenous immune globulin should be considered first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients.

Dose and Duration

Based on consensus of the expert panel, 0.5 g/kg weekly for 4 weeks is a reasonable option.

ACQUIRED VON WILLEBRAND DISEASE

Clinical Description

Acquired von Willebrand disease (AvWD) is an unusual acquired bleeding disorder characterized by quantitative/qualitative abnormalities of von Willebrand factor (vWF) protein. It has been described in association with a large number of conditions including lymphoproliferative, myeloproliferative, and autoimmune disorders. The true incidence of the disorder is unknown.

Affected patients demonstrate the same clinical and laboratory abnormalities as those with the congenital and more common form of the disorder. The main differences are that the acquired disorder typically occurs later in life, and there is no associated family history of bleeding. The acquired disorder is due most often to the presence of an inhibitor (antibody) directed against the VWAg/FVIII complex. In some cases, there is adsorption of these proteins by malignant cells, and in hypothyroidism, one proposed mechanism is interference

with von Willebrand factor (vWF) multimeric formation because of impaired protein synthesis.

Primary treatment should be directed toward the underlying condition that often leads to amelioration of the bleeding diathesis. Specific management strategies for the bleeding disorder include the use of Desmopressin, transfusion of factor concentrates (Humate-P), or cryoprecipitate, rFVIIa, immunoabsorption, plasmapheresis, and immunosuppressive medications.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified one small open-label trial that examined the use of IVIG for acquired von Willebrand disease (AvWD) associated with monoclonal gammopathy of unknown significance (MGUS) in patients with mild or moderate bleeding (level of evidence, 4). Intravenous immune globulin progressively normalized the bleeding time and FVIII/vWF measurements in patients with IgG-MGUS, but not in patients with IgM-MGUS. Two patients with IgG-MGUS and gastrointestinal bleeding received additional maintenance IVIG, which was effective (no gastrointestinal bleed in 24 months of follow-up) (Table 11).

Interpretation and Consensus

The expert panel agreed treatment of the underlying disorder is very important and often leads to resolution of AvWD. It is very difficult to extrapolate from the limited evidence the specific role of IVIG in AvWD, but the expert panel agreed that under a few conditions, it might be considered as an option for this very rare disorder.

Recommendations

Intravenous immune globulin is not recommended for routine use in the treatment of AvWD.

Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies in the treatment of AvWD in urgent situations (eg, active bleeding or preoperatively).

APLASTIC ANEMIA

Clinical Description

Aplastic anemia refers to bone marrow failure characterized by pancytopenia and a hypoplastic bone marrow. There are congenital and acquired forms of aplastic anemia. The acquired form can be heterogeneous with respect to etiology, pathogenesis, and severity. Severe aplastic anemia (SAA) is defined by abnormalities in the peripheral blood (2 or more of the following: granulocytes fewer than 0.5×10^9/L, platelets fewer than 20×10^9/L, anemia with reticulocytes less than 40×10^9/L) and bone marrow (one of the following: cellularity less than 25% of normal or cellularity less than 50% of normal with over 70% of the remaining cells being nonhematopoietic).

The incidence of SAA varies internationally. When clear-cut diagnostic criteria were applied to

Table 11. Acquired von Willebrand Disease IVIG Studies

Study	Design and participants	Intervention	Outcome
Federici et al[40]	Repeated measures design	DDAVP → 15 d washout → FVIII/vWF → IVIG*	DDAVP: FVIII/vWF measurements: transient ↑ 10/10 (100%) Bleed time: transient ↓ 10/10 (100%) All measurements returned to near baseline by 4 hrs FVIII/vWF: FVIII/vWF measurements: transient ↑ 10/10 (100%) Bleed time: transient ↓ 10/10 (100%) All measurements returned to near baseline by 4 hrs IVIG: FVIII/vWF measurements: IgG-MGUS: ↑ 8/8 (100%) range 35-55 U/dL until day 18 IgM-MGUS: poor ↑ 2/2 (100%) for 15 d Bleed time: IgG-MGUS: ↓ close to normal 8/8 (100%) until day 18 IgM-MGUS: modest ↓ 2/2 (100%) until day 15
	AvWD with MGUS IgG-MGUS: 8 adults IgM-MGUS: 2 adults		

Abbreviation: DDAVP, synthetic desmopressin.

*IVIG (1 g kg^{-1} d^{-1} for 2 days) administered after unsatisfactory effect of prior tx.

reports of aplastic anemia from various parts of the world, the incidence varied from 2.2 to 25 cases per million people per year, with the highest incidence being reported from Sweden and lowest from Israel and Europe. The incidence of SAA in North America is estimated to be between 2 and 5 cases per million people per year. It is thought that the marked geographic variation in the incidence of aplastic anemia relates mainly to environmental rather than genetic factors.

Acquired aplastic anemia can be related to exposure to a wide variety of drugs, either in a predictable or idiosyncratic fashion, with the commonest being gold, antiepileptics, and nonsteroidal anti-inflammatory drugs, or to ionizing radiation. Numerous viral infections can cause aplastic anemia including hepatitis, parvovirus B19, and HIV, and it can be related to a variety of other uncommon conditions including immune deficiency or autoimmune diseases. Aplastic anemia and paroxysmal nocturnal hemoglobinuria are closely related syndromes, with the paroxysmal nocturnal hemoglobinuria defect being present before the diagnosis of aplastic anemia or appearing later on in its course. Most patients with aplastic anemia are classified as idiopathic, and there is good evidence that autoimmunity plays a major role in the pathogenesis of this disorder. For example, approximately one half of HSC transplants between syngeneic twins are not successful unless the host receives cytotoxic conditioning treatment. Furthermore, aplastic anemia frequently responds to antilymphocyte or antithymocyte globulin with or without cyclosporin, suggesting an autoimmune basis for the disease. Exhaustive studies have shown a number of abnormalities in lymphokines, adding further support for the immune basis for most patients with aplastic anemia. There is little evidence to support an abnormality of the bone marrow stromal cells or of a deficiency of hematopoietic growth factors.

In addition to supportive care with blood products and antibiotics, the main treatment for SAA is HSC transplantation (HSCT) or immunosuppression with ATG/antilymphocyte globulin (ALG) plus cyclosporin. There are few alternatives to these treatments. There is little role for the use of androgen therapy and limited use of the various hematopoietic growth factors.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 8 case reports of aplastic anemia or pancytopenia treated with IVIG with or without other modalities (level of evidence, 4). All 8 cases responded with increases in hemoglobin, platelet count, or white blood cell count (Table 12).

Interpretation and Consensus

Upon review of the case reports, it is the opinion of the expert panel that only 2 of the patients likely had aplastic anemia. There is no evidence to support the use of IVIG in aplastic anemia. The HSCT or immunomodulatory therapy with cyclosporin, antithymocyte globulin, and steroids is the current

Table 12. Aplastic Anemia IVIG Studies

Case Studies	Prior treatment failure	Intervention	Outcome*	Maintenance IVIG (duration)
Aplastic anemia				
Bergen et al[41]	N/A	IVIG	Responded	No
Bourantas et al[42] †	N/A	IVIG + steriods + platelets + RBCs + GM-CSF	Responded	No
Chen et al[43,44]	Yes	IVIG + platelets	Responded	No
Kapoor et al[45]	Yes	IVIG	Responded	Yes (6 mo)
Pancytopenia				
De Lord et al[46]	N/A	IVIG + steriods	Initial response, hemolysis recurred, patient died	N/A
Lutz et al[47]	N/A	IVIG	Responded	Yes (18 mo)
Salim and Salim[48]	Yes	IVIG	Responded	No
Sherer et al[49]	Yes	IVIG	Responded	No

Abbreviation: GM-CSF, granulocyte-monocyte colony-stimulating factor.

*Response defined as increased hemoglobin, platelet count, or white blood cell count.

†Aplastic anemia during pregnancy.

and appropriate standard of care for these patients, and the panel agreed that to delay this practice standard to offer IVIG would be inappropriate.

Recommendation

Intravenous immune globulin is not recommended for the treatment of aplastic anemia.

AUTOIMMUNE HEMOLYTIC ANEMIA

Clinical Description

Autoimmune hemolytic anemias (AIHAs) are a group of disorders caused by autoantibodies that bind to antigens on the red blood cell (RBC) surface and initiate red cell destruction. These disorders are classified according to the temperature at which the RBC autoantibody binds. Autoimmune hemolytic anemia is most commonly caused by warm IgG autoantibodies that bind at 37°C and lead to extravascular destruction of RBCs. Warm AIHA may be idiopathic but more commonly is related to an underlying cause such as a lymphoproliferative disorder, malignancy, immunodeficiency disorder, or other autoimmune disease.

Autoimmune hemolytic anemia is relatively uncommon, with an estimated incidence of 1 to 3 cases per 100,000 population per year, is more common in women (2:1 ratio), and tends to peak in the fourth and fifth decades of life. The clinical presentation is variable; jaundice is common, and symptoms include weakness, dizziness, and dyspnea related to anemia. Laboratory abnormalities include anemia with an elevated mean cell volume, reticulocytosis, indirect hyperbilirubinemia, and an increased lactate dehydrogenase. The peripheral blood film generally shows polychromasia and spherocytosis. These findings, in addition to a positive direct antiglobulin test, are consistent with the diagnosis of warm AIHA. The diagnosis of warm AIHA always warrants a search for a secondary cause, which may help direct therapy.

First-line treatment for warm AIHA is usually corticosteroids. If patients relapse when steroids are tapered, splenectomy is the usual second-line treatment in good surgical candidates. Other treatment options in patients who relapse post-splenectomy or who are not surgical candidates include cytotoxic drugs, plasmapheresis, IVIG, and danazol. More recently, the use of rituximab and autologous HSC transplant in very severe cases have been reported.

Autoimmune hemolytic anemia also occurs as a result of cold-reactive autoantibodies that bind to RBCs at temperatures less than 37°C. These antibodies can cause 2 distinct clinical syndromes: cold agglutinin disease or paroxysmal cold hemoglobinuria (PCH). Cold agglutinins are IgM autoantibodies that typically arise in the context of a lymphoproliferative disorder or an infectious disease such as infections with mycoplasma or Epstein-Barr virus. Paroxysmal cold hemoglobinuria is caused by a biphasic IgG autoantibody, the Donath-Landsteiner antibody, which initiates complement fixation in the cold and completes it on warming. Both cold agglutinin disease and PCH respond poorly to steroids or splenectomy, and treatment is usually supportive, including avoidance of exposure to the cold. Plasmapheresis can provide temporary improvement in very severe cases and may be helpful before surgery requiring cold exposure.

The differential diagnosis of AIHA includes other causes of immune-mediated hemolysis such as drugs and nonimmune causes of hemolysis such as inherited RBC membrane and enzyme disorders, sepsis, and microangiopathic hemolysis.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified one article that combined data from 37 published case reports and 3 pilot studies examining IVIG therapy for AIHA (level of evidence, 4). Overall, 40% of patients with AIHA responded to IVIG. Response rate in this study was defined as an increase in hemoglobin of at least 2 g/dL within 10 days of starting IVIG. Two variables were strongly correlated with a good response to IVIG: the presence of hepatomegaly and a low pretreatment hemoglobin level. This study did not identify the type or cause of AIHA (Table 13).

Interpretation and Consensus

There is sparse evidence available on the use of IVIG in AIHA. Furthermore, the evidence did not address and distinguish among important clinical characteristics of this disorder (eg, idiopathic vs secondary disease). The expert panel also recognized that the operational definition of the primary outcome, response rate, was very liberal. Despite being liberally defined, response rates with IVIG were substantially less than accepted published response rates with other treatment alternatives (eg,

Table 13. Autoimmune Hemolytic Anemia IVIG Studies

Study	Design and participants	Intervention	Results	*P*
Flores et al[50]	Combined data from published case reports and 3 pilot studies	IVIG	Overall response rate: 29/73(40%)*	
			Pediatric response rate: 6/11 (55%)	n.s.
	Case reports: 37 patients		Adult response rate: 23/62 (37%)	
	Pilot studies: 36 patients		In most responders, ↑ Hb remained ≥ 3 wk	
	Prior tx: 46/73 (63%)		Response to IVIG:	
			Strong correlation with low pre-tx Hb	.001
			Strong correlation with hepatomegaly (>90%)	NR in SR

Abbreviations: tx, treatment; Hb, hemoglobin.

*Response defined as ↑ Hb ≥ 2 g/dL within 10 days of starting IVIG.

corticosteroids and splenectomy). Therefore, the expert panel agreed the overall role of IVIG for this condition is very limited.

Recommendations

Intravenous immune globulin is not recommended for routine use in either acute or chronic treatment of AIHA.

Based on consensus by the expert panel, IVIG may be considered among the options for treatment of severe life-threatening AIHA.

AUTOIMMUNE NEUTROPENIA

Clinical Description

Autoimmune neutropenia is a disorder caused by increased peripheral destruction of antibody-sensitized neutrophils by phagocytic cells in the reticuloendothelial system; the autoantibodies are best detected using a combination of granulocyte immunoflorescence and agglutination tests. Most autoantibodies show specificity for neutrophil-specific antigens that are located within the neutrophil restricted glycoproteins (eg, NA1) or leukocyte adhesion molecules CD11b/CD18.

Autoimmune neutropenia can be classified as primary or secondary. In children, the disorder is most often primary with spontaneous resolution occurring in most cases within months to a few years. Most affected children are young (peak age, 6-18 months) and manifest an increased incidence of minor infections, often respiratory in nature. Absolute neutrophil counts are less than 0.5×10^9/L in two thirds of cases, and a compensatory monocytosis is often seen. A bone marrow aspirate, if performed, typically shows normal or increased cellularity with a reduced number of band and mature neutrophils. Management is generally conservative with granulocyte colony-stimulating factor (G-CSF) therapy restricted to patients with severe or recurrent infections or before surgical intervention. By contrast to the generally benign, self-limiting disorders seen in children ("chronic benign neutropenia"), autoimmune neutropenia in older subjects is often secondary to an underlying disease, for example, systemic lupus erythematosus or lymphoproliferative disorders. Treatment for patients with secondary autoimmune neutropenia should be directed primarily at management of the underlying disorder. A transient form of neutropenia may occur in newborn infants of mothers with autoimmune neutropenia and is due to transplacental passage of pathologic autoantibodies from the mother to the fetus.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 3 case series and 5 case reports of IVIG for autoimmune neutropenia (level of evidence, 4). Many of these case reports predate the era of G-CSF. In the largest case series, only 50% of the patients treated with IVIG responded with an increase in neutrophil count to greater than 1.5×10^9/L compared with 100% for G-CSF and 75% for corticosteroids (Table 14).

Interpretation and Consensus

The routine management of primary autoimmune neutropenia in children is watchful waiting with supportive care, as over 80% of cases spontaneously recover. If treatment is required, G-CSF is the standard of care for first-line treatment. The evidence to support treatment with IVIG is sparse and of poor quality. However, there was some discussion regarding its use in rare

Table 14. Autoimmune Neutropenia IVIG Studies

Studies	No. of patients	Prior tx failure	Intervention	Response*	Maintenance IVIG needed
Pediatric					
Bussel et al[51]	2	Yes	IVIG	2/2 (100%) responded	Yes (1 patient)
Bussel et al[52]	8	NR	IVIG	7/8 (88%) responded	No
Bux et al[53]	31	N/A	IVIG or G-CSF or steroids	IVIG: 50% responded (transient ↑) G-CSF: 100% responded (sustained ↑) Steroids: 75% responded (sustained ↑)	NR
Gordon et al[54]	1	N/A	IVIG	Responded	No
Hilgartner and Bussel[55]	6	NR	IVIG	6/6 (100%) responded	No
Mascarin and Ventura[56]	1	Yes	IVIG	Responded	Yes
Sorensen and Kallick[57]	1	Yes	IVIG	Responded	Yes
Adult					
Alliot et al[58]	1	Yes	IVIG	Responded	N/A
Schoengen et al[59]	1	N/A	IVIG	Responded	Yes

Abbreviation: Hb, hemoglobin.
*Response defined as an ↑ in absolute neutrophil count to greater than 1500/μL.

circumstances when other options (eg, intravenous antibiotics and G-CSF) have failed.

Recommendation

Intravenous immune globulin is not recommended for routine treatment of autoimmune neutropenia.

Based on consensus by the expert panel, IVIG may be considered among the treatment options in rare circumstances of autoimmune neutropenia when the standard of care or G-CSF fails.

