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Interindividual Variability in IVIG Response in Kawasaki Disease: Pharmacokinetics, Immunology, and Clinical Outcomes

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ABSTRACT

Kawasaki disease (KD) is an acute, self-limited vasculitis of childhood and the leading cause of acquired heart disease in children in developed countries. Timely administration of high-dose intravenous immunoglobulin (IVIG) substantially reduces the incidence of coronary artery aneurysms, transforming the natural history of the disease. Nevertheless, approximately 10–20% of patients exhibit resistance to initial therapy, characterized by persistent or recrudescent fever and ongoing systemic inflammation. This subgroup is at markedly increased risk for coronary artery abnormalities, myocardial ischemia, and long-term cardiovascular morbidity. Interindividual variability in IVIG response arises from complex interactions among pharmacokinetic factors, immune activation pathways, genetic susceptibility, endothelial biology, and disease severity at presentation. Increasing evidence suggests that KD represents a heterogeneous spectrum of inflammatory phenotypes rather than a single uniform disorder, challenging traditional treatment paradigms based on standardized dosing. This comprehensive narrative review synthesizes current understanding of determinants of IVIG responsiveness, integrating insights from immunology, pharmacology, genetics, and clinical cardiology. Particular emphasis is placed on mechanisms of coronary artery injury, biomarkers of resistance, predictive models, and emerging targeted therapies. A deeper understanding of variability in treatment response is essential for developing personalized therapeutic approaches aimed at preventing irreversible cardiovascular damage and improving long-term outcomes.

Keywords: *Kawasaki disease; IVIG resistance; coronary artery aneurysm; pediatric vasculitis; pharmacokinetics; cytokines; immunogenetics; pediatric cardiology; coronary arteritis.*

INTRODUCTION

Kawasaki disease is an acute febrile illness characterized by systemic inflammation of medium-sized arteries, with particular predilection for the coronary circulation. Since its first description by Tomisaku Kawasaki in 1967, the disease has emerged as the most common cause of acquired heart disease in children in countries where rheumatic fever has declined (1). The condition predominantly affects infants and young

children, especially those under five years of age, although cases across a broader age spectrum are increasingly recognized. Epidemiological patterns demonstrate marked geographic variation, with the highest incidence reported in East Asian populations, particularly Japan, Korea, and Taiwan, suggesting an important genetic component in susceptibility (2).

The etiology of KD remains incompletely understood despite decades of investigation. Current evidence supports a multifactorial model in which environmental or infectious triggers provoke an exaggerated immune response in genetically predisposed individuals. Seasonal clustering, epidemic patterns, and the young age of affected patients all suggest exposure to a ubiquitous agent that induces disease only in susceptible hosts. Although numerous pathogens have been proposed, none has been consistently identified, reinforcing the concept that KD may represent a final common inflammatory pathway triggered by diverse stimuli (3).

The introduction of IVIG therapy in the 1980s dramatically altered the prognosis of KD. Prior to its widespread use, coronary artery aneurysms developed in approximately 20–25% of untreated patients. Administration of high-dose IVIG within the first 10 days of illness reduces this risk to below 5%, making it one of the most effective therapies in pediatric medicine (4). However, a clinically significant proportion of patients fails to respond adequately to initial treatment. These individuals experience persistent fever and inflammation, reflecting ongoing vasculitis, and are at substantially increased risk for coronary artery abnormalities, including giant aneurysms associated with long-term morbidity and mortality (5).

Recognition of IVIG resistance has profound clinical implications. Coronary artery damage begins early in the disease course and may progress rapidly in the presence of uncontrolled inflammation. Consequently, early identification of high-risk patients and timely escalation of therapy are essential. From a pediatric emergency medicine perspective, this necessitates vigilance in diagnosis and monitoring, as delayed treatment can result in irreversible vascular injury.

Increasing evidence indicates that variability in treatment response arises from differences in host biology rather than solely from timing of therapy. Factors influencing response include pharmacokinetic variability affecting drug distribution and clearance, heterogeneity in immune activation pathways, genetic polymorphisms influencing inflammatory responses, and baseline disease severity. These observations challenge the traditional assumption that a uniform therapeutic approach is adequate for all patients and highlight the need for individualized treatment strategies.

Immunopathogenesis of Kawasaki Disease

The pathological hallmark of KD is necrotizing vasculitis involving medium-sized arteries, particularly the coronary arteries. Early lesions are characterized by infiltration of the vascular wall by neutrophils, followed by monocytes, macrophages, and activated lymphocytes. This inflammatory process leads to destruction of the internal elastic lamina and smooth muscle cells, weakening the structural integrity of the vessel wall and predisposing to aneurysm formation (6).

