Review Article

Endo-tracheal tube associated bacterial infection, prevalence and their drug susceptibility pattern in NICU

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ABSTRACT

Aim of this article is to provide an overview of modifiable and non-modifiable factor in the development of Nosocomial Infections (NIs) in the Neonatal Intensive Care Units (NICUs).Endotracheal tube intubation/Mechanical ventilation is a lifesaving invasive procedure which is associated with their own potential complications, like ventilator associated pneumonia (VAP), sepsis, Ventilator associated-tracheo-bronchitis(VAT), acute respiratory distress syndrome, pulmonary embolism, Barotrauma and pulmonary edema, which can occur among the patients receiving mechanical ventilation. Among the above listed complication, Neonatal sepsis is the most common and VAP is the second most common encountered Nosocomial infection, which account for the most of the morbidity and mortality in the NICUs and ventilated patients. PubMed, Embase and google scholar have been searched for the articles meeting our criteria,total fourteen articles have been used. Neither any alterations or modifications nor any Software's were used in this article. In some recent research article and literature, some strategy have been mentioned, which are resulting in better control of Nosocomial infection due to ventilator or endotracheal tube intubation. Gram-negative bacteria are most prevalent in the developing countries and Gram-positive in the developed countries, Klebsiella pneumonia, E. coli and staphylococcus aureus are the most common reason for NIs. Increasing number of NIs and multidrug resistance bacteria are matter of concern for Neonatologist around the world.

Keywords: *Nosocomial infection in NICUs, VAP, VAT, bacterial prevalence, antimicrobial susceptibility*

Introduction

Nosocomial infections (NIs) is the serious problem worldwide in those neonates, who are admitted to Neonatal intensive care units (NICUs). It leads to higher morbidity and mortality under the age of 28 days, and prolonged length of hospital stay, also increases the cost of the treatment. [1]Among the preterm and low birth weight (VLBW less than 1500g) babies, rate of neonatal sepsis is much higher. [2] Neonates especially preterm and low birth weight have immature immune system and less efficient mucosal and cutaneous barriers, [3-4] which makes them more prone to acquired infections due to multiple invasive procedures, like use of ventilator /endotracheal tube (ETT), peripheral and central venous lineand broad-spectrum antimicrobials. [5]Use of ventilator increases the risk of getting VAP by 6-20 fold with crude mortality rate of 20%-40%,[6,7] the rate of incidence of VAP has been described as 3% per day for the 1st week , 2%

a day in the 2nd week and 1% a day in the coming weeks of mechanical ventilation. [8] Another lower respiratory tract infection due to ETT is VAT, which has similar sign and symptoms like VAP and similar diagnostic microbiological criteria based on quantitative or semi quantitative investigation of endotracheal aspirate. [9,10] Nosocomial infection has become a big challenge for the hospital and society as well, especially in the developing countries due to expenses during the longer hospitalstay. Incidence of nosocomial infection varies region to region, even in the same NICU at different point of time,usually incidence rate have been reported in between 18%-34% [11, 12] and leads to 40% of neonatal death in the developing countries. [13] Previous report from different countries reveals that one third of the Nosocomial infections can be prevented by effective infection control protocol and active surveillance of predominant organism and their drug susceptibility pattern. [12]

The incidence and prevalence of neonatal sepsis in NICUS

Neonatal sepsis is defined as a clinical syndrome in an infant of 28 days or younger, which has a systemic sign of inflammation and isolation of bacterial pathogens from the bloodstream. Diagnosis and management of sepsis is a great challenge in the NICUs for the neonatologist. Neonatal sepsis happening due to Gram-positive, Gram-negative and Candida, and it has variation in a different region and even in the same NICU over the time. [14] (Table 1)

Table 1: Incidence of neonatal sepsis in different published studies

STUDY NAME	STUDIES DESIGN	DIAGNOSIS	INCIDENCE
Afif Ahmad et al [15]	Retrospective studies	Neonatal sepsis	EOS 17% LOS 83%
D.Mohammed, O.S.E seifi et al [16]	prospective cohort study	Neonatal sepsis	58%
Sally AF El-sahrig et al[17]	Retrospective study	Neonatal sepsis	46.40%
Yalaz M, et al[18]	Retrospective study	Neonatal sepsis	9.10%
Shreshta S et al[19]	Descriptive prospective study	Neonatal sepsis	EOS 84.08% LOS 15.95%
EmanM.Rabieshehab El-Din et al[20]	prospective study	Neonatal sepsis	EOS 44.2% LOS 55.8%
Dal-Bo K,SilvaRM,et al[21]	Prospective cohort study	Neonatal sepsis	15.20%
MohammadAqeelkhan et al[22]	Descriptive study	Neonatal sepsis	19.30%
EOS= early onset sepsis, LOS= Late onset sepsis			

