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SUMMARY WITH CRITICAL APPRAISAL

Curosurf (poractant alfa) for the Treatment of Infants At Risk For or Experiencing Respiratory Distress Syndrome: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Abbreviations

BPD	broncho-pulmonary dysplasia
CI	confidence interval
CO2	carbon dioxide
CPAP	continuous positive airway pressure
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NRDS	neonatal respiratory distress syndrome
O2	oxygen
OR	odds ratio
RCT	randomized controlled trial
PDA	Patent ductus arteriosus
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
RR	relative risk
USA	United States of America

Context and Policy Issues

Infant respiratory distress syndrome

The risk of respiratory distress syndrome is associated with prematurity and is the leading cause of death in premature infants.[1] About 10% of the preterm infants in the US may develop respiratory distress syndrome.[2] At birth or within hours after birth, infants at risk may breathe rapidly and shallowly, pulling their chests sharply while breathing, and breathe with grunting sounds or nostril flaring.[2] The causes of respiratory distress can be differentiated based on diagnostic tests, such as X ray, blood tests, and endocardiography.[2]

Role of surfactant

The leading cause of respiratory distress syndrome in premature infants is the lack of surfactant.[1] Surfactant is secreted by the cells in pulmonary alveoli and decrease the surface tension in the aveoli.[3] The secretion of surfactant in fetus lungs begins at the third trimester of pregnancy.[2] With surfactant, the alveoli are less likely to collapse at low lung volume.[3] When infants are at risk of developing or have developed respiratory distress due to the lack of surfactant, surfactant can be supplemented externally for prophylaxis or treatment purposes.[4] For its importance in reducing mortality and morbidity in infants, surfactant is currently listed on the World Health Organization Model List of Essential Medicines, the essential and basic medications needed in health care.[4]

Exogenous surfactant can be produced from different sources.[4] Animal-derived surfactant is currently used for its effectiveness on reducing the mortality and morbidity associated with respiratory distress in infants.[4] Three animal-derived surfactants are commonly used: two derived from bovine lungs, beractant and calfactant, and one derived from porcine lungs, poractant alfa.[4] One notable difference between bovine- and porcine-derived surfactant is that porcine-derived surfactant contains a higher concentration of phospholipid and has a lower volume of administration.[4]

Effectiveness versus cost-effectiveness

There is some evidence that porcine-derived surfactant, poractant alfa, may be more effective than the bovine-derived calfactant in reducing deaths, need for oxygen, and mechanical ventilation. [4] However, the price of poractant alfa is higher and may not be cost-effective in clinical practice compared to bovine-derived alternatives.[5] For policymaking in health care, the adoption of interventions in medical practice requires considerations in clinical effectiveness and cost-effectiveness.[6] This review aims to systematically assess the clinical effectiveness and cost-effectiveness of poractant alfa, compared to bovine-derived surfactants.

Research Question

1. What is the clinical effectiveness of Curosurf (poractant alfa) for the treatment of infants at risk for or experiencing respiratory distress syndrome?
2. What is the cost-effectiveness of Curosurf (poractant alfa) for the treatment of infants at risk for or experiencing respiratory distress syndrome?
3. What are the evidence-based guidelines associated with the treatment of infants at risk for or experiencing respiratory distress syndrome?

Key Findings

One systematic review, one network meta-analysis, six randomized controlled studies, and three retrospective cohort studies were included in this review. Overall, poractant alfa was found to be similarly or more clinically effective for outcomes such as broncho-pulmonary dysplasia, and retinopathy of prematurity, compared to the following bovine lung extract surfactants: beractant, bovactant, lipid extract sufactant (BLES), and calfactant. However, larger studies may be needed to confirm whether poractant alfa is associated with higher mortality rates than BLES and whether poractant alfa is associated with more risks in pulmonary hemorrhage and bronchopulmonary dysplasia than surfactant TA. Lower mortality risks associated with poractant alfa may be attributable to higher initial doses of poractant alfa, compared to beractant. Information on the cost of poractant alfa in the US was identified, however no cost-effectiveness evaluations were identified. Authors of the study that included cost concluded that the cost of poractant alfa could be a limiting factor for its use in the US. No relevant evidence-based guidelines were identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were used to limit the retrieval by study type for question 1 and 2. A methodological filter was applied to limit retrieval to guidelines for question 3. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and August 16, 2018.

Selection Criteria and Methods

One reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Infants at risk for or having respiratory distress syndrome
Intervention	Curosurf (poractant alfa)
Comparator	Q1-2: Bovine lung extract (BLES) Q3: No comparator
Outcomes	Q1: Clinical effectiveness/clinical benefit (e.g., but not limited to, infant disposition, death/mortality, bronchopulmonary dysplasia, O_2 saturation, ventilation parameters, severe airway obstruction [SAO]), safety; Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies included in a selected systematic review were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SR) were critically appraised using the AMSTAR 2 tool.[12] The included network meta-analyses were assessed using the Questionnaire to assess the relevance and credibility of a network meta-analysis.[7] The quality of randomized clinical trials (RCTs) was assessed using the Cochrane Risk of Bias Tool.[14] The quality of non-randomized studies was assessed using the Downs and Black checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations assessed in each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 275 citations were identified in the literature search. Following screening of titles and abstracts, 253 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 11 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Additional details describing the characteristics of the included studies are reported in Appendix 2.

Study Design

The literature search aimed to identify SRs, RCTs, observational studies, economic analyses, and evidence-based guidelines. One SR was identified for inclusion in this report.[9,10]

Singh et al. was a Cochrane review and included 16 RCTs.[9] Zhang et al. performed a network meta-analysis and included 17 RCTs.[10] Six RCTs were included in both reviews and 27 RCTs were uniquely identified by the two SRs (overlap details available in Appendix 5).[9,10]

There were nine primary studies included: six RCTs and three retrospective cohort studies.[5,11-18] The RCTs had two or three arms, one of which adopted poractant alfa as intervention.[11,12,14-17] Bozdag et al., Eras et al., and Mussavi et al. were single-centre RCTs.[11,12,16] Najafian et al. was a two-centre RCT.[17] Lemyre et al. was a three-centre RCT.[14] Mirzarahimi et al. did not describe the number of collaborating NICUs.[15] Except for Najafian et al. that did not describe the type of wards,[17] the RCTs were conducted in neonatal intensive care units (NICUs).[11,12,14-16] The three retrospective cohort studies were single-centre studies.[5,13,18] Zayek et al. and Jeon et al. studies infants admitted in the NICUs.[5]

No relevant cost-effectiveness studies and no relevant evidence-based guidelines were identified.

