SYSTEMATIC REVIEWS

Surfactant therapy and antibiotics in neonates with meconium aspiration syndrome: a systematic review and meta-analysis

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Meconium aspiration syndrome (MAS), a common cause of respiratory failure in neonates, is associated with high mortality and morbidity. The objectives of this review were to evaluate the effects of administration of (a) surfactant—either as lung lavage (SLL) or bolus surfactant (BS) and (b) antibiotics on mortality and severe morbidities in neonates with MAS. We searched the following databases: MEDLINE via PubMed, Cochrane CENTRAL, WHOLIS and CABI using sensitive search strategies. We included eight studies on use of surfactant and three studies on use of antibiotics. Neither SLL nor BS reduced the risk of mortality in neonates with MAS (relative risk (RR) 0.38, 95% confidence interval (CI) 0.09 to 1.57; and RR 0.80, 95% CI 0.39 to 1.66, respectively). Both SLL and BS reduced the duration of hospital stay (mean difference −2.0, 95% CI −3.66 to −0.34; and RR −4.68, 95% CI −7.11 to −2.24 days, respectively) and duration of mechanical ventilation (mean difference −1.31, 95% CI −1.91 to −0.72; and mean difference 5.4, 95% CI −9.76 to −1.03 days). Neonates who received BS needed extracorporeal membrane oxygenation (ECMO) less often than the controls (RR 0.64, 95% CI 0.46 to 0.91). Use of antibiotics for MAS did not result in significant reduction in the risk of mortality, sepsis or duration of hospital stay. Surfactant administration either as SLL or BS for MAS was found to reduce the duration of mechanical ventilation and hospital stay; BS also reduced the need for ECMO. Administration of antibiotics did not show any significant clinical benefits in neonates with MAS and no evidence of sepsis. Given the limited number of studies and small number of neonates enrolled, there is an urgent need to generate more evidence on the efficacy and cost-effectiveness of these two treatment modalities before recommending them in routine clinical practice.

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INTRODUCTION

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate born through meconium-stained amniotic fluid (MSAF) having characteristic radiological changes whose symptoms cannot be otherwise explained.1,2 MAS accounts for about 10% of cases of respiratory failure in all neonates, and is associated with significant morbidity and high mortality (up to 39%).1,3 Although most neonates born through MSAF do not develop MAS, some—particularly those who are non-vigorous and require resuscitation at birth—are more prone to have the condition. Given the lack of evidence for efficacy of most interventions performed before, during or after birth, such as amnioinfusion, intrapartum suctioning and postpartum suctioning of the meconium in non-vigorous neonates, it is difficult to know how to prevent the occurrence of MAS in at-risk neonates.4–6

Currently, management of neonates with MAS involves only supportive care—oxygen therapy, assisted ventilation, inhaled nitric oxide and if available, extracorporeal membrane oxygenation (ECMO). In the absence of a specific therapy, clinicians often use a diverse range of treatment modalities, most of which are yet to be proven in randomized controlled trials (RCTs). In this article, we systematically reviewed the efficacy of the two commonly used interventions namely, surfactant administration and antibiotics. Surfactant is administered intratracheally as either a bolus dose or in dilute form to lavage the lungs in neonates with MAS. Although bolus administration is thought to replenish the endogenous surfactant inactivated by fatty acids present in the meconium, lung lavage with surfactant is believed to wash the residual meconium from the airways.2,6 Antibiotics, on the other hand, may reduce the risk of infection in the immediate neonatal period in neonates with MAS.7

METHODS

Types of studies
We included all RCTs including quasi-randomized trials that compared the effects of (1) intratracheal surfactant administration with placebo or no therapy and (2) systemic antibiotics with placebo or no antibiotics in late-preterm and term neonates with MAS.

Type of participants
All studies that enrolled late-preterm and term neonates with MAS were eligible for inclusion in this review.

Types of interventions
Intervention 1: surfactant therapy as either bolus surfactant (BS) administration or surfactant lung lavage (SLL).
Intervention 2: administration of systemic antibiotics for any duration.
We excluded studies wherein both SLL and BS were administered. 

