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ORIGINAL ARTICLE

Meconium aspiration syndrome remains a significant problem in the NICU: outcomes and treatment patterns in term neonates admitted for intensive care during a ten-year period

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Objective: The purpose of this study was to evaluate the demographic and treatment characteristics of neonates ($\geqslant$37 weeks' estimated gestational age) who were admitted to a neonatal intensive care unit (NICU) for a diagnosis of meconium aspiration syndrome (MAS) during the years 1997 to 2007. The goals in studying this group of neonates were to better estimate the magnitude of abnormal outcomes and to determine the proportion of these infants exposed to specific therapeutic interventions.

Study Design: Retrospective review of an administrative de-identified data set.

Result: A total of 415 772 neonates formed the starting data set and 162 075 (39%) were $\geqslant$37 weeks. Of the 162 075 term neonates, 7518 (1.8% of all neonates and 4.6% of term NICU admissions) had an admission diagnosis of MAS. In the 7518 neonates, the following outcomes were observed: 6124 (81.5%) were discharged home; 679 (9%) were acutely transferred to a higher level of intensive care; 416 (5.5%) were transferred to another clinical service within the hospital; 178 (2.4%) were transferred to another NICU for convalescent care and 88 (1.2%) died. There were 33 (0.4%) who did not have data on outcome at discharge. During the period between 2002 and 2005, acute transfer rates decreased (12.4 to 9%) and the reported rate for death remained relatively constant between 0.9 and 1.5%. There were 107 (1.4%) neonates who were treated ($n = 61$) with, or transferred, for extracorporeal membrane oxygenation (ECMO) ($n = 46$). Three of the sixty-one neonates (4.9%) who were treated with ECMO died.

Conclusion: Term neonates who are admitted with a diagnosis of MAS continue to represent a high-risk population with significant morbidity, and they often require intensive therapies.
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Introduction

Approximately 13% of live-born infants are delivered through meconium-stained amniotic fluid.[1] Meconium-stained amniotic fluid is an important risk factor for severe respiratory disorders in term neonates, and the reported incidence of neonates who require mechanical ventilation for meconium aspiration syndrome (MAS) is 0.61 per 1000 live births.[2] Wiswell *et al*.[1] reported that 7.1% of neonates born through meconium-stained amniotic fluid developed respiratory distress (3.0% had MAS and 4.2% had findings attributed to other disorders). Children who survive MAS are at risk later in life for exercise-induced airway hyperreactivity.[3]

Several large databases of information are available for both short- and long-term outcomes of prematurely born neonates[4,5] and earlier investigations have evaluated the perinatal and neonatal factors that are associated with poor outcomes.[6,7] In contrast, data on the outcomes of the full population of neonates $\geqslant$37 weeks' estimated gestational age who were admitted to a neonatal intensive care unit (NICU) for MAS are limited.[8–11] Most studies that review the outcomes of neonates with a diagnosis of MAS have focused on treatment with extracorporeal membrane oxygenation (ECMO) or inhaled nitric oxide (iNO).[12–14]

The purpose of this study was to evaluate the demographic characteristics of a large population of neonates $\geqslant$37 weeks' estimated gestational age who were admitted for neonatal intensive care, for a diagnosis of MAS during a ten-year period. Our goals in studying this group of neonates were to better estimate the magnitude of abnormal outcomes and to determine the proportion of these infants who were exposed to the specific therapeutic interventions that are used to treat this problem.

Methods

Study type

Retrospective analysis of an administrative data set.

Patient population

Neonates were included in our study sample if they: (a) were $\geqslant$37 completed weeks' estimated gestational age, (b) required admission

to an NICU and (c) had a diagnosis of MAS. This study included patients who were discharged between 1 January 1997 and 1 March 2007. The gestational age assignment was based on the best obstetrical estimate before delivery and was recorded as completed weeks. We excluded 414 preterm (<37 weeks) neonates in whom MAS was reported as our primary objective was to evaluate term neonates with MAS. This approach was used to reduce the confounding effect of gestational age on outcome and treatment.

