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APPROPRIATE USE OF IMMUNOGLOBULINS IN POLAND - Key Considerations and Treatment Paradigms

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immunoglobulins, appropriate use in Poland, unmet medical need, added therapeutic value, quality of evidence, treatment modalities, treatment paradigms

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Abstract

Common Position of Scientific Societies: Polish Society of Dermatology (PTD), Polish Society for Fundamental and Clinical Immunology (PTiDiK), Polish Society of Paediatric Oncology and Haematology (PTOHD)

Background and Objectives

This paper aims to analyse, assess and appraise appropriate use of Normal Polyvalent Immunoglobulins (IgGs) across multiple indications, wherever these therapies are known to be used and have been proven to be an effective therapeutic modality. This assessment is based on a framework proposed by a group of international experts in the recent Green Paper „Appropriate Use of Immunoglobulins in Europe".[1] Based on a systematic application of the framework's criteria to all IgG conditions and diseases, this paper presents a short-list of indications, where IgG use is appropriate, together with a guidance on optimal therapeutic paradigms. As such, this paper is aimed to assist the clinical community and policy makers in navigating the extremely complex clinical landscape of rare and ultra-rare diseases and conditions, which are either immune-mediated or stem from deficient, dysregulated or dysfunctional immune system. Some of the indications considered in this study are currently not registered for IgG use in Poland or, if registered, not fully covered with reimbursement. In cases where IgG use in such conditions or diseases is found to be appropriate, this study may be also considered by the relevant regulatory and/or HTA bodies as a contribution towards reassessment or reappraisal.

Materials and Methods

This paper was created using a hybrid methodology, including a literature review using PubMed and Scopus, comparative assessment of clinical trials and real-world evidence using Cochrane Library, and cross-referencing of International Guidelines (where available) with two robust sets of national protocols for the Use of Immunoglobulins (English NHS[2] and Australian National Blood Authority[3]). The results of the multi-source reviews were then triangulated with leading Polish experts (National Consultants, Heads of Professional Societies) through individual interviews and virtual correspondence, which rendered a short-list of appropriate IgG use indications for further investigation. The guidance on the appropriate use of IgGs, in a form of treatment paradigm tables, was a result of additional literature review of peer-reviewed papers indicated by the experts during interviews, as well as manual search strategy combining Medical Subject Headings (MeSH) terms and keywords such as "Immunoglobulins" with every identified indication e.g. Guillain-Barré Syndrome (GBS). This second review was then followed by written contributions from the experts in the field based on their real-world experience and local protocols, especially when different from international guidelines. The paper was then finalised by a second round of expert interviews and virtual correspondence to reach the final approval of the panel of all contributing experts.

1.1 INTRODUCTION

Normal Polyvalent Immunoglobulins: therapeutic value and medical need

Normal Polyvalent Immunoglobulins (IgGs) are a class of unique biological therapies derived from human plasma. IgGs bring value to patients across many indications in two distinct ways, either by compensating a significant immune deficiency or by modulating an aberrant immune system homeostasis. The former mode of action concerns the essential or life-saving treatment for primary and secondary immunodeficiencies (PIDs and SIDs respectively), and the latter refers to the radical improvements to the quality of life in a broad range of immune-mediated conditions, especially in neurology, haematology and dermatology. The IgG value, however, goes beyond the clinical benefit, and there is a growing body of evidence indicating that the use of IgGs either as treatment or as prophylaxis significantly reduces socio-economic and psycho-social burden of the disease.[4]

Key Issues: IgG Availability and Use, Regulatory Status, Clinical Practice

Medical need for the IgGs in Europe is growing at an estimated rate of 8-9% annually, due to demographics, better diagnostics, discovery of efficacy in new indications and a growing incidence of secondary immune deficiencies (SIDs), as a side-effect of modern B-cell depleting treatments. However, due to its unique and finite source material (human plasma), the collection of which in

Europe has been growing at only 4-6%[5] in recent years, the IgG availability is insufficient to cover the current need, whilst its donor-to-patient value chain is prone to disruptions, such as the ones seen during the COVID-19 pandemic. Assuming that medical need is similar and hence patient numbers are proportional across European countries, it is striking that the consumption of IgGs varies from 177.3 kg per capita in Sweden to as little as 32.9 in Poland or even less at 8.8 in Romania [see Fig 1]. In Poland, the IgG consumption) [see Fig. 2] is systemically divided between two Drug Programs with full reimbursement (PID and Neurology and use outside of these Programs (mix of in- and off-label, reimbursed and out of pocket) [see Table 1]. The widening gap between the IgG availability and the growing medical need is, as experts have consistently noted[6], additionally aggravated by the high heterogeneity between countries' IgG regulatory status and reimbursement coverage. All of the above indicates an urgent need for establishing evidence-based IgG appropriate use across all indications in order to optimise and harmonise the currently disparate policies and clinical practices.

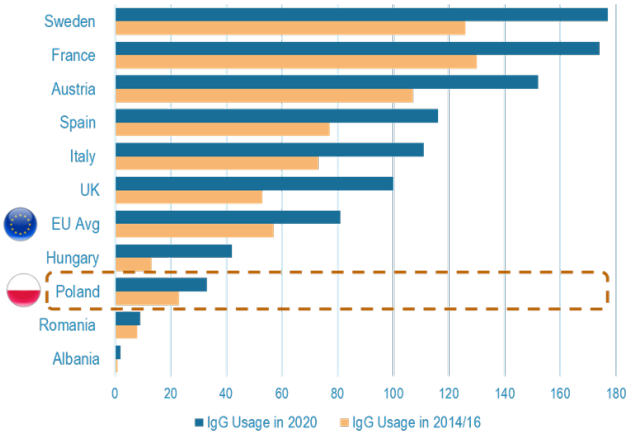


Figure 1. AVERAGE IgG CONSUMPTION BY COUNTRY* (2014 vs 2020, in Kg per Million Population)[5]

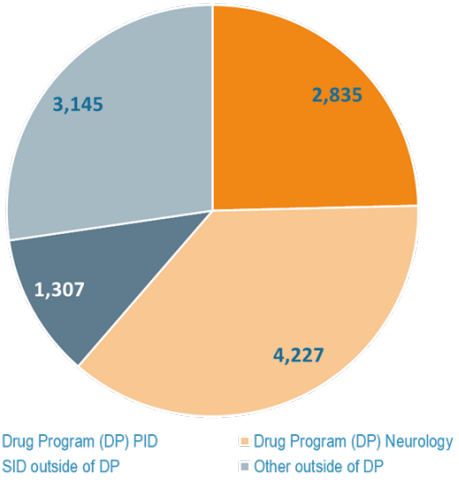


Figure 2. CONSUMPTION OF IgG IN POLAND by PROGRAM / INDICATION*(2020, in Kg)[5,7]

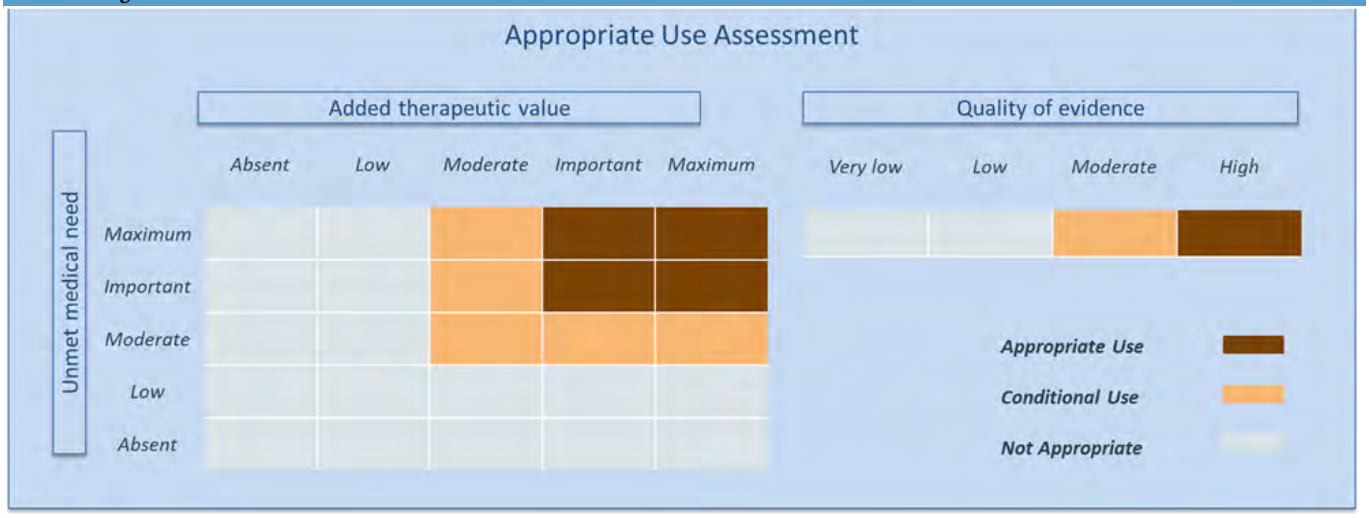
Table 1. IgG USE IN POLAND - Main Indications

Drug Program PID: main indications	Drug Program Neurology: main indications	Outside of Drug Program: main indications
Common variable immunodeficiency (CVID),	Chronic inflammatory demyelinating polyneuropathy (CIDP)	Idiopathic thrombocytopenic purpura (ITP)
Unspecified primary hypogammaglobulinemia	Multifocal motor neuropathy (MMN)	Secondary immunodeficiencies (SID)
Agammaglobulinemia	Guillain–Barre syndrome (GBS)	Alloimmune thrombocytopenia (FMAIT NAIT)
Significant subclass deficiency	Myasthenia gravis exacerbation (MG/MC)	Other Inflammatory Myopathies
Specific antibody deficiency	Idiopathic inflammatory myositis (polymyositis and dermatomyositis)	Pemphigus
	Encephalitis with antibodies to neuronal antigens	Kawasaki disease

Appropriate Use Framework: medical need/ therapeutic value/ quality of evidence

The framework for establishing appropriate use of IgGs across all potential indications is derived from a recent Green Paper [see Table 2, 3, 4, 5 and Fig. 3]. The framework proposed in the Paper derives from an international experts' consensus and is an adaptation of AIFA CTS Algorithm[1,8] using three dimensions: Level of (Unmet) Medical Need, Added Therapeutic Value, and Quality of Evidence.

Table 2. IgG APPROPRIATE USE FRAMEWORK



The Added Therapeutic Value, based on the consensus amongst the advisory members, has three criteria: Efficacy, Safety Profile/Adverse Effects, and Practicality. Whilst the first two are well-established concepts, the third one is specific to IgGs and concerns optimal mode of administration and point of care.

Table 3. CRITERIA FOR ADDED THERAPUTIC VALUE

LEVEL: / DIMENSION:	Maximum	Important	Moderate	Low	Absent
Clinically relevant outcomes	High efficacy and vital	High efficacy	Reasonable efficacy	Low efficacy	Absence of clinical benefit
Adverse effects & safety profile	High safety profile with very low or absent adverse effects	High safety profile with low or absent adverse effects	Reasonable safety profile	Poor safety profile	Poor safety profile
Practicalities	V. Practical (easy mode of administration and point of care, easy reimbursement procedure)	V. Practical (easy mode of administration and point of care, easy reimbursement procedure)	Practical (easy mode of administration or point of care and feasible reimbursement procedure)	Less practical (lack of easy mode of administration or point of care, difficult reimbursement procedure)	Not practical (lack of easy mode of administration, burdensome point of care, lack of/ difficult reimbursement procedure)

The second part of the framework, the Level of (Unmet) Medical Need, is a two-fold criterion based on availability of efficacious alternative treatments and the disease burden in the absence of IgG treatment. The maximum level of medical need would be in indications where no alternative treatments exist and where disease burden is the highest. Important medical need would occur when alternative treatments do exist but show low(er) efficacy. From this perspective, there are many IgGs uses, both in-label and off-label, that address maximum or important medical needs.

Table 4. CRITERIA FOR UNMET MEDICAL NEED

LEVEL: / DIMENSION:	Maximum	Important	Moderate	Low	Absent
Alternative Treatments	No alternative treatments available	Alternative treatments exist with inferior results (e.g. worse outcomes, lower efficacy, worse safety profile and higher complexity)	Alternative treatments exist with similar results (e.g. similar outcomes, efficacy, safety profile and complexity)	Alternative treatments exist with better results (e.g. better outcomes, higher efficacy, better safety profile and lower complexity)	Alternative treatments exist with much better results (e.g. better outcomes, higher efficacy, better safety profile and lower complexity)
Disease Burden	Very High DALY (severe disability and premature death)	High DALY (severe disability or high risk of premature death)	Moderate DALY (disability and risk of premature death)	Moderate to Low DALY (risk of disability)	Low DALY (minimal impact on Quality of Life)

Establishing level of unmet medical need and therapeutic benefit is conditional on the ability to provide compelling evidence. As most IgG indications are rare or ultra-rare, they share a challenge of data availability, quality and/or comparability. Whilst the last criterion, Quality of Evidence, would assign the highest value to RCTs and the lowest to individual case studies, in orphan indications, where RCT data is absent or not ethical to obtain, Real World Data and Outcomes Studies must also be carefully considered as potentially valuable insights constituting important evidence [see Table 5 and Fig. 3].

