

Development of an Iranian National Clinical Practice Guideline for the Prevention, Diagnosis, and Treatment of Cytomegalovirus Infection in Hematopoietic Stem Cell Transplant Recipients

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ABSTRACT

Cytomegalovirus (CMV) infection is one of the most important causes of mortality and morbidity in hematopoietic stem cell transplant (HSCT) recipients. There are many guidelines for CMV prevention, diagnosis, and treatment. However, in resource-limited settings, the implementation of international guidelines is constrained by some differences in epidemiology, diagnostic methods, and drug availability. This study develops a national guideline for CMV management based on the healthcare context in Iran. The Guideline Development Group (GDG) is a multidisciplinary team that consists of experts in hematology, oncology, infectious diseases, virology, pharmacology, epidemiology, and methodology that develops the guideline. To have a systemic approach, a literature review was conducted based on relevant studies about CMV management in HSCT recipients from 2000 to 2025. The quality of evidence is assessed through the GRADE methodology and Delphi process. The guideline includes recommendations for risk stratification, surveillance, diagnostic methods, prophylactic strategies, and management of resistant/refractory infections. However, considering limited access to anti-viral agents such as Letermovir in Iran, alternative approaches are designed to have a feasible and effective protocol. Therefore, the guideline integrates international evidence with local healthcare real settings to provide an implementable protocol for CMV management. The context-adapted guideline results in optimized resource utilization and reduces variability in practice. Considerably, the establishment of a national registry system and periodic updates can strengthen CMV control in Iran healthcare system.

Keywords: Cytomegalovirus; CMV; Hematopoietic stem cell transplantation; Hematopoietic stem cell transplant (HSCT); Guideline; Iran healthcare system

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT), using bone marrow, peripheral blood, or cord blood as stem cell sources, is performed to treat malignancies, immunodeficiencies, and autoimmune diseases (such as systemic lupus erythematosus or multiple sclerosis). The absence of both phagocytes and adaptive immune cells (T and B cells) immediately after transplantation results in a transient state of profound immunosuppression, rendering patients highly susceptible to infections. complete immunologic incompetence, resulting in the host being extremely susceptible to infection^{1, 2}. Cytomegalovirus (CMV) is a member of the beta herpesvirus family, which, following primary infection, establishes latency in leukocytes and may reactivate during post-transplant immunosuppression, becoming a major cause of morbidity and mortality among HSCT recipients^{3, 4}. This infection is frequently seen in the early post-engraftment period. Several risk factors for CMV reactivation have been identified, such as duration of immunosuppression, serostatus of the patients and the donors, conditioning regimen, use of T-cell depletion, and the presence of acute graft-versus-host disease (GVHD). Recognizing and managing these diverse risk factors are essential for the development of effective CMV prevention and treatment strategies for HSCT recipients⁵. Studies have emphasized that effective CMV prevention, early detection, and timely intervention are essential for reducing CMV-related complications and improving transplant outcomes^{6, 7}. Two primary strategies are used to prevent CMV infection in HSCT recipients: prophylaxis and preemptive treatment (PET). Prophylaxis is recommended for high-risk patients, which involves the administration of antiviral medications to prevent infection. In PET, CMV viral load is monitored regularly using polymerase chain reaction (PCR) assays, and treatment is initiated upon detection of viral reactivation^{6, 7}. In recently updated international guidelines, Letermovir is currently considered the standard of care for primary CMV prophylaxis for up to 200 days after HCT in high-risk patients and for secondary prevention in selected circumstances. PET involves initiation of antiviral

therapy, most commonly ganciclovir or valganciclovir, and in refractory or resistant (R/R) cases, maribavir is a safer and more effective alternative^{6, 8}.

Despite recommendations for the management of CMV having been published internationally and publicly, due to the lack of accurate epidemiological data in the country and limited diagnostic facilities, the use of valid and reference guidelines in Iran faces difficulties. In addition, although the latest guidelines recommend Letermovir, this drug is not available in Iran. Therefore, a national guideline will be prepared and adjusted according to the pharmaceutical conditions and diagnostic equipment in Iran.

MATERIALS AND METHODS

Guideline Development Group (GDG)

A National Steering Committee (NSC) was formed to define the scope of the guideline, coordinate the development process, and ensure methodological rigor in accordance with the established guideline development framework¹⁰. The Guideline Development Group (GDG) included hematologists, oncologists, infectious disease specialists, clinical virologists, clinical pharmacologists, epidemiologists, and methodologists. All members declared potential conflicts of interest, and recommendations were developed through structured discussion and consensus informed by the quality of available evidence¹¹.

