Myeloma in Focus:
A newsletter for healthcare providers

Hypogammaglobulinemia

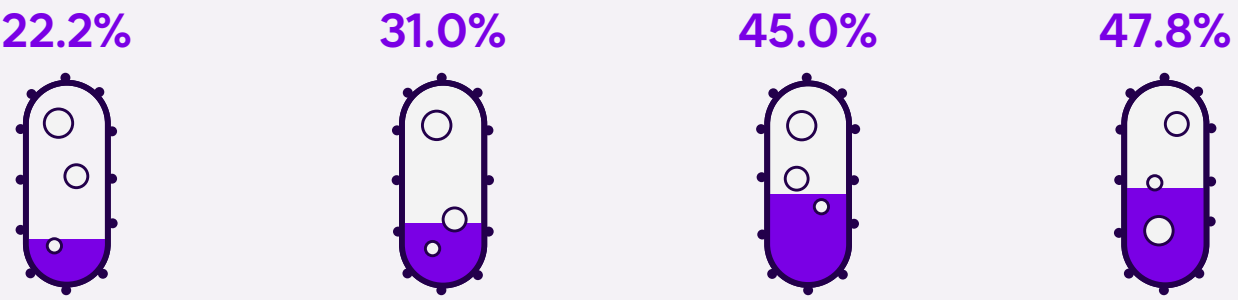
Welcome to this edition of the Sanofi quarterly newsletter! These newsletters, created by Sanofi, aim to provide education to healthcare providers on relevant topics in multiple myeloma (MM). This edition will focus on hypogammaglobulinemia (HGG) and will include an overview of the clinical impact of HGG-associated infections, current strategies for infection management, and future directions for the management of HGG in MM.

In this issue

Infections in MM

Infections are a substantial cause of early mortality in MM (Figure 1).

Figure 1: Percentage of deaths caused by infection reported across MM studies[1–4]



In addition, infections have a pronounced negative impact on patient quality of life (QoL) due to repeat hospitalizations, leading to limitations on everyday activity and increased stress for patients.[5,6] The impact of infection-related hospitalizations on healthcare systems is also a signficant financial burden, with high costs reported per patient.[7] A greater understanding of the risk factors for infection is crucial in order to negate the impact of infections on healthcare systems and patients alike.

As a disease of the immune system, MM is frequently associated with secondary immune deficiency (SID).[8] Patients show significant immune impairment and dysfunctional immune response due to the disease pathophysiology and/or anti-myeloma therapies, resulting in an increased susceptibilty to severe and recurrent infection.[8–10] Accumulation of malignant plasma cells within the bone marrow causes MM-related immune dysfunction, secretion of large quantities of an abnormal immunoglobulin, and suppressed production of healthy immunoglobulins (Figure 2).[8]

Figure 2: Pathogenesis of MM cells[11]

