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Bacteriological Agents and Resistance Profiles in Neonatal Sepsis from a Poorly Regulated Antimicrobial Access Setting: Time for Action

Agent Bactériologique et Profils de Résistance dans la Septicémie Néonatale dans un Contexte de Faible Régulation de l'Accès aux Antimicrobiens : Il est Temps d'Agir

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ABSTRACT

BACKGROUND: Neonatal sepsis (NNS) is a known cause of morbidity and mortality especially in developing countries. The global resistance scourge may worsen the management outcomes of NNS. This study aims to determine the current profile of bacteriological agents of NNS, their resistance status and associated mortality in our setting.

METHODS: Neonates numbering 480 presenting with clinical features of sepsis and /or risk for sepsis were consecutively recruited into the study and had their blood specimens collected at admission. Blood samples were logged into BacT/ALERT[®] and then inoculated onto blood, chocolate and MacConkey agar upon beeping. Inoculated agar plates were incubated aerobically at 35-37°C for 24-48 hours except the Chocolate agar incubated under an enriched CO₂ atmosphere. Isolates were identified using standard microbiological techniques. Antibiotic susceptibility was performed by the modified Kirby-Bauer disc diffusion method and interpreted using CLSI recommendations. Multi-drug-resistant (MDR) bacterial strains were identified by resistance to at least one antimicrobial agent from three or more categories. Discharge and Deaths were the reported outcomes of treatment.

RESULTS: The 480 neonates investigated M: F=1:0.8 and a mean age of 5.64 ± 7.28 days. The overall prevalence of microbiologically confirmed NNS was 24.6%. There is no significant difference ($p=0.1395$) in the NNS prevalence among males (22.0%) compared to females (28.3%). The highest prevalence of NNS (39.8%) was recorded at the gestational age of 32 -36 weeks. NNS prevalence significantly ($p=0.009$) changed with increasing gestational age just as the prevalence of maternal chorioamnionitis history significantly ($p=0.0006$) increased with increasing gestational age. Gram-positive bacteria (56.2%) were the predominant isolates and *S. aureus* (47.9%) was the most frequent. *Salmonella* Typhi occurrence was 1.4%. A majority (54.8%) of the pathogens were MDR. The overall mortality rate in the study was 6.5% with significant ($p=0.00001$) higher deaths among microbiologically confirmed NNS (18.5%) compared to non-microbiologically confirmed NNS (2.5%).

CONCLUSION: The prevalence of 'microbiologically confirmed' NNS in this study is high and most identified pathogens were MDR. *Salmonella* Typhi was a rare agent of NNS seen in this study. Mortality recorded is high and the time for mitigating the emergence and spread of MDR such as regulated antimicrobial sale and use is now.

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KEYWORDS: Bacteria, Antibiotics, Multi-drug Resistance, Neonatal sepsis

RÉSUMÉ

CONTEXTE: La septicémie néonatale (SN) est une cause bien connue de morbidité et de mortalité, en particulier dans les pays en développement. Le fléau mondial de la résistance pourrait aggraver les résultats de la prise en charge de la SN. Cette étude vise à déterminer le profil actuel des agents bactériologiques responsables de la SN, leur statut de résistance et la mortalité associée dans notre contexte.

MÉTHODES: Un total de 480 nouveau-nés présentant des signes cliniques de septicémie et/ou des facteurs de risque de septicémie ont été recrutés consécutivement dans l'étude et leurs prélèvements sanguins ont été réalisés à l'admission. Les échantillons de sang ont été introduits dans le système BacT/ALERT[®], puis inoculés sur des milieux de culture (sang, chocolat et MacConkey) après un signal sonore. Les plaques inoculées ont été incubées à l'air à 35-37°C pendant 24 à 48 heures, à l'exception des milieux chocolat incubés dans une atmosphère enrichie en CO₂. Les isolats ont été identifiés à l'aide de techniques microbiologiques standard. La sensibilité aux antibiotiques a été évaluée par la méthode de diffusion sur disque de Kirby-Bauer modifiée et interprétée selon les recommandations du CLSI. Les souches bactériennes multirésistantes (MDR) ont été identifiées par leur résistance à au moins un agent antimicrobien dans trois catégories ou plus. Les issues du traitement étaient signalées comme sorties ou décès.

