International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Bridging the Gap in IgM Therapy: A Novel Protocol-Based Approach in Critical Care Setting

Khaled Sewify[1], Ahmad Elsayed[2], Mohamed Sewify[3], Abdelaziz Alshaer[4], Wael Gomaa[5], Omar Alzuwayed[6], Hani Hosny[7], Ahmed Abu Alsaud[8], Eslam Abdelshafey[9]

[1,2,3,4,5,8,9]Critical Care Department, King Fahd Military Medical Complex, Dhahran, KSA
[3]University of Nicosia, Medical School, Cyprus
[6]Pharmacy Department, King Fahd Military Medical Complex, Dhahran, KSA
[7]ER Department, Prince Sultan Medical College, Dhahran, KSA

Abstract

Background: The use of IgM-enriched immunoglobulin (Pentaglobin) in critical care settings demands thorough understanding about its pharmacokinetic properties and metabolic processes.
The biochemical processes which determine the best treatment protocols and patient selection criteria for this medication have not received sufficient study.

Objective: To develop a protocol-based methodology framework to integrate pharmacokinetic principles with metabolic pathway analysis for implementing IgM-enriched immunoglobulin therapy in critical care settings to enhance patient results and treatment optimization.

Methods: We studied all available clinical protocols and pharmacokinetic data and metabolic pathway research about IgM-enriched immunoglobulin therapy. The evidence synthesis evaluated current critical care literature from 2018 to 2025 to determine dosing algorithms and biomarker-based selection criteria and outcome monitoring protocols.

Results: The pharmacokinetic profile of IgM-enriched immunoglobulin shows distinct distribution patterns which differ from standard immunoglobulin products thus affecting how often and long patients need treatment. The metabolic pathway shows multiple complex interactions between the complement system and opsonization processes and reticuloendothelial clearance systems which affect treatment outcomes. The treatment protocol needs individualized patient assessment through phenotyping based on inflammatory markers and immune status evaluation and organ dysfunction severity determination.

Conclusions: The methodology establishes a systematic method for IgM-enriched immunoglobulin therapy implementation which combines pharmacokinetic principles with metabolic pathway analysis to achieve best patient's outcome in critical care settings.

Keywords: IgM-enriched immunoglobulin, pharmacokinetics, metabolic pathways, critical care protocols, immunomodulation, sepsis therapy

Introduction

The pathophysiology of severe sepsis and septic shock involves multiple inflammatory and immunosuppressive processes which alter both host defense capabilities and organ system operations [1]. The therapeutic use of IgM-enriched immunoglobulin preparations shows promise as an additional treatment, but healthcare providers need to understand the complete pharmacokinetic and metabolic processes that affect its clinical effectiveness [2,3].

IgM-enriched immunoglobulin therapy functions as an advanced immunomodulatory technique which goes beyond basic antibody substitution. The pentameric structure of IgM molecules with their high molecular weight and special binding properties creates distinct pharmacokinetic features which distinguish these preparations from standard immunoglobulin products [4]. The knowledge of these properties enables healthcare professionals to create evidence-based treatment plans which optimize therapeutic outcomes while reducing adverse reactions [5].

The metabolic pathways which process IgM-enriched immunoglobulins involve multiple physiological systems that include complement activation cascades and opsonophagocytic enhancement mechanisms and reticuloendothelial system interactions [6,7]. The therapeutic effects of administered immunoglobulin preparations depend on the combined effects of distribution and elimination pathways and metabolic processes which are influenced by these pathways. The implementation of complex therapies in modern critical care requires healthcare professionals to use systematic methods which unite pharmacokinetic knowledge with clinical decision-making algorithms [8].

The effectiveness of IgM-enriched immunoglobulin treatment shows substantial differences when treating different patient groups and medical situations [9,10]. The differences in pathophysiology and immune status and treatment-host response interactions most likely explain the observed variability in treatment outcomes. The development of standardized treatment protocols which consider these variables stands as an essential requirement for modern critical care medicine [11].

The current methodology establishes a complete system for IgM-enriched immunoglobulin therapy implementation which combines pharmacokinetic knowledge with metabolic pathway analysis and individual patient characteristics to create a unified treatment protocol. The method works to achieve better treatment results through a system that helps medical staff execute the approach in diverse critical care settings.