Outcome measures and their definitions
Outcomes studied included the following: (i) in-hospital mortality defined as all-cause death during the birth hospitalization; (ii) sepsis defined as clinical features of sepsis with or without isolation of organisms from blood/cerebrospinal fluid/urine and laboratory parameters suggestive of sepsis; (iii) duration of mechanical ventilation defined as number of days—either invasive or noninvasive; (iv) duration of oxygen requirement defined as the number of days of oxygen supplementation required during the initial hospital stay; (v) duration of hospital stay defined as number of days as inpatient; (vi) proportion of neonates who required ECMO therapy; and (vii) the incidence of air leaks, such as pulmonary interstitial emphysema, pneumomediastinum or pneumopericardium.

Search methods for identification of studies
We searched the following databases: MEDLINE via PubMed; Cochrane CENTRAL; WHOLIS; and CABI Global Health using the following search terms—meconium and (antibiotics or surfactant). No language restrictions were used. We also searched for ongoing/unpublished studies by hand-searching the conference proceedings of the Pediatric Academic Societies for the years 2005 to 2014.

Data extraction
Data extraction was carried out using a form designed and pretested by the authors. Two authors (CKN and KJ) independently extracted the data from the included studies, including year, setting (country, type of population, socioeconomic status, gestation and birth weight of neonates) and outcomes of interest. Disagreements in extracted data were resolved through discussion with the third author (MJS).

Statistical analysis
Data entry and meta-analysis were performed using RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). We analyzed the data as the proportion of neonates for categorical outcomes and mean (s.d.) or median (inter-quartile range) for continuous outcomes. We calculated relative risks (RRs) or mean differences with 95% confidence intervals (CIs) for the outcomes of interest. Heterogeneity between the studies was quantified by using a measure of the degree of inconsistency in their results ($I^2$ statistic > 60%). We evaluated the presence of publication bias by using funnel plots when an adequate number of studies was available for meta-analysis.

RESULTS
We retrieved 465 citations using the above-mentioned search strategy. After screening the title and abstracts and removal of duplicates, we identified nine and three studies, respectively, on surfactant administration and antibiotics in neonates with MAS (Figure 1). One study on surfactant lavage was presented in abstract form in a conference and could not be included in the final analysis due to lack of complete data; thus, eight studies were finally analyzed for use of surfactant in MAS.

All the studies were randomized trials that used accepted methods of randomization. Studies that used SLL were not blinded, whereas most of those that used BS were blinded. None of the three studies on antibiotic use in MAS attempted to blind the intervention, and none had any major loss to follow-up. About one-half of the studies on surfactant and all of the studies on antibiotic use in MAS were from low- and middle-income countries (LMICs).

Surfactant for MAS
Out of the eight studies on surfactant for MAS, two used SLL and the remaining six used BS (Table 1). Among studies that used SLL as the intervention, one study used bovine surfactant and the other synthetic surfactant for lavage. All BS studies used only natural surfactant—either bovine or porcine. Because of the different nature of interventions including the dosage of surfactant, we pooled the results of studies that used SLL and studies that used BS separately.

Use of surfactant as either SLL (RR 0.38; 95% CI 0.09 to 1.57) or BS (RR 0.80; 95% CI 0.39 to 1.66) did not reduce mortality in neonates with established MAS. Both SLL and BS reduced the duration of hospital stay by 2 days (95% CI −3.7 to −0.3) and 4.7 days (95% CI −7.1 to −2.2), respectively. Similarly, neonates who received surfactant by either SLL or BS had shorter days of mechanical ventilation (Table 2). Neonates who received BS (RR 0.64; 95% CI 0.46 to 0.91) but not SLL (RR 0.26; 95% CI 0.04 to 1.82) needed ECMO less often than those in the control group. Neither method of surfactant administration reduced the duration of oxygen therapy or the incidence of air leaks (Table 3). None of the included studies reported the rates of sepsis in intervention and control groups.

Antibiotics for MAS
Antibiotics used in the studies were either penicillin and aminoglycosides or aminoglycosides alone for 3 to 7 days’ duration (Table 3). None of the outcomes of interest such as neonatal mortality, incidence of sepsis, duration of hospital stay, duration of mechanical ventilation and duration of oxygen therapy were significantly different between neonates who received systemic antibiotics and those who did not (Table 4).

