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NEONATAL SEPSIS IN RURAL GHANA: A CASE CONTROL STUDY OF RISK FACTORS IN A BIRTH COHORT

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ABSTRACT

Neonatal sepsis poses a major challenge to achieving the MDG-4 due to lack of facilities to implement proposed management guidelines. Identifying risk factors of neonatal sepsis will help put strategies in place to prevent sepsis. This prospective case control study investigated risk factors of neonatal sepsis in the Asutifi District a typical rural setting of the Brong Ahafo Region of Ghana. A semi-structured check list was used to collect clinical and demographic data from 196 neonates (96 with sepsis as case and 100 without sepsis as control) and respective mothers. Maternal factors that were significantly associated with neonatal sepsis were foul smelling liquor (p=0.001), meconium stained amniotic fluid (p= 0.000), parity (p=0.000), history of UTI/STI (p=0.002) and maternal age (0.017). Neonatal factors that were significantly associated with sepsis include male sex (p=0.040), preterm (p=0.000), not crying immediately after birth (p=0.001), low birth weight <2500g (p=0.000), APGAR score less than 7 (p=0.000) and resuscitation at birth (p=0.004). Priority attention must be given to neonates and mothers with the aforementioned characteristics during antenatal and postnatal care to prevent sepsis.

Key words: ***Neonatal sepsis, rural Ghana, MDG-4***

INTRODUCTION

Notwithstanding technological advances in diagnosis and therapeutics as well as strategies put in place to achieve MDG-4, neonatal sepsis is still a major cause of mortality and morbidity in Asia and Sub-Saharan Africa (Black et al., 2008; Brierkley et al., 2009; Tripathi & Malik, 2010; Adhikari et al., 2010, 2012; Martin et al., 2012; Yasmen et al., 2012). This rather disproportionate high morbidity and mortality from sepsis in these countries are explained by the high incidence of bacterial, parasitic and HIV infection combined with low hygienic standards and vaccination rates, widespread malnutrition and lack of resources (Becker et al., 2009; Yasmen et al., 2012). Guidelines for the management of severe sepsis and septic shock have been formulated (Dellinger et al., 2004, 2008; Adhikari et al., 2012). Implementation of essential guidelines together with timely administration of essential therapies (e.g., fluid resuscitation, antibiotics, source control measures) would effectively improve the management and outcome of neonatal sepsis (Ferrer et al., 2008; Levy et al., 2010; Adhikari et al., 2012). Similar initiatives have been undertaken in children resulting in comparable improvements in outcome (Brierley et al., 2009; Kissoon et al., 2010; Adhikari et al., 2012). Despite their benefits, these guidelines cannot be implemented in most middle- or low-income countries due to lack of resources (Santhanam et al, 2009; Bataar et al., 2010; Baelani et al., 2011; Kissoon, 2011). This leaves those clinicians caring for the majority of sepsis patients worldwide without standardized and adoptable guidance for sepsis care (Santhanam et al., 2009). Identification of risk factors and early institution of therapy can improve mortality and morbidity.

In numerous studies, certain predisposing factors related to pregnancy, deliveries as well as neonatal diseases have been identified as

important causes of sepsis in the newly born infant. Some of the maternal factors include; premature rapture of membrane, maternal fever within two weeks prior to delivery, meconium stained amniotic fluid (MSAF), foul smelling liquor and instrumental delivery. Identified foetal factors include birth weight, gestation and Apgar score (Rodrigo, 2002; Shah et al., 2006; Utomo et al., 2008; Satar & Ozlu, 2012; Yasmen et al., 2012). For many years attention has also been drawn to the risk of cross infection in Neonatal Intensive Care Units (nosocomial infection) (Yasmen et al., 2012). For neonates who have been admitted in health care facilities, age at admission and history of instrumentation or invasive procedures were notable risk factors (Nithin et al., 2008; Gargi et al., 2010; Mohammad, 2011; Yelda et al., 2012). Poor water supply, poor cord handling and birth outside the hospital with unsupervised antenatal care and delivery have also been documented (Nwankwo et al., 2011). In contrast to these observations a review of the literature does not show the exact impact of these factors in the development of neonatal sepsis in rural parts of the underdeveloped world. This study thus considered the risk factors of neonatal sepsis in a Ghanaian rural setting where quick laboratory facilities are not readily available. The study also identified other factors as well as therapeutic interventions that could play vital roles towards improving the survival of neonates with sepsis in least underprivileged communities.