Diagnosis

Meconium aspiration syndrome is defined as respiratory distress in an infant born through meconium stained amniotic fluid whose symptoms cannot be explained otherwise.[15] In this study, the diagnosis was based on the report of the attending neonatologist as recorded in the diagnosis table of the data set.

Administrative data set

Pediatrix Medical Group health care professionals (doctors and nurse practitioners) providing care to neonates admitted for intensive care use a proprietary software system to generate clinical admission, discharge and daily progress notes. These data are stored in a consolidated data set and then de-identified for quality assurance, research and billing purposes. By using the de-identified data set, from which several other observations have been reported,[16–18] we performed a retrospective case series review of neonates with a diagnosis of MAS. Cases were identified by searching the diagnosis table in our database for the term 'meconium aspiration syndrome.' Neonates who died in the delivery room or those who were not admitted for neonatal intensive care were not included in the data set.

Pediatrix Medical Group provides intensive care services in 244 hospitals in 32 states and Puerto Rico. Nine centers provide ECMO. The data in the electronic database are used for medical chart documentation, billing and quality improvement projects. Clinicians providing care to patients interact with the patients' data on a daily basis to generate progress notes and to provide billing information. Each day's notes are stored with diagnoses. The local data are consolidated within the Pediatrix Medical Group data warehouse, de-identified, and made compliant with the Health Insurance Portability and Accountability Act of 1996 regulations. Data are also configured into tables that can be joined and queried for statistical analyses. The Good Samaritan Hospital, San Jose, CA, institutional review board approved our research with the de-identified data set. Data on estimated gestational age represented the best estimates from both obstetrical data and neonatal examination findings.

Our analytical approach to these data was descriptive in nature. Specific database tables within the data warehouse used for this analysis were 'patients,' 'medication results,' 'admissions' and 'diagnoses.' All patients with a report of MAS collected within the diagnosis table were reviewed. In addition, data on the causes of death and problems at discharge were reviewed for determination of the 'primary' cause of death. The outcome data are based on what was collected before transfer. We do not have data on neonates who died after transport to another facility.

Differences in the demographic characteristics of patients who died and those who were discharged home were analyzed by comparing the two population samples with univariate analyses. Continuous variables (e.g., estimated gestational age and birth weight) were evaluated with two-tailed t-tests. Categorical variables (e.g., race and gender) were evaluated with two-tailed chi-square tests. Nonparametric data were assessed with Kruskal–Wallis analysis of variance. After bivariate analyses, multivariate logistic regression was used to calculate the adjusted odds ratio (OR) for death by comparing the neonates who died with those who were discharged home. Transferred patients were not included in this analysis, but they were included in the results table to show the differences in the demographic characteristics of the patients excluded from the analysis. We incorporated into the logistic regression analysis the variables found in bivariate analyses that were different for the treatment groups at a probability of <0.1. Birth weight and gestational age were entered into the model as continuous variables. Cases with missing values for any of the independent variables were excluded from the analyses. Changes in event rates over time were assessed with chi-square analysis. We also used the linear trend test and the Cochran–Armitage trend test to evaluate time-related changes. All statistical analyses were carried out by using JMP 7 (SAS Institute, Cary, NC, USA).

Results

Population sample

A total of 415 772 neonates comprised the starting data set and 162 075 (39%) were $\geqslant$37 weeks. Of the 162 075 term neonates, 7518 (1.8% of all neonates and 4.6% of term NICU admissions) had a diagnosis of MAS compared with 414 preterm (<37 weeks) neonates. As indicated in the methods, these neonates were not included in our analysis. The likelihood of a diagnosis of MAS increased with the advancing gestational age, from 1.1% of neonates with an estimated gestational age of 37 weeks to 24% of the 170 neonates with a gestational age of >42 weeks (Figure 1a). The diagnosis of MAS and/or pulmonary hypertension was relatively constant over the study decade at 4 to 6% of term neonates admitted for NICU care (Figure 1b).

