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IMMUNOGLOBULIN E ROLE IN PARASITIC DISEASES: AN OVERVIEW

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Abstract

Immunoglobulin E (IgE) is a type of antibody (or immunoglobulin (Ig) "isotype") that is found only in mammals. IgE is synthesized by plasma cells. Monomers of IgE consist of two heavy chains (ε chain) and two light chains, the ε chain containing four Igs-like constant domains (Cε1-Cε4). IgE is an important part of the immune response against infection by certain zoonotic worms, and protozoa. IgE may have evolved as a defense to protect against venoms. IgE also has an essential role in type I hypersensitivity, manifests in allergic diseases; allergic asthma, most sinusitis types, allergic rhinitis, food allergies, and chronic urticaria and atopic dermatitis specific types. IgE also plays a pivotal role in responses to allergens, such as anaphylactic reactions to drugs, bee stings, and antigen preparations used in desensitization immunotherapy.

IgE is the least blood serum levels in a non-atopic individual are only 0.05% of Ig concentration compared to 75% for IgGs at 10mg/ml. But, it can trigger anaphylaxis, one of the most rapid and severe immunological reactions. This reviewed IgE role of in some zoonotic parasites.

Key words: IgE, mammals, Helminthes, Protozoa, Overview

Introduction

Pathogenesis of many allergic diseases involves allergic antibody or IgE (Oettgen and Geha, 2001). IgE is important in defense against parasitic diseases, especially those caused by helminthes and some protozoa (McSharry *et al,* 1999). However, due in part to the redundancy of the immune system, low or absent levels of IgE don't predispose people to severe parasitic infections (Watanabe *et al,* 1988). IgE is not believed to play an important role in defense against bacterial infections, since it does not activate complement or participate in opsonization, but plays a key role in the pathogenesis of allergic diseases, especially mast cell/ basophil activation, and in antigen presentation (Stone *et al,* 2010).

Review, discussion, and conclusion

Immunoglobulin E is one of five isotypes of human immunoglobulins, IgG, IgA, IgM, IgD, and IgE, as well as all immunoglobulins are composed of 2 light chains and 2 identical heavy chains (Schroeder and Cavacini, 2010). The heavy chain differentiates the various immunoglobulin isotypes. The heavy chain in IgE is ε (epsilon). IgE is a monomer, and consists of four constant regions, in contrast to other immunoglobulins that contain only three constant regions. Due to this extra region, the weight of IgE is 190 kDa compared to 150 kDa for IgG (Lynch *et al,* 1998). The Cε2 constant domain is unique to IgE, while the Cε3 region binds to the low and high affinity IgE receptor. Of note, the anti-IgE monoclonal antibody omalizumab also binds to the Cε3 region, so the binding of omalizumab to IgE decreases the amount of “free” IgE available for binding to IgE receptor-bearing cells including mast cells and basophils (Vercelli, 2005).

Synthesis: Antibodies are produced by plasma cells. The cells are programmed to make IgM by default, but undergo “isotype switching” to produce IgE with the same antigenic specificity under specific conditions. This process requires cell surface interactions between B and T cells, as well as soluble factors from various cell types (Geha *et al,* 2003). During isotype switching, genomic DNA is spliced and rejoined in class switch recombination (Vercelli, 2009).

B cell isotype switching requires two signals: The first signal involves the soluble factors interleukin-4 (IL-4) and 13 (IL-13) released by Th2 cells, mast cells, and basophils. Interaction of these cytokines with their respective receptors on B cells activates transcription at the specific ε germline locus via signal transducer and activator of transcription (STAT) 6. Second signal is the interaction between B cell CD40 and T cell CD40 ligand (CD154), which results in DNA class switch recombination &IgE expression triggered by nuclear factor κB (NFκB). STAT6 and NFκB synergize to activate B cell activator protein (BSAP), promoting production of IgE (Smith and Ownby, 2009). The removal of the unwanted constant regions by splicing and rejoining of the DNA requires AID (activation-induced cytidine deaminase) and UNG (uracil DNA glycosylase). Accessory molecules that amplify IgE production include CD28/CD80-CD86 interactions. Also, there are negative signals reduce IgE production: ID2 (inhibitor of DNA binding 2) binds to E-box; BCL-6 (B cell lymphoma 6) competes with STAT6; and SOCS-1 (suppressor of cytokine signaling 1) also works on STAT-6. Interferon gamma can also inhibit IgE production via STAT1-mediated activation of SOCS1 (Takhar *et al,* 2007).