MATERIALS AND METHODS

This prospective case control study was conducted among 196 neonates (≤28 days old) born between January 2011 and December 2013 in the St Elizabeth Hospital Asutifi, in the Brong Ahafo Region of Ghana. A neonate was considered as a case if he/she was born during the study period, was aged less than a month and had been diagnosed with sepsis by the attending physician. Infection in the neonate was confirmed by laboratory data (blood cell examination, value of C-reactive protein and microbial blood culture). Such neonates were admitted in the Paediatric ward and the Neonatal Intensive Care Unit of the St. Elizabeth Hospital Asutifi (SMHA) in Ghana. For each case, a healthy neonate born within the study period was randomly selected at the post-natal clinic in the SMHA as a control.

Information was collected from cases and controls on a wide range of potential maternal and neonatal risk factors for neonatal sepsis. These included factors already identified in previous studies, and factors expected to predispose to neonatal sepsis in this study. A researcher developed semi-structured checklist was used to collect the data. The checklist was pretested in a pilot study before administering in the main study. Informed consent was obtained from the mothers before data collection. Trained midwives collected data and the instrument was administered by the midwives in the local dialect (i.e Twi) to obtain medical and obstetric history of the mothers of the neonates. Data on the neonates were mainly obtained from the medical records but in cases where data to be collected were not available in the medical records of the child, the midwives sought permission from the mothers and babies examined for accuracy and consistency of the information provided. Standard procedures were used to collect data that involved measurements, for example laboratory procedures and physical measurements.

Neonatal characteristics: All neonates who had been diagnosed with sepsis were reviewed and data were collected on the following characteristics; sex, gestational age, birth weight, Apgar score at minutes one and five, age at the time of admission and as to whether or not they cried immediately at birth. Resuscitation at birth and catheter access was also noted for all neonates.

Maternal characteristics: The obstetric and medical data collected from both mothers of neonates with sepsis and the control group were; history of premature rupture of membranes (PROM), antenatal attendance, educational and employment status, mode of delivery, maternal urinary tract infection/sexually transmitted infections (UTI/STI), bleeding during pregnancy/APH, previous abortion, pregnancy-induced hypertension (PIH), age of mother, parity, foul smelling liquor, and prolonged labor.

Conceptual Definitions

Neonatal sepsis: Neonatal sepsis is defined as a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life (Gomella et al., 2009; Utomo,

2010). Newborn infections, also called neonatal sepsis, may vary from subtle conditions to a very severe disease which could ultimately lead to death.

Premature infant: a live born infant delivered before 37 weeks of pregnancy (based on the Ballard score or from first day of last menstrual period).

Low birth weight: is a neonate whose birth weight is less than 2,500g.

Premature rupture of membranes (PROM): the time from membranes' rupture to onset of delivery more than 18 hours.

Meconium stained amniotic fluid (MSAF): was considered if the amniotic fluid was green in color or mixed with meconium, or appears meconium stained on the baby.

Congenital anomaly: any abnormality of anatomy and morphology detected during physical examination.

Fetal Inflammatory Response Syndrome (FIRS): defined as one of the following; tachypnea, hypo- or hyper-thermia, CRT >3seconds, WBC < 4.000 or >34.000, CRP >10mg/dl, IL-6 or IL-8 >70pg/ml, positive 16SrRNA PCR is found.

Statistical analysis: Data from the checklist were entered into the Statistical Package for Social Sciences Version 20.32 (SPSS ver. 20.32) for analysis. Pearson's chi-squared was used to determine associations between independent variables (maternal and neonatal characteristics) and the dependent variable, diagnosis on admission (sepsis/ no sepsis). Logistic regression analyses were used to determine the risk for neonatal sepsis, compared to a reference parameter of a variable. Differences between means were regarded as statistically significant at $p<0.05$.