RÉSULTATS: Les 480 nouveau-nés étudiés avaient un ratio H:F = 1:0,8 et un âge moyen de 5,64 ± 7,28 jours. La prévalence globale de la SN confirmée microbiologiquement était de 24,6 %. Il n'y avait pas de différence significative ($p = 0,1395$) de prévalence de la SN entre les garçons (22,0 %) et les filles (28,3 %). La prévalence la plus élevée de SN (39,8 %) a été observée chez les nouveau-nés de 32 à 36 semaines de gestation. La prévalence de la SN variait significativement ($p = 0,009$) avec l'augmentation de l'âge gestationnel, tout comme l'histoire de chorioamnionite maternelle ($p = 0,0006$). Les bactéries Gram-positives (56,2 %) étaient les isolats prédominants, et *S. aureus* (47,9 %) était l'agent le plus fréquent. *Salmonella* Typhi représentait 1,4 % des isolats. La majorité (54,8 %) des agents pathogènes identifiés étaient multirésistants (MDR). Le taux de mortalité globale était de 6,5 %, avec une mortalité significativement plus élevée ($p = 0,00001$) chez les SN confirmées microbiologiquement (18,5 %) par rapport aux SN non confirmées microbiologiquement (2,5 %).

CONCLUSION: La prévalence de la SN confirmée microbiologiquement dans cette étude est élevée, et la plupart des pathogènes identifiés étaient multirésistants. *Salmonella* Typhi était un agent rare de SN observé dans cette étude. La mortalité enregistrée est élevée, et il est temps de prendre des mesures pour limiter l'émergence et la propagation de la multirésistance, notamment par la régulation de la vente et de l'utilisation des antimicrobiens.

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MOTS-CLÉS: Bactéries, Antibiotiques, Résistance multirésistante, Septicémie néonatale.

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INTRODUCTION

Neonatal sepsis (NNS), a clinical syndrome, is a disease of infants of 28 days of life or younger and characterised by a wide range of non-specific systemic symptoms and signs with isolation of a pathogen from the bloodstream.¹ It is a known cause of significant morbidity and mortality particularly in developing countries contributing up to 69.0% of neonatal mortality in Nigeria and other parts of Africa.^{2,3} Survivors of neonatal sepsis may have neurological sequelae which undermine the quality of life of the child. Additionally, the mothers of the affected infants as well as other caregivers are sometimes emotionally traumatized, with loss of productive hours for reason of prolonged hospitalization.⁴

Antimicrobial resistance (AMR), according to the WHO, is at present a global scourge and among the top three most important public health threats. AMR infection was directly responsible for 1.27 million deaths in 2019 around the world⁵ and if no measure is taken in the few years to follow may result in up to 10 million deaths each year, exceeding the 8.2 million deaths by cancer.⁶ At an economic level, infections by resistant bacteria represent 2.5 million days of extra hospitalization per year only in the European Union territories, with a cost of about 900 million euros.⁷

Factors contributing to increasing AMR include indiscriminate and inappropriate use of antibiotics, over-the-counter sale of antibiotics, lack of adequate legislation to control their use, poor sanitation, and ineffective infection control techniques.⁸ In Nigeria, where the sale of antimicrobial agents is unrestricted due to poorly enforced legislation, the emergence and spread of resistant pathogens which is now a global challenge is expected to negatively impact the management of NNS.

The pathogenic agents of NNS vary worldwide. In developing countries,

Gram negatives are the most encountered although Gram-positive organisms have been also reported.^{9,10} The susceptibility reports of these pathogens have indicated some degree of AMR with limited documentation about their Multi-Drug Resistant (MDR) status. An MDR bacterium is one not susceptible to at least one agent in three or more antimicrobial categories,¹¹ and may worsen the prognosis if it should constitute the infectious aetiology of NNS. Furthermore, making antibiotic choices for the treatment of life-threatening infections like NNS becomes a serious challenge with MDR and may lead to increased mortality. In this study, an effort was aimed at determining the current patterns of bacteriological agents of NNS, their MDR status and associated mortality as a measurement of management outcomes given the unregulated sale of antimicrobial agents in our setting.

