Limitations of blood culture, cardiovascular sequelae and the emerging role of metagenomic next generation sequencing in early-onset neonatal sepsis among premature infants

Limitaciones del hemocultivo, secuelas cardiovasculares y el papel emergente de la secuenciación metagenómica de nueva generación (mNGS) en la sepsis neonatal de inicio temprano en prematuros

Leni Ervina[1*], Hendri Busman[2], Khairun Nisa Berawi[3], Bambang Irawan[4], Syazili Mustofa[5]
Email: [1]leniervina01@gmail.com*, https://orcid.org/0009-0001-5401-4577
[2]hendrabusman00@gmail.com, https://orcid.org/0000-0002-6475-8385
[3]knisaberawi@gmail.com, https://orcid.org/0000-0001-5707-464X
[4]bambang98irawan@gmail.com, https://orcid.org/0009-0001-4647-2682
[5]syazilimustofa905@gmail.com, https://orcid.org/0000-0002-7646-0869
[1,2,3,4,5]Program Studi Doktor MIPA, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Lampung, Lampung, Indonesia
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Abstract

Early-onset neonatal sepsis (EOS) is a leading cause of mortality and long-term morbidity in premature infants. The cornerstone of etiological diagnosis, blood culture, is critically limited in this population by low sensitivity, prolonged turnaround time, and a high rate of culture-negative results, often leading to prolonged empirical antibiotic use. This narrative review synthesizes current evidence on these diagnostic limitations and evaluates the emerging role of metagenomic next-generation sequencing (mNGS) as a transformative, culture-independent alternative. mNGS enables rapid, comprehensive pathogen detection directly from clinical samples, significantly improving diagnostic yield, especially in culture-negative sepsis, and holds promise for guiding targeted antimicrobial therapy. Crucially, this review also examines the established link between the systemic inflammatory insult of severe neonatal sepsis and subsequent cardiovascular dysregulation, including acute hypertensive crises and an elevated risk of chronic hypertension later in life. The integration of advanced diagnostics like mNGS is thus framed within a dual imperative: to optimize acute management through antimicrobial stewardship and to potentially mitigate the long-term programming of cardiovascular disease by enabling faster control of the inflammatory cascade. While challenges in standardization, cost, and interpretation remain, mNGS represents a pivotal step toward precision medicine in neonatology, aiming to improve not only immediate suravival but also the lifelong health trajectory of vulnerable premature infants.

Keywords: Neonatal hypertension, cardiovascular sequelae, early-onset neonatal sepsis, premature infants, blood culture, metagenomic next-generation sequencing.

Resumen

La sepsis neonatal de inicio temprano (SIT) es una de las principales causas de mortalidad y morbilidad a largo plazo en prematuros. El hemocultivo, la piedra angular del diagnóstico etiológico, se ve gravemente limitado en esta población por su baja sensibilidad, el prolongado tiempo de respuesta y la alta tasa de resultados negativos en los cultivos, lo que a menudo conlleva el uso prolongado de antibióticos empíricos. Esta revisión narrativa sintetiza la evidencia actual sobre estas limitaciones diagnósticas y evalúa el papel emergente de la secuenciación metagenómica de nueva generación (mNGS) como una alternativa transformadora e independiente del cultivo. La mNGS permite la detección rápida y completa de patógenos directamente en muestras clínicas, lo que mejora significativamente el rendimiento diagnóstico, especialmente en la sepsis con cultivo negativo, y es prometedora para guiar la terapia antimicrobiana dirigida. Fundamentalmente, esta revisión también examina el vínculo establecido entre la agresión inflamatoria sistémica de la sepsis neonatal grave y la posterior desregulación cardiovascular, incluyendo crisis hipertensivas agudas y un mayor riesgo de hipertensión crónica en etapas posteriores de la vida. La integración de diagnósticos avanzados como la mNGS se enmarca, por lo tanto, en un doble imperativo: optimizar el manejo agudo mediante la optimización del uso de antimicrobianos y mitigar potencialmente la programación a largo plazo de la enfermedad cardiovascular al permitir un control más rápido de la cascada inflamatoria. Si bien persisten los desafíos en la estandarización, el costo y la interpretación, la mNGS representa un paso fundamental hacia la medicina de precisión en neonatología, con el objetivo de mejorar no solo la supervivencia inmediata, sino también la trayectoria de salud a lo largo de la vida de los bebés prematuros vulnerables.