RESULTS

Table:1 Maternal Factors in Neonates with Sepsis

Parameters	Variables	Case (n=96)	Control (n=100)	Chi Square	Df	P-Value	Odd Ratio	CI Lower	CI Upper
Maternal Age	<20	14	20	10.207	3	0.017			
	21 – 30	36	54				1.052	0.461	2.352
	31 – 40	40	22				0.390	0.161	0.919
	>40	6	4				0.480	0.101	2.056
Educational	Illiterate	24	30	1.370	3	0.713			
Status	Primary	46	41				0.715	0.358	1.418
	Secondary	16	20				0.999	0.424	2.368
	Tertiary	10	9				0.724	0.246	2.104
Parity	Primi	80	59	14.062	1	0.000	3.436	1.784	6.884
	Multi	16	41						
PROM	Present	40	29	3.445	1	0.063	1.742	0.964	3.178
	Absent	56	71						
Maternal	Present	5	1	2.923	1	0.087	4.872	0.731	130.611
Fever	Absent	91	99						
MSAF	Present	30	11	12.141	1	0.000	3.625	1.730	8.103
	Absent	66	89						
PIH/Elampsia	Present	11	5	2.725	1	0.099	2.409	0.828	8.103
	Absent	85	95						
Mode of	S V D	62	72	1.252	2	0.535			
Delivery	C S	27	22				0.704	0.361	1.360
	ID	7	6				0.742	0.222	2.399
Foul Smelling	Present	13	1	11.616	1	0.001	13.599	2.606	5.655
Liquor	Absent	83	99						
ANC/History	<3	29	32	0.073	1	0.787	0.920	0.500	1.691
	≥ 3	67	68						
HO/STI/UTI	Present	30	13	9.526	1	0.002	3.007	1.477	6.425
	Absent	66	87						

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Maternal variables

Maternal age was a significant factor (p = 0.017). Specifically, women aged 21-30 years were 1.95 times less likely to have infants with neonatal sepsis compared to those aged less than 20 year (OR 1.052). Women aged 31-40 years were 61% less likely to have neonates with sepsis compared to those aged less than 20 years (OR O.390). Subjects aged over 40 years were 52% less likely to have infants with sepsis compared to those aged less than 20 years (OR 0.480).

Parity of the subject was significantly associated with the risk of neonatal sepsis. Specifically primigravidas were 3.56 times more likely to have neonates with sepsis compared to multifarious women (OR 3.436, p= 0.000).

Premature Rapture of Membrane (PROM) was significantly associated with the risk of neonatal sepsis. Women who had premature rapture of membrane were 1.26 times more likely to have infants with neonatal sepsis compared to those without premature rapture of membrane (OR 1.742, p=0.63).

Maternal fever was marginally associated with the risk of neonatal sepsis, specifically women who had maternal fever during labour had 4.13 times the odds of birthing neonates who suffered from neonatal sepsis compared to those who had no sepsis (OR 4.872, p= 0.087)

Meconium Stained Amniotic Fluid (MSAF) was significantly associated with the risk of neonatal sepsis. Specifically women who had meconium stained amniotic fluid were 3.375 times more likely to give birth to infants who suffered from neonatal sepsis compared to those without meconium stained amniotic fluid (OR 3.625, p = 0.000).

Pregnancy Induced Hypertension/or Eclampsia was marginally associated with the risk of neonatal sepsis. Women who had Pregnancy Induced Hypertension or Eclampsia were 2.591 times more likely to give birth to neonates who suffered from sepsis compared to those who did not have pregnancy Induced hypertension or Eclampsia (OR 2.409, p= 0.099)

Foul smelling liquor was significantly associated with the risk of neonatal sepsis. Specifically women who presented with foul smelling liquor were 13.401 times likely to give birth to infants with neonatal sepsis compared to those without foul smelling liquor (OR 13.599, p = 0.001). This variable had the largest effect on the likelihood of infants suffering from neonatal sepsis.

History of sexually transmitted injection (STI) or urinary Tract Infection (UTI) were significantly associated with risk of neonatal sepsis. Women with a history of sexually transmitted injections or urinary tract injections were 3.993 times likely to give birth to neonates who suffered from neonatal sepsis compared to those without a history of STI or UTI (OR 3.007, p=0.002).

