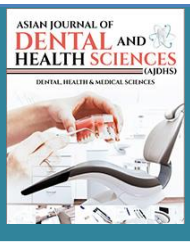

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Asian Journal of Dental and Health Sciences

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Gut Mucosal Immunity in HIV-Exposed Infants: A Review

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Article Info:

Article History:

Received 17 April 2024
Reviewed 28 May 2024
Accepted 24 June 2024
Published 15 July 2024

Cite this article as:

Obeagu EI, Obeagu GU, Gut Mucosal Immunity in HIV-Exposed Infants: A Review, Asian Journal of Dental and Health Sciences. 2024; 4(2):50-55

DOI: http://dx.doi.org/10.22270/ajdhs.v4i2.82

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Abstract

Gut mucosal immunity in infants exposed to Human Immunodeficiency Virus (HIV) presents a complex interplay of developmental processes, viral dynamics, and therapeutic interventions that significantly impact clinical outcomes. This review synthesizes current knowledge on the mechanisms, clinical implications, and therapeutic strategies concerning gut mucosal immunity in HIV-exposed infants. The gut mucosa serves as a critical site for immune maturation and defense against pathogens, but HIV infection disrupts this delicate balance, leading to compromised immune function and increased susceptibility to infections. Infants born to HIV-positive mothers experience unique challenges in gut mucosal immunity due to vertical transmission of the virus and exposure to antiretroviral therapy (ART). HIV infection disrupts gut-associated lymphoid tissue (GALT), resulting in early depletion of CD4+ T cells and compromised mucosal barrier function. These alterations contribute to microbial translocation, chronic inflammation, and immune dysregulation, impacting overall immune competence and increasing susceptibility to opportunistic infections. Despite advances in ART, persistent immune activation and residual gut mucosal damage pose ongoing challenges in achieving optimal immune reconstitution and preventing long-term complications in HIV-exposed infants. Clinical implications of compromised gut mucosal immunity in HIV-exposed infants extend beyond gastrointestinal health to encompass systemic immune dysfunction and increased risks of non-AIDS comorbidities. Impaired gut barrier function exacerbates microbial translocation, leading to systemic inflammation that may contribute to neurodevelopmental abnormalities and metabolic disorders.

Keywords: Gut, Immunity, HIV, Infants

Introduction

Human Immunodeficiency Virus (HIV) infection continues to pose significant global health challenges, particularly affecting vulnerable populations such as infants born to HIV-positive mothers. Vertical transmission of HIV remains a leading cause of pediatric HIV infections, highlighting the critical need for effective prevention, early diagnosis, and optimal management strategies. Infants exposed to HIV face unique immunological challenges, particularly in the development and maintenance of gut mucosal immunity, which plays a crucial role in immune maturation, defense against pathogens, and overall health outcomes.[1-2] The gut mucosa serves as a dynamic interface where complex interactions occur between the host immune system, commensal microbiota, and potential pathogens. In neonates and infants, the gut mucosa undergoes rapid development and maturation, crucial for establishing immune tolerance, regulating inflammatory responses, and shaping systemic immune function. However, in the context of HIV exposure, this delicate balance is disrupted early in life, impacting both local mucosal immunity and systemic immune responses. Understanding the mechanisms underlying gut mucosal immune dysfunction in HIV-exposed infants is therefore pivotal for developing targeted interventions to mitigate immune perturbations and improve clinical outcomes.[3-4] HIV infection profoundly affects gut-associated lymphoid tissue (GALT), comprising organized lymphoid structures such as Peyer's patches and gut-associated lymph nodes, as well as diffuse lymphoid aggregates in the lamina propria. These mucosal sites are critical for generating and maintaining adaptive immune responses against enteric pathogens. However, HIV selectively targets CD4+ T cells, particularly gut-homing CCR5+ CD4+ T cells, leading to their depletion and disruption of GALT architecture. Loss of CD4+ T cells compromise mucosal barrier integrity, impairs local immune surveillance, and promotes microbial translocation across the intestinal epithelium, contributing to chronic immune activation and systemic inflammation.[5-6]