Palabras clave: Hipertensión neonatal, secuelas cardiovasculares, sepsis neonatal de inicio temprano, bebés prematuros, hemocultivo, secuenciación metagenómica de nueva generación.

Introduction

Neonatal sepsis remains a critical global health challenge, representing a leading cause of morbidity and mortality in the first month of life, with the burden disproportionately high among premature infants[1,2]. Early-onset neonatal sepsis (EOS), typically manifesting within the first 72 hours, poses a particularly urgent diagnostic dilemma due to its rapid progression and nonspecific clinical presentation in a physiologically vulnerable host[3]. The imperative for swift and accurate pathogen identification is paramount to guide life-saving antimicrobial therapy and mitigate adverse outcomes.

The diagnostic landscape for EOS has long been anchored by blood culture, considered the conventional gold standard. However, its application in the neonatal intensive care unit, especially for premature infants, is fraught with significant limitations. Low circulating pathogen loads, the minimal blood volumes that can be safely obtained, and frequent administration of empirical antibiotics prior to sampling collectively contribute to poor sensitivity and a high rate of culture-negative results. This diagnostic uncertainty often compels clinicians to resort to prolonged courses of broad-spectrum antibiotics, a practice that fuels the global crisis of antimicrobial resistance and disrupts the nascent neonatal microbiome.

This scenario of diagnostic inadequacy necessitates a paradigm shift towards more precise, culture-independent technologies. In this context, metagenomic next-generation sequencing (mNGS) has emerged as a revolutionary tool. By enabling the direct detection and identification of microbial nucleic acids from clinical samples without prior cultivation, mNGS offers the potential to overcome the inherent delays and low yields of traditional culture. Its capacity to detect a wide array of pathogens—including fastidious bacteria, viruses, and fungi—in a single assay is particularly advantageous for diagnosing sepsis in neonates, where the etiological spectrum can be broad and atypical[1].

Simultaneously, a growing body of evidence underscores the profound and often long-term impact of severe neonatal infections on cardiovascular health. Systemic inflammation and hemodynamic instability during critical septic episodes can precipitate acute hypertensive crises and are increasingly recognized as potential instigators of long-term vascular remodeling and hypertension risk later in life[11,12]. This establishes a critical, yet underexplored, link between the immediacy of infectious diagnosis and the longitudinal trajectory of cardiometabolic health[13,14]. Therefore, improving the diagnostic precision for conditions like EOS is not only a matter of acute survival but also a potential intervention point for mitigating future cardiovascular morbidity, including hypertension, in this high-risk population.

The convergence of these two frontiers—advanced molecular diagnostics and the cardiometabolic sequelae of neonatal illness—forms the rational basis for this review[15,16]. We posit that the integration of sophisticated mNGS platforms into the diagnostic algorithm for EOS can serve a dual purpose: revolutionizing acute etiological clarification and, by enabling more targeted therapy, potentially attenuating the inflammatory cascade that contributes to future hypertensive risk. This review aims to synthesize current evidence on the limitations of traditional diagnostics, evaluate the emerging role of mNGS for EOS in preterm infants, and discuss this evolution within the broader imperative of improving both acute outcomes and long-term cardiovascular health in survivors of neonatal sepsis.

Materials and methods

This study was conducted as a structured narrative literature review designed to synthesize contemporary evidence across two interconnected domains: the evolving diagnostic landscape for early-onset neonatal sepsis in premature infants, and the emerging understanding of its implications for cardiovascular sequelae, including hypertension[17,18]. The primary objective was to critically appraise the limitations of conventional blood culture, evaluate the transformative potential of metagenomic next-generation sequencing (mNGS), and situate these diagnostic advancements within a broader framework of improving both acute outcomes and long-term cardiometabolic health in this vulnerable population.

