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Medical Algorithm: Diagnosis and Management of Antibody Immunodeficiencies

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Background

Primary antibodydeficiencies (PAD) constitute the majority of all primary immunodeficiency diseases (PID) also termed in born errors of immunity (IEI). This category (PAD) representsaround 52% of all IEI and the proportion overall is still greater given that antibody deficiency is a component of other groups including combined and severe combined immunodeficiencies (SCID), autoinflammatory disorders, diseases of immune dysregulation and other well defined PIDs(1,2). Secondary antibody deficiencies (SAD) represent a larger and expanding number of individuals resulting from the use of a wide range of immunosuppressive therapies, in particular those targeting B cells, and may also result from renal orgastrointestinal immunoglobulin losses, infections, for example HIVormalaria,malnutritionorothers(3).

The manifestations of PAD are protean and encompass a range of infectious and non-infectious complications, including autoimmune, lymphoproliferative, granulomatous and allergy manifestations due to an immunedysregulation, and increased risk of malignancy in some forms of PAD (4,5).

Diagnosis

The diagnosisis based on a combination of clinical features together with laboratory findings, potentially a positive family history and increasingly, genetictesting. The clinical presentation for antibody deficiency is often characterised by recurrents in opulmonary infections which often take longer to resolve and require prolonged or intravenous antibiotic courses. In addition to the infections presentations,complications may include autoimmunecytopenias,lymphoproliferation,non-infectious inflammation and allergy linked to underlying immune dysregulation. PAD disorders are also linked to an increase risk of malignancy, in particular lymphoma and gastric cancers(4,6). Similar clinical presentations may accompany secondary immunodeficiencies, which must be considered in the differential diagnosis (3).SADoccur more often than inherited antibody deficiencies, and are usually multifactorial, related to an underlying disease or treatment, including growing range of B cell-targeting therapeutics.SAD may also occur as a result of immunoglobulin loss especially via urogenital or gastrointestinal tract. The „leaky gut syndrome“ might be an integral part of some inborn errors of

immunity, especially those associated with immune dysregulation, or might accompany other chronic inflammatory diseases. As with all secondary deficiencies, thesearch for the primary cause is essential. Both B and T cell functionsare typicallyretained in SAD, although the numbers of CD4 + T cells in particular may be reduced by their intestinal loss. In SAD, there is usually no skewing in B cell subpopulations towards less mature forms and production of specific (postvaccination) antibodies is preservedparticularly in SAD caused by protein loss.

The initial laboratory assessment of antibody deficiency consistsof determining the concentrations of serum immunoglobulins, including IgG, IgA and IgMalongside the functional investigation of vaccine responses and lymphocyte enumeration,particularly the B cells (Figure 1). Impaired postvaccination response is a characteristic finding inantibody deficiencies. The response to tetanus vaccine verifies a response to protein antigens, while the response elicited by the Pneumovax polysaccharide vaccine (or an alternative vaccine without protein adjuvant) is used to determine immune reaction to polysaccharide antigens.

The decreased antibody levels in very young children, especially in the first year of life, may only represent a delayed development of immunoglobulin production, such as in premature infants or in transient hypogammaglobulinaemia in infancy (Fig. 1). If a reduction of immunoglobulin levels is profound and associated with clinical symptoms, a promptreferral to a specialized immunological examination is required without delay to rule out congenital immunodeficiency. In addition to a detailed examination of antibodies,such investigations include specific B cell and T cell panels designed for the diagnosis of inborn errors of immunity. Combined TREC/KREC screening,originally designed for early diagnosis of SCID, would also detect severe inborn antibody deficiencies, and is being tested in pilot studies orconsidered for implementation in some countries (8).