Table 5. QUALITY OF EVIDENCE SCALE

LEVEL:	Quality of Evidence Criteria
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

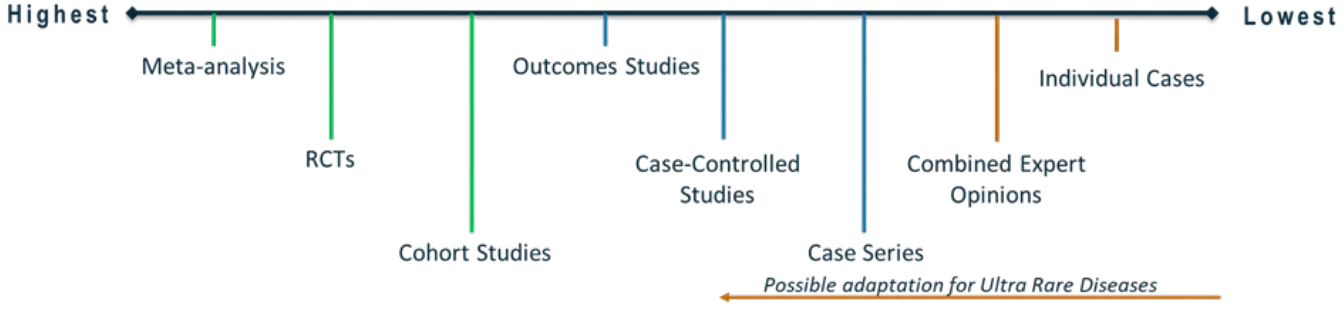


Figure 3. CEBM LEVELS OF EVIDENCE[9]

Shortlisting Indications for Appropriate Use Of IgGs: application of the Appropriate Use Framework

Based on the Framework outlined above, the experts conducted a deep analysis of multiple Indications, which in literature have all been considered for IgGs as a viable treatment, either as a first line or adjunct therapy and regardless of whether such treatment was on-label or off-label. A total of 35 distinct indications have been researched, out of which 21 were evaluated as "appropriate use" or "conditionally appropriate use" [see Table 6]. The appropriate use indications[10] were all characterised by a very high level of unmet medical need, corresponding to high mortality, disability or overall QALY shortfall, coupled with a very high added therapeutic benefit of IgGs, either as the only effective treatment or the most effective treatment, monotherapy and combinations alike. Majority of the appropriate and conditionally appropriate indications were already part of the Drug Programs, such as PID, MMN or CIDP. However, several conditions, such as Pemhigoid or a large spectrum of Secondary Immune Deficiencies (SIDs), which could be effectively treated with IgGs, had a less optimal or more complex reimbursement coverage and procedures, and ought to be considered for inclusion in relevant Drug Program in the future. The remaining indications, which were found to be "not appropriate" for the use of IgGs should be continuously monitored, as new evidences are emerging that may alter their place in the appropriate use framework.

Table 6. APPROPRIATE IgG USE in POLAND, SORTLISTED INDICATIONS

Unmet medical need \ Added therapeutic value	Absent	Low	Moderate	High	Maximum
Maximum				• Alloimmune thrombocytopenia • Toxic Eepidermal Necrolysis (TEN)	• PIDs associated with significant antibody defects
High		• Multiple Sclerosis (MS) in pregnant women • IgM Paraprotein-associated demyelinating neuropathy • ANCA-associated systemic vasculitides (AAV) • Autoimmune uveitis	• Autoimmune hemolytic anaemia (AIHA) • Stevens-Johnson syndrome • Scleromyxedema • Generalized morphea*	• Acquired hypogammaglobulinaemia secondary to haematological malignancies • Chronic Demyelinating Idiopathic Polyneuropathy (CIDP) • Guillain-Barré Syndrome (GBS) • Acquired red cell aplasia associated with chronic parvovirus B19	• Kawasaki Disease • Multifocal Motor Neuropathy (MMN) • Myasthenia gravis crisis (MC)
Moderate		• Myasthenia gravis (MG) • Rasmussen's Encephalitis • Opsoclonus-myoclonus syndrome - paediatric or adult non paraneoplastic • Autoimmune neutropenia • Pyoderma Gangrenosum (PG)	• Non-infective Autoimmune Encephalitides (AIE) • Autoimmune bullous dermatosis (AIBD): Pemhigoid, Pemphigus Vulgaris and LABD • Haemolytic disease of the newborn (HDFN) • Post-transfusion purpura*	• Idiopathic thrombocytopenic purpura (ITP) • Inflammatory Myopathies-Dermatomyositis (DM)/ Polymyositis (PM)/ Necrotizing autoimmune myopathy (NAM) • Cutaneous scleroderma*	
Low		• Acute idiopathic/ autoimmune dysautonomia/ ganglionopathy	• Acquired von Willebrand disease (vWD) • Neuromyelitis optica spectrum disorders (NMOSD)	• Systemic capillary leak syndrome (SCLS) • Chronic recurrent thrombosis	
Absent					

LEGEND:

Level of appropriateness is indicated by a shade of the tile:

- *Appropriate Use*
- *Conditional Use*
- *Not Appropriate*

Quality of evidence is indicated by colour of the text:

- Lipsum — High Quality
- Lipsum — Moderate Quality
- Lipsum — Low Quality
- Lipsum — V Low Quality

** Post-transfusion Purpura, Generalized morphea and Cutaneous scleroderma, due to scarce or low quality of evidence, and despite potential benefit, have not been investigated further in this paper*

Immunodeficiencies and Immune-Mediated Conditions: IgG mode of action and key principles of care

Immunodeficiencies

Immunodeficiencies are a highly heterogenous group of disorders stemming from either deficient, dysregulated or dysfunctional immune system. Each type requires a tailored therapeutic approach, but each type also shares the necessity of IgG use either to replace missing antibodies or to regulate aberrant homeostasis or, finally, to reconstitute immune system after radical aggressive procedures, such as stem cell transplant or gene therapy [see Fig. 4][10]

Immune-Mediated Conditions

Mechanisms underlying immunomodulation by IgGs are still mostly unknown, though there are some new considerations and regularities beginning to be revealed.[11] Stimulation of an immature myeloid population of dendritic cells (DC) that secretes IL-10 and the elucidation of Fc-specific, HLA-restricted natural regulatory T cells (Treg) provide insights into mechanisms of IVIg. The novel immune regulatory function of IgG in activating tolerogenic innate cells and expanding Treg reveals an important anti-inflammatory mechanism of action. Other potential mechanisms include provision of agent-specific neutralizing antibody, anti-idiotype and anti-cytokine antibodies, blockade of activating Fcγ receptors, and stimulation of the inhibitory FcγRIIb receptor. There is significant need to further explore the mechanisms of immunomodulation and neuromodulation to reveal alternative new treatments and more targeted and personalised therapies.

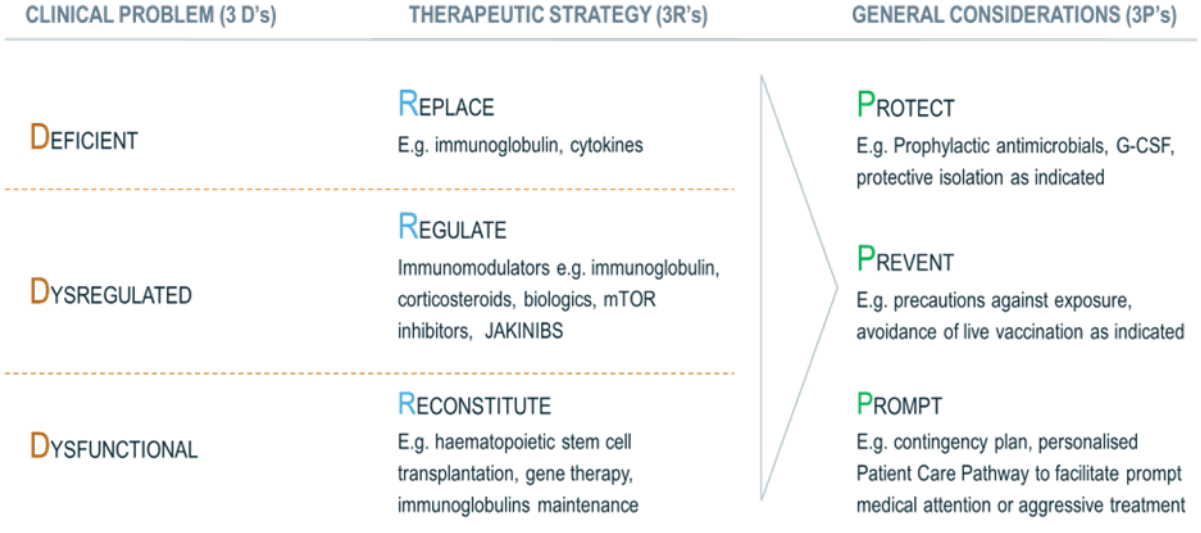


Figure 4. IMMUNODEFICIENCIES PRINCIPLES OF CARE[10]

1.2 INDICATIONS DEEP-DIVES: IMMUNOLOGY

PIDs associated with significant antibody defects:

OVERVIEW

Primary Immunodeficiencies (also known as IEI if molecular defect is found) with significant antibody defects are a heterogenous group of disorders, mostly genetically determined, and characterised by aberrant humoral immune function and deficient or depleted levels of antibodies. Common Variable Immunodeficiency (CVID) is the most prevalent form of PID, made distinct by a defective B-cell function, leading to impaired immunoglobulin production and causing very low immunoglobulin levels despite normal B-cell levels. In Poland the recorded prevalence of PIDs in 2016 was 7,2 thousands (18.9/100 thousands inhabitants), which is at the top end of the estimated European minimal prevalence range of 2-19 (e.g. 11 in France).[12]

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MAXIMUM]

Patients suffering from any form of PID experience more frequent and/or more severe infections (high individual disease burden), which require prolonged antiviral, antibiotic or surgical interventions coupled with frequent hospitalisations and consequent patient absenteeism (high socio-economic burden). Allergies, autoimmunities, non-neoplastic and neoplastic lymphoproliferations are other clinical manifestations of PID. Historically, before introduction of systematic IgG treatment, 20-year survival rates for CVID, the most common form of PID, have been as low as 30 % in 1979. IgG continues to be the only definitive treatment for PIDs, though multiple trials are ongoing testing viability of a single or adjunct therapeutic options (e.g. gene therapies). Disease Adjusted Life Years measure (DALY) for untreated PID patients has been estimated at 0.7-0.9 (significantly higher than most cancers) indicating very high medical need for effective treatment.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGHEST]

IgGs have a high efficacy/effectiveness in most forms of PIDs with significant antibody defects. Overall the IgG treatment has been historically credited with a recovery of 0.5-0.6 DALY/patient (treated patients DALY is estimated at 0.3). Multiple studies have shown that optimal use of IgGs in PID can alter the disease's natural history and result in highly meaningful improvements in both the primary endpoints and the overall quality of life including reduction in infections, hospitalisatons and absenteeism.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [HIGH]

There are numerous high-quality RCTs and Real-World studies covering the usage of IgGs in CVID. The most up-to-date and comprehensive data comes from 2212 patients with CVID from 28 medical centres contributing to the European Society for Immunodeficiencies Database.[13] Additionally, the Biotext 2004 meta-analysis confirms both the effectiveness and safety profile of IgG in PID.[14]

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Primary Immunodeficiency (PID) associated with significant antibody defects	• YES • D80-D89 indicated for IgG	• Intrinsic defects in immune cells, including B and T cells • Blood test (IgG, A, M nad IgG subclasses levels) • Humoral immune function test • Genetic test*	• A specific PID diagnosis must be established by a clinical immunologist	• First and only line of treatment	• Initiate at 0.2–0.8 g/kg/month
	REIMBURSEMENT COVERAGE				**OUTCOMES and MEASURES**
	• YES • Drug program PID				• Trough IgG • Reduction in number of infections • Treatment courses of antibiotics • Days in hospital

TREATMENT PARADIGM 1. PIDs associated with significant antibody defects

Acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) or B-cell depleting therapies (CAR-T and bispecific antibodies):

OVERVIEW

Acquired hypogammaglobulinemia is a type of secondary immune deficiency (SID), highly prevalent in heamatological malignancies, especially common in Chronic lymphocytic leukaemia (CLL), Multiple myeloma (MM), and Non-Hodgkin lymphoma (NHL), memory B cell deficiency secondary to haemopoietic stem cell transplantation (HSCT), In the recent years, following the introduction of modern therapies, such as anti-CD20, anti-CD19, anti-CD38 and CAR-T, all of which target and deplete B cells or plasma cells, the incidence of hypogammaglobulinaemia has significantly increased.[15] Additionally, therapeutic strategies targeting B cell receptor signalling pathway (e.g., Syk and PI3K enzymes or mTOR transcription factor) or B cell apoptosis inducers (e.g. navitoclax) are also contributing to the increased incidence.[16] This in turn is introducing additional complexity into the treatment paradigm, leading to additional burden in direct costs (e.g. cost of IgG and hospital visits) as well as indirect costs (e.g. travel to hospital, productivity loss, carer burden etc.)

