

**Mini-Review****Open Access****Prematurity as a secondary immunodeficiency disorder with increased risk of infections: A mini-review**\*<sup>1</sup>Ibraheem, R. M., and <sup>2</sup>Issa, A.<sup>1</sup>Department of Paediatrics and Child Health, University of Ilorin and University of Ilorin Teaching Hospital, PMB 1515, Ilorin, Nigeria<sup>2</sup>Department of Paediatrics, Children Specialist Hospital, Ilorin, Nigeria\*Correspondence to: [ibraheem.rm@unilorin.edu.ng](mailto:ibraheem.rm@unilorin.edu.ng); [rasheedahbidmus@yahoo.com](mailto:rasheedahbidmus@yahoo.com)  
+2348033704168; ORCID: [0000-0002-3960-9740](https://orcid.org/0000-0002-3960-9740)**Abstract:**

Prematurity significantly increases neonatal mortality in sub-Saharan Africa. Underdeveloped immune systems and prolonged hospitalization elevate the risk of secondary immunodeficiency leading to heightened vulnerability to healthcare-associated infections, including neonatal sepsis from various sources like intrauterine, intrapartum, and postnatal agents. This review explores the impact of prematurity on infection susceptibility and the role of immature immunity. A literature search using PubMed and Google Scholar identified relevant articles published between January 1980 and December 2022, focusing on terms such as "preterm," "prematurity," "neonatal sepsis," and "secondary immunodeficiency." Despite neonatal susceptibility to sepsis, accurate incidence estimates are lacking in many countries, and preterm infants face higher morbidity and mortality risks compared to full-term babies. Early-onset infections usually manifest within the first 72 hours post-delivery, while late-onset neonatal sepsis occurs after this period. Immaturity affects various immune system components, with gestational age influencing functionality. The compromised innate immune response in preterm infants involves factors such as fragile skin, reduced tear/mucus production, and low antimicrobial peptide levels. Complement deficiencies and impaired neutrophil function increase susceptibility to infections. Macrophages, dendritic cells, and natural killer cells exhibit reduced activity, impacting viral clearance. Preterm infants also have lower immunoglobulin (Ig) G levels, contributing to a weakened adaptive immune response. Hypogammaglobulinaemia heightens susceptibility to infections relying on antibody-mediated protection, while low secretory IgA production and delayed antibody response predispose to gastrointestinal and respiratory infections. The combined effect of immature immunity and medical interventions heightens preterm infants' susceptibility to pathogens. Recommendations for mitigating infection risks include antimicrobial stewardship, prompt initiation of exclusive breastfeeding, and timely administration of routine vaccinations.

**Keywords:** Secondary immunodeficiency; Preterms; Innate; Adaptive; Neonatal sepsis

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Copyright 2024 AJCEM Open Access. This article is licensed and distributed under the terms of the Creative Commons Attribution 4.0 International License [<a rel="license" href="http://creativecommons.org/licenses/by/4.0/">](http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided credit is given to the original author(s) and the source. Editor-in-Chief: Prof. S. S. Taiwo**La prématurité en tant que trouble d'immunodéficience secondaire avec risque accru d'infections: une mini-revue**\*<sup>1</sup>Ibraheem, R. M., et <sup>2</sup>Issa, A.<sup>1</sup>Département de Pédiatrie et de Santé Infantile, Université d'Ilorin et Hôpital Universitaire de Ilorin, PMB 1515, Ilorin, Nigeria<sup>2</sup>Département de Pédiatrie, Hôpital Spécialisé Pour Enfants, Ilorin, Nigeria\*Correspondance à: [ibraheem.rm@unilorin.edu.ng](mailto:ibraheem.rm@unilorin.edu.ng); [rasheedahbidmus@yahoo.com](mailto:rasheedahbidmus@yahoo.com)  
+2348033704168; ORCID: [0000-0002-3960-9740](https://orcid.org/0000-0002-3960-9740)**Résumé:**