The consequences of disrupted gut mucosal immunity in HIV-exposed infants extend beyond gastrointestinal health to impact overall immune competence and susceptibility to infections. Impaired gut barrier function allows for increased translocation of microbial products, such as lipopolysaccharides (LPS) and bacterial DNA fragments, into systemic circulation, triggering innate immune responses and perpetuating chronic inflammation. Persistent immune activation is associated with accelerated immune senescence, characterized by premature immune aging, reduced immune reconstitution, and heightened susceptibility to opportunistic infections and non-AIDS comorbidities.[7-8] Antiretroviral therapy (ART) represents a cornerstone of treatment in pediatric HIV infection, effectively suppressing viral replication and preserving immune function. Early initiation of ART in HIV-exposed infants is crucial for preventing disease progression and reducing the establishment of viral reservoirs. However, despite viral suppression, ART alone may not fully restore gut mucosal immunity or mitigate chronic inflammation in HIV-

infected children. Persistent immune activation and residual gut mucosal damage underscore the need for adjunctive therapies aimed at modulating immune responses and enhancing mucosal integrity.[9-10]

Gut Mucosal Immunity in HIV-Exposed Infants

The gut mucosa plays a pivotal role in immune development, acting as a barrier against pathogens while maintaining tolerance to commensal microbiota. However, HIV infection disrupts this delicate balance, leading to significant alterations in gut-associated lymphoid tissue (GALT), mucosal immune responses, and microbial composition.[11] HIV targets CD4+ T cells, particularly gut-homing CCR5+ CD4+ T cells, which are crucial for maintaining GALT integrity and regulating mucosal immunity. The depletion of these cells compromises mucosal barrier function, increases gut permeability, and facilitates the translocation of microbial products into systemic circulation. This process, known as microbial translocation, triggers chronic immune activation and inflammation, which are hallmarks of HIV pathogenesis and contribute to disease progression in infants.[12-13] Studies have shown that HIV-exposed infants exhibit early and persistent abnormalities in gut mucosal immunity, even in the absence of clinical symptoms. These abnormalities include reduced levels of GALT CD4+ T cells, altered cytokine profiles, and dysbiosis of the gut microbiota. Dysregulated immune responses in the gut mucosa not only impair local defenses against enteric pathogens but also impact systemic immune function, potentially influencing the course of HIV infection and complicating treatment outcomes.[14-15] The consequences of impaired gut mucosal immunity in HIV-exposed infants extend beyond gastrointestinal health to affect overall immune competence and susceptibility to infections. Chronic immune activation associated with gut mucosal damage may contribute to immune exhaustion, premature immune senescence, and impaired responses to vaccination. Addressing these challenges requires a multifaceted approach, including early initiation of antiretroviral therapy (ART), nutritional interventions to support gut health, and research into novel strategies to restore mucosal immune function and mitigate immune dysregulation.[16-17]

Clinical Implications

The clinical implications of altered gut mucosal immunity in HIV-exposed infants are profound and multifaceted, influencing both immediate management strategies and long-term health outcomes. Here, we explore these implications in detail:

1. **Increased Susceptibility to Infections:** Impaired gut mucosal integrity and dysregulated immune responses in HIV-exposed infants contribute to heightened susceptibility to enteric infections and systemic infections. The depletion of CD4+ T cells in gut-associated lymphoid tissue (GALT) compromises local immune defenses against pathogens, leading to frequent gastrointestinal infections such as diarrhea and opportunistic infections. These infections not only impact nutritional status and growth but also pose challenges in clinical management due to recurrent illness and the need for aggressive antimicrobial therapies.[18-20]
2. **Impact on Nutritional Status and Growth:** The gut mucosa plays a critical role in nutrient absorption and metabolism. HIV-associated gut mucosal damage can impair nutrient uptake, leading to malabsorption syndromes and nutritional deficiencies in infants. Persistent diarrhea and enteropathy further exacerbate nutritional challenges, affecting growth and development during a critical period of infancy. Optimizing nutritional support, including micronutrient supplementation and specialized formulas, is essential to mitigate these effects and support optimal growth in HIV-exposed infants.[21-23]
3. **Immune Dysregulation and Chronic Inflammation:** HIV-induced immune dysregulation in the gut mucosa contributes to chronic inflammation characterized by elevated levels of pro-inflammatory cytokines and microbial translocation. Chronic immune activation not only accelerates disease progression but also increases the risk of non-AIDS comorbidities, including cardiovascular disease, neurodevelopmental impairments, and metabolic disorders. Managing chronic inflammation in HIV-exposed infants requires a comprehensive approach that includes early initiation of antiretroviral therapy (ART), monitoring of inflammatory markers, and potentially anti-inflammatory interventions to mitigate long-term immune dysfunction.[24-26]
4. **Impact on Neurodevelopment and Cognitive Function:** Emerging evidence suggests a link between gut health, immune function, and neurodevelopment in HIV-exposed infants. Chronic inflammation and microbial dysbiosis in the gut may contribute to neuroinflammation and neurocognitive impairments, influencing cognitive development and behavioral outcomes. Addressing gut mucosal immunity as part of comprehensive pediatric HIV care is therefore crucial for optimizing neurodevelopmental outcomes and quality of life for affected infants.[27-28]
5. **Implications for Vaccine Responses:** Effective vaccination is essential for preventing opportunistic infections in HIV-exposed infants. However, impaired gut mucosal immunity and immune dysregulation may compromise vaccine responses, leading to reduced efficacy of routine childhood vaccines and vaccines against opportunistic infections such as pneumococcus and rotavirus. Strategies to enhance vaccine responses, including booster doses and novel adjuvanted vaccines, are needed to overcome these challenges and improve protective immunity in this vulnerable population.[29-31]
6. **Long-Term Health Monitoring and Management:** Longitudinal monitoring of gut mucosal integrity, immune function, and growth parameters is essential for optimizing clinical outcomes in HIV-exposed infants. Comprehensive health assessments, including screening for gastrointestinal complications, growth monitoring, and neurodevelopmental assessments, facilitate early detection and management of complications associated with impaired gut mucosal immunity. Multidisciplinary care teams, comprising pediatricians, infectious disease specialists, nutritionists, and developmental psychologists, collaborate to provide integrated care that addresses the complex health needs of HIV-exposed infants and supports long-term health and well-being.[32-35]