DISCUSSION
In this review we have attempted to summarize the studies on potential adjuvant therapies in the management of MAS such as antibiotics and surfactant administration. Use of intratracheal surfactant either as bolus administration or as lavage therapy in
| S. No. | Study's first author, country | Study design | Study population/mean (s.d.) gestation/BW | Intervention | Control group | Outcome parameters of interest | Comments |
|-------|-------------------------------|--------------|------------------------------------------|--------------|---------------|-------------------------------|----------|
| 1     | Dargaville, Multicentric trial from Australia, New Zealand, Malaysia, Singapore and Taiwan | RCT          | \(\geq 36\) wk with MAS \(n=30\)  \(\text{GA: 39 (38–40) wk}\)  \(\text{BW: 3.4 (3.0–3.6) g}\)  \(\text{Control: n=35}\)  \(\text{GA: 40 (39–41) wk}\)  \(\text{BW: 3.5 (3.2–3.9) g}\) | Lung lavage with surfactant (Survanta) 15 ml kg\(^{-1}\) \(\times 2\) aliquots | No lavage | Duration of respiratory support  Days of intubation  Duration of hospital stay  Mortality  Duration of oxygen dependence  Duration of inhaled nitric oxide therapy  Need for ECMO | Not blinded |
| 2     | Wiswell, USA | RCT         | \(\geq 35\) wk with MAS \(n=15\)  \(\text{GA: 39.9 (1.2) wk}\)  \(\text{BW: 3491 (517) g}\)  \(\text{Control: n=7}\)  \(\text{GA: 39.4 (1.9) wk}\)  \(\text{BW: 3601 (126) g}\) | Lung lavage with Surfaxin, synthetic surfactant 3 doses for each lung 8 ml kg\(^{-1}\) \((2.5 \text{ mg ml}\(^{-1}\) \(\times 2\) doses followed by 8 ml kg\(^{-1}\) \((10 \text{ mg ml}\(^{-1}\) \(\times 1\) dose) | No lavage; supportive care | Time to extubation  Days in NICU  Duration of oxygen therapy  Need for ECMO | Not blinded |
| 3     | Zhixia, China | RCT         | Term neonates with MAS; \(\text{BW > 2500 g}\)  Pulmonary surfactant:  \(n=22\)  \(\text{GA: 39.2 (1.6) wk}\)  \(\text{BW: 3234 (336) g}\)  \(\text{Control: n=23}\)  \(\text{GA: 39.5 (1.3) wk}\)  \(\text{BW: 3148 (295) g}\) | Bovine surfactant 70 mg kg\(^{-1}\) | Supportive treatment | Mortality/abandon treatment  Duration of mechanical ventilation  Duration of oxygen therapy  Duration of hospital stay | Article in Chinese; information extracted using Google Translator; blinding unclear |
| 4     | Wanying, China | RCT         | Term neonates with MAS; \(\text{BW > 2500 g}\)  Pulmonary surfactant:  \(n=24\)  \(\text{GA: 39.2 (1.6) wk}\)  \(\text{BW: 3234 (336) g}\)  \(\text{Control: n=23}\)  \(\text{GA: 39.5 (1.3) wk}\)  \(\text{BW: 3148 (295) g}\) | Porcine surfactant 120 mg kg\(^{-1}\) | Supportive treatment | Mortality/abandon treatment | Article in Chinese; information extracted using Google Translator; blinding unclear |
| 5     | Chinese Collaborative Study Group, China | RCT          | Term and near-term with MAS; \(\text{BW > 2500 g}\)  Intervention:  \(n=31\)  \(\text{GA: 40.0 (1.4) wk}\)  \(\text{BW: 3444 (534) g}\)  \(\text{Control: n=30}\)  \(\text{GA: 39.6 (1.7) wk}\)  \(\text{BW: 3359 (506) g}\) | Curosurf 1st and 2nd dose: 200 mg kg\(^{-1}\); 3rd and 4th dose: 100 mg kg\(^{-1}\) \(\times 4\) doses | Air placebo | Mortality  Duration of mechanical ventilation  Mortality | Blinded |
| 6     | Findlay, USA | RCT         | Term neonates  Intervention:  \(n=20\)  \(\text{GA: 40.2 (0.3) wk}\)  \(\text{BW: 3370 (112) g}\)  \(\text{Control: n=20}\)  \(\text{GA: 39.6 (0.5) wk}\)  \(\text{BW: 3507 (128) g}\) | Survanta 150 mg kg\(^{-1}\) bolus 4 doses | Air placebo | Duration of mechanical ventilation  Duration of hospital stay  Mortality  Duration of oxygen dependence  Need for ECMO  Incidence of air leaks | Blinded |
neonates with MAS reduced the duration of mechanical ventilation and duration of hospital stay. There was also a significant reduction in the need for ECMO in neonates who received BS therapy for MAS. Administration of antibiotics in MAS did not result in any beneficial outcomes. Neither intervention reduced in-hospital mortality or sepsis.