B cell isotype switching to produce antigen-specific IgE occurs primarily in mucosal lymphoid tissues, with the greatest amounts of antigen-specific IgE production in tonsils and adenoids, although some also occurs in peripheral tissues (Eckl-Dorna *et al,* 2012).

Local IgE: Antigen-specific IgE production occurs locally within bronchial and nasal mucosa, in addition to the lymphoid tissues and bone marrow, in patients considered nonatopic by skin testing and laboratory tests, and more than 99% of circulating allergen-specific IgEproduced within tissues (Balzar *et al,* 2007). Local IgE production phenomenon is termed entopy and may underlie some cases of chronic nonallergic rhinitis and severe asthma (Holgate *et al,* 2005).

Synthesis regulation: The genetic predisposition to develop allergic disease, or atopy, is a complex trait that is not fully understood. Total serum IgE levels and regulation of serum IgE production is strongly influenced by genetic factors. Less is known about other genetic factors important for allergic disease development (Fregonese *et al,* 2004).

Genome-wide associations identified several loci that may be important for IgE regulation, including loci in gene encoding the alpha chain of high affinity receptor for IgE (FCεRIa), STAT6, and in gene RAD50/IL-13 cluster (Granada *et al,* 2012).

IgE receptors: IgE functions by high and low affinity receptors on mast cells, basophils and other cells degranulation mast cells, basophils and antigen presentation. Expression of both receptors enhanced by IgE binding, so circulating IgE levels correlated positively with receptor levels (Moffatt *et al,* 2010).

The high affinity receptor for IgE is FcεRI. IgE binds to α chain exists in two forms: 1-A tetrameric form ($\alpha\beta\gamma_2$) of FcεRI is expressed on mast cells and basophils. In nonactivated state, these cells are coated with FcεRI receptors bound to various antigen-specific IgE molecules. If that multivalent antigen (allergen) enters cell's environment, it binds to the IgE, causing the FcεRI receptors to cluster on the cell surface and become cross-linked (Coker *et al,* 2003). The cross-linking leads to activation of the cell and release of preformed mediators from cytoplasmic granules (histamine), transcription and release of cytokines, and synthesis of leukotrienes and prostaglandins (Galli *et al,* 2008). The strength of the activation signal depends upon the polyvalency of allergen (IgE number binding sites) and the affinity of the IgE for allergen (Weidinger *et al,* 2008). The inflammatory mediators released by mast cells and basophils include histamine, tryptases, and tumor necrosis factor α, as well as leukotrienes and prostaglandins (LTC4 & PGD2, respectively). These mediators are responsible for signs and symptoms of immediate hypersensitivity as well as production of the

Th2 cytokines IL-4, IL-5, & IL-13 initiates late phase inflammation and promotes more IgE production. These mechanisms underlie the clinical manifestations of allergic diseases, such as allergic rhinitis and conjunctivitis, allergic asthma, food allergy, and anaphylaxis. 2- A trimeric form of FcεRI ($\alpha\gamma_2$) is expressed on Langerhans and dendritic cells, and monocytes as an important for antigen presentation. In humans, it is theorized that FcεRI on antigen-presenting cells permits the transpo-rt of antigens captured by IgE in tissues into peripheral lymph nodes to initiate immune responses (Hibbert *et al,* 2005).

The low IgE affinity receptor, FcεRII (CD23), is present on a variety of cells. The constitutively expressed form, CD23a, is present only on B cells, but inducible form, CD23b, is present on B-cells, T-cells, dendritic cells, monocytes, macrophages, neutrophils, eosinophils, intestinal epithelial cells, and platelets (Tsicopoulos and Joseph, 2000) Functions include regulation of IgE synthesis (binding of IgE to B cell CD23 inhibits IgE synthesis), antigen capture and presentation, and growth and differentiation of B cells. Epithelial cell CD23 transports IgE-allergen complexes from the lumen to mucosa to interact with mast cells that shed from the cell membrane (sCD23) by endogenous proteases causing a soluble form m that may be important for upregulation of IgE synthesis (Cooper *et al*, 2012).

Total IgE levels are always measured by a sandwich-type assay, anti-IgE antibody is bound to a solid support, a patient's serum is added, and then unbound protein is washed away (Bernstein *et al,* 2008). A second, labeled anti-IgE antibody is added, and amount bound to patient's IgE is measured. Total serum IgE levels (1 IU/ml= 2.44ng/ml) were given as international units or nanograms/ milliliter (Poole *et al,* 2005).

