REVIEW ARTICLE »»

# Antibiotic Administration for Prevention or Treatment of Meconium Aspiration Syndrome in Neonates: A Systematic Review

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## ABSTRACT

**Objectives:** To conduct a systematic review of the clinical trials evaluating the role of antibiotics for prevention or treatment of meconium aspiration syndrome (MAS). **Methods:** We searched several electronic databases including MEDLINE, EMBASE, CINAHL, SCOPUS (until September 2013), and CENTRAL (until August 2013). Additional citations were retrieved from the bibliographies of the selected articles. Studies were included if they were: Randomized or quasi-randomized trials, compared use of antibiotics with no antibiotics for treatment or prevention of MAS, and reported on clinical outcomes in the neonatal period. **Results:** Four randomized controlled trials (RCTs) were identified; three studies enrolled subjects for treatment of MAS and one study evaluated the prophylactic use of antibiotics in infants exposed to meconium stained amniotic fluid (MSAF). These trials enrolled 695 infants, with the duration of antibiotics between 3 and 7 days. All studies excluded subjects considered to be at higher risk for neonatal sepsis at onset. There were no differences noted for the outcomes of infection rates (relative risk [RR] [95% confidence interval: 0.85 [0.42, 1.73] for clinical sepsis, and 0.93 [0.36, 2.40] for culture-proven sepsis), need for mechanical ventilation (RR: 1.39 [0.68, 2.82]), air leaks syndrome (RR: 1.65 [0.68, 3.99]), hospital stay (mean difference − 0.34 days [−1.13, 0.45]), or mortality (RR: 1.25 [0.36, 4.39]) between the intervention and control groups. **Conclusions:** In neonates at low-risk for sepsis, insufficient evidence exists to support the routine use of antibiotics following exposure to MSAF or for the treatment of for suspected MAS. We discuss the implications and limitations of review findings for clinical practice.

**Key words:**
Antibiotics, meconium aspiration syndrome, meconium-stained amniotic fluid, meta-analysis, systematic review

## INTRODUCTION

Meconium aspiration syndrome (MAS) is a common cause of respiratory distress in neonates, especially in term and postterm infants and is associated with serious respiratory morbidities and mortality. 5–25% of all live births are associated with meconium-stained amniotic fluid (MSAF), but only 4–10% of infants born through MSAF develop MAS.[1-3] MAS is diagnosed in infants exposed to MSAF and presenting as respiratory distress with characteristic radiological findings and whose symptoms cannot be otherwise explained.[4,5]

The exact physiology of meconium passage into the amniotic fluid leading to the development MAS is unknown.[6] In addition, MAS could occur *in utero* or after delivery within first few breaths. Three potential mechanisms of meconium release have been postulated. First, meconium passage is likely related with gut maturation as it typically occurs in term and postterm infants. Second, meconium passage may present in the pathological event such as stress or infection. Finally, fetal hypoxia may reduce the clearance of defecated meconium because of impaired fetal swallowing.[7] It is unclear why some infants born through MSAF develop

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aspiration syndrome. Fetal hypoxia and acidosis may lead to fetal gasping and result in aspiration *in utero*.[7]

Meconium may affect infant's lungs in various ways. The pathophysiological mechanisms in MAS include: (1) Acute airway obstruction results in hypoxia, (2) surfactant dysfunction or inactivation, (3) chemical pneumonitis with release of vasoconstrictive and inflammatory mediators, and (4) persistent pulmonary hypertension of the newborn (PPHN).[5,8] Hyperinflation or atelectasis may present, depend on the consistency and the amount of meconium aspirated (partial or complete airway obstruction).

Antibiotics are widely used in MAS. Some studies have shown that meconium enhances bacterial growth by increasing the risk of intra-amniotic infection and by reducing host resistance.[9-11] Infection may aggravate stress causing infants to evacuate its bowels *in utero* and then lead to gasping, and therefore inhalation of meconium. Furthermore, routine use of antibiotics has been supported because the differentiation between MAS and pneumonia may be difficult and because of a risk of secondary infection in these cases.[12,13]

On the other hand, meconium itself is sterile and observational studies that assessed the development of sepsis in infants with MAS failed to demonstrate increased risk for bacteremia among meconium-stained neonates.[14] Some studies have proposed that routine antibiotics prophylaxis is not recommended in the management of MAS for those without perinatal risk factors. Antibiotics therapy did not affect the clinical course and outcome related to infection in MAS infants who did not require ventilation and were without risk factors for infection.[13] Nevertheless, antibiotics remain one of the medical therapies which are generously used in the management of MAS often leading to an extended hospital stay, higher health care costs, and the risk of greater antibiotics resistance.