Table:2 Neonatal Factors in Neonates with Sepsis

Parameters	Variables	Case (n=96)	Control (n=100)	Chi Square	Df	P-Values	Odd Ratio	CI Lower	Upper
Sex	Male	61	49	4.206	1	0.040	1.806	1.021	3.224
	Female	35	51						
Gestation	<37(Preterm)	51	17	29.644	2	0.000			
Weeks	37-42 (Term)	41	80				5.765	3.006	11.511
	>42 (Posterm)	4	3				2.243	0.381	11.815
Apgar Score	< 7	56	21	28.621	1	0.000	5.198	2.800	9.952
(1min)	≥ 7	40	79						
Birth Weight	<2.5kg	42	11	26.628	1	0.000	6.177	3.011	13.643
	≥2.5kg	54	89						
Cried	Yes	84	99	10.460	1	0.001	0.081	0.003	0.425
Immediately	No	12	1						
after Birth									
Resuscitation	Yes	14	3	8.296	1	0.004	5.274	1.630	24.558
at Birth	No	82	97						

Neonatal variables

Sex of the neonate was significantly associated with the risk of neonatal sepsis. Specifically males were 1.194 times more likely to suffer from neonatal sepsis compared with females (OR1.806, p = 0.040).

Gestational age of the infant was significantly associated with likelihood of neonatal sepsis. Specifically, infants aged 37 – 42 weeks were 5.235 times less likely to suffer from neonatal sepsis compared with those who were below 37 weeks gestation (OR 5.765, p=0.000) Infants who were aged above 42 weeks and post mature were 2.757 times less likely to suffer from neonatal sepsis compared to the preterm infants aged less than 37 weeks (OR 2.243, p=0.00).

Apgar score of the neonate one minute after birth was significantly associated with the likelihood of suffering from neonatal sepsis. Infants with scores less than 7 were 5.802 times more likely to suffer from neonatal sepsis compared to those who scored above 7 (OR 5.198, p = 0.000).

Birth weight was significantly associated with the likelihood of neonatal sepsis. Infants who weighed less than 2.5kg were 6.823 times more likely to suffer from neonatal sepsis. Compared with those who weighed over 2.5kgs (OR 6.177, p=0.00).

Immediate cry after birth was significantly associated with the risk of neonatal sepsis specifically infants who cried immediately following birth were 92 % less likely to suffer from neonatal sepsis compared to those who did not cry immediately (OR 0.081, p = 0.001).

Resuscitation at birth was significantly associated with the likelihood of neonatal sepsis. Infants who were resuscitated at birth were 5.726 times more likely to suffer from neonatal sepsis compared to those who were not resuscitated (OR 5.274, p = 0.004).

DISCUSSION

We examined the following as neonatal risk factors for developing sepsis; sex, Apgar score, crying immediately after birth, weight at birth, intravenous catheter access, resuscitation at birth, age at time of admission and gestational age. The results showed that neonatal characteristics which increased risk, significantly, for sepsis were; male sex, low Apgar score at 1st and 5th minute, IV catheter access, resuscitation at birth and not crying immediately at birth.

This study observed that intravenous cannula access and resuscitation at birth were risk factors for neonatal sepsis among the study population. Instrumentations, including intubations (endotracheal and mechanical ventilators) and catheterization (intravenous cannula and Foley's catheter), are long established risk factors for sepsis among clients with weak immunity, including hospitalized patients, neonates and the elderly (Shaikh et al., 2008; CDC, 2009; Leal et al., 2012). Thus pneumonia, blood stream infections and urinary tract infections are among the common infections in the hospital set up. Intravenous catheters are inserted to provide nutrition and also administer medications to the neonate when necessary. Unfortunately, such a procedure also provides a portal of entry for microorganisms into the bloodstream of the neonate if not done aseptically and therefore, putting clients at risk for the development of sepsis. Previous studies have indicated that nurses may not be knowledgeable about how to care for intravenous cannula in situ, regarding its cleaning or how long it is supposed to be in place. Consistent with Santhosh (2005) who indicated that resuscitation after birth was a significant risk factor for neonatal sepsis, it was observed in this study that neonates who were resuscitated at birth were at higher risk of developing sepsis compared to those who were not resuscitated (p=0.004). Resuscitation may be indicated at birth for neonates who may not have an established breathing pattern or those who may look asphyxiated at birth (Fraser et al., 2006). The aim of the procedure is to improve ventilation in the lungs of the neonates and help with tissue oxygenation, correct acidosis, prevent hypothermia and ensure effective circulation (Fraser et al., 2006). This is because the lumen of the peripheral airways of the newborn is narrow, and respiratory secretions are plentiful than in adults which could predispose the newborn to atelectasis (Fraser, Cooper and Nolte, 2006; Wilson and Lowdermilk, 2006). However, the procedure if done vigorously may cause bruises to the delicate and fragile mucous membrane of the neonate and serve as an entry point for microbial agents. Resuscitation if done with unsterile equipment may also introduce microbes

into the lungs of the neonate whose immune system is not yet well developed.