Of the 7518 neonates with MAS whose estimated gestational age was 37 weeks or more, 6124 (81.5%) were discharged home; 679 (9%) were acutely transferred to higher level of intensive care; 416 (5.5%) were transferred to another clinical service within the hospital; 178 (2.4%) were transferred to another NICU for convalescent care and 88 (1.2%) died. Thirty-three infants (0.4%) did not have data on outcome at discharge. Of the 7518 neonates with

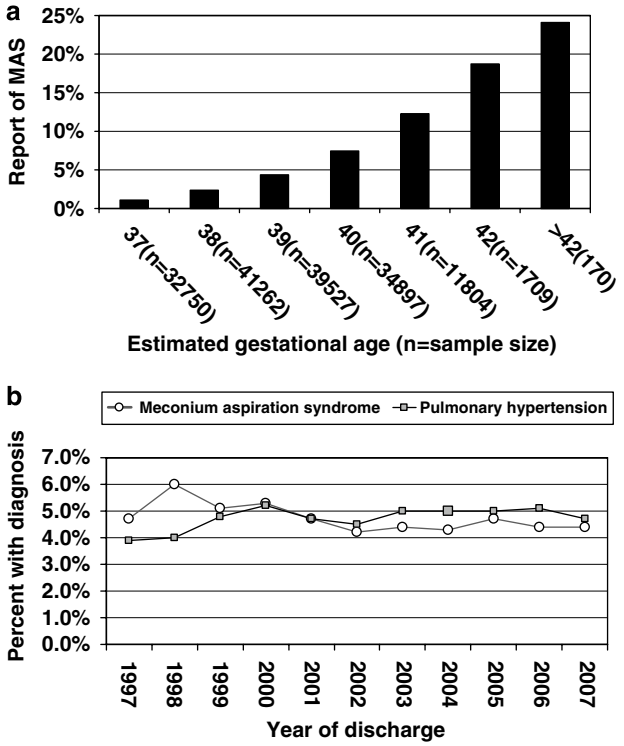

Figure 1 (**a**) The incidence of meconium aspiration syndrome (MAS) by estimated gestational age in term neonates admitted for neonatal intensive care. (**b**) The incidence of MAS and/or pulmonary hypertension by year in term neonates admitted for neonatal intensive care unit. ECMO, extracorporeal membrane oxygenation.

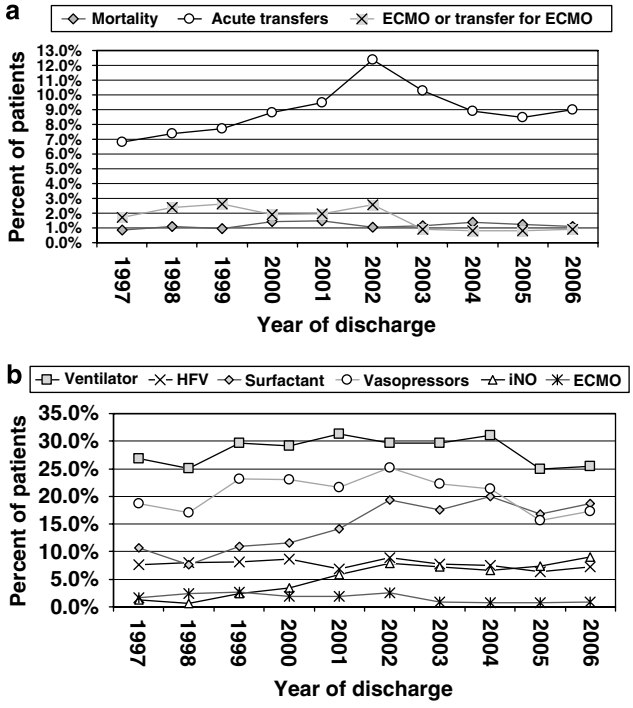

Figure 2 (**a**) The change in acute transfer and mortality rates over time in term neonates with meconium aspiration syndrome (MAS) who were admitted for intensive care. (**b**) The change over the use of specific therapies over time in term neonates with MAS who were admitted for intensive care. ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; HFV, high frequency ventilation.