La prématurité augmente considérablement la mortalité néonatale en Afrique subsaharienne. Un système

immunitaire sous-développé et une hospitalisation prolongée augmentent le risque d'immunodéficience secondaire conduisant à une vulnérabilité accrue aux infections nosocomiales, y compris la septicémie néonatale provenant de diverses sources telles que les agents intra-utérins, intrapartum et postnatales. Cette revue explore l'impact de la prématurité sur la susceptibilité aux infections et le rôle d'une immunité immature. Une recherche documentaire utilisant PubMed et Google Scholar a identifié des articles pertinents publiés entre janvier 1980 et décembre 2022, se concentrant sur des termes tels que "prématuré", "prématurité", "septicémie néonatale" et "immunodéficience secondaire". Malgré la susceptibilité néonatale au sepsis, des estimations précises de l'incidence font défaut dans de nombreux pays, et les nourrissons prématurés sont confrontés à des risques de morbidité et de mortalité plus élevés que les bébés nés à terme. Les infections précoces se manifestent généralement dans les 72 heures suivant l'accouchement, tandis que les infections néonatales tardives surviennent après cette période. L'immaturité affecte divers composants du système immunitaire, l'âge gestationnel influençant la fonctionnalité. La réponse immunitaire innée compromise chez les nourrissons prématurés implique des facteurs tels qu'une peau fragile, une production réduite de larmes/mucus et de faibles niveaux de peptides antimicrobiens. Les carences en complément et la fonction altérée des neutrophiles augmentent la susceptibilité aux infections. Les macrophages, les cellules dendritiques et les cellules tueuses naturelles présentent une activité réduite, ce qui a un impact sur la clairance virale. Les nourrissons prématurés ont également des taux d'immunoglobuline G plus faibles, ce qui contribue à affaiblir la réponse immunitaire adaptative. L'hypogammaglobulinémie augmente la susceptibilité aux infections reposant sur une protection médiée par les anticorps, tandis qu'une faible production d'IgA sécrétoires et une réponse retardée des anticorps prédisposent aux infections gastro-intestinales et respiratoires. L'effet combiné d'une immunité immature et d'interventions médicales augmente la sensibilité des nourrissons prématurés aux agents pathogènes. Les recommandations pour atténuer les risques d'infection comprennent la gestion des antimicrobiens, le début rapide de l'allaitement maternel exclusif et l'administration en temps opportun des vaccinations de routine.

Mots-clés: Déficit immunitaire secondaire; Prématurés; Innée; Adaptative; Sepsie néonatale

## Introduction:

Prematurity is a complex issue with wide-ranging socio-economic implications for individuals, families, and societies. Immaturity of the immune system and other challenges in the management of these babies affect the immediate health of premature infants but also have long-term consequences that can impact their quality of life and place a strain on the healthcare and social systems. Premature/preterm babies refer to babies born before the completion of 37 weeks of gestation (1). There are three groups based on gestational age; extremely preterm (< 28 weeks), very preterm (28-32 weeks), and moderate-to-late preterm (32-36 weeks) (2). The preterm delivery occurs due to maternal- or baby-related factors and may occur spontaneously or by caesarian section (1).

Approximately 15 million infants are born prematurely annually, constituting roughly 11% of all births globally (2). In sub-Saharan Africa, the prevalence of prematurity reportedly ranged from 3.4% to 49.4% (3). In 2019, there was a significant reduction in global newborn deaths, dropping from 5 million in 1990 to 2.4 million (4). Nearly half (47%) of all deaths among under-five children occurred during the neonatal period, with approximately one-third of these deaths occurring on the day of birth and nearly three-quarters occurring within the first week of life, with prematurity as one of the leading causes (2,4).

In 2019, sub-Saharan Africa had the highest neonatal mortality rate, with 27

deaths per 1,000 live births, closely followed by Central and Southern Asia, where the rate was 24 deaths per 1,000 live births. Nigeria ranked as the second country with the highest number of neonatal deaths after India, with 270,000 deaths in 2019 (4).

Despite neonates being particularly susceptible to sepsis, many countries lack accurate incidence estimates for this age group (5). A systematic review, involving 26 studies, identified a pooled neonatal sepsis incidence of 2,824 sepsis cases per 100,000 live births, and a mortality of 17.6% (5). These figures highlight the considerable contribution of neonatal sepsis to morbidity and mortality. Moreover, there were considerable regional differences in incidence, with the low-middle-income-countries (LMICs) having the highest burden, and preterm neonates are particularly affected (5). Indeed, sepsis in preterm infants is reported to be 1000-fold more common than in term infants, and associated with higher mortality and life-long neurodevelopmental handicaps (6,7).

