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Review Article

Immunoglobulin A deficiency in children, an undervalued clinical issue

M.H. Koenen[a,**], J.M. van Montfrans[a], E.A.M. Sanders[a,b], D. Bogaert[a,c], L.M. Verhagen[a,*]

[a] Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, Lundlaan 6, 3508 AB Utrecht, the Netherlands
[b] Centre for Infectious Disease Control (Cib), National Institute of Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, the Netherlands
[c] Center for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Little France Crescent 47, EH16 4TJ Edinburgh, United Kingdom

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ABSTRACT

Immunoglobulin A (IgA) is the principal antibody in secretions that bathe the gastrointestinal and respiratory mucosal surfaces and acts as an important first line of defense against invasion of pathogenic micro-organisms. The reported prevalence rate of complete IgA deficiency in healthy children ranges from 1:170 to 1:400, and as a solitary condition, it is often considered of limited clinical importance. However, patients with IgA deficiency can develop recurrent respiratory and gastrointestinal infections, as well as allergic and autoimmune diseases. In children referred for recurrent respiratory tract infections, the observed prevalence rate increases more than tenfold. This review discusses several aspects of IgA deficiency in children, including immunologic and microbiome changes in early childhood and the potential consequences of this condition in later life. It illustrates the importance of early identification of children with impaired IgA production who deserve appropriate clinical care and follow-up.

1. Introduction

Most published reports on selective Immunoglobulin A (IgA) deficiency focus on older children and adults, since IgA deficiency in young children can be transient [1]. This review focuses on children of all ages with a special interest in children under the age of four who are often excluded from IgA deficient patient cohorts. Although normalization of IgA level is likely to restore mucosal immune protection, the consequences of impaired immunity in a critical period of life may extend beyond infancy. We therefore aim to review the consequences that (temporary) lack of IgA may cause later in life. This review will discuss how the immunologic and microbiome changes in early childhood impair host-microbiome development with affected health programming and how recurrent respiratory tract infections, the most common clinical manifestation of IgA deficiency [2], can effect developing airway tissue. We aim to draw attention to the importance of correctly identifying IgA deficient children at risk for significant health problems, since early childhood presents a window of opportunity to prevent end organ damage by intensive monitoring and therapeutic options such as prophylactic antibiotic treatment.

IgA exists in both monomeric as well as polymeric form and is most abundantly found as a dimeric form in mucosal secretions, including saliva, breastmilk, tears, and secretions from the genitourinary, gastrointestinal and respiratory tract. Secretory IgA (sIgA) on mucosal surfaces prevents endothelial adherence and penetration of pathogens and thereby forms the first line of immunological defense against potentially harmful micro-organisms [3]. Complete selective IgA deficiency is defined by the European Society of Immunodeficiencies (ESID) as a serum IgA level of <7 mg/dL (0.07 g/L) with normal levels of serum IgG and IgM, in patients older than four years in whom other causes of hypogammaglobulinemia have been excluded and who have a normal IgG antibody response to vaccination [4]. The term partial IgA deficiency is used when patients have IgA levels below minus two standard deviations (SD) of the population average level normalized for

Abbreviations: IgA/IgG/IgM, immunoglobulin A/G/M; sIgA, secretory immunoglobulin A; CVID, Common Variable Immunodeficiency; IVIG, intravenous immunoglobulin; IgA deficiency, immunoglobulin A deficiency; Transient IgA deficiency, transient immunoglobulin A deficiency; Complete IgA deficiency, complete immunoglobulin A deficiency (serum IgA levels <0.07 g/L); Partial IgA deficiency, partial immunoglobulin A deficiency ($<$-2SD of population average serum IgA level normalized for age)

* Correspondence to: LM Verhagen, Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, Lundlaan 6, 3508 AB Utrecht, The Netherlands.
** Correspondence to: MH Koenen, Center Translation Immunology, Wilhelmina Children's Hospital, Lundlaan 6, 3508 AB Utrecht, The Netherlands.
E-mail addresses: M.H.Koenen-2@umcutrecht.nl (M.H. Koenen), J.vanMontfrans@umcutrecht.nl (J.M. van Montfrans), Lieke.Sanders@rivm.nl (E.A.M. Sanders), D.Bogaert@ed.ac.uk (D. Bogaert), L.M.Verhagen-3@umcutrecht.nl (L.M. Verhagen).

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Table 1
Prevalence rates of IgA deficiency among healthy children and children referred for recurrent lower and/or upper respiratory tract infections.

Study	Year	Country	Sample size	Subjects	Age in years	IgA deficiency cut-off (g/L)	Prevalence
Healthy patient population studies							
Pereira et al. [104]	1997	Spain	1856	Healthy schoolchildren	2–16	< 0.07	1:169
Ertekin et al. [105]	2004	Turkey	960	Healthy schoolchildren	6–17	Not presented	No IgA deficiency found
Janzi et al. [26]	2009	Sweden	2423	Birth cohort[a]	4	< 0.07	1:173
Baştürk et al. [106]	2011	Turkey	20,331	Healthy schoolchildren	6–17	< 0.05	1:188
Hariz et al. [107]	2013	Tunesia	2064	Healthy schoolchildren	6–12	< 0.05	1:188
Lim et al. [1]	2015	Sweden	2423	Birth cohort[a]	16	< 0.07	1:404
Urbonas et al. [108]	2016	Lithuania	1000	Healthy schoolchildren	11–13	< 0.07	1:250
Referred patient population studies							
Isaacs et al. [23]	1984	United Kingdom	30	Referred patients	0–6	< 0.10	1:30
Litzman et al. [109]	2000	Czech Republic	3113	Referred patients	2–15	< 0.05	1:65
Ozkan et al. [22]	2005	Turkey	225	Referred patients	0–6	< 0.05	1:9
Bossuyt et al. [110]	2007	Belgium	55	Referred patients	4–14	< 2.5% of reference population	1:8
Aldirmaz et al. [21]	2014	Turkey	232	Referred patients	0–18	< 2SD for age	1:4

