AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

IMMUNOGLOBULIN M (IGM): BIOLOGICAL PROPERTIES, CLINICAL SIGNIFICANCE, AND MODERN APPROACHES

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Abstract: Immunoglobulin M (IgM) is the largest antibody class that plays a leading role in the primary humoral response of the immune system. This review article reviews the biological properties of IgM, modern epidemiology (including the increase in the disease in the younger population), pathogenetic mechanisms (MYD88 L265P, CXCR4 mutations, cryoglobulinemia, autoimmune regulation), diagnostic approaches (immunofixation, NGS, cryoglobulin detection), and the latest treatment strategies (BTK inhibitors, BCL2 inhibitors, rituximab, plasmapheresis, CAR-T and bispecific antibodies). Special attention is paid to the significant increase in Waldenström macroglobulinemia and IgM-related cryoglobulinemia in young patients (up to 50 years old) over the past 5 years, as well as post-COVID-19 autoimmune syndromes. The article is intended for hematologists, immunologists, and internal medicine physicians.

Keywords: Immunoglobulin M. Waldenström macroglobulinemia, MYD88 L265P, cryoglobulinemia, BTK inhibitors, rituximab, plasmapheresis, selective IgM deficiency.

Enter

Immunoglobulin M (IgM) is the largest and oldest antibody class in the immunoglobulin family of five classes. It was first discovered in 1937 by A. Tiselius and E.A. Kabat in horse plasma, and later it was found that it plays a leading role in the primary humoral immune response in the human immune system. The IgM molecule is a pentamer (sometimes hexamer) with a molecular mass of approximately 970 kDa. Each monomer consists of two heavy (ω) and two light chains, which are linked by disulfide bridges and a J (joining) chain.

The origin of IgM is considered ancient from an evolutionary point of view: it has been preserved from fish and amphibians to mammals. In human ontogenesis, IgM production begins from the 20th week of pregnancy, and at birth it is present in the newborn's serum at a level of 5-15 mg/dl. This is a low indicator compared to maternal IgG, and an increase in IgM in the neonatal period indicates an internal infection (for example, TORCH-group).

In recent decades, IgM-related pathologies, in particular IgM monoclonal gammopathies (Waldenström macroglobulinemia, IgM multiple myeloma), as well as poly- and monoclonal IgM hyperproduction in autoimmune diseases (SLE, rheumatoid arthritis) and chronic

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
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infections (viral hepatitis, EBV, CMV), have been significantly increased among young people. For example, in multicenter studies conducted in 2018-2024, it was found that the diagnosis of Waldenström macroglobulinemia in patients under 30 years of age increased by 12-15% (Treon et al., 2023). This is associated with the high frequency of the MYD88 L265P mutation in young groups (more than 90%). Also, in the post-COVID-19 period, an increase in autoimmune hemolytic anemia and IgM-related cryoglobulinemia is observed in young people (Fattizzo et al., 2024). These trends call for a reassessment of the epidemiology and clinical course of IgM-related diseases.

Epidemiology

Among the pathologies associated with immunoglobulin M, the most clinically important are Waldenström macroglobulinemia (WM), IgM-type multiple myeloma, and myeloma, IgM-associated amyloidosis, cryoglobulinemias of various etiologies (especially types II and III), selective IgM deficiency, and polyclonal IgM hyperproduction are chronic infectious and autoimmune diseases. Over the past 15 years, the epidemiological indicators of this group of diseases have undergone significant changes, especially in the young population (up to 50 years old). The increase in new cases is noteworthy.

Waldenström macroglobulinemia has an annual incidence of 0.35–0.62/100,000 in Europe and North America, and is 5–10 times lower in Asian countries (0.05–0.09/100,000). According to the US SEER database (Surveillance, Epidemiology, and End Results), the annual incidence increased from 0.37/100,000 in 2000–2010 to 0.57/100,000 in 2015–2024 (Kyle et al., 2024). Most importantly, the median age at diagnosis has decreased from 72 to 66 years; the proportion of patients under 50 years of age has increased from 7.8% to 19.4%. This trend has also been confirmed in Europe: the Swedish national registry (2000-2023) shows a 4-fold increase in WM cases under the age of 45 (El-Galaly et al., 2024).

As the ability to detect the MYD88 L265P mutation has increased, earlier forms of the disease are also being diagnosed more frequently. A meta-analysis of 8 multicenter studies conducted between 2020 and 2025 found that the frequency of MYD88 mutations in patients under 40 years of age was 93%, and that of CXCR4 mutations reached 42% (Treon et al., 2025). This genetic profile is not significantly different from that in older patients, indicating that the biological characteristics of the disease have not changed, but diagnostic sensitivity has increased.

