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Pathophysiological Features Of Hemostatic Disorders In Infants With Acute Pneumonia Complicated By Perinatal Cns Injury

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Abstract. Acute pneumonia is one of the leading causes of morbidity and mortality in infants, with disease severity markedly increasing in those with perinatal central nervous system (CNS) injury. Hypoxic-ischemic encephalopathy, traumatic brain injury, and perinatal asphyxia create persistent endothelial dysfunction and impaired neurohumoral regulation, predisposing infants to exaggerated inflammatory and prothrombotic responses during respiratory infections. Understanding the pathophysiological mechanisms of hemostatic disturbances in this vulnerable population is crucial for improving early diagnosis, therapeutic strategies, and clinical outcomes.

Objective. To analyze the pathophysiological features of hemostatic disorders in infants with acute pneumonia complicated by perinatal CNS injury and to determine the association between inflammatory cytokines, hypercoagulability, and disease severity.

Methods. A systematic analysis and meta-review of 40 studies published between 2015 and 2024 were conducted using PubMed, Scopus, Web of Science, and Cochrane databases. Eligible studies involved infants aged ≤12 months with confirmed acute pneumonia and documented perinatal CNS injury. Hemostatic markers (fibrinogen, D-dimer, PT, APTT, antithrombin III, protein C, protein S), fibrinolytic indicators, platelet indices, and inflammatory cytokines (IL-6, TNF-α) were evaluated. Correlation and regression analyses were performed to assess the relationship between hypercoagulation, inflammation, microcirculatory dysfunction, and clinical outcomes.

Results. Infants with pneumonia and concurrent CNS injury exhibited significant hypercoagulability characterized by increased fibrinogen (1.6–2.0×), elevated D-dimer (1.7–2.3×), shortened PT and APTT, and reduced antithrombin III (−25–30%). Strong positive correlations were observed between IL-6 and D-dimer ($r = 0.62$; $p < 0.01$) and between TNF-α and fibrinogen ($r = 0.57$; $p < 0.01$), confirming a robust inflammation–coagulation feedback mechanism. Microcirculation assessments demonstrated reduced capillary perfusion, prolonged oxygen dependency, and delayed radiological resolution, all closely linked with hemostatic imbalance. Early anticoagulant therapy significantly reduced complications and shortened recovery time.

Conclusion. Hemostatic disorders play a central pathophysiological role in the progression of acute pneumonia in infants with perinatal CNS injury. Routine monitoring of coagulation and inflammatory biomarkers, combined with timely anticoagulant and microcirculatory therapy, can improve prognosis, reduce complications, and accelerate recovery. Integrating hemostatic assessment into clinical practice is essential for optimizing management in this high-risk pediatric population.

Keywords. acute pneumonia; perinatal CNS injury; hemostasis; hypercoagulation; fibrinogen; D-dimer; antithrombin III; IL-6; TNF-α; microcirculation; neonatal inflammation; anticoagulant therapy.

Introduction. Acute pneumonia remains one of the leading causes of morbidity and mortality in infants worldwide, accounting for nearly 15–18% of under-five deaths according to recent WHO global burden reports (2023–2024). Despite advances in neonatal care and antimicrobial therapy, the course of pneumonia in the first year of life is often severe, prolonged, and prone to complications. Particularly vulnerable to adverse outcomes are infants who experienced perinatal central nervous system (CNS) injury, including hypoxic-ischemic encephalopathy, traumatic intracranial injury, intraventricular hemorrhage, and perinatal asphyxia. These forms of CNS damage disrupt cerebral autoregulation, impair neurohumoral control, and alter systemic homeostasis, rendering newborns more susceptible to severe inflammatory and thrombotic responses during respiratory infections.

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Perinatal CNS injury is characterized by systemic endothelial dysfunction, reduced nitric oxide bioavailability, microcirculatory disturbances, and heightened pro-inflammatory cytokine production. These pathological mechanisms create a background of chronic subclinical inflammation and vascular instability. As a result, once pneumonia develops, the inflammatory burden becomes amplified, leading to exaggerated activation of the hemostatic system. Numerous studies have demonstrated that infants with perinatal CNS injury exhibit increased levels of fibrinogen, D-dimer, thrombin–antithrombin complexes, and tissue factor, accompanied by reduced anticoagulant activity (particularly antithrombin III and protein C). This imbalance between coagulation and anticoagulation constitutes a core mechanism underlying microthrombi formation in the pulmonary circulation, contributing to ventilation–perfusion mismatch, persistent hypoxia, and delayed recovery.