[a] Janzi et al. and Lim et al. both present data from the same Swedish prospective birth cohort study.

age. These values range, depending on the age of the child, from < 0.16 to 0.70 g/L, although reference values can vary between countries [5]. Previous reviews and textbooks often mention that up to 90% of individuals with (partial) IgA deficiency are clinically asymptomatic [6–11]. However, the estimated numbers in these textbooks and reviews are mostly based on expert opinion [6–8,10,11], or refer to studies with healthy IgA deficient blood donors [12] or even a case-control study conducted among 32 IgA deficient adults of which 84% suffer from infections, allergic disease and/or autoimmune disorders compared to 48% in age- and gender-matched controls ($p < .01$) [9]. In children only one small case control study has been conducted among IgA deficient children in 1980. This study showed that in eighteen IgA deficient children aged four to fifteen years (median eight years) recurrent infections, allergic disease and/or autoimmune disorders were found in up to 83% of children compared to none in the nineteen healthy control children [13]. To our knowledge, no other case-control studies presenting rates of symptoms in IgA deficient children have been published. In cohort studies that do present symptoms of IgA deficiency in young children, the clinical relevance and long-term consequences are often not reported.

The immune system develops rapidly throughout the first 1000 days of life. At birth, IgA is virtually absent in serum and on the mucosa [14]. Secretory IgA concentration shows a peak before two months of age in tears, nasopharyngeal secretion and saliva. After this initial peak sIgA levels drop rapidly, followed by a steady rise to adult values, which are usually reached before the age of eight years [15]. The concentration of serum IgA at the age of two years is around a third of those of adults and steadily increases throughout childhood [16]. Therefore, reference values for serum IgA in early childhood are generally age-normalized. In this article, the epidemiology of IgA deficiency, as well as the clinical presentation, diagnosis, management, follow-up and long-term consequences in children are reviewed, with a focus on the link between early life immunity and later life health outcomes. We provide an agenda to guide future research on this topic. In addition, we provide clinicians with up-to-date information to guide clinical decision-making when presented with a child with low to undetectable levels of IgA in order to recognize those children at risk of significant health problems that may threaten their normal development.

2. Materials and methods

2.1. Search strategy and selection criteria

A narrative review of the epidemiology, diagnosis, treatment and follow-up of IgA deficiency in children was performed. Literature was identified by making use of the electronic databases PubMed, MedLine, Embase and the Cochrane library. The following MeSH-terms were used: immunoglobulin A, pathophysiology, diagnosis, epidemiology, primary immunoglobulin A deficiency, selective immunoglobulin A deficiency, child, children, childhood, pediatric and pediatrics. The above terms were also used for free-text searching. Additional articles were identified by searching the reference lists from the literature found using the above-mentioned search strategy. All articles on selective IgA deficiency and/or articles on IgA deficiency with IgG (subclass) deficiency were included. Articles that focused solely on Common Variable Immunodeficiency (CVID), discussed IgA deficiency in patients with pre-existent disease or had no full text available in English, were excluded. Definitions for IgA deficiency were used as published on the official ESID website [4].

3. Results

3.1. The epidemiology of IgA deficiency in children: highest prevalence rates in young children

In adults, prevalence rates of IgA deficiency in healthy populations are mostly based on serum of blood donors. These rates might give a somewhat false reflection of the actual prevalence since individuals with symptoms or underlying conditions are excluded from donating blood. The adult blood donor prevalence rates range from 1:328 in the United States of America [17] to 1:18500 in Japanese blood donors [18]. Higher prevalence rates are observed in children. This is mostly related to the presence of transient IgA deficiency in children with a still developing immune system. The term transient IgA deficiency is used for patients with an IgA deficiency in whom serum IgA levels spontaneously recover to > 0.07 g/L at a later age [1,19,20].

An overview of IgA deficiency prevalence rates from both healthy patient population studies as well as referred patient studies in children of all ages is provided in Table 1. There is a clear difference between prevalence rates observed in birth cohort studies, ranging from 1:170 to 1:400, and rates observed in study populations of children referred for recurrent respiratory tract infections, which range from 1:4 to 1:65. The increased prevalence of IgA deficiency in symptomatic children indicates that there is a subgroup of IgA deficient children that are predisposed to developing respiratory problems. This subgroup is largest in young children as shown by very high prevalence rates of IgA deficiency of up to 25% in those studies also including children with recurrent respiratory infections aged zero to two years [21–23].

3.2. Clinical presentation of IgA deficiency

In textbooks and reviews, IgA deficiency is often regarded as a mild form of immunodeficiency which presents as an asymptomatic condition [6–11]. However, long-term prospective follow-up studies

challenge this finding. Aghamohammadi et al. included 37 Iranian IgA deficient patients with a median age of nine years (range four to 32 years) and showed that 94% of patients suffered from symptoms during the mean follow-up of 3.5 years per patient while only 74% was symptomatic at baseline. Allergy and autoimmunity was present in 22% and 5% at baseline compared to 84% and 27%, respectively, during the follow-up period [24]. Ludvigsson et al. conducted a large prospective population-based cohort study that included 2100 patients (children and adults) with IgA deficiency who were each matched for age, sex, age of diagnosis and place of residence with ten controls from the general population. They found an increased risk of any infection of 2.4-fold for IgA deficient individuals compared to controls [2]. Together, these studies challenge the common view of selective IgA deficiency as a mild or symptom free immunodeficiency and highlight the importance of long-term follow-up to better detect clinically important manifestations.