Measurement of allergen-specific IgE: The first allergen-specific IgE commercial assay was the radio-allergosorbent test or RAST (Miller *et al,* 1984). The bound allergen-specific IgE was detected with radio-iodinated polyclonal antihuman IgE & quantified with a gamma counter (Hamilton and Adkinson, 2004). The term RAST is still used to refer to *in-vitro* assays for allergen-specific IgE, although modern methods use enzymes instead of radionucleotides. Other technical advances in assay technology have dramatically improved the sensitivity and specificity IgE allergen-specific measurements. *In vitro* IgE antibody assay or allergen-specific IgE immunoassay was more accurate characterized three IgE antibody assays available only in North America (Hamilton and Williams, 2010): 1- HYTEC-288 is a colorimetric assay using a paper disc solid-phase support, 2- Immuno-CAP is a fluoroimmuno-assay with a cellulose sponge so- lid-phase matrix, and 3- Immulite chemiluminescent assay has a biotinylated-allergen and avidin particle solid-phase.

The three systems use extracts from different sources immobilized as the antigen capture allergosorbent, and thus the results are not interchangeable. These tests quantify allergen-specific IgE that may or may not correlate with allergic or specific symptoms (Popescu and Vieru, 2018). Lower detection limit for allergen-specific IgE was less than total IgE. Most labs have a lower limit of 0.1 to 0.35 IU/ml. (Takhar *et al,* 2005).

Omalizumab effect: Total serum IgE levels measured in the 2 ImmunoCAP assays were minimally reduced (2.4-9.0%) by omalizumab, but 5 other assays showed good reductions from 12.5% to 67.2% ($P < .001$), increased in proportion to total serum IgE levels. None used total serum IgE assays measured free IgE in omalizumab presence (Hamilton, 2006). IgE normal level gave least serum concentration of all IgGs ~150ng/ml compared to 10mg/ml for IgG, or 66,000-fold less. Normal levels were 0 to 100IU/ml (sometimes expressed in kU/L, depended on laboratory). IgE levels may be given in ng/ ml, and conversion between these units is 1 IU/ml = 2.44ng/ml. (Dullaers *et al,* 2012). The free IgE half-life in serum is about two days, but once IgE has bound to mast cells,

extended up to two weeks due to high affinity of this interaction (Arnold *et al,* 2007).

IgE childhood levels: IgE didn't cross the placenta. So, a woman's allergen sensitive is not passed on directly to her offspring via IgE transfer. But, allergens can pass transplacentally, and fetus can produce allergen-specific IgE. Routine allergen-specific IgE immunoassays cannot distinguish infant from maternal IgE, but a highly sensitive investigational microarray technique showed that infants can have IgE specific to food and inhalant allergens already present at birth (Kamemura *et al,* 2012). Preschool levels don't correlate well with those at older ages. Factors associated with increased total IgE levels include male, African-American race, poverty, increased serum cotinine, less than a 12th grade education, and obesity (Gergen *et al,* 2009). In atopic persons, total serum IgE levels may fluctuate. For example, in pollen-sensitized ones, serum IgE levels peak four to six weeks after pollen season height and decline until next pollen season (Underdown *et al,* 1976).

Breastfeeding: Human breast milk has negligible IgE levels (Duchén and Björkstén, 1996). However, IgE serum level of breastfeeding mother influences the serum level of her infant. Children of mothers with high IgE levels who breastfed the children for 4 months or longer had higher total IgE levels than bottle-fed infants or infants breastfed for less than 4 months (Wright *et al,* 1999). In contrast, breastfed infants of mothers with low IgE levels were more likely to have lower IgE levels than the bottle-fed or less than four months of breastfeeding infants. Paternal IgE levels did not have a detectable influence on children's IgE levels.

Decreased total IgE: Most assays can only detect IgE levels to 2 to 5 IU/ml. with lower levels characterized as undetectable. IgE deficiency was defined as levels <2.5 IU/ml. Decreased in humans IgE levels is associated with decreased levels of other immunoglobulins and with sinopulmonary disease as well as an increased autoimmune diseases (Schoettler *et al,* 1989). It was unclear, if isolated IgE deficiency in man was a clinically relevant immunodeficiency or more general immune dysregulation marker (Smith *et al,* 1997). Increased total IgE occurs in allergic diseases, some primary immunodeficiency, parasitic and viral infections, specific inflammatory diseases, some malignancies, and other disorders handful (Chan and Geland, 2015). Also, it is associated with allergic and respiratory diseases such as atopic dermatitis, allergic bronchopulmonary aspergillosis, asthma, persistent children wheezing, and airway hyper-responsiveness (Knutsen and Slavin, 2011).

Immunodeficiencies: Several primary immunodeficiencies are associated with elevated levels of IgE (Ozcan *et al,* 2008). It is unclear what pathologic role, if any, the increased IgE level has in these disorders.