Guideline development process and standards

The guideline will be developed to follow internationally recognized standards for guideline development by using a structured, transparent, and evidence-based approach¹⁰. The process conformed to established methodological frameworks to ensure rigor, reproducibility, and clinical relevance by using the AGREE II instrument¹².

Evidence identification and synthesis

A comprehensive systematic search was conducted to identify studies published between January 2000 and December 2024 in PubMed/MEDLINE, Embase, Cochrane Library, Scopus, and Web of Science. The search strategy combined MeSH and free text terms related to CMV and HSCT, such as "cytomegalovirus"

OR “CMV” AND “prevention” OR “prophylaxis” OR “antiviral therapy”. Boolean operators (AND, OR) and truncation were applied to maximize sensitivity. We included studies in humans within hematology-oncology settings (RCTs, observational studies, systematic reviews, and existing guidelines) that deal with the prevention, diagnosis, or treatment of CMV infection. Exclusion criteria comprised studies published only as abstracts (unless critical), studies without full text access, or those not relevant to the Iranian epidemiological context. Two independent reviewers screened and assessed their eligibility for inclusion. The quality of evidence for each intervention will be assessed with the use of the GRADE approach, and the synthesized evidence will be used to formulate the recommendations¹¹.

Recommendation formulation and consensus process

Recommendations will be prepared through structured discussions in the guideline development group. The quality of evidence, potential benefits and harms, and practical considerations will be integrated. The strength of each recommendation will be determined with the use of the GRADE approach. Where evidence will be limited or conflicting, consensus will be achieved through iterative expert panel discussions, following a modified Delphi process¹³.

Adaptation to the national context

Local epidemiology, resource availability, healthcare infrastructure, and feasibility of implementation will be considered to adapt to the Iranian healthcare setting. To enhance the relevance and usability of the guideline, context-specific factors, such as the national incidence of CMV in HSCT recipients, access to antiviral therapies, laboratory and diagnostic capabilities, and the distribution of hematopoietic stem cell transplant centers, will be incorporated. Local regulatory requirements, insurance coverage, and national clinical practice standards will also be reviewed to ensure that the recommended intervention will be realistically put into practice in different healthcare facilities in Iran. The guideline aims to provide practical, evidence-informed, and contextually appropriate recommendations by

integrating the national considerations to apply successfully in routine clinical practice across the country.

RESULT

The guideline development is expected to result in clearly defined clinical domains that address CMV infection in allo-HSCT recipients. Key outcomes will include risk assessment, surveillance strategies, preventive measures, and therapeutic interventions for complex clinical scenarios. However, the guideline focuses exclusively on transplant-related CMV infection to maximize clinical relevance and precision. Evidence quality and clinical relevance will be systematically assessed, and recommendations will be designed by integrating international studies and practice guidelines. Moreover, recommendations will be evaluated based on feasibility, safety, and anticipated clinical impact.

Additionally, structured expert judgment supports the results. Diagnostic thresholds, process of treatment selection, and duration of treatment will be presented in a standardized format to enhance consistency across all clinical settings. Considerably, context-specific pathways will be defined based on the national healthcare setting in Iran.

Due to limited local accessibility to diagnostic methods and antiviral agents, international recommendations will not be directly implemented. Thus, alternative recommendations will be employed to achieve the required clinical outcome while optimizing available resources. To improve practical application, the guideline will include some algorithms and management flowcharts. These data-based tools are intended to support timely decision-making and reduce variability across transplant centers.

DISCUSSION

CMV infection is one of the most common complications in the HSCT process. Several international guidelines have been developed for the prevention and treatment of CMV infection, but in many countries, there are challenges in implementing these guidelines. Variability in disease epidemiology, limited access to novel diagnostic

methods, and antiviral agents are some of the significant challenges⁹⁻¹¹.

However, considering the national limitations and opportunities, a structured, evidence-based, and adapted guideline could be developed to manage the prevention, diagnosis, and treatment of patients with CMV infection in the Iranian healthcare system. The guideline will integrate an international framework with local epidemiologic data and national availability^{12,13}. The guideline will be structured around risk stratification, monitoring strategies at the molecular level, prophylactic plans, managing resistant or refractory infections, and more efficient treatment selection^{14, 15}.

In addition, the development of a nationally adapted guideline not only makes a standardized framework for transplantation centers but also remains adaptive in various situations with different laboratories and pharmacological accessibilities. Despite international recommendations strongly emphasizing Letermovir-based prophylaxis, the Iranian guideline will provide alternative strategies considering the current availability in Iran^{12, 16}.

