CASE REPORT

Therapeutic Lung Lavage with Diluted Surfactant in Neonates with Severe Meconium Aspiration Syndrome

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Meconium aspiration syndrome (MAS) may result in considerable morbidity and mortality in newborn infants. The current standard treatment is still in need of improvement for the most severe patients. We report 3 cases with devastating MAS that was successfully treated with therapeutic lung lavage. These cases were all delivered in local obstetrics clinics or hospitals with meconium-stained amniotic fluid and non-vigorous appearance at birth. However, no endotracheal suction was performed when they were born. All of them suffered from severe hypoxia and unstable vital signs despite there being high ventilatory settings when they were transferred to the tertiary medical center. Therapeutic lung lavage with diluted surfactant (Survanta, 5 mg/mL, 30 mL/kg in 2 aliquots) was performed within 24 hours of age. Bloody fluid (about 40–50% of total lavage amount) was recovered in all 3 cases. Although brief desaturation and bradycardia were observed during the procedures, 2 of them tolerated the procedures well and improved soon after lavage. The other patient received lung lavage in a relatively unstable condition and needed chest tapping to relieve bilateral pleural effusion. Their respiratory condition improved after the procedures, and they were all discharged within 1 month without major respiratory complications. These successful experiences are compatible with previous animal studies and other case reports with different lavage protocols. We conclude that therapeutic lung lavage may improve the outcome in newborn infants with severe MAS, and there were no significant adverse side effects observed. Before performing lung lavage, stabilization and optimal support may prevent unexpected results during and after lavage. [*J Chin Med Assoc* 2008; 71(2):103–109]

Key Words: lavage, meconium, neonates, surfactant

Introduction

Meconium aspiration syndrome (MAS) is a complex disease of the newborn, and may result in considerable respiratory morbidity. It is also the most common disease in neonatal patients treated with extracorporeal membrane oxygenation (ECMO).[1] In the past decades, there has been a reduction in the incidence of MAS because of advances in perinatal care.[2] In a recent report, the incidence of severe MAS (infants who were intubated and mechanically ventilated with a primary diagnosis of MAS) was 0.43 per 1,000 live births. However, death related to MAS in these patients was still 2.5%.[2] Therefore, an effective therapy to improve outcome is crucial in treating neonates with severe MAS.

The pathophysiology of MAS includes airway obstruction,[3] surfactant inactivation,[4,5] inflammation,[6–8] and pulmonary hypertension.[9,10] Successful treatment of severe MAS relies on effective meconium removal without inactivating or washing out surfactant, followed with appropriate ventilatory care.

Inhibition of surfactant function in alveolar space may be mediated by aspirated meconium, plasma proteins, hemoglobin and edema fluid.[11] Bolus surfactant

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Table 1. Characteristics of the 3 cases

	Case		
	1	2	3
Birth weight (g)	3,634	3,350	3,480
Gestational age (wk)	39	40	41
Sex	F	M	M
Apgar score (1 min/5 min)	2/6	2/5	7/7
Delivery mode	Cesarean section	Vaginal delivery	Vaginal delivery
In/Out born	Out	Out	Out
Endotracheal suction in delivery room	No	No	No
Persistent hypertension of newborn	Yes	No	No
Oxygenation index when admitted	41.5	31.5	13.3
Total ventilatory days	7	3	2
Ventilatory mode (d)	HFOV(3) + IMV(4)	IMV(3)	HFOV(1) + IMV(1)
Nasal prong CPAP (d)	4	5	2
Inhaled nitric oxide (d)	2	0	0
Inotropics (d)	5	3	0
NICU stay (d)	15	12	5
Hospital stay (d)	23	23	9

CPAP = continuous positive airway pressure; HFOV = high frequency oscillatory ventilation; IMV = intermittent mechanical ventilation; NICU = neonatal intensive care unit.

therapy has been found to reduce the requirement for ECMO, but no diminution of air leak or ventilatory days.[11] Lung lavage using diluted surfactant has recently been shown to be an alternative to bolus therapy in treating MAS. That has the advantage of removing surfactant inhibitors from the alveolar space, in addition to augmenting surfactant concentration in alveolar space.[11] Good toleration and effective response were documented in animal models[12–18] and human infants with MAS.[19–23] The reported benefits of lung lavage in MAS included removing significant amounts of meconium and alveolar debris, and thereby improving oxygenation and pulmonary mechanics.[11]

We present 3 newborns with severe MAS, including 2 who fulfilled the criteria for ECMO (oxygenation index > 40).[24] All were successfully treated by therapeutic lung lavage with diluted surfactant.