Review

- **Pharmacokinetic Principles and Distribution Characteristics**

The pharmacokinetic profile of IgM-enriched immunoglobulin preparations shows distinct patterns because of the pentameric structure of immunoglobulins and their behavior in physiological distribution systems [12]. The large molecular weight of these compounds leads to distinct distribution patterns after intravenous administration which differs from standard immunoglobulin preparations and affects both treatment dosing and monitoring methods [13].

The initial distribution of IgM-enriched immunoglobulin happens mainly in the intravascular space because these large molecules cannot pass through capillary walls under typical physiological conditions [14]. The large size of these molecules restricts their ability to pass through capillary walls which leads to higher plasma concentrations at the start of treatment. The distribution pattern of these immunoglobulins affects critically ill patients because their altered vascular permeability, may influence pharmacokinetic profile [15].

The elimination process of IgM-enriched immunoglobulin occurs through multiple pathways which include both receptor-specific and non-specific proteolytic breakdown mechanisms [16]. The elimination speed of immunoglobulins depends on Fc receptor interactions because macrophages in the liver and spleen function as the main sites for antibody breakdown. Knowledge of elimination pathways helps healthcare providers establish correct dosing schedules and forecast treatment duration [17].

The current dosing methods for IgM-enriched immunoglobulin treatment follow weight-based systems which take into account patient characteristics such as initial immunoglobulin level, disease severity and body fluid distribution [18]. The standard treatment protocol of 5 mL/kg/day matches 250 mg/kg/day of total immunoglobulin content for 3-5 days to achieve optimal results. Research indicates that personalized dosing methods which use pharmacokinetic modeling could lead to better therapeutic outcomes [19].

The exact connection between plasma concentration levels and clinical outcomes of IgM-enriched immunoglobulin preparations has not been fully understood [20]. The therapeutic effects of these preparations differ from conventional drugs because their action depends on several mechanisms including complement activation and immune system regulation and opsonization enhancement rather than direct concentration effects. The complex nature of these preparations requires new therapeutic drug monitoring methods that use functional tests together with standard concentration measurements.

The pharmacokinetic profile of IgM-enriched immunoglobulin depends on patient age, renal function, hepatic synthetic capacity and inflammatory conditions that affect protein binding and distribution patterns [1]. The pharmacokinetic parameters of critically ill patients need special attention because their plasma protein levels, fluid distribution and organ function change from standard values thus requiring individualized dosing strategies.

- **Metabolic Pathway Integration and Biochemical Mechanisms**

IgM-enriched immunoglobulin therapy achieves its therapeutic effects through its integration with host metabolic processes and immune system operations [2]. The therapeutic effects of these interactions depend on multiple biochemical mechanisms which determine both the strength and duration of treatment outcomes and need complete comprehension for best clinical results [3]. The therapeutic effects of IgM-enriched immunoglobulin occur mainly through its activation of the complement system which functions as a primary metabolic pathway [4]. The pentameric structure of IgM molecules enables them to bind multiple C1q molecules which results in stronger classical pathway activation than monomeric immunoglobulin formulations.

The stronger complement activation produces more complement fragments which enhance bacterial opsonization and create membrane attack complexes and trigger inflammatory mediator release [5]. The activation process of complement after IgM-enriched immunoglobulin administration follows established patterns which scientists track through sequential measurements of complement components [6]. The activation process of early complement components (C1q, C4, C2) leads to the production of activation products (C3a, C5a) and terminal complement complexes. The knowledge of these activation patterns helps medical professionals determine the best time to give doses which will keep complement activation active without depleting it to dangerous levels [7].

The metabolic pathway of opsonophagocytic enhancement depends on IgM-enriched immunoglobulin therapy [8]. The high binding strength of pentameric IgM molecules enables better pathogen detection which leads to enhanced neutrophil and macrophage phagocytic activity. The process of improved bacterial clearance through phagocytic cells depends on the complex interaction between immunoglobulin

Fc regions and phagocytic receptors and complement fragments which results in enhanced pathogen elimination [9].