Moreover, in the middle-resource setting, healthcare protocols should be revised based on functional barriers. Furthermore, one of the most distinctive strengths of the guideline is its multidisciplinary approach, which involves specialists across fields such as hematology–oncology, infectious diseases, virology, pharmacology, epidemiology, and transplantation medicine^{17, 18}. Such multidisciplinary collaboration is expected to improve clinical outcomes and reduce potential biases. The guideline is further strengthened by grading recommendations using the GRADE framework in addition to structured consensus through the Delphi method to improve the relevance of the study. Despite all advantages, there are some limitations that should be considered. Lack of comprehensive Iranian epidemiological data, especially long-term data of HSCT recipients, is the most important limitation¹⁹. Moreover, various diagnostic and therapeutic modalities can lead to some inconsistencies in results. However, one of the critical plans is the development of a national CMV infection registry, which can resolve such problems at the national

level⁸. Therefore, the national guideline of CMV infection in Iran will provide an evidence-based framework for the management of CMV infection in HSCT recipients in Iran. To have the optimum resource utilization and improve clinical outcomes at the healthcare level, international evidence and local experiences should be integrated. Also, designing a national CMV registry, providing periodic updates, and conferencing educational panels could enhance CMV infection management in the long term^{20, 21}.

REFERENCES

1. Umarovich BM. Developing of viral infections in hematopoietic stem-cell transplant (HSCT) recipients. *WOM*. 2025; **3**(5): 568-573.
2. Centers for Disease Control and Prevention; Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2000;**6**(6a):7-83.
3. Jakharia N, Howard D, Riedel DJ. CMV Infection in Hematopoietic Stem Cell Transplantation: Prevention and Treatment Strategies. *Curr Treat Options Infect Dis*. 2021; **13**(3): 123-140.
4. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017; **64**(1):87-91.
5. Valadkhani B, Kargar M, Ashouri A, et al. The risk factors for cytomegalovirus reactivation following stem cell transplantation. *J Res Pharm Pract*. 2016;**5**(1):63-9.
6. Chung H. CMV infections after HSCT: prophylaxis and treatment. *Blood Res*. 2025;**60**(1):33.
7. Hiskey L, Madigan T, Ristagno EH, et al. Prevention and management of human cytomegalovirus in pediatric HSCT recipients: A review. *Front Pediatr*. 2022;**10**:1039938.
8. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis*. 2001;**33**(2):139-44.
9. Ljungman P, de la Camara R, Robin CH, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis*. 2019; **19**(8):e260-e272.
10. Organization WH. WHO Handbook for Guideline Development, 2nd edition. Geneva, Switzerland: World Health Organization; 2014.
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and

- strength of recommendations. *BMJ*. 2008;336(7650):924-6.
12. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):E839-42.
13. Ford BA. The Delphi Technique: Making Sense of Consensus. *Practical Assessment. Res Eval*. 2007;12(10):1-8.
14. Silva F, Martins A, Ferraz P, et al. [Management of Cytomegalovirus Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients]. *Acta Med Port*. 2024; **37**(10):733-740.
15. Keyvani HS, Taghinezhad Saroukalaei S, Mohseni AH. Assessment of the Human Cytomegalovirus UL97 Gene for Identification of Resistance to Ganciclovir in Iranian Immunosuppressed Patients. *Jundishapur J Microbiol*. 2016; 9(5): e31733.
16. Styczyński J. Prophylaxis vs preemptive therapy in prevention of CMV infection: new insight on prophylactic strategy after allogeneic hematopoietic cell transplantation. *Acta Haematologica Polonica*. 2020; 51(1):17-23.
17. Olayemi E, Asare EV, Benneh-Akwasi Kuma AA. Guidelines in lower-middle income countries. *Br J Haematol*. 2017; 177(6): 846-854.
18. Jones C,. Ritchwood TD, Taggart T. Barriers and Facilitators to the Successful Transition of Adolescents Living with HIV from Pediatric to Adult Care in Low and Middle-Income Countries: A Systematic Review and Policy Analysis. *AIDS Behav*. 2019; **23**(9):2498-2513.
19. Oshnouei S, Asadi-Lari M ,Jebraeily M, et al. Epidemiological Profile of Adult Hematopoietic Stem Cell Transplantation for Malignant Diseases: Experience from a Reference Service in Urmia, Iran (2010-2024). *Med J Islam Repub Iran*. 2025; 39: 89.
20. Emery V, Zuckerman M, Jackson G, et al. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. *Br J Haematol*. 2013;162(1): 25-39.
21. Piñana JL, Giménez E, Vázquez L, et al. Update on Cytomegalovirus Infection Management in Allogeneic Hematopoietic Stem Cell Transplant Recipients. A Consensus Document of the Spanish Group for Hematopoietic Transplantation and Cell Therapy (GETH-TC). *Mediterr J Hematol Infect Dis*, 2024; 16(1): e2024065.