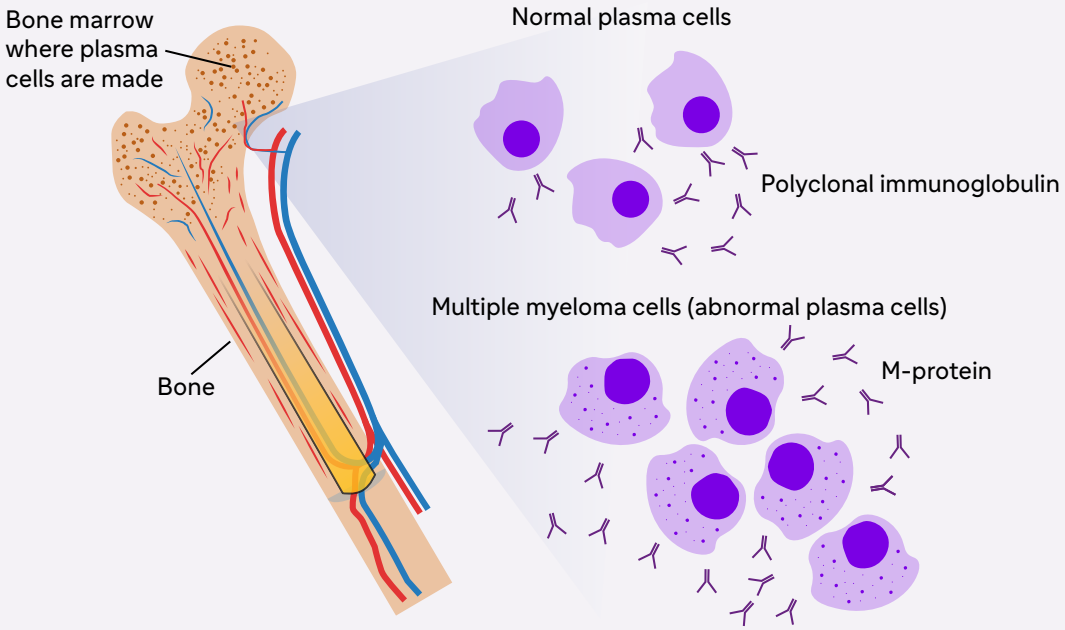


Figure adapted from: https://www.ncbi.nlm.nih.gov/books/NBK66001/ (c) 2014 Terese Winslow LLC.[11]

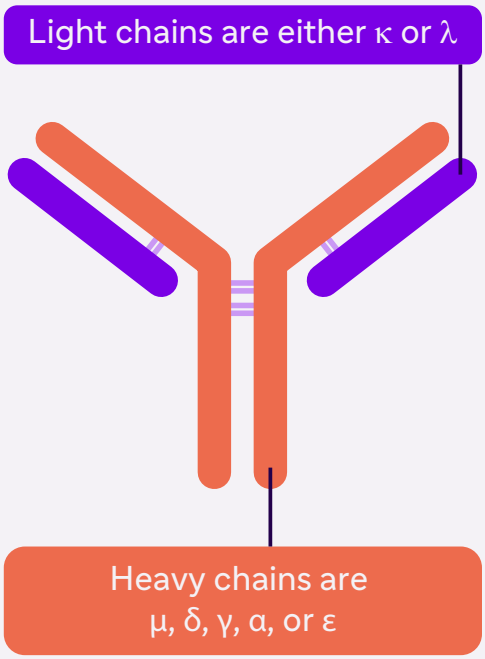
Abnormal immunoglobulin production is a hallmark of MM

Immunoglobulins comprise two identical light chains and two identical heavy chains (Figure 3) and are divided into five distinct classes: IgM, IgD, IgG, IgA, and IgE, according to the type of heavy chain (μ, δ, γ, α, and ε, respectively). There are only two types of light chain: kappa (κ) and lambda (λ). Either type of light chain may be found in any of the five immunoglobulin classes.[12]

Normal plasma cells secrete immunoglobulins to fight infection through diverse mechanisms, including direct pathogen binding and interaction with the adaptive and innate immune systems.[11,13] IgG is a central component of the adaptive immune system and protects against infection through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[14]

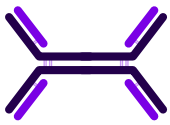
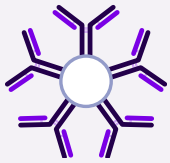
In MM, a clonal population of malignant plasma cells produces excessive amounts of one type of immunoglobulin (IgG, IgA, IgM, IgE, IgD, or light chain only). Referred to as monoclonal or M-protein, this abnormally-functioning immunoglobulin does not protect against infection, and its accumulation in the bone marrow can cause thickening of the blood, kidney damage and renal disease complications.[11,15,16]

Figure 3: Immunoglobulin structure[12]



The subtype of overexpressed M-protein corresponds with the subtype of myeloma. In rarer cases, patients may have IgD, IgM, IgE or non-secretory MM (i.e. plasma cells that do not secrete immunoglobulins); however, IgG, IgA, and light chain only are the most dominant subtypes (Table 1).[16,17]