MAS, 696 (9.3%) had brain imaging (ultrasound, magnetic resonance imaging, of computed tomography scan) and 5 (0.07%) had a report of severe intracranial hemorrhage. A total of 379 (5%) patients had a need for oxygen support at discharge or 28 days of life (whichever came first), 366 (4.9%) developed seizures and 4 (0.05%) patients had a report of necrotizing enterocolitis (one required surgical intervention). During the period between 2002 and 2005, acute transfer rates decreased (12.4 to 9%) and the reported rate for death was relatively constant between 0.9 and 1.5% (Figure 2a).

Deaths

Of the 88 neonates who died, 40 (45.5%) had a history of severe asphyxia; 21 (23.9%) had a history of a major anomaly (heart anomaly, $n=7$; trisomy, $n=3$; inborn error of metabolism, $n=3$; multiple congenital anomalies, $n=3$; congenital hydrocephalus, $n=1$; congenital diaphragmatic hernia, $n=1$; omphalocele, $n=1$; osteogenesis imperfecta, $n=1$ and pulmonary hypoplasia, $n=1$); 19 (21.6%) died acutely despite ventilator support (progressive respiratory failure, $n=13$; airleak, $n=4$ and pulmonary hemorrhage, $n=2$); 5 (5.7%) died of septic shock; 1 (1.1%) died with a large intracranial hemorrhage and 1 (1.1%) died of necrotizing enterocolitis. In one (1.1%) patient, a specific cause of death was not reported.

Only three of the patients who died were treated with ECMO. Of the 88 neonates who died, we estimated that 24 infants (those with acute deterioration and those with sepsis) may have been eligible for and benefited from ECMO, but they were not treated with ECMO. Ten of these 24 infants died within 24 h of birth.

Treatments

The degree of respiratory support during the first day after birth was noted as follows: room air in 844 (11%); oxygen by hood in 2468 (33%); nasal cannula in 788 (10%); continuous positive airway pressure in 492 (7%); conventional mechanical ventilation in 2111 (28%) and high-frequency ventilation in 565 (8%). In 250 (3%), the degree of respiratory support was not recorded (Table 2).

The large majority of neonates with MAS were treated with antibiotics ($n=6906$, 92%). Other commonly reported therapies include vasopressors (dopamine, dobutamine or epinephrine, $n=1502$, 20.0%); surfactant ($n=1203$, 16.0%); anticonvulsants ($n=680$, 9%) and iNO ($n=460$, 6.1%). Less commonly reported medications included dexamethasone ($n=344$, 4.6%) and hydrocortisone ($n=230$, 3.1%). One hundred seven (1.4%) neonates were treated ($n=61$) with or transferred for ECMO ($n=46$). Of the 61 patients treated with ECMO, the majority ($n=41$, 67.2%) were treated with veno-venous ECMO.

Three of the sixty-one neonates (4.9%) who were treated with ECMO died.

During the period of time from 2000 to 2006, the use of iNO and surfactant increased (Figure 2b). The use of high-frequency ventilation remained relatively consistent at 6 to 9% of term neonates with MAS. The use of vasopressors and ECMO decreased.