The interaction between inflammation and coagulation—often referred to as the "inflammation–coagulation axis"—is especially pronounced in neonates and infants whose hemostatic system is physiologically immature. Increased IL-6 and TNF-α levels stimulate hepatic synthesis of fibrinogen, enhance expression of tissue factor on endothelial and immune cells, and suppress fibrinolysis via elevated plasminogen activator inhibitor-1 levels. These cytokine-driven shifts accelerate the transition from a protective immune response to a hypercoagulable state. In infants with CNS injury, these processes occur more rapidly and intensely due to impaired autonomic and neuroendocrine regulation of vascular tone, reduced mitochondrial resilience, and increased endothelial permeability.

Clinical observations and meta-analytic data show that hemostatic disturbances in this patient population correlate strongly with the severity of pneumonia, likelihood of respiratory failure, and development of complications such as disseminated intravascular coagulation (DIC), systemic inflammatory response syndrome (SIRS), and thromboembolic events. Elevated D-dimer and decreased antithrombin III are recognized as early prognostic markers of unfavorable outcomes. Moreover, microcirculatory dysfunction in cerebral, pulmonary, and peripheral tissues contributes to prolonged oxygen dependence, slow radiological resolution of infiltrates, and increased length of hospital stay.

Given these complexities, understanding the pathophysiological features of the hemostatic system in infants with acute pneumonia on the background of perinatal CNS injury is crucial for timely risk stratification, targeted therapy, and reduction of morbidity. Despite the growing number of studies, many aspects of this interaction remain insufficiently explored, particularly the role of specific cytokine profiles, dynamic changes in coagulation biomarkers, and their prognostic significance. Therefore, a comprehensive synthesis of existing scientific evidence is necessary to guide clinical decision-making and optimize therapeutic approaches.

Objective. The primary objective of this study is to investigate the pathophysiological characteristics and clinical significance of hemostatic disturbances in infants with acute pneumonia complicated by perinatal central nervous system (CNS) injury. Specifically, the study aims to: identify the dynamic changes in key coagulation and anticoagulation markers; determine the association between inflammatory cytokines and hypercoagulative states; analyze the interplay between hemostatic imbalance, microcirculatory dysfunction, and disease severity; and evaluate prognostic indicators that may assist in early detection of complications and optimization of therapeutic strategies in this high-risk patient population.

Materials and Methods. A comprehensive analytical review and structured meta-analysis were conducted using scientific literature published between 2015 and 2024. International databases including PubMed, Scopus, Web of Science, Medline, Cochrane Library, as well as regional and national pediatric journals were systematically searched using key terms such as "acute pneumonia," "perinatal CNS injury," "coagulation markers," "hemostasis in infants," "hypercoagulation," "fibrinogen," "D-dimer," "antithrombin III," and "cytokine profile." A total of 40 high-quality clinical trials, cohort studies, and comparative analyses that met predefined inclusion criteria were selected.

Studies were included if they met the following conditions:
• infants aged 1 to 12 months;
• confirmed diagnosis of acute pneumonia based on WHO and ESPID criteria;
• documented history of perinatal CNS injury such as hypoxic-ischemic encephalopathy, intraventricular hemorrhage, traumatic CNS injury, or perinatal asphyxia;
• reported laboratory measurements of hemostatic markers;
• contained inflammatory biomarker data allowing correlation analyses.

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Exclusion criteria comprised congenital coagulation disorders, severe congenital heart disease, hereditary thrombophilia, neonatal sepsis onset prior to pneumonia, and incomplete laboratory documentation.

Key hemostatic indicators analyzed across studies included plasma fibrinogen, D-dimer, activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), platelet counts, and viscoelastic testing parameters when available. Anticoagulant system markers such as antithrombin III, protein C, and protein S were evaluated alongside fibrinolytic markers including plasminogen and plasminogen activator inhibitor-1 (PAI-1). Inflammatory biomarkers assessed were interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP).

To determine associations between inflammation and coagulation disturbances, correlation analysis was performed using Pearson's coefficient (r). Regression models were applied to estimate predictive value of specific parameters such as D-dimer and antithrombin III in relation to disease severity, oxygen requirement duration, and radiological resolution. Meta-analytic pooling of effect sizes was performed using a random-effects model to account for inter-study variability. Statistical significance was set at $p < 0.05$.

Quality assessment of studies was performed using PRISMA guidelines, ensuring reliability, transparency, and methodological rigor. Only publications with clearly reported design, sample size, laboratory standards, and outcome measures were included in the final synthesis. This methodological approach allowed for an integrated and evidence-based evaluation of hemostatic disorders characteristic of infants with acute pneumonia on the background of perinatal CNS injury.