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Acquired hypogammaglobulinemia effects reduced ability to mount antibody responses to a wide range of infectious agents and vaccines, thereby increasing risk of infection, and contributing to morbidity and mortality. Similar to PID, SID patients require prolonged antiviral, antibiotic or surgical interventions coupled with frequent hospitalisations and consequent patient absenteeism (high socio-economic burden). Unlike in PID, the efficacy of available treatments (antibiotic prophylaxis and IgG) is less evident and more heterogenous, depending on the underlying malignancy and other common co-morbidities, such as chronic heart failure, cerebrovascular disease or chronic lung disease. Overall disease burden is high, though it remains less severe than in PIDs associated with significant antibody defects.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

There are only two treatment modalities in acquired hypogammaglobulinaemia, namely IgG replacement therapy and antibiotic prophylaxis. IgG has been shown to be a superior treatment option to antibiotics in reducing the risk of clinically documented infections (CDI) by as much as 28%. However, there is still little evidence of IgG therapy meaningfully contributing to reduced mortality. Optimal dosing, based on a broad clinician consensus, is 0.2–0.8 g/kg/4 weeks at initiation, for a period of 8 to 12 months, after which, if there is clear evidence of benefit, maintenance should be at 0.2–0.6g/kg every four weeks to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range.[17,18,19]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE to HIGH]

The evidence of IgG effectiveness in acquired hypogammaglobulinemia is relatively low compared to PIDs, partially driven by greater patient heterogeneity and more complex etiology. Notably, there are no parallel randomised clinical trial comparing IgG with antibiotic prophylaxis (recent Phase II trial remains inconclusive[20]). However, recent meta-analysis[16] provides evidence indicating that pprophylactic IgG reduces the risk of clinically documented infection (CDI) by 28%, vaccination reduced the risk by 63%, whilst prophylactic antibiotics had no statistically significant impact on the risk. Overall, the evidence remains only moderate and more RCTs and RWE studies are necessary.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) or B-cell depleting therapies (CAR-T and bispecific antibodies)	• YES • C85, C91, C92, D47, D84 all indicated for IgG	• Differential diagnosis of patients with recurrent infections and abnormal immunologic evaluation • IgG <4 – 5 g/L (excluding paraprotein) • Blood test (IgG, A, M)	INCLUSION CRITERIA: • Hypogammaglobulinemia in patients diagnosed with chronic lymphocytic leukemia, multiple myeloma or non-Hodgkin lymphoma or • Hypogammaglobinaemia associated with therapies targeted at B cells (e.g. anti-CD20, and anti-CD19; such as: monoclonal antibodies, CAR-T or bispecific antibodies in patients with B-cell lymphoma, B-cell acute lymphoblastic leukemia or multiple myeloma and • IgG <4 – 5 g/L (excluding paraprotein) • severe or recurrent infections in medical history	• Antibiotic prophylaxis is typically the first line treatment • IgGs are second line after prophylaxis has been proven ineffective or subeffective after 6-9 months • Most recent evidence points to the highest efficacy of an early IgG treatment as adjunctive to prophylaxis after 3 months from initiation • IgGs replacement therapy should be used asj first line in severe B-cell aplasia	• Initiate at 0.2–0.8 g/kg/4 weeks for a period of 8 to 12 months • Maintenance treatment should depend on clear evidence of benefit • Maintenance at 0.2–0.6g/kg every four weeks to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range
	REIMBURSEMENT COVERAGE				**OUTCOMES and MEASURES**
	• YES • Reimbursed outside of Drug program • In some cases reimbursed outside of Drug Program under cost added to hospitalisation "1c - świadczenia do sumowania"				• Reduction in number of infections • Treatment courses of antibiotics • Days in hospital

TREATMENT PARADIGM 2. **Acquired hypogammaglobulinaemia secondary to haematological malignancies**

1.3 INDICATIONS DEEP-DIVES: HAEMATOLOGY

Immune Thrombocytopenic Purpura (ITP):

OVERVIEW

Immune thrombocytopenic purpura (ITP) is an autoimmune primary disorder of hemostasis characterized by a low platelet count (<100 G/L) in the absence of other causes. ITP) is the most common autoimmune cytopenia in children. Up to 25% of these children develop chronic ITP, and some have significant bleeding symptoms or bleeding risk that requires continuing therapy. The incidence of primary ITP is two to four cases per 100,000 individuals per year, in both adults and children. The prevalence is higher in adults (10 per 100,000 vs. 5 per 100,000 individuals in children) because the rate of chronicity is higher in adult population. About 400 children is newly diagnosed for ITP in Poland each year.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MAXIMUM]

There is a 15% probability of severe bleeding involving hospitalization within 5 years of diagnosis of ITP, even though only 5% of patients are present with severe bleeding at diagnosis. The clinical signs and symptoms of ITP can change depending on the severity of the platelet count and presence of any underlying medical disorders. The most common symptoms include purpura, bruising, nosebleeds, bleeding gums, petechiae, and heavy menstrual bleeding. In rare cases, ITP can cause severe bleeding, such as bleeding into the brain or abdomen. In children the risk of clinically significant bleeding is significantly lower (3%) and CNS bleeding less then 1 %.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGHEST]

Steroids are the standard first line treatment in children and adults. Intravenous immunoglobulin can be used periprocedurally or as first line therapy in combination with steroids. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests corticosteroids rather than IVIg, however this is a conditional recommendation based on low certainty in the evidence of effects.[21,22] IVIg are recommended for patients with active bleeding or when steroids are contraindicated or unsuccessful. The more widely used regimens are 1 g/kg administered 1 or 2 days, or 0.4 g/kg administered 3–5 days in patients >65 years old.[23,24] Nevertheless, alternative patterns have been suggested, such as a single dose of 0.2–0.4/kg, which could be repeated again 3 days afterward in the event of no response.[25] Initial response is good in 70-90%, however in majority of adults and partially in children, the disease relapses, reaching chronic phase (>12 months) in 20-30% of children.

QUALITY OF EVIDENCE:
CEBM scale, confidence in effect vs estimate of effect [MODERATE]

ASH recommendation are currently the most influential for treatment of adults and children with ITP. However, these are conditional recommendation based on low certainty in the evidence of effects.[21,22]

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Immune Thrombocytopenic Purpura (ITP)	• YES • D69.3 indicated for IgG	• Diagnosed using Complete Blood Count (CBC) specific to platelet count • Low platelet count, usually less than 40x10³/L • Blood film- large platelets and small platelet fragments • Platelet Coomb's test to detects anti-platelet antibodies fixed on the patient's platelets • Differential diagnosis to exclude haemolytic uremic syndrome, disseminated intravascular coagulation, paroxysmal nocturnal haemoglobinuria, myelodysplastic syndrome, lymphoproliferative disorders, and infection (HIV, Hepatitis C)	• Eligibility restricted to 4 specific cases: • Life-threatening bleeding • Immediate increase in platelet count is required e.g. emergency surgery • Patient is refractory to all other treatments to prevent haemorrhage (other second line treatments may need to be tested alongside IgG) • Moderate bleeding in patient with high risk of subsequent severe bleed e.g. mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding indicater higher risk of a subsequent severe bleed	• Systemic steroid therapy is the first line treatment • For steroid resistance or steroid dependence there are following options: splenectomy, rituximab or thrombopoietin receptor agonists • IgGs are typically a second- or third-line treatment tailored to specific situations (see Eligibility)	• Adults: 1 g/kg administered 1 or 2 days, or 0.4 g/kg administered 3–5 days in patients >65 years old • 2nd dose may be required if severe or life-threatening (intracranial, pulmonary) bleeding occurs • If a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5-7
	REIMBURSEMENT COVERAGE • YES • Reimbursed outside of Drug Programs				**OUTCOMES and MEASURES** • Increase in platelet count • Resolution of bleeding • Number of bleeding complications • Number of hospitalisations due to bleeding

TREATMENT PARADIGM 3. Immune Thrombocytopenic Purpura (ITP)

Alloimmune thrombocytopenia (foetal, maternal) (FMAIT NAIT):

OVERVIEW

Foetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare immune disorder. FNAIT occurs when the platelets of foetus/neonate are destroyed by the mother's immune cells in the blood stream. It is the leading cause of severe thrombocytopenia in the newborn. It occurs when a woman becomes alloimmunized against foetal platelet antigens inherited from the foetus's father (which are absent on maternal platelets), leading to foetal thrombocytopenia. Prevalence is assumed to be nearer to 1 in 1200 live births.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MAXIMUM]

FNAIT can cause severe complications and long-term disabilities. The main objective of screening is to reduce both the morbidity and mortality associated with FMAIT, primarily by preventing intracranial haemorrhage. The most common manifestation is bleeding into the skin, which may be the only clinical sign in up to 47% of cases. In severe cases, FMAIT may present with bleeding into the major organs, such as gastrointestinal, lung, or ICH, resulting in death or long-term disability. ICH affects between 7% and 26% of all cases of FMAIT. Most of these (nearly 80%) occur during intrauterine life and, of these, 42% occur before 30 weeks of gestation. Mortality rates vary from 1-10%, and long-term complications, including neurological sequelae such as mental retardation, cerebral palsy, cortical blindness, and seizures, may occur in 14-26% of cases.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

Prenatal: The antenatal management of FMAIT remains controversial, and currently involves three treatment options: maternal intravenous immunoglobulin (IVIg), maternal steroid administration, or serial intrauterine platelet transfusions (IUPT). Studies have shown that both maternal IVIg and IUPT can prevent severe thrombocytopenia in the foetus and its related complications.[25,26,27] As first-line treatment, many authors propose administering IVIg (1 g/kg body weight) to the mother at weekly intervals starting at 20 weeks of gestation, depending on the previous history. Some maternal-foetal medicine specialists have suggested using a lower dose of IVIg (0.5 g/kg) and starting treatment between 12 and 20 weeks of gestation. Maternal therapy with IVIg results in a foetal platelet count >50,000/mL in 67% of pregnancies with a history of a prior sibling affected by FMAIT.

Neonatal: Platelet transfusion is the treatment of choice. As additional therapy, some authors have suggested adding high-dose IVIg (400 mg/kg/d for 3-4 days or 1 g/kg/d for 1-3 days) to reduce the time taken for the platelet count to recover.[27,28] IVIg should not be the only treatment because it takes 18 to 24 hours to work.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

Evidence from limited clinical trials[29] shows that IVIg effectively modulates the course of the condition. Pacheco et al 2011, endorsed by Petersen et al, 2013, recommended[30,31] treatment algorithm based on risk stratification if previous pregnancies have been variably affected by FNAIT and maternal alloantibodies are demonstrated against current paternal/foetal antigens.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Immune Thrombocytopenic Purpura (ITP)	• YES • D69.3 indicated for IgG **REIMBURSEMENT COVERAGE** • YES • Reimbursed outside of Drug Programs	• Diagnosed using Complete Blood Count (CBC) specific to platelet count • Low platelet count, usually less than 40x10⁹/L • Blood film- large platelets and small platelet fragments • Platelet Coomb's test to detects anti-platelet antibodies fixed on the patient's platelets • Differential diagnosis to exclude haemolytic uremic syndrome, disseminated intravascular coagulation, paroxysmal nocturnal haemoglobinuria, myelodysplastic syndrome, lymphoproliferative disorders, and infection (HIV, Hepatitis C)	• Eligibility restricted to 4 specific cases: • Life-threatening bleeding • Immediate increase in platelet count is required e.g. emergency surgery • Patient is refractory to all other treatments to prevent haemorrhage (other second line treatments may need to be tested alongside IgG) • Moderate bleeding in patient with high risk of subsequent severe bleed e.g. mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding indicater higher risk of a subsequent severe bleed	• Systemic steroid therapy is the first line treatment • For steroid resistance or steroid dependence there are following options: splenectomy, rituximab or thrombopoietin receptor agonists • IgGs are typically a second- or third-line treatment tailored to specific situations (see Eligibility)	• Adults: 1 g/kg administered 1 or 2 days, or 0.4 g/kg administered 3–5 days in patients >65 years old • 2nd dose may be required if severe or life-threatening (intracranial, pulmonary) bleeding occurs • If a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5-7 **OUTCOMES and MEASURES** • Increase in platelet count • Resolution of bleeding • Number of bleeding complications • Number of hospitalisations due to bleeding

TREATMENT PARADIGM 4. **Alloimmune thrombocytopenia (foetal, maternal) (FMAIT NAIT)**

Autoimmune haemolytic anaemia (AIHA)

OVERVIEW

Autoimmune cytopenia can occur as a single lineage disorder or in combination with other cel lines. Severe autoimmune hemolytic anemia (AIHA) is usually defined by a decrease of haemoglobin concentration below 7 g/dL, and is mediated by the presence of auto-antibodies. AIHA occurring in combination with ITP (immune thrombocytopenic purpura) is known as Evans syndrome. The most frequent causes of AIHA are: infections, malignancies, drug-induced side effects, cellular therapies (e.g. 1-5% patients after allo-HCT), microangiopathies and transfusion of ABO-incompatible blood product. A rare cause of AIHA is the autoimmune lymphoproliferative syndrome (ALPS). AIHA can be presented as warm (wAIHA) or cold AIHA (cAIHA).