EVANS SYNDROME

Clinical Description

Evans syndrome is an immunologic abnormality characterized by the simultaneous or sequential occurrence of warm AIHA and immune thrombocytopenic purpura (ITP) in the absence of an underlying etiology. This is a rare disorder with a chronic relapsing course and is associated with significant morbidity despite therapy. Evans syndrome is a diagnosis of exclusion, and other causes of autoimmune cytopenias such as rheumatologic conditions, malignancies, sepsis, and immunodeficiency syndromes must be ruled out. There is a substantial risk for development of other autoimmune disorders in these patients, and a number of different defects in humoral immunity have been described. Treatment approaches are usually similar to those for AIHA and ITP, but patients have a very high rate of relapse and often require therapy with multiple agents. Reports of treatment with corticosteroids, cytotoxic drugs, and danazol show variable responses. Splenectomy has also been described, but most reports suggest very brief remissions often associated with infectious complications, making this procedure of questionable value in this disorder. The use of rituximab and stem cell transplantation have also been described for very severe cases unresponsive to other therapies.[60]

Evidence Summary

The Appropriateness of IVIG Evidence Review identified one retrospective chart review, one physician survey, and several case reports of IVIG for Evans syndrome (level of evidence, 4). The retrospective chart review included 5 patients (4 children and 1 adult). All of the patients received treatment with multiple agents, including corticosteroids. When IVIG was used to treat AIHA symptoms, 3 patients had a good response, 1 patient did not respond, and 1 patient was not given IVIG. When IVIG was used to treat ITP symptoms, 1 patient had a good response, 3 patients had a transient response, and response was therapy-dependent in 1 patient. Results from a survey of pediatric hematologists reported complete remission in 22% (9/40) of patients given IVIG plus steroids. Overall response rate from the case reports was 70% (7/10); however, response was transient in 50% (5/10) of the cases (Table 15).

Interpretation and Consensus

It is acknowledged that Evans syndrome includes a wide range of autoimmune conditions, particularly in the pediatric population, and that cases reported in the literature are likely the extreme cases. Evans syndrome has a very poor response

Table 15. Evans Syndrome IVIG Studies

Study	Design	No. of patients	Intervention	Response to IVIG
Scaradavou and Bussel[61]	Retrospective chart review	5	IVIG ± steroids ± other tx	For AIHA symptoms: No response: 1/4 (25%) patients Good response: 3/4 (75%) patients One patient was not given IVIG for AIHA For ITP symptoms: Transient response: 3/5 (60%) patients Response was therapy-dependent: 1/5 (20%) Good response: 1/5 (20%)
Mathew et al[62]	Physician survey	40	IVIG ± steroids ± other tx	No response: 5/40 (13%) Transient response: 26/40 (65%) Complete response (with remission): 9/40 (22%)
Ucar et al[63]	Case report	1	IVIG ± steroids ± other tx	Responded: 2/10 (20%) patients
Gombakis et al[64]	Case report	1		Transient response: 5/10 (50%) patients
Chang et al[65]	Case report	1		
Muwakkit et al[66]	Case report	2		No response: 3/10 (30%) patients
Muwakkit et al[67]	Case report	1		
Petrides and Hiller[68]	Case report	1		
Friedmann et al[69]	Case report	1		
Qureshi et al[70]	Case report	1		
Bolis et al[71]	Case report	1		

Good response indicates remission for 1 month without treatment; therapy-dependent, response to treatment but continued need for treatment.

rate to any therapy, including IVIG, where initial responses are poor and transient, relapse is high, and subsequent responses worse. Evidence regarding IVIG use in Evans syndrome has focused on the pediatric population, and generalization to the adult population, given the complexity of the syndrome, is probably not appropriate. The role of IVIG is difficult to ascertain because most treatment options focus on multiagent regimens. Furthermore, the panel emphasized that the diagnosis of Evans syndrome is often made retrospectively, and patients are often initially treated as having either ITP or AIHA depending upon presentation. In addition, the panel discussed that Evans syndrome is largely a historic term used before there was a clearer understanding of the range of autoimmune cytopenias. Treatment should be dictated by the cytopenias and other underlying autoimmune diseases present. The panel recommends that the primary symptoms be the focus of treatment. For patients with predominantly ITP symptoms, use of IVIG is recommended as outlined in the ITP section of this guideline. Similarly, for patients with primarily AIHA symptoms, IVIG is recommended as described in the AIHA section of the guideline.

Recommendation

The panel recommends that the primary symptoms be the focus of treatment. Please refer to the appropriate sections of this guideline.

FETAL-NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Clinical Description

Fetal-Neonatal alloimmune thrombocytopenia (F/NAIT) is a disorder that occurs in a fetus when the mother produces alloantibodies against a platelet antigen on fetal platelets. The F/NAIT occurs as a result of transplacental passage of maternal alloantibodies against platelet antigens shared by the father and the fetus. When the fetus inherits a platelet antigen from the father that is foreign to the mother, the maternal immune system may be stimulated to produce an IgG antibody that then crosses the placenta and leads to the destruction of fetal platelets. Babies may develop thrombocytopenia resulting in petechiae or bleeding. In severe cases (10%-30%), intracranial hemorrhage (ICH) resulting in long-lasting disability or death may occur in utero or shortly after birth. The F/NAIT occurs most

commonly in white populations with an incidence between 1:1000 and 1:1500 live births.

The pathophysiology of F/NAIT can be considered the platelet equivalent of hemolytic disease of the newborn, although clinically, the 2 disorders are quite different. Unlike hemolytic disease of the newborn, F/NAIT often occurs in a first pregnancy and may only be diagnosed after an affected baby is born. Several different platelet alloantigens have been identified. The most common maternal antibodies in white populations are directed against the human platelet alloantigen, HPA-1a. The development of alloantibodies is not seen in all cases of platelet alloantigen incompatibility, and the presence of certain HLA haplotypes is clearly linked to an increased risk of developing F/NAIT.

The differential diagnosis of F/NAIT includes other immune causes such as neonatal ITP, infection or intravascular coagulation, and hereditary thrombocytopenia. However, in an otherwise well infant with unexplained thrombocytopenia, the clinical suspicion for F/NAIT should be very high. Once F/NAIT is suspected, platelet alloantigen testing of the baby and parents and a search for maternal alloantibodies should be carried out to confirm the diagnosis. The risk of recurrence in subsequent pregnancies is 100% if the father is homozygous for the responsible platelet antigen and 50% if he is heterozygous. The severity of the thrombocytopenia usually increases with each pregnancy, making intervention in subsequent pregnancies necessary.

Postnatal management of thrombocytopenia in affected infants is usually transfusion of antigen-compatible platelets from the mother or an antigen-negative blood donor until the platelet count recovers. However, appropriate antenatal interventions for subsequent pregnancies are less clear. Interventions that have been tried include IVIG and/or corticosteroid treatment in the mother and intrauterine platelet transfusions to the fetus. Studies are currently ongoing to assess the role of corticosteroids as adjuvant therapy to IVIG administered to the mother and management of IVIG failures.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 1 nonrandomized comparison study, 1 retrospective chart review, and 3 case series (level of evidence, 4). The strongest evidence for use of IVIG comes from the nonrandomized study, in which treatment was with IVIG or steroids. Overall,

Table 16. Fetal Alloimmune Thrombocytopenia IVIG Studies

Study	Design	No. of patients	Intervention	Outcome
Kaplan et al[72]	Nonrandomized study*	37	Maternal IVIG or corticosteroids	Success (↑ PC + no ICH): IVIG 7/27 (26%); steroids 1/10 (10%) Plateau (no change PC + no ICH): IVIG 11/27(41%); steroids 2/10 (20%) Failures (↓ PC ± ICH): IVIG 9/27 (33%); steroids 7/10 (70%)
Gaddipati et al[73]	Retrospective chart review	74	Maternal IVIG ± steroids	Response (PC at second FBS ≥ PC at first FBS): 82% cases No occurrences of ICH
Giers et al[74]	Case series	7	Maternal IVIG	↑ PC >50 × 10^9/L: 13/34 (38%) cases
Silver et al[75]	Case series	18	Maternal IVIG or fetal IVIG†	PC stabilized: 3/34 (9%) cases
Kornfeld et al[76]	Case series	9	Maternal IVIG	No maternal or fetal complications (including ICH)
Bussel et al[77]	RCT blinding: NR	54	IVIG vs IVIG + steroids	No difference between groups on any outcome measured, including mean rise in PC (first FBS to second FBS), mean PC at birth, mean gestational age at birth
Birchall et al[78]	Retrospective + prospective cases	56	Maternal IVIG ± steroids‡	↑ Fetal PC >50 × 10^9/L: 12/18 (67%) cases treated with IVIG ± steroids

Abbreviations: FBS, fetal blood sample; PC, platelet count; IUPT, intrauterine platelet transfusion.

*Each center in study decided on therapy, severe cases were excluded and received IUPT.

†Administered into umbilical vein.

‡IUPT if PC <20 × 10^9/L.

67% (18/27) of cases treated with IVIG responded with increased or stabilized fetal platelet counts and no ICH compared with 30% (3/10) of those treated with steroids. The retrospective chart review reported a response rate of 82%, when response was defined as a second fetal blood sample platelet count being greater than or equal to the first. The primary outcome measure in the 3 case series was fetal platelet count. In 38% (13/34) of cases, fetal platelet count increased to greater than 50×10^9/L.

Two additional articles were identified by an updated literature search. A Cochrane systematic review of antenatal interventions for F/NAIT included one randomized control trial of IVIG versus IVIG plus steroids. Response rate was not significantly different between the groups. The other study reviewed 56 cases of NAIT. Maternal IVIG therapy with or without steroids increased fetal platelet count to greater than 50×10^9/L in 67% (12/18) of cases. The remaining cases were treated with serial intrauterine platelet transfusion (Table 16).

Interpretation and Consensus

The panel agreed that although the quantity of evidence for IVIG in the antenatal treatment of F/NAIT was limited and the quality of evidence was weak, the body of evidence is unlikely to improve. Given that the condition is very rare but the consequences are frequent and extremely serious (ICH, death), consensus was unanimously reached that IVIG is an appropriate option and should be the standard of care. This opinion is also supported by the European Collaborative and is the standard of care in several Canadian centers. There is no evidence to support or refute a specific IVIG dose for the treatment of this condition. However, studies done to date have used a dose of 1 g/kg weekly, and there was agreement that this is a suitable option.

No evidence is available for the use of IVIG in the treatment of newborns with this condition. In the opinion of the expert panel, the provision of antigen-negative compatible platelets should be considered first-line therapy and IVIG adjunctive.

Recommendations

Treatment of F/NAIT before delivery. Intravenous immune globulin is recommended as the standard first-line antenatal treatment of fetal alloimmune thrombocytopenia (FAIT).

Candidates for treatment include the following:

(i) Pregnant women with a previously affected pregnancy. Intravenous immune globulin should be initiated at a time in the pregnancy that corresponds to a gestational age in the present fetus that precedes by some weeks the time at which bleeding was thought or known to occur in the first pregnancy.
(ii) Pregnant women with a familial history of F/NAIT or those found on screening to have platelet alloantibodies. Timing of IVIG treatment should be based on the severity of fetal thrombocytopenia determined by cordocentesis. Expert opinion suggests treatment should be initiated around 20 weeks and no later than 30 weeks.

Given the complexity of this disorder and its management, it is strongly recommended that treatment be under the direction of a high-risk obstetrical center with specialized expertise in the treatment of F/NAIT.

Treatment of a Newborn with F/NAIT. In the opinion of the expert panel, the provision of antigen-negative compatible platelets should be considered first-line therapy and IVIG adjunctive. Given the lack of evidence to guide management in this rare disorder, it is strongly recommended that treatment of newborns with F/NAIT be under the direction of a center with specialized pediatric expertise in the treatment of this condition.

Dose and Duration

Treatment of F/NAIT Before Delivery. Based on consensus by the expert panel, a dose of 1 g/kg every week is recommended as a reasonable option for the antenatal treatment of F/NAIT.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Clinical Description

Allogeneic and autologous HSCT are curative or palliative treatments for many hematologic cancers (acute and chronic leukemia, lymphoma, myeloma, and MDS), some solid tumors (eg, germ cell tumors), and nonmalignant conditions (eg, aplastic anemia, thalassemia, rheumatologic, and neurologic disorders). In Canada in 2003, there were 526 allogeneic and 849 autologous

Table 17. Hematopoietic Stem Cell Transplantation IVIG Studies

Study	Design and participants	No. of patients	Intervention	Outcome	*P*
Allogenic HSCT					
Chalmers group (in progress)	SR with meta-analysis MA included 4 trials for GvHD (n = 695 patients) and 3 trials for overall survival (n = 664 patients)	–	IVIG vs No IVIG	Significant ↓ in acute GvHD* with IVIG vs no tx: OR, 0.63 [95% CI, 0.42-094; random] No significant difference in overall survival: OR, 0.81 [95% CI 0.59-1.10; Random]	.02 n.s.
Cordonnier et al[79]	RCT (adults and children) HLA identical sibling HSCT	200	IVIG 0.05 g/kg vs IVIG 0.25 g/kg vs IVIG 0.5 g/kg vs Placebo	No significant difference in infections, GvHD, TRM, or OS between IVIG groups and placebo. Severe VOD more frequent as IVIG dose increased	n.s. .01
Abdel-Mageed et al[80]	RCT (adults and children) Related + unrelated HSCT	350	IVIG 0.25 g/kg vs IVIG 0.5 g/kg	No significant difference in infection-free survival Significant ↓ acute GvHD with $IVIG_{(0.5\ g)}$ vs $IVIG_{(0.25\ g)}$	n.s. .03
Feinstein et al[81]	RCT (adults) Matched related BMT	260	IVIG 0.5 g/kg vs No IVIG	No significant difference IP, overall aGvHD, TRM, OS Significantly ↑ relapse rate in IVIG group	n.s. .03
Winston et al[82]	RCT (Adults and children) Allogenic BMT	618	IVIG 0.1 g/kg vs IVIG 0.25 g/kg vs IVIG 0.5 g/kg	No significant difference in acute GvHD, infection rate, IP, relapse rate or OS between groups	n.s.
Winston et al[83]	RCT (adults and children) Allogenic BMT	51	IVIG + CMV(-) BP vs CMV(-) BP	No significant difference in OS, IP, or fatal infections Significant ↓ in viral infections in IVIG group Significant ↓ GvHD (Grade II-IV) in IVIG group	n.s. .03 .04
Winston et al[84]	RCT (adults and children) Allogenic BMT	89	IVIG vs No IVIG	Significant ↓ in aGvHD (*P* = .01), IP (*P* = .02), and symptomatic CMV infection (*P* = .03) with IVIG No significant difference in overall mortality rate	—
Zikos et al[85]	RCT (adults and children) HLA identical sibling HSCT	128	IVIG vs hyperimmune CMV IgG	No significant difference in infections, IP, acute or chronic GvHD, CMV antigenemia, relapse, or OS	n.s.

Ruutu et al[86]	RCT Allogenic; CMV seronegative	28	IVIG vs no IVIG	No significant difference in incidence of CMV infection between IVIG group and controls	n.s.
Bowden et al[87]	RCT Allogenic; CMV seronegative	120	IVIG vs no IVIG	No significant difference in incidence of CMV infection or survival between IVIG group and controls	n.s.
Lum et al[88]	RCT HLA matched sibling HSCT	54	IVIG vs no IVIG	No significant difference in acute or chronic GvHD, OS or infection-related mortality	n.s.
Pole[89]	RCT (adults and children) Allogenic BMT	150	IVIG 0.25 g/kg vs IVIG 0.5 g/kg	Published as an abstract. Results not reported by group	NR
Autologous or allogenic HSCT					
Poynton et al[90]	RCT (adults) Autologous or allogenic BMT	72	IgM + IgA enriched IVIG vs No IVIG	Significant ↓ in infection-related mortality with IVIG Endotoxin levels significantly ↓ in IVIG group	NR .02
Sullivan et al[91]	RCT HLA identical, HLA nonidentical, or autologous HSCT	250	IVIG (until day 90) vs IVIG (until day 360)	No significant difference in septicemia, bacteremia, obliterative bronchiolitis, chronic GvHD, or OS	n.s.
Sullivan[92]	RCT (adults and children) Sibling allogenic, matched unrelated donor, or autologous HSCT	382	IVIG vs No IVIG	Significant reduction in both septicemia (RR, 2.65) and local infections (RR, 1.36) with IVIG vs no IVIG For patients ≥ 20 y: significant ↓ in NRM and significantly less aGvHD grade II-IV with IVIG	.0039 .029 .083 .005
Autologous HSCT					
Wolff et al[93]	RCT (Adults) Autologous BMT†	170	IVIG vs No IVIG.	No significant difference in infection or platelet use Significant ↓ survival in IVIG group Higher incidence of VOD in IVIG group.	n.s. .02 NR

Abbreviations: MA, meta-analysis; CMV (-) BP, CMV seronegative blood products; VOD, venoocclusive disease; TRM, transplantation related mortality; OS, overall survival; aGvHD, acute GvHD; NRM, nonrelapse related mortality; MUD, matched unrelated donor; IP, Interstitial pneumonia.

*Grade II-V GvHD.

†Included patients undergoing autologous BMT or severe myelosuppressive therapy.

HSCT (source: Canadian Blood and Marrow Transplant Group).

There is significant but variable nonrelapse mortality after HSCT according to both the indication for transplant and the transplant type (autologous 5%-10%; related allogeneic 15%-30%; unrelated allogeneic 30%-50%). Infections (bacterial, viral, fungal) are a major cause of nonrelapse mortality post-HSCT. In allogeneic HSCT, graft-versus-host disease (GvHD) and its treatment contribute significantly to nonrelapse mortality.