The objective of this systematic review is to determine the role of routine antibiotic administration in the prevention or treatment of MAS for neonatal outcomes.

## METHODS

Searches were conducted by a medical librarian (SC) using both controlled vocabularies (MESH, EMTREE, etc.) and keywords (meconium adj3 (aspir* or inhal*) and ((antibiotic* or anti-infect* or anti-infect*) or specific drug names)). We searched the following electronic databases: MEDLINE, EMBASE, CINAHL, SCOPUS, and ProQuest dissertations and theses (until September 23, 2013); CENTRAL (until August 2013), and ACP Journal Club (until September 2013). We also searched database of abstracts of reviews of effects, Health Technology Assessment, and NHS Economic Evaluation Database (all until third-quarter 2013), Cochrane Methodology Register (third-quarter 2012); and International Pharmaceutical Abstracts (until August 2013). Search results were not limited by language. Additional references will be sought from bibliographies of the selected articles.

### Study selection

All citations identified were screened independently by two reviewers (PP, GN). Studies were considered for this review if they satisfied the following criteria: Randomized or quasi-RCT; included term, and postterm neonates who were diagnosed with MAS or exposed to MSAF; compared between antibiotics treatment and no antibiotic treatment; and reported any of the following outcomes: (1) Development of infection (culture proven sepsis or clinical sepsis), (2) need for respiratory support (ventilation and/or oxygen treatment), (3) air leaks syndrome, (4) PPHN, (5) need for extracorporeal membrane oxygenation, (6) need for inhaled nitric oxide, (7) hospital stay, and (8) mortality. Discrepancies regarding inclusion were resolved through discussion among the review team.

### Quality assessment

Methodological quality of the included studies was assessed using Cochrane risk of bias tool.[15] These assessments were performed independently by two reviewers and discrepancies were resolved by discussion among the review team.

### Data extraction

Data were extracted by two reviewers (PP, GN) using a standardized form and check accuracy by a third reviewer (MK). Primary authors for the included studies were contacted for additional information if needed. We extracted the following information: Characteristic of the study population and setting; description of the intervention and comparisons (antibiotics treatment vs. no antibiotics treatment); outcome measures and results.

### Assessment of heterogeneity

*The* $I^2$ statistic was calculated for each analysis to quantify heterogeneity across studies. If substantial ($I^2$ > 50%) heterogeneity was detected, the potential causes for its existence were explored, and further sensitivity analysis undertaken.

## RESULTS

Figure 1 shows the flow of the studies through the selection process. We identified four randomized controlled trials (RCTs) published between the years 1995 and

2015, enrolling a total of 695 patients. Three studies enrolled subjects for treatment of MAS[12,13,16] and one study evaluated prophylactic use of antibiotics in infants exposed to MSAF (initially published as an abstract in 2012 followed by full-text publication listed for 2015).[17] A brief description and salient characteristics of the included studies trials are presented in Table 1 (studies listed by the first author's name and year of publication). All three studies of antibiotics treatment for MAS excluded subjects considered to be at higher risk for neonatal sepsis at the onset due to antenatal risk factors and/or positive sepsis screen. Three studies[12,13,16] used a combination of antibiotics from penicillin and aminoglycoside groups whereas one study[16] used aminoglycoside alone. Duration of antibiotics treatment was 3 to 7 days. Lin *et al*. study[13] provided data for infants at 2 months of age without providing data at the time of discharge from the hospital. The study by Goel *et al*.[17] reported data for the outcome of the prophylactic use of antibiotics in infants exposed to MSAF. In this study, 18.2% of the infants in the prophylactic antibiotic group subsequently developed MAS as compared to 15.5% of the infants not treated with antibiotics.

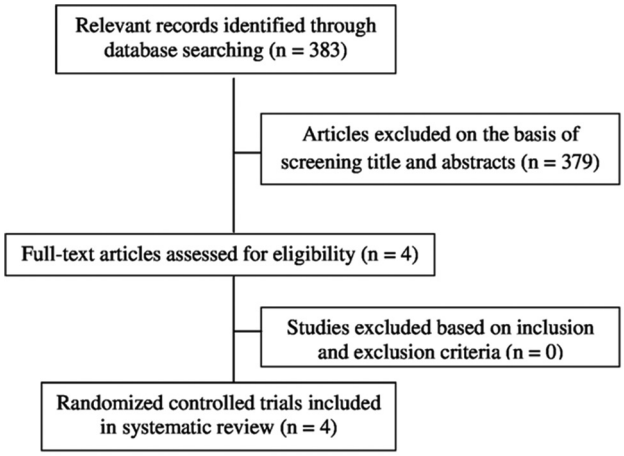


**Figure 1:** Flow of the studies through the select process

## Risk of bias assessments

Table 2 shows the risk of bias assessments of the included studies. Two studies did not adequately describe the methods used to generate the random sequence for participants.[13,16] Only one of the included studies described satisfactorily the method of allocation concealment.[12] None of the studies used a placebo in the control group or blinded intervention