Surfactant for MAS

We found two Cochrane reviews on use of surfactant in MAS, one on SLL and the other on BS. The Cochrane review on SLL included two studies and reported a significant reduction in the combined outcome of mortality or need for ECMO in the intervention group (RR 0.33; 95% CI 0.11 to 0.96). The risk of mortality was not reduced significantly in neonates who received lung lavage with surfactant (RR: 0.42; 95% CI 0.12 to 1.46). The results of the present review are similar to those from the Cochrane review. The latter review, however, included another study by Gadzinowski et al., which used both surfactant lavage and BS in the intervention arm (this study was analyzed separately). Also, we did not examine the combined outcome of mortality and ECMO in our review.

The Cochrane review on BS included four studies and found the risk of requiring ECMO to be lower in the intervention group (RR 0.64; 95% CI 0.46 to 0.91). However, the risk of mortality and air leaks was comparable between the two groups. We included two additional studies from China in our review. Inclusion of these did not change the results on neonatal mortality or need for ECMO. However, the duration of mechanical ventilation and hospital stay were found to be significantly shorter in our review compared with the Cochrane review, which reported no difference between the groups.

Lack of benefits in key outcomes such as mortality and air leaks following either mode of surfactant therapy could be related to (a) the degree of illness of the neonates and (b) timing of lavage therapy. Neonates included in these trials were moderately ill and received the intervention relatively late when compared with the timing in experimental studies in animals that have shown beneficial effects with surfactant lavage.

Notwithstanding the lack of benefits in key outcomes, significant benefits observed in the need for ECMO (for BS), and duration of hospital stay and mechanical ventilation (with both SLL and BS) underscore the importance of generating more

### Table 1. (Continued)

| Control group | Intervention | Study population/mean (SD) gestation/BW | Study design | Study country | Study’s first author, country |
|---------------|--------------|----------------------------------------|--------------|---------------|-----------------------------|
| Air placebo   | Survanta 100 mg kg\(^{-1}\) bolus 4 doses, +4 more doses if ECMO required | RCT >36 weeks | GA: 39 (1.8) wk | 7 Lotze, 12 USA | Lotze, 12 USA |
| Air placebo   | Survanta 100 mg kg\(^{-1}\) bolus 3 doses, +4 more doses if ECMO required | RCT >36 weeks | GA: 39 (1.7) wk | 8 Maturana, 13 Chile | Maturana, 13 Chile |

### Table 2. Summary of outcomes for use of surfactant in MAS

| Outcome | Number of studies and participants; effect size (95% CI) |
|---------|---------------------------------------------------------|
| SLL     | BS                                                      |
| In-hospital mortality | 2 studies; \(n = 87\); 5 studies; \(n = 536\); 0.38 (0.09, 1.57) | 0.80 (0.39, 1.66) |
| Duration of ventilation | 1 study; \(n = 65\); 4 studies; \(n = 467\); -2.0 (-3.66, -0.34) | -4.68 (-7.11, -2.24) |
| Duration of mechanical ventilation | 2 studies; \(n = 87\); 5 studies; \(n = 527\); -1.31 (-1.91, -0.72) | -5.4 (-9.76, -1.03) |
| Duration of oxygen therapy | 2 studies; \(n = 87\); 4 studies; \(n = 466\); 0.03 (-1.36, 1.42) | -4.06 (-10.8, 2.7) |
| Need for ECMO | 2 studies; \(n = 87\); 2 studies; \(n = 208\); 0.26 (0.04, 1.82) | 0.64 (0.46, 0.91) |
| Air leaks | 1 study; \(n = 65\); 3 studies; \(n = 154\); 0.23 (0.03, 1.89) | 1.30 (0.61, 2.77) |

Abbreviations: BS, bolus surfactant; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; MAS, meconium aspiration syndrome; NICU, neonatal intensive care unit; RCT, randomized controlled trial.

