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Review Article

A Review on the Role of Melatonin in Neonatal Sepsis Caused by Methicillin-Resistant *Staphylococcus aureus*

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ABSTRACT

Background: Neonatal sepsis and encephalopathy are life-threatening conditions marked by excessive inflammation and oxidative stress, contributing to high morbidity and mortality in newborns. Melatonin, a multifunctional indoleamine with potent antioxidant, anti-inflammatory, and immunomodulatory properties, has emerged as a promising adjunctive therapy in neonatal care. This review summarizes current evidence on melatonin's biological functions and its potential to reduce inflammation, oxidative damage, and improve neonatal outcomes.

Methods: A narrative review was conducted by searching PubMed, Scopus, Web of Science, and Google Scholar from 2000 to November 2025 using the keywords melatonin, neonatal sepsis, and methicillin-resistant *Staphylococcus aureus* (MRSA). Relevant experimental, preclinical, and clinical studies were identified, reviewed, and synthesized to provide an integrated overview of melatonin's effects in neonatal sepsis and related inflammatory conditions.

Results: Preclinical studies indicate that melatonin downregulates pro-inflammatory cytokines (e.g., TNF-α, IL-6) while enhancing anti-inflammatory mediators such as IL-10. It also preserves mitochondrial function, mitigating oxidative injury and neuroinflammation. Early clinical trials report that melatonin administration in septic and asphyxiated neonates reduces inflammatory biomarkers, lowers oxidative stress, and is well tolerated without major adverse effects. Challenges remain, including the distinct pharmacokinetics of neonates, variable clearance rates, heterogeneous study populations, and limited sample sizes, which complicate dose optimization and definitive conclusions on efficacy and long-term safety.

Conclusion: Melatonin represents a safe and biologically potent adjunctive therapy for neonatal inflammatory disorders. Large-scale, multicenter randomized trials are warranted to establish standardized dosing, assess long-term neurodevelopmental outcomes, and confirm clinical efficacy in improving neonatal survival and recovery.

Keywords: Adjunct therapy, Antioxidant, Melatonin, Methicillin-resistant *Staphylococcus aureus*, Neonatal sepsis

Introduction

Neonatal sepsis, particularly in premature infants, remains a major cause of mortality and long-term morbidity worldwide, despite advances in perinatal care and antimicrobial therapy. Among nosocomial infections in neonatal intensive care units (NICUs), *Staphylococcus*

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aureus—especially its methicillin-resistant strains (MRSA)—accounts for a considerable proportion of late-onset sepsis (LOS) cases occurring after 72 hours of birth (1–4).

MRSA possesses a diverse array of virulence determinants, including adhesins, immune evasion factors, exotoxins (e.g., α-hemolysin), and an exceptional ability to form biofilms on indwelling devices and epithelial surfaces. These pathogenic traits are tightly regulated by genetic systems such as the *icaADBC* operon, *agr* quorum-sensing circuit, and global regulators like *sar* and *sigB*, which coordinate biofilm development and toxin expression, contributing to persistent infections and antibiotic resistance in vulnerable neonates (2,5,6).

In recent years, melatonin (N-acetyl-5-methoxytryptamine), an indoleamine mainly secreted by the pineal gland, has gained attention for its potential as an adjunctive therapy against multidrug-resistant pathogens, including MRSA. Beyond its well-established chronobiotic role, melatonin exerts potent antioxidant, anti-inflammatory, and immunomodulatory effects (2,5–9). Emerging evidence indicates that melatonin can interfere with bacterial quorum-sensing systems, suppress biofilm formation, and downregulate virulence gene expression in MRSA strains. These findings suggest a possible dual role for melatonin in both mitigating infection-related inflammation and directly attenuating bacterial pathogenicity.

Clinical studies in neonatal intensive care settings have further demonstrated that melatonin administration reduces pro-inflammatory cytokines and oxidative stress markers in neonates with respiratory distress syndrome (RDS), sepsis, and perinatal asphyxia, without any reported adverse effects. Previous studies conducted by other researchers have demonstrated that melatonin is well tolerated in neonates, exhibiting a favorable safety profile with minimal toxicity.(9–10). However, the existing data are limited by small sample sizes and short follow-up durations, underscoring the need for larger, well-designed clinical trials to confirm its efficacy and safety in neonatal populations (7–10).