The study revealed that Apgar score and neonate crying at birth were significantly associated with neonatal sepsis. Apgar scores at first ($p<0.000$) and fifth minute ($p=0.000$) were strongly associated with neonatal sepsis and neonate crying at birth ($p=0.03$) was significantly associated with neonatal sepsis. Crying at birth is perhaps the most critical part of the physiological adjustment procedure for a newborn to survive the extra uterine life. Following the cutting of the umbilical cord, the newborn undergoes a series of cardiopulmonary changes with the first breath of air. Initial breathing is the result of a reflex triggered by pressure changes, temperature changes, noise, light and other sensations related to the birth process (Wilson and Lowdermilk, 2006). In most cases an exaggerated respiratory response follows within the first minute of birth, and the infant takes the first gasping breath and cries (Wilson and Lowdermilk, 2006). Thus it follows the physiological mechanism that having low Apgar scores or not crying at birth may be associated with neonatal sepsis, as they could also indicate poor adaptation to extra uterine life. Previous studies have also found that low Apgar scores to be associated with neonatal sespsis (Shah et al., 2006; Shitaye, 2008 and Al- Dasoky et al., 2009). Previous studies have not considered crying as a measure of infant wellbeing or as a possible risk for neonatal sepsis.

Many other studies as well as the present study have shown that the male gender is a significant risk factor for neonatal sepsis (Green and Daling, 1985; Mary and David, 2007; Thermiany et al., 2008; Al- Dasoky et al., 2009; Gargi et al., 2010; Onyedibe et al., 2011; Soman and Lucey, 2011 and Chandan et al., 2012). While the biological mechanism underlying why male babies are at higher risk than female in developing neonatal sepsis may not be clearly understood, some authors have suggested that circumcision, although may reduce the risk for contracting HIV/AIDS in the long round, could be a possible factor contributing to sepsis in males (CDC, 2011). Other authors suggest that since the male gender is a risk factor for prematurity and low birth weight (Utomo, 2010; Lawn, 2013) and as these factors have also been associated with neonatal sepsis, then it is likely that the relationship between sex and neonatal sepsis is mediated by birth weight and prematurity. Some people however, hold on to the myth that female babies may have stronger immunity than males, but evidence supporting this claim is scanty.

The study also revealed birth weight of the neonate ($p=0.000$) or preterm delivery ($p=0.000$) as significant risk factors for neonatal sepsis and in fact these factors have been well documented in previous studies (Shah et al., 2006; Shitaye et al., 2010; Utomo, 2010 and Haque, 2010). In an earlier review, Haque (2010) explained that neonates with low birth weight and preterm babies tend to have poor host defenses and are thus are more likely to suffer sepsis. In addition, clinicians may not have the ability to diagnose sepsis early and accurately among low birth weight or preterm babies due to lack of highly sensitive and specific markers, or clinicians` inadequate knowledge on the process of sepsis among neonates which make them tend to concentrate on “killing the pathogen” rather than concentrating on the consequences of the inflammatory process (Haque, 2010). Moreover, neonates with low birth weight and preterm babies are also more likely to receive parenteral nutrition via IV cannula or some form of medication via IV access. This may predispose them to higher risk of infections compared to babies of normal weight who otherwise do not receive such therapy.