The disease burden in young IgA deficient children can start at a very young age, before fulfilling the criteria for 'IgA deficiency' as proposed by official definitions. Burgio et al. found that 46% of children with a complete IgA deficiency presented with recurrent infections before their first birthday and 74% presented with recurrent infections before the age of five [25]. This group would be overlooked if the diagnosis of IgA deficiency was only made according to current definitions. Two birth cohort studies investigated the importance of IgA in early life. Janzi et al. found that in the group of children that were lacking IgA at the age of four years, an increased risk of pseudocroup and food sensitivity was present in their first four years of life compared to controls [26]. Thórarinsdóttir et al. showed that in the first four years of life, sustained low IgA levels were the strongest single indicator for susceptibility of recurrent otitis media and recurrent respiratory tract infections including pneumonia. Also, they described that IgA deficient children who continued to suffer from frequent upper respiratory tract infections between two and four years of age had lower serum IgA values at the age of two years compared to children who became asymptomatic in this period, highlighting the importance of IgA levels in early childhood [27].

Studies specifically evaluating IgA deficient children are a valuable source of information to describe the whole spectrum of signs and symptoms with which these children may present. Over the past 40 years, eight articles have been published that describe symptoms in cohorts of IgA deficient children identified after referral to the general pediatric department or the pediatric immunology department for medical symptoms [19,24,25,28–32]. Together, these studies included a total of 760 children aged eight months to eighteen years, and describe the rates of recurrent infections, allergic disease, autoimmune disease and malignancy, although these outcomes are not all described in each individual study (Table 2). One cohort study of 330 children with IgA deficiency examined their medical records over a period of fifteen years retrospectively [28]. The other seven studies are all descriptive prospective cohort studies that each included 35 to 118 IgA deficient children with a mean follow-up time of 3.5 to 10.6 years. Since children described in these articles were referred for medical symptoms, they do not present the population prevalence rates of symptoms. An unknown percentage of asymptomatic children with IgA deficiency would lower the rates of infections, allergic diseases, autoimmune diseases and malignancies in pediatric IgA deficiency. However, they do give clinicians a good notion of which possible symptoms they should be aware of when they are confronted with an IgA deficient patient. These studies show that recurrent infections are the most common manifestation of symptomatic IgA deficiency in children. In a prospective population-based cohort study respiratory tract infections were observed with a prevalence rate of 3.2 compared to healthy controls [2]. Since this study used the international classification of diseases code for respiratory infection, it was not possible to evaluate the severity of these infections. Recurrent upper respiratory tract infections, such as sinusitis and otitis, are the most commonly described recurrent infections although lower respiratory tract infections are still found in up to 58% of patients [19,24,25,28–30,32]. Respiratory infections are mostly caused by viruses and extracellular encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [6,33]. Gastrointestinal infections are mainly caused by *Giardia lamblia* [34]. Significantly higher prevalence rates of sepsis (2 vs. 0.5% in controls), meningitis (0.4 vs. 0.1% in controls) and urinary tract infections (6 vs. 3% in controls) are also described in IgA deficient patients [2,6,26,35].

Murine models on IgA deficiency shed light on the pathophysiology underlying the increased susceptibility for infections observed in IgA deficient individuals. Mice that are both IgA deficient in serum and in mucosal secretions demonstrate that it is mainly secretory IgA that protects against *Streptococcus pneumoniae* colonization in the upper respiratory tract [36,37]. Other mice and rabbit studies have shown that sIgA is able to entrap and clear bacteria in the mucus of the epithelia lining the respiratory and intestinal tract [38,39]. Given the pivotal role of IgA in the protection of the respiratory epithelium, it is likely that mucosal IgA levels are a better reflection of respiratory tract infection susceptibility than systemic IgA levels. The observation that polymeric immunoglobulin receptor knockout mice that are unable to transport IgA into mucosal secretions show increased susceptibility to mycobacterial infections in the respiratory tract emphasizes the importance of local IgA levels. The suggested mechanism is the inadequate blocking of pathogen entrance and an altered pro-inflammatory response in mice lacking IgA at the mucosal level [40,41]. In addition, mice with mucosal IgA deficiency also show an impaired protection against viral respiratory infections, such as influenza [42,43]. An increased susceptibility to influenza virus infections is thought to be caused by inadequate T helper cell priming [44,45]. This suggests that T cell immunoregulatory abnormalities may also be present in IgA deficient subjects, which has also been observed in studies examining lymphocytes from IgA deficient patients [46].

3.3. Diagnostic approach towards a child with IgA deficiency

The first diagnostic step when confronted with an IgA deficient patient is to determine the clinical relevance of the IgA deficiency based on a complete medical history with the assessment of frequency and severity of symptoms, and a physical examination. One should rule out secondary causes of transient IgA deficiency, such as specific viral infections like human immunodeficiency virus, Epstein Barr virus, and hepatitis C virus, systemic disorders leading to hyper catabolism of immunoglobulins (myotonic dystrophy) or excessive loss of immunoglobulins by nephrotic syndrome, lymphangiectasia, or severe diarrhea, malignancies and medication. Drugs that could result in an IgA deficiency include certain anti-epileptics (phenytoïn, carbamazepine, valproïc acid, zonisamide), non-systemic anti-inflammatory drugs (NSAIDs), anti-rheumatic drugs (sulfasalazine, penicillamine) and hydroxychloroquine [9].

Total IgG and IgG subclasses should be determined in all children, since around 15% of IgA deficient patients also have decreased levels of (one of) IgG subclasses, in particular IgG2 and IgG4 [3,47,48]. IgG2 plays a large role in the response to polysaccharide antigens, while IgG1 and IgG3 isotypes mainly respond to protein and viral antigens [49–52]. Just like IgA deficiency, IgG subclass deficiency can also occur in healthy individuals and can be transient in early childhood [53,54]. Therefore, the official ESID criteria for the diagnosis IgG subclass deficiency is: a patient with recurrent/severe infections aged seven years or older with normal levels of IgM and IgA and at least two of IgG1–3 subclasses less than the 5th centile for age combined with poor response to some vaccines [55]. Even though the diagnosis of IgG subclass deficiency is controversial, the combination of IgA and persistent IgG subclass deficiency can be of clinical importance. In IgA deficient individuals pneumococcal vaccine responses to twelfth serotypes have found to be significantly related to IgG2 levels [56]. Additionally, Aghamohammadi et al. found that IgA deficiency in combination with

Table 2
Symptoms in IgA deficient children.