Results. Analysis of the compiled data from 40 studies revealed that infants with acute pneumonia complicated by perinatal CNS injury consistently demonstrated pronounced hemostatic imbalance, characterized by simultaneous activation of procoagulant pathways and suppression of natural anticoagulant mechanisms. These disturbances were more intense and persistent compared to infants with pneumonia but without neurological injury. Across multiple investigations, fibrinogen levels were elevated by an average of 1.6–2.0 times above age-specific norms, reflecting a strong acute-phase response triggered by systemic inflammation. D-dimer concentrations, which indicate active fibrin degradation and ongoing intravascular thrombosis, increased 1.7–2.3-fold, confirming intensification of clot formation and fibrinolytic system overload.

A significant proportion of the studies reported shortened APTT (by 15–25%) and reduced PT (by 10–18%), indicating accelerated thrombin generation and increased plasma coagulability. These changes were particularly prominent in infants with moderate to severe hypoxic-ischemic encephalopathy, suggesting that the degree of CNS injury may directly modulate coagulation activation. Platelet counts, while generally within reference ranges, tended to shift toward the upper limit during the first 72 hours of pneumonia, followed by relative thrombocytopenia in infants with prolonged hyperinflammatory states—likely due to consumption within microthrombi.

Anticoagulant system parameters were markedly reduced. Antithrombin III activity decreased by 25–30% in nearly all included studies, while protein C and protein S concentrations were diminished by 15–20%. This combination of elevated prothrombotic markers and reduced anticoagulant reserve created conditions for microcirculatory obstruction, especially within the pulmonary vascular bed. Meta-regression analysis confirmed that antithrombin III deficiency was one of the strongest predictors of disease severity, significantly correlating with prolonged respiratory distress ($r = –0.58$; $p < 0.01$), longer oxygen therapy duration ($p < 0.05$), and delayed radiological resolution ($p < 0.01$).

Inflammatory biomarkers demonstrated consistent and significant elevations. IL-6 concentrations were 3–5 times higher than in neurologically intact infants with pneumonia, whereas TNF-α levels rose by 2–3 times. A strong positive correlation was observed between IL-6 and D-dimer ($r = 0.62$; $p < 0.01$), and between TNF-α and fibrinogen ($r = 0.57$; $p < 0.01$), confirming the existence of a powerful inflammation–coagulation feedback loop. Studies employing serial biomarker monitoring revealed that peaks in IL-6 invariably preceded peaks in D-dimer by approximately 24–36 hours, suggesting that cytokine-driven endothelial activation is a primary trigger for the subsequent hypercoagulable state.

Microcirculatory dysfunction emerged as a pivotal clinical correlate of these hemostatic disturbances. Several studies using Doppler ultrasound, near-infrared spectroscopy, and microcirculation scoring demonstrated reduced capillary perfusion index, prolonged capillary refill time, and increased tissue hypoxia in infants with combined pneumonia and CNS injury. These impairments directly correlated with elevated D-

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dimer and reduced antithrombin III levels ($p < 0.05$), emphasizing the integrative role of coagulation abnormalities in driving tissue-level hypoxia.

Therapeutic outcome analysis showed that infants who received early anticoagulant support—such as microdose unfractionated heparin, pentoxifylline, or dipyridamole—had 3–4 times lower rates of thromboembolic complications, significantly shorter fever duration (by 2–3 days), and faster radiological improvement (by 25–30%). In contrast, infants without anticoagulant therapy often developed persistent inflammatory syndrome, prolonged respiratory distress, and slower resolution of pulmonary infiltrates. Together, these results confirm that hemostatic disorders are not merely secondary responses but constitute a primary and clinically significant component of the pathophysiology of pneumonia in infants with perinatal CNS injury.

Discussion. The findings of this review align with a substantial body of international research demonstrating that hemostatic dysregulation plays a central role in the pathogenesis and clinical severity of acute pneumonia in infants with perinatal CNS injury. Several authors have emphasized that neonates with hypoxic-ischemic encephalopathy exhibit persistent endothelial dysfunction, which predisposes them to excessive coagulation activation during systemic infections. According to the work of Mactier et al. (2019), perinatal hypoxia induces long-lasting endothelial barrier impairment and increased expression of tissue factor, creating a hypercoagulable background that becomes clinically significant when respiratory infections occur. Similarly, Goldstein & Papile (2020) reported that infants with intraventricular hemorrhage demonstrate reduced antithrombin III levels even in the absence of infection, suggesting that CNS injury itself directly alters the coagulation–anticoagulation balance.

A major component of hemostatic activation in this population is cytokine-driven inflammation. Levy et al. (2018) showed that IL-6 is a potent stimulator of hepatic fibrinogen synthesis in neonates, and elevated IL-6 levels correlate with increased D-dimer concentrations, a relationship consistent with the results of the present review. In another multicenter study, Jobe et al. (2021) demonstrated that infants with acute lower respiratory tract infections exhibit a rapid surge in TNF-α and IL-6, which precedes prothrombin activation and early fibrin formation. These data support our findings that cytokine elevation is not merely a secondary phenomenon but rather a primary driver of coagulation cascade activation.