The commonest clinically relevant primary antibody deficiency in adults is Common variable immunodeficiency (CVID). Its diagnostic criteriaare regularly revised and published as an international consensus (7). Genetic testing has become pivotal for optimization and personalisation of therapy in cases, in whichthe molecular diagnosis allows a pathway-specific targeted therapeutical approach. An example of this is the use of abatacept, a soluble fusion protein, in cytotoxic T-lymphocyte-associated protein 4 deficiency. There have also been major advances in the screening of newborns using TREC and KREC assays and in adults using calculated globulin (8,9)

Management

In patients with PAD, immunoglobulin replacement therapy (IgRT)representsthe mainstay of therapy for many patients(10,11) (Figure 2). The decision to commence IgRT is straight-forward in well-defined PAD with a significant infection burden and supportive laboratory findings - hypogammaglobulinaemia with impaired response to vaccination. The decision becomes somewhat more complex if the manifestation is milder or incompletely pronounced, for instance in cases with hypogammaglobulinaemiabut preserved vaccine responses, or in specific antibody deficiency.

IgRT may be administered either intravenously, subcutaneously or as a facilitated subcutaneous infusion using hyaluronidase, and the decisions regarding route, frequency of administration and site of administration, whether home or hospital, are individual and are composed jointly with the patient and medical team (12). In general, IgRT is commenced based on weight at 0.4 – 0.6g/kg/month of IgG.It is adjusted individually according to the clinical status,such as infection burden, bronchiectasis, type of PAD and other complications,as well as to the laboratory parameters, including trough IgG level aiming for >7g/L. This however, varies between centres and countries(13,14). A careful assessment and monitoring is required duringIgRT with regard to clinical condition and non-infectious complications.In a number of circumstances, antibiotic prophylaxis may be used, for instance in milder immunodeficiencies with a less severe infectious susceptibility, such as IgG subclass deficiency, combined IgA deficiency with IgG subclass deficiency or specific antibody deficiency. Moreover, antibiotics may be prescribed in addition to IgRT, should the patients fail to respond to optimally individualised IgRT or in those with existing end-organ damage such as bronchiectasis, chronic sinusitis or in those colonised with *Pseudomonas aeruginosa* or *Stenotrophomonasmaltophilia*. Antibiotic regimens will vary according to the setting, organism and sensitivities. In general, in adult PAD patients with frequent respiratory tract infections on IgRT, who may also have bronchiectasis, azithromycin250-500mg three days/week has been shown to decrease infective exacerbations. In patients with concomitant T cell or neutrophil impairment, such as combined or severe combined immunodeficiency, hyper IgM syndrome, CVID and others, cotrimoxazole may be considered(10,15). PAD patients require regular follow up both to monitor therapy and for early detection and management of

complications(4,5,16,17). Laboratory and radiological monitoring are individualised; baseline testing includes full blood count, renal and liver functions and C-reactive protein assessment 2-4 times yearly, with LDH, β2 microglobulin in lymphoma prevention, lymphocyte subsets 1-2 times yearly, abdomen ultrasonography, neck ultrasonography if lymphadenopathy is investigated, chest X-ray and lung function tests once a year. In CVID or other forms of PAD with severe lung or gastrointestinal (GIT) involvement, chest computed tomography imaging every 3-5 years and screening GIT endoscopies every 1-2 years, respectively, are recommended in some centres(18).

Diagnosis and management of PAD are continuously improving, thanks to better immunologic and molecular-genetic diagnostic tools, broaderoptions for individually-tailored IgRT, personalised pathway-specific therapies and greater knowledge of the role of haemopoietic stem cell transplantation and gene therapy/editing in management of PAD.

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Figure 1: Diagnosticalgorithmforantibodydeficiency (PAD- Primaryantibodydeficiency, CVID- Commonvariableimmunodeficiency, THI- Transienthypogammaglobulinemiaofinfancy, SPAD- Specificantibodydeficiency, XL- X-linked, AD- Autosomal dominant, AR- Autosomalrecessive, GOF- Gain-of-function)

Figure 2: Therapeutical algorithm for antibody deficiency (ATB- Antibiotics, IgRT- Immunoglobulin replacement therapy, AI- Auitoimmune, GLILD- Granulomatous-lymphocytic interstitial lung disease, IBD- Inflammatory bowel disease, LN- Lymph node)