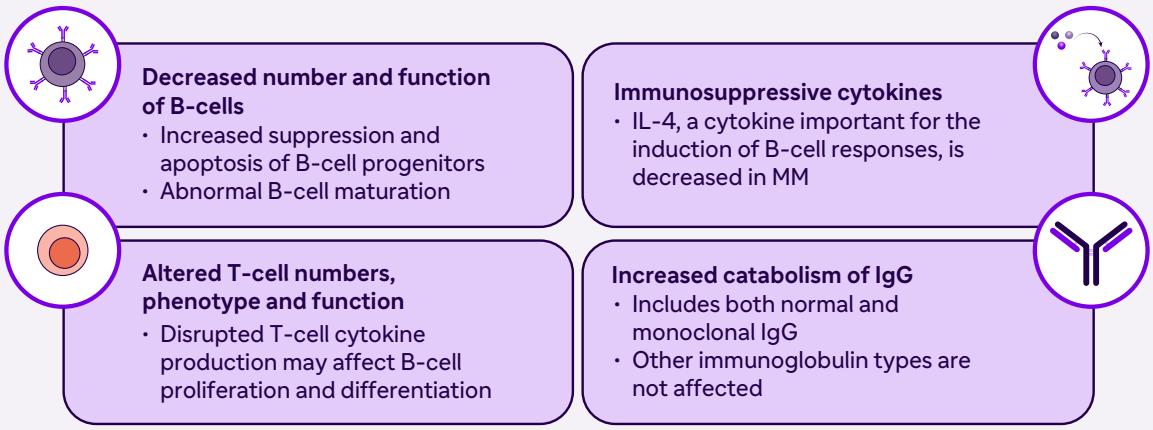
Table 1: Structure and function of different immunoglobulins and frequency of different MM subtypes[16–18]

Type of MM	Immunoglobulin structure	Myeloma prevalence	Function against infection
IgG (κ or λ subtypes) Monomer		Most common myeloma (~52% of cases)	• Complement activation • Neutralizes toxins and viruses • Opsonization and clearance of pathogens • Associated with a secondary immune response • Crosses placenta
IgA (κ or λ subtypes) Dimer		Second most common myeloma (~21% of cases)	• Secreted into saliva and colostrum • Protection of mucosal surfaces
IgM (κ or λ subtypes) Pentamer		Relatively rare (~0.5% of cases)	• Complement activation and opsonization • Associated with a primary immune response
IgD (κ or λ subtypes) Monomer		Relatively rare (~1–2% of cases)	• B-cell receptor • Suggested to regulate B-cell regulation
IgE (κ or λ subtypes) Monomer		Relatively rare (~0.01% of cases)	• Immunoglobulin of allergy and antiparasitic activity
Light chain only		Third most common myeloma (~16% of cases)	
Non-secretory		~2% of cases	

Ig, immunoglobulin; κ, kappa; λ, lambda

Alongside secretion of M-protein is the reciprocal suppression of healthy immunoglobulins, which contributes to the impaired immune response frequently observed in MM.[8] A variety of underlying mechanisms have been implicated in the supression of healthy immunoglobulins, including decreased number of circulating B-cells, the presence of suppressor B-cells, and impaired T-cell function.[19] Some of the mechanisms underlying suppressed immunoglobulin production are outlined in Figure 4 below.

Figure 4: Mechanisms underlying abnormal Ig production in MM[19]



Healthy immunoglobulins are also referred to as uninvolved protein, and several assays have been developed to quantify the proportion of uninvolved immunoglobulins to involved M-protein, known as the involved/uninvolved ratio.[20] The involved/uninvolved ratio has become an important diagnostic marker, as a higher ratio of M-protein often correlates with a higher risk of progression from smoldering MM to clinical disease.[21]

The supression of normal immunoglobulins and accumulation of M-protein can lead to HGG, a condition characterized by low immunoglobulin levels and an increased risk of infection.[8,22]

Definition of HGG

HGG can be a primary immunodeficiency, caused by a hereditary alteration of the immune system, or secondary to acquired nonhereditary factors, such as malnutrition, infections (e.g., human immunodeficiency virus), metabolic disorders, and hematological malignancies (HMs). One type of HM that commonly results in HGG is MM, which is associated with the suppression of functional polyclonal immunoglobulin levels, often termed immunoparesis.[8,22]

