Nosocomial Pneumonia in a Pediatric Intensive Care Unit

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Background: *Nosocomial pneumonia (NP) is the second most common hospital acquired infection. Understanding the pattern of occurrence, risk factors and etiological agents of NP in a PICU, is essential for developing effective infection control measures. This prospective observational study was conducted in a PICU of a tertiary care teaching hospital, to determine the incidence, etiology and risk factors for NP.* ***Materials and Methods:*** *Patients admitted to the PICU, over a period of 1 year who had endotracheal (ET) intubation, were enrolled consecutively into the study. Demographic details were recorded at the time of inclusion. Diagnosis of NP was based on CDC criteria (1988).Semiquantiative assay of endotracheal aspirate (ETA) with a colony count of > 10^5 cfu/mL was taken as evidence of infection. Colonisation was defined as isolation of organism with < 10^5 cfu/mL. Age, nutritional status, number and duration of intubations, duration of mechanical ventilation, sedation, nasogastric feeding were the risk factors studied for development of NP. Intubation attempts of more than one were defined as reintubation. Risk factors found significant on univariate analysis, were subjected to multiple regression analysis to determine the most important predictors of NP.* ***Results:*** *The study group comprised of 72 children with a median age of 3.7 years and boys: girls ratio of 1.9:1.Twenty two of 72 (30.5%) developed NP; the predominant isolates from ETA were Acinetobacter anitratus*(12)*, Pseudomonas aeruginosa* (5)*, Klebsiella sp*(3) *and Staphylococcus aureus and E.coli*(1) *each. Additionally 18(39%) had evidence of ET colonization, with Acinetobacter sp being the commonest 9(50%). Re-intubation, prolonged duration of intubation and mechanical ventilation were the significant risk factors on univariate analysis for development of NP.On multiple regression analysis, reintubation was the only independent risk factor for NP(OR 0.72, 95%CI 0.55-0.94).Overall mortality was 21%(15/72);7(47%)of these deaths were secondary to NP.* ***Conclusions:*** *NP developed in nearly one third of the intubated patients; Gram negative organisms were the predominant etiological agents and associated with high mortality. Re-intubation, prolonged duration of intubation and mechanical ventilation were the significant risk factors on univariate analysis for development of NP. On multiple regression analysis, reintubation was the only independent risk factor for NP*

Key words*: Endotracheal aspirate, Nosocomial pneumonia, Reintubation.*

NOSOCOMIAL pneumonia (NP) is the second most common hospital acquired infection, its incidence ranging from 7% to 14.6 %(1,2). Intubated patients with or without mechanical ventilation are the strongest risk factor for NP (3-5), others being prolonged hospital stay, underlying illness, impaired consciousness, bronchoscopy, neuro muscular disease and aspiration of gastric contents(4).

Compared to the exhaustive data on adult nosocomial infections (NI)(6) and NP, there are very few studies on pediatric NP especially from a developing country(7). Understanding the pattern of occurrence, risk factors and etiologic agents of NP in a pediatric intensive care unit (PICU) is an essential prerequisite for developing effective infection control measures and for assessing the impact of these control measures. With this in mind, we decided to conduct this study to determine the incidence, etiological agents, risk factors and outcome for nosocomial pneumonia in our PICU.

Subjects and Methods

This was a prospective study conducted in the PICU of multispecialty urban teaching and referral hospital of north India, over a period of one year from January to December 2003 after seeking approval from the Institute's Ethics Committee. PICU was an 8-bedded unit at that time with an annual admission average of 300-400 patients. It had a 24-hour

intensivist cover and was manned by 4 junior residents, 2 senior residents and 2 consultants. The nurse to patient ratio was 1:1 for ventilated and 1:2 for other patients. It was fully equipped for conventional mechanical ventilation and non-invasive and invasive continuous electronic monitoring of respiratory and hemodynamic status. Bedside *X*-ray, ultrasound and laboratory facilities were available round the clock.

All intubated patients admitted to PICU during the study period were enrolled into the study consecutively. Demographic details, admission diagnosis, indication for PICU admission, nutritional status, and PRISM scores were recorded for all at the time of inclusion. Infants <1 month, trauma and post surgical patients were excluded as they are not admitted in PICU.