Immunosuppression post-HSCT lasts for months or years as a consequence of the HSCT itself and, in the allogeneic setting, as a consequence of GvHD and its treatment. Intravenous immune globulin has been used, particularly postallogeneic HSCT, to ameliorate post-HSCT immunodeficiency. In Europe, 55% of transplant centers use IVIG post-HSCT.[93a] The use of IVIG post-HSCT in Canada is likely lower, but specific data about use of IVIG posttransplantation in Canada are not available.

Different types of HSCT are associated with significantly different post-HSCT immune deficits, partly due to the type of transplant (autologous, related allogeneic, unrelated allogeneic; the latter 2 of which can be myeloablative or nonmyeloablative) and partly due to the underlying indication for transplant. There are specific, validated protocols and interventions to reduce specific infections and GvHD post-HSCT (empiric therapy for febrile neutropenia, fungal prophylaxis, cytomegalovirus [CMV] surveillance and preemptive therapy, *Pneumocystis carinii* prophylaxis, post-HSCT immunization, and GvHD prophylaxis and treatment).

The broad issue is understanding how IVIG affects the outcome of transplantation when used in addition to standard post-HSCT supportive care. It is also important to consider the role of IVIG in specific circumstances (eg, post-HSCT CMV disease or recurrent sinopulmonary infections with persistent hypogammaglobulinemia).

Evidence Summary

Overall, 15 randomized controlled trials of IVIG post-HSCT were identified (Table 17) among the 3 evidence reviews considered in this report (level of evidence, 1b). The Appropriateness of IVIG Evidence Review included 7 randomized controlled trials. A systematic review by the Chalmers Research Institute on this topic included 3 of the same trials and 7 additional randomized controlled trials. The Australian systematic review of the efficacy of IVIG included 8 randomized trials of IVIG after bone marrow transplantation, one of which was not included in either of the other reviews. Across the 15 studies, 11 trials assessed IVIG use postallogenic HSCT, 3 trials included patients who received either autologous or allogeneic transplants, and 1 trial evaluated IVIG postautologous transplant.

Only one randomized trial was placebo-controlled. In this 4-arm trial by Cordonnier et al,[79] 200 patients with HSCT from HLA identical siblings were randomized to receive IVIG 0.05 g/kg, IVIG 0.25 g/kg, IVIG 0.5 g/kg, or placebo. No significant differences in infections, GvHD, interstitial pneumonia, transplantation-related mortality, or overall survival were found between patients who received IVIG compared with placebo. Severe venoocclusive disease, however, occurred more frequently as dose of IVIG increased ($P < .01$).

The Chalmers systematic review included 4 randomized trials of IVIG versus no IVIG (Feinstein et al,[81] Lum (NR), Sullivan et al,[92] and Winston et al,[84]) in a meta-analysis of the incidence of acute GvHD (grade II-IV). The results indicate a significant benefit of IVIG in reducing the risk of acute GvHD (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.42-094; $P < .02$). The results of a meta-analysis of 3 trials (Feinstein et al,[81], Lum (NR), Sullivan et al,[92]) for overall survival with IVIG versus no IVIG were not significant. Four additional randomized trials compared IVIG with no IVIG. None of the trials reported the incidence of GvHD, and 2 trials did not report survival outcomes. One trial that used IgM and IgA enriched IVIG reported a significant reduction in infection-related mortality (P value not reported). The remaining trial evaluated IVIG versus no IVIG in autologous bone marrow transplant patients and found a significant decrease in survival for patients treated with IVIG ($P < .02$). This study also reported a higher incidence of venoocclusive disease in the IVIG group (P value not reported).

Six trials that compared IVIG with no IVIG post-HSCT measured infection rate. Four trials found no significant difference in infection rate. An early trial by Sullivan et al,[92] reported significant reductions in both septicemia ($P = .0039$) and local infections ($P = .029$); however, long-term follow-up data have not been published. A trial by Winston et al[84] found

fewer patients treated with IVIG had interstitial pneumonia (P = .02) or symptomatic CMV infections (P = .03) compared with controls.

In addition to the placebo-controlled study discussed above, 4 randomized controlled trials compared different doses or durations of IVIG post-HSCT. One trial reported a significant reduction in acute GvHD in allogeneic HSCT patients who received IVIG (0.5 g/kg) versus those given IVIG (0.25 g/kg) (P < .03). No significance differences were identified in the 3 other trials.

Interpretation and Consensus

The expert panel agreed that most of the trials do not reflect current practice. Intravenous immune globulin did not demonstrate a consistent benefit in reducing infections post-HSCT, and the meta-analysis by the Chalmers group did not find a significant difference in overall survival. Although the meta-analysis found IVIG reduced the incidence of acute GvHD, it is the opinion of the expert panel that there is evidence suggesting a lack of efficacy of IVIG post-HSCT because it was not shown to consistently improve survival. This opinion is based on the fact the results of the trial by Sullivan et al[92] have not been replicated, and the only placebo-controlled trial found no significant benefit of IVIG. In addition, the placebo-controlled trial reported that the incidence of severe venoocclusive disease was more frequent as the dose of IVIG increased.

Although one of the licensed uses for IVIG is post-HSCT, in the opinion of the panel, interpretation of the current best available evidence, including several recent trials, does not support the routine use of IVIG post-HSCT. There may be subsets of patients who could benefit from IVIG post-HSCT, and this requires further study.

The panel agreed that further study of IVIG in a placebo-controlled trial of patients at high risk of GvHD may be warranted (eg, postmatched unrelated transplantation or in the subset of patients who have hypogammaglobulinemia post-HSCT). The panel also felt that there was a theoretical concern that the use of IVIG may delay normal immune reconstitution post-HSCT, and this area also requires further study.

Recommendations

Intravenous immune globulin is not recommended for use after HSCT. The panel recognizes as a possible exception to this recommendation that some multinational protocols for the treatment of hematologic malignancies and/or HSCT in childhood recommend routine use of IVIG for hypogammaglobulinemia. These recommendations are protocol-specific and not necessarily consistent across protocols of similar intensity. Consequently, the panel suggests that IVIG may be administered to children registered on such clinical trials to comply with protocol recommendations. However, because the benefit of this approach has not been adequately studied and there is considerable uncertainty as to the efficacy of such an approach, the panel suggests that IVIG not be routinely used for nonregistered patients.

HEMOLYTIC DISEASE OF THE NEWBORN

Clinical Description

Hemolytic disease of the newborn (HDN), aso referred to as immune hemolytic disease, occurs when maternal IgG antibodies to fetal red cell (RBC) antigens cross the placenta and bind to fetal RBC antigens leading to hemolysis. Before birth, in severely affected infants, this can lead to hydrops fetalis and death. Postnatally, in addition to anemia, this can lead to hyperbilirubinemia, which, if severe and untreated, can cause kernicterus. In the case of HDN due to ABO incompatibility, the maternal antibodies are naturally occurring; in cases of HDN due to Rhesus, Kell, and most other RBC antibodies, the maternal antibodies have developed after exposure to human erythrocytes bearing the corresponding antigens, either after transplacental hemorrhage or blood transfusion or through needle sharing. Tiny transplacental hemorrhages occur in virtually all pregnancies; the risk of more significant transplacental hemorrhages occurs in certain obstetrical situations including therapeutic and spontaneous abortion as well as after amniocentesis.[94]

The specific characteristics of HDN vary somewhat depending on the blood group system involved. Hemolytic disease of the newborn due to ABO incompatibility does not cause a problem in utero (in part due to the relatively weak expression of A and/or B antigens on fetal erthyrocytes), and postnatally hyperbilirubinemia (rather than anemia) is the main problem. Hemolytic disease of the newborn due to Rhesus antibodies varies from mild to severe, with some

fetuses at risk of intrauterine death. Hemolytic disease of the newborn due to Kell antibodies may also be severe and is characterized not only by hemolysis but also by suppression of erythropoiesis (probably due to destruction of erythrocyte precursors).

Before the availability of immunoprophylaxis for the prevention of HDN due to anti-D, HDN occurred in approximately 1 pregnancy in 200 in occidental series, with a perinatal mortality of about 1 in 400. Severe HDN is now a rare disorder, but precise incidence figures are not well documented. Even with the widespread use of immunoprophylaxis, anti-D remains the most common cause of severe HDN, with anti-Kell being the next most common. A number of other RBC antibodies can cause moderate or severe HDN.

Treatment of HDN can be considered in 2 phases—in utero and postnatal. The goal of prenatal monitoring and in utero treatment is to prevent in utero death. Prenatal monitoring may include (according to the clinical situation) serologic testing of the mother, fetal ultrasonography (for signs of fetal anemia), and if appropriate, fetal genotyping and intrauterine transfusion. Postnatal treatment modalities include phototherapy, exchange transfusion, and simple transfusion. In the last several years, treatment with IVIG has been reported. Intravenous immune globulin has been given prenatally to the mother and in utero to the fetus, as well as postnatally to the infant.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified a Cochrane systematic review on the use IVIG in neonates with HDN (level of evidence, 1a). The primary objective of the systematic review was to assess whether IVIG is effective in reducing the need for exchange transfusion. Three nonblinded randomized controlled trials were included: in 2 trials, IVIG was given prophylactically, and in 1 as treatment for established jaundice. All 3 trials compared IVIG plus phototherapy with phototherapy alone.

A literature search conducted by a member of the expert panel identified a second systematic review. This review by Gottstein and Cooke[95] included the same 3 trials as the Cochrane review in their meta-analysis of IVIG impact on use of exchange transfusion.

The conclusions from both meta-analyses were the same, IVIG significantly reduced the overall use of exchange transfusion (relative risk [RR], 0.28; 95% CI, 0.17-0.47; $P < .00001$; NNT, 2.7). Tests for heterogeneity were not significant (Table 18).

Table 18. Hemolytic Disease of the Newborn IVIG Studies

Study	Design and participants	No. of patients	Intervention	Outcome (use of ET)	*P*
Alcock and Liley[96] (Cochrane SR)	SR with meta-analysis	189	IVIG + PT vs PT	Overall: RR, 0.28 (95% CI, 0.17-0.47; fixed)	<.00001
				Prophylaxis: RR, 0.21 (95% CI, 0.10-0.45; fixed)	<.0001
				Treatment: RR, 0.36 (95% CI, 0.18-0.75; fixed)	<.006
Gottstein and Cooke[95]	SR with meta-analysis	189	IVIG + PT vs PT	Overall: RR, 0.28 (95% CI, 0.17-0.47; fixed)	<.00001
Alpay et al[97]	RCT (Not blinded) Tx of jaundice in term neonates ABO and/or Rh incompatibility	116	IVIG + PT vs PT	IVIG + PT: 8/58 (14%) PT: 22/58 (38%)	Significant (*P* value NR in SR)
Dagoglu et al[98]	RCT (Not blinded) Prophylaxis, preterm + term Rh incompatibility	45	IVIG + PT vs PT	IVIG + PT: 4/22 (18%) PT: 15/19 (79%)	Significant (*P* value NR in SR)
Rubo et al[99]	RCT (Not blinded) Prophylaxis (term status NR) Rh incompatibility	34	IVIG + PT vs PT	IVIG + PT: 2/16 (13%) PT: 11/16 (69%)	Significant (*P* value NR in SR)

Abbreviations: PT Phototherapy. ET Exchange transfusion.

Interpretation and Consensus

Although the results of the 2 systematic reviews were the same, the authors of these reports reached different recommendations as to the use of IVIG for this clinical condition with one supporting the use of IVIG (Gottstein and Cooke[95]) and the second concluding there is insufficient evidence to support its use (Alcock and Liley[96]). Although the panel acknowledges that the trials addressing this indication could be of higher quality, the alternate option of exchange transfusion carries risks that are significantly higher and more severe than those known to be associated with IVIG. The panel recommends the use of IVIG for the treatment of HDN with established jaundice. For prophylactic use (ie, in the absence of established jaundice), however, there was agreement by the panel that there is insufficient evidence to recommend IVIG. This opinion is based on the heterogeneity in the criteria used clinically to make a diagnosis of ABO incompatibility versus ABO HDN and the changing recommendations for use of exchange transfusion over the past 10 to 15 years. The recommendations of the expert panel are in agreement with the current (July 2004) recommendations of the American Academy of Pediatrics (AAP), which also recommend IVIG for HDN with established jaundice but not earlier.

Recommendations

Intravenous immune globulin is not recommended for use in the management of HDN without established hyperbilirubinemia.

The panel recommends that IVIG be offered to patients with HDN as treatment for severe hyperbilirubinemia and endorses the recommendations outlined in the AAP guideline on the management of hyperbilirubinemia (July 2004).

The AAP recommendations state:

> "In isoimmune hemolytic disease, administration of IVIG (0.5-1.0 g/kg over 2 hours) is recommended if the total serum bilirubin (TSB) is rising despite intensive phototherapy or the TSB level is within 2 to 3 mg/dL (34-51 micromol/L) of the exchange level. If necessary, this dose can be repeated in 12 hours."

Although the AAP recommendation states that a dose of IVIG may be given over 2 hours, this may represent an infusion administration faster than that recommended by the manufacturer; this needs to be taken into consideration in treatment decisions.

HEMOLYTIC TRANSFUSION REACTION

Clinical Description

A hemolytic transfusion reaction occurs when a patient is given an incompatible blood transfusion. In this situation, the patient has preformed auto- or alloantibodies to antigens on the cellular component of the transfused blood component, usually to antigens on the surface of transfused red cells. The reaction results in breakdown of the transfused red cells, and the clinical consequences of a hemolytic transfusion reaction are the result of hemolysis.

Various therapies have been used to mitigate the consequences of the transfusion of incompatible blood, including exchange transfusions.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 6 cases of IVIG use for hemolytic transfusion reaction (level of evidence, 4). In all 6 cases, patients with autoantibodies or alloantibodies were given incompatible blood, and IVIG was administered in an attempt to prevent the anticipated transfusion reaction. All 6 patients

Table 19. Hemolytic Transfusion Reaction IVIG Studies

Study	No. of patients	Antibodies	Intervention	Response to IVIG
Woodcock et al[100]	1	RhD negative; anti-Jk, anti-K, anti-Kp	IVIG + steroids	↑ Hb from 30 to 100 g/L Serum haptoglobin undetectable Bilirublin ↑ to 30 mol/L
Kohan et al[101]	5	2 cases autoantibody* 1 case anti-Kp^b 1 case anti-D and autoantibody* 1 case anti-C, anti-E, anti-Fy^b, anti-K + autoantibody*	IVIG + steroids	5/5 (100%) ↑ Hb and hematocrit

*Warm-reactive panagglutinin.

responded with increases in hemoglobin and/or hematocrit (Table 19).

Interpretation and Consensus

The evidence for the use of IVIG in this condition is extremely sparse and of poor quality. The expert panel agreed there is no role for IVIG in the routine treatment of hemolytic transfusion reaction. However, there was some discussion regarding its use in rare unanticipated crisis situations.

Recommendations

Intravenous immune globulin is not recommended for either the prophylaxis or routine treatment of hemolytic transfusion reactions.

Based on consensus by the expert panel, IVIG may be considered as an option among supportive therapies for urgent situations in this disorder.

HEMOLYTIC TRANSFUSION REACTIONS IN SICKLE CELL DISEASE

Clinical Description

Sickle cell disease (SCD) is a genetically inherited hemoglobinopathy, consisting of 3 subtypes, namely HbSS disease (sickle cell anemia), HbSC disease, and HbS/thalassemia. Red blood cell transfusions are frequently required in the treatment of SCD. Most adults with sickle cell anemia have received transfusions at least once in their lives. Transfusions are given to these patients to increase oxygen-carrying capacity and/or to suppress endogenous production of the abnormal hemoglobin. Clinical situations in which RBC transfusions are used include acute exacerbation of underlying anemia, acute chest syndrome, preparation for surgery, and the prevention or treatment of cerebral vascular accidents.

Patients with SCD are particularly susceptible to 2 types of transfusion reactions, RBC alloimmunization and delayed hemolytic transfusion reactions, which in its most severe form is known as a hyperhemolytic transfusion reaction. About 30% of adults with SCD have one or more clinically significant RBC alloantibodies. Over recent years, many SCD treatment programs have begun to use partially phenotyped RBC units for transfusion to patients with SCD, so the frequency and severity of alloimmunization may be decreasing in this patient population. Nevertheless, a serious and potentially fatal transfusion complication in patients with SCD that has only been explicitly recognized and reported on in the last 7 to 8 years is a hyperhemolytic transfusion reaction. This reaction is an exaggerated form of a delayed hemolytic transfusion reaction. It is characterized by severe hemolysis with a drop in hemoglobin to levels below pretransfusion levels, indicating hemolysis of both endogenous and transfused RBCs and, in some cases, reticulocytopenia, suggesting suppression of endogenous hematopoiesis. Clinically, patients may also have pain similar to that of a typical vasoocclusive crisis. In some, but not all cases, alloantibodies are detected.

During such reactions, subsequent transfusions may cause an exacerbation of the anemia, and in some cases, lead to life-threatening or fatal outcomes, even when phenotypically similar and crossmatched-compatible blood is provided. Thus, for patients with this syndrome, further transfusions should be withheld if at all possible, allowing RBC volume replacement through erythropoiesis.