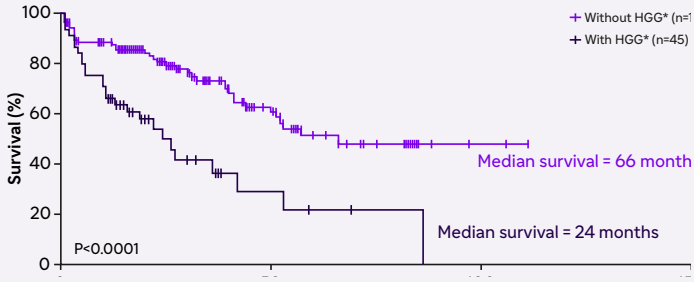
In recent clinical guidelines, HGG has been defined by the International Myeloma Working Group (IMWG) as IgG levels <400 mg/dL requiring treatment.[23] Similarly, a recent international expert panel consensus on HGG management recommended that serum IgG concentrations <400 mg/dL should be the threshold to define severe HGG, and 400–600 mg/dL should be defined as mild HGG.[22] However, a defined treatment threshold for HGG is lacking a definitive consensus, with differing IgG levels being adopted across clinical trials for HMs.[24]

Impact of HGG in MM

The risk of developing HGG is very high in MM (reported in up to 90% of MM cases),[22] with HGG-related mortality reported in up to 22% of MM cases.[10]

HGG has been reported to negatively impact survival outcomes and is thus identified as a negative prognostic marker. In a study of 148 MM patients with or without HGG, the median survival was 42 months shorter in patients with HGG (IgG <500 mg/dL) vs those without (Figure 5).[25]

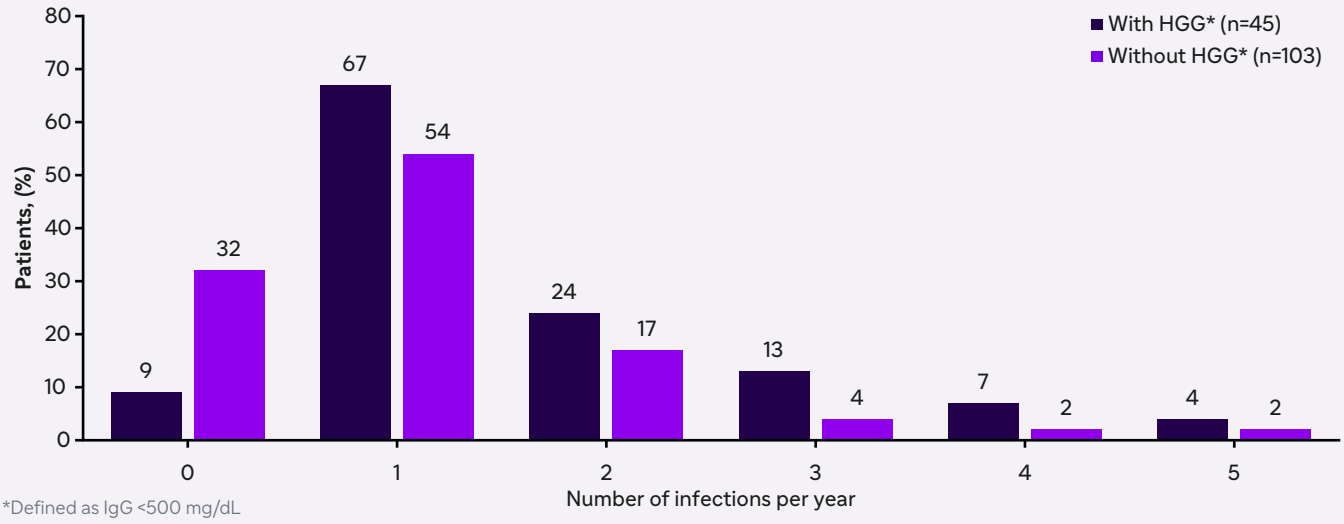
Figure 5: Survival outcomes in MM patients with HGG vs without HGG[25]



