



Contents lists available at SciVerse ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Benefits and risks of IgA in immunoglobulin preparations

Urs E. Nydegger*, Walter Fierz, Lorenz Risch

Labormedizinisches Zentrum Dr. Risch, Waldeggstrasse 37, CH-3097 Liebefeld bei Bern, Switzerland

ARTICLE INFO

Article history:

Available online xxxx

Keywords:

IVIG

IgA

Anaphylaxis

Laboratory analysis

ABSTRACT

The case of Immunoglobulin A (IgA) in transfusion medicine is unsettled: on one hand IgA is an important component of adaptive immunity and its deficiency may cause disease, on the other its presence in blood products might induce, in rare instances, allergy-like symptoms if not anaphylaxis.

The practice with i.v. immunoglobulins currently changes as up to 10% concentrated preparations are given at fast rates hence even trace amounts of IgA contained in these IgG preparations can cause unexpected (side-) effects. Fortunately, the spectrum of sensitive IgA assays, along with anti-IgA screening assays now permits laboratories to narrow down IgA-dependent transfusion reactions to the real cases, in which IgA was the decisive trigger of anaphylaxis, proven or not by the presence of anti-IgA of the IgG or even IgE class. Tolerance to allogenic IgA has recently been reported. The known association of HLA with IgA deficiency (IgAD) has now been completed with an association to the nonsynonymous variant in IFH11, allowing physicians to more precisely spot recipients at risk for an IgA-dependent transfusion reaction. Our review, along with our own experience here in Switzerland, allows us to conclude that IgA is a beneficial antibody rather than an allergen to be placed at the end of the list of non-infectious transfusion complications such as TRALI, febrile non-hemolytic reactions, purpura or volume overload.

© 2011 Elsevier Ltd. All rights reserved.

Contents

1. Introduction	00
2. IgA synthesis and location	00
3. Functional IgA performance	00
4. IgA deficiency	00
5. Laboratory procedures – current state	00
6. Anaphylactic reactions towards IgA, validation of lab results and risk assessment	00
7. The role of IgA-concentration in IVIg in IgA deficiency	00
8. Conflict of interest	00
References	00

1. Introduction

Transfusion therapy, particularly using polyclonal polypeptide immunoglobulin G (IgG) preparations, has been

under scrutiny with respect to the sensitization of IgA-deficient recipients (IgA deficiency, IgAD) by the passive transfer of IgA contained in the blood products. Vigilance directed at intravenous Ig (IVIg) is suggested because these preparations contain widely differing amounts of IgA [1,2]. Anaphylactic shock continues to be reported in single cases and while rare is still noteworthy. Recently, the IgA in IVIg

* Corresponding author. Tel.: +41 319790031; fax: +41 319790099.
E-mail address: nyu@lmz-risch.ch (U.E. Nydegger).

has been registered as a contaminant [3], and the side effects of IVIg therapy have led to the production of modified preparations using adapted purification procedures which are concentrated up to 10%.

The summary of the product characteristics (SmPC) with respect to IgA isotype/IgG issued by regulators, such as the EMA, does not stipulate maximal amounts of IgA; rather, this is left to the producer's discretion. Here, we discuss a topic that still lacks an international registry or requirement for mandatory reporting to the health authorities.