Year of Publication and Country of origin

The SRs were both published in 2015 the corresponding authors were based in the USA and China respectively.[9,10]

The six RCTs published between 2014[12] and 2018[15] were conducted in Iran,[15-17] Turkey,[11,12], and Canada.[14]

The three retrospective cohort studies were published in 2013,[18] 2015,[13] and 2018[5] respectively and were conducted in Australia ,[18] the USA,[5] and South Korea.[13]

Study population

The SR by Signh et al. included preterm infants at risk for or having RDS.[9] The SR by Zhang et al. included infants with neonatal RDS treated with exogenous pulmonary surfactants.[10]

All of the RCTs and retrospective cohort studies enrolled infants.[5,11-18] All RCTs included infants of gestational age of equal to or less than 37 weeks.[11,12,14-17] Bozdag et al., Eras et al., Najafian et al. specifically recruited infants of less than 32,[11] 32,[12] and 35 weeks of gestational age respectively.[17] Bazdag et al. and Najafian et al. also limited the birth weights to less than 1,500 g[11] and more than 750 g respectively.[17] Among six RCTs, the sample sizes ranged from 42[11] to 215.[12] Except for Bozdag et al. that included infants with pulmonary hemorrhage,[11] the other five RCTs recruited infants diagnosed with RDS.[12,14-17]

In the three retrospective cohort studies, there were 332,[13], 664,[18] and 1,194 infants included.[5] Jeon et al. reviewed patients diagnosed with RDS that required surfactant treatment.[13] Paul et al. and Zayek et al. selected infants treated with surfactant in the medical records.[5,18]

Interventions and Comparators

Singh et al. categorized the animal-derived surfactant extracts into four groups: bovine lung lavage surfactant extract, modified bovine minced lung surfactant extract, porcine minced lung surfactant extract, and porcine lung lavage surfactant.[9] Poractant alfa was considered a type of porcine minced lung surfactant extract.[9] The comparator was bovine lung surfactant.[9] Zhang et al. identified six exogenous pulmonary surfactants, two of which were uniquely identified by Zhang et al.: lucinactant and colfosceril palmitate that were synthetic, rather than bovine, and were not relevant to this review.[10] In the evidence network of the network meta-analysis by Zhang et al., the six surfactants were compared to each other, except for calfactant and lucinactant.[10] Poractant alfa and beractant were the most frequently compared in the included studies.[10]

Poractant alfa was the intervention evaluated in the six RCTs[11,12,14-17] and three retrospective cohort studies.[5,13,18]

Beractant, categorized as modified bovine minced lung surfactant extract in Singh et al., was the comparator in one retrospective cohort study[18] and five RCTs.[11,12,15-17] Bovine lipid extract surfactant (BLES), categorized as bovine lung lavage surfactant extract, was the comparator in one RCT.[14] Calfactant, categorized as bovine lung lavage surfactant extract, was the comparator in one retrospective cohort studies.[5,13] Surfacten that was not reviewed in the two SRs[9,10] was the other comparator in Jeon et al.[13]

The doses of poractant alfa were described in two retrospective cohort studies[5,13] and five RCTs.[11,14-17] The doses of poractant alfa were 100 milligrams per kilogram (mg/kg)[11,15,17] and 200 mg/kg.[14,9,16]

Outcomes

In one SR, the types of primary outcomes evaluated by Singh et al. included mortality and chronic lung disease.[9] The primary outcomes were assessed at 28 days of age, before hospital discharge, and at 36 weeks' postmenstrual age (postmenstrual age is equal to gestational age plus chronological age of the infant).[9] The secondary outcomes included surfactant doses, air leak syndrome, pulmonary hemorrhage, patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis, retinopathy of prematurity (ROP) and intraventricular hemorrhage.[9] In the other SR and network meta-analysis by Zhang et al., the outcome of interest was mortality.

In the retrospective cohort study by Jeon et al., outcomes were categorized based on the associations with RDS or prematurity.[13] RDS-associated outcomes were surfactant redosing, pulmonary hemorrhage, ventilation, and BPD.[13] Prematurity-associated outcomes included patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), ROP, infection, and mortality.[13]

Mortality was also the primary outcome in one RCT[14] and two retrospective cohort studies[5,18] Respiratory outcomes were directly studied through oxygenation index, bronchopulmonary dysoplasia,[11] extubation rate, respiratory support,[14,16] ventilation time,[15]

continuous positive airway pressure failure, ventilation dependency and blood gas profile in the RCTs.[16]

Chronic lung disease was assessed in two retrospective cohort studies.[5,18] and a retrospective cohort study.[18] Apgar score and infection were the outcomes of interest in one RCT.[17] Cognitive test scores and disability were also assessed in one retrospective cohort study.[18] In the RCT by Eras et al., neurological outcomes were primarily assessed through the occurrence of neurodevelopmental impairment and cerebral palsy.[12] Treatment cost was also summarized in one retrospective cohort study.[5]

Summary of Critical Appraisal

Additional details describing the critical appraisal of the included studies are reported in Appendix 3.

The SRs by Singh et al. and the network meta-analysis by Zhang et al. both described the study objectives, inclusion criteria and eligible study design, conducted comprehensive literature search, extracted data in duplicate, described the included studies in detail, adjusted for risk of bias of individual studies, conducted meta-analysis with appropriate methods, explained the outcomes based on the observed study heterogeneity, and declared conflict of interest.[9,10] The detailed description of study objectives, inclusion criteria, study design, meta-analysis, and methods to adjust for primary study heterogeneity could help to ensure the quality of the review. The adequate use of statistical methods was essential to draw appropriate statistical inference. However, both studies did not publish the research protocol *a priori*.[9,10] Singh et al. did not explain the study selection criteria in detail, document the funding sources of the primary studies, discuss the role of risk of bias for the results of meta-analysis, and assess publication bias.[9] In contrast, Zhang et al. explained selection criteria, listed the funding sources of the primary studies, discuss the role of risk of bias for the results of meta-analysis, and assessed publication bias.[10] It was not clear whether Zhang et al. selected the studies in duplicate and they did not describe the excluded studies.[10]

Specifically for the conduct of network meta-analysis, Zhang et al. described the rationale for the statistical methods, the network structure, the assessment of the consistency between direct and indirect contrasts, the minimal standard of RCT quality, the heterogeneity investigation, and the sensitivity analysis for potential confounders.[10] These measures ensured that the network meta-analysis was built on adequate modeling assumptions and statistical rigour. However, there was no description about the examination on within-study randomization, and agreement between direct and indirect comparisons.[10]

All RCTs included infants, did not have patients lost to follow-up, and did not seem to selectively report the results.[11,12,14-17] Randomization methods were described in four RCTs.[11,12,14,17] Allocation concealment was described in three RCTs.[11,14,16] Clinicians that assessed the outcomes were blinded in RCTs.[12,14-16] One, four and one RCTs were considered of good[14], fair,[11,12,15,16] and poor quality respectively.[17]

The three retrospective cohort studies described the study objectives, outcome measurement based on medical records, the characteristics of the patients, the interventions, distributions of principal confounders in different groups, findings, randomness of the results, related adverse effects, patient attrition, actual probability values, representativeness of the invited and included patients, representativeness of the

clinical settings, the lengths of follow-up periods, and statistical tests for main outcomes.[5,13,18] The compliance and outcome measurement were based on medical records and might be reliable.[5,13,18] The control and intervention groups were from the same populations.[5,13,18] However, only Jeon et al. and Paul et al. recruited patients with different treatment assignments at the same time.[13,18] Zayek et al. used historical cohorts from different time periods for comparison and there was no information on the changes in standard of care, except for the types of surfactants.[5] There was no lost to follow-up declared in the three retrospective cohort studies.[5,13,18] There were no estimates about the power or minimal sample sizes to detect the differences between groups in the three retrospective cohort studies.[5,13,18] The confounders were not adjusted for the outcome assessment.[5,13,18] It was unclear how much of the observed comparative effectiveness of poractant alfa could be contributed to the confounders. There was no randomization that could potentially eliminate the bias due to confounders in the three retrospective cohort studies.[5,13,18]

Summary of Findings

Clinical effectiveness of Curosurf (poractant alfa) for the treatment of infants at risk for or experiencing respiratory distress syndrome

Poractant alfa versus beractant[9-12,15-18]

One SR, one network meta-analysis, five RCTs, and one retrospective cohort study were included that compared poractant alfa and beractant.[9-12,15-18]