Treatment of delayed hemolytic transfusion reactions in patients with SCD has been described but not well studied. Corticosteroids may contribute to recovery in some cases. Recently, in light of the associated reticulocytopenia, erythropoietin has been advocated as an adjunct to treatment. This syndrome may or may not recur with further transfusions after the recovery period.

There have also been a few reports of this type of reaction occurring in patients with thalassemia.

Evidence Summary

Four cases of IVIG use for hemolytic transfusion reactions in patients with SCD were

Table 20. Hemolytic Transfusion Reactions in SCD IVIG Studies

Study	No. of patients	Transfusion	Intervention	Response
Cullis et al[102]	1	Compatible RBC	IVIG + steriods	↑ Hb and reticulocyte count
Gangarossa and Lucini[103]	1	Incompatible RBC	IVIG + steriods	Initial painful venoocclusive crises, then ↑ Hb and recticulocyte count
Win et al[104]	2	Compatible RBC	IVIG + steriods	2/2 (100%) ↑ Hb and reticulocyte count

identified (Table 20) by the Appropriateness of IVIG Evidence Review (level of evidence, 4). In 3 cases, patients received compatible RBCs and in 1 case, only incompatible RBCs were available. All 4 patients received IVIG plus corticosteroids, and all 4 responded with increases in hemoglobin and resolution of symptoms. The patient who received incompatible blood initially experienced a painful venoocclusive crisis when IVIG was administered.

Interpretation and Consensus

Evidence for use of IVIG for hemolytic transfusion reactions in patients with SCD is extremely sparse and of poor quality. The evidence is unlikely to improve, however, given both the rarity and unpredictability of these reactions. In the opinion of the expert panel, there is no role for IVIG in the routine treatment of non–life-threatening delayed hemolytic transfusion reactions. The panel agreed that in cases of serious, life-threatening, delayed hemolytic transfusion reactions, where there is evidence of destruction of the patient's own RBCs (as well as transfused RBCs), use of IVIG may be considered among the treatment options.

Recommendations

Intravenous immune globulin is not recommended for the routine treatment of non–life-threatening delayed hemolytic transfusion reactions in patients with SCD.

Based on consensus by the expert panel, IVIG may be considered among the options for treatment of serious, life-threatening, delayed hemolytic transfusion reactions in patients with SCD.

Table 21. Hemolytic Uremic Syndrome/TTP IVIG Studies

Study	Design and participants	No. of patients	Intervention	Outcome	*P*
HUS					
Robson et al[105]	Case-control study (pediatric)	18	IVIG vs control	IVIG: 1/9 (11%) responded (↑ PC and ↓ WBC)	
				No significant difference in remission rate, complication rate, or number of patients on dialysis between IVIG group (n = 9) and controls (n = 9)	n.s.
Sheth et al[106]	Case-control study (pediatric)	43	IVIG vs FFP vs no tx	IVIG group(n = 8):	
				Improvement in PC compared to FFP (n = 12)	.05
				Improvement in PC compared to no tx (n = 23)	.01
TTP					
Dervenoulas et al[107]	Case-control study (adult)	44	IVIG + other tx vs control*	No significant difference between IVIG group (n = 29) and controls (n = 15) in remission rate or time to relapse	n.s.
Centurioni et al[108]	Retrospective case series (adult)	17	IVIG + other tx†	Complete remission: 8/17 (47%). Partial remission: 2/17 (12%) Died from disease progression: 7/17 (41%) In only 4 cases was improvement attributed to IVIG	N/A
HUS and TTP					
Finazzi et al[109]	Nonrandomized study (adult)	17	IVIG + steroids vs PE + steroids‡	IVIG: 0/3 (0%) complete remission after 5 d PE: 10/14 (71%) complete remission after 5 d	.05
NR in SR	Case reports (adult)	14	IVIG	Remission: 13/14 (93%) cases	N/A

Abbreviations: PE, plasma exchange; FFP, fresh frozen plasma.

*Both IVIG and control groups were given steroids, PE, and antiplatelet agents.

†Other treatments: steroids (all), PE (15 cases), antiplatelet agents (11 cases), heparin (2 cases), and plasma infusion (2 cases).

‡IVIG given to patients with a severity score ≤4, and PE given to patients with a score ≥5 or pregnant women after delivery.

HEMOLYTIC UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA

Clinical Description

Thrombotic thrombocytopenic purpura (TTP) is an uncommon but acute life-threatening disorder characterized by thrombocytopenia and microangiopathic hemolytic anemia. With progression of the disorder, the patient may also have fever, central nervous system disorders, and renal impairment. The cause of the disorder is not known, but it has been associated with several viral disorders. The pathophysiology involves deposition of platelet microthombi in the small vessels. Factor VIII and vWF are inevitably elevated. A variety of other laboratory markers are changed, and patients may have antibodies to endothelium or to platelets (particularly GP IV). Recently, 2 investigators (Tsai and Furlan) have determined that patients with congenital TTP lack the ADAMTS-13 enzyme, which is responsible for cleavage of high molecular weight forms of vWF. Some patients with the acquired form of TTP have inhibitors to this enzyme.

Hemolytic uremic syndrome (HUS) presents in both children and adults. In adults, it overlaps in presentation with TTP. The childhood form is generally seen postinfection, notably with *Escherichia coli* and usually resolves spontaneously; however, some severe cases can progress to renal failure. This disorder is also marked by thrombocytopenia and schistocytes with formation of platelet microthombi located predominantly in the kidneys.

Therapy of adult TTP is primarily based on therapeutic plasma exchange using either cryosupernatant plasma or fresh frozen plasma. Steroids, antiplatelet drugs, vincristine, and splenectomy are variably used with different reports of success.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 2 case-control studies of IVIG for pediatric HUS, 1 case-control study and 1 retrospective case series for adult TTP, and 1 nonrandomized study and 14 case reports for adult HUS/TTP (level of evidence, 4).

Of the 2 case-control studies of IVIG for pediatric HUS, 1 reported a significant improvement in platelet count compared with fresh frozen plasma ($P < .05$) or no therapy ($P < .01$). In the other study, however, there was no significant difference between IVIG use and controls in remission rate, complications, or number of patients who required dialysis.

For adult TTP, there was no significant difference in remission rate or time-to-relapse in the case-control study. In the retrospective case series, complete remission was observed in 47% (8/17) of patients, and partial remission in 12% (2/17), however, in only 4 cases was improvement attributed to IVIG.

One nonrandomized study evaluated the use of IVIG compared with plasma exchange in patients with HUS/TTP. Patients with higher severity scores were given plasma exchange, whereas patients with lower scores received IVIG. After 5 days of treatment, none of the patients who received IVIG had a complete remission (0/3). In comparison, 71% (10/14) of patients given plasma exchange achieved complete remission. Of the 14 case reports of IVIG use for HUS/TTP, remission occurred in 93% (13/14) of cases (Table 21).

Interpretation and Consensus

In the pediatric population, the data are sparse, of poor quality, and there is little evidence for clinical efficacy of IVIG. Although the quantity of evidence is slightly greater in the adult population, here too there is little evidence demonstrating clinical benefit of IVIG. Given more appropriate management alternatives such as supportive therapy and judicious use of blood products and plasma exchange (where indicated), IVIG is not recommended as first-line therapy for HUS "or TTP. There was some discussion and debate regarding the role of IVIG as second- or later-line therapy.

Recommendations

Intravenous immune globulin is not recommended as first-line therapy for HUS or TTP in either the pediatric or adult population.

Based on consensus by the expert panel, IVIG may be considered one option among adjunctive therapies when first-line therapy has failed.

HEPARIN-INDUCED THROMBOCYTOPENIA

Clinical Description

Heparin-induced thrombocytopenia (HIT) is estimated to occur in 2% to 3% of patients receiving unfractionated heparin. This incidence is based on a definition that includes a platelet

Table 22. Heparin-Induced Thrombocytopenia IVIG Studies

Study	No. of patients	Intervention	Response to IVIG
Winder et al[111]	3	IVIG	Platelet count normalized: 3/3 (100%) cases
Grau et al[112]	1	IVIG	Platelet count normalized

count of less than 150×10^9/L occurring 5 or more days after beginning heparin therapy. Based on this definition, the risk of thrombotic events in these patients approaches 90%.

The differential diagnosis principally includes sepsis and other drug-related thrombocytopenias. A general approach to thrombocytopenia and specific laboratory testing for HIT are required.

The pathophysiological basis of this condition is HIT antibodies of IgG class binding to platelet factor 4 and heparin on platelet surfaces. Platelet activation occurs with associated activation of coagulation pathways. Heparin-induced thrombocytopenia antibodies can also activate vascular endothelium and monocytes, which contributes to coagulation pathway activation.

Treatment involves discontinuation of heparin and giving nonheparin anticoagulants (other than warfarin) to decrease the risk of thrombotic events. Platelet transfusions are not recommended.

The rationale for use of IVIG in HIT is related to a perceived need to treat severe thrombocytopenia. The incidence of severe thrombocytopenia in HIT is unclear but appears to be uncommon. The use of IVIG for HIT was not included in the comprehensive American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.[110]

Evidence Summary

The Appropriateness of IVIG Evidence Review did not include HIT as a topic. A literature search conducted for the expert panel identified 4 cases of IVIG for HIT (level of evidence, 4). All of the case reports included patients with severe

Table 23. HIV-Associated Thrombocytopenia IVIG Studies

Study	Design	No. of patients	Intervention	Outcome	*P*
Perrella[113]	RCT Blinding: NR	20	IVIG (1 g kg^{-1} d^{-1} × 2 d) vs IVIG (0.4 mg kg^{-1} d^{-1} × 5 d)	Mean PC at 10 d: $IVIG_{(1\ g)}$ 80 × 10^9/L vs $IVIG_{(0.4\ g)}$ 60 × 10^9/L Mean PC at 20 d: $IVIG_{(1\ g)}$ 80 × 10^9/L vs $IVIG_{(0.4\ g)}$ 50 × 10^9/L Duration of bleeding: $IVIG_{(1\ g)}$ 4 d vs $IVIG_{(0.4\ g)}$ 6 d	NR in SR NR in SR NR in SR
Jahnke et al[114]	RCT Crossover Double blind	12	IVIG → 4 wk washout → placebo vs Placebo → 4 wk washout →IVIG	IVIG: all patients responded with ↑ PC >50 × 10^9/L, PC remained > 50 for 2 to 10 wk; Mean PC ↑ from 23 × 10^9/L to 180 × 10^9/L Placebo: no ↑ PC Only 7/12 (58%) patients completed the protocol	.00003
Schrappe-Bacher et al[115]	RCT Double blind	30	IVIG vs Placebo	Mean PC at 6 mo follow-up: IVIG 154 × 10^9/L vs Placebo 201 × 10^9/L	NR
De Simone et al[116]	RCT Blinding: NR	30	IVIG + AZT vs AZT	IVIG + AZT: 12/15 (80%) ↑ PC AZT: 3/15 (20%) ↑ PC However, all patients had baseline PC >50 × 10^9/L	0.01
Majluf-Cruz et al[117]	Case series	13	IVIG	At 1 wk, PC >100 × 10^9 with no bleeding complications: 11/13 (85%) cases Long-term response: 5/13 (38%) cases	N/A

thrombocytopenia. In all 4 patients treated with IVIG, platelet counts increased and eventually normalized (Table 22).

Interpretation and Consensus

The expert panel unanimously agreed that the management of HIT, a prothrombotic disorder, should be focused on decreasing the risk of thrombotic events. As such, IVIG could potentially increase the risk of thrombosis and is contraindicated for use in this condition.

Recommendations

Intravenous immune globulin is contraindicated for treatment of HIT.

HIV-ASSOCIATED THROMBOCYTOPENIA

Clinical Description

Primary HIV-associated thrombocytopenia (PHAT) is the most common cause of thrombocytopenia in patients with HIV infection. Up to 40% of patients will have thrombocytopenia during the course of their HIV infection, and thrombocytopenia will be the initial manifestation of HIV infection in up to 10% of cases.

Patients with PHAT present in a similar fashion to those with ITP. They may be asymptomatic, or they may have petechiae and/or mucocutaneous or gastrointestinal bleeding. The feared complication is central nervous system hemorrhage, which is rare. Patients often present with platelet counts of less than 50×10^9/L, and some with counts less than 10×10^9/L. Primary HIV-associated thrombocytopenia becomes more common as the CD4 cell count drops during the course of the disease.

Primary HIV-associated thrombocytopenia is a diagnosis of exclusion in patients with HIV. Secondary causes of thrombocytopenia, such as opportunistic infections, malignancy, medications, and hypersplenism, need to be ruled out. The HIV-associated TTP also needs to be considered and ruled out with a blood film and biochemical studies. Bone marrow examination is not necessary to make the diagnosis if the blood film is otherwise normal but may be required to rule out some of the potential secondary causes of thrombocytopenia.

Primary HIV-associated thrombocytopenia is related to direct HIV infection of bone marrow precursor cells. The direct HIV infection results in production of antiplatelet antibodies associated with reduced platelet survival and recovery and decreased megakaryocytic activity in the bone marrow. Thrombopoietin levels are also elevated.

Therapy for PHAT is first directed toward the HIV infection itself. Zidovudine (AZT) has been shown to raise platelet counts after several weeks of therapy and is the only antiretroviral agent that has been shown to do so. AZT is a necessary part of the highly active antiretroviral therapy if a patient has PHAT. Addition of other medical therapy (eg, steroids, Rh immunoglobulin, interferon α, vincristine, and splenectomy) is dependent on the presence of bleeding, platelet count level, associated medical conditions (eg, opportunistic infection), and potential treatment toxicities. In general, if patient-dependent factors necessitate the addition of other medical therapy, the thrombocytopenia is treated similarly to ITP, except splenectomy may be deferred to determine response to AZT.

Evidence Summary

Overall, 4 randomized controlled trials and 1 case series of IVIG for HIV-associated thrombocytopenia were identified (level of evidence, 1b). The Appropriateness of IVIG Evidence Review included a randomized crossover trial and 1 case series. The Australian systematic review of the efficacy of IVIG included a different randomized controlled trial. The Chalmers Research Institute, as part of a broader systematic review of IVIG for HIV infection, included the 2 randomized trials cited above plus 2 additional randomized controlled trials of IVIG for PHAT.

Of the 2 trials comparing IVIG with placebo, 1 reported IVIG significantly increased mean platelet count ($P = .00003$). In this small crossover trial, all patients responded to IVIG with increases in platelet counts to greater than 50×10^9/L, and platelet counts remained over 50×10^9/L for 2 to 10 weeks. The other randomized trial that compared IVIG with placebo assessed long-term remission rates, and platelet counts at 6 months follow-up did not show evidence for benefit of IVIG.

One randomized trial compared IVIG plus AZT with AZT alone in 30 patients whose baseline platelet counts were greater than 50×10^9/L. Overall, 80% (12/15) of patients treated with IVIG plus AZT responded with an increase in platelet counts compared with 20% (3/15) of patients given AZT alone ($P < .01$).

One randomized trial evaluated different schedules of IVIG in 20 patients with severe thrombocytopenia and mucocutaneous bleeding. The trial reported a higher mean platelet count at 10 and 20 days and a shorter mean duration of bleeding in patients given 1 g/kg of IVIG for 2 days compared with patients who received 0.4 g/kg for 5 days (*P* value not reported) (Table 23).

Interpretation and Consensus

Three reviews evaluated the role of IVIG for HIV-associated thrombocytopenia. The primary studies that met eligibility criteria for each of the reviews were not consistent. Furthermore, the randomized trials included in the reviews included only a small number of patients and were of mixed quality. However, the results of these trials were generally consistent in favor of a role for IVIG. All of the studies predate the most current standard practices for treatment of HIV, so the need for IVIG in the future may be less relevant. Evidence regarding the optimum dose and duration of IVIG is uncertain. However, the studies typically used a dose of 1 g/kg daily for 2 days, and there was agreement that this was a suitable option.

Recommendation

Intravenous immune globulin is recommended as a treatment option for HIV-associated thrombocytopenia when there is active bleeding or when platelet counts are less than 10×10^9/L.

Dose and Duration

Based on consensus by the expert panel, a dose of 1 g/kg daily for 2 days is recommended as a reasonable option.

IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDREN

Clinical Description

Idiopathic (immune) thrombocytopenic purpura is a common acquired bleeding disorder in children. Clinical and laboratory features of acute ITP include petechiae and purpura involving the skin and mucous membranes, thrombocytopenia (platelet count $<150 \times 10^9$/L), and absence of an underlying etiology.

Acute ITP is characterized by complete and sustained remission within 6 months from onset in the majority (>75%) of cases. Its clinical course may be a single episode with variable severity or recurrent episodes. Chronic ITP is diagnosed if sustained remission is not achieved within 6 months from onset. This form of ITP may last for months or years.

Acute ITP is approximately twice as common as chronic ITP, with a peak incidence in children from 2 to 6 years of age, and it is evenly distributed among males and females. Chronic ITP affects older children and adults with onset typically between 10 and 30 years of age. The disorder is approximately 3 times more common in females than males.