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

AIHA are often highly resistant to standard therapy and can be associated with increased risks of high morbidity and mortality, particularly when coexisting with underlying disease or infections. Symptoms and signs include fatigue, pallor, icterus, dyspnea, and circulatory symptoms. AIHA after allo-HCT can be life-threatening and even fatal, and therefore in some patients early diagnosis and prompt intervention is mandatory. Supportive care includes transfusions of leukocyte-reduced and irradiated red blood cell (RBC) concentrates (or pathogen-reduced platelet concentrates, in case of Evans syndrome).

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE to HIGH]

First line treatment of warm AIHA include steroids (prednisolone 1 mg/kg/day) combined with rituximab (375 mg/m2/week) and intravenous immunoglobulins (2 g/kg). [32,33,34,35] The first-line treatment can be repeated in non-responding patients. IgGs are not used in treatment of cold AIHA.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW]

AIHA is a rare disease. Most evidence comes from observational retrospective studies. There is limited amount of guidelines. Most of the drugs used in therapy are off-label. An analysis of 73 patients with autoimmune haemolytic anaemia (AIHA) in 1993 based on three pilot studies and a literature review showed a 40 percent response to IVIg given together with corticosteroids.[36] A lower initial haemoglobin concentration and hepatomegaly were positive correlates of response. Several small case series have suggested a benefit for IVIg in AIHA associated with lymphoproliferative diseases, especially chronic lymphocytic leukaemia (CLL).

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Autoimmune hemolytic anaemia (AIHA)	• NO • D55.3 not indicated for IgG	• A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum lactate dehydrogenase is raised, and there is a reduction in serum haptoglobin	• Symptomatic or severe anaemia, except in patients with co-morbidities, refractory to conventional treatment with corticosteroids, • Corticosteroids contra-indicated, • As a temporising measure prior to splenectomy • Pregnant women with warm AHA refractory to corticosteroids OR with evidence of fetal anaemia.	• IgG are first line treatment of warm AIHA alongside steroids (prednisolone 1 mg/kg/day), combined with rituximab (375 mg/m2/week) • Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.	• 2g/kg in two to five divided doses • Repeated on 1st and 2nd relapse where alternative therapies are not indicated or are contraindicated
	REIMBURSEMENT COVERAGE				OUTCOMES and MEASURES
	• In specific cases reimbursed outside of Drug Programs in off-label procedure				• Rise in haemoglobin • Transfusion independence • Reduction in haemolysis markers (bilirubin, lactate dehydrogenase

TREATMENT PARADIGM 5. **Autoimmune haemolytic anaemia (AIHA)**

Acquired red cell aplasia associated with chronic parvovirus B19

OVERVIEW

Pure red cell aplasia (PRCA) is a syndrome defined by a normocytic normochromic anaemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow. Primary acquired PRCA is an autoimmune disorder that is frequently antibody-mediated. Infections, particularly with B19 parvovirus, are the main cause of secondary acquired PRCA. Human B19 parvovirus is responsible for the aplastic crisis seen in patients with chronic haemolytic disorders such as sickle cell anemia and can produce chronic PRCA in immunocompromised patients. B19 parvovirus directly infects human erythroid progenitors through the red cell surface P antigen (globoside).

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

The signs and symptoms are those associated with anemia, however patient has decreased quality of life and may require frequent blood transfusions. Every patient with diagnosis of PRCA should be tested for B19 parvovirus.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

A diagnosis of B19 parvovirus associated PRCA is an indication for intravenous immunoglobulin as specific and highly effective therapy. A course of intravenous immunoglobulin for this purpose uses the usual therapeutic dose employed for disorders such as immune thrombocytopenic purpura: 2 g/kg usually divided over 5 days (400 mg/kg/d). PRCA corrected after a first course of intravenous immunoglobulin in 93% of patients, but approximately one-third relapsed, at mean time to relapse of 4.3 months.[37]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE]

Secondary PRCA caused by parvovirus B19 is not frequent, however evidence from observational and retrospective study are relatively univocal with good response to treatment with IVIg. Whilst there is no randomised controlled trials for this condition there are many published case studies demonstrating benefit of Ig in the therapy of Parvovirus B19 associated Pure red cell aplasia (PRCA) in over 130 patients with defined Immunosuppressed states.[38,39] These case series suggest doses of 2g/kg are most effective, with most response demonstrated with 1–3 doses. Several small case series suggest potential benefit in patients receiving IgG therapy for refractory PRCA following immunosuppressive therapies.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Acquired red cell aplasia associated with chronic parvovirus B19	• NO • D60.0 not indicated for IgG **REIMBURSEMENT COVERAGE** • In specific cases reimbursed outside of Drug Programs in off-label procedure • Can be reimbursed under cost added to hospitalisation "1c - świadczenia do sumowania"	• Standard diagnosis by Haematologist	• Parvovirus B19 infection confirmed by PCR • Evidence of high viral load, usually above 109 IU/ml • Parvo B19 virus associated pure red cell aplasia (PRCA) in immunosuppressed patient proven by bone marrow biopsy	• Immunoglobulin is an adjunct to transfusion. Chronic parvovirus infection generally occurs on a background of immunosuppressive therapy, primary or HIV-related immunodeficiency and may resolve with a reduction in immunosuppression. • Acute parvovirus infection associated with transient aplastic crisis requires urgent transfusion rather than Immunoglobulin	• 2 g/kg given by divided doses over 2 or 5 days **OUTCOMES and MEASURES** • Rise in haemoglobin • Transfusion independence • Reticulocyte count

TREATMENT PARADIGM 6. Acquired red cell aplasia associated with chronic parvovirus B19

Haemolytic disease of the newborn (HDFN)

OVERVIEW

Haemolytic disease of the newborn (HDFN), also called erythroblastosis fetalis, is a blood disorder that occurs when the blood types of a mother and baby are incompatible. HDFN is relatively uncommon nowadays due to advances in early detection and treatment (In USA approximately 4,000 cases a year). Reported prevalence of HDFN due to any cause is 1695 per 100,000 live births. ABO incompatibility occurs in approximately 20% of births, though only 1% of these newborns develop HDFN. Although RhD immune globulin has become more standardized, approximately 0.1% to 0.4% of at-risk women still become sensitized during pregnancy, most likely due to antigens other than RhD.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MODERATE]

In patients with severe haemolytic anaemia secondary to Rh or ABO incompatibility, hydrops fetalis may develop (skin oedema, pericardial effusions, pleural effusions, and ascites). Additionally, untreated haemolytic anaemia in a neonate will progress from hyperbilirubinemia with jaundice to kernicterus due to unconjugated bilirubin accumulating in the basal ganglia and causing neuronal death.[40] Subsequently, kernicterus can result in neurodevelopmental impairment, sensorineural deafness, spastic cerebral palsy, and death.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE]

Prenatal Management: a maternal-foetal medicine specialist should be consulted when HDFN is identified or suspected in utero for management, including intrauterine transfusions and delivery. Newborn Management: requires blood transfusions, phototherapy and/ort an exchange transfusion. Other treatment modalities have been considered but are still controversial. Intravenous immunoglobulin (IVIg) in the infant may block Fc receptors on macrophages, thereby decreasing the breakdown of antibody-coated RBCs. The AAP recommends IVIg if total serum bilirubin continues to rise despite intensive phototherapy or is within 2 to 3 mg/dL of the exchange transfusion level.[41,42] Administration of IVIg to mothers before delivery has not been shown to be efficacious and is not currently recommended.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

A systematic review in 2014 by Louis et al, (including 12 randomised control trials [RCTs]) reported that combined results of all trials suggest that IVIg can reduce the incidence of exchange transfusion (ET) in infants with haemolytic disease of the foetus and newborn.[41] However, when only the trials at low risk of bias were considered, there was low/limited effect of IVIg on reducing incidence of ET or any other outcome of importance (e.g. peak bilirubin, duration of phototherapy or need for top-up transfusion). Additionally, the trials did not cover the adverse effects such as transfusion related acute lung injury (TRALI), which has a documented increased risk from transfusion of plasma products.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Haemolytic disease of the foetus and the newborn (HDFN)	• NO • NO separate ICD-10 code • ORPHA Code 275938 not indicated for IgG	• Standard diagnosis by Haematologist	• Rising bilirubin despite intensive phototherapy • Prevention of foetal haemolytic disease in women with a previous history of this and confirmed red cell antibodies to current paternal or foetal antigens, to delay the need for intrauterine transfusions • High risk of early foetal hydrops or death	• Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease	• Dose during pregnancy 1 g/kg • Dose for the newborn 0.5g/kg over 4 hours
	REIMBURSEMENT COVERAGE				**OUTCOMES and MEASURES**
	• In specific cases reimbursed outside of Drug Programs in off-label procedure • Can be reimbursed under cost added to hospitalisation "1c - świadczenia do sumowania"				• Bilirubin level • Need for exchange transfusion • Long term morbidity

TREATMENT PARADIGM 7 . Haemolytic disease of the newborn (HDFN)

1.4 INDICATIONS DEEP-DIVES: NEUROLOGY

Guillain-Barré Syndrome (GBS):

OVERVIEW

GBS is a group of acute autoimmune polyneuropathies and a heterogeneous clinical presentation, typically dominated by flaccid paralysis, loss of deep tendon reflexes, and paresthesia that reach maximum severity within up to 4 weeks since onset.[43,44] It is one of the most common causes of acute flaccid paralysis in highly developed countries with incidence 1 to 2/100,000/year.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Approximately 30% of patients with GBS are quadriplegic, another 30% lose ambulation, 33% of patients develop respiratory failure. Autonomic symptoms are present in 60% of cases. 3-10% of GBS patients die, 20% have residual neurological deficit, most will have long-term sequele such as fatigue or paresthesis that interfere with their daily activities.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

Most RCTs have been conducted in GBS patients who were unable to walk. Both IVIg and PLEX are effective treatments in GBS. PLEX was considered an effective treatment for GBS at the time of the first IVIg studies, IVIg was investigated as compared to PLEX. Current EAN/PNS guidelines[45] recommend starting IVIg as soon as possible in patients unable to walk unaided if still within the first 2 weeks from onset of weakness in the standard dose of IVIg (0.4 g/kg/day for 5 days). It is also advised to start IVIg (or PLEX) in patients who are still able to walk unaided within 4 weeks from onset of weakness, but who have a fast rate of deterioration, are at risk of requiring ventilatory support, have swallowing difficulties, autonomic disturbances or poor prognostic factors. In milder GBS patients IVIg can be considered. IVIg in the RCTs was as effective as PLEX, and is generally associated with fewer adverse events. In the patients with treatment-related fluctuations a second course of treatment (either IVIg or PLEX) may be needed. It is strongly recommended against treatment with PLEX followed by IVIg, compared with PLEX or IVIg alone.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE to HIGH]