Cytokine-mediated inflammation plays a central role in disease progression. Elevated serum levels of tumor necrosis factor-α, interleukin-1β, interleukin-6, and other proinflammatory mediators are consistently observed during the acute phase and correlate with disease severity and coronary artery involvement (7). These cytokines promote endothelial activation, increased vascular permeability, and recruitment of additional inflammatory cells, creating a self-perpetuating cycle of vascular injury. Innate immune activation appears to precede adaptive responses. Monocytes and neutrophils produce large quantities of cytokines and reactive oxygen species, contributing to endothelial damage. Subsequent activation of T cells and B cells sustains inflammation, while impaired regulatory T-cell function may hinder resolution. The

interplay between innate and adaptive immunity underscores the complexity of the inflammatory cascade in KD (8).

Endothelial dysfunction is a critical determinant of coronary artery pathology. Activated endothelial cells express adhesion molecules that facilitate leukocyte migration into the vessel wall. Matrix metalloproteinases degrade structural components of the arterial wall, while nitric oxide dysregulation contributes to vascular tone abnormalities. These processes collectively result in dilation, aneurysm formation, and potential thrombosis (9).

Mechanisms of Action of Intravenous Immunoglobulin

IVIG is a pooled preparation of immunoglobulin G derived from thousands of donors, containing a diverse repertoire of antibodies. Its therapeutic effects in KD are multifactorial and not fully elucidated. Neutralization of microbial toxins or superantigens has been proposed as one mechanism, although direct evidence is limited. More broadly supported mechanisms include modulation of Fc receptor expression on immune cells, suppression of proinflammatory cytokine production, inhibition of complement activation, and expansion of regulatory T cells (10).

IVIG also exerts protective effects on the vascular endothelium. Experimental studies demonstrate reduced expression of adhesion molecules and decreased leukocyte migration into the vessel wall following IVIG administration. Anti-idiotypic antibodies within IVIG preparations may neutralize pathogenic autoantibodies directed against endothelial antigens, further attenuating inflammation (11).

The rapid clinical improvement observed in most patients following infusion—often within 24 to 48 hours—reflects potent immunomodulatory activity. However, variability in these mechanisms among individuals likely contributes to differential treatment responses.

Pharmacokinetic Variability

Pharmacokinetics of IVIG are influenced by age, body composition, disease state, and genetic factors. In acute KD, systemic inflammation increases capillary permeability, allowing immunoglobulin to leak into interstitial spaces and reducing circulating levels. This phenomenon may result in subtherapeutic exposure despite standard dosing (12).

The neonatal Fc receptor plays a key role in protecting IgG from degradation and prolonging its half-life. Variations in FcRn function can alter serum immunoglobulin concentrations following infusion. Patients with severe inflammation may exhibit accelerated IgG catabolism, further reducing effective drug levels (13).

Hypoalbuminemia, common in severe KD, reflects protein leakage and correlates with treatment resistance. Elevated inflammatory markers such as C-reactive protein and neutrophil count similarly indicate high disease activity and have been associated with poor response to IVIG (14). These laboratory findings likely reflect both pharmacokinetic alterations and underlying disease severity.

Genetic Determinants of Response

Genetic susceptibility influences both disease risk and treatment response. Variants in genes regulating immune signaling pathways, apoptosis, and antibody receptor function have been associated with IVIG resistance. For example, polymorphisms in ITPKC affect calcium signaling in T cells, while variants in CASP3 influence apoptosis of activated immune cells (15).

Fc receptor polymorphisms may alter interactions between immunoglobulin and immune effector mechanisms, affecting the immunomodulatory effects of IVIG. Genome-wide association studies have identified additional loci related to cytokine regulation and vascular inflammation. These findings support the concept that KD is a genetically complex disorder with heterogeneous clinical manifestations.

Clinical Predictors of IVIG Resistance

Several clinical scoring systems have been developed to identify patients at high risk of treatment failure, particularly in Japan. Common predictors include young age, prolonged fever, elevated inflammatory markers, anemia, hypoalbuminemia, and hepatic dysfunction (16). However, these models demonstrate variable performance across different populations, limiting their universal applicability. Persistent fever following IVIG infusion remains the most practical indicator of resistance. Early recognition is essential because delayed control of inflammation significantly increases the risk of coronary artery abnormalities. Numerous clinical and laboratory factors have been associated with treatment resistance. These predictors are summarized in **Table 1**, which highlights the multifactorial nature of IVIG nonresponse.

Table 1. Factors Associated with IVIG Resistance in Kawasaki Disease

Category	Examples
Demographic	Younger age, male sex
Clinical	Prolonged fever, early coronary changes
Laboratory	Elevated CRP, anemia, hypoalbuminemia, elevated liver enzymes
Immunologic	High cytokine levels
Genetic	Variants in immune regulatory genes

As shown in **Table 1**, resistance arises from the convergence of multiple biological and clinical factors rather than a single determinant. Scoring systems based on these variables have been developed, particularly in Japanese populations, but their predictive accuracy varies across ethnic groups (14).