Case Reports

The basic characteristic data of the 3 cases are summarized in Table 1. All were full-term newborn infants, born in local obstetrics clinics or hospitals. Although they presented with meconium-stained amniotic fluid and non-vigorous activity at birth, none received endotracheal suction in the delivery room. Two of them (Cases 1 and 2) needed cardiopulmonary resuscitation right after birth. They were then transferred to our neonatal intensive care unit within 2 hours of age.

Case 1

This female baby presented with pulmonary hemorrhage on arrival. After endotracheal epinephrine administration, the hemorrhage stopped. However, hypoxia persisted even under high settings of high-frequency oscillatory ventilation (HFOV). Chest X-ray showed bilaterally diffuse patchy infiltration (Figure 1). Persistent pulmonary hypertension of the newborn was diagnosed with evidence of right-to-left shunts on echocardiography. Thus, inhaled nitric oxide was started. However, her condition continued to deteriorate, and the highest oxygenation index was as high as 66.7 when the patient was 14 hours old.

With the agreement of the baby's father and stabilization of the patient's condition (pH > 7.25, oxygen saturation higher than 90%, and mean blood pressure higher than 50 mmHg), the baby received therapeutic lung lavage when she was 20 hours of age according to the protocol of the *lessMAS* trial.[25] In brief, 2 aliquots of lavage fluid (15 mL/kg) with diluted surfactant (Survanta; Abbott Laboratories, North Chicago, IL, USA) were used for lung lavage. The baby was positioned with the chest right side down during the first lavage, and left side down during the second lavage. In each lavage, the diluted surfactant was instilled into the lungs within 20 seconds. Then, positive pressure ventilation was delivered for 10 seconds. After that, as much lavage fluid as possible was aspirated within 30–40 seconds. Brief desaturation (85% to 54%) was observed when the lavage procedure was

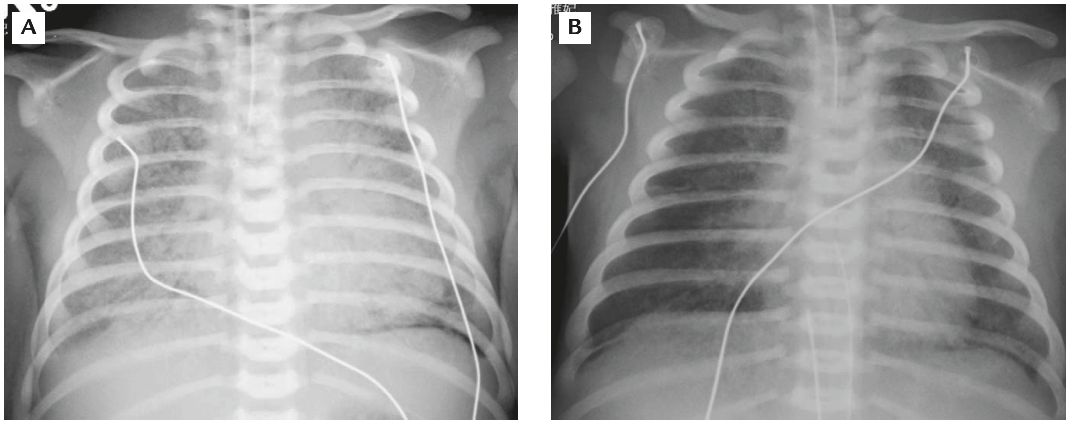

Figure 1. Chest X-ray of Case 1: (A) before lavage; (B) 24 hours after lavage.