*Defined as IgG <500 mg/dL

Further, patients with HGG experienced more infections per year compared with those who did not have low IgG levels (Figure 6).[25]

Figure 6: Number of infections per year in MM patients with HGG vs without HGG[25]

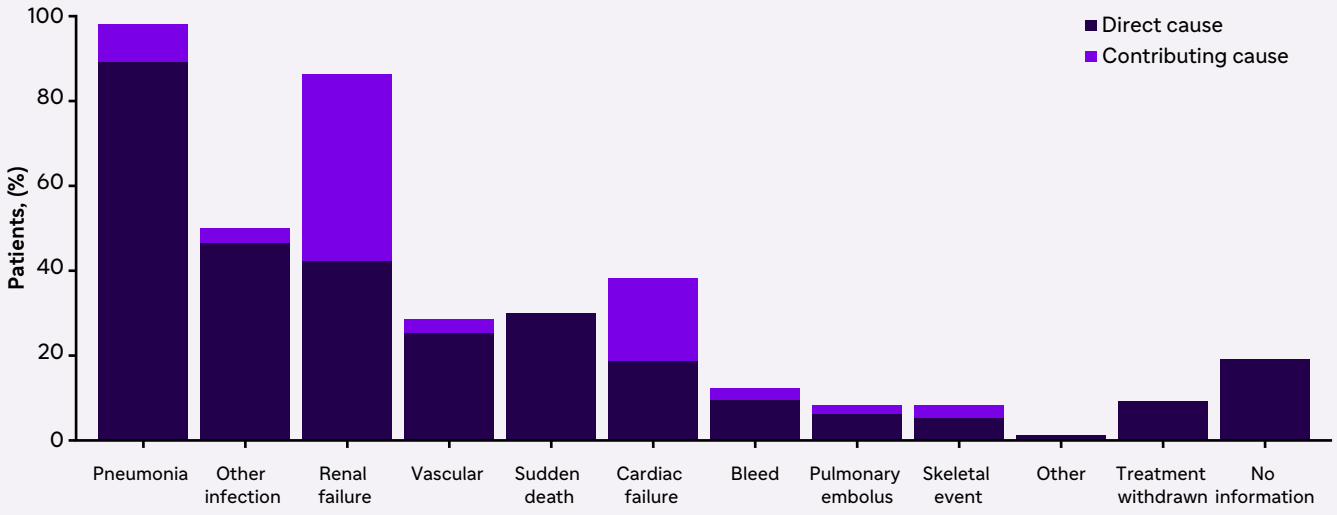


*Defined as IgG <500 mg/dL

HGG has been associated with an increased susceptility to infection, specifically by encapsulated organisms like *Haemophilus influenzae* and *Streptococcus pneumoniae*,[26] which can lead to conditions such as sepsis and pneunomia that have been linked to high mortality rates.[3,23]

The clinical impact of bacterial infections commonly associated with HGG is substantial, as shown in a retrospective analysis of 3107 patients with newly diagnosed MM (NDMM). Early death (defined as within 60 days of trial entry) occurred in 299 (10%) patients. Bacterial infection was the direct cause of early mortality in 45% of deaths, with pneumonia (due to *Pneumococcus pneumoniae* and *Staphylococcus aureus*) being the most common complication (Figure 7).[3]

Figure 7: Causes of early deaths in NDMM (<60 days of trial entry; N=299)[3]



The association between HGG and infection-associated deaths highlights the importance of utilizing effective management strategies against HGG and infection.

Infection prevention strategies in MM

The risk of infection varies throughout the disease course and is highest during the first 3 months after diagnosis;[23] therefore, strategies are focused at managing infection at the start of treatment.