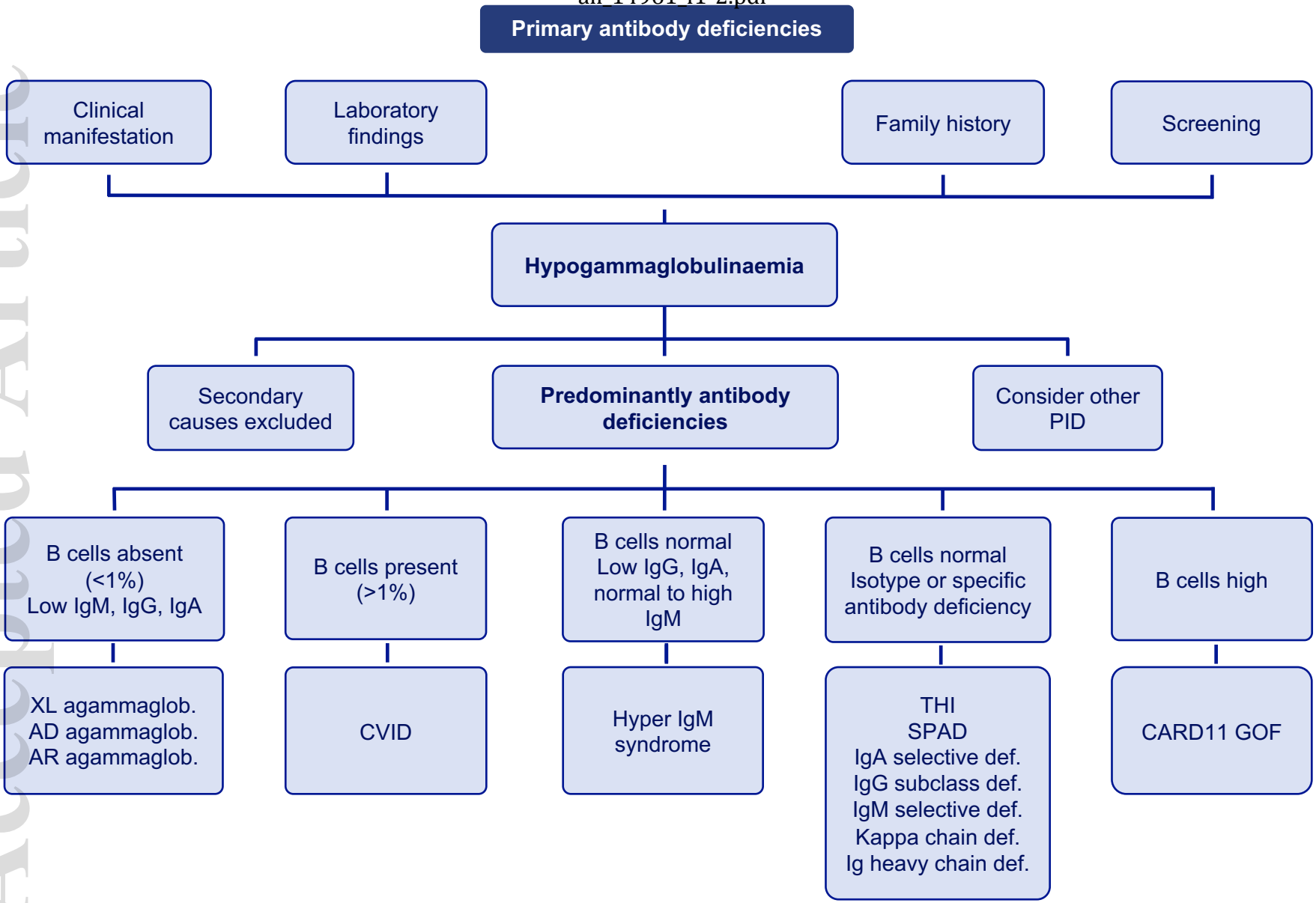

Figure 1