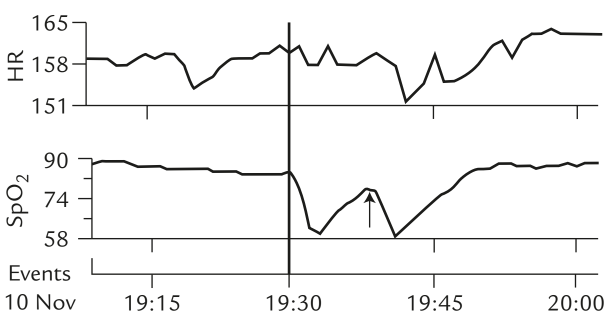

Figure 2. Case 1: real-time monitoring of heart rate and oxygen saturation during lung lavage. The vertical line indicates the start of the first lavage, and the arrow indicates the start of the second lavage.

begun, but it quickly returned to 80% as the mean airway pressure of HFOV increased. The second lavage was performed 5 minutes after the first. A similar desaturation pattern was noted (80% to 58%), but it also quickly returned to 80%. Brief bradycardia was observed during the second aliquot of lavage, but it also returned to normal very soon (Figure 2).

The patient's clinical condition improved soon after lung lavage. Chest X-ray taken after 24 hours showed significant improvement (Figure 1B). Table 2 summarizes the changes in oxygenation index, alveolar–arterial oxygen tension difference, heart rate and blood pressure before and after lavage. Inhaled nitric oxide was discontinued when the patient was 48 hours old, and she was successfully extubated 7 days later. She was discharged when she was 23 days old without respiratory or neurologic complications. After discharge, she was hospitalized 4 times within the first year of life due to respiratory tract infections.

Case 2

This male infant's condition was very critical when he arrived at our neonatal intensive care unit with the appearance of extreme hypotonia, hypoxia, hypotension, and very unstable vital signs. Profound metabolic and respiratory acidosis (pH 6.83) was also noted on arrival. Diffuse haziness with patchy infiltration and zones of hyperinflation were noted on the initial chest X-ray (Figure 3A). The oxygenation index was as high as 43.0.

With the agreement of the patient's father, lung lavage with diluted surfactant was tried to rescue his life, even though the general condition of this patient could not be stabilized (pH 6.84, oxygenation saturation 70%, mean blood pressure 22 mmHg). The same protocol as used in Case 1 was performed when this patient was 2 hours old. Significant overflow of the lavage fluid was observed during the instillation phase, and a total of 40 mL of bloody fluid was recovered (Table 2). Improvement in oxygenation was observed after lavage, but his condition deteriorated 1 hour later, with decreased oxygenation and hypotension. Chest X-ray revealed white-out lung (Figure 3B). Bilateral pleural effusion was suspected, and thoracocentesis was performed. Pleural fluid (47 mL on right side and 18 mL on left side, straw colored) was tapped out, and his condition improved again soon after the procedure.

Chest X-ray after chest tapping (Figure 3C) and on the second day (Figure 3D) both showed significant improvements. The patient was successfully extubated 3 days after lavage, and discharged smoothly at the age of 23 days. Although there were no respiratory complications in this case, mild developmental delay was observed, and brain imaging study revealed ventricular dilatation and periventricular leukomalacia.

Case 3

This male neonate was transferred to our hospital within 1 hour of birth. Central cyanosis, hypotonia and bradycardia were observed on his arrival, and we suctioned

Table 2. Descriptive data before and after lung lavage of the 3 cases

	Case		
	1	2	3
Age on arrival at tertiary hospital (hr)	2	1	1
Age when BAL performed (hr)	21	3	8
Lavage fluid (out/in), mL (%)	55/108 (51)	40/99 (40)	50/102 (49)
Appearance of lavaged-out fluid	Bloody, turbid	Bloody, turbid	Bloody, turbid
Maximum OI before lavage	66.7	43.0	26.2
Right before lung lavage			
OI	34.4	39.0	20.0
A-aDO_2 (mmHg)	619	457	613
HR (beats/min)	158	140	133
BP (systolic/diastolic) (mmHg)	60/46	32/29	80/21
4 hr after lung lavage			
OI	11.4	39.1	8.2
A-aDO_2 (mmHg)	548	571	319
HR (beats/min)	160	184	124
BP (systolic/diastolic) (mmHg)	59/48	68/50	64/40
24 hr after lung lavage			
OI	9.3	9.2	2.6
A-aDO_2 (mmHg)	237	389	82
HR (beats/min)	138	155	133
BP (systolic/diastolic) (mmHg)	68/51	61/44	67/42
48 hr after lung lavage			
OI	8.1	4.2	Extubated
A-aDO_2 (mmHg)	225	111	2.5
HR (beats/min)	154	112	134
BP (systolic/diastolic) (mmHg)	63/44	75/56	81/59