Definition of NP

Pneumonia developing after 48 hours of PICU stay was taken as nosocomial when the following criteria modified from CDC definition(8) were met:

1. Clinical (either fever, leucocytosis or purulent ET secretions).
2. Radiological features.
3. Semi quantitative culture of the endotracheal aspirate (ETA) positive for microorganisms.

In an already diagnosed case of pneumonia, super infection was defined as recurrence of fever, leucocytosis and radiological worsening after initial clinical and radiological improvement, along with isolation of different microorganism from theETA.

The ETA was obtained for microbiological semiquantitative assay after hand washing with soap and water for two minutes and wearing sterile gloves. The intracath was introduced through the ET and advanced beyond the carina, to collect the lower respiratory tract secretions into a mucus trap. The collected sample was sent to the laboratory within one hour of collection. Sample collected at night was stored at 4ºC overnight and sent to the laboratory by 10:00 am next day morning. In the laboratory 0.001 mL of sample was directly inoculated on the blood agar, chocolate agar and Mc Conkey's agar. Following overnight incubation at 37ºC, the media were examined for any growth and subsequently at 24, 48, 72, 96 hours and 7 days. Infection was defined by a semi quantitative count of more than 100 cfu/ 0.001 mL, equivalent to 10^5 cfu/mL of ETA.The sensitivity pattern was studied by "modified stroke's DISC DIFFUSION METHOD". Isolation of microorganism with a CFU of <100/0.001 mL was defined as colonization.The tip of the ET was also sent for microbiological assay when the patients were extubated, as per clinical need.

Concomitant blood cultures were collected whenever there was a suspicion of NP. The site of sampling was cleaned with povidone iodine and spirit and allowed to dry for two minutes. Two ml of blood was drawn and added to bile broth and trypticase soya broth (1 mL in each bottle). After overnight incubation at 37ºC it was inoculated on blood agar and Mc Conkey's agar.

Portable chest *X*-rays (AP view) were obtained in all patients with clinical suspicion of nosocomial pneumonia. The reporting of the *X*-rays was done by one consultant radiologist of our centre to minimize the interobserver bias.

Data of intubated patients with NP were compared with those without NP with respect to demographic details, nutritional status (based on criteria of weight, expressed as percentage of expected weight for age), frequency and duration of intubation, duration of mechanical ventilation, sedation, stress ulcer prophylaxis and neuromuscular paralysis to identify the risk factors for development of pneumonia.

The patients were followed up till recovery/ discharge/death .Outcome was measured as length of PICU stay and survival or death.

Statistical Analysis

Data are presented as mean ± SD. Numerical variables were compared using the Student's 't' test for parametric data and Mann Whitney U test for non parametric data. Categorical data were compared using the Chi-Square test. Variables significant on univariate analysis were subjected to multiple logistic regression to identify the significant risk factors for development of nosocomial pneumonia. The results were analyzed using the computerized statistical program (SPSS version 10.0)

Results

Of the total of 342 admissions during the study period, 72 children fulfilled the inclusion criteria and formed the study subjects. The mean age of the study population was 4.6 ± 3.6 [range 0.25-12 years] with boys: girl's ratio of 1.9:1. The salient baseline characteristics of the study subjects are as shown in *Table I.* Thirty-two of the total intubated patients were initially suspected to have NP based on clinical criteria and new or progressive infiltrates on chest *X*-ray. However, on the basis of the semi quantitative ETA, only 22 of these were proved to be definitive pneumonia; the incidence being 30.5% (22 out of 72).

Etiological organisms

The causative organisms for NP in our patients along with their antibiotic sensitivity pattern are as shown in *Table II.* All the isolates except one were Gram negative, with *Acinetobacter anitratus* being the most predominant isolate in 12 (54.5%), followed by *Pseudomonas aeroginousa* in 5 (22.7%), *Klebsiella* in 3 (13.6%) and *E.coli* in 1 (4.5%). *Staphylococcus aureus* (MRSA) was seen in one patient only. Our findings on antibiotic susceptibility revealed that sensitivity to third generation cephalosporins and quinolones was decreased for *Acinetobacter anitratus, Pseudomonas aeroginousa* and *Klebsiella.*

Eighteen (39%) of the intubated patients had evidence of endotracheal tube colonization; 9 (50%) of these were secondary to *Acinetobacter* species, 4 (22.2%) *MSSA*, 2 (11.1%) *Klebsiella* and one each due to *Pseudomonas, E. coli* and *Enterobacter* species.