The review process was initiated with a comprehensive and systematic search across major electronic databases, including PubMed/MEDLINE, Scopus, and Embase, supplemented by Google Scholar to capture a wide scope of relevant literature. While no strict start date was imposed to allow for the inclusion of foundational studies, a deliberate emphasis was placed on publications from the last decade to prioritize current technological advances and evolving clinical paradigms. The search strategy employed a combination of controlled vocabulary and free-text keywords. Core search strings were built by linking concepts related to the patient population ("early-onset neonatal sepsis," "preterm infant"), diagnostic modalities ("blood culture," "metagenomic next-generation sequencing," "Oxford Nanopore"), and clinical outcomes ("diagnostic yield," "antimicrobial stewardship," "neonatal hypertension," "cardiovascular sequelae") using Boolean operators to refine the results.

Following the database search, a two-stage screening process was implemented. Initially, two reviewers independently assessed the titles and abstracts of all retrieved records for topical relevance. Articles that passed this initial screen underwent a full-text evaluation against pre-defined eligibility criteria. Studies were included if they focused on the diagnosis or outcomes of early-onset sepsis in premature infants, reported on the performance or limitations of blood culture or mNGS, or discussed acute hemodynamic consequences or long-term cardiovascular risks post-sepsis. Original research, systematic reviews, and authoritative narrative reviews were all considered. Exclusions were made for studies focused solely on adult populations, case reports with limited generalizability, or publications not available in full text.

Data from the final selection of included articles were extracted using a standardized template, capturing details on study design, population, diagnostic methods compared, key performance metrics, and reported clinical or long-term outcomes. Given the narrative and integrative aim of this review, a quantitative meta-analysis was not performed. Instead, the extracted evidence was synthesized thematically. The analysis was structured to first establish the well-documented shortcomings of the current diagnostic gold standard, then explore the technical capabilities and early clinical evidence supporting mNGS as a disruptive alternative, and finally, to weave this diagnostic discourse into the growing narrative linking severe neonatal infection to adverse cardiovascular trajectories.

To visually anchor this synthesis and provide a novel comparative analysis, two new summary tables were conceptualized and developed based on the reviewed literature. The first table offers a direct, head-to-head comparison between blood culture and mNGS, framing their relative advantages and disadvantages specifically within the urgent context of neonatal sepsis and its management implications. The second table consolidates the scattered evidence from various studies reporting on the association between neonatal sepsis and subsequent cardiovascular outcomes, ranging from acute hypertensive episodes to long-term risk. These tables are presented in the following section to provide a clear, consolidated reference point before the detailed narrative discussion. Furthermore, the original figures from the manuscript, which illustrate diagnostic pathways and sequencing technology comparisons, will be integrated at appropriate points within the Results and Discussion to enhance conceptual clarity. This methodological approach ensures a rigorous, transparent, and coherent examination of the literature, bridging the gap between microbiological diagnosis and long-term patient health.

The systematic synthesis of the reviewed literature reveals three interconnected pillars of evidence: the critical limitations of traditional blood culture in diagnosing early-onset neonatal sepsis (EOS) in premature infants, the promising capabilities of metagenomic next-generation sequencing (mNGS) as a transformative diagnostic tool, and the established link between neonatal sepsis and subsequent cardiovascular morbidity, including hypertension. These findings collectively argue for a paradigm shift in diagnostic strategy with implications for both acute and long-term patient care.

Table 1: Head-to-Head Comparison of Blood Culture and Metagenomic NGS for EOS Diagnosis

Diagnostic Parameter	Blood Culture	Metagenomic NGS (mNGS)
Principle	Relies on *in vitro* microbial growth and subsequent identification.	Direct detection and sequencing of microbial nucleic acids from the sample.
Typical Time-to-Result	24-72 hours (often 48+ hours for final identification & sensitivity).	~6-24 hours with optimized pipelines (near real-time with ONT).
Reported Sensitivity in Neonates	Low (often 34-50%), highly volume-dependent.	Significantly higher, especially in culture-negative sepsis.
Spectrum of Detection	Limited to culturable bacteria and fungi. Primarily monomicrobial.	Broad: Bacteria (culturable & unculturable), viruses, fungi, parasites. Can detect polymicrobial infections.
Impact of Prior Antibiotics	Greatly reduces sensitivity (suppresses growth).	Minimal impact; detects microbial DNA even from non-viable organisms.
Information on AMR	Provides phenotypic antibiotic susceptibility testing (AST).	Can predict AMR through detection of resistance genes (genotypic), but does not replace phenotypic AST.
Key Limitation in Preterms	Very low blood volume drastically reduces yield.	Challenging bioinformatics to distinguish true pathogens from background in low-biomass samples.