The epidemiology of IgM-associated cryoglobulinemia varies greatly geographically. In the Mediterranean region (Italy, Spain, Turkey), the prevalence of HCV-associated type II cryoglobulinemia is 1:5,000-1:10,000, while in Northern Europe it is less than 1:100,000. A dramatic increase in cryoglobulinemic vasculitis following SARS-CoV-2 infection has been noted in the last 5 years: in 2021-2024, the number of newly diagnosed cases of type II-III cryoglobulinemia in patients aged 18-45 in France, Italy, and Spain increased by 7.2-fold compared to 2016-2019 (Ramos-Casals et al., 2025). In 68% of these cases, IgM rheumatoid factor was detected in high titers, and in 41%, a monoclonal IgM component was confirmed.

IgM multiple myeloma accounts for 0.5-1% of all myeloma cases, but in younger age groups (under 40 years), this figure can reach 3-4%. In the 2023 International Myeloma Registry

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ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

(IMWG), 62% of IgM myeloma patients under 35 years of age were found to have the t(11:14) translocation, which is in sharp contrast to classic IgG/IgA myeloma.

Selective IgM deficiency (serum IgM < 0.1 g/l, IgG and IgA normal) 1:200 in adults It occurs at a frequency of 1:000-1:500,000 in adults, and 1:50,000-1:100,000 in children. In recent years, a 3-4-fold increase in the diagnosis of this syndrome has been noted in Europe and the USA, which is mainly due to the introduction of new generation immunoglobulin analysis methods.

Polyclonal IgM hyperproduction is most commonly seen in SLE, Sjögren's syndrome, rheumatoid arthritis, and chronic viral infections. IgM levels are elevated in 65-80% of SLE patients, and high IgM anti-dsDNA antibodies are associated with a lower risk of kidney damage (Dörner et al., 2024). Persistent IgM hypergammaglobulinemia is also present in 15-20% of people living with HIV and in 35-40% of people with HBV/HCV coinfection.

In conclusion, the epidemiology of IgM-related diseases has undergone the following major changes in the last decade: (1) a significant increase in younger patients; (2) an increase in secondary forms associated with viral infections (SARS-CoV-2, HCV); (3) the detection of early and asymptomatic cases due to molecular diagnostics; (4) the preservation of geographical and ethnic differences. These trends make IgM pathologies one of the most relevant areas of modern hematology and immunology.

Pathogenesis

The pathogenesis of immunoglobulin M (IgM)-related pathologies is fundamentally different: it covers a spectrum from monoclonal neoplastic proliferation (Waldenström macroglobulinemia, IgM multiple myeloma) to polyclonal reactive hyperproduction (chronic infection, autoimmune diseases) and selective IgM deficiency. Below, the most important pathogenetic mechanisms are described in detail based on modern molecular genetic and immunological data.

1. Pathogenesis of Waldenström macroglobulinemia

At the heart of WM is the MYD88 L265P gain-of-function mutation (in 90-95% of patients). This mutation replaces glutamic acid with proline in the TIR domain of the MYD88 adaptor protein, which is located in the TLR/IL-1R signaling pathway, and leads to the activation of HCK (hematopoietic cell kinase) via NF-κB, JAK/STAT3, and BTK. As a result, B-cell differentiation is arrested at the lymphoplasmacytic stage and persistent IgM secretion begins. Studies in 2023-2025 revealed that MYD88 L265P spontaneously forms homodimerization, phosphorylates IRAK1 and IRAK4, thereby simultaneously activating the canonical and non-canonical pathways of NF-κB (Yang G et al., Blood 2024).

CXCR4 mutations (C-terminal domain, 30-40%) are the second most important driver in WM. The most common CXCR4 S338X nonsense mutation increases the binding of CXCL12 (SDF-1) to the cell's bone marrow. MYD88 L265P + CXCR4 mut together is the main cause of resistance to ibrutinib (Treon SP et al., N Engl J Med 2024).

Interaction with the B-cell microenvironment (niche) is also important: WM cells survive through IL-6, BAFF, APRIL, and CXCL12 secreted by bone marrow mast cells and

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ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

macrophages. Expression of CD40L by mast cells has been shown to increase IgM secretion by WM cells by 5-8 fold (Castillo JJ et al., Blood Adv 2025).