There were nine moderate-quality RCTs that compared modified minced lung surfactant extract (beractant or surfactant TA) and porcine minced lung surfactant extract (poractant alfa) included in the SR by Singh et al.[9] Six of them were also included in the network meta-analysis by Zhang et al.[10] Two of the primary studies adopted poractant alfa 100 mg/kg (Baroutis 2003 and Halahakoon 1999), one adopted both 100 and 200 mg/kg (Ramanathan 2004), one did not report the dose (Karadag 2014), and the other five adopted 100 mg/kg.[9] Compared to poractant alfa, it was found that modified bovine minced lung surfactant extract was associated with significant increases in the risk of mortality prior to hospital discharge (nine RCTs), death or oxygen requirement at 36 weeks of postmenstrual age (three RCTs), receiving more than one dose of surfactant, and patent ductus arteriosus (PDA) (three RCTs).[9] In the subgroup analysis, higher initial doses of poractant alfa were compared to beractant 100 mg/kg and were found to be associated with both lower risks of mortality prior to discharge and lower risks of death or oxygen requirement at 36 weeks of postmenstrual age.[9] Singh et al. considered the observed differences in clinical effectiveness between beractant and poractant alfa limited to the studies using a higher initial dose of poractant alfa.[9] Authors concluded that further research would reduce uncertainty regarding the causes of the differences in effectiveness.[9]

In the network meta-analysis by Zhang et al., the mortality risks of different surfactants were directly and indirectly compared based on the results from 17 high-quality RCTs on infants with RDS.[10] Six of them were also included in the SR by Singh et al.[9] Beractant (Survanta) was the comparator used for conclusion.[10] When compared to each other, there were no significant differences in mortality rates between poractant alfa and beractant.[10] When the mortality risks associated with the six surfactants were assessed together, beractant seemed to be related to the lowest mortality risks.[10]

Four fair-quality RCTs,[11,12,15,16] one poor-quality RCT,[17] and one good-quality retrospective cohort study[18] compared the effectiveness of poractant alfa and beractant. The doses of

poractant alfa were 100 mg/kg[11,15,17] or 200 mg/kg.[13,16] The doses of beractant were 100 mg/kg.[11,15-17] The doses were not mentioned in Eras et al. and Paul et al.[18,19]

Bozdag et al. did not find significant differences in oxygenation index until 24 hours of surfactant use, rates of bronchopulmonary dysplasia, and pulmonary hemorrhage-related mortality.[11] Eras et al. found similar rates of neurodevelopmental impairment and cerebral palsy.[19] Mirzarahimi et al. found poractant alfa associated with lower rates of redosing and longer duration of ventilation.[15] Mussavi et al. did not find significant differences in bronchopulmonary dysplasia, ROP, IVH, hospital-stay length, and mechanical ventilation requirement.[16] Najafian et al. found similar rates of the need for nasal continuous positive air way pressure (CPAP) and endotracheal tube, mortality and complications that included sepsis, pneumonia, necrotizing enteric colitis (NEC), IVH, ROP and pulmonary hemorrhage in two groups.[17] In subgroup analysis, proactant alfa was associated with less need of endotracheal tubes (more than 32 birth weeks only) and CPAP (29 to 32 birth weeks only).[17] However, the incidence of IVH and NEC was significantly higher in the poractant alfa group.[17]

In the retrospective cohort study by Paul et al., the infants receiving poractant alfa and beractant had similar baseline characteristics, except for that those receiving poractant alfa were 2.8 days younger.[18] The risks of mortality, chronic lung disease, and severe disability were similar for these two types of surfactant.[18]

Overall, similar mortality risks were found in the network meta-analysis by Zhang et al.[10] and two primary studies.[17,18] When limited to pulmonary hemorrhage-related mortality, the risk was similar for the two types of surfactants in one fair-quality RCT.[11] However, in the SR by Singh et al. proactant alfa was associated with reduced risks of mortality prior to discharge and at 36 weeks of postmenstrual age.[9] Higher initial doses of poractant alfa might be the cause, but authors concluded that further verification was warranted.[9]

The risk of boncho-pulmonary dysplasia was found to be similar in two fair-quality RCTs.[11,16] For cerebral palsy, neurodevelopmental impairment,[12] oxygenation index,[11] pulmonary hemorrhage,[16,17] IVH,[17] ROP, NEC,[17] pneumothorax,[16] need for CPAP,[17] chronic lung disease, and severe disability,[18] poractant alfa and beractant seemed to be similarly effective. However, there was conflicting evidence found for the need for mechanical ventilation in two fair-quality RCTs.[15,16]

However, higher initial doses of proactant alfa might be associated with reduced risks of oxygen requirement at 36 weeks of postmenstrual age.[9] There were also specific subgroups identified, infants of 29 to 32 weeks of gestational age, that may have lower risks in IVH and NEC if treated with poractant alfa in one poor-quality RCT.[17]

Poractant alfa versus bovactant[16]

In the fair-quality RCT by Mussavi et al., poractant alfa 200 mg/kg was also compared with bovactant 100 mg/kg.[16] Poractant alfa was found to be associated with similar rates of bronchopulmonary dysplasia, ROP, IVH, hospital-stay length, and the need for mechanical ventilation compared to bovactant or beractant.[16] However, bovactant was associated with higher incidence of pneumothorax and pulmonary hemorrhage.[16] Specifically for the neonates born younger than 32 weeks of gestational age, bovactant was also associated with higher incidence of PDA, hospital-stay length, and mechanical ventilation time than the other two surfactants.[16]

Poractant alfa versus bovine lipid extract surfactant (BLES)[14]

One good-quality RCT by Lemyre et al. compared poractant alfa 200 mg/kg and BLES 135 mg/kg in Canadian neonatal intensive care units (NICUs).[14] There was no significant difference observed in infants alive and extubated within 48 hours.[14] Lemyre et al. found similar rates of bronchopulmonary dysplasia, extubation, redosing, and severe airway obstruction within 48 hours.[14] However, poractant alfa was found to be associated with higher overall mortality and larger studies are needed in order to explore this association.[14]

Poractant alfa versus calfactant[13]

One good-quality retrospective cohort study compared poractant alfa 200 mg/kg and calfactant 105 mg/kg.[13] Jeon et al. found that poractant alfa was similarly effective when compared with calfactant in terms of the risks of surfactant redosing, pulmonary air leak, duration of mechanical ventilation, PDA, IVH (≥grade III), periventricular leukomalacia, high stage ROP, NEC (≥stage II), mortality, and duration of hospital stay.[13] Though poractant alfa was associated with more cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia.[13] Jeon et al. concluded that poractant alfa as effective as calfactant.[13]

Poractant alfa versus surfactant TA[13]

One good-quality retrospective cohort studies compared poractant alfa 200 mg/kg and surfactant TA 120 mg/kg. [13] Jeon et al. found that poractant alfa was similarly effective as surfactant TA in terms of the risks of surfactant redosing, pulmonary air leak, duration of mechanical ventilation, PDA, IVH (≥grade III), periventricular leukomalacia, high stage ROP, NEC (≥stage II), mortality, and duration of hospital stay.[13] However, poractant alfa was associated with more cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia.[13]

Cost-effectiveness of Curosurf (poractant alfa) for the treatment of infants at risk for or experiencing respiratory distress syndrome

No relevant cost-effectiveness analyses were identified, however one of the included retrospective cohort studies included costing information and the results are presented here.

One good-quality retrospective cohort study compared poractant alfa 200 mg/kg and calfactant 105 mg/kg in the US.[5] Zayek et al. conducted an cost analysis of these two surfactants assuming similar clinical effectiveness of the two surfactants based on their experiences.[5] Calfactant was associated with fewer doses, higher percentages of needing one dose.[5] The cost of treatment per patient for poractant alfa was US$1160.62 and 38% higher than that for calfactant.[5] The 22-month cost difference could reach US$202,732.75 in the hospital.[5] There was a strong pharmacoeconomic advantage of using calfactant for lower patient costs.[5]

Guidelines

There were no relevant evidence-based guidelines identified.