Difference in patients who survived and were discharged home and those that died

Bivariate analysis showed that, when compared with neonates who survived, neonates who died were: smaller; had lower Apgar scores; more often delivered by C-section; more often outborn (transferred from another hospital for care); more commonly treated with vasopressors, surfactant, nitric oxide, anticonvulsants, cefotaxime and steroids; and more often required assisted ventilation(Tables 1 and 2). Using multivariate analysis, the factors independently associated with death were: a 5-minute Apgar score <3 (adjusted OR = 7.5, 95% CI 4.6 to 12.2, $P<0.01$); the reported use of ventilator support during the first 48 h after birth (adjusted OR = 4.1, 95% CI 2.1 to 8.1, $P<0.01$); the reported use of vasopressors (adjusted OR = 3.8, 95% CI 2.2 to 6.4, $P<0.01$); a report of a major congenital anomaly (adjusted OR = 2.1, 95% CI 1.2 to 3.7, $P<0.01$) and the reported use of cefotaxime (adjusted OR = 2.1, 95% CI 1.4 to 3.4, $P<0.01$). Increasing gestational age, delivery by C-section and birth outside an ECMO site were not found to be independently associated with increased odds of mortality. The use of surfactant, iNO and steroids were not found to be associated with an increase in the odds of survival.

Table 1 Demographics of population sample by outcome type (*P*-values for bivariate analysis)

	Died	*Home*	*Transferred at 7 days or less*	*Transfer after 7 days of life*	*Died vs home P-value*
Number of patients	88	6124	1131	142	
Numeric data, median (25–75 percentile)					
Maternal age (years)	28 (22–33)	26 (22–31)	27 (22–32)	28 (21–32)	0.01
Estimated gestational age (weeks)	39.5 (39–40)	40 (39–40)	40 (39–40)	40 (39–40)	NS
Birth weight (kg)	3.3 (2.9–3.7)	3.4 (3.1–3.8)	3.4 (3.0–3.8)	3.4 (3.0–3.8)	0.04
Apgar 1 min	2 (0–4)	6 (3–8)	5 (2–7)	4 (2–7)	<0.001
Apgar 5 min	4.5 (0–7)	8 (7–9)	8 (6–9)	7 (6–8)	<0.001
Agar 10 min	3 (1–7)	8 (7–8)	7 (6–8)	7 (5–8)	<0.001
Pulmonary hypertension	49 (55.7)	1100 (18)	409 (36.2)	75 (52.8)	<0.001
Inborn	47 (53.4)	4546 (74.2)	905 (80)	55 (38.7)	<0.001
Major anomaly reported	20 (22.7)	477 (7.8)	123 (10.9)	39 (27.5)	<0.001
Male	51 (58)	3268 (53.4)	624 (55.2)	81 (57)	NS
Race					NS
American/Alaska native	0 (0)	30 (0.5)	8 (0.7)	9 (6.3)	
Asian	0 (0)	176 (2.9)	38 (3.4)	7 (4.9)	
Black	14 (15.9)	1211 (19.8)	242 (21.4)	18 (12.7)	
Hispanic	35 (39.8)	1696 (27.7)	235 (20.8)	44 (31)	
Missing data	3 (3.4)	256 (4.2)	49 (4.4)	12 (8.4)	
Other	1 (1.1)	130 (2.1)	24 (2.1)	2 (1.4)	
Pacific Islander	0 (0)	6 (0.1)	0 (0)	1 (0.7)	
White	35 (39.8)	2619 (42.8)	535 (47.3)	49 (34.5)	
Cesarean section	55 (62.5)	2806 (45.8)	633 (56)	87 (61.3)	0.03
Antenatal steroids	0 (0)	27 (0.4)	8 (0.7)	1 (0.7)	
Antenatal antibiotics	13 (14.8)	1441 (23.5)	218 (19.3)	27 (19)	
Multiples					
Single	88 (100)	6097 (99.6)			NS
Twin	0 (0)	26 (0.4)			
Triplet	0 (0)	1 (0)			
Positive blood culture reported	4 (4.5)	177 (2.9)	25 (2.2)	12 (8.5)	

Table 2 Treatments by outcome type (*P*-values for bivariate analysis)