Patients with hyper-IgE syndrome (Job syndrome) increased total IgE, usually range from 2000 to more than 50,000IU/ml. A syndrome characterized by eczema, retained primary teeth, joint hyper-extensibility, characteristic facies, and pathologic fractures. They were more susceptible to fungal and *Staphylococcus aureus* infections of skin abscesses and lungs, including pneumatoceles (Cameron *et al,* 2003).

Netherton syndrome (cutaneous ichthyosis) is a rare autosomal recessive disorder due to a deficiency in SPINK5 (skin specific protease inhibitor Kazal type 5) causing IgE sensitization by damaging skin barrier. IgE total levels were from 100 to >10.000IU/ml. This may be similar to hyper-IgE syndrome, except ichthyosis and bamboo hair (trichorrhexis invaginata) occurs in Netherton syndrome (Moltrasio *et al,* 2023).

The immunodysregulation polyendocrinopathy, enteropathy, X-linked (IPEX) is a rare X-linked primary immune deficiency with autoimmunity composed of a triad of enteropathy, endocrinopathy (diabetes or hypothyroid), and eczema, and patients have increased IgE & IgA with rare or absent of T regulatory cells (Spasevska *et al,* 2023).

Wiskott-Aldrich syndrome, a rare X-linked syndrome due to mutations in Wiskott-Aldrich syndrome protein (WASP), is associated with eczema, thrombocytopenia, variable T cell function and increased IgE levels (Buchbinder *et al*, 2014). Omenn syndrome with erythroderma failed to thrive, diarrhea, hepatosplenomegaly, lymphadenopathy, eosinophilia, increased IgE, but decreased IgG, IgA, & IgM, and combined B & T cell immunodeficiency due to hypomorphic mutations in *RAG1, RAG2*, or *ARTEMIS* altered receptor rearrangement (Al-Hammadi, 2015).

One phenotype of complete DiGeorge syndrome has oligoclonal T-cell expansion with elevated IgE levels, in addition to the classic midline deficits (thymic hypoplasia, cardiac defects, parathyroid disease, cleft palate, and classic facies (Ellertsen *et al,* 2009).

Infections with certain parasites and viruses are associated with an elevated serum IgE mainly in developing countries; parasites are the commonest cause of IgE elevations (Pien *et al,* 2008): 1- A primary role for IgE is combating parasitosis (Duarte *et al,* 2007). Parasites increasing serum IgE levels are *Ascaris, Echinococcus*, filariae, hookworms, *Schistosoma, Strongyloides, Toxocara,* and *Trichuris* that reflect parasite-specific IgE and total IgE (Varatharajalu *et al,* 2011). Increasing IgE levels were associated with increasing tissue invasion, and peripheral blood eosinophilia usually occurred in the children (Zar *et al,* 2002). 2- Human immunodeficiency virus type 1 patients have elevated IgE levels, and increased allergic reactions to drugs or environmental allergens (Bowser *et al,* 2007). In HIV-positive adults, elevated IgE levels may be partially related to various other conditions, such as I.V. drug use or alcohol intake (Miguez-Burbano *et al,* 1995). 3- Viral infections associated with elevated IgE levels are Epstein-Barr virus and cytomegalovirus. In EBV mononucleosis, IgE levels increase initially and return to baseline within weeks to months (Bahna *et al,* 1984). 4- Elevated IgE levels may be seen in infections with bacterial TB (Kutlu *et al,* 2008).

Inflammatory diseases: Churg-Strauss syndrome features elevated IgE (up to 5000IU/ml.), necrotizing small and medium-sized vessel vasculitis and eosinophilia associated with asthma (Marques *et al,* 2017).

Kimura disease is a rare benign chronic inflammatory disorder with lymphadenopathy and eosinophilic adenitis of head and neck regions of middle-aged Asian males with IgE levels greater than 1000 IU/ml, peripheral eosinophilia (Abuel-Haija and Hurford, 2007). Generally, much controversy existed as to the relationship between Kimura's disease and angiolymphoid hyperplasia with eosinophilia, and initially thought to give the same disease spectrum, but accepted as two separate diseases. Chong *et al.* (2006) reported that Kimura's disease and angiolymphoid hyperplasia were two separate diseases with eosinophilia coexisted in same patient. Angiolymphoid hyperplasia with eosinophilia (ALHE) is a benign vascular neoplasm affect mainly middle-aged women and whether AHLE and Kimura's disease might represent two variants of same disease entity.