**Table 1: Characteristics of the included RCTs**

| Study | Participants | Antibiotic group | Control group | Outcomes reported | Comments |
|---|---|---|---|---|---|
| Shankar *et al*. 1995[16] | Infants with MAS, defined as<br>Born through MSAF<br>Presence of meconium in trachea<br>Respiratory distress beyond 4 h<br>Abnormal X-ray findings | Gentamicin 6 mg/kg/day × 7 days ($n$=20) | No antibiotics ($n$=20) | Culture proven sepsis<br>Clinical sepsis<br>Duration and severity of respiratory distress<br>Need for ventilator<br>Pulmonary air leaks<br>Mortality | |
| Lin *et al*. 2005[13] | Infants with MAS, defined as<br>Presence of meconium in trachea<br>Respiratory distress<br>Abnormal X-ray findings | Ampicillin 100 mg/kg/day × 3 days<br>Gentamicin 5 mg/kg/day × 3 days ($n$=132) | No antibiotics ($n$=127) | Culture proven sepsis within 2 months of birth<br>Duration of tachypnea<br>Need for ventilator, CPAP, $O_2$<br>Pulmonary air leaks<br>Mortality | Outcomes presented for infants followed up until at 2 months of age instead of at primary discharge from hospital |
| Basu *et al*. 2007[12] | Infants with MAS, defined as<br>Born through MSAF<br>Presence of meconium in trachea<br>Respiratory distress within 4 h and persist beyond 24 h<br>Abnormal X-ray findings<br>No other cause of respiratory distress | Ampicillin 100 mg/kg/day × 7 days<br>Amikacin 15 mg/kg/day × 7 days ($n$=72) | No antibiotics ($n$=74) | Culture proven sepsis<br>Clinical sepsis<br>Duration of respiratory distress and $O_2$ requirement<br>Need for ventilator<br>Pulmonary air leaks<br>Hospital stay<br>Mortality | |
| Goel *et al*. 2015[17] | Infants born through MSAF (antibiotics used with the intent to prevent MAS) | Piperacillin-tazobactam 50 mg/kg/dose × 3 days<br>Amikacin 15 mg/kg/dose × 3 days ($n$=121) | No antibiotics ($n$=129) | Culture proven sepsis<br>Clinical sepsis<br>Need for ventilator, $O_2$<br>Pulmonary air leaks, PPHN<br>Hospital stay<br>Mortality | Study registered at clinicaltrials.gov (NCT01290003) |

RCT – Randomized controlled trial; MAS – Meconium aspiration syndrome; MSAF – Meconium stained amniotic fluid; CPAP – Continuous positive airway pressure; PPHN – Persistent pulmonary hypertension of the newborn

from the caregivers. Most studies were classified as "unclear" for the criterion of free of selective reporting, because it was difficult to make this judgment in the absence of availability of study protocols. Only one study registered its protocol online at clinicaltrials.gov.[17] The study by Lin *et al*.[13] had a large number of infants excluded (47 infants) following randomization.

## Outcomes

### *Development of Infections*

All studies reported the outcome of culture-proven sepsis whereas three studies also reported the rates of clinical sepsis. Figures 2 and 3 show the results of a meta-analysis of culture-proven and clinical sepsis, respectively. There was no difference between the treatment and the control groups in the rates of culture-proven sepsis (relative risk [RR]: 0.93 [0.36, 2.40]) or for clinical sepsis (0.85 [0.42, 1.73]). There was no heterogeneity in the estimates from the individual studies.

### *Respiratory outcomes*

There were no differences in any of the respiratory morbidities studied [Table 3]: The need for mechanical ventilation (RR: 1.39 [0.68, 2.82]) [Figure 4], the need for noninvasive ventilation (RR: 1.09 [0.71, 1.69]), and the incidence of air leaks syndromes (RR: 1.65 [0.68, 3.99]). The duration of respiratory support (ventilation or oxygen alone) was also not different between the intervention groups for studies that provided those data. One study[17] reported one infant in the antibiotics treatment group developed PPHN whereas two infants who were in control group diagnosed with PPHN.