One systematic review[45] of nine randomised controlled trials (RCTs) of moderate quality found that IVIg hastened recovery in adults with GBS to the same degree as plasma exchange. Cochrane Neuromuscular Disease Group Specialized Register in 2014[46] confirmed that in severe disease, IVIg started within two weeks from onset hastens recovery as much as plasma exchange. Three additional studies, including 75 children, suggested that IVIg significantly hastens recovery compared with supportive care. A randomised controlled trial investigating the effectiveness of a second dose of IVIg showed no benefit[44] and increased adverse events associated with the administration of a second dose.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Guillain-Barré Syndrome (GBS)	• YES • G61.0 indicated for IgG and PLEX	• Diagnosis in line with EFNS/International Peripheral Nerve Society Guidelines • Neurological examination including diminished or loss of deep-tendon reflexes. • Lumbar puncture • Nerve conduction study (NCS) • Other – as appropriate in clinical setting	• Any of the following: • Significant disability (GBS-DS grade 3 or more). • Disease progression towards intubation and ventilation • Patients with mild and/or non-progressive GBS may not require IgG but can be considered for treatment	• IgGs and PLEX (Plasma Exchange) are both first line treatments depending on availability and practicality • No other treatment options are known	• 2g/kg as soon as possible after the diagnosis, over 5 days. • IgG is less likely to be effective if given more than 4 weeks after the onset of symptoms • Second dose is recommended for treatment-related fluctuations only after favourable response to first IVIg treatment • However, if first dose is entirely not effective, then second dose is not recommended as it may be associated with significant potential harm (Walgaard et al., 2021)
	REIMBURSEMENT COVERAGE				OUTCOMES and MEASURES
	• YES • Drug Program Neurology				• No single established outcome measure • Variety of measures/ tools: • Medical Research Council (MRC) sum score, • GBS disability scale (GBS- DS) formerly also known as the Hughes Disability Scale • GBS-DS. grade 3 or more (van Doorn, EAN/PNS 2023) • Inflammatory neuropathy cause and treatment (INCAT) disability scale and sensory sum score and the inflammatory Rasch- built overall disability scale (I- RODS)

TREATMENT PARADIGM 8 . **Guillain-Barré Syndrome (GBS)**

Chronic inflammatory demyelinating polyneuropathy (CIDP) (IgG or IgA associated):

OVERVIEW

Chronic Immune Demyelinating Polyneuropathy (CIDP) is an acquired, immune-mediated neuropathy. It affects peripheral nerves and their roots. Symptoms develop during at least 8 weeks, the course may be relapsing-remitting or progressive. Monophasic course can be seen, especially in children. In rare cases CIDP may have acute (<4 weeks) or subacute (4-8 weeks) onset. Several clinical variants were defined, typical CIDP patient presents with symmetric weakness of proximal and distal muscles, absence of deep tendon reflexes and sensory deficit. CIDP prevalance ranges from 0.7 to 10.3 cases per 100,000 people, with male predminance. Incidence increases with age.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

CIDP patients often present with significant disability caused by muscle weakness and/or sensory ataxia. 30-50% are unable to walk at presentation, long term prognosis worsens with axonal loss. 20-30% of CIDP patients have diabetes or glucose intolerance that increase risk of side effects of treatment with corticosteroids. Currently IVIg, glucocorticoids, or plasma exchange are considered first-line therapies for CIDP, with 60-70% of patients showing favorable response to each of them. If first-choice therapy fails another first-line treatment should be offered. For maintenance therapy IVIg, SCIg, glucocorticoids, or plasma exchange are recommended[47], with option to add azathioprine, mycophenolate mofetil or cyclosporine or rituximab aiming to reduce dose/frequency of IVIg, PLEX or corticosteroids (EAN/PNS 2021, very low certainty evidence). For treatment induction, PLEX and IVIg seem equally effective. It may take up to 3 months for any treatment to show effectiveness (eg. administer three Ig courses). Treatment efficacy shouild be evaluated with objective measures.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

There is little data comparing efficacy of PLEX and IgG as a maintenance therapy. Glucocorticoids may be beneficial in some patients who do not respond to IgG. Long term side effects of chronic corticosteroid use should be considered and measures to reduce dose taken. PLEX is usually considered in the patients who failed to respond to IgG or glucocorticoids, due to practical reasons (vascular access, need for specialized equipment).

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE to HIGH]

Cochrane latest (2024) updated review of RCTs with a total of 332 participants showed significant proportion of patients had short term improvement in disability after IVIg compared with placebo (high quality evidence).[48] One study also confirmed long-term improvement over 24 and 48 weeks. Quality and statistical validity of all the short-listed RCTs were high and, as such, provide sufficient probability of the estimated therapeutic effect.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Guillain-Barré Syndrome (GBS)	• YES • G61.0 indicated for IgG and PLEX	• Diagnosis in line with EFNS/International Peripheral Nerve Society Guidelines • Neurological examination including diminished or loss of deep-tendon reflexes. • Lumbar puncture • Nerve conduction study (NCS) • Other – as appropriate in clinical setting	• Any of the following: • Significant disability (GBS-DS grade 3 or more). • Disease progression towards intubation and ventilation • Patients with mild and/or non-progressive GBS may not require IgG but can be considered for treatment	• IgGs and PLEX (Plasma Exchange) are both first line treatments depending on availability and practicality • No other treatment options are known	• 2g/kg as soon as possible after the diagnosis, over 5 days. • IgG is less likely to be effective if given more than 4 weeks after the onset of symptoms • Second dose is recommended for treatment-related fluctuations only after favourable response to first IVIg treatment • However, if first dose is entirely not effective, then second dose is not recommended as it may be associated with significant potential harm (Walgaard et al., 2021)
	REIMBURSEMENT COVERAGE				OUTCOMES and MEASURES
	• YES • Drug Program Neurology				• No single established outcome measure • Variety of measures/ tools: • Medical Research Council (MRC) sum score, • GBS disability scale (GBS- DS) formerly also known as the Hughes Disability Scale • GBS-DS. grade 3 or more (van Doorn, EAN/PNS 2023) • Inflammatory neuropathy cause and treatment (INCAT) disability scale and sensory sum score and the inflammatory Rasch- built overall disability scale (I- RODS)

TREATMENT PARADIGM 9 . Chronic inflammatory demyelinating polyneuropathy (CIDP) (IgG or IgA associated)

Multifocal motor neuropathy (MMN):

OVERVIEW

Multifocal motor neuropathy (MMN), previously called multifocal motor neuropathy with conduction block (MMNCB), is a rare, acquired, motor neuropathy characterized by progressive asymmetric weakness without sensory symptoms. It typically involves upper limbs more than the lower limbs. Electrodiagnostic studies reveal an asymmetric motor neuropathy with characteristic conduction block. However, some patients with MMN have no detectable conduction block. Other findings that support the diagnosis of MMN are increased signal intensities on T2-weighted magnetic resonance images of the brachial plexus, an increase in the cross-sectional area of the median and ulnar nerves may be seen with high-resolution US (HRUS) and elevated serum anti-GM1 antibodies present in about half of patients with MMN. The prevalence of the disease is estimated to be 0.6 to 2 per 100,000 population, with male predominance.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

MMN is the disease with no proven alternative treatments except for IVIg.[49,50,51] Majority of patients require cyclic IVIg for the whole life, remissions are rare. Different immunomodulatory agents such as cyclophosphamide, mycophenolate mofetil, azathioprine, and rituximab have been reported in the literature with variable results. Corticosteroids and plasmapheresis are ineffective in patients with MMN and may even worsen the clinical course. If untreated most patients develop a progressive worsening of strength, especially in the hands and arms, which can induce difficulties to perform even simple daily tasks. Legs also may be affected leading to difficulty in walking. In some cases the symptoms are mild and patients do not require any treatment.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

High efficacy – marked response to IVIg treatment is one of the characteristic clinical features of MMN and is included in diagnostic criteria. 70-90% MMN patients respond to IVIg treatment (non responders- inactive/ with axonal loss). High safety profile of IVIg with rare severe side effects has been reported in MMN.[50,52] IV administration require professionals (no self administration possibility). SCIg are not approved for MMN treatment and are not included in the drug program in Poland for this indication. IVIg access is available in drug program, limited by occasional IVIg shortages.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE to HIGH]

There is a significant body of evidence from double blind placebo controlled study[50,53] of IVIg treatment in 44 multifocal motor neuropathy (MMN) cases. Additional evidence comes from small to moderate sized unblinded long-term follow-up studies of both treated and treatment naïve cases. A significant difference (P = 0·005) in mean maximal grip strength was observed during IVIg treatment compared to placebo (decline 31.4%). In unblinded follow-up studies improvement was demonstrated in up to 70 percent of cases in grip strength and Medical Research Council (MRC) scores, confirming that IVIg is the most useful agent for initial and maintenance treatment of MMN.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Multifocal Motor Neuropathy (MMN)	• YES • G61.8 indicated for IgG	• Extensive nerve conduction tests to confirm motor conduction block, though it is not required to diagnose MMN, • IgM Anti-GM1 antibodies • MR brachial plexus • Nerve ultrasoud (HRUS) • Response to IVIg treatment is included in diagnostic criteria • Other – as appropriate for differential diagnosis	• Significant functional impairment interfering with normal daily activities and quality of life	• IgG is currently the first and only line of treatment	• Regimens to establish response might include: • 2g/kg given over 2 to 5 days and repeated after 4- 6 weeks. • 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later • If no significant measurable and functionally meaningful objective improvement has been achieved after 3 doses, IgG should be stopped/ considered ineffective • If there is response to treatment dosing in maintenance IgG treatment is guided by clinical response, total doses per month usually vary from 0.4 to 2g/ kg bw
	REIMBURSEMENT COVERAGE				OUTCOMES and MEASURES
	• YES • Drug Program Neurology				• Objective assessment is recommended • Clinically meaningful improvement in any of the following three: • MRC score • Power score from 7 pre-defined pairs of muscles including 4 most affected muscle groups neuro-physiologically • RODS for MMN • Hand dynamometry • INCAT scale • 6MWT instead of standard 10-m walk (in secs) or 6 minutes walk test

TREATMENT PARADIGM 10. Multifocal Motor Neuropathy (MMN)

Non-infective Autoimmune Encephalitides (AIE):

OVERVIEW

Autoimmune non-infective encephalitis (AIE) comprises a group of non-infectious immune-mediated inflammatory disorders of the brain parenchyma often involving the cortical or deep grey matter with or without involvement of the white matter, meninges or the spinal cord. Inflammatory reaction may have paraneoplastic, post-infectious, iatrogenic or idiopatic etiology. In recent years, an increasing number of antibodies targeting neuronal surface or synaptic antigens have been recognised. Epidemiological studies suggest that AIE is possibly as common as infectious encephalitis with an estimated prevalence rate of 13.7/100 000. The onset is usually acute or subacute, but chronic presentation is also possible. Clinical course is usually monophasic, but may be also reccurent. The immune reaction in AE is usually diffuse, resulting in multifocal clinical presentation depending on anatomical localisation and size of inflammation. Main diagnosic procedures includes MR imaging, cerebrospinal fluid (CSF), EEG analysis and antineuronal antibodies in serum and CSF. Some AIE patients do not have any identifiable antibodies (seronegative). Screen for associated neoplasm is necessary. Differential diagnosis is important.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MODERATE]

Early and aggressive immunotherapy is associated with better outcomes (based on several retrospective studies). High-dose corticosteroids (IVMP) are first line treatment in AE. In severe courses combined therapy with IVIg or PLEX is recommended.[54,55] IVIg or PLEX are indicated as an initial therapy in contradictions to IVMP and in lack of response to IVMP if it was used in monotherapy. There are no robust clinical trials comparing the different modalities of acute immunotherapy. If there is no clinical or radiological improvement 2–4 weeks after completion of combined acute therapy, a second-line include rituximab or cyclophosphamide. Ongoing treatment with IVIg may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/ rituximab) are ineffective or contra-indicated.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE]

IVIg is the most frequently used acute immunotherapy if corticosteroids are contraindicated, although some experts consider them less effective than corticosteroids or PLEX. The etiology of paraneoplastic AE associated with antibodies against intracellular antigens is thought to be cell-mediated rather than antibody-mediated, so IVIg in such cases may not always be effective.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW]

The heterogeneity of AE presentation and findings on ancillary testing create difficulties for providing clinical trials and limit the quality of evidence behind AE management.[56] Recommendations are primarily based on expert opinion.[54,55] In the systematic review (retrospective case series) by Nosadini et al (2015)[57], three tenets and common themes were reported:

1. Immune therapy is better than no immune therapy,
2. If a patient fails to respond to first line therapy, second line therapy improves outcomes. Steroids and IVIg are generally considered first line therapy although sometimes plasma exchange is used in addition, or instead of IVIg.
3. No treatment increases the risk of relapse.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Non-infective Autoimmune Encephalitides (AIE)	• YES • G04; G04.8 indicated for IgG	• Clinical judgment based on neurologic and psychiatric symptoms, antineural antibodies, CSF, EEG and MR imaging. • Differential diagnostic is important	• Non-infective encephalitis, with or without underlying malignancy • Functional disability caused by seizures, encephalopathy, motor or sensory deficits, cognitive dysfunction or other relevant neurological sequelae • Evidence of inflammatory CNS disorder including active CSF, EEG defined seizures, MRI imaging changes consistent with AIE, known antibodies etc in the absence of infection	• Prednisolone is first line, with or without Plasma Exchange • In severe courses IVIg may be used in stead of PLEX in combined therapy • IVIg or PLEX are indicated as an initial therapy in contradictions to IVMP and in lack of response to IVMP if it was used in monotherapy. • Ongoing treatment with IVIG may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/ rituximab) are ineffective or contra-indicated	• 2g/kg bw in total or divided (0.4 g/kg/day) for 5 days initially • Futher treatment depends on clinical course – no strict recommendations: doses 1-2g/ kg .
	REIMBURSEMENT COVERAGE				**OUTCOMES and MEASURES**
	• YES • Drug Program Neurology • In some cases G04 reimbursed outside of Drug Program under cost added to hospitalisation "1c - świadczenia do sumowania"				• No validated outcome measures are established- clinical response with MR or CSF assessment: • Reduction of seizure activity • Improvement on one or more validated tests of memory or executive tasks • Clinical neurological examination • Resolution of MR signal change (when present)