Neoplasms were association with IgE elevations include Hodgkin and non-Hodgkin lymphoma (Eckschlager *et al,* 2004), especially nodular sclerotic histology, cutaneous T cell lymphoma/Sezary syndrome (Scala *et al,* 2012), and IgE myeloma (Hua *et al,* 2012). IgE myelomas are extremely rare (0.01% of plasmacytomas) with serum IgE levels from 0.6 to 63g/L (Wang *al,* 2009).

Other disorders: 1- Patients with bone marrow transplantation, IgE levels can increase up to 2000-fold, even without graft-versus-host disease (Ringdén *et al,* 1983), 2- Nephrotic syndrome associated with different glomerulonephritis forms is associated with increased IgE levels that decrease with thera py (Tan *et al,* 2011), 3- Cigarette smokers often have increased IgE levels compared to nonsmokers, especially in men (Arnson *et al,* 2010), & 4- Alcoholism increases serum IgE levels (González-Quintela *et al,* 2002).

Anti-IgE therapy: Omalizumab (Xolair) is a recombinant humanized monoclonal antib-

ody that binds to the Cε3 portion of free serum IgE. It treated perennial moderate to severe chronic persistent allergic asthma, was effective for other IgE-mediated diseases as well (Friedrich *et al,* 2008).

Reddel *et al*. (2021) in Austria added that clinical nurse specialists can monitor for signs of anaphylaxis, such as urticaria, hypotension, and shortness of breath. Pharmacists can monitor patients for adverse drug reactions from drug therapy. Immunologists can monitor patients with severe asthma and add omalizumab (Anti-IgE) therapy when indicated according to GINA guidelines.

Conclusion

IgE is a critical defense against some parasitosis and in mast cell and basophil degranulation and antigen presentation, and central to many allergic diseases pathogenesis.

IgE is produced by plasma cells. Isotype switching of B cells to produce antigen-specific IgE requires interleukins 4 & 13, and interactions between B & T cells. Antigen-specific IgE production takes place in mucosal lymphoid tissues, particularly tonsils and adenoids.

IgE functions via its high (FcεRI) and low (FcεRII) affinity receptors on mast cells, basophils and other cells causing mast cells degranulation, and basophils and antigen presentation. Expression of both receptors positively correlated to circulating IgE levels.

Total IgE levels are measured by sandwich-type assays that detect IgE levels as low as 2 to 5 IU/ml, with lower levels characterized as undetectable. Normal serum levels range from undetectable to 100 IU/ml.

IgE don't pass via placenta, its levels increase from birth with peak between 16 to 19years old. IgE deficiency is levels of total IgE <2.5 IU/ml. Decreased IgE levels can be associated with deficiencies of other immunoglobulins or sinopulmonary disease and autoimmune diseases. But, it is unclear if isolated IgE deficiency in humans is a clinically relevant immunodeficiency or a mark er of more general immune dysregulation.

IgE total serum increases in allergic diseases, some primary immunodeficiencies, para sitic and viral infections, and some inflamm a tory diseases or malignancies, or other disorders. Block and decrease receptor expression is a strategy in allergic disease treatment.

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References

Abuel-Haija, M, Hurford, MT, 2007: Kimura disease. Arch. Pathol. Lab. Med.131:650-6.

Al-Hammadi, S, 2015: Unusual presentation of Omenn syndrome: Case report. World Allergy Organ J. 8, 1:SA248 doi:10.1186/1939/45518/S.

Arnold, JN, Wormald, MR, Sim, RB, *et al,* 2007: The impact of glycosylation on the biological function and structure of human immunoglobulins. Ann. Rev. Immunol. 25:2-8.

Arnson, Y, Shoenfeld, Y, Amital, H, 2010: Effects of tobacco smoke on immunity, inflammation and autoimmunity. J. Autoimmun. 34:258-62.

Bahna, SL, Heiner, DC, Horwitz, CA, 1984: Sequential changes of the five immunoglobulin classes and other responses in infectious mononucleosis. Int. Arch. Allergy Appl. Immunol. 74: 1-8.

Balzar, S, Strand, M, Rhodes, D, Wenzel, SE, 2007: IgE expression pattern in lung: Relation to systemic IgE and asthma phenotypes. J. Allergy Clin. Immunol. 119:855-62.

Bernstein, IL, Li, JT, Bernstein, I, *et al,* 2008: Allergy diagnostic testing: An updated practice parameter. Ann. Allergy Asthma Immunol. 100: S1-10.

Bowser, CS, Kaye, J, Joks, RO, *et al,* 2007: IgE and atopy in perinatally HIV-infected children. Pediatr. Allergy Immunol. 18:298-308.

Buchbinder, D, Nugent, DJ, Fillipovich, AH, 2014: Wiskott-Aldrich syndrome: Diagnosis, current management, and emerging treatments. Appl. Clin. Genet. 3, 7:55-66.