Limitations

There are several limitations to this report. The information on the surfactant doses was not reported in one network meta-analysis, one RCT, and one retrospective cohort studies.[10,12,18] Basic information on the dose, frequency, and duration[20] has not been

described in several studies.[10,12,18] Higher initial doses of poractant alfa, 200 mg/kg versus 100 mg/kg, could be associated with the observed differences in mortality risks when compared to beractant, but this needed to be verified.[9] Additionally, there were different methods developed to administer the surfacants.[21] The administration methods might influence the effectiveness of the surfactants.[21]

There was heterogeneity in the inclusion criteria of the included studies. The impact of the differences in the basic characteristics of the preterm infants included in the SRs and primary studies remained unclear. For example, there were differences in the age eligibility and limitations in birth weights. The standard of care in most studies was not described in detail and it is therefore difficult to compare conditions. In the retrospective cohort study by Zayek et al., cohorts of different time periods were compared and there was no statement about the consistency or inconsistency of standard of care.[5] A variety of outcomes had been reported and this led to some difficulties in assessing the outcomes across different studies.

Conclusions and Implications for Decision or Policy Making

One SR, one network meta-analysis, six RCTs and three retrospective cohort studies were identified regarding the comparative clinical effectiveness of poractant alpha and bovine lung extract surfactants.[5,9,10,14-18] Surfactants were usually administered once, but could be repeated at the same or lower doses.[9] The most commonly used doses of poractant alfa were 100 and 200 mg/kg,[9] but the exact doses were not reported in several studies.[10,12,18] Overall, routes of administration were not reported. Inconsistency in the reporting of outcomes as well as a lack of clarity regarding the standard of care in the studies makes comparisons across trials difficult. No relevant evidence-based guidelines were identified.

Poractant alfa versus beractant[9-12,15-18]

Poractant alfa (100[11,15,17] or 200 mg/kg[13,16]) was associated with similar risks of mortality,[10,17,18] pulmonary hemorrhage-related mortality,[11] bonchopulmonary dysplasia,[11,16] cerebral palsy, neurodevelopmental impairment,[12] oxygenation index,[11] pulmonary hemorrhage,[16,17] IVH,[17] ROP, NEC,[17] pneumothorax,[16] need for CPAP,[17] chronic lung disease, and severe disability when compared with beractant (100 mg/kg).[18] Singh et al. found poractant alfa associated with lower mortality risks, but they considered this effect potentially attributable to higher initial doses of poractant alfa.[9]

Poractant alfa versus bovactant[16]

For bronchopulmonary dysplasia, ROP, IVH, hospital-stay length, and the need for mechanical ventilation, poractant alfa was similarly effective; for pneumothorax and pulmonary hemorrhage, poractant alfa was found to be more effective; and for neonates of less than 32 weeks gestational age, poractant alfa was more effective for outcomes including PDA, hospital-stay length, and mechanical ventilation time.[16]

Poractant alfa versus bovine lipid extract surfactant (BLES)[14]

Lemyre et al. found similar rates of bronchopulmonary dysplasia, extubation, redosing, and severe airway obstruction in alive infants within 48 hours of birth.[14] However, poractant alfa was found to be associated with higher overall mortality and this needed to be confirmed in larger studies.[14]

Poractant alfa versus calfactant[13]

Poractant alfa was found to be similarly effective as calfactant in terms of the risks of surfactant redosing, pulmonary air leak, duration of mechanical ventilation, PDA, IVH (≥grade III), periventricular leukomalacia, high stage ROP, NEC (≥stage II), mortality, and duration of hospital stay.[13] Even though poractant alfa was associated with more cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia.[13] Authors concluded that poractant alfa was as effective as calfactant.[13]

Poractant alfa versus surfactant TA[13]

Jeon et al. found that poractant alfa was similarly effective as surfactant TA in terms of the risks of surfactant redosing, pulmonary air leak, duration of mechanical ventilation, PDA, IVH (≥grade III), periventricular leukomalacia, high stage ROP, NEC (≥stage II), mortality, and duration of hospital stay.[13] However, poractant alfa was associated with more cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia.[13]

CostingThe cost of treatment per patient for poractant alfa was $1160.62 and 38% higher than that for calfactant in the US.[5] The 22-month cost difference could reach $202,732.75 in the hospital.[5] There was a strong pharmacoeconomic advantage of using calfactant for lower patient costs.[5]

Overall, poractant alfa was found to be similarly or more effective for several outcomes, such as broncho-pulmonary dysplasia and retinopathy of prematurity, compared to the following bovine lung extract surfactants: beractant,[9,10] bovactant,[16] BLES,[14] and calfactant.[13] However, larger studies were necessary to confirm whether poractant alfa was associated with higher mortality rates than BLES[14] and whether poractant alfa was associated with more risks in pulmonary hemorrhage and bronchopulmonary dysplasia than surfactant TA.[13] It is possible that the lower mortality risks associated with poractant alfa might be attributable to higher initial doses of poractant alfa, compared to beractant, thus further study would reduce uncertainty.

The high cost of poractant alfa (based on costs from one non-randomized study in the US) may be a limiting factor for use.[5] However, policy makers may be interested in whether some subgroups may benefit more from the use of poractant alfa to tailor the strategy of adopting poractant alfa in clinical use.

Cost-effectiveness studies in the Canadian setting would reduce uncertainty regarding the cost-effectiveness of poractant alfa versus bovine options.

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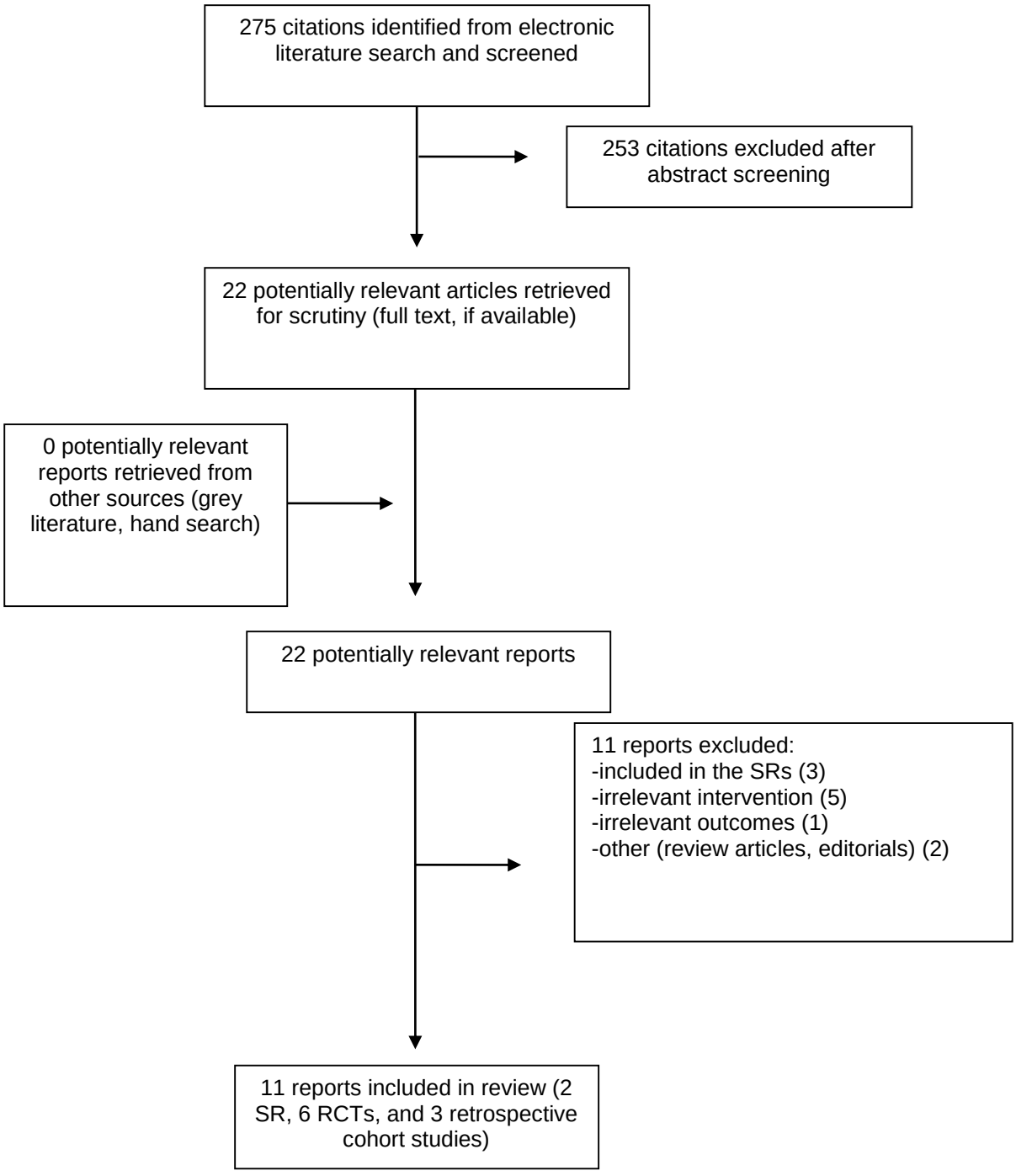
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Systematic Reviews and Network Meta-analyses