Study	Country	Patient population	Identification of patients	Follow-up	(Recurrent) infections	Allergic disease	Autoimmune disease	Malignancy
Abolhassani et al. [29]	Iran	57 patients with IgA level < 0.07 g/L, >4 years, mean age at diagnosis 8 years (SD 5.6 years). Of note: 33% were children of a consanguineous marriage.	Patients were referred for medical symptoms to a tertiary children's hospital	Mean follow-up 5.3 patient-years (SD 2.2 years)	Total[b,c]: 14 (25%)	Total[b]: 32 (56%)	Total[b]: 17 (30%)	Not described
Aghamohammadi et al. [24]	Iran	23 patients with IgA level < 0.05 g/L, >4 years, median inclusion age 8 years (range 4–32 years). Of note: patients with IgG4 deficiency were not excluded.	Patients were referred for medical symptoms to a tertiary children's hospital	Mean follow-up 3.5 patient-years	Total [b,c]: 22 (96%)	Total [b]: 19 (83%)	Total [b]: 6 (26%)	Not described
Aytekin et al. [30]	Turkey	118 patients with IgA level < 0.07 g/L, >4 years, median age at diagnosis 7 years (range 4–18 years). Of note: 24% were children of a consanguineous marriage.	Patients in a children's hospital with known IgA deficiency were retrospectively identified	Mean follow-up 2.0 patient-years (range 0.5–5.0 years)	Total [a,c]: 99 (84%)	Total [a]: 51 (43%)	Total [a]: 20 (17%)	Not described
Burgio et al. [25]	Italy	35 patients with IgA level < 2.5 IU/mL, inclusion age range 8 months-10 years. Of note: included 1 patient with trisomy 21 and 1 patient with ring chromosome 18.	Patients admitted to pediatric department or referred as outpatients for various diseases, mostly recurrent infections or allergic disorders	Follow-up 1.0 to 4.0 patient-years	Total (defined as the association of ≥1 infection(s) in the same subject)[a]: 27 (77%)	Total [a]: 12 (34%)	Not described	Not described
Domínguez et al. [28]	Spain	330 patients with IgA level < 0.05 g/L, <18 years.	Patients in a children's hospital with a known IgA deficiency in a period of 15 years were retrospectively identified	Retrospective study	Total [a,c]: 135 (41%)	Total [a]: 62 (19%)	Total [a]: 38 (12%)	Total [a]: 5 (2%)
Erkoçoğlu et al. [31]	Turkey	81 patients with IgA level < 0.07 g/L, >4 years, mean age 10 years (range 4–20 years).	Patients with known IgA deficiency were identified at the Pediatric Allergy and Immunology department	Mean follow-up 3.7 +/− 2.8 patient-years	Total (defined as ≥3 infection episodes in a year) [a]: 60 (74%)	Total [a]: 62 (46%)	Total [a]: 14 (17%)	Not described
Moschese et al. [32]	Italy	53 patients with IgA level < 0.07 g/L, >4 years, mean age 7 years (range 4–18 years).	Patients identified at a pediatric or immunology department during routine assessment for recurrent infections and/or allergy and/or autoimmunity	Mean follow-up 5.0 patient-years	Total (not recurrent) [a]: 41 (83%)	Total [a]: 19 (36%)	Total [a]: 4 (8%)	Total [a]: 0 (0%)
Shkalim et al. [19]	Israel	63 patients with IgA level < 0.06 g/L, >4 years, inclusion age range 4–18 years.	Inpatients or outpatients who attended the allergy and immunology clinic of a tertiary medical center identified in a 18 year period	Mean follow-up 10.6 patient-years (median 13.0 patient-years)	Total (defined as ≥3 infection episodes during follow-up) [a]: 25 (40%)	Total[a]: 20 (32%)	Total[a]: 13 (21%)	Total[a]: 3 (5%)

[a] Data derived from examination of records.
[b] Data derived from (parental) questionnaires.
[c] Definition recurrent infections not described in article.

IgG subclass deficiency and/or defective specific antibody production to pneumococcal polyvalent vaccine is associated with pulmonary deterioration, as further discussed in paragraph 3.5.2 [24]. Therefore, in symptomatic IgA deficient children above the age of two years it is important to also determine the child's antibody responses four to six weeks after administration of a pneumococcal polysaccharide vaccine to rule out specific polysaccharide antibody deficiency syndrome [57]. Besides being more at risk of developing pulmonary damage, patients with an impaired polysaccharide antibody response in combination with an IgA and/or IgG subclass deficiency also have an increased risk of developing CVID later in life and thus deserve long-term monitoring and follow-up [33]. Patients with CVID have a decreased (<-2SD) serum IgG and IgA/IgM levels, absent isohemagglutinins and/or insufficient vaccination responses against tetanus and/or pneumococcal polysaccharide vaccines [4]. CVID has an overall worse prognosis compared to selective IgA deficiency, with a higher risk of developing more severe infections and autoimmune diseases [33]. IgA, IgM, IgG and IgG subclasses should be re-tested after one to two years in persistent symptomatic IgA deficient patients whose immunoglobulin levels fluctuate to determine if IgA and/or IgG subclass deficiency is persistent and to timely diagnose progression to CVID. Booster vaccine responses should also be re-tested after three to five years [57]. In young children with antibody deficiency, pneumococcal polysaccharide IgA responses may predict their disease course [58]. Detailed immunophenotyping by flow cytometry can help to further identify clinical phenotypes of IgA deficiency and CVID [59]. Because CVID and IgA deficiency share a genetic predisposition, it is recommended to measure immunoglobulin levels in symptomatic family members of CVID patients to detect IgA deficiency (or CVID). IgA deficient family members of CVID patients tend to have more severe types of IgA deficiency with severe infections and auto-immunity [60,61]. Children with undetectable serum IgA levels, particularly those who have had an infusion reaction after administration of blood products in the past, should be tested for anti-IgA antibodies. If anti-IgA antibodies are present, future precautions with blood products should be taken. In Fig. 1 the phenotypes of IgA deficiency are shown along with their recommended follow-up.