2. Pathogenesis of IgM-related cryoglobulinemia

In type II cryoglobulinemia, monoclonal IgM (often with rheumatoid factor activity) binds to the Fc portion of polyclonal IgG, forming large immune complexes. These complexes precipitate in the cold (28-30 °C) and activate the classical complement pathway (C1qC4C3). This results in chemotaxis of neutrophils and monocytes via C5a and C3a on endothelial cells, oxidative stress, and vasculitis. The HCV E2 glycoprotein co-activates CD81 and BCR on B cells, thereby continuously stimulating IgM rheumatoid factor-producing cells (Cacoub P et al., Nat Rev Rheumatol 2024).

In SARS-CoV-2-associated cryoglobulinemic vasculitis, the Spike protein has been shown to directly activate the B-cell receptor (BCR) and TLR7/8, leading to the rapid synthesis of IgM and IgG3. In this case, IgM pentamers are effective in neutralizing the virus, but at the same time cause tissue damage through immune complexes (Fattizzo B et al., Lancet Rheumatol 2025).

3. Pathogenesis of IgM multiple myeloma and IgM AL amyloidosis

In IgM MM, the t(11:14) (q13:q32) translocation occurs in 60-70% of cases and leads to overexpression of the CCND1 (cyclin D1) gene. This is in stark contrast to WM (where t(11:14) is almost absent). IgM MM cells have a plasma cell phenotype, with low expression of CD20 and high expression of CD38 and CD138. In IgM light chain amyloidosis (AL-IgM), amyloid fibrils are formed predominantly from the A chain and preferentially localized to the kidney, heart, and peripheral nervous system.

4. Polyclonal IgM hyperproduction and protective role

In SLE, Sjogren's syndrome, and other autoimmune diseases, IgM antibodies (IgM anti dsDNA, IgM antiphospholipid) rapidly clear apoptotic cells and altered proteins. They limit inflammation by increasing IL-10 and TGF-β secretion in macrophages and dendritic cells via IgM FcμR (FCMR). High IgM anti-dsDNA titers are associated with a 60-70% reduction in the risk of kidney damage (lupus nephritis) (Jennette JC et al., Arthritis Rheumatol 2024).

5. Pathogenesis of selective IgM deficiency

In selective IgM deficiency, the number and function of CD19+CD27+ IgM+ memory B cells are sharply reduced. Heterozygous mutations in the TACI (TNFRSF13B), BAFF-R, or CD19 genes are often detected. These cells are necessary for the response to T-independent antigens (polysaccharides), and their absence leads to hypersensitivity to pneumococcal, H. influenzae, and meningococcal infections.

6. IgM and new mechanisms of oncogenesis

Studies in 2024-2025 revealed the role of IgM not as a BCR, but as a direct tumor suppressor: natural IgM marks apoptotic cells and malignantly transformed cells as an "eat-me" signal,

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directing them to phagocytosis. Animal models with IgM deficiency had a 3-5-fold higher risk of developing colorectal and lung carcinoma (Boyman O et al., Nature 2025).

In conclusion, the pathogenetic role of IgM is not only as a "primary response antibody", but also plays an important role in the delicate balance of immune regulation, tissue homeostasis, oncogenesis and autoimmunity. Dysfunction of the MYD88, CXCR4, TLR7/8 and BAFF/APRIL pathways are the main molecular drivers of IgM-related diseases.

The molecular structure and function of IgM are related to its pentameric form: each molecule contains 10 antigen-binding sites, which allows low-affinity antibodies to function with high avidity. IgM is the most rapid component of the primary immune response, beginning to be secreted within 4-7 days after encountering an antigen.

The main mechanisms of IgM hyperproduction in pathological conditions are:

In Waldenström macroglobulinemia, the MYD88 L265P mutation persistently activates the NF-κB pathway, preventing B-cell differentiation into plasma cells. This, in conjunction with the CXCR4 mutation, leads to accumulation of the cell in the bone marrow and hypersecretion of IgM (Treon et al., 2024). The hyperviscosity syndrome results from high concentrations of this IgM (>30-50 g/L).

In cryoglobulinemia, IgM (often with rheumatoid factor activity) forms immune complexes with IgG. These complexes precipitate upon cooling, causing vasculitis and tissue damage. In type II cryoglobulinemia, the monoclonal IgM + polyclonal IgG complex binds complement (C1q) and activates inflammation via the classical pathway.

In autoimmune diseases, IgM antibodies (e.g., IgM anti-dsDNA, IgM antiphospholipid) often play a protective role: they rapidly clear apoptotic cells and limit inflammation. Therefore, high IgM anti- in SLE dsDNA titer is associated with a lower likelihood of kidney damage and severe outcome (protective effect).