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Singh et al. 2015,[9] USA	16 RCTs, Cochrane review	Preterm infants at risk for or having RDS	Animal-derived surfactant extracts including 1) Bovine lung lavage surfactant extract [calfactant (100 mg/kg), Bovine Lung Expanding Substance, (BLES, 137 mg/kg), cow/calf lung surfactant extract (CLSE) or SF-RI 1 (bovactant, 50 mg/kg)] 2) modified bovine minced lung surfactant extract [beractant, 100 mg/kg or surfactant TA(Surfacten, 120 mg/kg)] 3) porcine minced lung surfactant extract (poractant alfa, 100 to 200 mg/kg) 4) Porcine lung lavage surfactant (Surfacen)	Bovine lung surfactant	1) Neonatal mortality (mortality < 28 days of age) from any cause 2) Mortality prior to hospital discharge (from any cause) Chronic lung disease 3) Oxygen requirement at 28 to 30 days of age 4) Oxygen requirement at 36 weeks' postmenstrual age Death or chronic lung disease 5) Death or oxygen requirement at 28 to 30 days of age 6) Death or oxygen requirement at 36 weeks' postmenstrual age Secondary outcomes 1) Doses of surfactant 2) pneumothorax 3) Air leak syndromes (including pulmonary interstitial emphysema, pneumothorax, pneumomediastinum) 4) Pulmonary hemorrhage 5) Patent ductus arteriosus (PDA) (that has been treated with cyclo-oxygenase inhibitor or surgery) 6) Culture-confirmed bacterial sepsis 7) Culture-confirmed

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					fungal sepsis 8) Necrotizing enterocolitis (any stage) 9) Periventricular leukomalacia (in infants who received neuroimaging) 10) Retinopathy of prematurity in subjects examined. - all stages 11) retinopathy of prematurity (ROP) stage 3 or greater Intraventricular hemorrhage (in infants who received neuroimaging). 12) Intraventricular hemorrhage (any grade) 13) Severe intraventricular hemorrhage (grade 3 or greater)
Zhang et al. 2015,[10] China	17 RCTs, network meta-analysis	57,223 infants with NRDS treated with various exogenous pulmonary surfatant (Survanta, n = 27,017; Alveofact, n = 159; Infasurf, n = 20,377; Curosurf, n = 20,911; Surfaxin, n = 646; Exosurf, n = 1640).	6 exogenous pulmonary surfactants: beractant (Survanta), bovactant (Alveofact), calfactant (Infasurf), poractant alfa (Curosurf), lucinactant (Surfaxin), and colfosceril palmitate (Exosurf) Doses not mentioned Lucinactant (Surfaxin), and colfosceril	Surfactants compared to each other	1) mortality

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
			palmitate (Exosurf) are not bovine-derived and not eligible for this review.		

BLES = bovine lung expanding substance; CLSE = cow/calf lung surfactant extract; kg = kilogram; mg = milligram; NRDS = neonatal respiratory distress syndrome; PDA = Patent ductus arteriosus);RCT = randomized controlled trial; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; USA = United States of America

Table 2: Characteristics of included primary studies

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Randomized Controlled Trials					
Mirzarahimi et al. 2018,[15] Iran	RCT, 2-arm, NICU	N = 150 infants Inclusion criteria 1) gestational age <37 week 2) HMD [not explained in the article, supposedly hyaline membrane disease, a synonym for Infant Respiratory Distress Syndrome (IRDS)]	Poractant alfa (Curosurfor), 100mg/kg administered by injection at the distal tracheal tube up to two hours	Beractant (Survanta). 100mg/kg administered by injection at the distal tracheal tube up to two hours	Ventilation time, hospitalization time,
Lemyre et al. 2017,[14] Canada	RCT, three-centre, 2-arm, NICU	N = 87 infants Inclusion criteria 1) between 24+0 and 31+6 weeks gestational age (GA) 2) RDS requiring intubation and surfactant therapy within their first 48 hours of life	Poractant alfa (Curosurf1, Chiesi Farmaceutici, Parma, Italy); 2.5 mL/kg (200mg/kg of phospholipids) for the first dose and 1.25 mL/kg (100mg/kg) for repeat doses	Bovine lipid extract surfactant (BLES® Biochemicals, London, Ontario); 5 mL/kg (135 mg/kg of phospholipids) per dose	Primary outcomes 1) alive and extubated at 48 hours postsurfactant administration Secondary outcomes 1) duration of respiratory support (respiratory support via an endotracheal tube and non-invasive respiratory support) 2) extubation success rates, 3) need for additional surfactant doses, 4) death and 5) pulmonary morbidities up to 36 weeks corrected GA
Mussavi et al. 2016,[16] Iran	RCT, triple-blind, single-centre, NICU	N = 165 infants Inclusion criteria 1) born between January 1, 2012, and December 31, 2013	Poractant alfa (200 mg/kg) (group 2)	Bovactant (Alveofact) (100 mg/kg) (group 1); beractant (Survanta) (100 mg/kg) (group III)	Primary outcomes 1) continuous positive airway pressure (CPAP) failure, 2) ventilator dependence until 7

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		2) gestational age 37 weeks or younger 3) RDS			days after birth, 3) blood CO2 and O2 levels (SO2 in the texts, possibly a typo), and 4) base excess (BE) Secondary outcomes: intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), pneumothorax, broncho-pulmonary dysplasia (BPD), pulmonary hemorrhage, sepsis, and length of hospitalization.
Najafian et al. 2016,[17] Iran	RCT, 2-centre, 2-arm	N = 112 infants Inclusion criteria 1) RDS 2) birth weight more than 750 gr; gestational age less than 35 weeks 3) O2 saturation 85% to 96%; 4) informed consent by parents, 5) age ≤ 6 h at the time of randomization	Poractant alfa (Curosurf) (group one) 100 mg/kg after intubation	Beractant (Survanta) 100 mg/kg (group two)	1) Apgar score: calculated using heart rate, respiratory effort, muscle tone, reflex irritability, and color given values of 0, 1, or 2 2) sepsis: based on positive blood culture 3) pneumonia by chest radiography, seeing bilateral alveolar densities with air bronvhograms or irregular patchy infiltrates 4) intraventricular hemorrhage (IVH) by cranial ultrasonography.
Bozdag et al. 2015,[11] Turkey	RCT, 2-arm, single-centre, NICU	N = 42 infants Inclusion criteria: 1) gestational age of < 32 weeks or birth-weight of < 1,500 g at birth	Poractant alfa, 100 mg/kg (1.25 mL/kg), a single dose after the 2nd hour of pulmonary hemorrhage	Beractant, 100 mg/kg (4 mL/kg), a single dose after the 2nd hour of pulmonary hemorrhage	Primary outcomes 1) respiratory status: change in oxygenation index and other respiratory variables.