Nine (40.9%) patients with NP also had concomitant blood culture positivity with *Klebsiella* being the commonest in 3 (33.3%) patients followed by *Acinetobacter* and *Enterobacter* in 2 each (22.2%) and *MRSA* and *E. coli* in 1 each (11.1%). Only 3 patients had same organisms on both ETA and blood culture (2 *Acinetobacter* and 1 *Klebsiella*) while the rest had different organisms isolated from ETA and blood culture.

Risk Factors for NP

Intubated patients who developed NP were compared with those who did not, with respect to age, sex, PRISM scores, nutritional status, duration and frequency of intubation (reintubation) and duration of mechanical ventilation, nasogastric feeding ,sedation and use of H_2 blockers to identify risk factors for NP *Table III.*

Univariate analysis revealed that patients with NP had a significantly higher duration of mechanical ventilation and higher proportion and frequency of reintubation. There were, however, no statistically

TABLE I– *Baseline Characteristics of Study Patients*

	Total N = 72	Pneumonia N = 22	No pneumonia N = 50	P value
Age (years) mean + SD	4.6 + 3.6	4.5 + 3.5	4.7 + 3.6	0.79
Sex (M:F)	3:1	2.6:1	3.2:1	0.76
PRISM III mean + SD	16.6+10.6	14.4+8.3	17.6+11.4	0.11
Nutritional status				
No PEM	52	15	37	0.84
Grade 1	15	5	10	0.79
Grade 3	5	2	3	0.63
Indication for PICU admission				
Resp	37	16	21	0.04*
CVS	18	4	14	0.37
CNS	17	2	15	0.05*

*P <0.05byChi-square test.

TABLE II–*Organisms Isolated In ETA and Their Sensitivity Pattern*

	Acinetobacter (n=12)	*Pseudomonas* (n=5)	*Klebsiella* (n=3)	*Staphyloccoccus* (n=1)	*E.coli* (n=1)
Amoxycillin	1/12	0/5	0/3	0/1	0/1
Erythromycin	0/12	0/5	0/3	0/1	0/1
Gentamycin	2/12	1/5	3/3	1/1	1/1
Amikacin	3/12	1/5	0/3	0/1	1/1
Isepamycin	1/12	0/5	0/3	0/1	1/1
Cefotaxime	2/12	2/5	0/3	0/1	0/1
Cefoperazone	1/12	3/5	0/3	0/1	0/1
Ceftazidime	2/12	2/5	0/3	0/1	0/1
Ciprofloxacin	1/12	2/5	0/3	0/1	0/1
Piperacillin	5/12	4/5	3/3	1/1	0/1
Ticarcillin	1/12	1/5	0/3	0/1	0/1
Clindamycin	0/12	0/5	0/3	1/1	0/1
Vancomycin	0/12	0/5	0/3	1/1	0/1
Imipenem	1/12	0/5	2/3	0/1	0/1

Note: Susceptibility of each organism to each antibiotic is indicated in X/Y where, X = number of isolates susceptible to the particular antibiotic and Y = Total number of isolates for which susceptibility was studied.

TABLE III–*Risk Factors for Nosocomial Pneumonia (Univariate analysis)*

Variables	Pneumonia (n = 22)	No pneumonia (n = 50)	'p' value
Age (years) mean ± SD	4.5 + 3.5	4.7 + 3.6	NS
Age ≤1 year (no. of patients)	5	7	NS
PEM (no. of patients)	7	13	NS
PRISM score (mean ± SD)	14.4 ± 8.3	17.6 ± 11.4	NS
Duration of intubation (days) mean ± SD	16.4 ± 13.9	12.1 ± 6.3	*
Duration of mechanical ventilation (days) mean ± SD	16.3 ±15.7	9.4 ± 5.4	*
Reintubation (number of times)	2.7 ± 3.2	0.74 ± 1.6	*
Nasogastric feeding (days) mean ± SD	5.09 ± 5.06	3.8 ± 6.6	NS
Duration of stress ulcer prophylaxis (days) mean ± SD	6.8 ± 5.7	4.0 ± 3.9	NS
Duration of neuromuscular paralysis (days) mean ± SD	5.0±5.1	4.9 ± 5.6	NS

*p <0.05 by Student's 't' test.