TREATMENT PARADIGM 11. Non-infective Autoimmune Encephalitides (AIE)

Myasthenia Gravis (MG) Crisis (MC):

OVERVIEW

Myasthenia gravis is an autoimmune disease of the neuromuscular junction (NMJ). NMJ abnormalities are caused by antibodies against acetylcholine receptor (ACHR) or MuSK protein. MG patients can present with a wide spectrum of severity and variable pattern of muscle weakness and fatiguability ranging from ocular symptoms, to generalized weakness with bulbar symptoms and respiratory compromise. Acute respiratory insufficiency, so called myasthenic crisis (MC), develops in 10-15% of MG patients. This life-threatening event requires acute intervention. IVIg and PLEX have been proven to be effective in MC and imminent MC. Although MG is a lifetime disease for most, 30-50% of patients can reach remission. All others will require variable treatment regimens ranging from symptomatic to long-term immunosuppression. Novel FnRc inhibitor has also recently been added to the drug program B.157 as a second line treatment.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Acute exacerbation of MG can lead to life-threatening episodes, 3-5% of MG patients die due to MC. Availability of rescue treatment in the form of IVIg is therefore a medical necessity.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGHEST]

Treatment options for myasthenia gravis include symptomatic treatment (e.g. anticholinesterase agents), long-term immunosuppressive therapy (e.g. corticosteroids, azathioprine, mycophenolate mofetil), and rapid immunomodulating treatments (e.g. IVIg, PLEX). Studies indicate that IVIg and PLEX are comparable in effectiveness for MC. IVIg, are more accessible and potentially cost-effective option.[58] Alternative highly effective treatment options include involve novel drugs such as C5 inhibitors, FnRc inhibitors. However, these treatments are not widely available in Poland yet, and currently not recommended for acute exacerbations.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE to HIGH]

A number of controlled trials (7) have demonstrated the efficacy of short-term IVIg use (1 to 5 days) in the management of acute exacerbation of moderate to severe myasthenia gravis.[58,59] There is insufficient placebo-controlled evidence for the use of IVIg as a steroid-sparing agent or before thymectomy in stable MG. Current international guidelines recommend the use of immune globulin IV as adjunctive therapy for the treatment of acute exacerbation of myasthenia gravis based on controlled trials and expert consensus.[60,61,62]

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Myasthenia Gravis (MG) Crisis (MC)	• YES • G70.0, G73.2 indicated for IgG and PLEX	• Antibody testing (anti ACHR, anti-MuSK) • Electrophysiology (Repetitive Nerve Stimulation, SFEMG) • CT or MRI of mediastinum (thymus evaluation)	• As rescue treatment in myasthenic crisis or imminent myasthenic crisis, for exacerbations during pregnanacy, as a bridging therapy. • Not for chronic MG treatment	• IVIg or PLEX can be used as rescue therapy • IVIg prefered for pregnant women and children	• 2g/kg bw in total or divided (0.4 g/kg/day) for 5 days initially • Additional treatment course can be administered based on clinical course –: doses 1-2g/ kg . • If no significant measurable and functionally meaningful improved in abilities has been achieved, IVIg should be stopped and PLEX considered as rescue therapy
	REIMBURSEMENT COVERAGE				OUTCOMES and MEASURES
	• YES • Drug Program Neurology (as rescue therapy)				• No obligatory efficacy criteria • Clinical stabilization/ improvement (eg. MGFA class, MG-ADL, other scales can be used) • Respiratory function and dysphagia screening recomended

TREATMENT PARADIGM 12. Myasthenia Gravis (MG) Crisis (MC)

1.5 INDICATION DEEP-DIVES: RHEUMATOLOGY / INFLAMMATION

Kawasaki Disease:

OVERVIEW

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute (FEBRILE) systemic vasculitis of the medium-sized arteries (inflammation of the blood vessels) that mainly affects children. Symptoms include fever, chapped lips, strawberry tongue, red eyes (bulbar conjunctival injection), rash, redness, swollen hands and feet and enlarged cervical lymph nodes.[63] High fevers and systemic inflammation characterise the acute phase. Inflammation of the coronary arteries causes the most serious complication of the disease, coronary artery abnormalities or aneurysms (CAAs), often leading to sudden death. KD is the leading cause of acquired heart disease in children in developed countries.[64] The acronym FEBRILE denotes the following manifestations: Fever, Enanthem (mucous membrane rash), Bulbar conjunctivitis, Rash, Internal organ involvement, Lymphadenopathy, Extremity changes.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Approximately 25% of untreated patients develop cardiac sequelae, including CAAs. Aneurysms develop in 3-5% of patients treated with IVIg before the 10th day of illness. Other serious cardiovascular complications include: diffuse coronary artery ectasia, heart failure or myocardial dysfunction, myocardial infarction, pericarditis with small pericardial effusions (occurs in 25% of patients with acute illness), systemic arterial aneurysms and rupture of coronary artery aneurysms with hemopericardium. Rarely, patients may also be shocked and have features of toxic shock syndrome, termed 'Kawasaki disease shock syndrome.[65] Without the IgG treatment the unmet medical need is high, as no alternative treatment modality has proven effective.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGHEST]

IgG is currently the only known effective treatment, with 85-90% of KD patients responsive, 80% of whom reaching fever resolution within 1.5-2 days. IgG relieves acute inflammation and has been shown to reduce the rate of CAAs from approximately 25% in untreated patients to 3-5% in treated patients.[63,64,66] The available evidence also indicates that high-dose IVIg regimens are associated with a reduced risk of CAA formation compared to medium- or low-dose IVIg regimens.[66]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [HIGH to MODERATE]

The body of evidence concerning the efficacy and safety of IgG treatment for KD is extensive, with at least 59 RCTs.[63,66] The meta-analysis of IVIg versus placebo, including all children, showed a significant decrease in new coronary artery abnormalities (CAAs) in favour of IVIg, at thirty days RR (95% CI) = 0.74 (0.61 to 0.90). Additionally, the 2017 international guidelines[64] provide further detailed comparisons including dosing variations and adjunct treatment modalities.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Kawasaki Disease	• YES • M30.3 indicated for IgG **REIMBURSEMENT COVERAGE** • YES • Reimbursed outside Drug Program	• Exact etiology is unknown • Hyperinflammation syndrome, a form of vasculitis, of unknown cause that results in fever and mainly affects children under 5 years of age • Clinical diagnosis of PIMS-TS in children • Clinical diagnosis of PIMS-TS in an adult (MIS-A or AIMS-TS) • Diagnosis of complete KD requires fever of at least 5 days' duration along with 4 or 5 of the principal clinical features: extremity changes, polymorphous rash, oropharyngeal changes, bilateral, nonexudative, limbic sparing, painless bulbar conjunctival injection, acute unilateral nonpurulent cervical lymphadenopathy with lymph node diameter greater than 1.5 cm • Echocardiography is the study of choice to evaluate for coronary artery aneurysms CAAs	• The are strong similarities between PIMS (paediatric multisystem inflammatory syndrome) and Kawasaki disease: the use of IVIg ought to be considered for any child fulfilling diagnostic criteria for PIMS • Therapy should be initiated within 10 days of fever onset; however, children who present after 10 days of fever still should be treated if fever or other signs (including raised acute phase markers, such as CRP) of persistent inflammation are present • No contraindications known to date	• IVIg in combination with anti-inflammatory doses of Aspirin is the treatment of choice • Medium- (30-50 mg/kg/day) to high- (80-100 mg/kg/day) dose aspirin divided four times daily in the acute phase, typically first 14 days • IV methylprednisolone can be administered prior or after IVIg (not concurrently)	• 2g/kg single dose, in conjunction with high-dose aspirin; a second dose may be given if no response, or if relapse within 48h • Impaired cardiac function necessitates the administration of a prolonged treatment dose **OUTCOMES and MEASURES** • Resolution of fever • Improvement in acute phase markers

TREATMENT PARADIGM 13. Kawasaki Disease

Inflammatory Myopathies-Dermatomyositis (DM)/ Polymyositis (PM)/ Necrotizing autoimmune myopathy (NAM):

OVERVIEW

Inflammatory myopathies are a heterogeneous group of idiopathic disorders, characterized by muscle cell infiltrations and specific alterations of the muscle fibres. These disorders are commonly divided into polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myopathy (NAM) and inclusion body myositis IIBM). DM typically occurs in both children and adults, whilst other myositis mostly develop in middle aged or elderly individuals. Majority of patients with myositis typically present with a subacute onset of weakness of arms and legs and clearly elevated creatine kinase in the serum. PM, DM and most patients with NM usually respond to immunosuppressive medicines, especially if IgG is also administered as an adjunct therapy.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MODERATE to HIGH]

All forms of inflammatory myopathies (DM, PM and NAM) are associated with an increased risk of malignancy, 2-7 times higher than general population. Additionally extramuscular organs can be affected including lung, heart, and joints. The association with malignancy and multi-organ pathology indicates a moderate to high disease burden. Specific to DM, patients present with signs of inflammation of the skin such as a Gottron papules, a periorbital oedema, and erythema of the face, heliotrope rash of the eye lids, shawl and V-sign.[67] Both the DM and PM manifest muscle inflammation which causes proximal weakness and impaired walking and/or climbing stairs as well as lifting their arms or heavy objects, with elevation of muscle enzymes. Unlike DM, a rash or other signs of inflammation of the skin do not occur in PM. Necrotizing autoimmune myopathy (NAM) is often more acute and more severe compared to DM and PM, especially in terms of acute or subacute proximal weakness of arms and legs and the elevation of muscle enzymes; usually very high, 20–50 times elevated. Severe NAM in most cases leads to dysphagia, cardiomyopathy, muscular atrophy and interstitial lung disease (ILD). In most of the available case studies, corticosteroid and/or immunosuppressive treatments are only moderately effective as monotherapy; with significant improvement when IgG is added to the treatment modality. The disease burden and the status of alternative therapies all indicate a moderate to high unmet medical need across all myopathies.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

Based on limited evidence, IgG significantly improves treatment results with glucocorticosteroids and/or immunosuppressive therapy.[68] Between 60-80%[68,69] of DM and PM patients treated with the combination of steroids and IgG show significant improvement in muscle power, muscle disability scores and creatine kinase levels. Additionally inclusion of IgG allows for reduction of the otherwise high steroid dosing or for complete discontinuation of the steroid therapy.[70] In NAM, specifically, IgG have been reported as an important rescue therapy in some patients, until other immunosuppressive agents become effective.[69]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

The evidence pertaining to IgG efficacy and safety is of moderate quality, highest for DM and lowest for NAM: only one double-blind, placebo-controlled trial of 15 patients with biopsy-confirmed, treatment-resistant DM; several case series for PM (totalling 35 refractory patients) and only small-scale case studies for NAM, without specific IgG focus.[69]

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Inflammatory Myopathies-Dermatomyositis (DM)/ Polymyositis (PM)/ Necrotizing autoimmune myopathy (NAM)	• YES • G72.4, M31, M33.1, M33.2, indicated for IgG **REIMBURSEMENT COVERAGE** • YES • Drug Program Neurology • Some cases reimbursed outside of Drug Program (M31)	• PM, DM and NAM are a group of multisystemic autoimmune disorders, characterised by muscle cell infiltrations and specific alterations of the muscle fibers • PM, DM and NAM belong to a spectrum of syndromes known as myositis disorders or inflammatory myopathies • They are diagnosed by muscle biopsy showing muscle cell infiltrations and specific alterations of the muscle fibers • Electromyogram (EMG) is also used alongside biopsy • In younger children, the combination of a characteristic rash, raised muscle enzymes, an objective measure of muscle weakness e.g. Childhood Myositis Assessment Scale (CMAS) are sufficient as diagnosis with or without the biopsy	• Any of the following: • Patients with significant muscle weakness or dysphagia unresponsive to corticosteroids and other immunosuppressant agents in adults with biopsy-proven PM or DM or NAM or children with clinical, biochemical and imaging abnormalities consistent with definite PM or DM or NAM • Also, DM patients with refractory skin involvement	• If progression is not rapid steroids should be considered the first line • IVIg should be used as an adjunct to any second line immunosuppressive therapy • Patients with myositis-specific antibodies: rituximab should be considerd second line • Patients with refractory idiopathic myositites: abatacept should be considered second line or third line after rituximab, alongside the adjunct IVIG therapy	• An initiation of a maximum 4g/kg divided into two or three courses of 1-2 g/kg each, and delivered within 8-week period • Assessment after 6-8 weeks since initiation • After initiation continue with 2g/kg delivered over 4 to 5 days and repeated after 6 weeks • The need for maintenance treatment in resistant juvenile dermatomyositis should be determined on an individual basis **OUTCOMES and MEASURES** • DM: functional/disability scores (ADLs): ○ semi-quantitative muscle scores (MRC sumscore) ○ other quantitative muscle strength (MMT8) ○ up and go 10-m walk (in secs) ○ CDASI, CAT or DAS, FVC, CHAQ • PM and NAM: functional/disability scores (ADLs): ○ semi-quantitative muscle scores (MRC) ○ other quantitative muscle strength (MMT8) ○ up and go 10-m walk (in secs) ○ HAQ, FVC • PM,DM and NAM: ○ Improvement in symptoms of dysphagia incl. speech pathology, tolerance of food textures and/or reduced episodes of aspiration

