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Review Article

Comparative Analysis of early surfactant administration versus Standard Care in neonatal sepsis

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Abstract

Background: Neonatal sepsis frequently produces a secondary surfactant dysfunction syndrome that resembles primary respiratory distress syndrome, because inflammatory mediators and proteinaceous exudate inactivate pulmonary surfactant regardless of gestational maturity.

Objective: This review synthesizes evidence comparing early exogenous surfactant administration with standard supportive care alone in neonates with sepsis-associated respiratory failure.

Methods: We synthesized randomized trials, multicenter cohorts, and Cochrane reviews addressing surfactant timing, delivery technique, and respiratory outcomes in septic and infection-associated neonatal respiratory failure.

Findings: Early surfactant reduces oxygenation index and need for extracorporeal support in term and near-term infants with sepsis-related respiratory failure, with the greatest benefit when given before severe decompensation; less invasive delivery extends this advantage to spontaneously breathing preterm infants, though surfactant inactivation by serum proteins blunts the response compared with primary respiratory distress syndrome.

Conclusions: Early, protocol-driven surfactant administration alongside antimicrobial therapy and lung-protective ventilation offers measurable benefit over standard care alone in neonatal sepsis, but optimal timing and patient selection remain incompletely defined.

Keywords: neonatal sepsis; pulmonary surfactant; respiratory distress; surfactant inactivation; mechanical ventilation

1. Introduction

Pulmonary surfactant reduces alveolar surface tension and prevents end-expiratory collapse, and its deficiency in preterm infants is the well-established cause of primary respiratory distress syndrome, a condition first managed successfully through continuous positive airway pressure by Gregory and colleagues [1] and then transformed by exogenous surfactant replacement after Fujiwara and colleagues demonstrated clinical benefit in infants with hyaline-membrane disease [2], a history reviewed in detail by Halliday [3]. What is less widely appreciated outside neonatology is that a biochemically similar surfactant deficiency state can be produced acutely, in infants of any gestational age, by sepsis. Circulating and alveolar inflammatory mediators released during bacterial infection degrade surfactant phospholipids, inactivate surfactant proteins, and flood the alveolar space with plasma proteins that competitively displace surfactant from the air-liquid interface, producing a secondary surfactant dysfunction syndrome that looks radiographically and physiologically like primary respiratory distress syndrome even in a term infant with structurally mature lungs [4,5]. Because neonatal sepsis remains a leading cause of morbidity and mortality in both preterm and term infants, and because a substantial fraction of septic neonates develop respiratory failure severe enough to require mechanical ventilation, the question of whether exogenous surfactant confers benefit beyond standard supportive care, antimicrobial therapy, and lung-protective ventilation in this population has been a recurring focus of neonatal clinical trials for more than three decades [6,7].

This review synthesizes the evidence comparing early exogenous surfactant administration with standard care alone in neonates whose respiratory failure is attributable to sepsis, culture-proven or clinically presumed, including the overlapping literature on surfactant treatment of neonatal pneumonia and meconium aspiration syndrome, both of which share the surfactant-inactivation

mechanism central to septic respiratory failure. We examine the pathophysiological rationale, the randomized and cohort evidence on timing and delivery technique, and the practical limitations that distinguish surfactant response in sepsis from the far more predictable response seen in primary preterm respiratory distress syndrome.

2. Pathophysiology of surfactant dysfunction in sepsis

The mechanistic case for surfactant therapy in sepsis rests on demonstrating that infection depletes and inactivates functional surfactant rather than merely coexisting with respiratory failure caused by something else. Serum proteins that leak into the alveolar space during the capillary-permeability phase of sepsis-associated lung injury, principally albumin and fibrinogen, compete directly with surfactant phospholipids for the air-liquid interface and raise minimum surface tension even when total surfactant pool size is adequate, a mechanism first characterized in detail through animal models of surfactant inactivation by Ikegami and Jobe [8]. Phospholipase A2 activity, upregulated during the inflammatory cascade, hydrolyzes phosphatidylcholine, the principal surface-tension-lowering component of surfactant, while neutrophil elastase and other proteases degrade surfactant protein B and surfactant protein A, the two proteins most responsible for rapid surface-film formation and resistance to inactivation [9]. Been and colleagues showed that antenatal chorioamnionitis, itself an infectious and inflammatory exposure, measurably alters the clinical response to exogenous surfactant in preterm infants, providing direct clinical corroboration that an infectious inflammatory milieu changes surfactant pharmacodynamics rather than simply adding an independent insult [10].