TABLE IV–*Outcome of Patients with Nosocomial Pneumonia*

Outcome	Pneumonia (n = 22)	Non-pneumonia (n = 50)	'p' value
Duration of hospital stay (days)	22	14	*
Median (range)	(6-90 days)	(5-63 days)	
Survived, n (%)	14(63.6)	42(84)	NS
Died , n (%)	7 (31.8)	8(16)	NS

* p<0.05 by Mann Whitney U test.

significant differences between the two groups with respect to age, sex, nutritional status, feeding and duration of sedation, paralysis and stress ulcer prophylaxis.

On subjecting the significant variables to multiple logistic regression, we found that reintubation was the only independent risk factor for development of NP (OR 0.72, 95% CI 0.55-0.94, p = 0.017).

Outcome

The outcome of patients in terms of length of stay, survival and death are depicted in *Table IV*. The median duration of PICU stay was significantly longer in patients with NP as compared to those without [22 days Vs 14 days; p = 0.021].

The percentage mortality in the group with NP and no NP was 31.8% and 16% respectively. However this difference was not statistically significant. All the deaths in the group with NP were secondary to Gram negative infections with *Pseudomonas* contributing to 4 (57.1%) deaths followed by *Klebsiella, E. coli* and *Acinitobacter* in one patient each.

Discussion

The incidence of NP in our study was 30.5%, similar to the trend reported previously (7,9). Most studies on nosocomial pneumonia in intensive care units have been carried out in the developed countries, which reveals an incidence ranging from 7 to more than 40%.(10-13). Most studies on NP have used objective diagnostic criteria based on the combination of quantitative culture samples obtained with fiberoptic bronchoscopy using the protected specimen brush (PSB) or the bronchoalveolar lavage (BAL)(5,14-16). Both these methods have been shown in literature to have a specificity and sensitivity of greater than 95% in the diagnosis of NP(17,18). The quantitative bacteriologic methods have increased the reliability of sputum specimens for the diagnosis of lower respiratory tract infections when compared with conventional qualitative cultures because of more careful collection of sputum and the method of dilution which eliminates contaminating oropharyngeal secretions(13). However, Marquette, *et al.* (1993) in their study comparing ETA aspirate cultures with PSB found that at the cut off value of 10^6 cfu/mL, the former technique could be used as a reliable alternative to PSB(19). These findings compare favorably with our study where we had used the semiquantitative cultures of the ETA aspirates at a cut off point of 10^5 cfu/mL. Since the technique of PSB and BAL are not readily available to us in our ICU, the ET aspirate quantitative technique can be used as an alternative diagnostic tool for NP. It may be helpful in differentiating infection from colonisation and can thus reduce the overuse of antibiotics in PICU. Moreover, it is a simple, inexpensive and non-invasive technique and suited to our set up where cost becomes a major limiting factor.

We observed Gram-negative predominance as causative factor for NP in our study,a finding similar to that reported previously(7,20). Though it has been observed by some authors that the community acquired organisms such as S*treptococcus pneumoniae, H. influenzae* and *MSSA* were frequent cause of early onset NP (developing within 5 days of hospitalization) as against the resistant *Enterobacter, Pseudomonas* and *Acinetobacter* species encountered in late onset group (*i.e.*, after 5 days of hospitalization)(21), Ibrahim, *et al.* in their study reported that this distinction did not hold true for an ICU setting and the organisms for both early and late NP were similar(20). Though we had not divided our NP into early and late infections, majority of them occurred within 3-10 days of PICU stay and the organisms encountered were mostly resistant *Acinetobacter*, *Klebsiella*, *Pseudomonas* and *Enterobacter* species.