The diagnostic utility of blood culture, the longstanding gold standard, is severely constrained in the neonatal intensive care setting. Its sensitivity is frequently reported to be below 50% in cases of suspected EOS, primarily due to the minimal blood volumes obtainable from preterm infants and the common administration of empirical antibiotics prior to sampling. This low yield results in a high rate of culture-negative sepsis, leaving clinicians without an etiological diagnosis. Consequently, management relies heavily on prolonged, broad-spectrum antibiotic therapy, a practice that exacerbates the global threat of antimicrobial resistance and disrupts the vulnerable neonatal microbiome.

Table 2: Cardiovascular Sequelae Linked to Neonatal Sepsis: Clinical Evidence

Type of Sequelae	Clinical Manifestation	Supporting Evidence & Proposed Mechanisms
Acute / Short-Term	**Hemodynamic Instability & Neonatal Hypertension:** Fluctuations in blood pressure requiring vasoactive support or antihypertensive therapy.	Common in severe sepsis due to cytokine storm, endothelial dysfunction, and dysregulated vascular tone[13]. Associated with acute kidney injury.
Long-Term / Programming	**Increased Risk of Childhood Hypertension:** Higher systolic and diastolic blood pressure percentiles observed in survivors of severe neonatal sepsis.	Cohort studies linking proven sepsis with higher BP at school age[14]. Mechanisms may involve permanent vascular remodeling and altered renal development.
	Endothelial Dysfunction: Impaired vascular reactivity and arterial stiffness.	Studies showing altered flow-mediated dilation in ex-preterm infants with a history of severe infection[15].
	Metabolic Syndrome Component: Association with insulin resistance and altered lipid profiles.	Systemic inflammation may disrupt developing metabolic pathways, creating a predisposing phenotype[16].

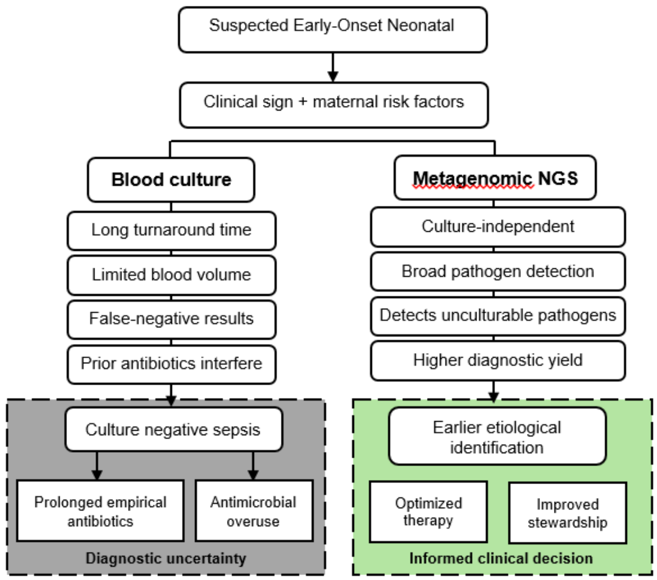
Metagenomic next-generation sequencing presents a compelling alternative by directly detecting microbial nucleic acids without the need for cultivation. This culture-independent approach bypasses the key limitations of blood culture, offering a significantly higher diagnostic yield. mNGS can identify a vast array of pathogens—bacteria, viruses, fungi, and parasites—from a single sample, proving particularly valuable for detecting fastidious or uncultivable organisms. Emerging evidence indicates that mNGS can identify causative pathogens in a substantial proportion of culture-negative sepsis cases. Furthermore, third-generation platforms like Oxford Nanopore Technology enable real-time sequencing and provide longer read lengths, which enhance the accuracy of identification and can simultaneously reveal genetic markers of antimicrobial resistance, potentially guiding targeted therapy more swiftly.