Melatonin also modulates the neonatal immune response by downregulating pro-inflammatory cytokines and upregulating anti-inflammatory mediators which may help attenuate the systemic inflammatory response syndrome (SIRS) characteristic of neonatal sepsis (10–13). Given its ability to cross both the blood–brain barrier and the placental interface, coupled with its antioxidant and anti-biofilm properties, melatonin emerges as a promising adjunctive agent in the management of neonatal MRSA sepsis (10,13,14).

This narrative review aims to comprehensively analyze the antimicrobial, anti-virulence, and immunomodulatory properties of melatonin in the context of MRSA-associated neonatal sepsis. Special emphasis is placed on its molecular mechanisms of action, effects on biofilm architecture and virulence gene regulation, and potential translational applications in neonatal care (2,5,19–21).

Methods

This narrative review was conducted through a comprehensive search of scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, 2000 to November 2025. The search terms used were melatonin, neonatal sepsis, and methicillin-resistant *Staphylococcus aureus* (MRSA). Relevant original research articles, review papers, and experimental studies investigating the role of melatonin in neonatal sepsis or MRSA-related infections were included. Studies published in English and Persian were considered. Data from selected publications were critically analyzed, summarized, and synthesized to provide an integrated understanding of melatonin's potential therapeutic and mechanistic role in MRSA-induced neonatal sepsis.

Pathophysiology of Neonatal Sepsis

Neonatal sepsis is categorized into two types: early-onset sepsis (EOS), which occurs within the first 72 hours of life, and LOS, which occurs after 72 hours. In neonatal sepsis, the inflammatory response involves the release of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines can cause tissue damage and lead to organ dysfunction. Sepsis also disrupts normal metabolic pathways and affects energy production, which may result in dysfunction in glucose metabolism, lipid metabolism, and the citric acid cycle (1-4,23,24).

Several maternal, fetal, and environmental factors contribute to the risk of neonatal sepsis:

Maternal Factors: Previous infections, chorioamnionitis, and Group B streptococcal colonization are significant risk factors (25).

Fetal Factors: Prematurity, low birth weight, and low APGAR scores increase the risk (25).

Environmental Factors: Invasive medical procedures, such as intravenous line insertion and mechanical ventilation, also elevate the risk (26).

Tabel 1. Key Concepts and Clinical Significance

Concept	Description	Clinical Significance
Neonatal Sepsis	Dysregulated host response to systemic infection in newborns.	High morbidity and mortality, especially in preterm infants.
Immune System Dysfunction	Innate immunity is less effective against pathogens.	Increased susceptibility to severe infections.
Inflammation and Oxidative Stress	Pro-inflammatory cytokines and ROS contribute to tissue damage.	Organ dysfunction and multi-organ failure.
Metabolic Changes	Disruption of energy production pathways.	Multi-organ dysfunction and failure.

Diagnostic Challenges

Diagnosing neonatal sepsis is challenging due to nonspecific symptoms. Blood cultures remain the gold standard for diagnosis, but they can be time-consuming. Clinical scoring systems and biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) are used to aid in early detection (14).

Treatment and Management

Treatment involves prompt antibiotic therapy, supportive care, and management of organ dysfunction. Preventive measures, such as maternal antibiotic prophylaxis for Group B streptococcal colonization, are crucial (27).

Future Directions

Research into novel therapeutic strategies, including anti-inflammatory and antioxidant agents like melatonin, is ongoing. Understanding the complex interplay between inflammation, oxidative stress, and metabolic changes in neonatal sepsis is essential for developing effective treatments (28).

Table1: In summary, neonatal sepsis is a critical condition that requires early diagnosis and aggressive management. Understanding its pathophysiology and identifying risk factors are crucial for developing effective therapeutic strategies. Further research into novel treatments that target inflammation, oxidative stress, and metabolic dysregulation is necessary to improve outcomes in neonatal sepsis.