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		2) pulmonary hemorrhage within the first 2 weeks of life			Secondary outcome 1) bronchopulmonary dysplasia (the need for oxygen at 36 weeks of postmenstrual age) and mortality related to pulmonary hemorrhage (within 72 hours after pulmonary hemorrhage).
Eras et al. 2014,[19] Turkey	RCT, 2-arm, single-blinded, single-center, NICU	N = 215 infants Inclusion criteria 1) gestational age of 32 weeks born between January 2008 and January 2009 2) RDS: symptoms (a need for supplemental oxygen, tachypnea, grunting, and intercostal retractions) and confirmation with diagnostic tests (typical X-ray: uniform reticulogranular pattern accompanied by peripheral air bronchograms; blood gas findings (pH ≤ 7.25 and PCO2 ≥ 55 mm/Hg)) Exclusion criteria 1) major congenital anomalies 2) no parental consent	Poractant alfa	Beractant	1) neurodevelopmental impairment (NDI): presence of one or more of the following events: (1) cerebral palsy with functional deficits, (2) bilateral hearing loss and/or blindness, and (3) mental developmental index (MDI) or psychomotor developmental index (PDI) of < 70 on the Bayley Scales of Infant Development II (BSID II) 2) cerebral palsy: nonprogressive motor disorder with abnormal muscle tone, persistent or exaggerated primitive reflexes, or a positive Babinski sign associated with delayed motor development

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Non-Randomized Studies					
Zayek et al. 2018,[5] USA	Retrospective cohort study, single-centre, NICU, treatement strategy change	N = 1,194 Inclusion criteria 1) patients treated with surfactant	Poractant alfa was the surfactant used from July 24, 2013, to June 7, 2015 Dose: 200 mg/kg (2.5 mL/kg) for initial dose; 100 mg/kg (1.25 mL/kg) for repeat doses	Calfactant was used before and after the poractant alfa era Dose: 105 mg/kg (3 mL/kg) body weight for initial and a repeat dose	1) mortality, 2) chronic lung disease, or 3) acute pulmonary complications 4) treatment costs
Jeon et al. 2015,[13] South Korea	Retrospective cohort study, single-centre, NICU	N = 332 infants Inclusion criteria 1) 24–31 weeks' gestation 2) admitted to the neonatal intensive care units (NICU) between January 2009 and December 2012 3) RDS requiring pulmonary surfactant replacement therapy Exclusion criteria 1) chromosomal abnormality or life-threatening major congenital malformation	Group 3, poractant alfa (Curosurf®), 2.5 mL/kg (200 mg/kg)	Group 1, Surfacten®, 4 mL/kg (120 mg/kg).; Group 2, calfactant (Infasurf®), 3 mL/kg (105 mg/kg)	Outcomes associated with RDS: 1) a need for surfactant redosing, 2) pulmonary air leak, 3) pulmonary hemorrhage, 4) mechanical ventilation (including non-invasive ventilation such as nasal continuous positive airway pressure), 4) invasive ventilation (or intubation), 5) postnatal steroids therapy, and 6) broncho-pulmonary dysplasia. Outcomes associated with prematurity 1) patent ductus arteriosus (PDA), 2) intraventricular hemorrhage (IVH), 3) periventricular leukomalacia (PVL), 4) retinopathy of prematurity (ROP),

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					5) necrotizing enterocolitis (NEC), 6) sepsis, duration of hospital stay, and mortality.
Paul et al. 2013,[18] Australia	Retrospective cohort study, single-centre	N = 664 Inclusion criteria 1) <32 weeks gestation 2) administered surfactant for the treatment of RDS 3) "27-month period between October 2005 and December 2007 during which time the unit policy was to alternate between using poractant alfa and beractant on a monthly basis" (p. 840)	Poractant alfa	Beractant	Primary outcome 1) death before discharge or moderate to severe chronic lung disease Secondary outcomes 1) pulmonary haemorrhage, 2) air leak, 3) patent ductus arteriosus (PDA) requiring treatment, 4) moderate to severe disability and 5) cognitive test scores in survivors.

BPD = broncho-pulmonary dysplasia; CO2 = carbon dioxide; IVH = intraventricular hemorrhage; CPAP = continuous positive airway pressure; NEC = necrotizing enterocolitis; NICU = neonatal intensive care unit; O2 = oxygen; PCO2 = partial pressure of carbon dioxide; PDA = Patent ductus arteriosus; RCT = randomized controlled trial; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; USA = United States of America

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[12]

Strengths	Limitations
Singh et al. 2015[9]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described • Reasons for study exclusion listed in the flowchart • Comprehensive search with the Cochrane Central Register of Controlled Trials, MEDLINE via PubMed, EMBASE, and CINAHL • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies not provided • Potential studies in all languages screened • Included studies described • Critical appraisal with a tool developed by the Cochrane Neonatal Group • Meta-analysis conducted with RevMan 2014 • Heterogeneity considered for the outcomes • Conflict of interest declared	• Protocol not established *a priori* • Study selection criteria not explained in detail • Funding sources of the included studies not mentioned • Risk of bias not explicitly tested in the meta-analysis • Risk of bias in individual studies not discussed regarding the results of meta-analysis • Publication bias not assessed

PICO = population, intervention, comparator, and outcome

Table 4: Strengths and Limitations of Network Meta-Analyses using the Questionnaire for quality assessment[7]

Strengths	Limitations
Zhang et al. 2015[10]	
• PICO components included in the research questions or study inclusion criteria • Comprehensive search for RCTswith PubMed, Ovid, EBSCO, Springerlink, Wiley, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang and VIP databases • Study contexts described • RCTs connected in one network • No poor-quality RCTs included for analysis • Selective reporting not likely • Systematic differences in treatment effect modifiers not found • Contrasts between direct and indirect comparisons mentioned • Consistency in closed loops between direct and indirect comparisons studied • Study quality and sample sizes considered in sensitivity analysis • Random-effects and fixed-effect models considered	• Within-study randomization not addressed • Agreement between direct and indirect comparisons not described • Results of direct and indirect comparisons not reported separately • Protocol not established *a priori* • A list of excluded studies not provided

Strengths	Limitations
• Heterogeneity investigated for random-effects models • Comparison network in Figure 3 • Individual studies reported • 95% confidence intervals reported • Ranking of interventions provided • Age and sex distributions in RCTs reported • Conclusion possibly fair and balanced • No conflict of interest reported	

PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial

Table 5: Strengths and Limitations of RCTs using the Cochrane Risk of Bias checklist[14]

Strengths	Limitations
Mirzarahimi et al. 2018[15]	
• Infants could not be blinded • Clinicians probably blinded, but the details not described • No attrition reported in the texts • No loss to follow-up • Selective outcome reporting not likely	• Randomization mentioned, but the exact method not described • Allocation concealment not described
Lemyre et al. 2017[14]	
• Randomization method mentioned • Allocation concealment described • Infants could not be blinded • Clinicians blinded • Attrition reported in Figure 1 • No loss to follow-up • Selective outcome reporting not likely	
Mussavi et al. 2016[16]	
• Allocation concealment described • Infants could not be blinded • Clinicians blinded • No attrition reported in Figure 1 • No loss to follow-up • Selective outcome reporting not likely	• Randomization mentioned, but the exact method not described
Najafian et al. 2016[17]	
• Randomization method described • Infants could not be blinded • No attrition reported in Figure 1 • No loss to follow-up • Selective outcome reporting not likely	• Allocation concealment not described • Clinicians not blinded
Bozdag et al. 2015[11]	
• Randomization method mentioned • Allocation concealment described • Infants could not be blinded • Attrition reported in the texts	• Clinicians not blinded