Relationship of nosocomial infection with ventilator associated pneumonia (VAP)

The centers for disease control and prevention (CDC, Atlanta, GA, USA) defines

VAP as 'a nosocomial infection diagnosed in patients undergoing Mechanical ventilation for at least 48 h'. [23] Diagnosis of VAP requires a combination of radiological, clinical and laboratory criteria. However, CDC/NNIS criteria refer to infant younger than 1 year and do not defines specific criteria for the newborn period in term or preterm infants. In spite of this lack of specificity,most of the studies over VAP in NICUs are based on CDC criteria. [24] Due to difficulties in getting non-contaminated sample from the infant's airways, the CDC permits the diagnosis of 'clinically defined pneumonia' based on only clinical and radiological findings, without any isolated pathogen. On the other hand, isolation of pathogens without clinical and radiological sign is not diagnostic of VAP and could just represent the colonization of the airways. The incidence of VAP is shown in table 2.

Table 2: Incidence of VAP in different published studies

Studies	Design	Diagnosis	Incidence %
M A badar et al [25]	Prospective studies	VAP	57.10
El-kholy et al [26]	Prospective studies	VAP	20.50
Yuan et al [27]	Retrospective cohort study	VAP	20.10
Afjieh et al [28]	Prospective cohort	VAP	17.30
Tripathi et al [29]	Prospective cohort	VAP	30.60
Deng et al [30]	Retrospective	VAP	33.50

Ventilator associated tracheobronchitis (VAT)

Lower respiratory tract is a sterile structure, generally bacteria enter here from colonized oropharynx through the lumen of the endotracheal tube or around the cuff of tube, diagnosis of VAT and VAP is bit complicated due to their similar sign and symptoms and same micro biological criteria for tracheal aspirate. In contrast to VAP, VAT does not require new and persistent infiltration over the chest radiograph andcavitation or consolidation. Developing VAT or VAP, depends on the virulence, number of Bacteria and colonization. Body has own defense mechanism against the colonization by cilia, macrophages, polymorphonuclear leukocytes and their cytokines and antibodies (IgM, IgG, and IgA) and compliment's fixation protect from tracheal colonization to VAT or VAP. [6,31]

Incidence and pathogenesis of Gram-negative and positive bacteria

Most of the studies from the developing countries reported that Gram negative bacteria is the main culprit for the NI infection in the NICUs, although their prevalence varies from one country to other, even in the same NIUC. Incidence is shown in Table 3. But klebsiella and E.coli having highest prevalence among the gram-negative and S. aureus among gram-

positive, [16, 22, 29]in contrast to developing world, developed countries having more Gram-positive bacterial infection. Group B streptococci were reported as the most common pathogens in terminfant in United States by National Institute of child health and development [32] as shown the incidence in Table 4. Invasion of sterile lower respiratory tract by the colonizing bacteria in the naso-/oropharynx, Gastric fluid and tracheal secretions lead to VAT or VAP and other respiratory tract infections. However pathogens can also be transmitted through hands of healthcare workers and ventilator circuit and the biofilms of endotracheal tube. [33]

Table 3: Incidence of Bacteria in different studies

Studies	Gram-positive %	Gram-negative %
Sally AF El-sahrig et al [17]	35.70	75
Afif Ahmad et [15]	66	16
Yalaz M et al [18]	49.40	31.40
Shrestha S et all [19]	39.36	60.64
Eman M.Rabie shehab El-Din et al [20]	58.57	38.57

Table 4: Incidence of individual bacteria in the published articles included in our study