Antibiotics	78 (88.6)	5760 (94.1)	935 (82.7)	133 (93.7)	0.03
Ampicillin	77 (87.5)	5697 (93)	913 (80.7)	130 (91.5)	0.04
Gentamicin	46 (52.3)	4764(77.8)	754 (66.7)	109 (76.8)	
Cefotaxime	42 (47.7)	1143 (18.7)	167 (14.8)	39 (27.5)	<0.001
Surfactant	27 (30.7)	844 (13.8)	284 (25.1)	47 (33.1)	<0.001
Vasopressor	60 (68.2)	963 (15.7)	392 (34.7)	83 (58.5)	<0.001
Dopamine	53 (60.2)	937 (15.3)	382 (33.8)	81 (57)	<0.001
Dobutamine	35 (39.8)	443 (7.2)	192(17)	46(32.4)	<0.001
Epinephrine	24 (27.3)	70 (1.1)	37 (3.3)	9 (6.3)	<0.001
Dexamethasone	10 (11.4)	264 (4.3)	25 (17.6)	40 (3.5)	<0.001
Age first dose (days)	1.5 (0.75–5.2)	4 (1–8)	1 (0–4.75)	4 (1–6)	
Hydrocortisone	12 (13.6)	162 (2.6)	34 (3)	22 (15.5)	<0.001
Age first dose (days)	1 (0.25–2.75)	1 (1–2)	1 (0–1)	1 (0–3.5)	
Inhaled nitric oxide	18 (20.5)	305 (5)	95 (8.4)	41 (28.9)	<0.001
Age first dose (days)	1 (0–1.25)	1 (0–1)	1 (0–1)	1 (0–1)	NS
Duration (days)	1 (0–6.5)	4 (3–7)	1 (0–4)	5 (2.5–7)	
ECMO	3 (3.4)	37 (0.6)	51 (4.5)	16 (11.3)	0.01
Age ECMO started (days)	0 (0–1)	1 (1–4)	2 (0.5–2.5)	2 (1–5)	NS
ECMO type					
Type not reported	0 (0)	3 (0)	0 (0)	2 (1.4)	
Transferred for ECMO	0 (0)	0 (0)	46 (4.1)	0 (0)	
V–A	3 (3.4)	10 (0.2)	1 (0.1)	1 (0.7)	
V–V	0 (0)	24 (0.4)	4 (0.4)	13 (9.2)	
Phenobarbital and/or Phenytoin	35 (39.8)	476 (7.8)	59 (41.5)	108 (9.5)	<0.001
Seizures	17 (19.3)	264 (4.3)	28 (19.7)	56 (5)	<0.001
Highest degree of respiratory support in first 48 h of age					<0.001
Room air	1 (1.1)	746 (12.2)	91 (8)	1 (0.7)	
Hood O_2	10 (11.4)	2176 (35.5)	257 (22.7)	16 (11.3)	
Nasal cannula	0 (0)	406 (6.6)	57 (5)	9 (6.3)	
High flow nasal cannula	0 (0)	277 (4.5)	29 (2.6)	7 (4.9)	
CPAP	0 (0)	426 (7)	57 (5)	8 (5.6)	
Vent	45 (51.1)	1516 (24.8)	490 (43.3)	51 (35.9)	
HFV	30 (34.1)	364 (5.9)	137 (12.1)	30 (21.1)	
FiO_2 day of admission	1 (0.96–1)	0.6 (0.31–1)	1 (0.45–1)	1 (0.64–1)	<0.001
Age at discharge (days)	2 (1–7)	7 (4–10)	1 (0–2)	14 (9.25–24)	<0.001

Abbreviation: CPAP, continous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFV, high frequency ventilation; Vent, ventilator; FiO_2, fractional inspired oxygen; V-A veno-arterial; V-V veno-venous.