The microbial flora associated with NP reflects the common organisms present in the gut, oropharynx and environment *i.e.*, Gram-negative(22). Colonization in ICU patients has been recognized as an important source for Gram-negative infections(23). Frequent use of broad spectrum empiric antimicrobials in an ICU setting further enhances the risk of colonization with resistant organisms(22). This was shown in a study where the incidence of NP was 23% in colonised as against 3% in non-colonised patients(24). Our findings revealed that of the 18 patients having ET colonization, 14 were secondary to Gram-negative pathogens

What this Study Adds

- Nosocomial Pneumonia in intubated patients was a significant problem encountered in our PICU.
- The predominant pathogens responsible for this infection were Gram negative with Acinetobacter being the commonest.
- Reintubation was the most significant risk factor identified for development of NP.
- Mortality was high; especially in patients with NP due to Pseudomonas species.

with Acinetobacter being the commonest (50%). Hence, the increased incidence of Gram-negative NP in our study population is a reflection of the pattern of colonization seen in our intubated patients.

Eleven (34.4%) of patients with NP in our study were less than one year. Though this number was not significantly different from the non-pneumonia group, it is well known that extremes of age are a high risk because of relative immaturity of the immunological system(1). Also the use of uncuffed ET enhances the risk of aspiration of upper GIT flora thus contributing to the development of NP(1).Other points borne out by the analysis of risk factors were that prolonged intubation and mechanical ventilation and reintubations were associated with a significantly high risk for NP.

Repeated intubations carried the maximum risk for development of NP on multivariate analysis, a finding similar to the one reported previously wherein 19 (47%) of the cases developed pneumonia following reintubation compared to 4 (10%) of the controls(9). The increased incidence of NP following reintubation was probably related to an enhanced risk of aspiration of the colonised oropharyngeal contents during each episode of intubation. The glottic dysfunction associated with prolonged intubation further aggravates this.Most patients in our study group were reintubated for falling SpO_2, accidental extubations and rarely as an elective procedure. Our findings of increased risk of NP with reintubation imply that this procedure should not be included as a routine protocol in all mechanically ventilated patients. Also, it is safer to intubate patients (who have been extubated for some reason) as soon as possible to minimize the risk of aspiration during the interval between extubation and reintubation.

The relationship between prolonged duration of endotracheal intubation and ventilation and the development of NP has been examined by several authors(15,25-27).Our data suggests a similar trend for increasing lengths of endotracheal intubation and an interestingly high rate of acquisition of NP in the first 10 days of intubation.Though significant on univariate analysis both prolonged intubation and ventilation failed to show independent effect on multivariate analysis.

The overall mortality of NP in our study was 60% and is comparable to the mortality rates of 30-70% reported in several studies(7,14,16). A strong association between mortality rate and the infecting organism has been well documented. It has been shown that the attributable mortality in pneumonia due to Pseudomonas and Acinetobacter species exceeded 40%(10). *Pseudomonas*, *Enterobacter*, other Gram-negative bacilli and *Staphylococcus aureus* have been characterized as "high risk" since they are associated with high mortality(4). Our findings of organism specific mortality are in concordance with the previous study; with the highest mortality seen in *Pseudomonas* infection. NP not only increases incidence of mortality but also prolongs the length of ICU stay; thereby enhancing the cost of hospitalization(16). Just like organism specific mortality, increased length of ICU stay specially so with NP secondary to *Pseudomonas* and *Acinetobacter* species has also been observed(10). Our patients with NP had a significantly longer duration of ICU stay as compared to others. In a developing country like ours with limited resources this prolonged hospitalization imposes a significant economic burden.

Conclusions

NP in intubated patients was a significant problem encountered in our PICU. The predominant

pathogens responsible for this infection were resistant Gram negatives with *Acinetobacter* being the commonest. Reintubation was the most significant risk factor identified for development of NP. Mortality was high; especially in patients with NP due to *Pseudomonas* species. The knowledge of common organisms and their antibiotic susceptibility is important for institution of appropriate antimicrobial therapy thus restricting the use of empiric broad spectrum antibiotics which predisposes to colonization.

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