Strengths	Limitations
• No loss to follow-up • Selective outcome reporting not likely	
Eras et al. 2014[12]	
• Randomization method mentioned • Infants could not be blinded • Clinicians blinded • Attrition reported in the texts • No loss to follow-up • Selective outcome reporting not likely	• Allocation concealment not described

Table 6: Strengths and Limitations of non-randomized studies using Downs and Black checklist[8]

Strengths	Limitations
Zayek et al. 2018[5]	
• Objectives described • Outcomes defined in the Methods • Patients characteristics described in the Results • Interventions described • Principal confounders, such as demographic characteristics, compared between groups • Main findings clearly described • Random variability of the results estimated • Adverse effects reported • No lost to follow-up • Actual p values reported • Infants considered for recruitment representative of the patients in the NICU • Infants recruited representative of the patients in the NICU • Staff and the NICU probably representative of usual practice • Infants could not be blinded • Lengths of follow-up the same for the patients • Statistical tests appropriate • Patient compliance recorded by clinicians • Main outcomes recorded by clinicians • Different groups recruited from the same populations	• Clinicians not blinded • Data dredging not identified • Different groups of patients recruited at different time periods • No randomization • No allocation concealment • Confounders not taken into account for the outcome analysis • The power to detect the differences between groups not determined before study • Patients recruited in different time periods
Jeon et al. 2015[13]	
• Objectives described • Outcomes defined in the Methods • Patients characteristics described in the Results • Interventions described • Principal confounders, such as demographic characteristics, compared between groups • Main findings clearly described • Random variability of the results estimated • Adverse effects reported • No lost to follow-up	• Clinicians not blinded • Data dredging not identified • Different groups of patients recruited at different time periods • No randomization • No allocation concealment • Confounders not taken into account for the outcome analysis • The power to detect the differences between groups not determined before study • Patients recruited in different time periods

Strengths	Limitations
• Actual p values reported • Infants considered for recruitment representative of the patients in the NICU • Infants recruited representative of the patients in the NICU • Staff and the NICU probably representative of usual practice • Infants could not be blinded • Lengths of follow-up the same for the patients • Statistical tests appropriate • Patient compliance recorded by clinicians • Main outcomes recorded by clinicians • Different groups recruited from the same populations	
Paul et al. 2013[18]	
• Objectives described • Outcomes defined in the Methods • Patients characteristics described in the Results • Interventions described • Principal confounders, such as demographic characteristics, compared between groups • Main findings clearly described • Random variability of the results estimated • Adverse effects reported • No lost to follow-up • Actual p values reported • Infants considered for recruitment representative of the patients in the NICU • Infants recruited representative of the patients in the NICU • Staff and the NICU probably representative of usual practice • Infants could not be blinded • Lengths of follow-up the same for the patients • Statistical tests appropriate • Patient compliance recorded by clinicians • Main outcomes recorded by clinicians • Different groups recruited from the same populations • Treatment assigned to patients based on alternating time periods	• Clinicians not blinded • Data dredging not identified • Different groups of patients recruited at different time periods • No randomization • No allocation concealment • Confounders not taken into account for the outcome analysis • The power to detect the differences between groups not determined before study

NICU = neonatal intensive care unit

Appendix 4: Main Study Findings and Author's Conclusions

Table 7: Summary of Findings of Systematic Reviews and Network Meta-analysis

Main Study Findings	Author's Conclusions
Singh et al. 2015[9]	

Modified bovine minced lung surfactant extract (beractant or surfactant TA) compared to porcine minced lung surfactant extract (poractant alfa)
• 9 RCTs that compared beractant and poractant alfa
• Significant increase associated with modified bovine minced lung surfactant extract:
  • risk of mortality prior to hospital discharge (typical RR 1.44, 95% CI 1.04 to 2.00; 9 studies and 901 infants; moderate quality evidence);
  • death or oxygen requirement at 36 weeks' postmenstrual age (typical RR 1.30, 95% CI 1.04 to 1.64; 3 studies and 448 infants; moderate quality evidence);
  • receiving more than one dose of surfactant (typical RR 1.57, 95% CI 1.29 to 1.92; 6 studies and 786 infants); and
  • patent ductus arteriosus (PDA) requiring treatment (typical RR 1.86, 95% CI 1.28 to 2.70; 3 studies and 137 infants)
Subgroup analysis based on initial dose of surfactant
• Beractant (100 mg/kg) compared to higher initial dose of porcine minced lung surfactant (> 100 mg/kg)
  • Higher mortality prior to discharge (typical RR 1.62, 95% CI 1.11 to 2.38) and
  • Risk of death or oxygen requirement at 36 weeks' postmenstrual age (typical RR 1.39, 95% CI 1.08 to 1.79).
	• "Significant differences in clinical outcome were noted in the comparison trials of modified minced lung surfactant extract (beractant) compared with porcine minced lung surfactant extract (poractant alfa) including a significant increase in the risk of mortality prior to discharge, death or oxygen requirement at 36 weeks' postmenstrual age, PDA requiring treatment and "receiving > 1 dose of surfactant""
	• "The difference in these outcomes was limited to studies using a higher initial dose of porcine minced lung surfactant extract."
	• "It is uncertain whether the observed differences are from differences in dose or from source of extraction (porcine vs. bovine) because of the lack of dose-equivalent comparison groups with appropriate sample size." (p. 2)

Zhang et al. 2015[10]	
• 17 high quality RCTs on neonatal respiratory distress syndrome (NRDS) infants for this network meta-analysis. • Network meta-analysis: mortality rates associated with Alveofact, Infasurf, Curosurf, Surfaxin, Exosurf not significantly different compared to Survanta (Alveofact: OR = 1.163, 95% CI = 0.645 to 2.099, P = 0.616; Infasurf: OR = 0.985, 95% CI = 0.777 to 1.248, P = 0.897; Curosurf: OR = 0.789, 95% CI = 0.619 to 1.007, P = 0.056; Surfaxin: OR = 0.728, 95% CI = 0.477 to 1.112, P = 0.142; Exosurf: OR = 0.960, 95% CI = 0.698 to 1.319, P = 0.799). • Surface under the cumulative ranking curves (SUCRA) value: Surfaxin group significantly higher than the other five groups (Surfaxin: 80.4%; Survanta: 37.0%; Alveofact: 24.4%; Infasurf: 40.0%; Curosurf: 73.9%; Exosurf: 44.2%), suggesting that infant mortality rate in Surfaxin group was the lowest among the six groups.	• "Surfaxin could effectively reduce the mortality rate of infants with NRDS and may have a better efficacy in NRDS treatment, compared to Survanta, Alveofact, Infasurf, Curosurf and Exosurf" (p. 46)

CI = confidence interval NRDS = neonatal respiratory distress syndrome;;RCT = randomized controlled trial; RR = relative risk