Cameron, L, Gounni, AS, Frenkiel, S, *et al,* 2003: S epsilon S mu and S epsilon S gamma switch circles in human nasal mucosa following ex vivo allergen challenge: Evidence for direct as well as sequential class switch recombination. J. Immunol. 171:3816-21.

Chan, SK, Gelfand, EW, 2015: Primary immunodeficiency masquerading as allergic disease. Immunol. Allergy Clin. N. Am. 35:767-78.
Chong, WS, Thomas, A, Goh, L, 2006: Kimura's disease, and angiolymphoid hyperplasia with eosinophilia: Two disease entities in same patient: Case report and review of the literature. Int. J. Dermatol. 45, 2:139-45.
Coker, HA, Durham, SR, Gould, HJ, 2003: Local somatic hypermutation and class switch recombination in the nasal mucosa of allergic rhinitis patients. J. Immunol.171:5602-8.
Cooper, AM, Hobson, PS, Jutton, MR, *et al,* 2012: Soluble CD23 controls IgE synthesis and homeostasis in human B cells. J. Immunol. 188: 3199-204.
Duarte, J, Deshpande, P, Guiyedi, V, *et al,* 2007: Total and functional parasite specific IgE responses in *Plasmodium falciparum*-infected patients exhibiting different clinical status. Malar. J. 6:1-8.
Duchén, K, Björkstén, B, 1996: Total IgE levels in human colostrum. Pediatr. Allergy Immunol. 7: 44-50.
Dullaers, M, De Bruyne, R, Ramadan, F, *et al,* 2012: The who, where, and when of IgE in allergic airway disease. J. Allergy Clin. Immunol. 129:635-42.
Eckl-Dorna, J, Pree, I, Reisinger, J, *et al,* 2012: The majority of allergen-specific IgE in blood of allergic patients does not originate from blood-derived B cells or plasma cells. Clin. Exp. Allergy 42: 1347-52.
Eckschlager, T, Průsa**, R, Hladíková, M, *et al,* 2004:** Lymphocyte subpopulations and immunoglobulin levels in Hodgkin's disease survivors. Neoplasma 51:261-64.
Ellertsen, LK, Storla, DG, Diep, LM, *et al,* 2009: Allergic sensitization in tuberculosis patients at the time of diagnosis and following chemotherapy. BMC Infect. Dis. 9:100-10.
Fregonese, L, Patel, A, van Schadewijk, A, *et al,* 2004: Expression of the high-affinity IgE receptor (FcepsilonRI) is increased in fatal asthma. Am. J. Respir. Crit. Care 169:A297-304.
Friedrich, N, Husemoen, LL, Petersmann, A, *et al,* 2008: The association between alcohol consumption and biomarkers of alcohol exposure with total serum IgE levels. Alcohol Clin. Exp. Res. 32:983-8.
Galli, SJ, Tsai, M, Piliponsky, A, 2008: Development of allergic inflammation. Nature 454: 445-54.
Geha, RS, Jabara, HH, Brodeur, S, 2003: The regulation of immunoglobulin E class-switch recombination. Nat. Rev. Immunol. 3:721-8.
Gergen, PJ, Arbes, SJ, Jr, Calatroni, A, *et al,* 2009: Total IgE levels and asthma prevalence in the US population: Results from the National Health and Nutrition Examination Survey 2005-2006. J. Allergy Clin. Immunol. 124:447-54.
González-Quintela, A, Vidal, C, Gude, F, 2002: Alcohol-induced alterations in serum immunoglobuline (IgE) levels in human subjects. Front. Biosci. 7:e234-8.
Granada, M, Wilk, J, Tuzova, M, *et al,* 2012: A genome-wide association study of plasma total IgE concentrations in the Framingham Heart Study. J. Allergy Clin. Immunol.129:840-8.
Hamilton, RG, 2006: Accuracy of US Food and Drug Administration-cleared IgE antibody assays in the presence of anti-IgE (omalizumab). J. Allergy Clin. Immunol. 117:759-66.
Hamilton, RG, Adkinson, FN, Jr, 2004: In vitro assays for the diagnosis of IgE-mediated disorders. J. Allergy Clin. Immunol. 114:213-9.
Hamilton, RG, Williams, PB, 2010: Specific IgE Testing Task Force of the American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma and Immunology. Human IgE antibody serology: A primer for the Practicing North American allergist/immunologist. J. Allergy Clin. Immunol. 126:33042.
Hibbert, R, Teriete P, Grundy G, *et al,* 2005: The structure of human CD23 and its interactions with IgE and CD21. J. Exp. Med. 202:751-9.
Holgate, S, Casale, T, Wenzel, S, *et al,* 2005: The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J. Allergy Clin. Immunol.115:459-65.
Hua, J, Hagihara, M, Inoue, M, Iwaki, Y, 2012: A case of IgE-multiple myeloma presenting with a high serum Krebs von den Lungen-6 level. Leuk. Res. 36:e107-11.
Kamemura, N, Tada, H, Shimojo, N, *et al,* 2012: Intrauterine sensitization of allergen-specific IgE analyzed by a highly sensitive new allergen microarray. J. Allergy Clin. Immunol. 130: 113-9.
Knutsen, AP, Slavin, RG, 2011: Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis. Clin. Dev. Immunol. Apr 5:843763.doi: 10.1155/2011/843763.
Kutlu, A, Bozkanat, E, Ciftçi, F, *et al,* 2008:

Effect of active tuberculosis on skin prick allergy tests and serum IgE levels. J. Investig. Allergol. Clin. Immunol. 18:113-9.

Lynch, NR, Hagel, I, Palenque, M, *et al*, 1998: Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. J. Allergy Clin. Immunol. 101:217-24.

Marques, CC, Fernandes, EL, Miquelin, GM, Colferai, MMT, 2017: Cutaneous manifestations of Churg-Strauss syndrome: Key to diagnosis. An. Bras. Dermatol. 92, 5:S56-8.

McSharry, C, Xia, Y, Holland, CV, Kennedy, MW, 1999: Natural immunity to *Ascaris lumbricoides* associated with immunoglobulin E antibody to ABA-1 allergen and inflammation indicators in children. Infect. Immun. 67:484-94.

Miguez-Burbano, MJ, Shor-Posner, G, Fletcher, M, *et al,* 1995: Immunoglobulin E levels in relationship to HIV-1 disease, route of infection, and vitamin E status. Allergy 50:157-64.

Miller, SP, Marinkovich, VA, Riege, DH, Sell, WJ, Baker, DL, *et al,* 1984: Application of the MAST immunodiagnostic system to determination of allergen-specific IgE. Clin. Chem. 30, 9: 1467-72.

Moffatt, MF, Gut, I, Demenais, F, *et al,* 2010: A large-scale, consortium-based genome wide association study of asthma. N. Engl. J. Med. 363:1211-9.

Oettgen, HC, Geha, RS, 2001: IgE regulation and roles in asthma pathogenesis. J. Allergy Clin. Immunol. 107:429-34.

Moltrasio, C, Romagnuolo, M, Riva, D, Colaveto, D, Ferrucci, SM, *et al,* 2023: Netherton syndrome caused by heterozygous frame shift mutation combined with homozygous c.1258A > G polymorphism in *SPINK5* Gene. Genes (Basel). May 14;14(5):1080. doi:10.3390/genes1405.

Ozcan E, Notarangelo LD, Geha R, 2008: Primary immune deficiencies with aberrant IgE production. J. Allergy Clin. Immunol.122:1054-9.

Pien, GC, Orange, JS, 2008: Evaluation and clinical interpretation of hypergammaglobulinemia E: Differentiating atopy from immunodeficiency. Ann. Allergy Asthma Immunol. 100: 392-8.

Poole, JA, Meng, J, Reff, M, *et al*, 2005: Anti-CD23 monoclonal antibody, lumiliximab, inhibited allergen-induced responses in antigen-presenting cells and T cells from atopic subjects. J. Allergy Clin. Immunol.116:780.

Popescu, FD, Vieru, M, 2018: Precision medicine allergy immunoassay methods for assessing immunoglobulin E sensitization to aeroallergen molecules. World J. Methodol. 8, 3:17-36.

Reddel, HK, Bacharier, LB, Bateman, ED, Brightling, CE, Brusselle, GG, *et al,* 2021: Global Initiative for Asthma Strategy: Executive summary and rationale for key changes. Am. J. Respir. Crit. Care Med. 205, 1:17-35.

Ringdén, O, Persson, U, Johansson, SG, *et al,* 1983: Markedly elevated serum IgE levels following allogeneic and syngeneic bone marrow transplantation. Blood 61:1190-4.

Scala, E, Abeni, D, Palazzo, P, *et al,* 2012: Specific IgE to allergenic molecules is a new prognostic marker in patients with Sézary syndrome. Int. Arch. Allergy Immunol.157:159-62.

Schoettler, JJ, Schleissner, LA, Heiner, DC, 1989: Familial IgE deficiency associated with sinopulmonary disease. Chest 96:516.