BAL = bronchoalveolar lavage; OI = oxygenation index; A-aDO_2 = alveolar-arterial oxygen tension difference; HR = heart rate; BP = blood pressure.

out some meconium from the patient's trachea. Bilateral patchy infiltration was observed on chest X-ray (Figure 4A). His condition deteriorated gradually in spite of adequate mechanical ventilation. The maximal oxygenation index was 26.2.

With the parents' agreement, lung lavage with the same protocol as in Case 1 was performed when this patient was stabilized at the age of 8 hours. Brief desaturation and bradycardia were also noted during the lavage procedures, but with rapid recovery. Bloody fluid was recovered from endotracheal suction (Table 2). His general condition and laboratory data improved soon after lavage (Table 2). Chest X-ray also demonstrated significant improvement (Figure 4B).

The patient was extubated successfully 41 hours after lavage, and discharged 7 days later. There were no respiratory or neurologic complications during the first year of his life.

Discussion

Direct endotracheal suction of the aspirated meconium right after birth in meconium-stained and non-vigorous newborns has been suggested in neonatal resuscitation programs.[26,27] Unfortunately, all of our presented newborns were born in local obstetrics clinics or hospitals without standby pediatric care, and none received immediate endotracheal suction even though they were all meconium-stained and non-vigorous at birth. Therefore, there remains much room for improvement in perinatal care in Taiwan. Maternal transportation for high-risk and post-term pregnancies to centers with well-trained neonatal care personnel and high-quality facilities should be seriously considered for the safety of pregnant women and their expected newborns, because meconium may result in serious complications.[28,29]