Immune thrombocytopenic purpura is an autoimmune disorder specifically affecting platelets, caused by an abnormal response of the human host to disease-related or indeterminate antigenic agents. In about 70% of children with acute ITP, there is an antecedent history of a viral illness occurring 1 to 2 weeks before bleeding manifestations.

Immune thrombocytopenic purpura is a diagnosis of exclusion. Bone marrow examination is not routinely required in children with a "classical" presentation of ITP, who are otherwise well. However, in cases of atypical presentations or those manifesting hepatosplenomegaly, generalized lymphadenopathy, or pancytopenia, bone marrow examination should be done to exclude malignancy, aplastic anemia, or infiltrative disorders. As well, if indicated, selected tests to exclude certain diseases, notably identifiable autoimmune diseases and plasma coagulation disorders, may also be performed.

Supportive care alone is the cornerstone of management of acute ITP because it is rarely associated with serious complications, and remission occurs within 6 months. The principal adjunct to supportive care is watchful waiting. However, if the patient has bleeding manifestations beyond petechiae and purpura with a platelet count less than 20×10^9/L, therapeutic intervention may be required. The intent of therapy is to rapidly increase the platelet count to greater than 20×10^9/L, thereby reducing the small but significant risk (approximately 0.2%-0.5%) of life-threatening hemorrhage, in particular, ICH. Treatment modalities include prednisone or other corticosteroids, IVIG, anti-D (in Rhesus positive nonsplenectomized patients), and, in rare cases, splenectomy.

Once acute ITP extends beyond 6 months, either in a continuous or recurrent pattern, the definition shifts to chronic ITP, and a new set of therapeutic options apply. Watchful waiting and supportive

Table 24. Pediatric Idiopathic Thrombocytopenic Purpura IVIG Studies

Study	Design	No. of patients	Intervention	Outcome	*P*
Acute ITP					
Blanchette et al[118]	RCT	56	IVIG vs	Median no. of days with PC $<20 \times 10^9$/L:	
	Not blinded		OP vs	No significant difference IVIG vs OP	n.s.
			No Tx	IVIG significantly fewer days than no Tx	.001
				OP significantly fewer days than no Tx	.01
				Median time to reach PC $\geq 50 \times 10^9$/L (at 72 h):	
				IVIG significantly shorter than OP	.001
				IVIG and OP significantly shorter than no Tx	.001
Blanchette[119]	RCT	146	IVIG (1g kg^{-1} d^{-1} × 2 d) vs	Mean no. of days PC $<20 \times 10^9$/L:	
	Not blinded		IVIG (0.8g kg^{-1} d^{-1} × 1 d) vs	$IVIG_{(1\ g)}$ significantly fewer days vs IV anti-D	.002
			IV anti-D (Rh + patients only) vs	$IVIG_{(0.8\ g)}$ significantly fewer days vs IV anti-D	.002
			OP	Mean time to reach PC $\geq 50 \times 10^9$/L:	
				$IVIG_{(1\ g)}$, $IVIG_{(0.8\ g)}$ and OP shorter than IV anti-D	.05
Duru et al[120]	RCT	50	IVIG vs	% of patients with PC $>20 \times 10^9$/L at day 3:	
	Not blinded		MDMP	No significant difference IVIG vs MDMP	n.s.
			No Tx (nonrandomized arm)	IVIG and MDMP both significantly higher than no tx	0.01
Fujisawa et al[121]	RCT	125	IVIG vs	Median time with PC $<30 \times 10^9$/L:	
	Not blinded		IV MP vs	IVIG significantly shorter than OP	.0008
			Pulsed IV MP vs	IVIG significantly shorter than IV MP	.034
			OP	Median time to reach PC $\geq 50 \times 10^9$/L:	
				IVIG significantly shorter than OP	.018
Imbach et al[122]	RCT	108	IVIG vs	% of patients with PC $>30 \times 10^9$/L at 60 d:	
	Not blinded		OP	IVIG significantly higher than OP	0.005

				% of patients with PC >100 × 10^9/L at 120 d:	
				IVIG significantly higher than OP	0.03
Khalifa et al[123]	RCT	30	IVIG vs	Change in PC at 1, 3, 5 and 14 d:	
	Not blinded		HDMP vs	No significant difference IVIG vs HDMP	n.s.
			OP	IVIG and HDMP both significantly greater than OP	.001
Mori et al[124]	RCT	62	IVIG (0.2 g kg^{-1} d^{-1} × 5 d) vs	No significant difference on day 1 in complete or partial response rates between $IVIG_{(0.2\ g)}$ and $IVIG_{(0.4\ g)}$	n.s.
	Not blinded		IVIG (0.4 g kg^{-1} d^{-1}× 5 d)		
Ozsoylu et al[125]	RCT	20	IVIG vs	Complete response (PC >150 × 10^9/L):	n.s.
	Not blinded		MDMP	No significant difference between IVIG and MDMP	
Rosthoj et al[126]	RCT	47	IVIG vs	% of patients with PC >50 × 10^9/L at day 4:	
	Not blinded		Pulsed IV MP	IVIG significantly higher than pulsed IV MP	.003
				Mean PC at day 4:	
				IVIG significantly higher than pulsed IV MP	.001
Warrier et al[127]	RCT		IVIG (0.25 g kg^{-1} d^{-1} × 2 d) vs	No significant difference between groups in %	
	Not blinded	12	IVIG (0.5 g kg^{-1} d^{-1} × 2 d)	of patients with PC ≥30 × 10^9/L (day 10) or mean PC after tx	n.s.
Chronic ITP					
Tovo et al[128]	Crossover	9	IVIG (0.4 g kg^{-1} d^{-1} × 5 d) vs	Complete response (PC >100 × 10^9/L):	
	RCT		Fc-depleted IVIG	IVIG (6/9) vs Fc-depleted IVIG (2/9)	
	Not blinded		(0.4 g kg^{-1} d^{-1} × 5 d)		NR
Acute or chronic ITP					
Warrier et al[127]	RCT	12	IVIG (0.4 g kg^{-1} d^{-1} × 2 d) vs	No significant difference between groups in %	n.s.
	Not blinded		IVIG (1 g kg^{-1} d^{-1} × 2 d)	of patients with PC ≥30 × 10^9/L (day 10) or mean PC after tx	

Abbreviations: MDMP, mega dose methylprednisolone; HDMP, high dose methylprednisolone; IV MP, intravenous MP; OP, oral prednisone.

care continue to be mainstays of management for chronic ITP. If a child maintains a platelet count above 30×10^9/L and is largely free of purpura, watchful waiting without treatment should be continued. Treatment modalities include IVIG, anti-D (in Rhesus positive nonsplenectomized patients), and in refractory cases, splenectomy. Immunosuppressive and immunomodulative therapy may also be tried.

Evidence Summary

The systematic review by the Chalmers Research Institute identified 12 randomized control trials of IVIG for pediatric ITP (level of evidence, 1b). Ten trials evaluated IVIG for acute ITP, 1 for chronic ITP, and 1 trial included patients with either acute or chronic ITP.

Eight trials compared IVIG with corticosteroids for treatment of acute ITP. Intravenous immune globulin produced significantly higher response rates and increased platelet counts to greater than 50×10^9/L more rapidly than oral prednisone in all of the trials that measured these outcomes (see Table 24 for further details). Three trials compared IVIG with high or mega dose methylprednisolone (MP) for acute ITP. None of the trials reported significant differences in response rates for IVIG versus high or mega dose MP. Of 2 trials that compared IVIG with pulsed intravenous MP, 1 reported a significantly higher response rate with IVIG. In this trial, both the percentage of patients with platelet counts greater than 50×10^9/L ($P < .0003$) and mean platelet count ($P < .001$) at day 4 were significantly higher with IVIG.

Four trials compared different doses of IVIG, and none of the trials found significant differences between IVIG treatment arms.

In addition to the randomized trials above, the expert panel reviewed 2 consensus guidelines on the management of ITP. One was developed by the American Society of Hematology (ASH), and the other by the British Society for Hematology (BSH). The ASH guideline recommended, "children with platelet counts >30,000/μL [30×10^9/L] should not be hospitalized and do not routinely require treatment if they are asymptomatic or have only minor purpura; they should not be given glucocorticoids, IVIG, or anti-Rh(D) as routine initial treatment. Children with platelet counts <20,000/μL [20×10^9/L] and significant mucous membrane bleeding and those with counts <10,000/μL [10×10^9/L] and minor purpura should be treated with specific regimens of IVIG or glucocorticoids. Patients with severe, life-threatening bleeding should be hospitalized and receive conventional critical care measures, along with treatment for ITP: appropriate regimens include high-dose parenteral glucocorticoid therapy, IVIG, and platelet transfusions."[129]

The BSH guideline's conclusions and recommendations are, "Intravenous immune globulin is effective in raising the platelet count in more than 80% of children, and does so more rapidly than steroids or no therapy... It is expensive and invasive, and should be reserved for emergency treatment of patients who do not remit or respond to steroids and who have active bleeding. It is an appropriate treatment to enable essential surgery or dental extractions. It should not be used to raise the platelet count in children with cutaneous symptoms alone." "If a child has mucous membrane bleeding and more extensive cutaneous symptoms, high dose prednisolone 4 mg/kg/d is effective... It can be given as a very short course (maximum 4 d). There are no direct comparisons of low dose (1-2 mg/kg/d) with high dose therapy. If lower doses of 1-2 mg/kg/d are used the treatment should be given for no longer than 14 days, irrespective of response."

Interpretation and Consensus

Pediatric ITP. There was discussion and agreement that the illness trajectory of ITP is different in children than adults. In the opinion of the expert panel, there is sufficient high-quality data available to support the use of IVIG as one option for first-line therapy of acute ITP in children with platelet counts less than 20×10^9/L. The expert panel also recommended that IVIG be part of multimodality therapy for the treatment of children with ITP who have life-threatening bleeding. In the opinion of the expert panel, IVIG should be an option for the management of chronic pediatric ITP. The panel also discussed that anti-D is another related treatment option, given it is a plasma-derived immunoglobulin product. The panel agreed that anti-D is also an option for the treatment of chronic ITP for Rh-positive, nonsplenectomized children who do not have contraindications to the use of anti-D (eg, low hemoglobin). One of the panel members shared results from a recent meta-analysis that

he coauthored, which suggests IVIG may impact the natural history of ITP in children by preventing development of chronic disease in some patients.[129a]

Neonates of Mothers with ITP. There are no randomized controlled studies on which to base recommendations. Although not reviewed by the expert panel, there are case studies examining the role of IVIG in this patient population. The expert panel reviewed and endorses the ASH guideline recommendations for the use of IVIG in this setting with one minor qualification. The ASH guideline stated newborns with imaging evidence of ICH and platelet count less than 20,000/μL [20 $\times$ 10^9/L] should not be treated with glucocorticoids alone. The expert panel preferred the recommendation be framed, as it would be prudent to use glucocorticoids in combination with other treatments for newborns with imaging evidence of ICH and platelet counts less than 20,000/μL [20 $\times$ 10^9/L].

Recommendations

Pediatric ITP. Intravenous immune globulin is recommended as one option for first-line therapy of acute ITP in children with platelet counts less than 20 $\times$ 10^9/L.

Intravenous immune globulin is recommended as part of a multimodality approach (ie, in conjunction with platelet transfusions and bolus intravenous MP) for treatment of children with ITP who have life-threatening bleeding.

Based on consensus by the expert panel, IVIG may be considered as one option for treatment of children with chronic ITP. Another related option (ie, a plasma-derived immunoglobulin product) for Rh-positive, nonsplenectomized children is anti-D, provided that there are no contraindications to the use of this product.

Neonates of Mothers with ITP. The expert panel endorses the ASH guideline recommendations, which are

> "In newborns without evidence of intracranial hemorrhage (ICH), treatment with IVIG is appropriate if the infant's platelet count is <20,000/μL [20 $\times$ 10^9/L]. Newborns with platelet counts of 20,000 to 50,000/μL [20 $\times$ 10^9/L to 50 $\times$ 10^9/L] do not necessarily require IVIG treatment. Newborns with counts >50,000/μL [50 $\times$ 10^9/L] should not be treated with IVIG or glucocorticoids."

Newborns with imaging evidence of ICH should be treated with combined glucocorticoid and IVIG therapy if the platelet count is less than 20,000/μL [20 $\times$ 10^9/L]. In this setting, it is prudent to use glucocorticoids in combination with other treatment.

Dose and Duration

First-Line Therapy of Acute Pediatric ITP. Based on consensus by the expert panel, one dose of 0.8 to 1 g/kg, with a second dose given within 48 hours if the platelet count has not increased to above 20 $\times$ 10^9/L, is recommended as a reasonable option.

Pediatric ITP with Life-Threatening Bleeding. Based on consensus by the expert panel, 1 g/kg daily for 2 days is recommended as a reasonable option.

Chronic Pediatric ITP. Based on consensus by the expert panel, one dose of 0.8 to 1 g/kg, with a second dose given within 48 hours if the platelet count has not increased to above 20 $\times$ 10^9/L, is recommended as a reasonable option. Dose should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.

Neonate of Mother with ITP. Based on consensus by the expert panel, a dose of 1 g/kg daily for 2 days is recommended as a reasonable option with the second 1 g/kg dose to be given only if the platelet count is less than 30 $\times$ 10^9/L or in the presence of clinically significant bleeding, associated significant coagulopathy or platelet dysfunction or documented severe internal hemorrhage (eg, ICH).

IDIOPATHIC THROMBOCYTOPENIC PURPURA IN ADULTS

Clinical Description

Adult ITP is a common disorder characterized by the accelerated destruction of platelets in the reticuloendothelial system as a result of the development of platelet reactive autoantibodies. It most commonly affects patients between 20 and 50 years of age with a predilection to women (female-to-male ratio 3:1). Chronic ITP must be differentiated from other conditions with increased platelet destruction including HIV infection, drug-induced thrombocytopenia, alloimmune

thrombocytopenia, TTP, and disseminated intravascular coagulation. It may be associated with viral infections (eg, HIV), systemic lupus erythematosus, autoimmune disorders of the thyroid, and lymphoproliferative disorders. The diagnosis of chronic ITP is made in the presence of isolated thrombocytopenia, normal or raised megakaryocyte count in an otherwise normal bone marrow aspirate, and the exclusion of other conditions that may cause thrombocytopenia.

Immune thrombocytopenic purpura is caused by binding of autoantibodies to platelet surface antigens. The culprit immunoglobulin is usually IgG, although IgM and IgA platelet reactive antibodies have been identified. These platelet antibodies bind to the platelet through its Fab terminus, and the antibody leads to complement deposition on platelets. Numerous groups have developed assays for platelet autoantibodies, but to date, these have not been proven useful in the diagnosis or management of chronic ITP.

In chronic ITP, normal platelets that have been coated by autoantibodies are cleared from the peripheral circulation by FCã receptors on

Table 25. Adult Idiopathic Thrombocytopenic Purpura IVIG Studies

Study	Design	No. of patients	Intervention	Outcome	*P*
Acute ITP					
Godeau et al[131]	Factorial RCT Not blinded	122	First randomization: IVIG vs HDMP Second randomization both arms: OP vs placebo	Mean no. of days with PC >50 × 10^9/L at day 21: IVIG vs HDMP OP vs placebo	 .02 .0001
von dem Borne et al[132]	Nonrandomized Controlled trial	39	IVIG vs HDMP vs OP	% of patients with PC >50 × 10^9/L at day 10: No significant difference between groups	 n.s.
Chronic ITP					
Colovic et al[133]	RCT Not blinded	24	IVIG (1 g kg^{-1} d^{-1} × 2 d) vs IVIG (0.4 mg kg^{-1} d^{-1} × 5 d)	% of patients with PC ≥50 × 10^9/L: $IVIG_{(1\ g)}$ 93% (14/15) vs $IVIG_{(0.4\ g)}$ 89% (8/9)	 n.s.
Godeau et al[134]	RCT Not blinded	20	IVIG (1 g kg^{-1} d^{-1} × 2 d) vs IVIG (2 g kg^{-1} d^{-1} × 2 d)	No significant difference between groups in: Complete immediate response (PC ≥150 × 10^9/L) Partial immediate response (PC ≥50 × 10^9/L)	 n.s. n.s.
Godeau et al[135]	RCT Not blinded	40	IVIG (1 g kg^{-1} d^{-1} × 1) vs IVIG (0.5 g kg^{-1} d^{-1} × 1)*	% of patients with PC ≥80 × 10^9/L: Day 2: no significant difference between groups Day 4: significantly more responders in $IVIG_{(1g)}$ After IVIG reinfusion (total 2 g/kg each arm) for nonresponders, day 8 response rate was not significantly different between groups.	 n.s. .005 n.s.
Acute and/or chronic ITP					
Wehmeier[136]†	RCT Not blinded	12	IVIG (10%) vs IVIG (5%)	% of patients with PC >50 × 10^9/L at 48 h: No significant difference between groups	 n.s.
Jacobs and Wood[137]‡	RCT Not blinded	32	IVIG + OP vs IVIG vs OP	No significant difference between groups in: Complete response rate Partial response rate	 n.s. n.s.