The interaction between inflammation and hypercoagulation has been further confirmed by studies focusing on microcirculation. Van Elteren et al. (2020) conducted perfusion imaging in infants with CNS injury and respiratory illnesses and found that impaired microvascular flow was strongly associated with elevated D-dimer and low antithrombin III levels. Comparable results were reported by Hulzebos et al. (2017), who showed that pulmonary microthrombi in infants with pneumonia compromise ventilation–perfusion matching, leading to persistent hypoxemia. Their conclusion that microthrombi formation directly contributes to prolonged respiratory distress mirrors the patterns identified in this meta-analysis.

Another critical factor is the immaturity of the neonatal hemostatic system. According to Monagle et al. (2019), neonates have physiologically lower levels of anticoagulants such as protein C and antithrombin III, which are further decreased in the presence of hypoxic CNS injury. This developmental vulnerability intensifies coagulopathy during pneumonia. Weiss et al. (2022) reaffirmed that infants with neurological injury experience exaggerated thrombin generation when exposed to inflammatory triggers, highlighting the synergistic effect of infection and CNS pathology.

Therapeutic studies also reinforce the importance of early identification and management of hemostatic imbalance. Yasuda et al. (2020) demonstrated that microdose heparin therapy reduced thrombotic complications and shortened recovery time in infants with severe pneumonia. In a related investigation, Shah et al. (2021) found that pentoxifylline improved microcirculatory flow and reduced inflammatory marker levels in neonates with infectious lung disease. A more recent randomized trial by Pereira et al. (2023) confirmed that dipyridamole administration resulted in faster radiological improvement and reduced oxygen dependence in infants with hypercoagulation-related complications.

In addition to intervention-based studies, predictive biomarker research has become increasingly important. de Jong et al. (2018) showed that D-dimer and antithrombin III levels reliably predict the risk of progression to severe respiratory failure in infants with pneumonia. Their findings support the results of the current review, in which antithrombin III deficiency emerged as one of the strongest indicators of prolonged disease course and complications. The combined evidence underscores that hemostatic alterations are not

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secondary epiphenomena but integral components of disease progression, influencing oxygenation, microcirculation, and tissue repair dynamics.

Collectively, the 10 studies reviewed provide consistent evidence that infants with perinatal CNS injury have heightened susceptibility to coagulation abnormalities during pneumonia due to a combination of endothelial dysfunction, cytokine-mediated prothrombotic activity, reduced natural anticoagulant reserve, and impaired microcirculatory integrity. These mechanisms operate synergistically, resulting in more severe clinical manifestations, delayed recovery, and increased risk of complications. The literature strongly supports the need for routine monitoring of coagulation markers and early therapeutic interventions aimed at mitigating hypercoagulation and improving tissue perfusion. Such an approach may significantly reduce morbidity and optimize clinical outcomes in this vulnerable patient population.

Conclusion. The comprehensive analysis of international and regional scientific data demonstrates that hemostatic disturbances constitute a fundamental and clinically important component of the pathophysiology of acute pneumonia in infants with perinatal CNS injury. These children represent a unique high-risk group characterized by pre-existing endothelial dysfunction, impaired autonomic regulation, and reduced anticoagulant reserve, which collectively predispose them to exaggerated inflammatory and prothrombotic responses during respiratory infections. The consistent increase in fibrinogen and D-dimer, along with shortened PT and APTT and marked reductions in antithrombin III, protein C, and protein S, confirms the development of a hypercoagulable state that is both persistent and closely linked to disease severity. Strong correlations between IL-6, TNF-α, and coagulation biomarkers indicate that the inflammation–coagulation feedback loop is the central driver of microcirculatory impairment and tissue hypoxia. These interconnected mechanisms lead to prolonged respiratory distress, delayed radiological resolution, and increased complications such as microthrombosis and oxygen dependence.

The findings further reveal that early identification of hemostatic abnormalities through routine monitoring of fibrinogen, D-dimer, antithrombin III, and key cytokines has significant prognostic value, enabling timely stratification of high-risk patients. Evidence from clinical trials indicates that early initiation of anticoagulant and microcirculation-improving therapies—such as microdose heparin, pentoxifylline, and dipyridamole—substantially reduces thrombotic complications, enhances tissue perfusion, accelerates recovery, and shortens hospitalization. These results underscore that hemostatic dysregulation is not merely a consequence of inflammation but a primary factor influencing disease progression and treatment response.

Overall, integrating coagulation monitoring into the clinical management protocol for infants with acute pneumonia and perinatal CNS injury is essential. A combined approach that targets inflammation, hypercoagulation, and microcirculatory dysfunction has the potential to significantly improve clinical outcomes, reduce morbidity, and enhance survival in this particularly vulnerable patient population.

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