Bacteria	Shreshta et al [19]	Tripathi et al [29]	Afif Ahmad et al [15]	Eman M.Rbie shehab El-Din et al [20]	Yalaz M et al [18]	D.Mohammmed OSE seifi et al [16]
Klebsiella Pneumoniae	28.72%	32.87%	21.40%	14.29%	10.50%	34.20%
Escherichia coli	6.38%	23.28%	21.40%	2.86%	2.30%	11.20%
P. aeruginosa	9.57%	10.95%	17.30%	1.43%	4.70%	14.90%
Acinetobacter baunnii	5.30%	17.80%	7.10%	5.00%	2.30%	-
CONS	9.57%	6.84%	7.10%	52.86%	-	-
S.aureus	18.10%	2.73%	14.30%	2.14%	13%	26.10%
Enterobacter	3.20%	2.73%	-	-	8.20%	-
Streptococcus	3.20%	-	-	-	-	3.70%
CONS = coagulase-negative Staphylococci						

Risk factor and prevention strategy

NIs depends on multiple factors like prematurity, Low birth-weight and Days of mechanical ventilation (MV). Extremely low birth-weight neonates need prolonged use of MV, which is an independent risk factor for developing VAP. [28] Other contributing factors in developing VAP and Neonatal sepsis are immature immune system of neonates, re-intubation, primary blood

stream infection, prior antibiotics use, sedation parenteral nutrition, endo-tracheal suctioning peripheral intravenous line and Genetic syndrome. [34]

Following strategy have been tested in the prevention of NIs.

Hand washing

A ten second of hand washing prior to touch a patient and after, have been shown a significant reduction in the rate of transmission of infection by the health worker. A previous surveillance intervention with NICU patients for 2 years by increased hands hygiene compliance (from 43 to 80%) significantly decreases the incidence of respiratory infection from 3.35 to 1.06 infection per 1,000 patient days. [35] Frequent hand washing with or even without any antiseptic containing soap has shown good control of microbial flora over the hands. Any alcohol containing product or chlorhexidine containing soap can be used for disinfection.

Planed extubation

Re-intubation increases the chance of aspiration so clinician must calculate the benefit of extubation and risk of prolonged ventilation. [36]

Antiseptic for skin

Use of antiseptic over the skin before any invasive procedure, like venous puncture, central line and catheter has shown significant reduction of infection related to these procedures.

Bed of Head elevation and lateral position

Putting of head slightly higher to abdomen reduces the chance of aspiration of gastric content. Several studies showed that elevation of bed head up to 45 degree [37] or semi-recumbent position reduces the VAP significantly in adult. It is clear now by different studies that supine position should be avoided in intubated patients, degree of elevation still remains controversial, but clinical practice guideline now recommend the elevation of more than 30 degree is protective against aspiration. [37]

Types of ETT

There is no specific recommendation for newborn infant about types of ETT and sub-glottic suction. However CDC and healthcare infection control advisory committee suggest the use of ETT with dorsal lumens to allow drainage of respiratory secretion, oro-tracheal instead of naso-tracheal, types of ETT being used with regard to Uncuffed and cuffed, Uncuffed one being traditionally used since many years but studies suggest that it has increased incidence of VAP, in other hand cuffed one has less need of ETT changes and stridor after extubation but need prolonged ventilation. [38]In the study, machado et al. [39] shows that ETT with nano-modified coating apparently reduces the incidence of VAP through preventing biofilm formation and colonizing of tube through free radical destructionand replacement of respiratory circuit only if they are contaminated. [40]

Immunoprophylaxis

Preterm infants are already have reduced endogenous synthesis of immunoglobulin G and less trans-placental transfer of Immunoglobulin make more prone to neonates for NIs. Ohlsson and lacy [41] meta-analysis showed that prophylactic use of Intravenous immunoglobulin (IVIG) reduce the incidence of sepsis by 3% but there is no

any reduction in mortality rate, therefore, use of IVIG benefit is marginal so cost should be considered before using. Granulocyte colony stimulating factor (G-CSF) and Granulocyte-macrophage colony stimulating factors (GM-CSF) are recombinant hematopoietic cytokines should be considered which boost up the host defense immune system against sepsis by increasing circulating neutrophils and to augment the bactericidal activity of neutrophils and macrophage against pathogens. Some studies showed significant decrease in sepsis, but further more evidence based studies are needed. [42]