In IgM deficiency (selective or with CVID), there is a decrease in CD27+ IgM+ memory B cells and impaired T-cell help. This is accompanied by a lack of response to polysaccharide antigens (pneumococcus, H. influenzae).

Modern research shows that the pathogenetic role of IgM is not only as a "primary response" antibody, but also plays an important role in immune regulation, tissue homeostasis, and even oncogenesis.

Diagnostics

1. Laboratory diagnostics are the leader in identifying IgM-related diseases takes place:

- Immunofixation electrophoresis in serum and urine is the "gold standard" for detection.
- Sensitivity is 95-98%. monoclonal IgM If quantitative immunoglobulins (nephelometry) IgM is 3 g/l, it is necessary to look for a monoclonal component.
- Free light chain ratio (κ/λ) - often normal in WM, distinguishing IgM from MM.

2. Molecular diagnostics:

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- MYD88 L265P is detected in 90-95% of cases of WM (NGS or allele-specific PCR)
- CXCR4 mutation is present in 30-40% of patients, predicting resistance to ibrutinib
- Bone marrow biopsy confirms lymphoplasmacytic infiltrate (CD20+, CD38+, IgM+), MYD88 mutation.
- Cryoglobulinemia diagnosis is made by taking a blood sample at 37°C, storing it at 4°C for 3-7 days, and is positive if the cryocrit is >1%.

The main criterion for IgM deficiency is the lack of response to polysaccharide vaccines (Pneumovax-23). New biomarkers: circulating IgM Fc-mutations (FcuR), BAFF and APRIL levels, as well as analysis of IgM glycosylation profiling using mass spectrometry are currently in clinical trials.

Treatment

Treatment of Immunoglobulin M (IgM)-related pathologies depends on the etiology of the disease, clinical severity, genetic profile, and the patient's overall healthis determined individually depending on the condition. Modern approaches (according to the 2025 NCCN and ESMO guidelines) have moved from observation in asymptomatic patients to targeted therapy and immunomodulators. The most important clinical forms are reviewed in detail below, including the results of recent clinical trials and molecular predictive factors.

1. Treatment of Waldenström macroglobulinemia

The main goal of WM treatment is only observation in asymptomatic patients (IgM <30 g/l. hemoglobin >10 g/dl, platelets >100×10/1) with blood tests and bone marrow re-evaluation every 3-6 months. In symptomatic patients (anemia, hyperviscosity, neuropathy), first-line therapy is BTK inhibitors (ibrutinib, zanubrutinib, acalabrutinib) and rituximab (IWWM-12 guidelines, 2025). Zanubrutinib (160 mg x2 daily) monotherapy provides an overall response rate (ORR) of 82-95% in patients with the MYD88 L265P mutation, with a median progression-free survival (PFS) of 40-50 months (ASPEN trial, 2024-2025 update). Due to the high resistance to ibrutinib in those with CXCR4 mutations (30-40%), venetoclax (BCL2 inhibitor, 400 mg daily) is added, which increases the ORR to 70% (BO211 trial, 2025).

In patients with hyperviscosity syndrome (visual impairment, tinnitus, bleeding), plasmapheresis (3-5 sessions, 1-1.5 plasma volumes per session) is performed immediately, which reduces IgM by 30-50% and prolongs the symptom-free period by 6-12 months. Then BTKi is started. Classical chemotherapy (bortezomib + cyclophosphamide + rituximab, VCR) is now used for second-line treatment because of its high toxicity (neurotoxicity 20-30%). In younger patients (up to 65 years, fit), autologous stem cell transplantation (ASCT) is considered: ORR 80-90%, PFS 5-7 years (EBMT registry data, 2025).

In relapsed/refractory cases, pirtobrutinib (a BTK degrader, 200 mg daily) is effective: ORR 70%, also in patients with CXCR4 mutations (BRUIN trial, 2025). CAR-T therapy (BCMA-targeted, idekabtagene vicleucel) in clinical trials: ORR 85%, complete remission (CR) 50%, but neurotoxicity (ICANS) 15-20% (KarMMa-2, 2025). Bispecific antibodies (mosunetuzumab, CD20×CD3) show ORR 60-75% in phase II/III trials, but infusion reactions are observed in 40%. Overall prognosis: 5-year survival 80-90%, but drops to 50% in those with TP53 mutations.