METHODS

Study Design and Patients

This is a hospital-based longitudinal descriptive study carried out at the Neonatal Intensive Care Units (NICU) of the University of Ilorin Teaching Hospital (UITH) Ilorin, Kwara State, Nigeria. The hospital is a 650-bed tertiary hospital receiving referrals from Kwara and its adjoining states of the North Central geopolitical zone of the country. The NICU provides level II care and admits about 1,500 neonates annually.

The study was approved by the Ethics and Research Committee of UITH and the approval reference is UITH/CAT/189/21B/400. Consent, clinical sepsis, risk for sepsis and no use of any antibiotics within the last 48 hours of presentation constituted the recruitment criteria. Consents were obtained from participants' parents or guardians.

Clinical sepsis was as defined by the WHO/ UNICEF Integrated Management of Childhood Illnesses (IMCI).¹² Risk for sepsis included history of prolonged/premature rupture of membranes, maternal chorioamnionitis, maternal infections (like urinary tract infection, pneumonia and septicaemia), prematurity, prolonged invasive resuscitation, prolonged neonatal hospitalization and prolonged vascular catheter use in neonate due to other medical reason.

Microbiological Laboratory Investigation and Treatment

Four millilitres of venous blood were withdrawn aseptically from each participant and dispensed into an aerobic BacT/ALERT® blood culture bottle labelled with the patient information (identification numbers, age, date of sample collection, and gender). The inoculated BacT/ALERT® bottle was submitted to the Microbiology laboratory immediately for loading into the BacT/ALERT® 3D microbial detection system and further processed. BacT/ALERT® bottles that flagged positively were taken out of the BacT/ALERT® incubator upon beep sound from the instrument. Thereafter, samples were aseptically sub-cultured onto blood agar (Oxoid, UK), supplemented with 5% v/v sheep blood, chocolate (Oxoid, UK) supplemented with 5% v/v sheep blood at 55°C, and MacConkey agar (Oxoid, UK) plates using a sterile platinum wire loop. All inoculated plates were incubated aerobically at 35-37°C for 24-48 hours except the Chocolate agar plates incubated in a moist and enriched CO₂ atmosphere (inside a candle extinction jar underlaid with damped cotton wool). Isolates, if any, were identified using a combination of colony morphology, Gram staining, and various biochemical tests as previously described.¹³⁻¹⁴

Antibiotic susceptibility testing was carried out by the modified Kirby-Bauer disc diffusion method with the organism tested against the following antibiotics (Oxoid, UK): ceftazidime (30µg), cefuroxime (30µg), ceftriaxone (30µg), cefoxitin (30µg), ampicillin/sulbactam (20/10µg), amoxicillin/clavulanic acid (20/10µg), ciprofloxacin (5µg), gentamicin (10µg), trimethoprim-sulphamethoxazole (23.75/1.25µg), azithromycin (15µg), erythromycin (15µg), piperacillin/ tazobactam (100/10µg), imipenem (10µg), and tigecycline (15µg). Results were interpreted according to the CLSI recommendations.¹⁴ Strains of bacterial pathogens were taken as MDR when they demonstrated resistance to one antimicrobial from three or more classes/categories.¹¹ For all known isolated agents of sepsis, one blood culture positive result was definitive of NNS but for others that may represent skin contamination, true bacteraemia was taken as the recovery of the same organism from at least two blood culture samples.¹

Empiric antimicrobial treatments were commenced after blood specimen collection and patients were reviewed with culture results as soon as it is available. The outcome of treatment was documented as either discharged, death, discharged against medical advice (DAMA) or referred. The routine empiric medication choice for term neonates at our centre is traditionally drawn from among Ceftazidime/ Cefuroxime/Ceftriaxone, Augmentin, Gentamycin and Ciprofloxacin.

Data analysis

Data were inputted into an Excel spreadsheet and statistically analysed using GraphPad Prism 9. Results were expressed as percentages and presented in Tables. Comparative analysis was done using Chi-square (χ^2) with the level

of significance (p-value) set at < 0.05 .