Control of premature birth and Nutrition

Term delivery and control of premature delivery will decrease the sepsis significantly as studies showed that preterm infant has high risk of sepsis. Maintenance of proper nutrition and no alteration of hyper alimentation solutions after preparation, early enteral feeding and specially promotion of use of human milk have much beneficiary effect and reduction of sepsis and better boost up of host defense system. Probiotics have been used in some studies which show that critically ill patients who received lactobacillus rhamnosus had significantly less cases of microbiologically confirmed case of VAP and clostridium difficile associated diarrhea. [43]

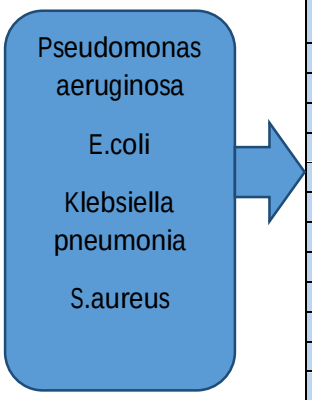
Sampling techniques

Many types of sampling techniques have been applied to avoid the contamination of the sample, some technique like Broncho-alveolar lavage (BAL) need a trained medical personal for the effective result as it is an invasive technique. In contrast to this procedure, tracheal aspirate (TA) is a noninvasive technique which does not require a specialized trainee and easy to use, but has got high change of over diagnosis and resulting into the irrational use of antibiotics. [44] In addition to this, Protected specimen brush(PSB) have been largely adopted for sample collection in VAP suspected adults, it is a very reliable technique and has less chance of contamination which also meet the standard of microbiological sampling for respiratory airways. [45] BAL and PSB, both techniques are quite safe, having minor complication such as minimal bronchial hemorrhage, a moderate increase in oxygen and transient fever also reported. [46] Due to the smaller diameter of ETT in neonates, unfortunately PSB and Bronchoscopic BAL cannot be performed in neonates so in the neonates Blind-protected BAL seems to be the best choice for reliable sampling. [47]

Antimicrobial susceptibility pattern in our reviewed articles

Antimicrobial susceptibility varies significantly according to their use in the hospital in a one region and in the different department of the same hospital. It is totally depends of the sensible use of antimicrobial and knowledge of current prevalence of pathogen. Here are some common medicine, which being used specially in the NICUs around the world and their susceptibility pattern. Beta-lactamantibiotic's sensitivity decreasing as per most of the studies [48] and methicillin resistant coagulase negative staphylococcus (MRCoNS) are most common emerging bacteria in the ICU. A Multidrug resistant Gram negative bacterium has been reported from NICUs around the world. [49, 50] Table 5, illustrates the percentage range

of sensitivity of four Bacteria in these five different studies.



Antimicrobial tested in these bacteria	Muhammas Aqeel khan et al[22]%	D.Mohmmed, O.S El Seifi et al %[16]	Afif Ahmed et al %[15]	Shrestha S et al %[19]	Sally AF El-sahrigy et al %[17]
Ampicillin	7-22	0-50	0	12-23	-
Amikacin	66-80	14-100	100	11-92	77-100
Cefotaxime	5-66	0	93-100	0-67	20-100
Vancomycin	83-100	0-45	-	100	-
Ciprofloxacin	55-88	0-50	-	10-80	-
Meropenem	91-97	-	100	-	-
Cetazidime	50-83	-	-	-	-
Cefepime	71-82	-	93-100	-	-
Imepenem	-	42-100	-	89-100	80-100
Aztreonam	-	0-25	-	0	-
Gentamycin	-	41-60	93-100	0-85	-
Penicillin	-	0-50	-	-	-
Amox/cv	-	50-100	-	-	-
Pipira/TZ	-	-	87-100	-	-

Conclusion

Neonatal sepsis and VAP is a most common and second most common NIs among the neonates. Prematurity, low birth-weight and Prolonged MV are the major reason, along with peripheral and central catheterization, Crowded NICU and Immature immune system of newborn. Frequent surveillance and antimicrobial susceptibility test could provide a better control over NIs and Multidrug resistance bacteria. Therefore good weaning protocol, proper patients care and less invasive investigation procedure can bring down the rate of NIs and mortality in this fragile age group. My aim of this review was to draw an attention over the modifiable factors and strategy to control the progression NIs and antimicrobial resistance.

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