TREATMENT PARADIGM 14. Inflammatory Myopathies-Dermatomyositis (DM)/ Polymyositis (PM)/ Necrotizing autoimmune myopathy (NAM)

1.6 INDICATION DEEP-DIVES: DERMATOLOGY

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN):

OVERVIEW

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, acute, T-cell mediated, adverse cutaneous drug reactions on a severity spectrum primarily defined by the extent of epidermis detachment from dermis and the increasing mortality rate. SJS is characterised by less than 10% body surface area skin detachment and has been reported to have a mortality rate between 1% and 5%[71] (some early studies suggest significantly higher mean mortality rate of 10% amongst the elderly[72]). SJS/TEN overlap refers to detachments between 11% and 29% of the body surface area, with mortality of 20-25%. TEN has the greatest skin detachment area of >30% and has a mortality ranging from 25% to as much as 50%. In over 90% of SJS and TEN cases 2 or more mucous membranes are also involved. Common complications concern a large range of organ systems: respiratory, gastrointestinal/hepatic, oral, otorhinolaryngologic, gynaecologic/genitourinary, and renal. Morphologically, both SJS and TEN are characterised by necroptosis and apoptotic keratinocyte cell death, mediated by Fas receptor and its ligand FasL. Main mortality co-variants are the extent of epidermis detachment area and age of the patient.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH to HIGHEST]

SJS and TEN patients experience high to extremely high individual disease burden, exponentially increasing across the severity spectrum. Mortality rates of up to 50% (can exceed 50% in the immunocompromised and the elderly) and patient reported quality of life at the onset of the disease at 0.1-0.3 (on a scale from 0 to 1 where 0 means death) indicate high to maximum unmet medical need. SJS and TEN numerous complications, including multi-organ failures, extend the duration of the disease burden beyond the acute phase of the disease and severely impact patient's psycho-social functioning.[73,74,75]

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

There is no single effective treatment modality, but options include one of, or a combination of the following: systemic steroid, plasmapheresis, cyclosporin, anti-tumor necrosis factor-alpha (TNF-alpha), and intravenous immunoglobulin (IVIg). IVIg efficacy is best documented[71,73,74], whereby early, high-dose infusions are reported to have the greatest efficacy in cessation of epidermal and mucous detachment (as quickly as 2 days from initiation of treatment), and are linked to a significant decrease in mortality by ~15-20%. Overall, IVIg use in SJS and TEN has not been reported to have any significant safety or tolerability issues. Most studies suggest that efficacy is further improved if IVIg is combined with corticosteroid therapy - network meta-analysis (NMA) showed that IVIg and corticosteroids combination therapy was the only treatment with significant survival benefits (standardized mortality ratio, 0.53; 95% CI, 0.31-0.93).[76]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

All the reported clinical data regarding the use of IVIg are based on isolated cases or series of cases in a form of observational studies. The rarity of TEN cases makes it extremely challenging to achieve high-standard randomized controlled clinical trials to test the efficacy of the IVIg and combination treatment modalities. A 2013 paper analysing survival rates[77] and the most recent meta-analysis (2016)[74] provide a useful perspective on IVIg efficacy in TEN versus SJS, whereby the former shows greater magnitude of therapeutic effect.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	• NO • L51.2 not indicated for IgG	• Histological evaluation of the skin biopsy • Immunofluorescent analysis to differentiate TEN from other dermatological diseases • No specific blood tests for TEN or SJS but erythrocyte sedimentation rate, coagulation studies, urea and electrolytes, and liver function should be used to establish full therapy (e.g. organ failure) • The main differential diagnosis is erythema multiforme major (EMM) • The score of TEN (SCORTEN scale)[1] can also be used to assess the severity of illness and to predict mortality rate	• Reported efficacy is highest in early IVIG interventions, typically no later than 72h since the first skin detachment symptoms • Disease progression towards intubation and ventilation	• PLEX administered for 3 days and prior to IVIG to enhance the elimination of the causative medication • First line treatment for TEN (skin detachment >30%) and SJS/TEN (skin detachment >10%<30%) • Second line or adjunct treatment for SJS where extent of skin detachment is <10% • In both cases, IVIG should be accompanied by steroids, and/or plasmapheresis • Cyclosporin should be avoided in patients with kidney injury (kidney function is a critical component of SCORTEN scale) • TNF- alpha inhibitors can be considered if TNF- alpha is overexpressed in the affected keratinocytes	• For TEN consider very high dose of IVIG at 3 g per kg body weight distributed over 3 days; following detachment cessation a dose of 1g per kg body weight for subsequent 2 days • For SJS/TEN a high dose of IVIG at 2g per kg body weight distributed over 3-4 days • For SJS a dose of IVIG at 1g per kg body weight distributed over 3 days
	REIMBURSEMENT COVERAGE • CONDITIONAL • Off-label severe TEN cases reimbursed outside of Drug Program (M31) • Off-label SJS typically not reimbursed				**OUTCOMES and MEASURES** • Reduction in secondary infections • Reduction in lesions • Re-epithelialisation of the papuloerythematous and ampullary lesions • Mean time to cessation of skin and mucosal detachment • Survival rate

TREATMENT PARADIGM 15. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Autoimmune bullous dermatoses (AIBD) incl. Pemphigus Vulgaris (PV), Pemphigoid and Linear IgA bullous dermatosis (LABD):

OVERVIEW

Autoimmune bullous dermatoses (AIBDs) are an immunopathologically heterogeneous group of diseases with varied etiology, including medication triggers, skin trauma, malignancy and gastrointestinal disorders, characterised by blisters or erosions of the skin and/or mucous membranes. These dermatoses are further sub-divided into pemphigus, when the blistering is intraepidermal, and pemphigoid when the blistering is subepidermal.[78,79] Apart from the pemphigus/pemphigoid division, a separate pathology has been recently identified as Linear IgA bullous dermatosis (LABD), characterised by subepidermal blisters and unique linear IgA basement membrane antibody deposition.[80,81] Many of the LABD cases are drug-induced, the disease course is acute and resolves best if the culprit medication is swiftly discontinued. Pemphigoid and Pemphigus are chronic diseases with high morbidity, whereby protein and fluid loss and systemic infections contribute to mortality.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MODERATE to HIGH]

In pemphigus vulgaris (PV), the mucous membranes are always affected, including primarily the oral cavity, with erosions manifest on the mucosa of the pharynx, larynx, esophagus, and genitalia. In about half of the cases, flaccid blisters and erosions also appear on the skin, which may involve large areas and often leads to secondary infections. Prior to the use of corticosteroids, PV had a mortality of over 80%[78], with current mortality still approximately three times higher than in the general population. In bullous pemphigoid the mucous membranes of the mouth and the conjunctiva are particularly affected, less frequently mucous membranes of the nose, pharynx, anogenital region, larynx, esophagus, and trachea, with only 25-30% of patients also presenting erosions and blisters on the skin. The scarring following the healing of the lesions can lead to blindness, difficulties in breathing, dysphagia, and, in most severe cases, aphasia. Bullous Pemphigoid, prior to the introduction of systematic IgG therapy, had a 5-year probability of death of 60%. The overall unmet medical need in PV and Pemphigoid is considered moderate as multiple effective treatment modalities are available, including recent EMA-approved use of rituximab for severe cases. Linear IgA bullous dermatosis (LABD), if severe, can present as toxic epidermal necrolysis (TEN), a cutaneous adverse drug reaction, with mortality rate of as much as 50%. However, for mild and moderate cases, the disease usually improves or clears when treated with dapsone, an immunomodulatory sulphone, within just 2 to 3 days of drug initiation.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE to HIGH]

IgG has been evaluated as a useful therapeutic alternative to conventional modalities, especially if administered in high doses early after diagnosis.[82,83] IgG is most commonly used as a second- or third-line treatment in majority of the autoimmune dermatoses (e.g. pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita and systemic lupus erythematosus). However, the most recent literature[80,82,84] suggests IgG as the first-line treatment, warranted in special circumstances like concomitant malignancy, a foudroyant clinical course, and contraindications against and/or side effects of alternative treatments.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [MODERATE]

Due to the rarity and severity of autoimmune skin blistering diseases, well-designed prospective trials are generally lacking. There is, however, a growing body of evidence based on meta-analyses and series of case studies from the last 10-15 years of systematic use of IgG treatments across different jurisdictions.[85,86,87,88] Two randomized controlled trials demonstrated efficacy in treating pemphigus and bullous pemphigoid with IVIg at 4-week intervals in combination with conventional therapies of systemic steroids and immunosuppressants.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Autoimmune bullous dermatoses (AIBD) incl. Pemphigus Vulgaris (PV), Pemphigoid and Linear IgA bullous dermatosis (LABD)	• YES • L10 indicated for IgG • L12.0 not indicated for IgG • L13.9 not indicated for IgG **REIMBURSEMENT COVERAGE** • YES for L10 • CONDITIONAL for L12, L13 • Reimbursed outside of Drug Program	• Joint clinical, histopathologic, and laboratory studies • Direct IF allows a differentiation between pemphigoid diseases with linear deposits on the basement membrane, pemphigus diseases with intercellular fluorescence in the epithelium and LABD with linear deposits of IgA at the dermoepidermal junction along the basement membrane • Serum IgG against Dsg 1, Dsg 3	• Reported efficacy is highest in LABD and severe or refractory Pemphigus Vulgaris • IVIG typically used as adjunctive therapy due to the possibility of symptom rebound upon weaning or discontinuation	• Pemphigus Vulgaris first line treatment is typically corticosteroids, alone or in combination with steroid-sparing immunosuppressants or infusions with rituximab (moderate to severe) • Pemhigoid first line is topical clobetasol proprionate (mild cases) or prednisolone plus dapsone or doxycycline (severe cases) • IgG until recently has been considered an adjunct therapy or third line therapy for patients not responding rituximab • High dose IgG alongside steroids can be considered first line treatment in severe or refractory Pemhigus and Pemphigoid • High dose IgG as a first line in LABD is also widely accepted	• 1-2 g per kg body weight distributed over 2–5 days • Maintenance IgG every 4 weeks for patients unresponsive to rituximab **OUTCOMES and MEASURES** • Reduction in secondary infections • Reduction in lesions • Resolution of blisters/ healing affected skin • Resolution of pruritus • Decrease on a scale of Pemphigus Disease Area Index (PDAI)

TREATMENT PARADIGM 16. Autoimmune bullous dermatoses (AIBD) incl. Pemphigus Vulgaris (PV), Pemphigoid and Linear IgA bullous dermatosis (LABD)

Scleromyxedema

OVERVIEW

Scleromyxedema is a rare cutaneous mucinosis. Its initial manifestation is often in middle-aged patients with papules and sclerodermiform indurations of the skin. It is virtually always associated with monoclonal gammopathy and often transitions to hematooncological diseases such as multiple myeloma. The disease may affect extracutaneous organs and has an unpredictable course, though in majority of cases it will progress over a number of years with increasing severity of multi-system co-morbidities, which may ultimately lead to death.[89]

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Scleromyxedema is a rare condition with an estimated prevalence of approximately 1 in 1,000,000 individuals. Whilst the pathogenesis information is limited, the most widely explored is the relationship between the mucin deposition and the monoclonal immunoglobulins. The disease has a relatively large number of complications impacting patient quality of life, such as affection of the nervous system and the cardiovascular system, and less frequently the gastrointestinal system and the respiratory system. Febrile neurological complications can also progress to epileptic seizures and coma and may result in death. The actual mortality rate is difficult to establish given the very limited data, coming predominantly from case studies. According to the guidelines, the first and the most effective line of treatment is high-dosed IVIg. The second line is typically Thalidomide as monotherapy or, more commonly in combination with IVIg. Other therapies reported in case studies as suggesting promise included bortezomib and stem cell transplantation.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [HIGH]

The best evidence for treatment efficacy comes from high-dose intravenous immunoglobulin (IVIg), supported by two small, uncontrolled prospective trials. In addition to these prospective studies, there are two retrospective multicenter studies involving 8 and 30 patients, respectively, who were treated with IVIg, systemic corticosteroids, thalidomide, melphalan, and stem cell transplants.[90,91] Based on the results of the aforementioned studies, about 35% of patients treated with IVIg achieved a complete response with no residual signs of scleromyxedema, while 65% showed a partial response. However, the response is not permanent and maintenance infusions are required.[91] The type and frequency of adverse effects associated with IVIg treatment did not differ significantly from those observed in patients treated with IVIg for other medical indications. For this reason, the European consensus recommends IVIg as the first-line treatment for scleromyxedema.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

Since scleromyxedema is very rare, randomized, controlled clinical trials are not feasible. Prognostic outcomes of therapy in this condition are poorly understood as the literature is limited to case reports or small series.