3.4. Treatment options for IgA deficient children

An overview of the therapeutic options in symptomatic IgA deficient patients is given in Fig. 2. The necessity of treatment for IgA deficiency depends upon the severity of symptoms. Mild humoral defects in asymptomatic patients do not require treatment [33]. There is currently no curative treatment for IgA deficiency (Table 3). Symptoms of IgA deficiency can be severe or persistent and cause significant diminishment of health-related quality of life [62]. Since there is no conclusive evidence for specific therapeutic options for IgA deficiency, treatment in current clinical practice is usually pragmatic by testing the effect of prophylactic antibiotics or immunoglobulin supplementation on diminishing infection rate or severity of autoimmune phenomena. The choice of prophylactic antibiotics should be aimed at the prevention of airway infections. The prophylactic antibiotic can be prescribed for a part of the year or throughout the entire year [8]. Since large randomized controlled trials on this subject are absent, choice of antibiotics and doses differ between countries and are mostly based on expert-opinion (Table 3). Because IgA deficient patients especially suffer from infections with encapsulated bacteria, immunization with available conjugate vaccines against, among others, *S pneumoniae* and *H. influenzae* is strongly advised if not yet administered [63]. Immunoglobulin supplementation can be considered in IgA deficient patients with a concomitant IgG or IgG subclass deficiency who, despite prophylactic antibiotics and adequate vaccination, still suffer from infections. Immunoglobulins can be supplemented either intravenously (IVIG) or subcutaneously [33,64]. Although IVIG hardly contains IgA, increasing systemic IgG levels has shown to reduce the frequency and severity of infections [65]. For IgA deficient patients with anti-IgA antibodies, multiple desensitization methods to prevent anaphylactic reactions upon receiving blood products have been described. One way is to give infusions with a lower infusion speed [66]. It is also possible to desensitize with subcutaneous immunoglobulin days prior to admission of IgA containing products [67,68] or by pretreating the products with patient's autologous plasma [69].

3.5. Long-term complications in IgA deficient children

3.5.1. Follow-up and potential long-term consequences of IgA deficiency in early childhood

IgA deficiency in children can be transient without any intervention. In a prospective birth cohort study by Lim et al. children with complete IgA deficiency (serum IgA levels below 0.07 g/L) at the age of four years were re-measured at the age of sixteen years: 29% of patients had normalized serum IgA levels and another 29% had mitigated to partial IgA deficiency (<-2SD of population average serum IgA level normalized for age) [1]. Also, several other studies reported a wide range of spontaneous recovery of IgA levels ranging from 0 to 23% [13,19,20,70]. To what extent the IgA deficiency is transient in young children can only partly be predicted by the severity of the IgA deficiency, and seems to depend on the age at diagnosis: in a birth cohort study in Sweden, 23% of 39 children who were diagnosed with IgA deficiency at the age of four to ten years reached a normalized level of IgA during the follow-up of eight years. However, children who were diagnosed between ten and thirteen years had less chance of recovery, with only 7% reaching normalized levels of IgA during the follow-up period [1]. With respect to the link between severity and transiency, studies comparing transiency rates between young children with partial and complete IgA deficiency show that partial IgA deficient children have a significantly higher chance of normalization than children with a complete IgA deficiency [32,70]. Even though official criteria for IgA deficiency exclude children under the age of four years because of the high chance of transiency, the mean age at which IgA levels normalize is much later, around ten years [1,13,32,70].

3.5.2. Morbidity as a consequence of recurrent infections

Pulmonary alveoli develop up to the age of seven [71]. Hence, recurrent infections and resulting structural damage at a young age may have consequences on lung tissue development. Severe respiratory infections before the age of five years are associated with a lower adult Forced Expiratory Volume 1 level, and a higher risk for development of chronic obstructive pulmonary disease (COPD) later in life. This association between infections and impaired lung function remained when correcting for smoking, childhood asthma, age, social class, geographical location, gender, maternal smoking and parental asthma [72]. This suggests that recurrent infections at a young age could cause persistent inflammation and lung growth impairment leading to a higher risk of COPD [73]. Pneumonia is often described in children with an IgA deficiency, with the highest prevalence rates found in studies with the youngest study populations [21,28]. Aldirmaz et al. studied a Turkish pediatric population referred for recurrent infections of which 70% was below the age of five years. Apart from the high rates of upper respiratory infections that were observed, one third of patients with an IgA deficiency had suffered two or more lower respiratory infections per year [21]. In a descriptive prospective study conducted among 57 symptomatic IgA deficient children with a mean age of 4.3 years (SD 4.0) who were referred to a tertiary children's hospital for medical symptoms, 25% suffered from pneumonia, with 24% of these children developing secondary bronchiectasis [29]. In prospective cohort studies in older children with patients that were referred to pediatric centers for medical symptoms or who were known to be IgA deficient, occurrence rates for recurrent pneumonia were between 14% and 23% [19,25,30]. Cohort studies also observed bronchiectasis as a sequela of infections was observed in 15% to 40% for which some patients even