Secondary immunodeficiencies occur due to an external factor affecting the host's immune response, which may be a transient or persistent impairment of the function of cells or tissues of the immune system (8). The secondary immunodeficiency disorder of prematurity is associated with the immaturity of the immune system (8,9). Virtually all immune system compartments are affected, and there is a correlation between the GA and the function of these compartments (10). The younger the GA, the higher the infection susceptibility (9). Furthermore, preterm bab-

ies need intensive care with or without ventilator support, intravenous access, parenteral feeding with attendant prolonged hospital stay, and antibiotic use predispose them to healthcare-associated infections (HCAI). Hence, this study reviewed the burden of prematurity and neonatal sepsis and highlighted the different pathogens responsible for neonatal sepsis and their modes of transmission. Also, the study delves into various aspects of immunity (innate and adaptive), including the anti-infective components of breastmilk, and how each aspect is compromised in preterm babies, thus predisposing them to infections.

## Methodology:

A comprehensive literature search was conducted on PubMed and Google Scholar to identify relevant articles on prematurity and infections. The search terms were "preterm", "prematurity", "neonatal sepsis", "infections", and "secondary immunodeficiency". We confined our search to articles published in English language between January 1980 and December 2022 and identified relevant articles through a systematic process that included screening of article titles, abstracts, and full texts. Manual searches of reference lists of relevant articles provided additional articles.

Inclusion criteria for the review were articles that discussed prematurity and infections, neonatal sepsis and immunity. Two reviewers independently performed the data extraction and synthesis, with the resolution of any discrepancies through discussion.

## Results and Discussion:

### Neonatal sepsis

Neonatal sepsis (NS) refers to a systemic infection affecting a neonate, of bacterial, viral, or fungal (yeast) origin, that is associated with haemodynamic changes and other clinical manifestations, and results in substantial morbidity and mortality (11). Neonatal sepsis has been classified as either early-onset or late-onset depending on the age of onset and timing of the sepsis episode (11,12). Clinical manifestations of early-onset infections usually appear within the first 72 hours

of life while those occurring after 72 hours are regarded as late-onset (11). Bacteria are the most common pathogen of NS. Acquisition of these organisms may occur in utero, during delivery or postnatally (11,12). The infection may be systemic or localised. The implicated organism may be a commensal or opportunistic pathogen. The bacterial agents of early and late-onset NS are shown in Table 1.

Intrauterine infections can be caused by pathogens such as rubella, cytomegalovirus (CMV), parvovirus B19, varicella-zoster virus, *Treponema pallidum* (causes syphilis), and *Toxoplasma gondii*. The most common mode of transmission of hepatitis B and hepatitis C virus, human immunodeficiency virus (HIV), and herpes simplex virus (HSV) is intrapartum, although transplacental transmission also occurs (12). The maternal genitourinary and lower gastrointestinal tract flora can cause intrapartum and postpartum infections. The common bacterial agents are enteric Gram-negative organisms, Group B streptococcus (GBS), *Neisseria gonorrhoeae*, and *Chlamydia* spp while the common viruses are HSV, HIV and CMV (12). The bacterial agents that cause healthcare associated infections (HCAIs) in neonates include coagulase-negative staphylococci (CoNS), Gram-negative bacilli, *Staphylococcus aureus*, and *Candida* (Table 1), while viruses commonly causing neonatal HCAIs are enteroviruses, respiratory syncytial virus (RSV), adenovirus, rhinovirus, influenza and parainfluenza viruses.

### Defect in innate immune response in neonates

#### Physical barrier:

Preterm babies have fragile skin and mucosa, easily breachable with consequent bacterial invasion (12). Organisms such as CoNS (skin commensals) can gain entry from minute breaches in the skin (13). The enteric Gram-negatives can translocate across the gastrointestinal epithelium to cause infections (13). In preterm babies, there is decreased tear and mucus production and lack of access to the contents such as lysozyme (14,15). Thus, eye infections with discharge due to *S. aureus*, *N. gonorrhoeae* and *Chlamydia trachomatis* are common in this age group, having come across these organisms during passage through the birth canal.