Alongside anti-infective behaviors like regular hand washing that patients are encouraged to adopt, approaches to prevent infection include vaccines and prophylactic antibiotics.[22] Vaccines that confer protection against viruses, like influenza and pneumococcal, which represent a significant risk in MM, are recommended for all patients before the initiation of anti-myeloma therapies (Table 2).[27]

Table 2: Recommendations across clinical guidelines for vaccination in MM[27]

Infections	Vaccine type	Recommendation
Influenza	Trivalent or quadrivalent (strains selected according to seasonal prevalence)	All patients, nonimmune family members, close contacts and HCPs
Hepatitis A	Inactivated hepatitis A vaccine	Patients traveling to areas of high endemicity
Hepatitis B	Recombinant hepatitis B vaccine	Patients traveling to areas of high endemicity, behavioral/occupational exposure, hemodialysis
Pneumococcal	PCV13	All patients
	PPV23	>2 months, or 6–12 months after PCV13
Haemophilus influenzae	Haemophilus influenza type B conjugate	All patients
Meningococcal	Meningococcal conjugate	Patients with asplenia, complement deficiency, recurrent episodes of bacterial infections
Diptheria-tetanus-pertussis	Tetanus and diphtheria toxoids, and acellular pertussis	Patients who did not receive a primary vaccination for diptheria-tetanus-pertussis, or a booster dose of tetanus and diphtheria toxoid vaccine. May be limited to tetanus only based on epidemiological prevalence
Herpes zoster	Recombinant zoster virus (VZV) glycoprotein E vaccine	All patients
	Live-attenuated VZV vaccine	All patients

HCP, healthcare professional; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; and pertussis; VZV, zoster virus

Patients may also be given antibiotic prophylaxis against bacterial infection within the first 2 to 3 months after myeloma treatment initiation, based on evidence from clinical trials.[22,28]

A UK-based randomized trial (TEAMM, Tackling EArly Morbidity and Mortality in Myeloma) in NDMM demonstrated that the number of deaths was significantly reduced in patients receiving prophylactic levofloxacin alongside anti-myeloma treatment compared with patients receiving placebo in the first 12 weeks, without increasing antibiotic-resistant infections. However, long-term findings revealed that the survival benefit was not extended to a year.[28] As such, prophylactic antibiotics for bacterial infections are routinely recommended in the newly diagnosed setting, during the first 12 weeks of treatment initiation for all patients. Further, patients receiving certain anti-myeloma therapies are also recommended for antimicrobial prophylaxis.[23,29,30]

In patients with documented bacterial infection with no or insufficient response to antibiotic therapy, IgRT may be considered to manage HGG.[22]

Current guideline recommendations for IgRT in MM

IgRT uses a concentrate of pooled IgG derived from healthy donors to replenish immunoglobulins to healthy levels and restore immune response.[31]

Many guidelines don't recommend the routine use of IgRT and suggest it is only used in patients with MM who have severe HGG (IgG <400 mg/dL) and recurrent and/or severe infections (Table 3).

Table 3: Guideline recommendations for IgRT therapy in MM[23,29,30]

NCCN	IMWG	ESMO-EHA
IgG <400 mg/dL and recurrent life-threatening infections	IgG <400 mg/dL and severe/ recurrent infections by encapsulated bacteria	Not routinely recommended; IgG <400–500 mg/dL and ≥2 severe infections within 1 year