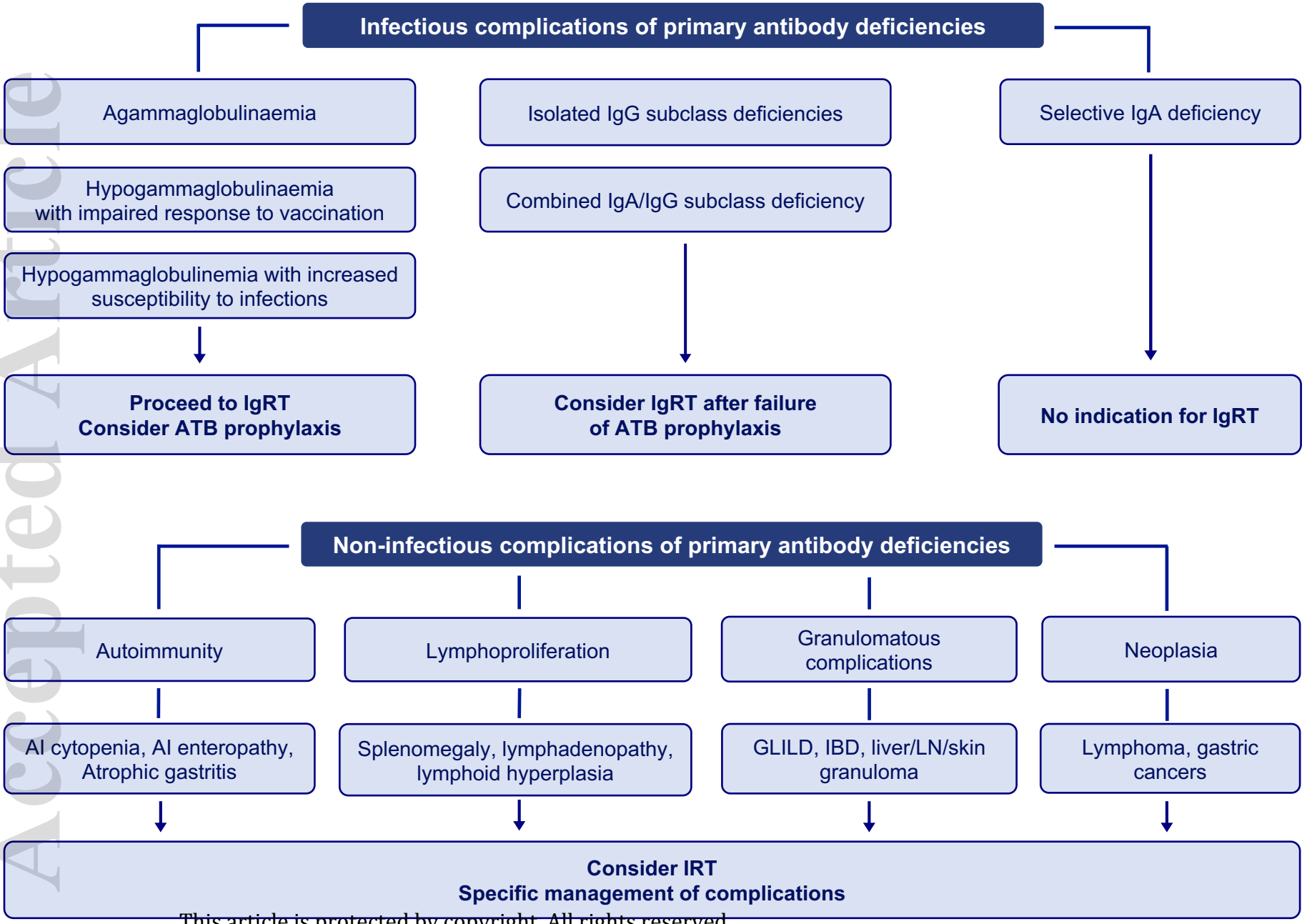

Figure 2