Table 1: Bacterial causes of infections in neonates

Bacteria	Early-onset	Late-onset (HCAI)	Late-onset (CAI)
<b>Gram-positive</b>	+++	+	
Group B streptococcus	+++	+	+
Other streptococci	++		+
<i>Enterococcus</i>	+	++	
<i>Streptococcus pneumoniae</i>	+		
<i>Listeria monocytogenes</i>	+		
Viridian streptococci	+	++	
<i>Clostridia</i>	+		+
<i>Staphylococcus aureus</i>	+	++	
Coagulase-negative staphylococci	+	+++	
<b>Gram-negative</b>			
<i>Escherichia coli</i>	+++	+	++
<i>Klebsiella</i> spp		++	
<i>Haemophilus influenzae</i>	+	+	
<i>Neisseria gonorrhoeae</i>	+		
<i>Neisseria meningitidis</i>	+	+	
<i>Proteus</i> spp		+	
<i>Salmonella</i> spp			+
<i>Pseudomonas</i> spp		+	
<i>Serratia</i>		+	
<i>Enterobacter</i>		+	
<i>Citrobacter</i>		+	+
<i>Bacteroides</i>	+	+	
<b>Others</b>			
<i>Treponema pallidum</i>	+		

+ connotes the relative frequency of occurrence; HCAI=Healthcare associated infection; CAI=Community associated infection; Source: (ref 12)

### Soluble factors and complements:

The levels of some antimicrobial peptides (AMPs) such as bactericidal permeability-increasing protein (BPI), defensins and collectins increase with gestational age (10). These substances produced by epithelial cells and phagocytes have direct bactericidal effects. Defensins and BPI can disrupt bacterial cell membranes. BPI is also fungicidal, thus, its deficiency contributes to *Candida* infection (16).

Mannose-binding lectin (MBL) opsonises bacteria, binds to C1q receptors on the macrophage to initiate phagocytosis and is a component of the MBL pathway of complement activation (17). Also, surfactants are crucial in the host defence against infection. The surfactant-associated proteins (SP), SP-A and SP-D, are collectins that enhance bacterial and viral clearance (18). SP-A and SP-D proteins can also bind to fungi to facilitate agglutination and phagocytosis by host cells (18). The low levels of these soluble factors in neonates increase their susceptibility to infections with poor organism clearance.

Breast milk contains a lot of anti-infective substances (Box 1) effective in combating various pathogens involved in respiratory

and gastrointestinal infections (19,20). Pre-term infant faces challenges in utilizing these substances because of difficulties in breastfeeding and the underdeveloped suck and swallow reflexes. Hence, the risk of preterm babies for sepsis increases.

The levels and functional capacity of the complement system components are decreased in newborns, especially preterms (17). The complements are involved in opsonisation, chemotaxis, and killing of microbes. These deficiencies increase the infection risk from encapsulated organisms such as *S. pneumoniae*, *N. meningitidis*, and Gram-negative bacteria (15).

### Neutrophils:

Preterm babies have decreased neutrophil precursor pool and low intracellular killing by reactive oxygen intermediaries (ROIs) compared with term babies (21). Furthermore, neutrophils cannot cast the neutrophil extracellular traps (NETs), which therefore compromise the preterms' innate defensive ability to bind some Gram-positive and Gram-negative bacteria and fungal hyphae (17,22).