Schroeder, HW, Jr, Cavacini, L, 2010: Structure and function of immunoglobulins. J. Allergy Clin. Immunol. 125:S41-8.

Smith, JK, Krishnaswamy, GH, Dykes, R, *et al,* 1997: Clinical manifestations of IgE hypogammaglobulinemia. Ann. Allergy Asthma Immunol. 78:313-9.

Smith, P, Ownby, DR, 2009: Clinical significance of IgE. In: Middleton's allergy: Principles and Practice, 7th ed, Adkinson NF, Bochner BS, Busse WW, et al (Eds), Mosby Elsevier.

Spasevska, I, Sharma, A, Steen, CB, Josefsson, SE, Blaker, YN, *et al,* 2023: Diversity of intratumoral regulatory T cells in B-cell non-Hodgkin lymphoma. Blood Adv. 7, 23:7216-30.

Stone, KD, Prussin, C, Metcalfe, D, 2010: IgE, mast cells, basophils, and eosinophils. J. Allergy Clin. Immunol. 125:S73-82.

Takhar, P, Corrigan, CJ, Smurthwaite, L, *et al,* 2007: Class switch recombination to IgE in bronchial mucosa of atopic and nonatopic patients with asthma. J. Allergy Clin. Immunol. 119: 213-9.

Takhar, P, Smurthwaite, L, Coker, HA, *et al,* 2005: Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. J. Immunol.174:5024-9.

Tan, Y, Yang, D, Fan, J, *et al,* 2011: Elevated levels of immunoglobulin E may indicate steroid resistance or relapse in adult primary nephrotic syndrome, especially in minimal change nephrotic syndrome. J. Int. Med. Res. 39:2307-10.

Tsicopoulos, A, Joseph, M, 2000: CD23 role in

allergic disease. Clin. Exp. Allergy 30: 602-8.
Underdown, BJ, Knight, A, Papsin, FR, 1976: Relative paucity of IgE in human milk. J. Immunol. 116:1435-42.
Varatharajalu, R, Parndaman, V, *et al,* 2011: *Strongyloides stercoralis* excretory/secretrory protein strongylastacin specifically recognized by IgE antibodies in infected human sera. Microbiol. Immunol. 55:115-9.
Vercelli, D, 2005: Genetic regulation of IgE responses: Achilles and the tortoise. J. Allergy Clin. Immunol. 116:60-9.
Vercelli, D, 2009: Immunobiology of IgE. In: Middleton's allergy: Principles & Practice 7th ed, Adkinson NF, *et al* (Eds), Mosby Elsevier.
Wang, ML, Huang, Q, Yang, TX, 2009: IgE myeloma with elevated level of serum CA125. J. Zhejiang Univ. Sci. B, 10:559.
Watanabe, N, Katakura, K, Kobayashi, A, *et al,* 1988: Protective immunity and eosinophilia in IgE-deficient SJA/9 mice infected with *Nippostrongylus brasiliensis* and *Trichinella spiralis.* Proc. Natl. Acad. Sci. USA 85:4460-9.
Weidinger, S, Gieger, C, Rodriguez, E, *et al,* 2008: Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. PLoS Genet. 4:e1000166.
Wright AL, Sherrill D, Holberg CJ, *et al,* 1999: Breast-feeding, maternal IgE, and total serum IgE in childhood. J. Allergy Clin. Immunol. 104:589-96.
Zar, H, Latief, Z, Hughes, J, Hussey, G, 2002: Serum immunoglobulin E levels in human immunodeficiency virus-infected children with pneumonia. Pediatr. Allergy Immunol.13:328-34.

Table 1: Conditions associated with elevated serum IgE

Diseases	Agent	Name
Infectious	Parasitic	Ascariasis, Schistosomiasis & Strongyloidiasis
	Bacterial or viral	Human immunodeficiency virus (HIV) infection *Mycobacterium tuberculosis* , Cytomegalovirus & Epstein-Barr virus (EBV)
Atopic		Allergic fungal rhinosinusitis, Atopic dermatitis, Allergic asthma &Allergic rhinitis
Immunodeficiencies		Hyperimmunoglobulin E syndrome , Wiskott-Aldrich syndrome, Netherton disease, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Omenn syndrome &Atypical complete DiGeorge syndrome
Inflammatory		Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) & Kimura disease
Neoplasms		Hodgkin lymphoma & IgE myeloma
Others		Tobacco smokers, Cystic fibrosis, Nephrotic syndrome, Bone marrow transplantation & Bullous pemphigoid

Explanation of figures

Fig. 1: Immunoglobulin E structure, Fig. 2: Allergen-specific IgE production and dissemination, Fig. 3: Main causes of IgE serum elevation.