2. IgA synthesis and location

The glycoprotein IgA is present in the systemic compartment, in plasma, and in the secretory compartment, which encompasses various body secretions, such as milk, cerebrospinal fluid, endolymphatic and perilymphatic, gastric juice, mucus (including nasal drainage), pleural and peritoneal fluids, saliva, semen, sweat, tears and vaginal secretions. Daily production of IgA is ~66 mg/kg body weight and exceeds all other Ig isotypes combined; notably, IgA is found in exocrine secretions at mucosal surfaces. Such secretory IgA (sIgA) will not appear in Ig fractions from healthy human donor plasma pools. Two different subclasses, IgA1 and IgA2, exist, and the ratio IgA1/IgA2 is higher in the systemic compartment. IgA is synthesized by activated B cells. In germ-free mice, IgA production is low but increases after colonization with intestinal bacteria which shapes the ecology of the microbial flora – thus, the gut is the largest antibody-producing organ in the body because >80% of the activated B cells reside in its mucosal tissues. The signals required for class switch recombination of IgM-positive B cells to IgA occur in the Peyer's patches where the committed plasma B cells will recirculate via the lymph, thoracic duct and bloodstream to the lamina propria with the majority of the sIgA expressing restricted antigen-specificity [4–6]. As such, sIgA antibodies play an essential role as sentinels for the recognition and clearance of enteric pathogens at mucosal sites. IgA circulates as a monomer, but it is dimeric in bodily fluids. Normal serum reference ranges span from 0.7 to 4 g/L. The two monomeric IgA partners are linked end-to-end on their N terminal with a J-chain, and the Fc-portions are intermingled with the secretory components. The molecule is glycosylated, and unstable O-linked glycans in the IgA1 hinge region favor molecular transformation to form deposits in the glomerular mesangium and IgA nephropathy [7].

3. Functional IgA performance

Among the immunobiological functions of IgA so far investigated, the following are notable.

- (1) sIgA and sIgA-antigen immune complexes are selectively transported across Peyer's patches to underlying dendritic cells in the mucosa-associated lymphoid tissue independent of antigen specificity [8].
- (2) Immune complex formation occurs for the neutralization/removal of pathogenic foreign material. The range of antigenic recognition might approach the variety of IgG proper (i.e., $\sim 10^{12}$). For

example, the IgA1 subtype can specifically recognize staphylococcal alpha toxin. sIgA is the predominant Ig present in tears and protects the ocular surface against various antigens [9].

- (3) In the gut, IgA along with defensins and beneficial bacteria (e.g. bifidobacteria), keeps sulfate-reducing bacteria latent [10,11]. IgA prepared from human serum by Cohn fraction II and ion-exchange chromatography contains high IgA titers against *Escherichia coli* 0111, *Salmonella typhimurium* and clostridia [12]. Oral administration of IgA prevents gastrointestinal disease in patients at risk [12] and reduces viral infections [13].
- (4) IgA neutralizes the proliferative and cytokine-inducing capacity of group A streptococcal superantigens [11].
- (5) IgA downregulates the release of inflammatory cytokines, such as IL-1 β , TNF α and IL-6 from *Haemophilus influenzae* or endotoxin stimulated human monocytes. IgA induces IL-1RA in activated monocytes, IgA thus has anti-inflammatory activity that prevents an uncontrolled release of noxious sequelae in acute and chronic inflammation [14,15].
- (6) Human B cells express the Toll-like receptor-9, which gets restored upon IVIg treatment in certain inflammatory conditions and leads to increased synthesis of IgA-, IgM- and IgG-secreting cells. One might argue that IVIg treatment augments the patient's own IgA secretion and improves tolerance to IgA [16].

4. IgA deficiency

Selective IgA deficiency (IgAD) and common variable immunodeficiency (CVID) are the most common primary immune deficiencies in humans [17]. The prevalence of selective IgA deficiency is ~1/500 (IgAD) and is defined as decreased or absent serum levels of IgA in the presence of normal levels of IgG and IgM in individuals in whom other causes of hypogammaglobulinemia have been excluded. Most IgA-deficient people are asymptomatic because of compensatory increases in secreted IgG and IgM. Should affected patients suffer from recurrent infections, then sinusitis, otitis, and bronchitis are the most frequent. Some cases of IgAD spontaneously remit. When IgG2 subclass deficiency occurs in combination with IgAD, the affected patients are more susceptible to encapsulated bacteria. Atopic disease and autoimmune disorders can be associated with IgAD and occasionally a sprue-like syndrome with steatorrhea has been associated with an isolated IgAD. Treatment with IVIg is ineffective because IgA and IgM are present only in trace quantities in these preparations. Frequent transfusions of plasma containing IgA or unwashed blood cell transfusions may be hazardous like IVIg since recipients may become sensitized as with IVIg (see below). Although combined IgAD/CVID patients do not show Mendelian segregation in families, they exhibit a high degree of familial clustering, with marked differences in the population prevalence among ethnic groups, ranging from ~1/500 in Caucasians to 1/18500 in Japanese [18,19].