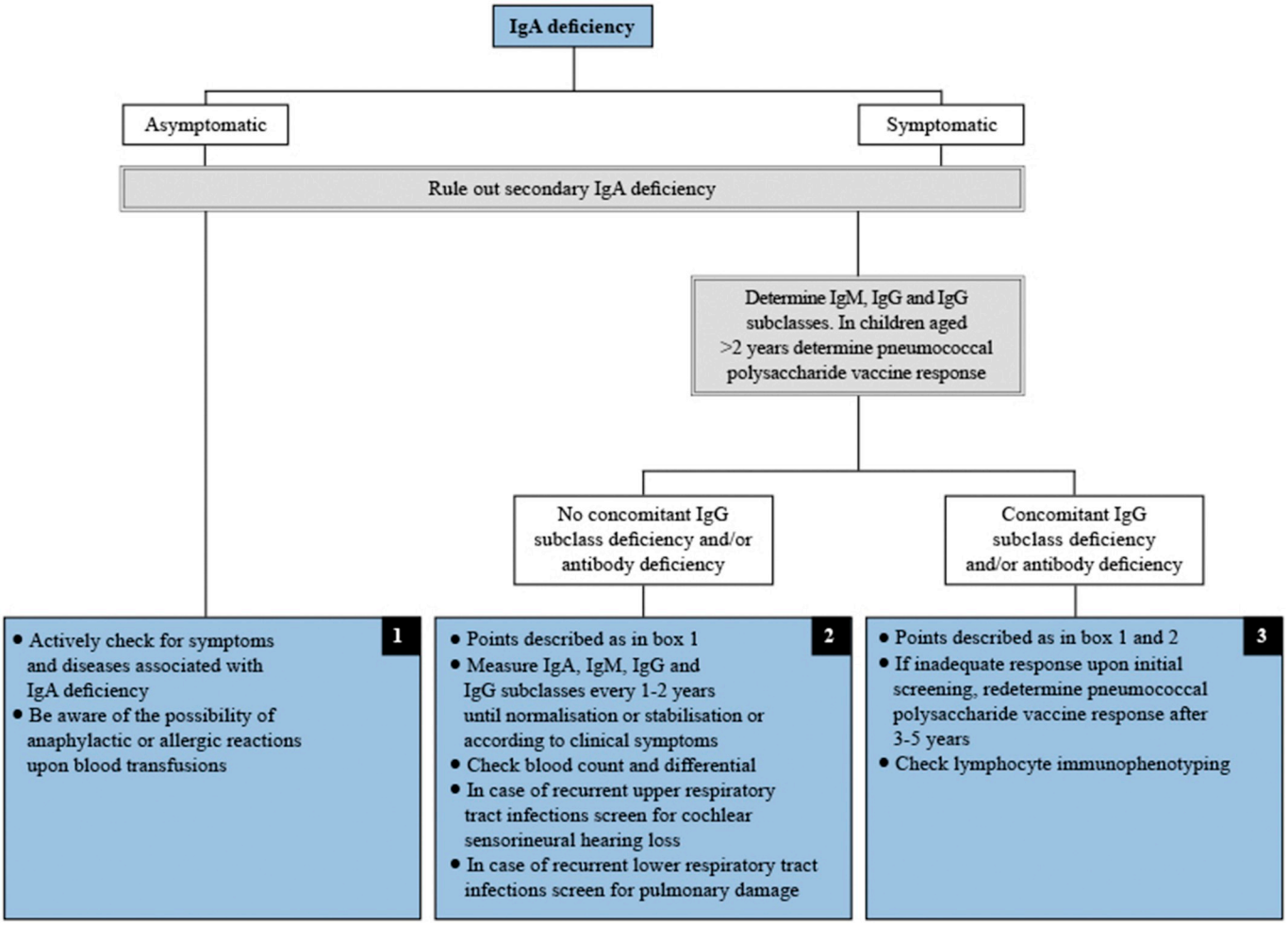

Fig. 1. IgA deficiency subtypes and recommended follow-up in blue boxes 1, 2 and 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

had to undergo a lobectomy [25,28,30]. The combination of IgA deficiency with other immune deficiencies increases the risk of lung damage further as shown by Aghamohammadi et al. in a study including 37 patients referred to a tertiary children's hospital for medical symptoms with a median age of nine years and a mean follow-up period of 3.5 years per patient. Patients with IgA deficiency with an accompanied IgG subclass deficient and/or defective specific antibody production to pneumococcal polyvalent polysaccharide vaccine had a

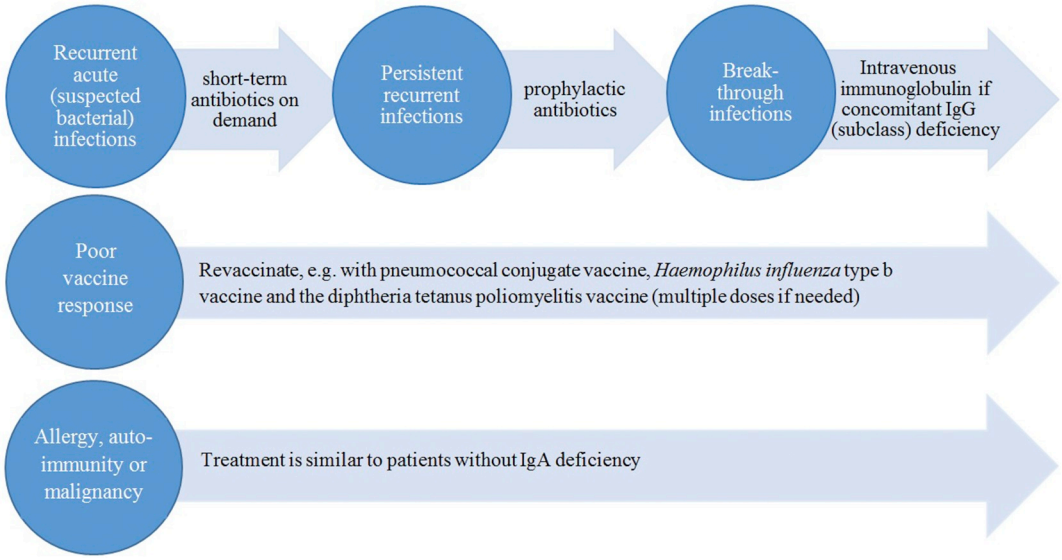

Fig. 2. Therapeutic options in symptomatic IgA deficient patients.