Table 8: Summary of Findings of RCTs

Main Study Findings	Author's Conclusions
Mirzarahimi et al. 2018[15]	
• Repeated doses: higher in Survanta group (67.7%) than in Curosurf group (32.3%, *P* = 0.043) • Mean duration of ventilation: lower in Survanta group (8 days) than in Curosurf group (10.5 days, *P* = 0.001).	• Side effects: similar in two groups (data not shown) • Need for repeated doses: less in Curosurf group • Need for ventilation: less in Survanta group
Lemyre et al. 2017[14]	
• Extubation rates at 48 hours: 21/42 (50%) in the poractant alfa group vs 26/45 (57.8%) in the bovine lipid extract surfactant group; adjusted OR 0.76 (95% CI 0.30±1.93) (p = 0.56) • Need to re-dose: no differences • Duration of oxygen support: reduced in infants who received poractant alfa (41.5 vs 62 days respectively; adjusted OR 1.69 95% CI 1.02±2.80; p = 0.04) • Bronchopulmonary dysplasia: favoring poractant alfa among survivors (51.5% vs 72.1%; adjusted OR 0.35 95%CI 0.12±1.04; p = 0.06) • Death: 9 in the poractant alfa group and 3 in the bovine lung extract group • Severe airway obstruction following administration: 0 (poractant alfa) and 5 (bovine lipid extract surfactant) infants (adjusted OR 0.09 95%CI <0.01±1.27; p = 0.07)	• "No statistically significant difference was observed in the proportion of infants alive and extubated within 48h between the two study groups." • "Poractant alfa may be more beneficial and associated with fewer complications than bovine lipid extract surfactant." • "higher mortality in the poractant alfa group" (p. 2)
Mussavi et al. 2016[16]	
• Clinical parameters (bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, hospital-stay length, and mechanical ventilation requirement): no significant differences between the groups before and after surfactant administration • incidence rates of pneumothorax: higher in the bovactant (Alveofact) group (P = 0.03) • incidence rates of pulmonary hemorrhage: higher in the bovactant (Alveofact) group (P = 0.03) Neonates ≤ 32 weeks • Incidence of pneumothorax: significantly higher in the Alveofact group Neonates > 32 weeks • Incidences of PDA, mean hospital-stay length, and mean mechanical ventilation time: significantly higher in the Alveofact group	• "No significant differences were observed in most of the clinical variables between the three types of natural surfactant": poractant alfa, beractant, and bovactant • "Curosurf and Survanta replacement therapies among premature neonates with RDS perform better than Alveofact replacement therapy" (p. 1)
Najafian et al. 2016[17]	
• Complications including sepsis, pneumonia, IVH, NEC, pulmonary hemorrhage, ROP: similar in two groups; 18 neonates (32.1%) of Curosurf group and 20 neonates (35.7%) of Survanta group (RR = 0.922, 95% CI = 0.617 to 1.379) • Mortality: similar between the two groups • Needing nasal CPAP and endotracheal tube: similar between the two groups	• "no significant difference in complications or mortality between those two groups" • "however Curosurf was associated with less need of endotracheal tube (in >32 birth weeks subgroup) and nasal CPAP (in 29 to 32 birth weeks subgroup) (p = 0.008)" (p. 55)

Main Study Findings	Author's Conclusions
Neonates with gestational age of 29 to 32 weeks • IVH and NEC incidence: significantly more in Curosurf group compared to Survanta group (27.8% vs 0% and 22.3% vs 0%, P < 0.05)	
Bozdag et al. 2015[11]	
Poractant alfa versus beractant • Oxygenation index until 24 hours of surfactant: no significant difference between the groups at all time points (p > 0.05) • Rates of bronchopulmonary dysplasia (BPD): similar in both groups • Mortality related to pulmonary hemorrhage: similar in both the groups.	• "Both natural surfactants improved oxygenation when administered for pulmonary hemorrhage in very low-birth-weight infants." • "The type of surfactant seems to have no effect on BPD and mortality rates in these patients" (p. 211)
Eras et al. 2014[12]	
• Neurodevelopmental impairment: 33 of 113 infants (29.2%) in the poractant alfa group compared to 36 of 102 (35.2%) in the beractant group (p = 0.339) • Percentages of cerebral palsy: no significant difference (11.5 vs. 16.7%, respectively; p = 0.275)	• "poractant alfa and beractant are similar in terms of neurodevelopmental outcomes when used for the treatment of RDS in preterm infants" (p. 463)

BPD = broncho-pulmonary dysplasia; CI = confidence interval; IVH = intraventricular hemorrhage; CPAP = continuous positive airway pressure; NEC = necrotizing enterocolitis; OR = odds ratio; PDA = Patent ductus arteriosus; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity

Table 9: Summary of Findings of Non-Randomized Studies

Main Study Findings	Author's Conclusions
Zayek et al. 2018[5]	
• Number of doses: 1.6 administrations for calfactant and 1.7 for poractant alfa, p = 0.03 • Percentages of needing 1 dose: higher for calfactant (53%) than poractant alfa (47%) • Number of doses in four categories (1, 2, 3, and >3): significantly lower for calfactant than for poractant alfa (p < 0.001) • Role of gestational age: no consistent effect on the number of doses • Per patient cost: higher for poractant alfa than for calfactant in all birth weight cohorts • Average per patient cost: $1160.62 for poractant alfa, 38% higher than the average per patient cost for calfactant ($838.34) • 22-month cost difference: $202,732.75 more using poractant alfa than using calfactant in the hospital	• "a strong pharmacoeconomic advantage for the use of calfactant compared to the use of poractant alfa because of similar average dosing and lower per patient drug costs"
Jeon et al. 2015[13]	
• Instances of surfactant redosing and pulmonary air leaks, as well as duration of mechanical ventilation: not different. • Rates of patent ductus arteriosus, intraventricular hemorrhage (≥grade III), periventricular leukomalacia, high stage retinopathy of prematurity, necrotizing enterocolitis (≥stage II), mortality, and duration of hospital stay: similar	• "Calfactant is equally as effective as surfactant-TA and poractant alfa"

Main Study Findings	Author's Conclusions
• Cases of pulmonary hemorrhage and moderate to severe bronchopulmonary dysplasia increased for poractant alfa (Curosurf)	
Paul et al. 2013[18]	
• Age: infants in the poractant alfa group 2.8 days younger than beractant (27.0 ± 2.3 vs. 27.4 ± 2.3 weeks; P = 0.03) • All other baseline characters including Clinical Risk Index for Babies II scores: similar for both groups • Death or chronic lung disease: similar (78/212 vs. 59/200; P = 0.28) • Death: similar (24/214 vs. 15/201, P = 0.24) • Moderate to severe chronic lung disease: similar (63/212 vs. 46/200; P = 0.45) • Moderate to severe disability: similar (20/163 vs. 19/151, P = 0.98) between poractant alfa and beractant, respectively	• "The results of our study do not support the need for preferential use of poractant alfa or beractant" (p. 839)

Appendix 5: Overlap between Included Systematic Reviews

Table 10: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Zhang 2015[10]	Singh 2015 [9]
Karadag 2014		X
Trembath 2013	X	
Ramanathan 2013	X	
Dizdar 2012	X	X
Fujii 2010	X	X
Gharehbaghi 2010	X	X
Proquitte 2007	X	
Bloom 2005		X
Lam 2005		X
Malloy 2005		
Moya 2005	X	
Sinha 2005	X	
Sanchez-Mendiola 2005		X
Attar 2004		X
Hammoud 2004		X
Ramanathan 2004	X	X
Yalaz 2004		X
Baroutis 2003	X	X
Giannakopoulou 2002	X	
Kukkonen 2000	X	
David E. da Costa 1999	X	
Halahakoon 1999		X
Bloom 1997	X	X
Hudak 1997	X	
Hudak 1996	X	
Christian 1995	X	
Speer 1995		X

X = included

Appendix 5: Additional References of Potential Interest

Guidelines with unclear methodology or methodology without sufficient rigour

Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. *Neonatology.* 2017;111(2):107-125.

Walsh BK, Daigle B, DiBlasi RM, Restrepo RD. AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013. *Respiratory care.* 2013;58(2):367-375.