A predominant inheritance pattern in multiple-case pedigrees explains the shared genetic predisposition [20]. In the setting of blood transfusion, IgA-related major adverse reactions are quoted to be approximately 1 in 50,000 and major adverse reactions may occur in ~2.5% of patients with identified anti-IgA antibodies [21]. These data are based on serum IgA measurements and might someday be compiled by genetic screening assays even though the IgAD/CVID susceptibility locus, which is called IGAD1, stretches across the major histocompatibility locus (MHC) on chromosome 6. Thus, no single locus, but rather a constellations of haplotypes, like A1-B8-DR3, A28-B28-B14-DR1 and B44-DR7 predict IgAD [22].

In a recent genetic study, 772 individuals of European ancestry with selective IgAD were compared to 1976 individuals without IgAD. A less common C version of rs1990760 in the IFIH1 gene was associated with 0.67 times lower risk of the condition. The variant has also been implicated in autoimmune diseases, such as type 1 diabetes and systemic lupus erythematosus, suggesting that autoimmunity may be in some way related to IgAD. Anyone can be genotyped for these conditions with a saliva sample (www.23andme.com) [20].

Several studies have noted a higher frequency of mother-to-child inheritance of IgAD compared to father-to-child. One explanation is the possible transplacental passage of anti-IgA antibodies, which could result in IgAD in the infant [17].

5. Laboratory procedures – current state

Some laboratory techniques in use for clinical diagnostic purposes are summarized in Table 1. Nephelometry is the most popular method [23]. In men, the total IgA is higher compared to women, and the 95% central intervals, which

are used for interpretive and diagnostic purposes are 0.72–3.89 g/L for both genders. With aging, human serum IgA levels tend to increase by ~10% [23] but updates are lacking, which is why the Seniorlabor-Study (www.seniorlabor.ch) is currently evaluating the reference ranges for IgA in advanced age [24]; measured IgA serum levels <0.1 g/L (<10 mg/dl) point to selective IgAD. The lowest detectable serum IgA level at our institution reached 0.1 g/L (10 mg/dl) if the analyzed serum was used undiluted (nephelometric method using ProSpec, Siemens Healthcare Diagnostics, Germany, June 2008). When a serum level is >1 g/L (>100 mg/dl) of IgA but remains 2 SD below normal for age (~0.7 g/L (70 mg/dl)), the propositus presents with partial IgAD. The conventional clinical laboratory definition of IgAD is less than 1–3% of the normal value (i.e., <0.5 g/L (<50 mg/dl)).

Using the database accrued by the Human Genome Project, such as www.genetests.org, www.23andme.com, www.orchid.com or www.alerchek.com, more than 2000 genetic tests are now available. The right genetic information on recipients of IgA-containing blood products [20,25,26] (www.broadinsitute.org) might help physicians to order the most informative lab test or prescribe the appropriately prepared blood product with a known IgA content.

6. Anaphylactic reactions towards IgA, validation of lab results and risk assessment

The hallmark cutaneous symptoms of anaphylaxis, which is associated with dyspnea, visceral edema and hypotension, are caused by the degranulation of mast cells and circulating basophilic granulocytes (basophils). Inundation of the microenvironment with histamine, proteoglycans, proteases, leukotrienes, and preformed cytokines, such as IL-33 [27], with overflow into the circulating blood takes

Table 1
The spectrum of laboratory analysis for IgA deficiency and the presence of anti-IgA.

Analyte	Technique	Normal range	Reference/Link	Comment
1. IgA				
<i>Protein based</i>				
Human IgA1 and IgA2 assays	ELISA-Kit available		Commercial methods on the market [53]	Better sensitivity when using free IgA in an indirect ELISA
	Radioimmunoassay			Obsolete
	Nephelometry	80–440 mg/dl 0.8–4 g/l	[54]	Today's standard
	Particle-enhanced nephelometric immunoassay (PENIA)	16.9–414.5 mg/L	[55]	
	Radial immunodiffusion		[35,56]	Good for developing countries
<i>Genome based</i>				
IgA	Tally on public websites		www.23andme.com, www.genetests.com	Are these tests safe and effective?
IgA	IFIH1 gene sequenced	Genome-wide threshold defined by HapMap	[20]	This is the future in documenting IgAD
2. Anti-IgA				
<i>Anti-IgA ELISA</i>				
IgG	Passive hemagglutinin inhibition	Defined titers	[57]	Simple
	Biotin-avidin ELISA	Defined background signal	[45]	In-house system
IgG	ELISA with inhibition step		[1]	In-house system inhibition step adds specificity
IgG	ImmunoCAP	Suggested cutoff: 300 U/ml	[39]	In development by Phadia™
IgG	ID-PaGIA		[38]	Available through BioRad™