### *Other outcomes*

There was no significant difference in the outcome of mortality (RR: 1.25 [0.36, 4.39]) between the antibiotics treatment group as compared to the control group [Figure 5]. Similarly, there was no difference in the duration of hospital stay (mean difference −0.34 days [−1.13, 0.45]) between two groups.

## DISCUSSION

Through this systematic review of the RCTs, we evaluated the role of antibiotics treatment in prevention or treatment of MAS in neonates. The main outcomes studied were the

**Table 2: Risk of bias assessments of the included studies**

| Study | Adequate sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome data addressed | Free of selective reporting | Free of other bias | Comments |
|---|---|---|---|---|---|---|---|
| Shankar *et al*. 1995[16] | Unclear | Unclear | No | Yes | Unclear | Yes | |
| Lin *et al*. 2005[13] | Unclear | Unclear | No | No | Unclear | No | Data at discharge not provided. Significant postrandomization exclusions (47 infants) |
| Basu *et al*. 2007[12] | Yes | Yes | No | Yes | Unclear | Yes | Two infants excluded after randomization |
| Goel *et al*. 2015[17] | Yes | Unclear | No | Yes | Yes | Yes | |

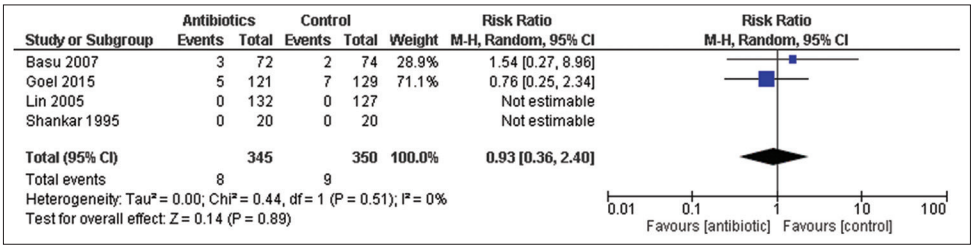


**Figure 2:** Antibiotics versus control. Pooled estimates for culture-proven sepsis rates

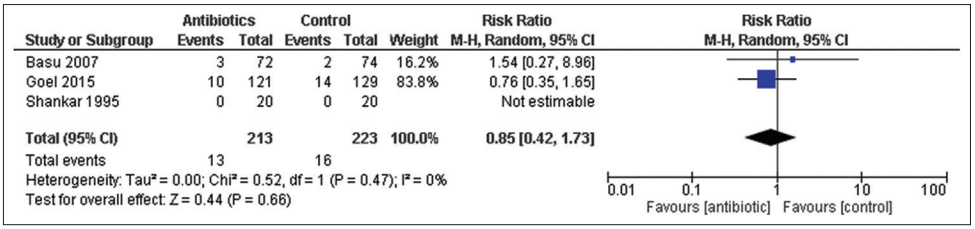


**Figure 3:** Antibiotics versus control. Pooled estimates of the clinical sepsis rates

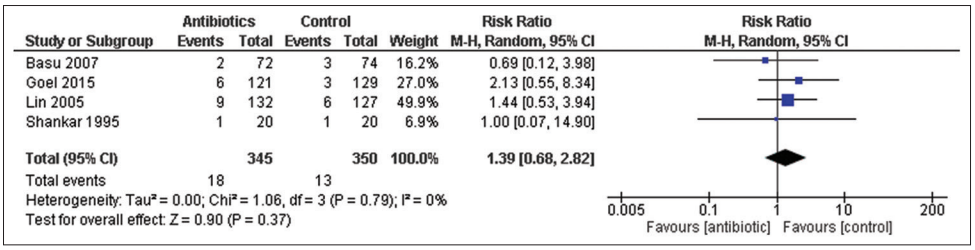


**Figure 4:** Meta-analysis for the outcome of need for mechanical ventilation

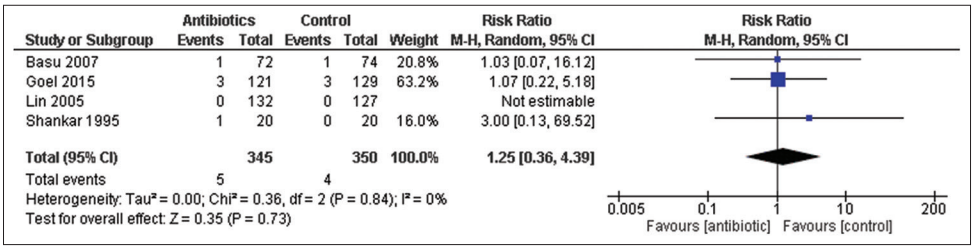


**Figure 5:** Meta-analysis for the outcome of mortality

**Table 3: Pooled estimates of the study outcomes measured in the included studies**

| Outcomes | Number of studies | Participants | Statistical method | Effect estimate (95% CI) |
|---|---|---|---|---|
| Culture-proven sepsis | 4 | 695 | Risk ratio (M-H, random, 95% CI) | 0.93 (0.36, 2.40) |
| Clinical sepsis | 3 | 434 | Risk ratio (M-H, random, 95% CI) | 0.85 (0.42, 1.73) |
| Need for mechanical ventilation | 3 | 695 | Risk ratio (M-H, random, 95% CI) | 1.39 (0.68, 2.82) |
| Need for noninvasive ventilation | 1 | 259 | Risk ratio (M-H, random, 95% CI) | 1.09 (0.71, 1.69) |
| Air leaks syndrome | 4 | 695 | Risk ratio (M-H, random, 95% CI) | 1.65 (0.68, 3.99) |
| Hospital stay (days) | 2 | 394 | Mean difference (IV, random, 95% CI) | −0.34 (−1.13, 0.45) |
| Mortality | 4 | 695 | Risk ratio (M-H, random, 95% CI) | 1.25 (0.36, 4.39) |

CI – Confidence interval

development of neonatal sepsis which included culture positive sepsis and clinical sepsis, respiratory morbidities, duration of hospital stay, and mortality. The included studies were assessed at high-risk of bias due to lack of blinding. The three trials[12,13,16] that enrolled subjects for treatment of established MAS, excluded infants with higher baseline risk for neonatal sepsis assessed based on presence of antenatal risk factors and/or positive sepsis screen following birth. We did not find any difference between antibiotics treatment and control groups for any of the outcomes evaluated. There was no heterogeneity in the pooled estimates of data from the individual trials.