Box 1: Anti-infective contents of breast milk

<b>Cells</b> <ul style="list-style-type: none"> <li>Granulocytes</li> <li>Macrophages</li> <li>Lymphocytes (B and T cells)</li> </ul>	<b>Carbohydrates</b> <ul style="list-style-type: none"> <li>Oligosaccharides and polysaccharides- Prevent bacteria from binding to a mucosal surface</li> <li>Fibronectin- increase macrophage antimicrobial activity</li> </ul>
<b>Enzymes</b> <ul style="list-style-type: none"> <li>Lysozymes- bacteriostatic against <i>Enterobacteriaceae</i></li> <li>Lactoperoxidase- bactericidal</li> <li>Lipase- disrupts viral envelope</li> <li>Amylase- digests polysaccharide</li> </ul>	<b>Cytokines and chemokines</b> <ul style="list-style-type: none"> <li>Interferon-<math>\gamma</math>- antiviral activity</li> <li>IL-10- anti-inflammatory</li> <li>TGF-<math>\beta</math> (transforming growth factor-<math>\beta</math>- role in intestinal defence</li> <li>CXC chemokines- chemotactic activity for intraepithelial lymphocytes, crucial for defence against bacterial and viral infection</li> </ul>
<b>Proteins</b> <ul style="list-style-type: none"> <li>Lactoferrin- binds iron and prevents bacterial growth, especially of <i>S. aureus</i> and <i>E. coli</i></li> <li>Alpha-1-antitrypsin- anti-inflammatory</li> <li><math>\alpha</math>-Lactalbumin- has antimicrobial activity against bacteria and fungi</li> <li>Complements</li> <li>Bifidus factor- promotes growth of <i>Lactobacillus bifidus</i>, deficiency promotes <i>E. coli</i> growth</li> <li>Vitamin B12 binding protein (haptocorrin)- it binds to Vitamin B12 thereby preventing gut bacteria from utilizing it for their growth.</li> <li>Osteoprotegerin- essential for regulating Th1/Th2 balance in newborn immune system development</li> </ul>	<b>Growth factors</b> <ul style="list-style-type: none"> <li>Examples epidermal growth factor, bifidus bacteria growth factor</li> <li>Stimulates the maturation of the epithelium, hence reducing its vulnerability to pathogens</li> <li>Colony-stimulating factors (CSF) are responsible for regulating the proliferation, differentiation, and survival of milk neutrophils and macrophages</li> <li>e.g. epidermal growth factor, bifidus bacteria growth factor</li> </ul>
<b>Antibodies</b> <ul style="list-style-type: none"> <li>IgA prevents bacteria adherence in the mucosa</li> <li>Others are IgM, IgG, IgE, antiviral antibodies</li> </ul>	<b>Lipids</b> <ul style="list-style-type: none"> <li>Free fatty acids (FFAs) and monoglycerides- have lytic effects on various viruses. The FFAs have an antiprotozoal effect, especially against <i>Giardia lamblia</i></li> <li>Mucins- prevent attachment of bacteria and viruses to the epithelium by binding to organisms</li> <li>Ganglioside- protects against endotoxin-induced diarrhoea</li> </ul>

Source: (ref 19, 20)

### Macrophages, dendritic cells and natural killer (NK) cells:

Monocytes are phagocytic cells that differentiate into macrophages and dendritic cells (DCs) in tissues (10,23). Besides being capable of phagocytosis, monocytes and macrophages have bactericidal mechanisms and are potent antigen-presenting cells (APCs) to the T cells (23). Monocytes of preterm infants have reduced ability for cytokine production and a decreased ability to activate the adaptive immune system. This ability is due to the reduced expression of the major histocompatibility complex (MHC) class II molecules on leukocytes in preterm neonates (10,23).

There is also decrease in the quantity of DCs and their antigen-presenting capabilities (10). This decrease correlates with the gestation age although the levels are still low compared to adults (10). Furthermore, the preterms have decreased natural killer (NK) cell activity, which plays a significant role in viral clearance through expression of interferon-gamma (IF- $\gamma$ ) (24). The reduced NK cell activity increases susceptibility to viral infections such as RSV and adenovirus. Also, the poor activity of the alveolar macrophages predisposes to increased susceptibility to viral infections. There is also reduction in the Toll-

like receptor (TLR) signaling of the innate immune system, resulting in antigen recognition impairment and decreased cytokine production (25).

### Defect in adaptive immune response in neonates

The maturation of the adaptive immunity occurs mainly after term birth. Hence there are deficiencies in T-cell activation and cytokine production, B-cell activation and immunoglobulin production, and interactions between T- and B-cells in newborns, which is worse in preterm compared to term birth (23).

#### B-cells:

A direct relationship exists between the amount of immunoglobulin (Ig) G transferred across the placenta to the baby and the gestational age (26). Maternal transfer of IgG to the fetus commences in the third trimester (26). Thus, early preterms have low IgG compared to late preterms. These IgG are essential in the defence against extra-cellular organisms; therefore, hypogammaglobulinaemia increases susceptibility to infections such as tetanus and GBS, in which

protection is antibody-mediated (12). The type-specific IgG levels against GBS are 0.3 µg/ml, 0.5 µg/ml and 1.0µg/ml at 28 weeks, 32 weeks and term respectively (10,12). The low levels contribute to GBS susceptibility.