place and their quantitative estimation can improve the lab diagnosis of anaphylaxis [21,28,29]. The formation of antibodies against IgA is brought about by IgG and IgE isotypes, which likely express epitope specificity against the hinge region on IgA. This hinge region is now a suspected allotypic exposition site of the IgA molecule for immune complex formation [30,31]. For patients at risk of developing IgE induced anaphylaxis upon treatment with IgA-containing blood/plasma products, the IgA serum level must be <0.5 g/L, which is classified as severe IgAD. An IgA level above this threshold rules out absolute IgAD and makes anaphylaxis due to anti-IgA unlikely [32].

Right or wrong [33], demonstration of anti-IgA antibodies is regarded as a prerequisite for the diagnosis of anaphylactic transfusion reactions in IgAD. The IgA molecule as a target for the anti-IgA adaptive immune response was first described in Transfusion Medicine by Vyas et al. [34] soon followed by others [35] and more recently reviewed by Sandler et al. [36]. The spontaneous occurrence of anti-IgA in healthy blood donors has been estimated to be up to 1 in 1200 individuals [37]. Practical tests to detect anti-IgA antibodies using a particle gel immunoassay were developed [38] (Table 1). With one of these, as an example, 10 patients expressed an anti-IgA titer ranging from 1:2 to 1:256. One patient had a history of anaphylaxis, and this was related to the administration of Rh(D) prophylaxis (anti-D immunoglobulin). The beads did not show nonspecific agglutination and could be used repeatedly for longer than 6 months. The test is now commercialized by BioRad® laboratories, formerly DiaMed® (Cressier sur Morat, Switzerland). Other providers, such as Phadia® (Uppsala, Sweden), are currently developing screening tests to detect IgG antibodies against IgA based in their case on the commercially available EliA platform [39]. Such techniques could be useful for screening purposes.

IgA-related anaphylactoid reactions are rare; thus, the medical literature reports only single cases based on different good clinical practice evaluation criteria, and the majority of clinical diagnoses are not confirmed by detecting anti-IgA in the patients' plasma (Table 2). For example, of 354 blood samples from patients with a suspected IgA-related reaction who were referred to the ARC National Reference Laboratory, only 18% contained IgA antibodies; the majority of the reactions were caused by other factors [21].

Between 1968 and 2006, ~40 cases of anti-IgA-related anaphylaxis to blood transfusions, Ig replacement therapy and other plasma products have been summarized following library searches (Table 2).

Three of these cases were attributed to IVIg treatment [40,41]. Reviewing the literature between 1987 and 2006

on CVID patients, in whom severe IgAD is often associated with anti-IgA formation, eleven cases of an anti-IgA associated anaphylactic reaction to IVIg were reported [1,42]. A study carried out by the Quebec Public Health Institute, Montreal, evaluated the risk associated with the passive transfer of anti-IgA to recipients (with normal IgA serum values) during the transfusion of anti-IgA-containing blood products from IgA-deficient donors: no evidence for increased risk of adverse events compared to anti-IgA-free blood products was found [40]. Nevertheless the possibility of anaphylaxis due to IgA is now being listed in the package inserts of most IVIg products.

7. The role of IgA-concentration in IVIg in IgA deficiency

Among the possible side effects of IVIg therapy [43] one might deduce that this stable plasma fractionation product containing IgA in trace amounts elicits a reaction between IgA and anti-IgA. A recent report from Florida, USA, alluded to this possibility in a timely review article [3] on the new generation of liquid IVIg preparations now concentrated up to 10%. The following contraindication warnings have been officially implemented for each IVIg: "IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (FDA) and hypersensitivity to human immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA(EMA).