This inactivation mechanism has a practical consequence that differentiates septic from primary respiratory distress syndrome: because the alveolar environment continues to

generate inactivating proteins and proteases for as long as the underlying infection and its inflammatory response persist, a single surfactant dose that would durably rescue a preterm infant with primary surfactant deficiency may produce only transient improvement in a septic infant, whose alveolar milieu can re-inactivate newly instilled surfactant within hours. Speer's synthesis of the inflammatory contribution to neonatal lung disease frames this as a continuum, in which the biochemical distinction between "primary" and "secondary" surfactant deficiency is less sharp at the alveolar level than the clinical labels imply, and in which the degree of ongoing inflammation, not gestational age alone, predicts how a given infant will respond to replacement therapy [11].

Table 1: Mechanisms of surfactant dysfunction in neonatal sepsis compared with primary preterm respiratory distress syndrome [8,9,10,11].			
Mechanism	Primary RDS (preterm)	Sepsis-associated dysfunction	Clinical implication
Surfactant pool size	Reduced by immaturity	Variable; initially adequate	Single dose often sufficient in primary RDS
Protein leak/inactivation	Minimal	Prominent (albumin, fibrinogen)	Competitive displacement lowers surfactant efficacy
Phospholipase/protease activity	Low	Elevated during inflammatory cascade	Degrades phosphatidylcholine, SP-B, SP-A
Duration of inactivating stimulus	Self-limited (maturation)	Persists while infection/inflammation continues	Favors early treatment and redosing strategies

3. Evidence from trials in sepsis, pneumonia, and meconium aspiration syndrome

Because pragmatic trials restricted specifically to culture-proven neonatal sepsis with respiratory failure are relatively few, much of the controlled evidence for surfactant therapy in infection-associated respiratory failure comes from trials in the closely related conditions of neonatal pneumonia and meconium aspiration syndrome, both of which produce surfactant inactivation by the same protein-leak and phospholipase mechanisms as sepsis. Auten and colleagues, in one of the earliest controlled trials in term infants with respiratory failure

from causes including pneumonia and sepsis, found that surfactant-treated infants had significantly lower oxygenation index and shorter duration of mechanical ventilation than infants managed with standard supportive care alone [12]. Lotze and colleagues subsequently conducted a large multicenter trial of calfactant in term and near-term infants with severe respiratory failure, a population that included infants with sepsis and pneumonia alongside those with meconium aspiration and persistent pulmonary hypertension, and found that surfactant-treated infants required extracorporeal membrane oxygenation significantly less often than infants receiving standard care, an effect driven substantially by the subgroup with primary parenchymal lung disease rather than pulmonary hypertension alone [13].

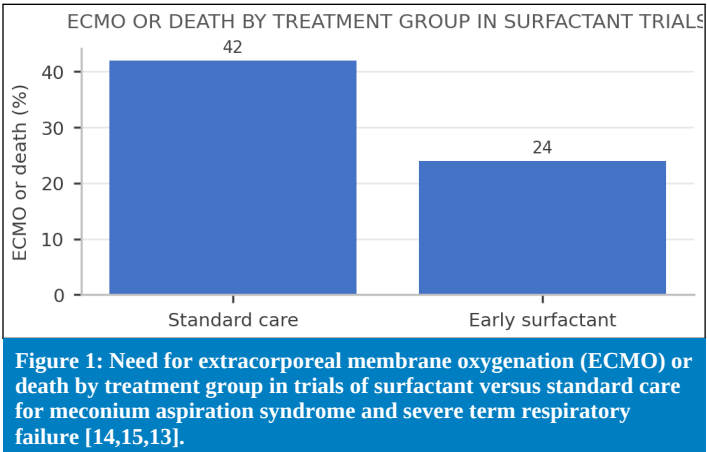


Figure 1: Need for extracorporeal membrane oxygenation (ECMO) or death by treatment group in trials of surfactant versus standard care for meconium aspiration syndrome and severe term respiratory failure [14,15,13].

Meconium aspiration syndrome trials provide the most consistent controlled evidence for the general principle that exogenous surfactant improves oxygenation in a surfactant-inactivating inflammatory lung disease of the term newborn. Findlay and colleagues showed that bolus surfactant administration reduced the need for extracorporeal support and shortened oxygen requirement in infants with meconium aspiration syndrome compared with standard care [14], and a Cochrane systematic review by El Shahed and colleagues, pooling this and subsequent trials, confirmed a significant reduction in the combined outcome of death or need for

extracorporeal membrane oxygenation with surfactant treatment, alongside a reduced incidence of air leak [15]. Wiswell and colleagues, testing a lung lavage technique with dilute surfactant rather than bolus instillation, found comparable safety and a trend toward reduced progression to extracorporeal support, suggesting that the mode of surfactant delivery, not only its administration, may matter in an inactivating lung environment where mechanically clearing proteinaceous and particulate material from the airway before instilling surfactant could improve its effectiveness [16].