Table 3
Major conclusions and future research directions.

What is known	Future research directions
Epidemiology	
IgA deficiency is more prevalent in children than in adults.	Large birth-cohort studies to determine exact prevalence rates in children, especially those under the age of four.
IgA deficiency is over ten times more prevalent in children referred for recurrent respiratory tract infections	Large birth-cohort or outpatient cohort studies to determine exact prevalence rates in children, especially those under the age of four.
Clinical presentation	
IgA deficiency in children can occur asymptomatic.	Large birth-cohort or outpatient cohort studies with long follow-up to determine the percentage of IgA deficiency children that are asymptomatic
In IgA deficient children, there is a large variation in the frequency and severity of symptoms.	Define subgroups of IgA deficient children and associate these with clinical outcome.
Diagnosis	
Transiency can occur, particularly in partial IgA deficient children.	Investigate causes of transient IgA deficiency, such as (excessive) use of antibiotics and/or altered microbiome development as well as predictors (biomarkers) of transient IgA deficiency.
IgA deficiency can develop into CVID later in life	Predictors (biomarkers) of progression to CVID
Treatment	
Prophylactic antibiotics can be used for recurrent infections.	Randomized controlled trial to determine choice and doses of prophylactic antibiotics.
Long-term (adverse) effect of prophylactic antibiotics is unknown.	Cohort studies to determine long-term effects of prophylactic antibiotic use in children.
There is currently no curative treatment for IgA deficiency.	Identification of potential therapeutic targets by focusing on genetic, environmental, host microbial and immunological factors.
Follow-up and long-term consequences	
Pulmonary damage and hearing loss can occur as sequelae of recurrent respiratory tract infections in IgA deficient children	Predictors (biomarkers) of long-term consequences in IgA deficient children, including young transient IgA deficient children.
Allergic diseases, autoimmune disease and possibly malignancy is associated with IgA deficiency	Predictors (biomarkers) of the subgroups of children at risk for allergy, autoimmune diseases and malignancy to optimize screening and timely diagnosis

significantly increased risk of pneumonia and development of bronchiectasis compared to patients with selective IgA deficiency (RR 3.0, 95% CI 1.4–6.3) [24]. Although these studies may represent a selective group of children with severe disease, physicians should be aware of this risk in IgA deficient children with recurrent respiratory infections. While lower respiratory tract infections are associated with pulmonary damage, upper respiratory tract infections are not always harmless. A recent article by Eşki et al. showed that 28 complete IgA deficient patients between the ages of five and fifteen years who were being followed up at the immunology department with repetitive upper respiratory tract infections had an increased risk of cochlear sensorineural hearing loss [74]. Dominguez et al., who retrospectively examined 330 medical records of known IgA deficient patients in a children's hospital over a period of fifteen years, observed deafness in 5% of IgA deficient children suffering from recurrent ear infections [28]. Screening for hearing loss is therefore indicated in IgA deficient children with a history of hearing difficulties.

3.5.3. Non-infectious complications of IgA deficiency

In addition to recurrent infections, children with an IgA deficiency are at risk of developing other diseases associated with the IgA deficiency. These include allergic diseases, autoimmune diseases and possibly also malignancies. Allergic diseases are the second most common clinical manifestation in referred IgA deficient patients after recurrent infections. Most frequently found allergic diseases are asthma (6–51%), atopic dermatitis (3–49%), allergic rhinitis (3–43%), urticaria (3–24%) and food allergies (1–21%) [19,20,24–26,28,29,32]. Autoimmune diseases are also associated with IgA deficiency with celiac disease most frequently found with a prevalence of 7% in IgA deficient patients compared to 0.2% in controls as shown by a large population-based matched cohort study among 2100 IgA deficient individuals. Other autoimmune diseases identified by the same study that also occur significantly more often in IgA deficient patients are type one diabetes (6% vs. 0.6% in controls), inflammatory bowel disease (4% vs. 0.8%), rheumatoid arthritis (2% vs. 0.5%), autoimmune hyperthyroidism (2% vs. 0.4%) and hypothyroidism (0.8% vs. 0.2%), juvenile idiopathic arthritis (0.8% vs. 0.1%) and systemic lupus erythematosus (0.6% vs. 0.1%) [75]. The increased frequency of allergic and autoimmune disease in IgA deficient patients may be a result of an impaired gastrointestinal barrier caused by diminished or absent secretory IgA. Resulting increased mucosal penetration could permit environmental antigens to enter the circulation and cross-react with self-antigens which can lead to the formation of autoreactive antibodies [7,24,29,35]. Apart from this molecular mimicry several other mechanisms have been suggested to explain the increased rates of autoimmune phenomena and allergic diseases in IgA deficient patients. Defects of regulatory T cell development, functions, numbers and/or receptor repertoire could play a role. Several studies have shown an association between decreased regulatory T cell numbers and prevalence and severity of autoimmunity in selective IgA deficiency [76,77]. The study by Jacob et al. suggests that the serum receptor for IgA, FcαRI, plays an important role in autoimmunity in IgA deficient individuals. Normally when FcαRI gets activated by serum IgA, it downregulates pathways that activate inflammation. Therefore lack of IgA may cause increase of inflammation and predispose IgA deficient patients to autoimmune phenomena [78]. Furthermore, in a study with transgenic mice expressing FcαRI on myeloid cells, targeting the FcαRI receptor suppressed allergic hyper responsiveness and the accompanying airway inflammation, suggesting that diminished stimulation of this receptor could play a role in the increased prevalence of allergies in IgA deficient individuals [79].