This rule is applicable to all commercially available IVIg preparations independent of the amount of IgA given; in patients with CVID, administration of IVIg is a life-saving treatment that reduces the frequency and severity of infections. Therefore, strategies are now developed to prevent IgA-related anaphylaxis in patients with a history of hypersensitivity [40,44].

The case reports on anaphylaxis upon IVIg treatment used IVIg preparations containing variable amounts of IgA, ranging from 2.5 to 0.015 mg/ml [1,40,45]. These preparations have been reported to induce IgA-related adverse reactions independently of their IgA content. This can be explained, at least in part, by the antigen-antibody ratio of IgA that forms in the recipient immediately following venous inflow [46]. With regard to IgA as an allergen, it is well known that desensitization protocols use incremental amounts of an allergen over time. With allergies to chemical drugs, desensitization usually involves the preparation of three different concentrations of a drug (solutions A, B, and C) with a 10-fold increase in concentration between A and C. This desensitizing capacity can be explained by incremental allergen/IgE antibody ratios

Table 2
IgA as a cause of anaphylaxis; proven or supposed.

Number of patients	Anti-IgA isotype	No Anti-IgA	Product	Literature reference
5	+		IVIg	[40]
2	Both IgE			[45]
83		3		[58]
5/8	IgG		Platelet concentrates, red blood cell concentrates	[1]
1				[48]
8/40				[36]
1	IgG			[35]

[47]. If we accept the view that IgA similarly acts as an allergen in transfusion-induced IgA anaphylaxis, its induction when contained in IVIg must have played a crucial role in the reported cases independent of the IVIg–IgA content [1,40]. In the same cases, the transfusion rate among the different preparations should be traced. Some authors recommend that, in patients with a history of a severe anaphylactic transfusion reaction and a laboratory-confirmed diagnosis of IgA deficiency, the IgA content of the IVIg to be administered should be below 0.0012 mg/ml [32].

In one case series of five patients with CVID and a previous history of IgA anaphylaxis following treatment with IVIg, reinfusion was recommenced using different preparations but under standard infusion conditions (i.e., 10 g in 1 h). Subsequently, all patients developed a complete tolerance to IVIg [40]. Anti-Ig did not seem to result from allogenic stimulation in these cases. The infusion rate clearly impacts the reaction, especially in patients with high anti-IgA titers. The most probable explanation for the elimination of anti-IgA activity in the patient's plasma is that IgA forms complexes with anti-IgA *in vivo*, thus diminishing anti-IgA activity completely without rebound. Moreover, anti-IgA has not been reported to be augmented by IVIg transfusions even upon repeated administration (no booster effect). There is one report on tolerance induction in a sensitized patient suffering from end-stage hepatic failure requiring transplantation by using a continuous infusion of an IgA-enriched Ig preparation (IgA: 6 mg/ml) [48]. IgA-related anaphylaxis in CVID patients following the administration of IVIg are hardly predictable in respect to the IgA content of the preparations. The management of these patients is promising if the infusion rate of IVIg is low and if reduction or complete elimination of the anti-IgA titer is accomplished. The relationship between IgA concentration in IVIG and adverse events was also analyzed in children treated for juvenile dermatomyositis [2]. In this study, patients with IgA deficiency were excluded and, they did not receive IVIg. Adverse events here (seen in a total of 9% of the infusions) included fever, headache, nausea or vomiting, and lethargy and were different according to the IgA content in the IVIg preparations whereby the study gauged the time to assess anti-IgA (8% for IVIg <0.01 mg/ml and 15% for an IVIg of 0.27 mg/ml). It has been speculated that in sensitive patients, exposure to exogenous IgA may trigger Fc alpha receptor-mediated metabolic activation of mast cells leading to the release of histamines, TNF-alpha, and heparin, all of which are potent pyrogens. The observation made in this retrospective study may be disease specific to treating pediatric dermatomyositis and it is premature to accept this observation as representative for other clinical conditions. There is no evidence of a difference in the tolerability of IVIg treatment due to the content of IgA in patients lacking anti-IgA in the plasma.