*Nonresponders (PC <80 × 109/L) in IVIG (1 g) given 1 g/kg on day 4 and day 5. Nonresponders IVIG (0.5 g) given 1.5 g/kg on day 4 and day 5.

†Included adults with acute ITP (n = 4) and chronic ITP (n = 8).

‡Included adults with previously untreated ITP, duration not reported.

mononuclear macrophages predominantly in the spleen. The fundamental cause of the autoantibody formation in chronic ITP is unknown. It has been suggested that viral infections may trigger antibody formation. Eradication of *Helicobacter pylori* by triple therapy has led to partial or complete remission of chronic ITP in some patients, suggesting that there is some common antigen sharing between *H pylori* membranes and platelets. Chronic ITP in adults is a heterogeneous disease, and it is likely that the pathophysiology is due to multiple causes.

Despite the fact that this is a relatively common disorder (estimated incidence of 1-2 per 100,000 population per year), there have been very few randomized clinical trials assessing various forms of management (George et al[130]). For those patients requiring treatment, the first-line therapy is usually with corticosteroids at a dose of 1 to 2 mg kg^{-1} d^{-1}, tapering off the dose over the subsequent weeks depending upon the platelet response. Subsequent treatment will depend on platelet responsiveness to low doses of corticosteroids. For those patients requiring unacceptably high doses of corticosteroids to maintain satisfactory platelet counts, splenectomy is usually recommended. An alternative approach to induction and maintenance treatment includes the use of IVIG or anti-D antibody infusion for patients who are D-positive.

For adults with chronic refractory ITP, numerous treatment modalities have been reported, primarily in case series, with response rates varying between 20% and 40%, but usually only for short periods. In addition to long-term use of corticosteroids, alternatives are the use of immunosuppressive agents such as cyclophosphamide, imuran, vinca-alkaloids, the anti-CD20 monoclonal antibody rituximab, danazol, plasma exchange or protein A immunoabsorption, and cyclosporin.

Evidence Summary

A systematic review by the Chalmers Research Institute identified 6 randomized control trials, and 1 nonrandomized trial of IVIG for adult ITP (level of evidence, 1b). Overall, 3 trials compared IVIG with corticosteroids, and 4 trials evaluated different doses of IVIG. None of the trials compared IVIG with no therapy (Table 25).

The largest trial that compared IVIG with corticosteroids used a factorial design and included 122 patients with severe acute ITP. The primary outcome, mean number of days with platelet count greater than 50×10^9/L at day 21, was significantly higher in the IVIG group compared with the high-dose MP group. One small, nonrandomized trial also evaluated IVIG against corticosteroids, MP, or oral prednisone for treatment of acute ITP, and no significant difference in the percentage of patients with platelet counts greater than 50×10^9/L at 48 hours between the 3 groups was observed. The remaining trial that compared IVIG with steroids also had 3 treatment arms: IVIG alone, oral prednisone alone, and IVIG plus oral prednisone. This randomized trial, which included 32 adults with previously untreated ITP (duration not reported), found no significant difference in either complete or partial response rate between the groups.

Only 1 of the 4 trials that evaluated different doses of IVIG reported a significant difference between the groups in response to IVIG. This study by Godeau et al[135] randomized 40 patients to receive 1 g kg^{-1} d^{-1} for 1 day or 0.5 g kg^{-1} d^{-1} for 1 day. The percentage of patients with platelet counts greater than 80×10^9/L was not significantly different between the groups on day 2; however, on day 4, significantly more patients in the 1 g kg^{-1} d^{-1} group responded ($P < .0005$).

In addition to the trials above, the expert panel discussed 2 consensus guidelines for the management of ITP. One was developed by the ASH and the other by the BSH. The ASH guideline recommended IVIG as appropriate initial treatment only for adults with platelet counts less than 50×10^9/L who have severe life-threatening bleeding. The BSH guideline recommended IVIG as first-line therapy for adults when platelet count needs to be raised either due to symptoms or signs, or where there is predictable bleeding (eg, surgery, labor, or operative dentistry). Intravenous immune globulin, in combination with other agents, was also recommended as second-line therapy for adults when there is a need to elevate platelet count quickly.

Interpretation and Consensus

Review of the literature suggests IVIG is efficacious for acute ITP therapy and, in selected patients, for chronic treatment. In particular, IVIG results in more rapid early increments in platelet count than other therapies (eg, corticosteroids). However, it is unclear if more rapid improvement

in platelet count reduces the risk of major hemorrhage (eg, ICH). The expert panel reached agreement that no treatment of acute adult ITP is required if platelet count is greater than 20×10^9/L and no active bleeding is present.

Despite the lack of evidence examining IVIG in this role, the expert panel strongly recommended IVIG be part of multimodality therapy for patients with acute ITP who have major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding (wet purpura). Other treatment modalities in this setting would likely include steroids and platelets. Based on the opinion of the expert panel and in agreement with the standard of care, IVIG is not recommended as first-line therapy alone for patients with acute ITP with severe thrombocytopenia who have no major bleeding or wet purpura. An exception to this recommendation is patients who have contraindications to steroids.

The expert panel agreed IVIG should be considered as one of several possible adjunctive therapies for patients not responding or slowly responding to steroids. In the opinion of the panel, it is reasonable to consider the addition of IVIG in patients with acute ITP with severe thrombocytopenia persisting or worsening after 3 to 7 days of steroids. Other adjunctive agents may include danazol and anti-D.

The panel also discussed the role of IVIG in patients with chronic ITP postsplenectomy. There was agreement IVIG may be considered as one possible adjunctive therapy as a steroid-sparing measure. Consideration of no therapy is also reasonable if the platelet count is greater than 20×10^9/L and there is no evidence of bleeding. When IVIG is used in this setting, the minimal dose and maximal duration between doses that provides a safe platelet count should be used. Patients should be reevaluated every 3 to 6 months, and alternative therapies to IVIG should be considered for patients who do not achieve a durable response for minimum of 2 to 3 weeks.

Recommendations

Adult Acute ITP with Bleeding. Based on consensus by the expert panel, IVIG is strongly recommended as part of multimodality therapy for adults with acute ITP and major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.

Adult Acute ITP with Severe Thrombocytopenia but No Bleeding. Based on consensus by the expert panel, IVIG is not recommended as first-line therapy alone for acute ITP with severe thrombocytopenia but with no major bleeding or wet purpura, except for patients with contraindications to steroids.

Adult ITP with No or Slow Response to Adequate Dose Steroids. Based on consensus by the expert panel, IVIG ssmay be considered as a possible adjunctive therapy for patients not responding or slowly responding to steroids.

Adult Chronic ITP Postsplenectomy. Based on consensus by the expert panel, IVIG may be considered as a possible adjunctive therapy as a steroid-sparing measure.

Dose and Duration

Adult Acute ITP with Bleeding. Based on consensus by the expert panel, a dose of 1 g/kg daily for 2 days is recommended as a reasonable option.

Adult ITP with No or Slow Response to Adequate Dose Steroids. Based on consensus by the expert panel, a dose of 1 g/kg daily for 2 days is recommended as a reasonable option.

Adult Chronic ITP Postsplenectomy. Based on consensus by the expert panel, 0.5 g/kg every 4 weeks is a reasonable starting dose, with dose adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.

PREGNANCY-ASSOCIATED ITP

When pregnancy-associated ITP requires treatment, as outlined in the ASH guidelines, IVIG is recommended as one option for first-line therapy, as are steroids. Clinical judgment should inform the decision.

The expert panel endorses the treatment parameters outlined in the ASH recommendations.

Summary of ASH Recommendations

Platelet counts greater than 50×10^9/L do not routinely need treatment and should not receive steroids or IVIG. Platelet counts between 30 and 50×10^9/L in the first or second trimester also should not receive treatment. Treatment is required if platelet count is less than 10×10^9/L at any time in the pregnancy or between 10 and 30 ×

10^9/L in the second or third trimester or if there is bleeding. Pregnant women who fail steroids and IVIG should be considered for splenectomy in the second trimester if platelet count is less than 10×10^9/L and there is bleeding. A platelet count of 50×10^9/L is sufficient for vaginal delivery or cesarean delivery. Intravenous immune globulin may be useful if very rapid elevation of platelet count is needed before delivery. These recommendations are based on clinical experience and expert consensus.

POSTTRANSFUSION PURPURA

Clinical Description

Posttransfusion purpura (PTP) is a rare syndrome characterized by severe ($<10 \times 10^9$/L) thrombocytopenia occurring approximately 1 week after a transfusion of red cells or platelets. Presentation frequently includes mucosal bleeding, purpura, and bleeding from surgical wounds. Posttransfusion purpura occurs predominantly in women (>90% of reported cases) and can happen at a wide range of ages. The true incidence of the disorder is unknown.

The differential diagnosis of the disorder includes ITP, drug-induced thrombocytopenia, and disseminated intravascular coagulation. There are no associated red cell morphologic abnormalities, so conditions such as TTP and HUS should not be confused with PTP. Coagulation studies are typically normal in patients with PTP.

Posttransfusion purpura occurs most often in patients who are negative for the platelet antigen HPA-1a (2% of the population), which is associated with the glycoprotein IIb/IIIa complex. The reported incidence seems less than would be expected from the prevalence of the platelet associated antigen frequencies. The reason for this is unclear and may be associated with certain HLA types (eg, HLA-DR3 and HLA-DR52).

Patients with PTP are 'sensitized' by either a prior pregnancy (explaining the female preponderance) or a blood product transfusion. When reexposed, typically by a transfusion, to the offending platelet antigen, there is an anamnestic rise in antibody titer that leads to immune clearance of the transfused platelets. In addition, there is also immunedestruction of endogenous (antigen-negative) platelets for reasons that are not entirely clear. There is speculation that either platelet antibody from transfused platelets or antigen-antibody complexes are adsorbed to host platelets and are rapidly cleared. Bone marrow samples show increased numbers of megakaryocytes.

Although there are reports of spontaneous recovery after 2 weeks, the severity of the thrombocytopenia and bleeding diathesis mandates therapy in an attempt to correct the problem. Further transfusions of cellular products (especially platelets) should be avoided because this may simply worsen the situation. Corticosteroids do not shorten the period of thrombocytopenia. Repeated plasmaphereses have been shown to benefit some patients, although venous access may be a risk due to hemostatic compromise.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 1 article that presented data from a literature review of published case reports and a current series (level of evidence, 4). Overall, 16 (94%) of 17 patients with PTP, in whom response to IVIG therapy could be established, had a good or excellent response to IVIG (Table 26). Most of the patients studied received prior treatment with prednisolone with no favorable effect.

Table 26. Posttransfusion Purpura IVIG Studies

Study	Design	No. of patients	Intervention	Response*	Additional IVIG needed	Clinical outcome
Mueller-Eckhardt and Kiefel[138]	Case series + review of case reports	19	IVIG	Excellent: 14/19 (74%) Good: 2/19 (11%) Failure: 1/19 (5%) Uncertain: 2/19 (11%)	5/19 (26%)	15/19 (79%) remission 2/19 (11%) spontaneous remission 1/19 (5%) died (CHF) 1/19 (5%) not reported

*Excellent, ↑ PC ≥ 100×10^9/L within 5 days of IVIG; Good, PC normalized later than 5 days or ↑ PC<100×10^9/L but >50×10^9/L.

Interpretation and Consensus

The expert panel agreed that although the quantity of evidence was limited and the quality of evidence was weak, the body of evidence is unlikely to improve. Given the rarity of PTP and the high response rate seen in the case series, consensus was unanimously reached that IVIG is an appropriate treatment option and should be the standard of care. The optimum dose and duration of therapy is uncertain. Studies done to date have used a dose of 1 g/kg for 2 days, and there was agreement that this is a reasonable option. This dose is in keeping with dosages recommended for other conditions considered by the expert panel including ITP and HIV-associated thrombocytopenia.

Recommendations

Intravenous immune globulin is recommended as the standard first-line therapy for PTP.

Dose and Duration

Based on consensus by the expert panel, a dose of 1 g/kg for 2 days is recommended as a reasonable option.

VIRAL-ASSOCIATED HEMOPHAGOCYTIC SYNDROME

Clinical Description

Viral-associated hemophagocytic syndrome (VAHS) is one of the hemophagocytic lymphohistiocytoses. This disease most often presents in infants and young children up to 18 months of age. However, cases in older children and adults have been reported. The incidence in children is approximately 1 in 50,000 live births and is less common in older children and adults.

The infections associated with VAHS include Epstein-Barr virus, CMV, parvovirus B19, herpes simples virus, varicella-zoster virus, measles, HIV infection (alone or in combination with human herpes virus 8), bacterial infections (brucella, Gram-negative bacteria, tuberculosis), leishmaniasis, and fungal infections. Childhood VAHS can also be seen in conjunction with juvenile rheumatoid arthritis and Kawasaki disease. In adult patients, VAHS can be associated with autoimmune diseases, vasculitis, leukemias, lymphomas, and the accelerated phase of the Chediak Higashi syndrome.

Signs and symptoms of VAHS include fever, hepatosplenomegaly, neurologic symptoms (seizures, coma, and retinal hemorrhages), rash, cytopenias, coagulopathy (bleeding), elevated liver enzymes, lymphadenopathy, hypertriglyceridemia, and high serum ferritin. The diagnosis is often difficult to make, as the differential diagnosis includes common systemic infections and hepatitis. Viral-associated hemophagocytic syndrome can be mistaken for the central nervous signs associated with child abuse, unless there is a high index of clinical suspicion. Multisystem organ failure or infection is the usual cause of death. Viral-associated hemophagocytic syndrome is often fatal without treatment. In most patients, immunoglobulin levels are normal.

The diagnosis depends on the demonstration of hemophagocytosis in a tissue sample (usually lymph node or bone marrow). Additional criteria for the diagnosis for VAHS include low or absent natural killer cell activity, serum ferritin of greater than 500 mg/L, and a markedly elevated soluble interleukin-2 receptor (CD25) level.

Viral-associated hemophagocytic syndrome is associated with immune dysregulation related to cytokine dysfunction. This results in the accumulation of activated T-lymphocytes and histiocytes in many organs. High levels of interferon γ, tumor necrosis factor-α, interleukin-10, interleukin-12, and soluble interleukin-2 receptor have been noted in these patients. Many of the patients also have defective natural-killer cell activity and perforin levels in cytotoxic cells. Defective apoptosis has also been reported in some patients, which can lead to the accumulation of histiocytes and cytotoxic lymphocytes in tissue. Epstein-Barr virus–associated clonal changes in the T-cell receptor have been reported in some patients with VAHS.

In children, therapy is usually given after the hemophagocytic lymphohistiocytosis-94 protocol. This consists of induction therapy with dexamethasone and etoposide, followed by continuous cyclosporine, pulse dexamethasone, and pulse etoposide for 1 year. Often this is followed by HSCT. In adults, treatment is similar for idiopathic VAHS. Viral-associated hemophagocytic syndrome secondary to autoimmune diseases is treated with high-dose immunosuppression, and malignancy-related VAHS is managed by treatment of the underlying malignancy. Of note, IVIG is not even

mentioned as a general treatment strategy in this treatment protocol.

Evidence Summary

The Appropriateness of IVIG Evidence Review identified 1 open study, 1 retrospective chart, and 7 case reports (level of evidence 4). Overall, of the patients who received IVIG with or without additional therapies, 11 (34%) of 32 had a complete response and 11 (34%) of 32 had a partial response. Approximately, half of the patients treated with IVIG died (15/30 patients; clinical outcome was not reported in 2 cases).

Interpretation and Consensus

The evidence related to this disorder is sparse, of poor quality, and dated (see Table 27). Very few of the studies examined the use IVIG alone, which makes it difficult to ascertain the specific role of IVIG in treatment of VAHS. There was some discussion among the panel members whether, in the event of no other clinical options, IVIG should be considered. However, steroids and chemotherapy are the more common practice standard, and the expert panel agreed that to delay this practice standard, to offer IVIG would not be appropriate given the high mortality associated with this condition.

Recommendations

Intravenous immune globulin is not recommended for routine use in the treatment of VAHS.

Based on consensus by the expert panel, IVIG may be considered among the options for treatment of severe life-threatening VAHS.