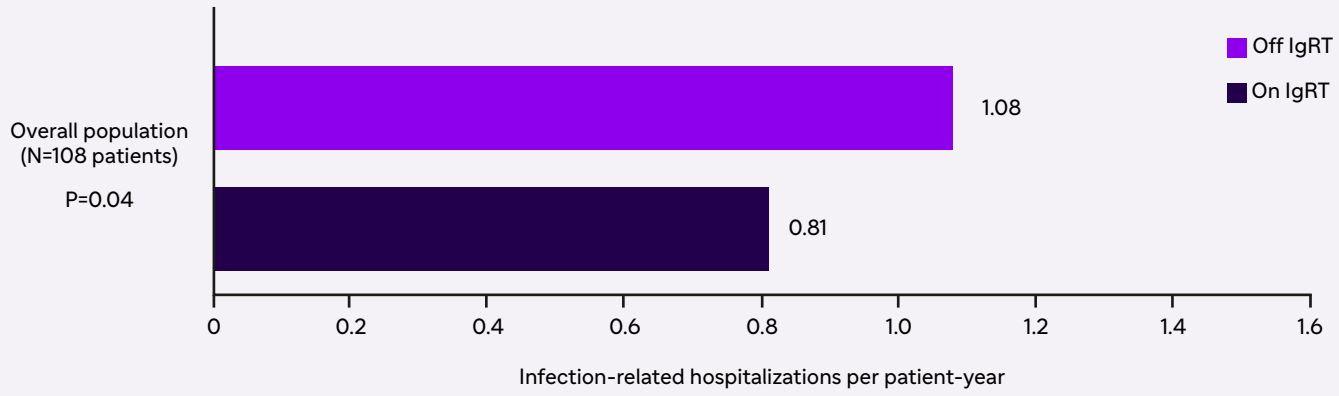
ESMO-EHA, European Society for Medical Oncology-European Haematology Association; Ig, immunoglobulin; IMWG, International Myeloma Working Group; NCCN, National Comprehensive Cancer Network

However, guidelines for IgRT vary at international and institutional levels, which has led to challenges with this treatment, including inappropriate use and supply shortages.[32] This issue has been made worse by a global increase in demand, with the number of patients worldwide receiving IgRT estimated to have increased by 19% between 2013 and 2015. Moreover, IgRT is costly, translating to a significant financial burden on healthcare organizations.[33] With this in mind, further refinement of patient selection for IgRT has been recommended by experts in order to conserve resources and ensure patients are receiving optimal care.[34]

Evidence for IgRT in HGG-related infections

Recent studies have demonstrated a clear benefit of IgRT in decreasing the risk of infection in patients with MM. Specifically, studies have shown an 80–90% reduction in Grade 3 to 5 infections when patients with HGG were treated with IgRT (HGG was defined as IgG <700 mg/dL and severe HGG as IgG <200 mg/dL).[35,36] An additional retrospective analysis exploring the impact of IgRT on infection-related hospitalizations in 108 patients with MM (81% had severe HGG [IgG <400 mg/dL]) demonstrated fewer patients were hospitalized due to infection compared with patients who did not receive IgRT (Figure 8).[37]

Figure 8: Infection-related hospitalizations in MM per patient-year on and off IgRT (N=108)[37]



By reducing infection-related hospitalizations, IgRT may improve health-related QoL as well as being cost-effective by reducing hospitalizations and antibiotic use,[38] highlighting the potential economic and clinical benefits of this therapeutic approach.

While there is evidence that IgRT can be an effective infection management strategy in patients with MM and HGG, it is noteworthy that other studies have not identified HGG as a significant risk factor for infection.[8,39] Further, as previously mentioned, clinical trials use inconsistent treatment thresholds for HGG. A lack of expert consensus hinders research and the generation of robust data from clinical trials assessing the benefit of IgRT against infection in patients with MM and HGG.[24]

A greater understanding of the mechanisms and factors that underline HGG-associated infection may help to improve management strategies. One consideration that may impact HGG-associated infection is the type of anti-myeloma therapy patients receive.