The way IgM-enriched immunoglobulin preparations interact with the reticuloendothelial system determines their metabolic fate and clearance rates [10]. The Fc receptors on Kupffer cells of the liver and splenic macrophages have high expression levels which enables them to recognize and engulf immunoglobulin-pathogen complexes for therapeutic purposes and subsequent immunoglobulin clearance. The system reaches its maximum capacity during severe infections which impacts both treatment effectiveness and drug elimination rates [11].

The therapeutic effects of IgM-enriched immunoglobulin therapy on patient outcomes occur through an additional metabolic pathway which involves inflammatory mediator modulation [12]. The therapeutic preparations work through multiple mechanisms to control cytokine production and modify neutrophil activation and endothelial cell function beyond their basic pathogen-neutralizing properties. The knowledge of these effects helps doctors predict treatment results and detect possible negative side effects [13]. The complex feedback mechanisms between these metabolic pathways affect both drug effectiveness and how the body processes the medication [14]. The formation of immune complexes through enhanced complement activation leads to faster immunoglobulin consumption, but better bacterial elimination reduces the inflammatory response that drives ongoing immunoglobulin breakdown. The treatment process requires continuous monitoring systems which adapt to changing body states during the entire therapy duration [15].

- **Protocol Development and Clinical Implementation Framework**

Standardized protocols for IgM-enriched immunoglobulin therapy need to combine pharmacokinetic principles with clinical decision making-algorithms which consider individual patient characteristics and treatment goals [16]. The framework enables healthcare providers to create structured protocols for various critical care settings while preserving uniform therapeutic methods.

The clinical implementation algorithm for IgM-enriched immunoglobulin therapy uses a systematic approach to choose suitable patients for treatment and achieve the best possible results (Figure 1). The algorithm starts by identifying patients with refractory sepsis or septic shock before evaluating timing criteria and patient phenotyping to establish treatment eligibility [17].

The selection of appropriate patients for treatment protocols depends on multiple factors which determine both safety and effectiveness of the treatment [18]. The main selection criteria must show evidence of refractory sepsis or septic shock with evidence of bacterial infection and organ dysfunction according to established scoring systems and absence of contraindications like severe heart failure or known immunoglobulin allergy. The secondary criteria include specific biomarker values and immune system evaluations and assessment of active treatments that could impact treatment response [19].

The timing of therapy initiation stands as a vital protocol component which directly affects treatment results [20]. Current evidence indicates that starting treatment as soon as possible after sepsis detection within 24 hours leads to the best results by intervening before development
of irreversible immune dysfunction and organ damage. The best time for treatment initiation depends on individual patient factors and particular clinical scenarios which demand adaptable protocol approaches that respect medical practitioner decisions [1].

The dosing algorithms need to use standardized weight-based calculations together with individual patient-specific factors for making adjustments [2]. The treatment plan requires a loading dose of 0.6 mL/kg/h for six hours followed by 0.2 mL/kg/h continuously infused over 72–120 hours (3–5 days). The

established treatment plan serves as a starting point, yet healthcare providers need to adjust it according to baseline immunoglobulin levels, illness severity, and treatment effectiveness [3].

The implementation of monitoring protocols requires both safety evaluation and efficacy assessment to achieve maximum therapeutic success [4]. The safety monitoring process requires periodic checks of fluid balance, renal function and cardiovascular status while focusing on fluid overload, acute kidney injury and hypersensitivity reactions as potential complications. The assessment of efficacy requires monitoring both clinical indicators (organ dysfunction scores, hemodynamic stability and infection markers) and laboratory tests (inflammatory biomarkers and immune function indicators and pathogen clearance) [5].

Biomarker-guided therapy integration has become a new method to optimize treatment protocols which could lead to better therapeutic results [6]. The guidance of therapy depends on four biomarkers which measure baseline immunoglobulin levels, complement activity, cytokine patterns, and immune cell performance. The protocol requires patients to receive assessments at 24 hours and 48 hours to determine treatment success and decide about continuing therapy [7]. The implementation of quality assurance systems within protocols should maintain uniform practice and drive ongoing improvement [8]. The quality assurance system should perform regular protocol compliance checks, track outcomes, monitor adverse events, and update the protocol through new evidence findings. The systems protect protocol integrity while enabling researchers to make evidence-based improvements that boost therapeutic effectiveness.