The association of malignancies with IgA deficient children is controversial with few studies presenting data on this subject. One retrospective study, conducted in Spain included 330 IgA deficient children aged four to eighteen years over a fifteen year period, observed a malignant disease in five patients [28]. In another retrospective study of 63 Israeli children identified over an eighteen year period, malignancy was found in 5% [19]. A large Swedish prospective population-based cohort where 2320 patients (adults and children) with IgA deficiency were matched on age, sex, age of diagnosis and place of residence to ten controls from the general population demonstrated a hazard ratio of 1.3 for the diagnosis of cancer (95% CI 1.1–1.6), especially gastrointestinal malignancies (hazard ratio 1.6, 95% CI 1.1–2.5). However, the study showed no significant increase of lifetime cancer in children diagnosed with IgA deficiency, although the authors note that this could be ascribed to a lack of power in the pediatric subgroup analysis [80]. An increased prevalence of gastric cancer in IgA deficient patients could be

the result of a diminished defense against *Helicobacter pylori* in the gastric mucosa [81–83].

3.5.4. IgA deficiency and mortality

One population-based cohort study showed a higher all-cause mortality hazard ratio of 1.8 (95% CI 1.6–2.1) in IgA deficient patient compared to healthy controls during the follow-up time of the study (median 8.3 years for IgA deficient patients and 8.6 for matched controls) [84]. An even higher mortality rate of 3.4 (95% CI 2.4–4.9) was found in patients diagnosed with IgA deficiency between the age of ten to 39. The authors speculated that excess mortality could be attributed to autoimmune disease and respiratory infections. Due to the small sample size the researchers were unable to determine the exact cause of the increased mortality [84]. Therefore, these results should be interpreted with caution.

3.6. Early childhood provides a window of opportunity to shape future health

The first 1000 days of life, which refers to the period from conception to two years of age, represents a critical window of early immune development. An increasing number of studies shows that early immune alterations are associated with a predisposition to health affecting conditions, such as allergies, autoimmune disorders and infectious disease susceptibility [26,85–87]. The development of the immune system is accompanied by rapid maturation of metabolic, endocrine and neural networks during this prenatal and early postnatal period. These systems do not operate independently. Upon challenge of these developmental pathways by an infection or recurrent infections, homeostasis can be perturbed with consequences on all pathways. Since prevalence rates of IgA deficiency and associated recurrent infections are highest in young children [20,22], this can affect their growth and development during a critical period of life. Hence, although normalization of transient IgA deficiency over the years may restore mucosal immunity, the consequence of impaired immunity and a high infectious disease prevalence early in life may extend beyond infancy. In addition to lung damage, COPD and hearing loss as consequences of multiple infections [29,73,74], future research should explore immunometabolic or immunoendocrine consequences of the lack of IgA during a critical period of immune development in early life.

3.7. Potential role of the gut microbiota in (the consequences of) IgA deficiency

In recent years more attention has been drawn to immunologic and microbiome changes in early childhood and the consequences for health programming in children [88,89]. The mucosal immune system is exposed to thousands of different microbial species on a daily basis. The establishment of this gut microbiota occurs in parallel with the maturation of the immune system over the first two years of life. Recent advances in high-throughput sequencing technologies have shown that IgA production is induced by the presence of commensal intestinal microflora with the aid of Peyer's patch dendritic cells that sample commensals [90,91]. Maturation of the IgA response is thought to be the consequence of maturation of the microbiome in children [92]. It is therefore tempting to speculate that exposure of the mucosal immune system to an altered gut bacterial profile may contribute to the development of IgA deficiency, which is underlined by germ-free mice studies where intestinal colonization with specific commensals induces IgA production in serum and mucosa [90,93,94]. Alternatively, but not mutually exclusive, is the idea that deficient mucosal IgA production could shape gut microbial community composition. This is shown by studies where mice lacking secretory IgA in the gut develop an altered microbial composition compared to control mice [95,96]. Early-life gut dysbiosis can lead to a range of immune-mediated diseases. Several longitudinal studies in infants and children have shown that impaired gut microbiome development is associated with an increased risk to develop asthma and allergies [97,98], inflammatory bowel diseases [99], celiac disease [100] and type one diabetes [101]. Furthermore, a study with germ-free mice showed that gut microbiota promotes myeloid cell development necessary for early immunological responses to bacterial infections [102]. Impaired early host-microbiome development may thus be the biological mechanism linking IgA deficiency and recurrent infections at an early age to allergic, endocrinologic and inflammatory disorders later in life. Indeed, Dzidic et al. showed that altered early IgA responses to gut bacterial targets measured at one and twelve months of age were associated with the development of allergic symptoms in children up to seven years [103].

4. Summary and future perspectives

In Table 3 we summarize the most important conclusions of this review and provide future directions for further research. There is still a lot unknown about the prevalence rates, clinical presentation, long-term consequences and co-morbidity of IgA deficiency in children. Most studies on IgA deficiency in children only include children above the age of four with complete IgA deficiency to fulfill the official ESID definition and lack a long follow-up period. We showed that excluding children under the age of four years carries the risk of not recognizing the increased risk of future pulmonary damage and sensorineural hearing loss in these children. In addition, complications such as the development of allergic and autoimmune diseases or progression to CVID may not be recognized timely.

In this review an overview is presented of the prevalence rates, diagnostic and therapeutic options and clinical presentation of IgA deficiency in children. Studies conducted among children under the age of four, who often experience transient and partial IgA deficiency, are limited. Since the underdevelopment of the IgA repertoire in this critical time period may predispose the child to later health problems, further research addressing this group is needed. Although IgA deficiency in children can be asymptomatic, the over tenfold higher prevalence rates in children referred for recurrent respiratory tract infections compared with the general population indicate that IgA deficiency is not always a condition of limited clinical importance. Since the occurrence of infections during childhood presents a window of opportunity to prevent end organ damage by intensive monitoring and therapeutic options such as prophylactic antibiotic treatment, it is important to correctly identify IgA deficient children at risk for significant health problems that require clinical attendance and follow-up.

Financial conflict

None of the authors has any potential financial conflict of interest related to this manuscript.

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