Coronary Artery Injury and Long-Term Outcomes

Coronary artery aneurysm formation is the most serious complication of KD. Persistent inflammation damages the vascular wall, leading to structural weakening and dilation. Aneurysms may regress, remain stable, or progress to stenosis and thrombosis. Giant aneurysms carry the highest risk of myocardial infarction and sudden death (5). Even patients without persistent aneurysms may exhibit long-term vascular abnormalities, including endothelial dysfunction and increased arterial stiffness. These findings suggest that KD may predispose to premature cardiovascular disease later in life, emphasizing the importance of optimal acute management and long-term surveillance (17).

Adjunctive Therapies for Resistant Disease

Management of IVIG-resistant KD includes repeat IVIG infusion, corticosteroids, tumor necrosis factor inhibitors, and interleukin-1 blockade. Early adjunctive therapy in high-risk patients may reduce coronary complications, although optimal treatment strategies remain under investigation (18).

Management of IVIG-resistant KD includes repeat IVIG infusion, corticosteroids, tumor necrosis factor inhibitors, and interleukin-1 blockade. **Table 2** summarizes commonly used second-line therapies.

Table 2. Adjunctive Treatments for IVIG-Resistant Kawasaki Disease

Therapy	Mechanism	Clinical Considerations
Repeat IVIG	Additional immunomodulation	Common first step
Corticosteroids	Broad anti-inflammatory	Useful in high-risk patients

TNF inhibitors (e.g., infliximab)	Cytokine blockade	Rapid fever resolution
IL-1 blockers (e.g., anakinra)	Targeted pathway inhibition	Promising for refractory cases

As indicated in **Table 2**, treatment strategies increasingly target specific inflammatory pathways, reflecting growing recognition of disease heterogeneity (16).

Discussion

Interindividual variability in response to intravenous immunoglobulin therapy in Kawasaki disease represents one of the most clinically consequential and biologically complex aspects of this pediatric vasculitis. Although IVIG has dramatically reduced the incidence of coronary artery aneurysms, treatment resistance persists in approximately 10–20% of patients and remains the strongest predictor of adverse cardiovascular outcomes (1,2). The persistence of this resistant subgroup despite standardized therapy underscores the heterogeneity of KD pathobiology and challenges the notion that the disease represents a uniform inflammatory process. Instead, accumulating evidence suggests that KD encompasses a spectrum of immunologic phenotypes characterized by differing patterns of cytokine activation, endothelial injury, and vascular remodeling.

From a pharmacologic perspective, variability in drug exposure appears to be a critical determinant of treatment success. The conventional dosing regimen of 2 g/kg was established empirically rather than through individualized pharmacokinetic modeling. In the setting of acute systemic inflammation, increased capillary permeability facilitates extravasation of immunoglobulin into interstitial spaces, reducing effective intravascular concentrations (3). Concurrent hypoalbuminemia reflects protein leakage and may further diminish oncotic pressure, exacerbating distributional changes. Studies have demonstrated that patients with higher inflammatory markers often exhibit faster clearance of infused immunoglobulin, suggesting that standard dosing may be insufficient for those with severe disease (4). These observations raise the possibility that therapeutic drug monitoring or weight-adjusted pharmacokinetic models could improve outcomes, although such approaches are not yet routinely implemented in clinical practice.

Immunologic heterogeneity provides an additional explanatory framework. KD involves activation of multiple inflammatory pathways, including both innate and adaptive immune responses. Elevated levels of interleukin-1β, interleukin-6, tumor necrosis factor-α, and other mediators correlate with disease severity and risk of coronary artery involvement (5). IVIG exerts broad anti-inflammatory effects, but its mechanisms may not adequately suppress all pathogenic pathways in every patient. In particular, interleukin-1–driven inflammation has been implicated in refractory cases, consistent with clinical trials demonstrating benefit from interleukin-1 blockade in IVIG-resistant disease (6). This finding supports the concept that KD encompasses distinct inflammatory endotypes, some of which may respond poorly to nonspecific immunomodulation.