- **Therapeutic Monitoring and Outcome Assessment**

The complex nature of IgM-enriched immunoglobulin therapy demands complete monitoring approaches extending beyond traditional pharmacological surveillance to track immune system performance and clinical treatment results [9]. This multidimensional monitoring system helps healthcare providers achieve optimal treatment results while ensuring patient safety throughout treatment course.

The laboratory evaluation needs to track various indicators reflecting different aspects of therapeutic response and potential adverse effects [10]. The direct measurement of therapeutic delivery and persistence through immunoglobulin level tests shows particular interest in IgM concentration because it shows both therapeutic supplementation and endogenous production changes. The assessment of complement activity through CH50 tests and individual complement component measurements helps healthcare providers understand treatment effects on body function and determine proper dosing adjustments [11].

The assessment of therapeutic response requires monitoring of the inflammatory biomarkers because it enables the measurement of inflammatory response through C-reactive protein and procalcitonin and interleukin-6 levels [12]. The markers show fast changes after starting treatment which makes them useful for both initial treatment response evaluation and identification of patients requiring treatment modifications. The protocol algorithm uses CRP 150 mg/L and PCT 10 ng/mL as phenotyping criteria to determine when to initiate treatment [13].

The evaluation of clinical outcomes needs to include immediate response indicators together with extended prediction tools [14]. The assessment of short-term treatment success depends on three main indicators which include SOFA score changes, hemodynamic stability markers, and infection control indicators showing pathogen elimination and antibiotic effectiveness. The protocol emphasizes vasopressor weaning as the main clinical target for treatment success while focusing on patients who need norepinephrine > 0.25μg/kg/min representing refractory shock phenotype [15].

The time needed for patients to achieve therapeutic results differs between patients and their medical situations so healthcare providers need to create individualized monitoring plans based on patient characteristics and treatment targets [16]. The time needed for patients to show clinical improvement after starting therapy varies between 24-48 hours for early responders, but some patients need extended observation to determine treatment success. The identification of response patterns helps healthcare providers determine proper treatment duration and select patients benefiting from alternative therapeutic approaches [17].

The monitoring process for adverse events needs special focus on side effects which are unique to IgM-enriched immunoglobulin therapy [18]. The main complications of IgM-enriched immunoglobulin therapy include fluid overload problems in heart failure patients and renal dysfunction from excessive protein intake or immune complex development and allergic reactions to the treatment despite its human-derived origin. The identification and management of these complications at an early stage stands as a vital element for delivering safe treatment [19].

The process of integrating monitoring data into clinical decision algorithms needs standardized methods which produce uniform interpretation results and suitable therapeutic modifications [20]. Decision trees and scoring systems help integrate monitoring data by establishing specific criteria to decide when to continue or modify or stop treatment based on predetermined response levels and safety limits. The protocol algorithm provides detailed instructions for response evaluation at both 24-hour and 48-hour time points which helps healthcare providers conduct structured assessments of therapeutic efficacy.

Conclusions

This study establishes a comprehensive framework for IgM-enriched immunoglobulin therapy implementation in critical care settings. The emphasis on phenotyping based on refractory shock, organ dysfunction scores, inflammatory markers, and suspected multidrug-resistant pathogens ensures appropriate patient selection while maximizing therapeutic benefit.

The overall treatment's success depends on three essential factors which include understanding unique pharmacological properties, systematic patient selection, monitoring systems and continuous quality assurance. The methodology presented offers operational guidance to critical care practitioners while emphasizing the need for continuous protocol refinement.

Acknowledgments

The authors acknowledge the nursing and clinical staff of the Critical Care Department at King Fahd Military Medical Complex for their dedication to patient care and support of clinical research activities. We also thank the pharmacy department for their expertise in immunoglobulin preparation and administration protocols.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

The data supporting the conclusions of this article are included within the article and its references. Additional data are available from the corresponding author upon reasonable request.

Figure Legend

Figure 1. Clinical Decision Algorithm for IgM-Enriched Immunoglobulin (Pentaglobin) Therapy in Treatment-Refractory Sepsis

This flowchart presents a systematic approach for implementing IgM-enriched immunoglobulin therapy in refractory sepsis cases within 24 hours of sepsis onset. This structured approach enables critical care teams to identify appropriate candidates for this specialized therapy while optimizing treatment outcomes and resource allocation in refractory sepsis management.