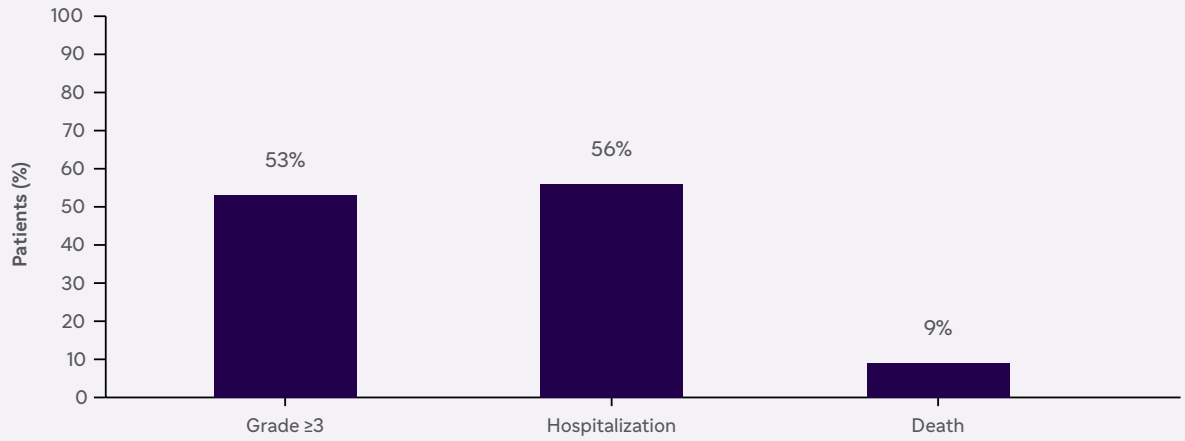
Infections in the era of novel anti-myeloma therapies

Despite being highly effective, novel anti-myeloma therapies have diverse mechanisms of action that can suppress immune function and increase infection risk.[22]

A real-world study of 229 patients with relapsed/refractory MM (RRMM) reported high rates of Grade ≥3 infections and infections requiring hospitalization, as shown in Figure 9.[40]

The impact of novel anti-myeloma therapies on increasing infection risk is multifactorial and includes HGG, which has been frequently reported in patients treated with such therapies.[22] As the use of immunotherapies is increasing in MM,[41] further research to understand the profile of these different therapies, alongside optimization of prophylactic infection strategies, is recommended.[42]

Figure 9: Rate of Grade ≥3 infections and infections resulting in hospitalization or death reported in RRMM patients treated with novel therapies[40]



Unmet need and future directions

It is important to highlight that the available evidence on newer anti-myeloma therapies is limited by factors such as study size and duration. Longer-term prospective follow-up studies are needed to determine the cumulative, long-term impact of such therapies on immunoglobulin production and infection.[9] Similarly, none of current MM diagnostic and staging criteria include routine diagnostic assessment of HGG.[22]

An expert panel on secondary antibody deficiency (SAD) – a term used to describe HGG and associated immunoglobulin dysfunction – recommended routine assessment of immunocompetency/deficiency at diagnosis in patients with MM, stratifying them based on SAD risk and infection. The panel proposed a diagnostic algorithm, integrating immune response and HGG severity, to establish an immunodeficiency baseline. Such algorithms could be used to inform individualized treatment plans based on infection risk, incorporating HGG and anti-infective strategies alongside anti-myeloma treatments.[22]

These algorithms could be supplemented in the future by risk stratification systems for infection, which have been explored to help support decision-making around the implementation and timing of anti-infective measures.

This includes the Multiple Myeloma Index for Risk of Infection model, which incorporates factors such as gender, disease stage and duration, and therapy type.[43] While there is currently limited evidence for such models, future implementation of a universal risk stratification system, alongside refinement of HGG diagnosis, could allow doctors to implement a personalized care plan based on HGG-related individual risk of infection.[22]

Summary

Infection is a leading cause of mortality in MM due to several underlying disease-related immunodeficiencies, such as HGG, which is frequently observed in patients.

Several anti-infection strategies, such as routine vaccinations and prophylactic antibiotics, have been adopted before initiating treatment.[22,27] IgRT is specifically reserved for patients with severe HGG experiencing recurrent or life-threatening infections based on evidence from clinical trials.[23,29,30] However, varying treatment thresholds for HGG across clinical trials has impeded research and there is a need for consistent definitions to be implemented across the board.[24]

Anti-myeloma immunotherapies with novel mechanisms of action may exacerbate HGG in MM,[22] and high rates of high-grade infection requiring hospitalization have been reported among patients treated with such therapies.[41]

Early and standardized HGG testing, coupled with further research on the impact of novel therapies on immunoglobulins, may enhance understanding of various treatment profiles and their correlation with HGG and infections. Together, this may help to optimize anti-infection strategies and reduce the impact of HGG and infection-related mortality in MM.

References:

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