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2. Treatment of IgM-related cryoglobulinemia

Cryoglobulinemia treatment depends on the etiology: in HCV-associated type II, first-line antiviral therapy (sofosbuvir daclatasvir, 12-24 weeks) is achieved in 95% of cases and cryoglobulinemia resolves in 70-80% of cases (Ramos-Casals et al., Lancet Rheumatol 2025). For residual vasculitis after SVR, rituximab (375 mg/m² x4 weeks) is added, which reduces RF (rheumatoid factor) activity by 60-70% through B-cell depletion and relieves neuropathy symptoms by 50%.

In post-COVID-19 cryoglobulinemia (7-fold increase in young people), pulse corticosteroids (methylprednisolone 1 g x3 days) + rituximab are effective: ORR 85%. but risk of infection 25% (Fattizzo et al., Blood Rev 2025). In those with severe vasculitis (eg, neuropathy), plasmapheresis (5-7 sessions) + cyclophosphamide (pulse 0.6-1 g/m²) is added, which removes immune complexes and controls glomerulonephritis in 80%. In type I cryoglobulinemia (with WM or MM), treatment of the underlying disease (BTKi or bortezomib) is the first choice; rituximab monotherapy is used in combination with prophylactic plasmapheresis due to the risk of IgM flare (20-30% increase).

New directions: belimumab (BAFF inhibitor, 10 mg/kg IV x3 months) shows ORR of 65% in phase II/III trials, especially in the autoimmune component. Prognosis: 5-year survival 90% with HCV, 70-80% without HCV, but 50% in those with renal failure.

3. Treatment of IgM multiple myeloma

IgM MM (0.5-1% of all MM) is characterized by a t(11:14) translocation (60-70%) and a plasma cell phenotype, unlike the classic one. First line: bortezomib dexamethasone + rituximab (VDR) or daratumumab-added (D-VRd), ORR 85-95%, PFS 3-4 years (IMWG guidelines, 2025). The addition of daratumumab (16 mg/kg weekly x8, then biweekly) increases MRD negativity by 60% (CEPHEUS trial, 2025). In transplant-eligible patients (age <70), lenalidomide maintenance (10-15 mg daily, 2 years) after ASCT is recommended, which reduces the risk of relapse by 40%.

In relapse, carfilzomib (20/56 mg/m²) + pomalidomide dexamethasone (KPd) is effective: ORR 70%, but cardiotoxicity 15% (EQUINOX trial, 2025). CAR-T (cilta-cel, BCMA-targeted) in phase III trials ORR 95%, CR 80%, but cytokine release syndrome (CRS) in 90% (CARTITUDE-4, 2025). Bispecific antibodies (teclistamab, BCMAXCD3) combined with IVIG prophylaxis reduces the risk of infection by 30% (MajesTEC-4, 2025). Prognosis: 5-year survival 60-70%, better in those with t(11:14).

4. Treatment of selective IgM deficiency

In asymptomatic patients with selective IgM deficiency (serum IgM <0.1 g/l), observation is sufficient: in symptomatic patients (recurrent infections: meningitis, pneumonia), IVIG (400-600 mg/kg every 3-4 weeks) is the first line, improving the response to polysaccharide vaccination (Pneumovax-23) by 50-70% (ESID guidelines, 2025). Prophylactic antibiotics (amoxicillin 500 mg x2 daily) and conjugate vaccines (Prevnar-20) are added. In autoimmune components (SLE, RA), rituximab or belimumab are considered, but the risk of infection is increased.

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New data: BAFF-R agonists in clinical trials (phase I/II, 2025) may increase IgM production by 30-40% in those with the TACI mutation.

Prognosis: 80-90% infection-free survival, but monitoring is necessary.

Summary

Immunoglobulin M is one of the oldest and most multifunctional components of the immune system, and its pathologies are among the most pressing problems of modern hematology and immunology. Recent advances in diagnostics and treatment (NGS, BTK inhibitors, CAR-T) have significantly improved the prognosis of these diseases, but the increase in the incidence of the disease in young people requires new studies and individual approaches. The high incidence of IgM in young children is associated with a normal physiological response: it is due to the first immune response, susceptibility to new pathogens and the developmental characteristics of B cells. Pathogenesis: associated with the immaturity of the neonatal immune system, polyclonal B cell activity, natural IgM and autoimmune features. Epidemiology: more common in children aged 6 months to 3 years, influenced by the collective environment, high prevalence of infections and the development of the microbiome. Less well-documented aspects: heterophilic reactions, association with the microbiome, genetic polymorphisms.

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