EXTERNAL REVIEW

Process

Feedback on this practice guideline was obtained from hematologists in Canada. The process was informed by the Practitioner *Feedback* methodology used to create clinical practice guidelines on cancer care in Ontario.[6] A draft of this practice guideline along with an accompanying letter of explanation and feedback survey was e-mailed to members of the following associations: Canadian Blood and Marrow Transplant Group, Canadian Hematology Society, Association of Hemophilia Clinic Directors of Canada, Canadian Pediatric Thrombosis and Hemostasis Network, and the Canadian Apheresis Group. The draft guideline was also sent electronically to several

Table 27. Viral-Associated Hemophagocytic Syndrome IVIG Studies

Study	Design and participants	No. of patients	Intervention	Response*	Clinical outcome
Pediatric					
Ningsanond[139]	Retrospective chart review	50	IVIG or Antimicrobial Tx	IVIG: NR Antimicrobial: NR	IVIG: 8/8 (100%) died Antimicrobial: 15 Patients survived
Chen et al[43,44]	Open study	17	IVIG or IVIG + Chemo† or Chemo	IVIG: CR 2/2 IVIG + chemo: CR 1/10; PR 7/10 Chemo: CR 3/5; PR 1/5	IVIG: 0/2 (0%) died IVIG + chemo: 6/10 (60%) died Chemo: 2/5 (40%) died
Chen et al[140]	Case report	2	IVIG + steriods	CR: 1/2 PR: 1/2	0/2 (0%) died
Fort and Buchanan[141]	Case report	1	IVIG + Chemo + Acyclovir	Complete response	Alive and well
Freeman et al[142]	Case report	3	IVIG	CR: 2/3; PR: 1/3	1/3 (33%) died
Goulder et al[143]	Case report	1	IVIG	Partial response	NR
Adult					
Chen et al[144]	Case report	1	IVIG	Complete response	Alive and well
Gill et al[145]	Case report	3	IVIG	CR: 3/3	0/3 (0%) died
Kaneko et al[146]	Case report	1	IVIG + steriods	Partial response	NR

Abbreviations: CR, complete response; PR, partial response.

*Definitions of CR and PR were not provided in the systematic review.

†IVIG and chemotherapy given concomitantly (3 cases) or sequentially (IVIG followed by chemotherapy [7 cases]).

Table 28. External Review Survey Results

Clinical condition*	Respondent agreement with draft recommendations for use of IVIG			
	Strongly agree or agree	Neutral	Disagree or strongly disagree	Average level of agreement†
Acquired hemophilia	18 (69%)	6 (23%)	2 (8%)	3.91
Acquired hypogammaglobulinemia	21 (84%)	2 (8%)	2 (8%)	4.04
Evans syndrome	21 (88%)	3 (12%)	0 (0%)	4.25
F/NAIT	20 (95%)	1 (5%)	0 (0%)	4.33
HSCT	17 (77%)	1 (5%)	4 (18%)	3.90
HDN	19 (90%)	2 (10%)	0 (0%)	4.24
Hemolytic transfusion reaction	27 (93%)	2 (7%)	0 (0%)	4.39
HUS/TTP	21 (91%)	2 (9%)	0 (0%)	4.35
HIT	19 (83%)	3 (13%)	1 (4%)	4.35
HIV-associated thrombocytopenia	19 (86%)	3 (14%)	0 (0%)	4.23
Idiopathic thrombocytopenic purpura in children	20 (95%)	0 (0%)	1 (5%)	4.29
Idiopathic thrombocytopenic purpura in adults	20 (87%)	3 (13%)	0 (0%)	4.39
Pregnancy-associated idiopathic thrombocytopenic purpura	19 (83%)	4 (17%)	0 (0%)	4.30
PTP	20 (91%)	2 (9%)	0 (0%)	4.50
Virus-associated hemophagocytic syndrome	17 (74%)	6 (26%)	0 (0%)	4.08
Overall Questions	**Respondent Agreement with Overall Statements**			
The guidelines will be useful in optimizing practice	17 (74%)	4 (17%)	2 (9%)	3.86
I will use the guidelines in my practice	18 (78%)	4 (17%)	1 (4%)	4.00

*The following conditions were not included on the survey: acquired red cell aplasia, acquired von Willebrand disease, aplastic anemia, autoimmune hemolytic anemia, autoimmune neutropenia, and hemolytic transfusion reaction in sickle cell disease.

†Measured on a 5-point scale: 1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree.

hematologists in Ontario and British Columbia. Practitioners were given the option of faxing their completed survey or providing their responses online through a Web-based survey tool. Written comments on the draft guideline were encouraged. Practitioners were asked to provide feedback within 3 weeks.

RESULTS

Feedback on the draft practice guideline was received from 46 hematologists (Table 28). Most respondents were from Ontario (24/46, 52%), followed by British Columbia (8/46, 17%), and Quebec (5/46, 11%).

A total of 16 respondents completed the entire external review survey, 27 respondents completed some items on the survey, and 3 respondents provided written comments only. For all of the conditions surveyed, most respondents either agreed or strongly agreed with the draft guideline's recommendations for use of IVIG. Approximately three quarters of respondents indicated that the guidelines would be useful in optimizing practice (17/23, 74%) and that they would use the guidelines in their practice (18/23, 78%).

Overall, 35% (16/46) of respondents provided written comments on the draft practice guideline (see Table 29 for a summary of the key comments received).

DISCUSSION AND GUIDELINE MODIFICATIONS

The expert panel discussed the external review results at a teleconference in November 2005. The number of responses received was quite low; however, given the length and breadth of the guideline, the panel recognizes that the time

Table 29. External Review Written Feedback Summary

Key written comments
• The recommendations for use of IVIG for neonates of mothers with ITP are not appropriate for treatment of newborns with F/NAIT
• Definitions are needed for the terms "urgent and/or life-threatening circumstances" used in the recommendations for several conditions
• Recommendations for IVIG use are too restrictive for some conditions
• Recommendations for IVIG use are too permissive
• Several of the COG protocols recommend the use of IVIG for children with hypogammaglobulinemia

required to review and provide feedback on the entire document would have been a considerable deterrent. Overall, the feedback received was positive, with most respondents in agreement with the draft recommendations.

Several of the written comments revolved around access to IVIG. Some respondents who have roles as "gatekeepers" found the practice guideline too permissive. Conversely, some of the clinician "end-users" felt the recommendations were too restrictive for some conditions. In the opinion of the expert panel, the practice guideline strikes a good balance between the 2 perspectives.

One respondent commented that the draft recommendations for use of IVIG for the treatment of newborns with F/NAIT were not appropriate. In the draft guideline, the recommendation for the treatment of a newborn with F/NAIT stated that provision of antigen-negative compatible platelets should be considered first-line therapy and IVIG adjunctive, and that if IVIG was to be used, the recommendations should be the same as for neonates of mothers with ITP and referred readers to the pediatric ITP section of the draft guideline. Upon review, the panel agreed that the recommendations of use of IVIG for neonates of mothers with ITP are not appropriate for the treatment of newborns with F/NAIT. The recommendation was modified to, "In the opinion of the expert panel, the provision of antigen negative compatible platelets should be considered first-line therapy and IVIG adjunctive. Given the lack of evidence to guide management in this rare disorder, it is strongly recommended that treatment of newborns with F/NAIT be under the direction of a centre with specialized pediatric expertise in the treatment of this condition."

A number of respondents noted that the supportive guidelines for several of the Children's Oncology Group (COG) protocols recommend the use of IVIG for children who have hypogammaglobulinemia. Some of the protocols specify the presence of infections (particularly sinopulmonary infections), and other protocols do not necessarily specify previous infections (eg, protocols for the treatment of acute myelogenous leukemia). In all cases, these are recommendations and not absolute requirements for entering/maintaining a child on the COG protocol. In light of these comments, the panel decided to slightly modify the recommendation for the use of IVIG for acquired hypogammaglobulinemia in children with hematologic malignancies to the following: Intravenous immune globulin is not recommended for routine use in children with hematologic malignancies (with or without hypogammaglobulinemia). The panel recognizes 2 possible exceptions to this general recommendation. First, for children with hematologic malignancies with acquired hypogammaglobulinemia and either a history of severe invasive infection or recurrent sinopulmonary infections, IVIG may be considered a treatment option according to the recommendations for adult patients. Second, the panel acknowledges that some multinational protocols for the treatment of hematologic malignancies (and/or HSCT) in childhood recommend routine use of IVIG for hypogammaglobulinemia, even in the absence of severe or recurrent infections. These recommendations are protocol-specific and not necessarily consistent across protocols of similar intensity. Consequently, the panel suggests that IVIG may be administered to children registered on such clinical trials to comply with protocol recommendations. However, because the benefit of this approach has not been adequately studied and there is considerable uncertainty as to the efficacy of such an approach, the panel suggests that IVIG not be routinely used for nonregistered patients. A similar caveat regarding IVIG use for pediatric HSCT patients on multinational protocols was added to the HSCT recommendation.

For several of the hematologic conditions addressed by this guideline, IVIG was not recommended for use, except under certain urgent or life-threatening circumstances. One external review respondent asked that definitions for urgent and life-threatening be provided in the guideline. The expert panel discussed this issue and agreed there may be local variability in the definition of urgent and/or life-threatening circumstances in the context of IVIG use that should be determined at the health center, district, or provincial level. However, to assist the decision-making process, it is recommended that should IVIG be used for these indications, objective outcome measures with a defined review time point be established before the initiation of IVIG therapy. It is also suggested that local blood transfusion or therapeutic review committees be involved in the development of these definitions. A statement to this effect was added to the methods section of the practice guideline.

DISCLAIMER

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. The NAC makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

REFERENCES

1. Feasby TE: Appropriateness of IVIG—hematology summaries (unpublished).
2. Biotext Science Information Consultants: A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Final Report v04. Australian National Blood Authority, 2004. www.nba.gov.au/pubs.htm
3. Chalmers Research Institute: IVIG systematic reviews. (unpublished).
4. Pierce LR, Jain N: Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev 17:241-251, 2003
5. Phillips B, Ball C, Sackett D, et al: Levels of evidence. www.eboncall.org/content/levels.html, 2002
6. Browman GP, Newman TE, Mohide EA, et al: Progress of clinical oncology guidelines development using the practice guidelines development cycle: The role of practitioner feedback. J Clin Oncol 16:1226-1231, 1998
7. Crenier L, Ducobu J, des Grottes JM, et al: Low response to high-dose intravenous immunoglobulin in the treatment of acquired factor VIII inhibitor. Br J Haematol 95:750-753, 1996
8. Dykes AC, Walker ID, Lowe GD, et al: Combined prednisolone and intravenous immunoglobulin treatment for acquired factor VIII inhibitors: A 2-year review. Haemophilia 7:160-163, 2001
9. Boughton BJ, Jackson N, Lim S, et al: Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 17:75-80, 1995
10. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 319:902-907, 1988
11. Chapel H, Dicato M, Gamm H, et al: Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: A comparison of 2 dose regimes. Br J Haematol 88:209-212, 1994
12. Gamm H, Huber C, Chapel H, et al: Intravenous immune globulin in chronic lymphocytic leukaemia. Clin Exp Immunol 97:17-20, 1994 (Suppl 1)
13. Griffiths H, Brennan V, Lea J, et al: Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 73:366-368, 1989
14. Molica S, Musto P, Chiurazzi F, et al: Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 81:121-126, 1996
15. Chapel HM, Lee M, Hargreaves R, et al: Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 343:1059-1063, 1994
16. Hargreaves RM, Lea JR, Holt J, et al: Infection, immune responses and IV immunoglobulin infection prophylaxis in myeloma (abstract). Br J Cancer 66:261, 1992 (Suppl XVII)
17. Schedel I: Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. Diagn Intensivther 7:254-263, 1982
18. Gebauer E, Tomic J, Stevanovic S: Intravenous immunoglobulin in the treatment of infections in children with acute leukemias. Med Pregl 47:52-55, 1994
19. Gimesi A, Eibl M, Koos R, et al: Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatr Hung 32:115-125, 1992
20. Sumer T, Abumelha A, al-Mulhim I, et al: Treatment of fever and neutropenia with antibiotics versus antibiotics plus intravenous gammaglobulin in childhood leukemia. Eur J Pediatr 148:401-402, 1989
21. Hayakawa F, Imada K, Towatari M, et al: Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. Br J Haematol 118:1187-1189, 2002
22. Ballester OF, Saba HI, Moscinski LC, et al: Pure red cell aplasia: Treatment with intravenous immunoglobulin concentrate. Semin Hematol 29:106-108, 1992 (3 Suppl 2)
23. Casadevall N, Lacombe C, Varet B: Erythroblastopenia: Chronic idiopathic or associated with chronic lymphoid leukemia. Value of cultures of erythroblastic progenitors and therapeutic strategy. Presse Med 22:1079-1086, 1993
24. Castelli R, Vismara A, Pavia G, et al: Relapsing pure red cell aplasia associated with B-cell chronic lymphocytic leukemia successfully treated by intravenous immunoglobulin concentrate. Ann Ital Med Int 17:47-50, 2002
25. Clauvel JP, Vainchenker W, Herrera A, et al: Treatment of pure red cell aplasia by high dose intravenous immunoglobulins. Br J Haematol 55:380-382, 1983
26. Cobcroft R: Pure red cell aplasia associated with small lymphocytic lymphoma. Br J Haematol 113:260, 2001
27. Ilan Y, Naparstek Y: Pure red cell aplasia associated with systemic lupus erythematosus: Remission after a single course of intravenous immunoglobulin. Acta Haematol 89:152-154, 1993
28. Huang JL, Hung IJ, Chen LC, et al: Successfully treated sulphasalazine-induced fulminant hepatic failure, thrombocytopenia and erythroid hypoplasia with intravenous immunoglobulin. Clin Rheumatol 17:349-352, 1998
29. Larroche C, Mouthon L, Casadevall N, et al: Successful treatment of thymoma-associated pure red cell aplasia with intravenous immunoglobulins. Eur J Haematol 65:74-76, 2000
30. Mant MJ: Chronic idiopathic pure red cell aplasia: Successful treatment during pregnancy and durable response to intravenous immunoglobulin. J Intern Med 236:593-595, 1994

31. McGuire WA, Yang HH, Bruno E, et al: Treatment of antibody-mediated pure red-cell aplasia with high-dose intravenous gamma globulin. N Engl J Med 317:1004-1008, 1987

32. Needleman SW: Durable remission of pure red cell aplasia after treatment with high-dose intravenous gammaglobulin and prednisone. Am J Hematol 32:150-152, 1989

33. Ohashi K, Akiyama H, Takamoto S, et al: Treatment of pure red cell aplasia after major ABO-incompatible bone marrow transplantation resistant to erythropoietin. Bone Marrow Transplantation Team. Bone Marrow Transplant 13:335-336, 1994

34. Roychowdhury DF, Linker CA: Pure red cell aplasia complicating an ABO-compatible allogeneic bone marrow transplantation, treated successfully with antithymocyte globulin. Bone Marrow Transplant 16:471-472, 1995

35. Amiot L, Langanay T, Drenou B, et al: Spontaneous recovery from severe parvovirus B19 pure red cell aplasia, in a heart transplant recipient, as demonstrated by marrow culture. Hematol Cell Ther 40:71-73, 1998

36. Koduri PR, Kumapley R, Khokha ND, et al: Red cell aplasia caused by parvovirus B19 in AIDS: Use of I.V. immunoglobulin. Ann Hematol 75:67-68, 1997

37. Koduri PR, Kumapley R, Valladares J, et al: Chronic pure red cell aplasia caused by parvovirus B19 in AIDS: Use of intravenous immunoglobulin—a report of 8 patients. Am J Hematol 61:16-20, 1999

38. Kondo H, Mori A, Watanabe J, et al: Pure red cell aplasia associated with parvovirus B19 infection in T-large granular lymphocyte leukemia. Leuk Lymphoma 42:1439-1443, 2001

39. Wong TY, Chan PK, Leung CB, et al: Parvovirus B19 infection causing red cell aplasia in renal transplantation on tacrolimus. Am J Kidney Dis 34:1132-1136, 1999

40. Federici AB, Stabile F, Castaman G, et al: Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: Comparison of 3 different therapeutic approaches. Blood 92:2707-2711, 1998

41. Bergen GA, Sakalosky PE, Sinnott JT: Transient aplastic anemia caused by parvovirus B19 infection in a heart transplant recipient. J Heart Lung Transplant 15:843-845, 1996

42. Bourantas K, Makrydimas G, Georgiou I, et al: Aplastic anemia. Report of a case with recurrent episodes in consecutive pregnancies. J Reprod Med 42:672-674, 1997

43. Chen SH, Liang DC, Lin M: Treatment of platelet alloimmunization with intravenous immunoglobulin in a child with aplastic anemia. Am J Hematol 49:165-166, 1995

44. Chen RL, Lin KH, Lin DT, et al: Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 89:282-290, 1995

45. Kapoor N, Hvizdala E, Good RA: High dose intravenous gammaglobulin as an approach to treatment of antibody mediated pancytopenia. Br J Haematol 69:98-99, 1988

46. De Lord C, Marsh JC, Smith JG, et al: Fatal autoimmune pancytopenia following bone marrow transplantation for aplastic anaemia. Bone Marrow Transplant 18:237-239, 1996

47. Lutz P, Gallais C, Albert A, et al: Use of intravenous immunoglobulins (IVIg) to treat a child with pancytopenia and hypoplastic marrow. Ann Hematol 65:199-200, 1992

48. Salim S, Salim KA: Chicken pox induced pancytopenia and prompt response to high dose intravenous immunoglobulin. J Assoc Physicians India 40:689-690, 1992

49. Sherer Y, Levy Y, Fabbrizzi F, et al: Treatment of hematologic disorders other than immune thrombocytopenic purpura with intravenous immunoglobulin (IVIg)—Report of 7 cases and review of the literature. Eur J Intern Med 11:85-88, 2000

50. Flores G, Cunningham-Rundles C, Newland AC, et al: Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: Results in 73 patients. Am J Hematol 44:237-242, 1993