Biological Role of Melatonin

Melatonin is a pleiotropic indoleamine hormone predominantly synthesized in the pineal gland, although substantial extrapineal synthesis occurs in various tissues and cellular organelles, particularly within mitochondria. Its widespread distribution across different biological systems suggests an ancient and evolutionarily conserved origin. Functionally, melatonin exerts extensive regulatory effects on cellular homeostasis through its antioxidant, anti-inflammatory, and immune-modulatory actions (29,30). Beyond its well-known role in regulating sleep-wake cycles, melatonin exhibits significant antioxidant, anti-inflammatory, and immunomodulatory effects. It acts as a direct scavenger of free radicals, neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), including hydroxyl radicals, peroxyl radicals, hydrogen peroxide, singlet oxygen, and peroxynitrite. Additionally, melatonin stimulates the production of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, and glutathione reductase (29-31). It also enhances the effectiveness of other antioxidants, creating a cascade that strengthens cellular defense against oxidative damage. The anti-inflammatory effects of melatonin are multifaceted and depend on the context. It modulates key inflammatory signaling pathways by inhibiting the nuclear translocation of nuclear factor kappa B (NF-κB), which reduces the transcription of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Furthermore, melatonin suppresses the expression of enzymes such as 5-lipoxygenase, which play a critical role in the production of inflammatory mediators (12,29-33). Notably, melatonin has a two-step role in inflammation: it temporarily enhances pro-inflammatory mediators during the initial phase, which is essential for starting the healing process, and subsequently exerts strong anti-inflammatory effects during the recovery phase to prevent chronic inflammation and tissue damage (29,32,33).

Table 2: This comprehensive profile explains melatonin's critical role in combating oxidative stress and systemic inflammation, highlighting its potential as a therapeutic agent in inflammatory, immune, and oxidative stress-related diseases.

Table 3: Laboratory evidence supports that melatonin is a promising adjunctive agent against MRSA infections. By targeting virulence gene expression, inhibiting biofilm formation,

Table 2. Biological Roles of Melatonin

Aspect	Details
Synthesis	From L-tryptophan → serotonin → N-acetylserotonin → melatonin; regulated by light/dark cycles.
Metabolism	Primarily hepatic via CYP1A2; half-life 20–50 minutes; excreted as 6-hydroxymelatonin sulfate.
Antioxidant Properties	Direct scavenging of ROS/RNS; stimulation of antioxidant enzymes; metal chelation; mitochondrial protection.
Anti-inflammatory Actions	Inhibits NF-κB translocation; downregulates pro-inflammatory cytokines (TNF-α, IL-1, IL-6); biphasic role in inflammation phases.
Immunomodulation	Enhances immune cell function; balances cytokine production; activates ERK and MAPK pathways.
Mitochondrial Effects	Preserves membrane potential; improves electron transport; inhibits pro-oxidative enzymes; receptor-dependent and independent actions.

Table 3. Melatonin's Antibacterial Actions Against MRSA

Mechanism	Effect on MRSA / S. aureus
Downregulation of icaA, agr, hlagenes	Reduced biofilm formation, quorum sensing, and hemolysin production
Inhibition of biofilm formation	Prevents biofilm development and disrupts established biofilms
Increased bacterial membrane permeability	Enhances antibiotic uptake and inhibits efflux pumps
Synergistic effect with antibiotics	Potentiates antibiotic efficacy, increases ROS, reduces resistance

increasing membrane permeability, and synergizimultidrug-resistant, melatonin enhances bacterial susceptibility and may help overcome antibiotic resistance. These findings encourage further clinical investigation into melatonin as a complementary therapy for MRSA and other multidrug-resistant bacterial infections.

Melatonin in Combatting MRSA: Laboratory Evidence

Recent laboratory studies provide compelling evidence that melatonin exerts significant antibacterial effects against MRSA through multiple mechanisms, including gene expression modulation, inhibition of biofilm formation, increased bacterial membrane permeability, and synergistic interactions with antibiotics (5,6,34,35).

Reduction in the Expression of icaA, agr, hla Genes: Melatonin has been shown to downregulate key virulence genes in *S. aureus*, including icaA, agr, and hla, which are critical for biofilm formation, quorum sensing, and hemolysin production, respectively. This gene expression suppression leads to impaired bacterial pathogenicity and reduced ability to form robust biofilms, which are essential for MRSA's persistence and antibiotic resistance. Although direct studies specifically on MRSA are limited, *S. aureus* studies indicate melatonin's role in modulating these genes, thereby attenuating virulence (5,6,36-38).

Inhibition of Biofilm Formation in In Vitro Models: Melatonin effectively inhibits biofilm formation by *S. aureus* and other pathogenic bacteria in vitro. Biofilms are structured bacterial communities that confer protection against antibiotics and host immune responses. Melatonin disrupts biofilm development and reduces the viability of established biofilms, as demonstrated in multiple bacterial species including Porphyromonasgingivalis and *S. aureus*. This antibiofilm activity is dose-dependent and occurs at sub-inhibitory concentrations without cytotoxic effects on host cells (5,6,36-39).