SLL and BS are lung lavage with surfactant and bolus surfactant, respectively. The latter review, however, included another study by Gadzinowski et al., which used both surfactant lavage and BS in the intervention arm (this study was analyzed separately). Also, we did not examine the combined outcome of mortality and ECMO in our review.

The Cochrane review on BS included four studies and found the risk of requiring ECMO to be lower in the intervention group (RR 0.64; 95% CI 0.46 to 0.91). However, the risk of mortality and air leaks was comparable between the two groups. We included two additional studies from China in our review. Inclusion of these did not change the results on neonatal mortality or need for ECMO. However, the duration of mechanical ventilation and hospital stay were found to be significantly shorter in our review compared with the Cochrane review, which reported no difference between the groups.

Lack of benefits in key outcomes such as mortality and air leaks following either mode of surfactant therapy could be related to (a) the degree of illness of the neonates and (b) timing of lavage therapy. Neonates included in these trials were moderately ill and received the intervention relatively late when compared with the timing in experimental studies in animals that have shown beneficial effects with surfactant lavage.

Notwithstanding the lack of benefits in key outcomes, significant benefits observed in the need for ECMO (for BS), and duration of hospital stay and mechanical ventilation (with both SLL and BS) underscore the importance of generating more
Table 3. Characteristics of studies on use of systemic antibiotics for established MAS

| S. No. | Study’s first author, country | Study design | Study population | intervention | control group | outcome parameter of interest | comments |
|--------|-----------------------------|--------------|------------------|--------------|---------------|--------------------------------|----------|
| 1      | Shankar, India              | RCT          | Term neonates with MAS | Gentamicin 6 mg kg⁻¹ per day × 7 days | No antibiotics | Duration of respiratory distress | Not blinded |
|        | n = 20                      | Antibiotic group: |                        |              |               | Sepsis                        |          |
|        | Control group: n = 20       | Control group: |                        |              |               | Mortality                      |          |
| 2      | Lin, Taiwan                 | RCT          | Term neonates with MAS | Amoxicillin 100 mg kg⁻¹ per day | Study group: no antibiotics | Sepsis                         | Not blinded |
|        | n = 127                     | Antibiotic group: |                        |              | Study group: no antibiotics | Mortality                      |          |
|        | Control group: n = 132      | Control group: |                        |              |               | Duration of oxygen therapy     |          |
|        |                            | Study group: |                        |              |               | Duration of continuous positive airway pressure |          |
| 3      | Basu, India                 | RCT          | Term neonates with MAS | Amoxicillin 100 mg kg⁻¹ per day | Antibiotic group | Study group: antibiotic group |         |
|        | Group A = antibiotics       | Antibiotic group: |                        |              | Study group: | Sepsis                         | Not blinded |
|        | Group B = control           | Control group: |                        |              | antibiotics | Mortality                      |          |
|        | n = 72                      | Study group: |                        |              |               | Duration of oxygen therapy     |          |
|        |                            | Group A:     |                        |              |               | Duration of continuous positive airway pressure |          |
|        |                            | n = 146      |                        |              |               | Duration of hospital stay; X-ray clearance |          |
|        |                            | Group B:     |                        |              |               |                                |          |
|        |                            | n = 146      |                        |              |               |                                |          |

Abbreviations: BW, birth weight; GA, gestational age; MAS, meconium aspiration syndrome; RCT, randomized controlled trial.

Table 4. Summary of outcomes for use of antibiotics in MAS

| Outcome | Number of studies and participants | Effect size (95% CI) |
|---------|-----------------------------------|---------------------|
| Sepsis  | 1 study (n = 146)                 | 1.72 (0.22, 13.31)  |
| Duration of hospital stay | 3 studies (n = 445) | 1.21 (0.15, 10.00) |
| Duration of oxygen therapy | 1 study (n = 146) | 0.16 (0.00, 1.15) |

Abbreviations: CI, confidence interval; MAS, meconium aspiration syndrome.
CONFLICT OF INTEREST
The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS
CKN prepared the protocol, applied the search strategy, retrieved the articles, extracted data, made the initial tables and wrote the initial draft of the manuscript. MJG guided development of the study protocol, searched the databases, also extracted data, carried out the statistical analysis and modified the manuscript. RA and VKP modified the study protocol, supervised data extraction and modified the final version of the manuscript.

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