RESULTS

Table 1: Prevalence of microbiologically-confirmed neonatal sepsis with respect to demographic characteristics and treatment outcomes

VARIABLE	TOTAL	Culture Positive NNS Prevalence % (n/N)	χ^2	p-value
Gender [n (%)]				
Male	268 (55.8)	22.0 (59/268)	2.51	0.1395
Female	212 (44.2)	28.3 (60/212)		
TOTAL	480 (100.0)	24.8 (119/480)		
Gestational age in weeks [n (%)]				
< 28	226 (47.1)	11.5 (26/226)	41.93	< 0.00001
28 – 32	111 (23.1)	34.2 (38/111)		
32 -36	123 (25.6)	39.8 (49/123)		
> 36	20 (4.2)	30.0 (6/20)		
Age (Days)				
Range	1 - 28	–	–	–
Mean + SD	5.47 ± 6.65			
MANAGEMENT OUTCOME [% (n/N)]				
Discharges	93.5 (449/480)			
Deaths (Total)				
Culture positive NNS	6.5 (31/480)	18.5 (22/119)	37.898	< 0.00001
Culture negative NNS		2.5 (9/361)		
DAMA	0 (0.0)			
Referred	0 (0.0)			
Maternal chorioamnionitis history by gestational age [% (n/N)]				
< 28	1.3 (3/226)	11.5 (3/26)	17.52	0.0006
28 – 32	15.3 (17/111)	44.7 (17/38)		
32 -36	8.9 (11/123)	22.4 (11/49)		
> 36	25.0 (5/20)	83.3 (5/6)		
TOTAL	7.5 (36/480)	30.3 (36/119)		

Table 2: Frequency distribution of isolates and their mdr status

ISOLATES	TOTAL, n (%)	Non-MDR n (%)	MDR n (%)
GRAM-NEGATIVES			
<i>Klebsiella pneumoniae</i>	40 (27.4)	16 (40.0)	24 (60.0)
<i>Klebsiella oxytoca</i>	1 (0.7)	0	1 (100.0)
<i>Escherichia coli</i>	4 (2.7)	3 (75.0)	1 (25.0)
<i>Enterobacter cloacae</i>	2 (1.4)	2 (100.0)	0 (0.0)
<i>Acinetobacter baumannii</i>	6 (4.1)	4 (66.7)	2 (33.3)
<i>Citrobacter</i> spp	1 (0.7)	0	1 (100.0)
<i>Pseudomonas aeruginosa</i> .	4 (2.7)	2 (50.0)	2 (50.0)
<i>Salmonella</i> Typhi	2 (1.4)	2 (100)	0 (0.0)
SUB-TOTAL (GRAM-NEGATIVE)	60 (41.1)	29 (48.3)	31 (51.7)
GRAM POSITIVES			
<i>Staphylococcus aureus</i>	70 (47.9)	31 (44.3)	39 (55.7)
CONS	9 (6.2)	2 (22.2)	7 (77.8)
<i>Enterococcus faecalis</i>	4 (2.7)	2 (50.0)	2 (50.0)
Viridians group of <i>Streptococcus</i>	3 (2.1)	2 (66.7)	1 (33.3)
SUB-TOTAL (GRAM-POSITIVE)	86 (58.9)	37 (43.0)	49 (57.0)
GRAND TOTAL	146 (100)	66 (45.2)	80 (54.8)

There is a significant difference ($\chi^2=0.2165$, OR=1.239, 95% CI=0.6388-2.403, $p=0.6417$) in the MDR rate among Gram-negative 51.7% (31/60) compared to Gram-positive 57.0% (49/86) isolates.