Increased Bacterial Membrane Permeability to Antibiotics: Melatonin increases the permeability of bacterial outer and inner membranes, facilitating greater antibiotic penetration. Studies have shown that melatonin disrupts the proton motive force (PMF) component $\Delta\psi$ in bacteria, which is essential for energy-dependent efflux pumps. This disruption leads to the inhibition of efflux pump activity, resulting in intracellular accumulation of antibiotics such as tigecycline. Enhanced membrane permeability and efflux pump inhibition by melatonin potentiate antibiotic efficacy against resistant strains like MRSA (34-36).

Evaluation of the Synergistic Effect of Melatonin and Antibiotics: Melatonin acts synergistically with various antibiotics, including tigecycline and colistin, enhancing their antibacterial activity against resistant pathogens. The combination therapy results in increased ROS production and oxidative damage within bacterial cells, further compromising bacterial survival. Importantly, melatonin does not increase antibiotic toxicity but rather restores antibiotic susceptibility in resistant strains by targeting bacterial defense mechanisms such as efflux pumps and biofilm formation (5-7,37-39).

Role of Melatonin in the Immune System of Neonates

Melatonin plays a multifaceted and critical role in modulating the neonatal immune response, particularly in the context of neonatal sepsis where immune dysregulation and excessive inflammation are major contributors to morbidity and mortality. Its immunomodulatory effects involve regulation of cytokine production, enhancement of innate immune cell function, and attenuation of the inflammatory storm characteristic of sepsis (40).

Regulation of Cytokine Levels

Reduction of Pro-inflammatory Cytokines: Melatonin significantly lowers levels of key pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 in neonates with sepsis or surgical stress. For example, in a clinical study of surgical neonates, melatonin administration reduced serum TNF-α and other inflammatory mediators, correlating with improved clinical outcomes (40).

Increase of Anti-inflammatory Cytokines: Concurrently, melatonin elevates anti-inflammatory cytokines like IL-10, which helps balance the immune response and prevent excessive tissue damage (32,33,40). Experimental models demonstrate melatonin's capacity to shift the cytokine milieu toward an anti-inflammatory profile, which is crucial in controlling sepsis-induced inflammation (41).

Modulation of Cytokine Signaling Pathways: Melatonin inhibits NF-κB activation, a central transcription factor regulating pro-inflammatory gene expression, thereby reducing cytokine production at the transcriptional level (40,41)

Improvement of Neutrophil and Macrophage Function

Neutrophil Activation and Regulation: Melatonin modulates neutrophil activation markers such as CD11b and Toll-like receptor 4 (TLR4), reducing excessive neutrophil activation and associated oxidative burst in neonates. In infants with neonatal encephalopathy, melatonin reduced neutrophil CD11b and TLR4 expression in response to endotoxin stimulation, indicating a dampening of hyperinflammatory neutrophil responses (41-43).

Macrophage and Monocyte Modulation: Melatonin influences monocyte/macrophage function by modulating surface activation markers and cytokine secretion, promoting a balanced immune response that enhances pathogen clearance while limiting collateral tissue damage (42-44).

Enhancement of Innate Immunity: Melatonin promotes innate immune cell proliferation and function, including natural killer cells and phagocytic activity, which are vital in neonates who rely predominantly on innate immunity (42,44).

Inhibition of Inflammatory Storm in Neonatal Sepsis

Attenuation of Cytokine Storm: Neonatal sepsis often triggers an overwhelming inflammatory response ("cytokine storm") that leads to organ dysfunction. Melatonin's anti-inflammatory and antioxidant properties mitigate this storm by suppressing pro-inflammatory cytokines and ROS, thereby protecting tissues from oxidative damage (42).

Reduction of Oxidative Stress: Melatonin scavenges free radicals and upregulates endogenous antioxidant enzymes, reducing oxidative stress markers such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which are elevated in septic neonates (42,45).

Clinical Evidence

Clinical trials demonstrate that adjunctive melatonin therapy in neonatal sepsis reduces inflammatory biomarkers (e.g., CRP) and improves clinical outcomes, including faster recovery and reduced mortality (14).