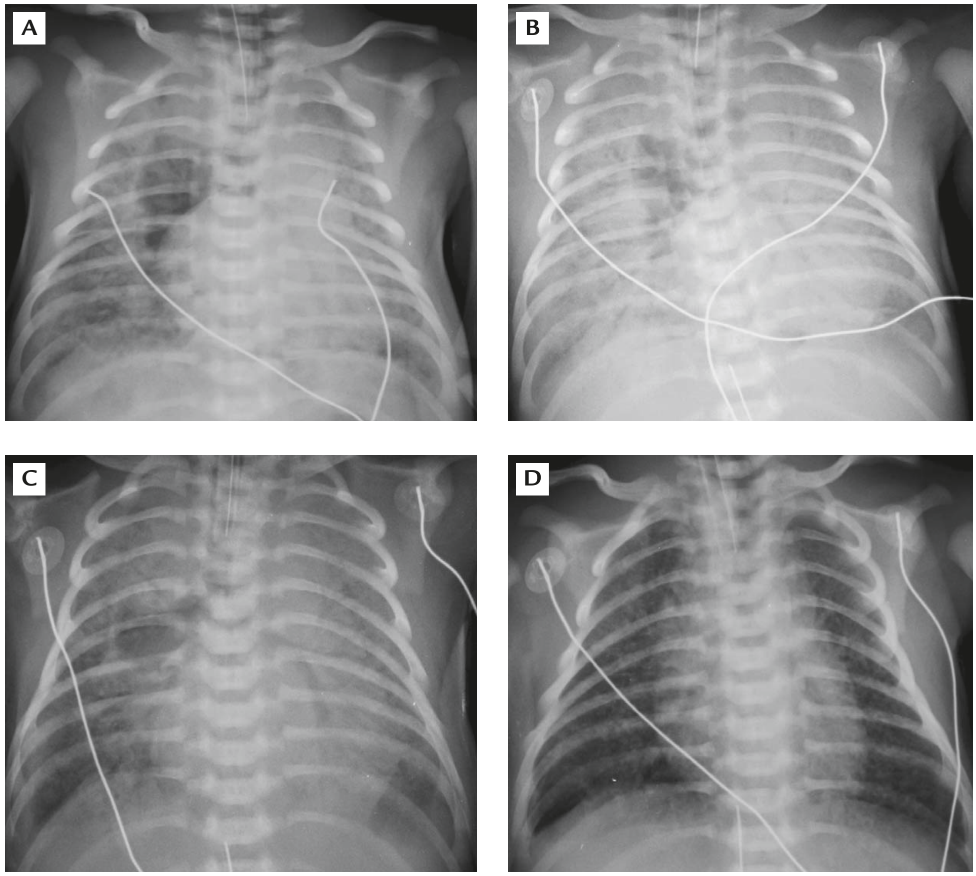

Figure 3. Chest X-ray of Case 2: (A) before lavage; (B) 2 hours after lavage, before chest tapping; (C) 5 hours after lavage, after chest tapping; (D) 24 hours after lavage.

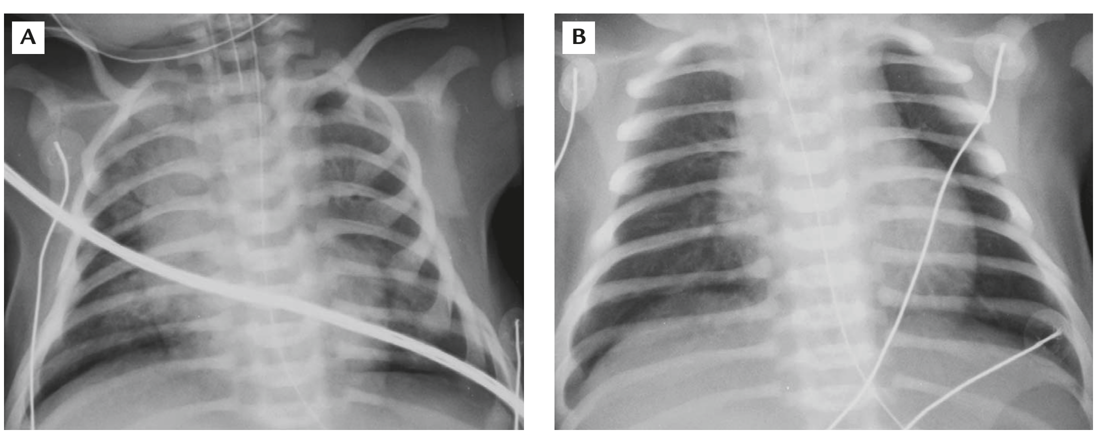

Figure 4. Chest X-ray of Case 3: (A) before lavage; (B) 24 hours after lavage.

Therapeutic lung lavage has been investigated for treating MAS in recent years. Isotonic saline bronchoalveolar lavage has been experimented with, revealing detrimental effects.[13] Full-strength and diluted surfactants have also been investigated as possible lavage fluids.[14–16] The total lavage volumes in these studies have varied. Large-volume diluted surfactant lavage seemed to show the most beneficial effects, with improvements in gas exchange and decreases in proinflammatory cytokines.[12,17] In our 3 cases, a total of 30 mL/kg diluted surfactant in 2 aliquots was used to perform lung lavage. This amount was based on the suggestion of Dargaville et al[17] and Dargaville and Copnell,[25] and the clinical outcomes of our cases were excellent. Although brief desaturation and bradycardia were observed during lavage, there was rapid improvement after the procedure was completed in Cases 1 and 3.