In conclusion, IgA is a beneficial antibody rather than an allergen when administered appropriately [12,49]. Based on personal experience and on this review article and on the risk of transfusions in general, IgA should not be seen as harmful by physicians and their patients. The likelihood of IgA-mediated anaphylaxis is at the end of the list of non-infectious transfusion complications, including TRALI,

febrile non-hemolytic reactions, purpura or volume overload [50–52].

8. Conflict of interest

None declared.

References

- [1] Horn J, Thon V, Bartonkova D, Salzer U, Warnatz K, Schlesier M, et al. Anti-IgA antibodies in common variable immunodeficiency (CVID): diagnostic workup and therapeutic strategy. *Clin Immunol* 2007;122:156–62.
- [2] Manlhiot C, Tyrrell PN, Liang L, Atkinson AR, Lau W, Feldman BM. Safety of intravenous immunoglobulin in the treatment of juvenile dermatomyositis: adverse reactions are associated with immunoglobulin A content. *Pediatrics* 2008;121:626–30.
- [3] Stein MR. The new generation of liquid intravenous immunoglobulin formulations in patient care: a comparison of intravenous immunoglobulins. *Postgraduate Med* 2010;122:176–84.
- [4] Kadaoui KA, Corthesy B. Secretory IgA mediates bacterial translocation to dendritic cells in mouse Peyer's patches with restriction to mucosal compartment. *J Immunol* 2007;179(11):7751–7.
- [5] Wells JM, Rossi O, Marijnen M, VanBaaren P. Epithelial crosstalk at the microbiota-mucosal interface. *Proc Natl Acad Sci USA* 2011;108(suppl1):4607–14.
- [6] Benckert J, Schmolka N, Kreschel C, Zoller MJ, Sturm A, Wiedenmann B, et al. *J Clin Invest* 2011;pii:44447.
- [7] Tanaka M, Seki G, Someya T, Nagata M, Fujita T. Aberrantly glycosylated IgA1 as a factor in the pathogenesis of IgA nephropathy. *Clin Dev Immunol* 2011;10.1155(open access).
- [8] Duc M, Johansen FE, Corthesy B. Antigen binding to secretory immunoglobulin A results in decreased sensitivity to intestinal proteases and increased binding to cellular Fc receptors. *J Biol Chem* 2010;285(2):953–60.
- [9] Lan J, Willcox MD, Jackson GD. Detection and specificity of anti-staphylococcus intermedius secretory IgA in human tears. *Aust N Z J Ophthalmol* 1997;25(S1):S17–9.
- [10] Danese F, Danese S. Intestinal microbiota in inflammatory bowel disease: friend or foe? *World J Gastroenterol* 2011;17(5):557–66.
- [11] Norrby-Teglund A, Ihendyane N, Kansal R, Basma H, Kotb M, Andersson J, et al. Relative neutralizing activity in polyspecific IgM, IgA and IgG preparations against group A Streptococcal superantigens. *Clin Infect Dis* 2000;31:1175–82.
- [12] Eibl MM, Wolf HM, Fuernkranz H, Rosenkranz A. Prevention of necrotizing enterocolitis in low-birth-weight infants by IgA-IgG feeding. *New Engl J Med* 1988;319(1):1–7.
- [13] Moon SS, Wank Y, Shane AL, Nuyuen T, Ray P, Dennehy P, et al. Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. *Pediatr Infect Dis J* 2010;20(10):919–23.
- [14] Wolf HM. Human serum IgA downregulates the release of inflammatory cytokines (Tumor Factor alpha, Interleukin-6), in human monocytes. *Blood* 1994;83:1278–88.
- [15] Wolf HM. Anti-inflammatory properties of human serum IgA: induction of IL-1 receptor antagonist and Fc alpha R (CF89) - mediated down-regulation of tumor necrosis factor-alpha (TNF-alpha) and IL-6 in human monocytes. *Clin Exp Immunol* 1996;105:537–43.
- [16] Giordani L, Quaranta MG, Marchesi A, Straface E, Pietraforte D, Villani A, et al. Increased frequency of immunoglobulin (Ig)-A-secreting cells following Toll-like receptor (TLR)-9 engagement in patients with Kawasaki disease. *Clin Exp Immunol* 2011;163(3):346–53.
- [17] Cunningham-Rundles C, Mestecky J, Lamm ME, Strober W, Bienenstock J, McGhee JR, et al. *Immunodeficiency and Mucosal Immunity*. Mucosal Immunology. 2005;3rd Ed(ISBN-0-12-491543-4):1145–58.
- [18] Burrows PD, Cooper MD. IgA deficiency. *Adv Immunol* 1997;65:245.
- [19] Palmer DS, O'toole J, Montreuil T, Scalia V, Yi QL, Goldman M, et al. Screening of Canadian blood services donors for severe immunoglobulin A deficiency. *Transfusion* 2010;50(7):1524–31.
- [20] Ferreira RC, Pan-Hammarstrom G, Graham RR, Gateva V, Fontan G, Lee AT, et al. Association of IFIH1 and other autoimmune risk alleles with selective IgA deficiency. *Nat Genet* 2010;42(9):777–80.