Discussion

These data show that MAS remains an important cause of admission for intensive care among term neonates, and reveal little change during the last decade. The prevalence of MAS was particularly high among post-term neonates. Ten per cent of the infants with MAS died or needed to be acutely transferred to a higher level of intensive care. The development of necrotizing enterocolitis and intraventricular hemorrhage was rare (<1%), but the need for oxygen support at 28 days or discharge (5%) as well as seizures (4.9%) was common. These numbers show that term neonates with MAS remain at risk for significant morbidity.

During the last decade, surfactant replacement, high-frequency ventilation and iNO have been used with increasing frequency, whereas ECMO use has decreased in the management of critically ill infants with severe respiratory failure.[19] Similar trends in the management of term neonates with MAS were also noted in the current data. Most (92%) neonates received antibiotics. Between 2000 and 2006, the use of iNO and surfactant had increased, but the use of vasopressors and ECMO had decreased (Figure 2b). The use of high-frequency ventilation remained relatively constant at 6 to 9% of term neonates with MAS. Apart from a knowledge of the frequency and timing of specific treatments, how those treatments might influence patient outcomes is essential for planning and conducting any clinical trial involving neonates with MAS.

The changes in care reported were not associated with an increase in mortality. The term 'hidden mortality' has been used to

describe the death of a patient who meets the criteria for ECMO or other rescue therapy, but expires before the treatment is initiated.[20] We found very little 'hidden mortality.' Of the 88 patients who died, most of them ($n = 64$) had a major anomaly, a history of hypoxic-ischemic injury, or another complication that would have been a contraindication to ECMO. Twenty-four neonates (those with acute deterioration and those with sepsis) may have been eligible for and benefited from ECMO, but they were not treated with ECMO. Ten of these twenty-four died within 24 h of birth and may have been too sick for transport. Nonetheless, these 24 represent the potential hidden mortality associated with severe MAS. Although this represents only 0.3% of our study population, it serves as a reminder that neonates who might benefit from ECMO may die before it can be offered or provided in this clinical condition. The estimated hidden mortality of 0.3% is very similar to our earlier study of near-term and term neonates who require assisted ventilation.[11]

Factors associated with mortality included the following: a 5-min Apgar score <3; the need for ventilator support during the first 48 h after birth; the need for vasopressors; the presence of major congenital anomalies and the use of cefotaxime. In the population of neonates with MAS, the use of surfactant, iNO and steroids was not found to be associated with an increase in the odds of survival. The factors that we found to be associated with death are surrogates for the severity of illness and in general suggest an obvious truth – 'sick neonates are at risk of dying.' However, markers of severity of illness can be used to identify neonates who should be rapidly moved to ECMO centers if they are appropriate candidates for this life-saving therapy.

The one exception in our list of risk factors is the finding of the association between cefotaxime use and mortality. We have reported earlier that the use of ampicillin/cefotaxime (in the NICU) during the first 3 days after birth may be associated with an increased risk of death (adjusted OR 1.5, 95% confidence interval (CI) 1.4 to 1.7), compared with the use of ampicillin/gentamicin.[21] The finding of similar results in our current study cohort further confirms the evidence that cefotaxime may increase the risk of mortality in neonates admitted to intensive care.

We realize that retrospective reviews have limitations. Proxies for selection bias may not reflect adequately the true severity of illness or the therapeutic approach. There may be variations in the process of care other than those that we report, and those variations may influence our observations. Retrospective studies are also limited by some incompleteness of data, and the evaluation of factors altering outcome is often better when carried out prospectively. The retrospective reviews of extensive data collections such as this one, however, may provide important insights that cannot be generated by prospective trials, or they may assist in the identification of processes for further evaluation.

Conclusions

Meconium aspiration syndrome remains an important source of morbidity and mortality in term newborns. Mortality was 1.2 per cent, and 9 per cent of the term neonates admitted with MAS needed to be acutely transferred to another intensive care facility. A significant proportion required intensive therapies such as vasopressors, surfactant, high-frequency ventilation, iNO and ECMO. Surfactant, iNO and/or steroid use were not associated with improved survival.

Conflict of interest

All the authors declared no conflict of interest.

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