Biomarker Role: Elevated endogenous melatonin levels in septic neonates correlate with inflammatory markers and may serve as a biomarker for sepsis severity and prognosis (45).

Table 4: Melatonin acts as a critical immunomodulator in the neonatal immune system by finely tuning cytokine production, enhancing innate immune cell function, and suppressing the hyperinflammatory state characteristic of neonatal sepsis. Its antioxidant properties further protect against oxidative damage, contributing to improved clinical outcomes. These multifaceted roles make melatonin a promising adjunctive therapy for managing neonatal sepsis and other inflammatory conditions in neonates. Continued clinical research is warranted to optimize dosing and fully integrate melatonin into neonatal care protocols.

Clinical Potential and Challenges of Melatonin Use in Neonates

Effective Therapeutic Dose and Need for

Table 4. Melatonin's Immunomodulatory Effects in Neonates

Mechanism	Effect	Supporting Evidence
↓ TNF-α, IL-6, IL-8	Reduced systemic inflammation and tissue damage	Clinical studies in septic neonates
↑ IL-10	Enhanced anti-inflammatory response	Experimental and clinical data
Modulation of NF-κB and TLR4	Suppression of pro-inflammatory signaling pathways	In vitro and ex vivo studies
Regulation of neutrophil activation (CD11b, TLR4)	Prevention of excessive neutrophil activation and oxidative burst	Neonatal encephalopathy model
Enhancement of macrophage function	Balanced immune response promoting pathogen clearance	Immunomodulatory studies
Reduction of oxidative stress	Decreased lipid peroxidation and ROS-mediated damage	Clinical and experimental
Clinical improvement in sepsis	Lower CRP levels, improved survival and faster recovery	Meta-analyses and clinical trials

Clinical Trials: Determining the optimal therapeutic dose of melatonin in neonates remains challenging due to variability in pharmacokinetics and a lack of standardized dosing protocols. Clinical studies have used a wide dose range—from microgram per kilogram levels in pharmacokinetic studies (0.04–0.6 μg/kg) to milligram per kilogram doses (up to 70 mg/kg) in efficacy trials. Pharmacokinetic data indicate neonates have a prolonged melatonin half-life (approximately 8–17 hours) and higher peak plasma concentrations than adults, likely due to immature hepatic metabolism and renal clearance. This suggests that lower or less frequent dosing may suffice to maintain therapeutic levels (46,47).

Despite promising preclinical neuroprotective and anti-inflammatory effects, current clinical data remain insufficient. Meta-analyses highlight very low-quality evidence due to small sample sizes and heterogeneity, especially in neonatal encephalopathy. Well-designed, adequately powered, multicenter RCTs are urgently needed to establish effective dosing regimens, confirm efficacy, and assess long-term safety in neonatal populations (14,46,47).

Challenges in Translating Laboratory Models to NICU Settings

Several challenges complicate the translation of melatonin's laboratory and animal model benefits into routine NICU practice:

Physiological Differences: Neonates, especially preterm infants, differ markedly from animal models in organ maturity, metabolism, and disease pathophysiology, affecting melatonin's pharmacodynamics and pharmacokinetics (46-48).

Population Heterogeneity: Variability in gestational age, birth weight, and comorbidities among neonates complicates standardization of dosing and treatment protocols (46).

Dosing and Administration Routes: Optimal routes (intravenous, oral, enteral) and timing of administration remain to be standardized, with absorption and bioavailability differing by method (46,49).

Concomitant Therapies: Many neonates receive other interventions (e.g., therapeutic hypothermia, sedation) that may interact with melatonin's effects or metabolism (1,50).

Limited Long-term Outcome Data: Most studies focus on short-term biochemical or clinical endpoints; data on neurodevelopmental and long-term outcomes are scarce (1,50,51).

Pharmacokinetics of Melatonin in Neonates

Pharmacokinetic studies in preterm and term neonates reveal distinct characteristics compared to adults:

Half-life: Melatonin elimination half-life ranges from approximately 8 to 17 hours in neonates, significantly longer than in adults (typically 20–50 minutes) (44-47,51-53).

Clearance and Volume of Distribution: Neonates exhibit slower clearance (e.g., ~0.045 L/h) and larger volume of distribution (~1.1 L), influenced by gestational age, gender, and race (52-54).