- [21] Vassallo Rr. IgA anaphylactic transfusion reactions: Part I: laboratory diagnosis, incidence, and supply of IgA-deficient products. *Immunohematology*. 2004;20:226–233.
- [22] Kralovicova J, Hammarstrom L, Plebani A, Webster AD, Vorechovsky I. Fine-scale mapping at IGAD1 and genome-wide genetic linkage analysis implicate HLA-DQ/DR as a major susceptibility locus in selective IgA deficiency and common variable immunodeficiency. *J Immunol* 2003;170(5):2765–75.
- [23] Berth M, Delange J, Langlois M, DeBuyzere M. Reference values of serum IgA subclasses in caucasian adults by immunonephelometry. *Clin Chem* 1999;45:309–10.
- [24] Sakem B, Nydegger U, Medina P, Risch L, Risch M. Determining laboratory reference intervals for serum immunoglobulins and C-reactive protein in the elderly. *Proc Swiss Society Gerontology Swiss Med Forum Suppl* 55 2011; 11(18).
- [25] Lander ES. Initial impact of the sequencing of the human genome. *Nature* 2011;470:187–97.
- [26] Offer SM, Pan-Hammarstrom Q, Hammarstrom L, Harris RS. Unique DNA repair gene variations and potential associations with the primary antibody deficiency syndromes IgAD and CVID. *PLoS* 2010;5(8):e12260.
- [27] Enokson M, Lyberg K, Moller-Westerberg C, Fallon PG, Nilsson G, Lunderius-Andersson C. Mast cells as sensors of cell injury through IL-33 recognition. *J Immunol* 2011;186(4):2523–8.
- [28] Sanz ML, Gamboa PM, Garia-Figueroa BE, Ferrer M. In vitro diagnosis of anaphylaxis. *Chem Immunol Allergy* 2010;95:125–40.
- [29] Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007;120(1):S2–S24.
- [30] Mestecky J, Suzuki H, Yanagihara T, Moldoveanu Z, Tomana M, Matousovic K, et al. IgA nephropathy: current views of immune complex formation. *Contrib Nephrol* 2007;157:56–63.
- [31] Phillips-Quagliata JM. Mouse IgA allotypes have major differences in their hinge regions. *Immunogenetics* 2002;53(12):1033–8.
- [32] Sandler GS. How I manage patients suspected of having had an IgA anaphylactic transfusion reaction. *Transfusion* 2006;46:10–3.
- [33] Gilstad CW. Anaphylactic transfusion reactions. *Curr Opin Hematol* 2003;10(6):419–23.
- [34] Vyas GN, Perkins HA, Fudenberg HH. Anaphylactoid transfusion reactions associated with anti-IgA. *Lancet* 1968;2(7563):312–5.
- [35] Schmidt AP, Taswell HF, Gleich GJ. Anaphylactic transfusion reactions associated with anti-IgA antibody. *New Engl J Med* 1969;280:188–93.
- [36] Sandler SG, Zantek ND. IgA anaphylactic transfusion reactions Part II. clinical diagnosis and bedside management. *Immunohematology* 2004;20 (234–238).
- [37] Sandler GS, Mallory D, Malamout D, Eckrich R. IgA anaphylactic transfusion reactions. *Transfus Med Rev* 1995;9(1):1–8.
- [38] Salama A, Schwind P, Schonhage K, Genth R, Cotting C, Hustinx H, et al. Rapid detection of antibodies to immunoglobulin A molecules by using the particle gel immunoassay. *Vox Sang* 2001;81(1):45–8.
- [39] Knosgaard B, Hinnerfeldt F, Kristensen B, Fiedler R. Development and evaluation of a new assay for anti-IgA antibody measurement based on the EliA platform on ImmunoCAP I and ImmunoCAP 100 systems. Poster-Exhibit. 2010.