INDICATION	REGULATORY STATUS	DIAGNOSTICS	IgG ELIGIBILITY	IgG POSITION vs. ALTERNATIVE THERAPIES	DOSING and MAINTENANCE
Scleromyxedema	• NO • L98.5 • ORPHA: 167635 **REIMBURSEMENT COVERAGE** • CONDITIONAL for L98.5 • Reimbursed outside of Drug Program	• Diagnosis made by Dermatologist • Joint clinical, histopathologic, and laboratory studies • Skin biopsy and confirmed absence of thyroid disease • Systemic manifestations of disease are present	• Moderate to severe scleromyxedema proven by skin biopsy and confirmed absence of thyroid disease OR • Unresponsive to standard corticosteroid therapy and at least one other immunosuppressant • Immunosuppressant medication resulted in unacceptable side effects or significant toxicity • Corticosteroid and/or immunosuppressant medication are contraindicated	• First and the most effective line of treatment	• Induction dose (IVIg) - 2 g/kg over 5 days • Maintenance dose (IVIg) - 0.5 to 2 g/kg over 2 to 5 days, four to six weekly, or longer. • A maximum dose of 2 g/Kg may be given in any 4 week period. **OUTCOMES and MEASURES** • Reduction in the number of lesions and severity of disease compared to the last assessment • Improvement in or stabilisation of disease compared to the previous assessment

TREATMENT PARADIGM 17. Scleromyxedema

1.7 DISCUSSION

The application of the Appropriate Use Framework to the current IgG therapeutic landscape in Poland has revealed several important considerations. Firstly, the list of diseases and conditions that ought to be routinely treated with IgG (as first-line or adjunctive therapy) significantly exceeds the scope of the two main Drug Programs (Primary Immunodeficiencies and Neurology). This clearly indicates the need to either consider the creation of new Drug Programs for Secondary Immunodeficiencies, Haematology, Rheumatology and Dermatology, or the reformulation of the general reimbursement rules applicable to these disease areas. These new Programs, to maximise their clinical, academic and socio-economic benefits, should be systemically combined with RCTs and/or Real World studies to generate robust local evidences, where data is currently limited, and to boost local research into alternative treatment modalities and protocols, thus contributing to the Polish and, potentially, the European guidelines. To make these new or updated guidelines maximally effective, they need to be better correlated with the specific ORPHA codes, instead of the general ICD-10 codes, to ensure the correct link to the right diagnostic tools and differential diagnosis, to the delineated eligibility criteria and to the detailed IgG dosing regimens as well as the precise sets of measures and outcomes. All in all, the above steps and actions should also help estimate the actual volume of IgGs required in Poland, not driven simply by their current use (i.e. demand), but rather quantified using objective epidemiological data (i.e. medical need).

1.8 CONCLUSIONS

This paper has been designed to systematise current knowledge and orchestrate current therapeutic approaches to immune deficiencies and immune-mediated conditions in Poland. As such, it should not be treated as the final and the definitive set of guidelines, but rather as an initial guidance and as a starting point for a deeper evaluation of IgGs and research into new and promising indications where IgGs might be used appropriately. The final guidance on the appropriate use of IgGs is a result of a robust methodology, whereby after the extensive literature review experts in the field were asked to contribute real-world experience and local protocols, especially when different from international guidelines, and were then followed by a series of individual interviews and virtual correspondence to reach the final approval of the panel of all contributing experts.

The growing medical need for plasma derived medicines and the finite and often insufficient supply of Immunoglobulins should also be seen as an urgent call for action for policy-makers to work towards a radical improvement in plasma collection and fractionation to reach strategic autonomy; a situation where all patients will always receive appropriate and reimbursed access to these life-saving and essential medicines.

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2.0 APPENDIX:

OVERVIEW OF INDICATIONS SUGGESTING BENEFIT OF IgG, WHERE EVIDENCE IS TOO LIMITED TO ASSIGN "APPROPRIATE USE" AND

TREATMENT PAREADIGMS

Post-transfusion purpura

OVERVIEW

Post-transfusion purpura (PTP) is a delayed adverse reaction to a blood transfusion or platelet transfusion that occurs when the body has produced alloantibodies to the allogeneic transfused platelets' antigens. These alloantibodies lead to thrombocytopenia. PTP usually presents 5–12 days after transfusion, and is a potentially fatal condition in rare cases. Approximately 85% of cases occur in women. Occurring in roughly 1 in 100,000 transfusions, posttransfusion purpura (PTP) is a rare, self-limited thrombocytopenia occurring 5 to 10 days after transfusion in patients lacking a specific platelet antigen, usually HPA-1a (GPIIIa, CD61).[93,94] After reexposure with transfusion, patients can develop potent antibodies against the platelet-specific antigen that they are lacking but which is present on donor platelets. Severe thrombocytopenia can help distinguish PTP from heparin-induced thrombocytopenia, which can also be considered in the differential diagnosis when thrombocytopenia develops 5 to 10 days after combined heparin exposure and blood transfusion.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [MODERATE]

The thrombocytopenia can be marked with a platelet count falling below 10,000/mL. The onset is sudden, although self-limited, and usually resolves in 2 weeks.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE]

IVIg appears to be an effective treatment, although plasma exchange, steroids, and splenectomy also may be useful.[95,96] Patients with acute bleeding and needing platelet support should receive platelets without the platelet-specific antigen, if possible. If random donor platelets are given, patients can develop severe inflammatory reactions.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW]

The evidence is limited to cases and case series. Due to the rarity and acute presentation RCTs are not available.

Generalized morphea

OVERVIEW

The generalized variant of circumscribed scleroderma is diagnosed when at least three anatomical localizations are affected. The most common localizations are the trunk, the thighs and the lumbosacral region. Compared to localized morphea, generalized morphea is characterized by a much more rapid progression. Disabling pansclerotic morphea presents an extraordinary variant of generalized morphea, which are associated with significant impairment in activities of daily life, quality of life and significant risk of death due to respiratory failure caused by fibrosis of the skin and subcutaneous tissue, which impairs the function of the respiratory muscles of the chest.[97] Treatment of generalized morphea is challenging due to the rarity, the heterogeneous clinical spectrum and the variable course of disease.

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Generalized morphea is a rare disease with an incidence of approximately 0.5 cases per 100,000 people annually.[98] Generalized morphea patients experience high to extremely high individual disease burden. The condition significantly reduces patients' quality of life. Fibrotic skin restricts both active and passive joint mobility, making it impossible to perform daily activities. Moreover, fibrotic skin tends to crack, leading to the formation of painful wounds and increasing the risk of secondary, including systemic, infections. Involvement of the skin, subcutaneous tissue, and chest wall muscles may result in respiratory failure and death.[97] First-line treatment for generalized morphea involves systemic glucocorticoids (typically administered as pulses) combined with methotrexate.[99] However, for many patients, this approach is suboptimal, and the disease continues to progress.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE]

To date, the efficacy and safety of intravenous immunoglobulins (IVIg) in patients with generalized morphea have been confirmed based on the presentation of several case reports and small case series.[100] Almost all patients treated with IVIg had previously undergone systemic glucocorticoid therapy combined with methotrexate or mycophenolate mofetil, which failed to halt disease progression. In the reports, patients received IVIg doses of 2 g/kg per cycle, administered over 3–5 days. The cycles were typically repeated monthly for 6–8 consecutive months. Following this treatment, complete remission of skin and subcutaneous tissue lesions was observed in just over 50% of the patients. Partial improvement was reported in approximately 25% of cases. The treatment was well-tolerated and not associated with significant adverse effects. [101,102,103]

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW]

All the reported clinical data regarding the use of IVIg are based on isolated cases or series of cases in a form of observational studies. The rarity of generalized morphea makes it extremely challenging to achieve high-standard RCTs to test the efficacy of the IVIg and combination treatment modalities.

Cutaneous scleroderma

OVERVIEW

Scleroderma or systemic sclerosis (SSc) is a multisystem autoimmune disease that though rare, affects 30–240 people/million worldwide, and is associated with significant morbidity and mortality. Though incompletely understood, the pathogenesis of SSc is thought to result from both a genetic predisposition and environmental exposure that together dysregulate the immune system, leading to excessive collagen production and microvasculopathy. This results in progressive fibrosis of the skin and internal organs, leading to multiple disease manifestations.[104]

(UNMET) MEDICAL NEED: disease burden and alternative treatments [HIGH]

Systemic sclerosis is a disease that can involve not only the skin but also various internal organs. It is suggested that treatment should be individualized for each patient, taking into account both the disease activity and the specific internal organs affected. For the management of interstitial lung disease associated with systemic sclerosis, systemic cyclophosphamide, mycophenolate mofetil, and more recently, nintedanib are recommended. In cases of coexisting pulmonary hypertension, phosphodiesterase

type 5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs are advised.[105] Treating skin involvement poses a significant challenge. First-line therapy includes methotrexate or mycophenolate mofetil. However, in some patients, skin sclerosis continues to progress despite treatment.

ADDED THERAPEUTIC VALUE: efficacy, safety and practicality [MODERATE to HIGH]

To date, the efficacy and safety of IVIg in treating skin sclerosis in systemic sclerosis have been evaluated in 11 scientific studies (7 retrospective, 3 prospective, including 1 randomized double-blind trial, and 1 case series), involving a total of 344 patients. In most of the patients described in these studies, no improvement was observed following first-line treatment. IVIg was typically administered at a dose of 2 g/kg/month in the majority of the studies.[106] Although most studies demonstrated an immediate effect within weeks of IVIg administration, several studies suggested that repeated dosing may be required. Greater reductions in mean skin thickness were observed after a second dose of IVIg, with ongoing benefits noted at 6, 12, 18, and 24 months. Furthermore, the reduction in mRSS (modified Rodnan Skin Score) was significantly greater at 12 months compared to 6 months.

QUALITY OF EVIDENCE: CEBM scale, confidence in effect vs estimate of effect [LOW to MODERATE]

Systemic sclerosis is a disease with a heterogeneous clinical presentation and varying degrees of disease activity in the affected internal organs. This variability poses a significant challenge in designing clinical trials for drug treatments in this condition.

3.0 ABBREVIATIONS:

AIBD: Autoimmune Bullous Dermatoses
AIHA: Autoimmune Hemolytic Anemia
ALPS: Autoimmune Lymphoproliferative Syndrome
ASH: American Society of Hematology
CAAs: Coronary Artery Aneurysms
CDI: Clinically Documented Infection
CEE: Central and Eastern Europe
CEBM: Centre for Evidence-Based Medicine
CIDP: Chronic Inflammatory Demyelinating Polyneuropathy
CVID: Common Variable Immunodeficiency
DALY: Disability-Adjusted Life Year
EMA: European Medicines Agency
ET: Exchange Transfusion
FNAIT: Fetal and Neonatal Alloimmune Thrombocytopenia
GBS: Guillain-Barré Syndrome
HCT: Hematopoietic Cell Transplantation
HDFN: Hemolytic Disease of the Newborn
HPA-1a: Human Platelet Antigen-1a
HRQoL: Health-Related Quality of Life
HTA: Health Technology Assessment
ITP: Immune Thrombocytopenic Purpura
IgGs: Immunoglobulins
IVIg: Intravenous Immunoglobulin
KD: Kawasaki Disease
LABD: Linear IgA Bullous Dermatosis
MeSH: Medical Subject Headings
MMN: Multifocal Motor Neuropathy
MuSK: Muscle-Specific Kinase
NHL: Non-Hodgkin Lymphoma
NMJ: Neuromuscular Junction
OMP: Orphan Medicinal Product
PIDs: Primary Immunodeficiencies
PLEX: Plasma Exchange
PRCA: Pure Red Cell Aplasia
PTP: Post-Transfusion Purpura
PV: Pemphigus Vulgaris
RCTs: Randomized Controlled Trials
SIDs: Secondary Immunodeficiencies
SJS: Stevens-Johnson Syndrome
TEN: Toxic Epidermal Necrolysis
TRALI: Transfusion-Related Acute Lung Injury
US: Ultrasound

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