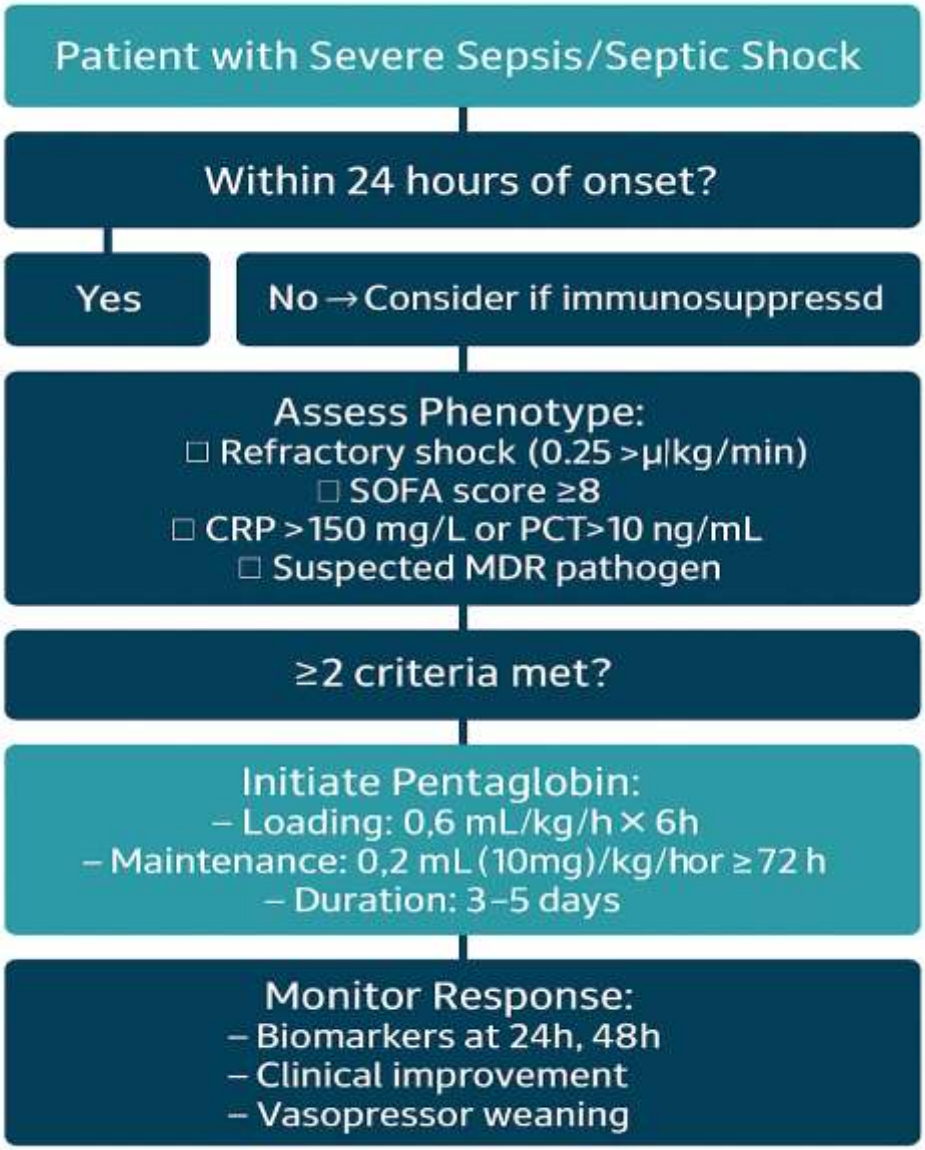

Figure 1 Flowchart for initiating Pentaglobin therapy

Abbreviations: NE, norepinephrine; SOFA, Sequential Organ Failure Assessment; CRP, C-reactive protein; PCT, procalcitonin; MDR, multidrug-resistant.