Different lavage protocols have been reported in recent years.[19,22,28] Lejeune and Pfister reported a newborn infant who underwent lavage with a small volume of diluted surfactant (Curosurf, 5 mg/mL, a total of 15 mL/kg, in aliquots of 2 mL), in whom they achieved a successful result.[19] Lista et al reported 8 newborn infants with MAS who underwent lung lavage with diluted surfactant (Curosurf, 5.3 mg/mL, a total of 15 mL/kg, in aliquots of 2.5 mL), and found similar improvements without the lavage causing major adverse effects.[22] In addition, Hung et al reported 11 newborns who underwent lavage with a small volume of diluted surfactant (Survanta, 10 mg/mL, a total of 20 mL, in aliquots of 2 mL), and another 9 infants who underwent lavage with a larger volume of diluted surfactant (Survanta, 5 mg/mL, a total of 40 mL, in aliquots of 2 mL); they found similar benefits from the 2 treatment protocols.[30] Our 3 cases underwent lavage with large-bolus lavage volumes (15 mL/kg/dose) with a total of only 2 aliquots. This is different from the protocol used in other case reports, and we found it to be safe when performed in infants with severe MAS when the patients are stabilized before lavage. Although several randomized controlled trials of surfactant lavage in MAS have been conducted,[25] there are no conclusive results yet. However, we believe there will be evidence-based results in the near future. In addition, some of the above reported cases received adequate endotracheal suction in the delivery room, and still obtained benefits from diluted surfactant lavage.

In our reported cases, only 1 (Case 2) had an unexpected course during and after lavage, due to the presence of bilateral pleural effusion. Since there was significant overflow of the lavage fluid and initial chest X-ray showed bilateral haziness, congenital pleural effusion was highly suspected. Also, the straw-colored pleural effusion was quite different from the bloody fluid recovered from therapeutic lavage. There has been no such similar complication reported in previous animal or human studies of diluted surfactant lung lavage. Furthermore, the lavage procedure in Case 2 was performed when a stable condition could not be achieved. This may have contributed to why we could not demonstrate a similar pattern of improvement as observed in the other 2 cases (Figure 2). The success of treating this case relied on lung lavage to remove meconium debris and chest tapping to remove bilateral pleural fluid. Therefore, detailed evaluation of underlying pulmonary pathology and patient stabilization before lung lavage are crucial for best outcome.

In conclusion, therapeutic lung lavage with diluted surfactant in severe MAS may improve outcome without significant adverse side effects. Before performing lung lavage, stabilization and optimal support may prevent unexpected results during and after lavage.

References

1. Hansell DR. Extracorporeal membrane oxygenation for perinatal and pediatric patients. *Respir Care* 2003;48:352–62.
2. Dargaville PA, Beverley C. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies, and outcome. *Pediatrics* 2006;117:1712–1.
3. Tran N, Lowe C, Sivieri EM, Shaffer TH. Sequential effects of acute meconium obstruction on pulmonary function. *Pediatr Res* 1980;14:34–8.
4. Moses D, Holm BA, Spitale P, Liu MY, Enhorning G. Inhibition of pulmonary surfactant function by meconium. *Am J Obstet Gynecol* 1991;164:477–81.
5. Janssen DJ, Carnielli VP, Cogo P, Bohlin K, Hamvas A, Luijendijk IH, Bunt JE, et al. Surfactant phosphatidylcholine metabolism in neonates with meconium aspiration syndrome. *J Pediatr* 2006;149:634–9.
6. de Beaufort AJ, Bakker AC, van Tol MJ, Poorthuis BJ, Schrama AJ, Berger HM. Meconium is a source of pro-inflammatory substances and can induce cytokine production in cultured A549 epithelial cells. *Pediatr Res* 2003;54:491–5.
7. Lindenskov PH, Castellheim A, Aamodt G, Saugstad OD. Meconium induced IL-8 production and intratracheal albumin alleviated lung injury in newborn pigs. *Pediatr Res* 2005;57:371–7.
8. Castellheim A, Lindenskov PH, Pharo A, Aamodt G, Saugstad OD, Mollnes TE. Meconium aspiration syndrome induces complement-associated systemic inflammatory response in newborn piglets. *Scand J Immunol* 2005;61:217–25.
9. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome: an update. *Pediatr Clin North Am* 1998;45:511–29.
10. Berger S, Konduri GG. Pulmonary hypertension in children: the twenty-first century. *Pediatr Clin North Am* 2006;53:961–87.
11. Dargaville PA, Mills JF. Surfactant therapy for meconium aspiration syndrome: current status. *Drugs* 2005;6518:2569–91.
12. Jeng MJ, Soong WJ, Lee YS, Chang HL, Shen CM, Wang CH, Yang SS, et al. Effects of therapeutic bronchoalveolar lavage and partial liquid ventilation on meconium-aspirated newborn piglets. *Crit Care Med* 2006;34:1099–105.
13. Marraro G, Bonati M, Ferrari A, Barzaghi MM, Pagani C, Bortolotti A, Galbiati A, et al. Perfluorocarbon broncho-alveolar lavage and liquid ventilation versus saline bronchoalveolar lavage in adult guinea pig experimental model of meconium inhalation. *Intensive Care Med* 1998;24:501–8.
14. Paranka MS, Walsh WF, Stancombe BB. Surfactant lavage in a piglet model of meconium aspiration syndrome. *Pediatr Res* 1992;31:625–8.
15. Cochrane CG, Revak SD, Merritt TA, Schraufstatter IU, Hoch RC, Henderson C, Andersson S, et al. Bronchoalveolar lavage with KL4-surfactant in models of meconium aspiration syndrome. *Pediatr Res* 1998;44:705–15.
16. Lam BC, Yeung CY, Fu KH, Wong KY, Chan FL, Tsoi NS. Surfactant tracheobronchial lavage for the management of a rabbit model of meconium aspiration syndrome. *Biol Neonate* 2000;78:129–38.
17. Dargaville PA, Mills JF, Headley BM, Chan Y, Coleman L, Loughnan PM, Morley CJ. Therapeutic lung lavage in the piglet model of meconium aspiration syndrome. *Am J Respir Crit Care Med* 2003;168:456–63.