Challenges

Addressing the challenges associated with gut mucosal immunity in HIV-exposed infants is crucial for optimizing clinical management and improving long-term health outcomes. These challenges span various aspects of care and research:

1. **Early Diagnosis and Access to Care:** One of the primary challenges is ensuring early diagnosis of HIV infection in infants born to HIV-positive mothers. Access to early infant diagnosis (EID) services remains limited in many resource-limited settings, delaying the initiation of antiretroviral therapy (ART) and potentially compromising immune reconstitution. Timely identification of HIV-exposed infants is essential to mitigate the impact of viral exposure on gut mucosal immunity and overall health outcomes.[36-37]

2. **Impact of Vertical Transmission and Breastfeeding:** Vertical transmission of HIV remains a significant mode of infection in infants. Breastfeeding poses additional challenges, as it provides nutritional benefits while also potentially exposing infants to the virus. Balancing the nutritional advantages of breastfeeding with the risk of HIV transmission requires careful counseling and support for mothers, as well as adherence to ART regimens to reduce viral load and minimize transmission risk.[38-39]

3. **Gut Mucosal Damage and Immune Dysfunction:** HIV infection disrupts gut-associated lymphoid tissue (GALT), leading to early depletion of CD4+ T cells and compromised mucosal barrier function. This damage contributes to microbial translocation, chronic immune activation, and systemic inflammation, which in turn increase the risk of opportunistic infections and non-AIDS comorbidities. Addressing gut mucosal damage and immune dysfunction requires targeted interventions to preserve mucosal integrity and enhance immune reconstitution.[40-41]

4. **Antiretroviral Therapy (ART) Challenges:** While ART is effective in suppressing viral replication and preserving immune function, challenges such as adherence, drug resistance, and side effects impact treatment outcomes in HIV-exposed infants. Pediatric formulations of ART may be limited, leading to dosing challenges and suboptimal adherence. Optimizing ART regimens and developing pediatric-friendly formulations are critical to ensure sustained viral suppression and mitigate the long-term effects of HIV on gut mucosal immunity.[42-43]

5. **Nutritional and Developmental Implications:** Impaired gut mucosal immunity in HIV-exposed infants can lead to malabsorption syndromes, nutritional deficiencies, and growth faltering. Nutritional interventions are essential to support gut health and promote optimal growth and development. However, access to adequate nutrition, especially in resource-limited settings, remains a challenge and can exacerbate the impact of HIV on immune and overall health outcomes.[44-45]

6. **Research and Resource Limitations:** Research into gut mucosal immunity in pediatric HIV infection faces challenges related to funding, infrastructure, and access to specialized laboratories and expertise. Longitudinal studies are needed to understand the long-term effects of HIV on gut health, immune function, and neurodevelopment in infants. Collaborative efforts among researchers, healthcare providers, policymakers, and community stakeholders are essential to address these challenges and advance knowledge in pediatric HIV care.[46-47]

7. **Social and Psychosocial Factors:** Stigma associated with HIV/AIDS can hinder access to healthcare services and adherence to treatment regimens, impacting overall health outcomes in HIV-exposed infants. Addressing social determinants of health, promoting maternal and family support, and integrating psychosocial support services into pediatric HIV care are crucial to improving treatment adherence, reducing stigma, and supporting holistic care for affected infants and their families.[48-49]