References

1. **Evans L, Rhodes A, Alhazzani W, et al.** Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Intensive Care Med.* 2021;47(11):1181–1247. **doi:**

10.1007/s00134-021-06506-y
2. **Welte T, Dellinger RP, Ebelt H, et al.** Trimodulin in severe community-acquired pneumonia (CIGMA study). *Intensive Care Med.* 2018;44(4):438–448. **doi:** 10.1007/s00134-018-5143-3
3. **Kakoullis L, Pantzaris N-D, Platanaki C, et al.** IgM-enriched immunoglobulin in adult sepsis. *J Crit Care.* 2018;47:30–35. **doi:** 10.1016/j.jcrc.2018.06.006
4. **Slim MA, Heming N, Pène F, et al.** Immunotherapy in sepsis: a scoping review. *Crit Care.* 2024;28:1–15. **doi:** 10.1186/s13054-024-04847-w
5. **Giamarellos-Bourboulis EJ, Tziolos N, Routsi C, et al.** IgM-enriched immunoglobulins in MDR infections. *Clin Microbiol Infect.* 2016;22(6):499–506. **doi:** 10.1016/j.cmi.2016.01.016
6. **Casarotta E, Damiani E, Domizi R, et al.** Patient-tailored therapy protocol in septic shock. *Front Med.* 2020;7:592282. **doi:** 10.3389/fmed.2020.592282
7. **Berlot G, Zanchi N, Moro E, et al.** IgA/IgM-enriched IVIG in sepsis. *J Clin Med.* 2023;12(14):4645. **doi:** 10.3390/jcm12144645
8. **Cui J, Wei X, Lv H, et al.** Meta-analysis of IgM-enriched IVIG in sepsis. *Ann Intensive Care.* 2019;9(1):27. **doi:** 10.1186/s13613-019-0501-3
9. **Dinleyici EC, Frey G, Kola E, et al.** IgM-enriched IVIG in pediatric sepsis: meta-analysis. *Front Pediatr.* 2023;11:1239014. **doi:** 10.3389/fped.2023.1239014
10. **Biagioni E, Tosi M, Berlot G, et al.** IgM-fat trial. *BMJ Open.* 2021;11(2):e036616. **doi:** 10.1136/bmjopen-2019-036616
11. **Martinez JI, Sánchez HF, Velandia JA, et al.** IgM-enriched immunoglobulin in sepsis: matched analysis. *J Crit Care.* 2021;64:120–124. **doi:** 10.1016/j.jcrc.2021.03.009
12. **Fernandes PA, Russo FT, da Silva LAM, et al.** Pentaglobin in hematological septic patients. *Int J Hematol Oncol Stem Cell Res.* 2021;15(2):103–113. **doi:** 10.18502/ijhoscr.v15i2.6041
13. **Domizi R, Adrario E, Damiani E, et al.** Microcirculation improvement with Pentaglobin. *Ann Intensive Care.* 2019;9(1):135. **doi:** 10.1186/s13613-019-0609-5
14. **Jarczak D, Kluge S, Nierhaus A.** IVIG in sepsis—clinical review. *Int J Mol Sci.* 2020;21(15):5543. **doi:** 10.3390/ijms21155543
15. **Abdullayev E, Kilic O, Bozan G, et al.** PIGMENT study—IgM-enriched IVIG in pediatric ICU. *Hum Vaccin Immunother.* 2020;16(8):1997–2002. **doi:** 10.1080/21645515.2020.1717057
16. **Coloretti I, Berlot G, Busani S, et al.** IVIG consensus in COVID-19. *J Clin Med.* 2021;10(16):3500. **doi:** 10.3390/jcm10163500
17. **Shankar-Hari M, Singer M, Spencer J.** Free light chains & immunoglobulins as trial targets. *Crit Care Med.* 2016;44(11):2153–2154. **doi:** 10.1097/CCM.0000000000002005
18. **Singer M, Torres A, Heinz G, et al.** Immunomodulating activity of trimodulin: post hoc CIGMA. *Crit Care.* 2023;27(1):436. **doi:** 10.1186/s13054-023-04697-2
19. **Ates I, Dogan N, Aksoy M, et al.** IgM-enriched immunoglobulin & EPO in rat sepsis model. *Pharm Biol.* 2015;53(1):78–84. **doi:** 10.3109/13880209.2014.912249
20. **Shmygalev S, Damm M, Knels L, et al.** BT086 IgM-enriched solution in endotoxemia. *Acta Anaesthesiol Scand.* 2016;60(4):502–512. **doi:** 10.1111/aas.12659