18. Ohama Y, Ogawa Y. Treatment of meconium aspiration syndrome with surfactant lavage in an experimental rabbit model. *Pediatr Pulmonol* 1999;28:18–23.
19. Lejeune T, Pfister RE. Surfactant lavage for extracorporeal membrane oxygenation-requiring meconium aspiration syndrome: a cheap alternative. *Eur J Pediatr* 2005;164:331–3.
20. Lam BC, Yeung CY. Surfactant lavage for meconium aspiration syndrome: a pilot study. *Pediatrics* 1999;103:1014–8.
21. Wiswell TE, Knight GR, Finer NN, Donn SM, Desai H, Walsh WF, Sekar KC, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics* 2002;109:1081–7.
22. Lista G, Bianchi S, Castoldi F, Fontana P, Cavigioli F. Bronchoalveolar lavage with diluted porcine surfactant in mechanically ventilated term infants with meconium aspiration syndrome. *Clin Drug Invest* 2006;26:13–9.
23. Dargaville PA, Mills JF, Loughnan PM, Campbell NT, McDougall PN. *Large Volume Therapeutic Pulmonary Lavage in Meconium Aspiration Syndrome*. Abstract presented at the Annual Scientific Conference of the Royal Australasian College of Physicians, Brisbane, May 2002.
24. Cook LN. Update on extracorporeal membrane oxygenation. *Paediatr Respir Rev* 2004;5:S329–37.
25. Dargaville PA, Copnell B. *Controlled Trial of Therapeutic Lung Lavage in Meconium Aspiration Syndrome (the lessMAS trial)*. Available at: http://www.rch.org.au/neonatal_rch/lessmas [Date accessed: June 11, 2007]
26. AAP/AHA. Initial steps in resuscitation. In: Kattwinkel J, ed. *Textbook of Neonatal Resuscitation*, 5th edition. American Academy of Pediatrics and American Heart Association, 2006; 2.6–2.7.
27. Halliday HL. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database Syst Rev* 2001;1:CD000500.
28. Wang YJ, Chen HC, Chi CS. Meconium peritonitis in neonates. *J Chin Med Assoc* 1994;53:49–53.
29. Yang CJ, Hung DS. Meconium peritonitis complicated with *Enterobacter aerogenes* infection: a case report. *J Chin Med Assoc* 1989;43:71–4.
30. Hung HY, Jim WT, Hsu CH, Chang JH, Peng CC, Shih SL, Chang HY, et al. Small versus large volume dilute surfactant lavage for meconium aspiration syndrome. *Acta Paediatr Tw* 2006;47:181–6.