Table 3: Potential Clinical Impact Pathway: From mNGS Diagnosis to Long-Term Cardiovascular Health

Stage of Care	Impact of Precise mNGS Diagnosis	Potential Downstream Effect on Cardiovascular Risk
Acute Management	**Faster, Accurate Pathogen ID:** Enables earlier targeted or appropriate antibiotic therapy.	**Mitigates Excessive Inflammation:** Precise therapy may more rapidly control the infectious and inflammatory insult, potentially reducing the severity and duration of the cytokine-mediated damage to the cardiovascular system.
	Antimicrobial Stewardship: Facilitates earlier de-escalation or cessation of unnecessary broad-spectrum drugs.	**Preserves Microbiome:** May help protect the developing gut microbiome, which is implicated in immune and metabolic programming, indirectly influencing long-term cardiovascular health.
Follow-up & Monitoring	**Etiological Clarity:** Identifies high-risk infections (e.g., those causing severe inflammation or end-organ damage).	**Risk Stratification:** Allows for targeted long-term follow-up. Survivors of sepsis with specific pathogens or severe inflammatory markers could be enrolled in specialized cardiovascular monitoring programs (e.g., periodic BP checks, endothelial function tests).
Research & Understanding	**Discovery of Novel Pathogens:** Uncovers previously unrecognized infectious causes of sepsis and inflammation.	**Elucidates Mechanisms:** Helps researchers define clearer links between specific infectious/inflammatory insults and distinct patterns of cardiovascular programming, leading to potential preventive strategies.

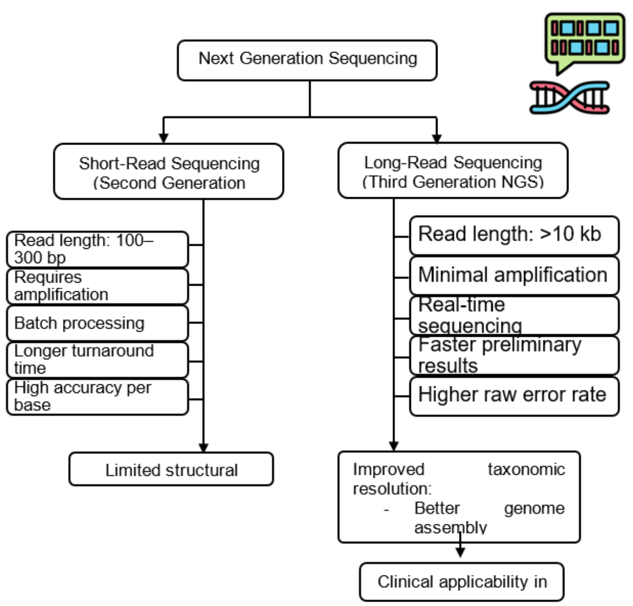
A crucial dimension illuminated by this review is the robust association between neonatal sepsis and cardiovascular dysregulation. The systemic inflammatory response during sepsis can induce acute hemodynamic instability, including neonatal hypertension, requiring immediate intervention. Perhaps more significantly, a growing body of evidence suggests that severe neonatal sepsis is an independent risk factor for the development of hypertension and other cardiovascular diseases later in childhood and adulthood. Proposed mechanisms include sepsis-induced endothelial damage, vascular remodeling, and persistent low-grade inflammation, which may irreversibly alter cardiovascular homeostasis. This link positions EOS not merely as an acute infectious crisis but as a potential early-life determinant of long-term cardiometabolic health. To provide a consolidated overview of the evidence, the following analytical summaries are presented.

Figure 1. Proposed diagnostic pathways for early-onset neonatal sepsis highlighting the limitations of blood culture and the potential role of metagenomic next-generation sequencing (NGS)



The figures illustrating the diagnostic pathway (Figure 1) and sequencing technology comparison (Figure 2) from the initial manuscript remain integral to visualizing these concepts and will be incorporated into the subsequent discussion section. Blood culture is constrained by prolonged turnaround time, limited blood volume, and high false-negative rates, whereas metagenomic NGS enables culture-independent and broader pathogen detection, potentially supporting earlier etiological identification and improved clinical decision-making.

Figure 2. Comparison between short-read and long-read sequencing technologies in clinical diagnostics.



Short-read sequencing offers high per-base accuracy but is limited by shorter read lengths and longer turnaround times. Long-read sequencing, including third-generation platforms such as Oxford Nanopore Technology, enables real-time analysis and improved taxonomic resolution, supporting its potential clinical utility in early-onset neonatal sepsis.