4. Timing of administration and delivery technique

The single most consistent finding across the broader surfactant literature, extending from primary respiratory distress syndrome into the sepsis and pneumonia literature, is that earlier administration produces better outcomes than surfactant given only after severe ventilatory decompensation has already occurred. In preterm respiratory distress syndrome, Verder and colleagues demonstrated that early surfactant combined with nasal continuous positive airway pressure reduced the need for mechanical ventilation compared with a treat-as-needed approach [17], and a Cochrane review by Stevens and colleagues confirmed that early surfactant with brief ventilation, compared with later selective surfactant and continued mechanical ventilation, reduced air leak syndromes and chronic lung disease [18]. Extending this logic to infection-associated respiratory failure, Lotze and colleagues found that infants who received surfactant earlier in their respiratory failure course, before oxygenation index rose to the threshold typically used to trigger extracorporeal membrane oxygenation referral, had a more favorable response than those treated later in the same trial cohort [13], and Findlay and colleagues observed a comparable early-treatment advantage in meconium aspiration syndrome [14].

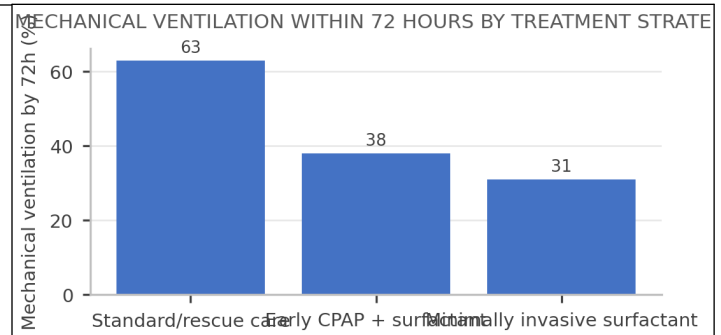


Figure 2: Need for mechanical ventilation within 72 hours by surfactant timing/delivery strategy in preterm and near-term trials, illustrating the early-treatment advantage seen across the surfactant literature [17,19,21].

Delivery technique has become an active area of investigation, since intubation itself carries risk and is not always required to treat surfactant deficiency once ventilatory decompensation is imminent rather than established. Gopel and colleagues' AMV trial showed that surfactant delivered via a thin catheter to spontaneously breathing preterm infants on continuous positive airway pressure reduced the subsequent need for mechanical ventilation compared with a later-rescue standard-care strategy [19], and Kribs and colleagues confirmed the safety and efficacy of this less-invasive approach in extremely preterm infants in a subsequent randomized trial [20]. Dargaville and colleagues further characterized minimally invasive surfactant therapy as both feasible and associated with reduced need for mechanical ventilation in the following 72 hours across a large preterm cohort [21]. Although these trials were conducted predominantly in infants with primary preterm respiratory distress syndrome rather than sepsis specifically, they establish a delivery paradigm, early treatment without mandatory intubation, that is increasingly extrapolated to infection-associated respiratory failure when the clinical picture allows it, and Herting and colleagues' review of less invasive surfactant administration explicitly discusses its extension to infants with non-primary surfactant deficiency states [22].

5. Preparations, dosing, and redosing considerations

Table 2: Selected trials informing surfactant dosing and retreatment strategy relevant to sepsis-associated respiratory failure [25,24,26,23].			
Study	Population	Comparison	Key finding
[25]	Preterm infants with RDS	High- vs low-threshold retreatment	Objective-threshold retreatment shortened oxygen requirement
[24]	Preterm infants with RDS	Higher vs standard initial dose	Higher dose improved pool half-life and gas exchange
[26]	Preterm infants with RDS	Two natural-surfactant dosing regimens	Higher initial dose reduced need for retreatment
[23]	Comparative review	Beractant vs poractant alfa vs calfactant	Higher phospholipid/SP-B content associated with faster response