Maternal characteristics that were observed to be significantly associated with neonatal sepsis in this study were; maternal age, history of foul smelling liquor, MSAF, history of maternal UTI/STI. Earlier studies have identified PROM (Chacko and Sohi, 2005; Shah et al., 2006; Al-Dasoky et al., 2009; Vinodkumar et al., 2009; Giorgiana et al., 2010; West & Tabansi, 2012), maternal UTI/STI (Chacko and Sohi, 2005; Al-Dasoky et al., 2009) and foul smelling liquor (Chacko and Sohi, 2005; Shah et al., 2006; West and Tabansi, 2012) as significant risk factors for neonatal sepsis. PROM, sometimes referred to as preterm prelabour rupture of the membranes, refers to a condition where rupture of fetal membranes occurs without the onset of spontaneous uterine activity resulting in cervical dilation (Fraser et al., 2006). Risk factors for PROM include cervical incompetence, cord prolapse and malpresentation associated with prematurity. After membrane rupture,

microorganisms from the vagina could ascend into the amniotic sac, causing chorioamnionitis or placentitis to develop (Wilson and Lowdermilk, 2006). But there could be other times when microorganisms may ascend and cause PROM (Wilson and Lowdermilk, 2006). This in essence predisposes the baby to infection in utero. The present study did not find PROM as a significant risk probably due to intervention put in in place to manage such cases.

The presence of meconium in amniotic fluid is a significant predictor of neonatal infection (Wilson and Lowdermilk, 2006). Normally it is expected that the amniotic fluid should remain clear. However, in times of fetal hypoxia, it could be stained with meconium. There is also recent evidence supporting that when there is meconium in amniotic fluid there is a greater chance of the fetus being born with low Apgar score, which unfortunately has earlier been associated with neonatal sepsis (Shah et al., 2006; Shitaye, 2008 and Al- Dasoky et al., 2009).

Maternal education and employment status were not significant risk factors for neonatal sepsis. This is inconsistent with earlier findings by Shah et al., (2006) who observed in a case control study in Nepal that maternal literacy and employment state were related to neonatal sepsis. Women with formal education are more likely to understand issues related to childcare and hygiene better than their illiterate counterparts (Onyedibe et al., 2011). Furthermore, it is believed that employed and financially empowered women may be well placed to cater for their needs and the needs of their babies such as good nutrition which goes the long run to improve their immunity and ability to fight infections (Orwenyo, 2011).
Maternal history of STI/UTI has been previously associated with increased risk for neonatal sepsis (Emamghorashi et al., 2012). Maternal UTI/STI is often associated with early onset neonatal sepsis, especially if untreated during the third trimester or labor, as it is a risk for PROM. Another mechanism by which untreated maternal UTI or STI may be associated with neonatal sepsis is this; following the colonization of the birth canal by the infectious agent, the baby is likely to ingest some of these bacteria as it is being delivered through the birth canal, thus increasing his risk (Al-Inany, et al, 2011; Emamghorashi et al., 2012)
This study observed maternal history of abortion as a significant risk factor for neonatal sepsis (p=0.002). In the famous EUROPOP case control survey that aimed to investigate the relationship between history of induced abortion and preterm delivery in the Europe, it was shown that previous induced abortions were significantly associated with preterm delivery and the risk of preterm birth increased with the frequency of abortions (Ancel et al., 2004). The sample size for this study was very large (N= 2938 cases and 4781 controls), multinational (n= 10 European countries) and had a sufficiently rigorous design. Although this study did not investigate whether the frequency of abortion is likely to influence neonatal sepsis, and generate an unlikely causal relationship between abortion and neonatal sepsis, it is reasonable to assume that the relationship between maternal history of abortion and neonatal sepsis is mediated by preterm delivery.

This study did not observe antenatal care attendance as a risk factor for neonatal sepsis (p=0.787). While the importance of antenatal care regarding minimizing the risk factors for adverse birth outcomes including neonatal sepsis is not doubted, this study did not observe significant differences in neonatal sepsis between women who attended antenatal care and mothers who did not. The interpretation of this, the indifference in neonatal sepsis by maternal antenatal care is likely to be hampered by small numbers but is provocative.

CONCLUSION

This study established a strong association between the following; low Apgar score, IV cannula use, resuscitation at birth, male sex, preterm, not crying immediately at birth, low birth weight and neonatal sepsis. This suggests the possibility of routine sepsis evaluation in neonates born with the aforementioned characteristics. Results of this study also suggest that empowering mothers through education and employment may be effective in minimizing risk for neonatal sepsis, as much as the role of screening mothers with UTI/STI for early treatment of infections and measures to curtail MSAF cannot be overemphasized.

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