Discussion

The findings of this review converge on a critical juncture in neonatal care, where diagnostic technology, acute infectious disease management, and long-term cardiovascular health intersect. The well-documented inadequacy of blood culture for early-onset neonatal sepsis (EOS) in premature infants is more than a technical shortfall; it represents a systemic failure that perpetuates antimicrobial overuse and obscures the true etiology of life-threatening illness. In this context, the emergence of metagenomic next-generation sequencing (mGS) is not merely an incremental improvement but a fundamental shift towards precision medicine in the neonatal intensive care unit. By providing a rapid, culture-independent, and comprehensive microbiological profile, mNGS directly addresses the core diagnostic void, offering a path to de-escalate empirical therapy and tailor antimicrobial treatment.

However, the most profound implication of this diagnostic evolution may extend beyond the immediate hospitalization. The robust evidence linking neonatal sepsis to acute hypertensive crises and, more significantly, to an elevated risk of chronic hypertension and endothelial dysfunction in later life, reframes our understanding of the disease. Severe sepsis is now recognized as a potent inflammatory and hemodynamic insult during a critical window of developmental plasticity. The cytokine storm and vascular injury sustained during infection appear to “program” the cardiovascular system for long-term dysfunction. This establishes a compelling biological rationale for hypothesizing that earlier, more precise pathogen identification and targeted therapy with mNGS could, by mitigating the severity and duration of the inflammatory cascade, also attenuate this damaging programming effect. While direct evidence for this causal chain is still emerging, the logical pathway is clear: reducing uncontrolled inflammation may protect the developing endothelium and vascular smooth muscle, thereby potentially lowering the lifetime risk of hypertension in this vulnerable population.

The integration of platforms like Oxford Nanopore Technology, with its real-time analysis capability, further closes the loop between diagnosis and action. The potential to not only identify a pathogen but also detect its resistance genes within hours transforms sepsis management from a reactive to a proactive endeavor. This aligns perfectly with the principles of antimicrobial stewardship and, by extension, with the goal of preserving the nascent microbiome—another factor implicated in long-term metabolic and immune health. It is crucial to acknowledge, however, that the clinical adoption of mNGS faces hurdles, including bioinformatic complexity, cost, and the challenge of interpreting results in low-biomass samples where contamination must be ruled out. Therefore, its optimal role in the near future is likely as a complementary tool within a refined diagnostic algorithm, triggered by high clinical suspicion or negative conventional cultures, rather than as a wholesale replacement.

Ultimately, this synthesis argues for a holistic view of neonatal sepsis management. The goal is no longer simply survival of the acute episode, but the promotion of lifelong health. Investing in advanced diagnostics like mNGS is an investment in two key outcomes: optimizing acute care through stewardship and targeted therapy, and potentially intervening in the early-life origins of cardiovascular disease. Future research must rigorously evaluate this dual benefit, measuring not only time to effective therapy and antibiotic days saved, but also long-term cardiovascular parameters in survivors managed with mNGS-informed protocols versus standard care.

Conclusions

This review underscores that the diagnosis and management of early-onset sepsis in premature infants stand at a pivotal crossroads. Blood culture, the traditional cornerstone of diagnosis, is insufficient for the task, leading to diagnostic uncertainty, protracted antibiotic use, and missed opportunities for targeted treatment. Metagenomic next-generation sequencing emerges as a transformative technology capable of overcoming these limitations by providing rapid, comprehensive, and culture-independent pathogen detection. Its integration into clinical practice promises to revolutionize antimicrobial stewardship in the NICU, leading to more precise and timely therapy.

Critically, the discussion must expand beyond the microbiology laboratory to encompass the lifelong health trajectory of the premature infant. The established link between neonatal sepsis and subsequent cardiovascular morbidity, including hypertension, demands that we view severe infection as a formative event with lasting consequences. Therefore, the imperative for precise diagnosis is twofold: it is essential for managing the immediate life-threatening infection and represents a potential strategic point for mitigating long-term cardiovascular risk. While challenges in standardization and interpretation remain, mNGS and related technologies offer a powerful tool to address both these urgent and enduring priorities. Embracing this advanced diagnostic paradigm is not merely a technical upgrade but a necessary step towards ensuring that survivors of neonatal sepsis do not face a future compromised by preventable chronic disease. The path forward requires a concerted effort to validate these approaches, refine their implementation, and continually assess their impact on both survival and long-term quality of life.

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