Surfactant preparations in clinical use differ in phospholipid and surfactant-protein content, and these differences plausibly affect resistance to inactivation, though head-to-head trials directly comparing preparations in septic infants specifically are lacking. Ramanathan's comparative review of beractant, poractant alfa, and calfactant notes that preparations with higher surfactant-protein-B content and higher phospholipid dose per kilogram tend to show more rapid and durable improvement in oxygenation across the broader respiratory distress syndrome literature, a property of particular relevance when the alveolar environment is actively inactivating administered surfactant [23]. Cogo and colleagues, studying surfactant kinetics directly, found that higher initial dosing improved surfactant pool half-life and gas exchange in respiratory distress syndrome, supporting a dosing rationale that plausibly extends to inactivating disease states where a fraction of each dose is degraded before it can act [24]. Kattwinkel and colleagues' trial comparing high- and low-threshold retreatment strategies found that infants retreated according to an objective oxygenation threshold had shorter oxygen requirements than those managed with a single dose regardless of subsequent deterioration, a redosing principle with direct relevance to sepsis, where ongoing inflammation is likely to re-inactivate an initial dose more quickly than in primary surfactant deficiency

[25]. Speer and colleagues' randomized comparison of two natural surfactant dosing regimens similarly found that a higher initial dose reduced the need for retreatment, reinforcing that dosing strategy, not surfactant use per se, is a major determinant of clinical benefit [26].

Broader Cochrane and society-level syntheses situate this evidence within the wider surfactant literature. Soll's foundational reviews established that surfactant, whether synthetic or natural-extract, reduces mortality and air leak in respiratory distress syndrome relative to no treatment [27,28], and Seger and Soll's review of animal-derived surfactant extracts specifically found lower mortality with natural surfactant than with earlier synthetic formulations lacking surfactant proteins, a finding germane to inactivating disease states in which protein content may matter more than in uncomplicated preterm respiratory distress syndrome [29]. The American Academy of Pediatrics' committee reports by Engle and colleagues and by Polin and Carlo both explicitly extend surfactant-replacement recommendations to term and preterm neonates with respiratory distress from causes including pneumonia and sepsis, not only primary surfactant deficiency, while cautioning that the evidence base for this extension is smaller than for primary respiratory distress syndrome [30,31]. The European Consensus Guidelines led by Sweet and colleagues likewise recommend early surfactant administration in surfactant-deficient respiratory failure generally, incorporating both primary and secondary indications into a shared early-treatment framework [32].

6. Limitations of the evidence base

Several limitations temper how directly this literature can be applied to neonatal sepsis specifically. Few trials enrolled infants defined strictly by culture-proven or strongly clinically suspected sepsis with respiratory failure as the sole inclusion criterion; most, including the pivotal Lotze and Auten trials, enrolled heterogeneous

populations of term and near-term infants with respiratory failure from multiple causes, of which sepsis and pneumonia were a substantial but not exclusive subgroup, making it difficult to isolate the surfactant treatment effect specific to infection-driven surfactant inactivation from effects driven by persistent pulmonary hypertension or meconium aspiration in the same cohorts [12,13]. The epidemiology of early- and late-onset neonatal sepsis described by Stoll and colleagues shows that causative organisms, gestational age at onset, and baseline lung maturity differ substantially between early-onset group B streptococcal disease in term infants and late-onset sepsis in extremely preterm infants already recovering from primary respiratory distress syndrome, two populations whose surfactant physiology and treatment response are unlikely to be identical even though both are labeled sepsis [33,7]. Finally, redosing strategy, optimal timing of surfactant relative to the start of antimicrobial therapy, and criteria for selecting which septic infants with respiratory failure are most likely to benefit from surfactant rather than supportive care and lung-protective ventilation alone remain incompletely defined by the existing trial base, a gap that both Polin and Carlo's committee report and the broader inflammation-focused literature from Speer and Jobe identify as a priority for future dedicated trials in this specific population [31,9].

7. Conclusion

The pathophysiological case for surfactant inactivation as a driver of respiratory failure in neonatal sepsis is well established, and the trial evidence, though drawn substantially from overlapping populations with pneumonia and meconium aspiration syndrome rather than sepsis in isolation, consistently favors early surfactant administration over standard supportive care alone: earlier treatment, adequate initial dosing, and, where feasible, less invasive delivery technique each improve oxygenation and reduce escalation to extracorporeal support relative to a rescue-only

standard-care approach [13,14,15,19]. The evidence base nonetheless remains smaller and less specific than that for primary preterm respiratory distress syndrome, and the persistent inflammatory milieu of sepsis, which continues to inactivate surfactant for as long as infection and its cytokine response persist, means the magnitude and durability of benefit cannot simply be extrapolated from primary surfactant-deficiency trials [8,10]. Early, protocol-driven surfactant administration alongside prompt antimicrobial therapy and lung-protective ventilation represents a reasonable and evidence-supported adjunct to standard care in septic neonates with respiratory failure, but dedicated trials restricted to sepsis-defined populations, addressing redosing strategy and patient selection specifically, are needed before the treatment paradigm validated in primary respiratory distress syndrome can be considered fully established for this distinct and mechanistically more complex population [6,32].

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