The results of this review show insufficient evidence to support the practice of routine use of antibiotics in neonates exposed to MSAF or with MAS, who are otherwise considered at low-risk for neonatal sepsis. Based on these data, we suggest that the use of antibiotics in asymptomatic infants merely exposed to MSAF is not needed. This would prevent delay in hospital discharge for these otherwise healthy infants and result in saving health care resources.

However, similar recommendation for symptomatic neonates with respiratory distress could be problematic, as pneumonia is usually considered in the differential diagnosis and cannot be excluded with certainly based on normal blood counts, or unremarkable sepsis screen and/or the lack of characteristic chest X-ray findings. In addition, the wide confidence intervals (CIs) for point estimates of the outcomes studied in this review mean that a definite statement in favor of withholding antibiotics in these symptomatic infants would not be feasible based on current evidence. For such infants, we suggest that the use of antibiotics could be restricted to a shorter duration lasting 48–72 h if appropriate investigations for infection are negative.

Our systematic review has a few limitations. First, the individual studies included for this review were relatively small trials with a low event rate for the important binary outcomes assessed such as sepsis rates, need for ventilation or mortality. Thus, as discussed above, the estimates for those outcomes are imprecise (as reflected in their wide 95% CIs) and we could have missed a clinical significant effect that may have existed due to a β-error. Second, the included studies were methodologically of poor quality with none employing blinding of interventions through the use of placebo in the control arm. In addition, one

of the included studies[13] reported a large dropout rate postrandomization, a potential source of additional bias. Lastly, we could have missed an important study that may have changed the results of this review. However, it seems unlikely as our search strategy, undertaken with the help of a research librarian was broad, and we did not use any language restrictions. We could not assess for publication bias using a formal test or through funnel plots, in view of a small number of trials included in this review.

## CONCLUSIONS

In summary, the neonates who are otherwise at low risk for neonatal sepsis, there is insufficient evidence to support the routine use of antibiotics for treatment of MAS or for prophylaxis in infants exposed to MSAF. The use of antibiotics in asymptomatic infants exposed to MSAF should thus be avoided. For symptomatic infants with a diagnosis of probable MAS, if appropriate investigations for infection are negative the use of antibiotics could be restricted to a short course of 2–3 days. Further, placebo control RCTs are warranted to elucidate the risk-benefit of antibiotics administration to infants with established MAS.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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