Endogenous Levels: Baseline endogenous melatonin is low or undetectable in preterm infants due to lack of maternal transfer and

Table 5. Clinical Potential and Challenges of Melatonin in Neonates

Aspect	Current Evidence	Challenges / Gaps
Safety	Generally safe in neonates at doses up to 70 mg/kg/day; no serious adverse events reported.	Limited large-scale safety data; long-term effects unknown.
Therapeutic Dose	Variable dosing in studies (0.04 µg/kg to 70 mg/kg); longer half-life in neonates.	Optimal dose and regimen not established; requires trials.
Translation to NICU	Promising preclinical neuroprotection and anti-inflammatory effects.	Physiological differences and heterogeneity complicate use.
Pharmacokinetics	Longer half-life (8–17 h), slower clearance, good absorption; influenced by gestational age.	Need for individualized dosing; interactions with other treatments.
Clinical Trials	Few small RCTs with limited sample size; meta-analyses show low-quality evidence.	Need for large, multicenter, well-powered clinical trials.

immature pineal secretion; circadian rhythms develop weeks after birth (52-56).

Absorption and Peak Concentrations: Oral and enteral melatonin is well absorbed, with peak plasma concentrations (Cmax) reached between 2 to 8 hours post-dose, though Tmax varies widely among neonates (52-56).

Dosing Implications: The prolonged half-life and pharmacokinetic variability suggest that dosing intervals may be extended compared to adults, but individualized dosing strategies are needed (52-56).

Table 5: Melatonin shows significant clinical potential as a safe and effective adjunctive therapy in neonatal care, particularly for oxidative stress and inflammation-related conditions such as neonatal sepsis and encephalopathy. However, challenges remain in defining optimal dosing, understanding pharmacokinetics across diverse neonatal populations, and translating preclinical findings into standardized NICU protocols. Robust, large-scale clinical trials are essential to confirm melatonin's efficacy, safety, and long-term benefits in neonates.

Furthermore, recent studies indicate that melatonin plays a significant role in improving clinical outcomes and reducing oxidative stress in neonates with sepsis. Gitto et al. (Italy, 2001) conducted the first human study showing that intravenous melatonin injection in septic neonates reduced oxidative stress and improved clinical status (57). El Frargy et al. (Egypt, 2015) examined clinical melatonin administration at 20 mg alongside antibiotics, reporting significant improvement in septic neonates(58). El-Gendy et al. (Egypt, 2017) confirmed the beneficial effects of melatonin in treating septic neonates (59). Abdelaziz et al. (Egypt, 2024) studied plasma melatonin levels as a diagnostic marker for late-onset neonatal sepsis and highlighted melatonin's protective effects (60). He et al. (China, 2021) using an animal model, demonstrated melatonin's anti-inflammatory and antibacterial effects against MRSA (61). Sun et al. (China, 2025) reported the efficacy of melatonin as adjunctive therapy for sepsis in neonatal patients (62). Additionally, Pavlyshyn et al. (Ukraine, 2022) identified urinary melatonin as a predictor of sepsis onset (63). These studies collectively reveal that melatonin plays a significant therapeutic and diagnostic role in neonatal sepsis, especially in antibiotic-resistant infections such as MRSA.

Conclusion

Melatonin demonstrates considerable potential as a safe and effective adjunctive therapy in neonatal care, particularly for conditions associated with oxidative stress and excessive inflammation, such as sepsis and neonatal encephalopathy. Preclinical and early clinical evidence suggests that melatonin can modulate inflammatory responses, reduce oxidative tissue damage, and potentially improve clinical outcomes without major adverse effects. Nevertheless, the translation of these findings into routine clinical practice is limited by the lack of standardized dosing protocols, variability among neonatal populations, and the small scale and short duration of existing studies. To fully establish its therapeutic role, future research should focus on well-designed, multicenter, randomized controlled trials that determine optimal dosing, timing, and administration routes. Such studies should also investigate melatonin's synergistic potential with standard interventions, including antibiotics and therapeutic hypothermia, while assessing both immediate biochemical and clinical outcomes and long-term neurodevelopmental and survival metrics. Collectively, these efforts will be crucial to confirm melatonin's efficacy, safety, and clinical utility, ultimately supporting its integration as a standard

adjunctive treatment in neonatal intensive care settings.

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None.

Conflicts of interest

The authors declared that they have no conflict of interest.

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