The role of regulatory immune mechanisms is equally important. Successful IVIG therapy is associated with expansion of regulatory T cells and suppression of activated effector cells. Patients who fail to exhibit this regulatory shift may experience persistent inflammation despite treatment. Polymorphisms affecting Fc receptor function can alter immune cell responses to immunoglobulin, influencing therapeutic efficacy (7). These variations highlight the complex interplay between host immunogenetics and pharmacologic intervention. Genetic susceptibility further contributes to variability in treatment response. Genome-wide association studies have identified variants in genes involved in calcium signaling, apoptosis, and immune regulation that correlate with both disease risk and resistance to IVIG (8). For example, polymorphisms in ITPKC influence T-cell activation pathways, while variants in CASP3 affect apoptosis of immune cells. Differences in Fc receptor genes may modify interactions between IVIG and immune effector mechanisms. Although genetic testing is not yet standard practice, these findings suggest that individualized therapy based on genetic profiling may eventually become feasible.

Clinical predictors of resistance largely reflect underlying biological processes rather than independent causal factors. Younger age, prolonged fever, elevated C-reactive protein, anemia, and hypoalbuminemia are consistently associated with poor response to therapy (4). Several scoring systems have been developed to identify high-risk patients, particularly in East Asian populations where disease incidence is highest. However, these models often perform poorly in other ethnic groups, emphasizing the influence of genetic and environmental differences (9). From a clinical standpoint, persistent fever after IVIG infusion remains the most reliable indicator of resistance and should prompt reassessment and consideration of additional therapy.

The relationship between treatment resistance and coronary artery outcomes is central to the clinical significance of this variability. Persistent inflammation damages the vascular wall, leading to structural weakening, dilation, and aneurysm formation. Histopathological studies demonstrate progressive destruction of elastic laminae and smooth muscle cells in untreated or refractory disease (10). Patients who respond promptly to IVIG typically experience rapid resolution of inflammation and a low risk of coronary complications, whereas resistant patients exhibit significantly higher rates of aneurysm formation, particularly giant aneurysms associated with long-term morbidity and mortality (1).

Even in the absence of persistent aneurysms, evidence suggests that KD may have lasting effects on vascular function. Endothelial dysfunction, increased arterial stiffness, and altered lipid metabolism have been documented years after the acute illness, raising concerns about accelerated atherosclerosis in adulthood (11). These findings underscore the importance of optimal acute management to minimize long-term cardiovascular risk.

Adjunctive therapies for IVIG-resistant KD have evolved considerably over the past two decades. Repeat IVIG infusion remains a common approach, but corticosteroids, tumor necrosis factor inhibitors, and interleukin-1 antagonists are increasingly used based on emerging evidence (6,12). Early use of adjunctive therapy in high-risk patients may prevent progression of coronary artery involvement, although optimal treatment algorithms remain under investigation. The diversity of available therapies reflects the multifactorial nature of the disease and the need for tailored approaches. From a pediatric emergency medicine perspective, timely recognition and initiation of treatment are critical. Many patients present with incomplete clinical features, delaying diagnosis and increasing the risk of coronary complications. Awareness of risk factors for IVIG resistance can inform decisions regarding hospitalization, monitoring, and early consultation with cardiology specialists. Serial echocardiography is essential for assessing coronary artery involvement and guiding management.

Future directions in research emphasize precision medicine. Integration of pharmacokinetic data, cytokine profiles, genetic markers, and clinical features could enable the development of predictive models capable of identifying patients likely to benefit from specific therapies. Advances in systems biology and machine learning may facilitate this approach by analyzing complex datasets to uncover patterns not apparent through traditional methods.

Conclusion

Interindividual variability in response to IVIG therapy in Kawasaki disease reflects a multifaceted interplay of pharmacokinetic factors, immune dysregulation, genetic susceptibility, and disease severity. Although IVIG has transformed the prognosis of KD, resistance to therapy remains a major determinant of coronary artery complications and long-term cardiovascular morbidity. Recognition that KD represents a heterogeneous spectrum rather than a single uniform disease has important implications for clinical management.

Effective treatment requires early diagnosis, prompt initiation of therapy, and vigilant monitoring for persistent inflammation. Patients who fail to respond to initial IVIG infusion should be considered at high risk for coronary involvement and evaluated for additional immunomodulatory therapy. Advances in

understanding the underlying mechanisms of resistance have led to targeted treatments addressing specific inflammatory pathways, marking a shift toward personalized medicine. Long-term outcomes depend not only on acute management but also on ongoing cardiovascular surveillance. Even patients without persistent aneurysms may experience subtle vascular abnormalities that predispose them to future disease. Consequently, KD should be regarded as a condition with potential lifelong implications. Future research should focus on identifying reliable biomarkers of resistance, optimizing pharmacokinetic dosing strategies, and refining predictive models that incorporate genetic and immunologic data. Such efforts hold promise for reducing treatment failure and preventing irreversible coronary damage. Ultimately, improving outcomes in KD requires a comprehensive approach that integrates advances in immunology, pharmacology, and clinical cardiology while maintaining vigilance for this potentially devastating disease in the pediatric population.

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