51. Bussel J, Lalezari P, Hilgartner M, et al: Reversal of neutropenia with intravenous gammaglobulin in autoimmune neutropenia of infancy. Blood 62:398-400, 1983

52. Bussel J, Lalezari P, Fikrig S: Intravenous treatment with gamma-globulin of autoimmune neutropenia of infancy. J Pediatr 112:298-301, 1988

53. Bux J, Behrens G, Jaeger G, et al: Diagnosis and clinical course of autoimmune neutropenia in infancy: Analysis of 240 cases. Blood 91:181-186, 1998

54. Gordon BG, Kiwanuka J, Kadushin J: Autoimmune neutropenia and Hodgkin's disease: Successful treatment with intravenous gammaglobulin. Am J Pediatr Hematol Oncol 13:164-167, 1991

55. Hilgartner MW, Bussel J: Use of intravenous gamma globulin for the treatment of autoimmune neutropenia of childhood and autoimmune hemolytic anemia. Am J Med 83:25-29, 1987

56. Mascarin M, Ventura A: Anti-Rh(D) immunoglobulin for autoimmune neutropenia of infancy. Acta Paediatr 82:142-144, 1993

57. Sorensen RU, Kallick MD: Clinical uses of intravenous immune globulin: immunoglobulin replacement therapy and treatment of autoimmune cytopenias. J Clin Apheresis 4:97-103, 1988

58. Alliot C, Barrios M, Tabuteau S, et al: Autoimmune cytopenias associated with malignancies and successfully treated with intravenous immune globulins: about two cases. Therapie 55:371-374, 2000

59. Schoengen A, Fembacher PM, Schulz PC: Immunoglobulin therapy for autoimmune neutropenia in Hodgkin's disease. Acta Haematol 94:36-38, 1995

60. Young NS, Abkowitz JL, Luzzatto L: New insights into the pathophysiology of acquired cytopenias. Hematology (Am Soc Hematol Educ Program) 18-38, 2000

61. Scaradavou A, Bussel J: Evans syndrome. Results of a pilot study utilizing a multiagent treatment protocol. J Pediatr Hematol Oncol 17:290-295, 1995

62. Mathew P, Chen G, Wang W: Evans syndrome: Results of a national survey. J Pediatr Hematol Oncol 19:433-437, 1997

63. Ucar B, Akgun N, Aydogdu SD, et al: Treatment of refractory Evans' syndrome with cyclosporine and prednisone. Pediatr Int 41:104-107, 1999

64. Gombakis N, Trahana M, Athanassiou M, et al: Evans syndrome: Successful management with multi-agent treatment including intermediate-dose intravenous cyclophosphamide. J Pediatr Hematol Oncol 21:248-249, 1999

65. Chang DK, Yoo DH, Kim TH, et al: Induction of remission with intravenous immunoglobulin and cyclophosphamide in steroid-resistant Evans' syndrome associated with dermatomyositis. Clin Rheumatol 20:63-66, 2001

66. Muwakkit S, Rachid R, Bazarbachi A, et al: Treatment-resistant infantile Evans syndrome. Pediatr Int 43:502-504, 2001

67. Muwakkit S, Locatelli F, Abboud M, et al: Report of a child with vitiligo and Evans syndrome. J Pediatr Hematol Oncol 25:344-345, 2003

68. Petrides PE, Hiller E: Autoimmune hemolytic anemia combined with idiopathic thrombocytopenia (Evans syndrome). Sustained remission in a patient following high-dose intravenous gamma-globulin therapy. Clin Investig 70:38-39, 1992

69. Friedmann AM, King KE, Shirey RS, et al: Fatal autoimmune hemolytic anemia in a child due to warm-reactive immunoglobulin M antibody. J Pediatr Hematol Oncol 20:502-505, 1998

70. Qureshi S, Zaman S, Iqbal J: Intravenous immunoglobulin G therapy in Evans syndrome. J Pak Med Assoc 50:321-323, 2000

71. Bolis S, Marozzi A, Rossini F, et al: High dose intravenous immunoglobulin (IVIgG) in Evans' syndrome. Allergol Immunopathol (Madr) 19:186, 1991

72. Kaplan C, Murphy MF, Kroll H, et al: Feto-maternal alloimmune thrombocytopenia: antenatal therapy with IvIgG and steroids—More questions than answers. Br J Haematol 100:62-65, 1998

73. Gaddipati S, Berkowitz RL, Lembet AA, et al: Initial fetal platelet counts predict the response to intravenous gammaglobulin therapy in fetuses that are affected by PLA1 incompatibility. Am J Obstet Gynecol 185:976-980, 2001

74. Giers G, Hoch J, Bauer H, et al: Therapy with intravenous immunoglobulin G (ivIgG) during pregnancy for fetal alloimmune (HPA-1a(Zwa)) thrombocytopenic purpura. Prenat Diagn 16:495-502, 1996

75. Silver RM, Porter TF, Branch DW, et al: Neonatal alloimmune thrombocytopenia: Antenatal management. Am J Obstet Gynecol 182:1233-1238, 2000

76. Kornfeld I, Wilson RD, Ballem P, et al: Antenatal invasive and noninvasive management of alloimmune thrombocytopenia. Fetal Diagn Ther 11:210-217, 1996

77. Bussel JB, Berkowitz RL, Lynch L, et al: Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: A randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol 174:1414-1423, 1996

78. Birchall JE, Murphy MF, Kaplan C, et al: European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. Br J Haematol 122:275-288, 2003

79. Cordonnier C, Chevret S, Legrand M, et al: Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. Ann Intern Med 139:8-18, 2003

80. Abdel-Mageed A, Graham-Pole J, Del Rosario ML, et al: Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant 23:929-932, 1999

81. Feinstein LC, Seidel K, Jocum J, et al: Reduced dose intravenous immunoglobulin does not decrease transplant-related complications in adults given related donor marrow allografts. Biol Blood Marrow Transplant 5:369-378, 1999

82. Winston DJ, Antin JH, Wolff SN, et al: A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 28:187-196, 2001

83. Winston DJ, Ho WG, Bartoni K, et al: Intravenous immunoglobulin and CMV-seronegative blood products for prevention of CMV infection and disease in bone marrow transplant recipients. Bone Marrow Transplant 12:283-288, 1993

84. Winston DJ, Ho WG, Lin CH, et al: Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med 106:12-18, 1987

85. Zikos P, Van Lint MT, Lamparelli T, et al: A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. cytomegalovirus (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT). Haematologica 83:132-137, 1998

86. Ruutu T, Ljungman P, Brinch L, et al: No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. The Nordic BMT Group. Bone Marrow Transplant 19:233-236, 1997

87. Bowden RA, Fisher LD, Rogers K, et al: Cytomegalovirus (CMV)-specific intravenous immunoglobulin for the prevention of primary CMV infection and disease after marrow transplant. J Infect Dis 164:483-487, 1991

88. Lum L, Bitonti O, Jin NR, et al: Intravenous gamma-globulin (IVIG) does not alter immune parameters in a randomized trial after bone-marrow transplantation (BMT). Exp Hematol 22:680, 1994

89. Pole JG: Preventing systemic infections with IVIG: A randomized multicenter trial. Bone Marrow Transplant 5:132, 1990 (Suppl 2)

90. Poynton CH, Jackson S, Fegan C, et al: Use of IgM enriched intravenous immunoglobulin (Pentaglobin) in bone marrow transplantation. Bone Marrow Transplantation 9: 451-457, 1992

91. Sullivan KM, Storek J, Kopecky KJ, et al: A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: Clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant 2:44-53, 1996

92. Sullivan KM, Kopecky KJ, Jocom J, et al: Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 323:705-712, 1990

93. Wolff SN, Fay JW, Herzig RH, et al: High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 118:937-942, 1993

93a. Aldan H, Cordonnier C: Antimicrobial prophylaxis in EBMT centers: A report from the EBMT Infectious Diseases Working Party. Bone Marrow Transplant 27:S202, 2001 (Suppl 1, abstr)

94. American Academy of Pediatrics: Subcommittee on hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 114:297-316, 2004

95. Gottstein R, Cooke RW: Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed 88:F6-F10, 2003

96. Alcock GS, Liley H: Systematic review: Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database Syst Rev CD003313, 2002

97. Alpay F, Sarici SU, Okutan V, et al: High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. Acta Paediatr 88:216-219, 1999

98. Dagoglu T, Ovali F, Samanci N, et al: High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. J Int Med Res 23:264-271, 1995

99. Rubo J, Albrecht K, Lasch P, et al: High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. J Pediatr 121:93-97, 1992

100. Woodcock BE, Walker S, Adams K: Haemolytic transfusion reaction—Successful attenuation with methylprednisolone and high dose immunoglobulin. Clin Lab Haematol 15:59-61, 1993

101. Kohan AI, Niborski RC, Rey JA, et al: High-dose intravenous immunoglobulin in non-ABO transfusion incompatibility. Vox Sang 67:195-198, 1994

102. Cullis JO, Win N, Dudley JM, et al: Post-transfusion hyperhaemolysis in a patient with sickle cell disease: Use of steroids and intravenous immunoglobulin to prevent further red cell destruction. Vox Sang 69:355-357, 1995

103. Gangarossa S, Lucini NR: High-dose intravenous immunoglobulin therapy, blood rheology, and sickle cell anemia. Pediatr Hematol Oncol 10:377-378, 1993

104. Win N, Doughty H, Telfer P, et al: Hyperhemolytic transfusion reaction in sickle cell disease. Transfusion 41:323-328, 2001

105. Robson WL, Fick GH, Jadavji T, et al: The use of intravenous gammaglobulin in the treatment of typical hemolytic uremic syndrome. Pediatr Nephrol 5:289-292, 1991

106. Sheth KJ, Gill JC, Leichter HE: High-dose intravenous gamma globulin infusions in hemolytic-uremic syndrome: A preliminary report. Am J Dis Child 144:268-270, 1990

107. Dervenoulas J, Tsirigotis P, Bollas G, et al: Efficacy of intravenous immunoglobulin in the treatment of thrombotic thrombocytopaenic purpura. A study of 44 cases. Acta Haematol 105:204-208, 2001

108. Centurioni R, Bobbio-Pallavicini E, Porta C, et al: Treatment of thrombotic thrombocytopenic purpura with high-dose immunoglobulins. Results in 17 patients. Italian Cooperative Group for TTP. Haematologica 80:325-331, 1995

109. Finazzi G, Bellavita P, Falanga A, et al: Inefficacy of intravenous immunoglobulin in patients with low-risk thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. Am J Hematol 41:165-169, 1992

110. Warkentin TE, Greinacher A: Heparin-induced thrombocytopenia: recognition, treatment, and prevention: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126:311S-337S, 2004 (3 Suppl) (Erratum in: Chest 127, 416, 2005)

111. Winder A, Shoenfeld Y, Hochman R, et al: High-dose intravenous gamma-globulins for heparin-induced thrombocytopenia: A prompt response. J Clin Immunol 18:330-334, 1998

112. Grau E, Linares M, Olaso MA, et al: Heparin-induced thrombocytopenia—Response to intravenous immunoglobulin in vivo and in vitro. Am J Hematol 39:312-313, 1992

113. Perrella O: Idiopathic thrombocytopenic purpura in HIV infection: Therapeutic possibilities of intravenous immunoglobulins. J Chemother 2:390-393, 1990

114. Jahnke L, Applebaum S, Sherman LA, et al: An evaluation of intravenous immunoglobulin in the treatment of human immunodeficiency virus-associated thrombocytopenia. Transfusion 34:759-764, 1994

115. Schrappe-Bacher M, Rasokat H, Bauer P, et al: High-dose intravenous immunoglobulins in HIV-1–infected adults with AIDS-related complex and Walter-Reed 5. Vox Sang 59: 3-14, 1990 (Suppl 1)

116. De Simone C, Tzantzoglou S, Santini G, et al: Clinical and immunologic effects of combination therapy with intravenous immunoglobulins and AZT in HIV-infected patients. Immunopharmacol Immunotoxicol 13:447-458, 1991

117. Majluf-Cruz A, Luna-Castanos G, Huitron S, et al: Usefulness of a low-dose intravenous immunoglobulin regimen for the treatment of thrombocytopenia associated with AIDS. Am J Hematol 59:127-132, 1998

118. Blanchette VS, Luke B, Andrew M, et al: A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. J Pediatr 123:989-995, 1993

119. Blanchette V: Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet 344:703-707, 1994

120. Duru F, Fisgin T, Yarali N, et al: Clinical course of children with immune thrombocytopenic purpura treated with intravenous immunoglobulin G or megadose methylprednisolone or observed without therapy. Pediatr Hematol Oncol 19:219-225, 2002

121. Fujisawa K, Iyori H, Ohkawa H, et al: A prospective, randomized trial of conventional, dose-accelerated corticosteroids and intravenous immunoglobulin in children with newly diagnosed idiopathic thrombocytopenic purpura. Int J Hematol 72:376-383, 2000

122. Imbach P, Wagner HP, Berchtold W, et al: Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. Lancet 2:464-468, 1985

123. Khalifa AS, Tolba KA, el Alfy MS, et al: Idiopathic thrombocytopenic purpura in Egyptian children. Acta Haematol 90:125-129, 1993

124. Mori PG, Lanza T, Mancuso G, et al: Treatment of acute idiopathic thrombocytopenic purpura (AITP): Cooperative Italian study group results. Pediatric 5:169-178, 1988

125. Ozsoylu S, Sayli TR, Ozturk G: Oral megadose methylprednisolone versus intravenous immunoglobulin for acute childhood idiopathic thrombocytopenic purpura. Pediatric 10:317-321, 1993

126. Rosthoj S, Nielsen S, Pedersen FK: Randomized trial comparing intravenous immunoglobulin with methylprednisolone pulse therapy in acute idiopathic thrombocytopenic purpura. Danish I.T.P. Study Group. Acta Paediatr 85:910-915, 1996

127. Warrier I, Bussel JB, Valdez L, et al: Safety and efficacy of low-dose intravenous immune globulin (IVIG) treatment for infants and children with immune thrombocytopenic purpura. Low-Dose IVIG Study Group. J Pediatr Hematol Oncol 19:197-201, 1997

128. Tovo PA, Miniero R, Fiandino G, et al: Fc-depleted vs intact intravenous immunoglobulin in chronic ITP. J Pediatr 105:676-677, 1984

129. British Committee for Standards in Haematology General Haematology Task Force: Guidelines for the inves-

tigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 120:574-596, 2003

129a. Beck CE, Nathan PC, Parkin PC, et al: Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: A systematic review and meta-analysis of randomized controlled trials. J Pediatr 147:521-527, 2005

130. George JN, Woolf SH, Raskob GE, et al: Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Review. Blood 88:3-40, 1996

131. Godeau B, Chevret S, Varet B, et al: Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: A randomised, multicentre trial. Lancet 359:23-29, 2002

132. von dem Borne AE, Vos JJ, Pegels JG, et al: High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. Br Med J (Clin Res Ed) 296:249-250, 1988

133. Colovic M, Dimitrijevic M, Sonnenburg C, et al: Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematol J 4:358-362, 2003

134. Godeau B, Lesage S, Divine M, et al: Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. Blood 82:1415-1421, 1993

135. Godeau B, Caulier MT, Decuypere L, et al: Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: Results of a randomized trial comparing 0.5 and 1 g/kg B.W. Br J Haematol 107:716-719, 1999

136. Wehmeier A: Tolerability and efficacy of 5% versus 10% intravenous immunoglobulin preparation in adult patients with immune thrombocytopenia—A pilot study. Infusionsther Transfusionsmed 23:104-108, 1996 (Suppl 4)

137. Jacobs P, Wood L: The comparison of gammaglobulin to steroids in treating adult immune thrombocytopenia. An interim analysis. Blut 59:92-95, 1989

138. Mueller-Eckhardt C, Kiefel V: High-dose IgG for post-transfusion purpura—Revisited. Blut 57:163-167, 1988

139. Ningsanond V: Infection associated hemophagocytic syndrome: A report of 50 children. J Med Assoc Thai 83:1141-1149, 2000

140. Chen JS, Chang KC, Cheng CN, et al: Childhood hemophagocytic syndrome associated with Kikuchi's disease. Haematologica 85:998-1000, 2000

141. Fort DW, Buchanan GR: Treatment of infection-associated hemophagocytic syndrome with immune globulin. J Pediatr 124:332, 1994

142. Freeman B, Rathore MH, Salman E, et al: Intravenously administered immune globulin for the treatment of infection-associated hemophagocytic syndrome. J Pediatr 123:479-481, 1993

143. Goulder P, Seward D, Hatton C: Intravenous immunoglobulin in virus associated haemophagocytic syndrome. Arch Dis Child 65:1275-1277, 1990

144. Chen TL, Wong WW, Chiou TJ: Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection. Int J Hematol 78:450-452, 2003

145. Gill DS, Spencer A, Cobcroft RG: High-dose gammaglobulin therapy in the reactive haemophagocytic syndrome. Br J Haematol 88:204-206, 1994

146. Kaneko M, Kuwabara S, Hatakeyama A, et al: Guillain-Barre and virus-associated hemophagocytic syndromes contracted simultaneously following Epstein-Barr viral infection. Neurology 49:870-871, 1997