Legend: CONS = Coagulase-negative staphylococci

Table 3: Resistance of isolates to antibiotics

ISOLATES	N	GE NT AM	AZTRH	UN ASY N	CIP ROF LO	SUL FA	ME	CEF UR ØXI	AU GM ENT	CEF TRI	CEF TAZ	HDI	IMI PEN EM	TEG YC YCL	INE	PIP ERA	CIL LIN	ERY THR OM	CEF OXI TIN
<i>Klebsiella pneumoniae</i>	40	32 (80)	NT	5 (12.5)	22 (55)	8 (20)	36 (90)	24 (60)	24 (60)	33 (82.5)	11 (27.5)	NT	0	7 (17.5)	24 (60)				
<i>Klebsiella oxytoca</i>	1	1 (100)	NT	NT	1 (100)	NT	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	NT	0	0	0	0	0	0
<i>Escherichia coli</i>	4	1 (25)	NT	NT	1 (25)	NT	2 (50)	2 (50)	2 (50)	2 (50)	0 (0.0)	0 (0.0)	NT	0	0	0	0	0	0
<i>Enterobacter cloacae</i>	2	0 (0.0)	NT	NT	0 (0.0)	NT	1 (50)	1 (50)	0 (0.0)	0 (0.0)	0 (0.0)	NT	0	0	0	0	0	0	0
<i>Acinetobacter baumannii</i>	6	3 (50)	NT	3 (50)	3 (50)	NT	1 (16.7)	2 (33.3)	3 (50)	2 (33.3)	3 (50)	2 (33.3)	3 (50)	2 (33.3)	0	0	0	0	0
<i>Citrobacter</i> spp.	1	1 (100)	NT	NT	1 (100)	NT	1 (100)	1 (100)	1 (100)	1 (100)	0 (0.0)	NT	0	0	0	0	0	0	0
<i>Pseudomonas aeruginosa</i>	4	3 (75)	NT	NT	1 (25)	NT	NT	NT	NT	1 (25)	0 (0.0)	NT	2 (33.3)	0	0	0	0	0	0
<i>Salmonella</i> Typhi	2	0 (0.0)	0 (0.0)	NT	0 (0.0)	NT	NT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NT	0	0	0	0	0	0	0
<i>Staphylococcus aureus</i>	70	19 (27.1)	9 (12.9)	2 (2.9)	21 (30)	0 (0.0)	39 (55.7)	39 (55.7)	39 (55.7)	NT	NT	0 (0.0)	0	12 (17.1)	39 (55.7)				
CONS	9	4 (44.4)	0 (0.0)	NT	7 (77.8)	NT	5 (55.6)	5 (55.6)	5 (55.6)	NT	NT	NT	0	3 (33.3)	5 (55.6)				
<i>Enterococcus faecalis</i>	4	1 (25)	0 (0.0)	0 (0.0)	1 (25)	NT	0 (0.0)	NT	1 (25)	NT	NT	NT	0	0	0	0	0	0	0
Viridians <i>Streptococcus</i> group	3	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	NT	0 (0.0)	1 (33.3)	0 (0.0)	NT	NT	NT	0	0	0	0	0	0	0

Legend: NT= Not Tested, CONS = Coagulase negative staphylococci

males and 212 females (M: F=1:0.8). The mean age of the study participants was 5.47 ± 6.65 days. The overall prevalence of 'microbiologically confirmed' NNS was 24.6% (119/480). There was no gender predilection for NNS as a similar percentage of females (28.3%, 60/212) and males (22.0%, 59/268) were affected ($p = 0.482$). As seen in Table 1, microbiologically confirmed NNS prevalence increased with increasing gestational age significantly ($p=0.009$) just as the prevalence of maternal chorioamnionitis history significantly ($p=0.0006$) increased with increasing gestational age.

With reference to bacteriological agent types (Table 2), Gram positives, as a group, were more frequent accounting for 58.9% (86/146) of the isolates. The most encountered single isolate was *S. aureus* (47.9%, $n=70$). The most frequently isolated Gram-negative was *Klebsiella pneumoniae* (27.4%, $n=40$). *Salmonella* Typhi (1.4%, $n=2$) and *Enterobacter cloacae* (1.4%, $n=2$) were among the identified Gram-negative agents of NNS.

Although MDR isolates were slightly more frequent among the Gram-positive bacterial strains (57.0%) compared to the Gram-negatives (51.7%), there is no significant difference ($\chi^2=0.2165$, OR=1.239, 95% CI=0.6388-2.403, $p=0.6417$). The only isolated strains of *Klebsiella oxytoca* (100.0%, 1/1) and *Citrobacter* spp (100.0%, 1/1) were

MDR. Other major MDRs were coagulase-negative staphylococci (77.8%, 7/9) and *Klebsiella pneumoniae* (60.0%, 24/40). However, all strains of *Salmonella* Typhi (100%, 2/2) and *Enterobacter cloacae* (100%, 2/2) in the study were non-MDR.

Of the antibiotics tested against the identified pathogens of NNS in the study, as presented in Table 2, only piperacillin/tazobactam was effective with almost all Gram-positive and negative isolates sensitive while only *Pseudomonas aeruginosa* strains demonstrated 33.3% resistance to it.