Therapeutic Strategies

Therapeutic strategies for addressing gut mucosal immunity in HIV-exposed infants aim to mitigate immune dysfunction, preserve mucosal integrity, and improve long-term health outcomes. These strategies involve a combination of medical interventions, nutritional support, and supportive care approaches tailored to the unique needs of pediatric patients. Here are key therapeutic strategies:

1. **Early Initiation of Antiretroviral Therapy (ART):** Early initiation of ART is critical to suppress viral replication, preserve CD4+ T cell counts, and prevent further damage to gut mucosal immunity. ART reduces viral load, which in turn decreases viral-induced immune activation and inflammation in the gut mucosa. Pediatric ART regimens, including fixed-dose combinations and age-appropriate formulations, ensure optimal dosing and adherence in infants.[50]

2. **Nutritional Support:** Optimal nutrition is essential for supporting gut mucosal health and immune function in HIV-exposed infants. Malnutrition and nutrient deficiencies can exacerbate immune dysfunction and impair growth. Nutritional interventions include breastfeeding promotion with adherence to ART by the mother, provision of infant formula when necessary, and supplementation with essential micronutrients such as vitamins and minerals. Nutrition counseling for caregivers ensures adequate dietary intake and growth monitoring.[51]

3. **Management of Opportunistic Infections:** Preventing and treating opportunistic infections are crucial components of pediatric HIV care. Infants with compromised gut mucosal immunity are at increased risk of gastrointestinal infections and systemic infections. Prophylactic antibiotics, antifungals, and vaccines (e.g., pneumococcal and rotavirus vaccines) help prevent infections. Early recognition and prompt treatment of infections reduce morbidity and mortality, supporting overall immune health.[52]

4. **Promotion of Breastfeeding with ART:** Breastfeeding provides essential nutrients and immune factors that support infant health. The benefits of breastfeeding must be balanced against the risk of HIV transmission. Exclusive breastfeeding with maternal ART adherence significantly reduces the risk of vertical transmission. Counseling mothers on safe breastfeeding practices and ensuring viral suppression through ART are critical to minimize transmission risk while promoting infant health.[53]

5. **Immune Modulation Therapies:** Innovative therapies aimed at modulating immune responses in HIV-exposed infants are under investigation. These include interventions to reduce chronic immune activation and inflammation, such as anti-inflammatory agents or immune checkpoint inhibitors. Research into probiotics and prebiotics to restore gut microbial balance (microbiota) and enhance mucosal immunity is also promising for improving gut health and immune function.[54]

6. **Monitoring and Management of Gut Health:** Regular monitoring of gut mucosal integrity and immune function is essential for early detection of complications and timely intervention. Biomarkers of gut mucosal damage, such as fecal calprotectin and zonulin levels, can aid in assessing mucosal health. Endoscopic evaluations and histopathological assessments provide insights into mucosal inflammation and damage, guiding therapeutic decisions.[55-56]

7. **Psychosocial Support:** Addressing psychosocial factors, including stigma associated with HIV/AIDS, is crucial for promoting adherence to treatment and overall well-being in affected infants and their families. Supportive care services, including counseling, peer support groups, and community outreach programs, help reduce stigma, improve treatment adherence, and enhance quality of life for HIV-exposed infants and their caregivers.[57-58]

8. **Research and Development:** Continued research into novel therapeutic approaches, including vaccines targeting

mucosal immunity and immune modulation therapies, is essential to advance pediatric HIV care. Collaborative efforts among researchers, healthcare providers, and pharmaceutical companies are needed to develop new treatment options tailored to the unique immunological challenges of HIV-exposed infants.[59]

Conclusion

Gut mucosal immunity in HIV-exposed infants represents a critical area of research and clinical management, with profound implications for immune development, infectious disease susceptibility, and long-term health outcomes. HIV infection disrupts the delicate balance of gut-associated lymphoid tissue (GALT), leading to early depletion of CD4+ T cells, compromised mucosal barrier function, and chronic immune activation. These immunological perturbations contribute to increased susceptibility to infections, nutritional challenges, and systemic inflammation, impacting overall health and quality of life in affected infants. Addressing the challenges associated with gut mucosal immunity in HIV-exposed infants requires a multifaceted approach that integrates early diagnosis, optimized antiretroviral therapy (ART), nutritional support, management of opportunistic infections, and innovative immune modulation strategies. Early initiation of ART is pivotal in suppressing viral replication, preserving immune function, and mitigating mucosal damage. Nutritional interventions, including breastfeeding with ART adherence and nutrient supplementation, support optimal growth and immune health, while management of opportunistic infections reduces morbidity and mortality.

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