- [40] Ahrens N, Hoflich C, Bombard S, Lochs H, Kiesewetter H, Salama A. Immune tolerance induction in patients with IgA anaphylactoid reactions following long-term intravenous IgG treatment. *Clin Exp Immunol* 2007;151:455–8.
- [41] Yu H, Sandler SG. IgA anaphylactic transfusion reactions. *Transfus Med Hemother* 2003;30:214–20.
- [42] Robitaille N. Allergic transfusion reactions from blood components donated by IgA deficient donors with and without anti-IgA: a comparative study. *Vox Sang* 2010;99:136–40.
- [43] Nydegger U. Immunoglobulins. In: Simon TL, Snyder EL, Solheim BG, Stowell CP, Strauss RG, Petrides M, editors. *Principles of Transfusion Medicine*. 4th ed. Oxford UK, Bethesda MD, USA: Wiley, AABB Blackwell; 2009.
- [44] Salama A. A new strategy for the prevention of IgA anaphylactic transfusion reactions. *Transfusion* 2004;44:509–11.
- [45] Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. *New Engl J Med* 1986;314(9):560–4.
- [46] Nydegger UE. Immune complex pathophysiology. *Ann N Y Acad Sci USA* 2007;1109:66–83.
- [47] Krishna MT, Huissoon AP. Clinical immunology review series: an approach to desensitization. *Clin Exp Immunol* 2010;163:131–46.
- [48] Kiani-Alikhan S. Successful desensitization to immunoglobulin A in a case of transfusion-related anaphylaxis. *Transfusion* 2010;S1–5.
- [49] Kreyman Kg, DeHeer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med*. 2007;35(12):2677–2685.
- [50] Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus pane. *Transfusion* 2004;44(12):1774–89.
- [51] Heddle NM. Pathophysiology of febrile nonhemolytic transfusion reactions. *Curr Opin Hematol* 1999;6(6):420–6.
- [52] Zhou L, Giacherio D, Cooling L, Davenport RD. Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. *Transfusion*. 2005;45(jul2005):1056–1063.
- [53] Sinclair D, Saas M, Turk A, Goble M, Kerr D. Do we need to measure total serum IgA to exclude IgA deficiency in coeliac disease? *J Clin Pathol* 2006;59(7):736–9.
- [54] Mali B, Armbruster D, Serediak E, Ottenbreit T. Comparison of immunoturbidimetric and immunonephelometric assays for specific proteins. *Clin Biochem* 2009;42(15):1568–71.
- [55] Booth CK, Dwyer DB, Pacque PF, Ball MJ. Measurement of immunoglobulin A in saliva by particle-enhanced nephelometric immunoassay: sample collection, limits of quantitation, precision, stability and reference range. *Ann Clin Biochem* 2009;46(5):410.
- [56] Padilla-Docal B, Dorta-Contreras AJ, Moreira JM, Martini-Robles L, Muzzia-Aroca J, Alarcon F, et al. Comparison of major immunoglobulins intrathecal synthesis patterns in Ecuadorian and Cuban patients with angiostrongyliasis. *Am J Trop Med Hyg* 2011;84(3):406–10.
- [57] Lum G, Szuflad P, Damarino M. A patient with a low IgA level requiring transfusion during CABG surgery. *Labmedicine* 2005;36(6):353–6.
- [58] Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. *Haematologica*. 1993;78(6suppl2):35–40. Benefits and risks of IgA in immunoglobulin preparations.