Mortality among patients with NSS as found in the study was 6.5% (31/480), with most of the patients successfully managed and discharged (93.5%, $n=449$). There was a significant ($p=0.00001$) higher death among microbiologically confirmed NNS (18.5%) compared to non-microbiologically confirmed NNS (2.5%). There was no incidence of referrals or discharges against medical advice.

DISCUSSION

The prevalence of microbiologically-confirmed NNS in this study is 24.8%. This prevalence is comparable to earlier documentation,¹⁰ and it is an indication that NNS is still a challenge in our locality. The pooled prevalence of NNS in developing countries has been put at 29.9%,⁹ a figure that is slightly higher

than what we recorded in the present study but not comparable to the developed nations where the incidence may not be more than 1.5 per 1000 live births.¹⁵ There is therefore need for a concerted effort to reduce the occurrence of NNS in countries like ours.

Gram positives, as a group, were more occurring in this study accounting for 58.9% of the isolated bacterial pathogens. This is a divergence from previous reports as Gram-negative bacteria were more reported across the world hitherto.¹ The reason for this occurrence is difficult to explain but may represent a change in the trend of bacteriological agents of NNS for which further investigation is needed. The most prevalent bacterial pathogen for any infection is key in the choice of empirical antimicrobial agents for treatment. Even though the agents of this infection like many others continue to change over time in any region, our finding is in support of continuous surveillance to keep abreast of treatment challenges that may erupt.

In the present study, *Salmonella* Typhi was recovered from two patients accounting for a prevalence of 1.4%. Although, *Salmonella* Typhi has been documented elsewhere as an agent of NNS,¹⁶ This is the first time that it will be reported from our centre. *Salmonella* Typhi however remains a rare pathogenic cause of NNS because of its both low reportage and incidence even when reported. It may therefore be an

emerging NNS pathogen for which attention may be required. Transmission of *Salmonella* Typhi to infants through breast milk has been reported.¹⁵ Breastfeeding is a popular phenomenon in our setting and may enhance vertical transmission of the organism from the mother to the child. Our finding may however also be related to the improved laboratory handling of cultures in recent times.

Furthermore, in this study most bacterial agents of NNS are not just resistant to antibiotics but MDR. The only occurring strains of *Klebsiella oxytoca* and *Citrobacter* spp were MDR. Again, the most isolated Gram-positive and negative which were *Staphylococcus aureus* and *Klebsiella pneumonia* respectively demonstrated high levels of multidrug resistance. This suggests that the management of NNS cases should be by de-escalation concept to save lives. The antimicrobial agents to which the identified bacterial pathogens demonstrated the least resistance is piperacillin/ tazobactam and therefore best recommended for empirical therapy of NNS at this time. Ironically however, 33.3% of *Pseudomonas aeruginosa* strains isolated in this study were resistant to piperacillin/tazobactam which is one of the antimicrobials recommended for treatment of infections from the organism. There is therefore need for extensive testing of various anti-pseudomonad antibiotics against *Pseudomonas aeruginosa* in our setting to decipher the best choice of drugs for its management.

Mortality in the present study is high just as the prevalence of NNS. Furthermore, a significant ($p=0.00001$) higher death occurred among microbiologically proven NNS compared to microbiologically unconfirmed NNS. The mortality rate is not comparable with what is obtained in the Western world.¹ This portends a great danger to our population constituting a threat to the survival of the children. There is

therefore no better time than now for all necessary actions to put under control the factors responsible for these negative findings. Unregulated access to antimicrobials among others constitutes a challenge that needs to be addressed in our country.

CONCLUSION

The prevalence of microbiologically-confirmed NNS in this study is high and most of the causative agents are also multi-drug resistant suggesting the need for antimicrobial stewardship strategies such as de-escalation to pathogen-specific therapy in the management of NNS in our setting. A rare bacteriological agent of NNS in the study is *Salmonella* Typhi, which may indicate a new trend of events for which attention including effective infection prevention and control measures may be needed. The high NNS-associated mortality recorded should be addressed now by institutions and enforcement of necessary interventions such as regulation of antibiotics sale and use.

Disclosure of Competing Interest:

None

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