Preterms are predisposed to early Gram-negative enteric infections as these organisms are affected mainly by specific bactericidal and opsonic antibodies of the IgM and IgA classes (12,15). Meanwhile, IgM and IgA are not transferred across the placenta, although the baby produces them in response to in-utero infections such as toxoplasmosis, rubella, CMV, varicella, and syphilis (12). Local secretory IgA production does not start till the first six to eight weeks of life, which, coupled with the lack of breast milk intake (which is rich in IgA content), predisposes preterm babies to respiratory and gastrointestinal infections (15,27).

Neonates develop their antibodies following stimulation by the various organisms after birth. The B lymphocytes are responsible for antibody production (23). In the preterm, there are decreased marginal zone B cells in the secondary lymphoid organs, reducing the B-specific responses generated (9). The secondary lymphoid organs (spleen, lymph nodes, mucosa-associated lymphoid tissue and gut-associated lymphoid tissue) are also immature (9). Furthermore, preterms have decreased ability to produce antibodies against polysaccharide antigens.

#### **T cells:**

The T-cells involved in cell-mediated immunity consist of two main types; cytotoxic T-lymphocytes (CTL, CD8<sup>+</sup>) and helper T-lymphocytes (Th, CD4<sup>+</sup>). The T-cells recognize pathogens via presentation of peptide segments of the pathogen on MHC of either macrophages or dendritic cells to their T-cell receptors (23). The CD8<sup>+</sup> CTLs are involved in eradicating intracellular pathogens, such as viruses, following antigen presentation through MHC class I expression (23). The effector mediators for intracellular killing are perforins and granzymes (26). The CD4<sup>+</sup> T-helper (Th) cells, with Th1, Th2 and Th17 subsets, are activated by antigens presented through MHC class II molecules. The Th1 subset produces the major cytokines; interferon-γ (IFN-γ), interleukin (IL)-2, and tumour necrosis factor -alpha (TNF-α), regarded as inflammatory cytokines (23). The Th2 subset is anti-inflammatory, producing IL-4, IL-5, IL-10 and IL-13 cytokines (23).

The Th1 subset play a crucial role in mediating the killing of intracellular organisms while the Th2 subsets are responsible for

coordinating the clearance of extracellular organisms including protozoans and helminths (23,26). The Th17 subset is essential for maintaining mucosal homeostasis and activating neutrophils for the clearance of extracellular pathogens (23,26). Additionally, the regulatory T cell (T-reg) subsets are vital for preserving immune homeostasis, maintaining self-tolerance and controlling inflammation (23,26).

Without maternal infections, the baby is not exposed to antigens in-utero, therefore, it lacks "immunological memory" (27). This lack prohibits their ability to mount an adequate T-cell response soon after exposure to a pathogen (27). Also, preterms have an exaggerated expression of the genes controlling the negative regulation of IFN-γ production, T cell proliferation, and IL-10 secretion (26). Indeed, when there is an imbalance of CD4<sup>+</sup> T cells, γδ T-cells, Th17, and T-reg subsets and their associated cytokine production in the gut of preterms, necrotising enterocolitis (NEC) tends to occur. In a healthy intestine, the production of IL-17 by the γδ T-cells in the epithelial layer protects the intestinal layer and prevents bacterial translocation. However, γδ T and T-reg cells are lost in babies with NEC, while Th17 and CD4<sup>+</sup> T cells increases (26).

#### **Vaccination response:**

Studies have found that the absolute primary antibody responses to antigens in the routine vaccination schedule are lower in preterm infants vaccinated according to chronological age than in term infants (28). However, majority achieve concentrations generally accepted to correlate with protection (28). Indeed, the responses to scheduled immunisations are adequate, except for the hepatitis B vaccine, where there is a need for a repeat of the full schedule in infants who received their first dose when they weighed less than 2000 g (29).

#### **Conclusion:**

The combination of immune system immaturity and the various interventions to improve the survival of the preterm baby increases their susceptibility to pathogens. Prompt human breast milk feedings and appropriate antimicrobial use through antimicrobial stewardship program, are crucial to promote the maturation of the preterm immune system and healthy microbiome. Commencement of routine vaccination in preterms without any delay is vital.

## Contributions of authors:

RMI conceived the review idea, designed the outline, and wrote the initial draft of the manuscript. AI wrote the abstract, introduction and conclusion segment of the manuscript. Both authors approved the final manuscript.

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No conflict of interest is declared.

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