Brief Report

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Nosocomial pneumonia: Search for an empiric and effective antibiotic regimen in high burden tertiary care centre

Nitin Gupta[1], Manish Soneja[1,*], Yogiraj Ray[1], Monalisa Sahu[1], Kutty Sharada Vinod[1], Arti Kapil[2], Ashutosh Biswas[1], Naveet Wig[1], Rita Sood[1]

[1] *Department of Medicine, All India Institute of Medical Sciences, New Delhi, India;*
[2] *Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India.*

Summary **The clinical practice guidelines on nosocomial pneumonia recommends an empirical regimen that would work in 95% of the patients based on the local antibiogram. The aim of the study was development of an antibiogram for guiding empiric therapy in settings with high prevalence of multi-drug resistant organisms. A retrospective review of electronic health records (e-hospital portal) was done to analyze all respiratory isolates from patients admitted in medical wards and intensive care unit between May 2016 and May 2017. The samples included brocho-alveolar lavage (BAL), mini broncho-alveolar lavage (mini-BAL) and endotracheal aspirate. The sensitivity pattern (combined and individual) of all bacterial isolates were analysed for commonly used antibiotics and their combinations. Out of the 269 isolates, the most common organisms were *Pseudomonas aeruginosa* (125, 46%), *Acinetobacter baumanni* (74, 27%) and *Klebsiella pneumoniae* (50, 19%). Cefoperazone-sulbactam (43%) had the best sensitivity pattern overall. Cefoperazone-sulbactam plus amikacin (56%) was the combination with the best combined sensitivity overall. There is a high prevalence of resistance in the commonly implicated organisms to the available antibiotics. There is an urgent need for implementation of effective anti-microbial stewardship programmes and development of newer antimicrobials.**

Keywords: Hospital acquired pneumonia, ventilator associated pneumonia, polymyxins

1. Introduction

Ventilator-associated pneumonia (VAP) is defined as a pneumonia that develops at least after 48 hours of mechanical ventilation in an intubated patient (*1*). Hospital acquired pneumonia (HAP) develops only after 48 hours of admission in a non-intubated patient (*2*). The clinical practice guidelines on hospital acquired and ventilator associated pneumonia (VAP) by Infectious Disease Society of America (IDSA) recommends generation of local antibiograms to guide the optimal choice of empiric antibiotics (*3*). The regimen should be chosen in such a way that it should work in more than 95% of the patients (*3*). A single anti-pseudomonal that covers methicillin sensitive *Staphyloccus aureus* (MSSA) should be chosen in the empiric regimen. In patients with risk factors for multi-drug resistant organisms (MDR), two anti-pseudomonals of different classes should be used. A methicillin resistant *Stapylococcus aureus* (MRSA) coverage should be added when the patient has received prior antibiotics in the last 90 days or if > 20% of *S. aureus* isolates are methicillin resistant (*3*). The anti-pseudomonals that are used in empiric therapy include betalactams like piperacillin tazobactam (P/T), cefoperazone sulbactam (C/S) and carbapenems. The second anti-pseudomonal that is usually added is either a fluoroquinolone (FQ) or an aminoglycoside (AG). The problem in Indian settings is high prevalence of resistance limiting the number of antibiotics available for clinical use (*4,5*). The aim of the study was to, therefore, generate a local antibiogram for nosocomial

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*Address correspondence to:
Dr. Manish Soneja, Department of Medicine, 3rd floor, Teaching block, All India Institute of Medical Sciences, New Delhi, India.
E-mail: manishsoneja@gmail.com

pneumonia and choose an empiric regimen that would meet the above mentioned requirements.

2. Materials

A retrospective review of electronic health records (e-hospital portal) was done to analyze all the bacterial isolates from brocho-alveolar lavage (BAL), mini broncho-alveolar lavage (mini-BAL) and endotracheal aspirates. These were routine diagnostic samples collected from patients with suspected nosocomial pneumonia admitted in medicine wards and the medicine intensive care unit between May 2016 and May 2017. Non-duplicative significant isolates from each patient was included in the analysis. The samples were processed on a blood agar and a Mac Conkey agar plate. After 24 hours of incubation, they were only processed further if the colony count was > 10^5 CFU/mL for endotracheal aspirate and > 10^3 for bronch-alveolar lavage samples. The microbiologically significant isolates were further identified using conventional biochemicals. The antibiotic susceptibility was done using the Kirby Bauer disc diffusion method on a Muller Huenton agar. The isolates were deemed sensitive and resistant based on the Clinical and Laboratory Standards Institute (CLSI) guidelines, 2016 (*6*). Following antibiotics were tested- piperacillin-tazobactam, amikacin, cefoperazone/sulbactam, ciprofloxacin, meropenem, imipenem, amoxicillin-clavulanic acid, cefotaxime and ceftazidime. The results of sensitivity were analysed using the WHONET software (*www.whonet.org/software.html*). The combined empiric sensitivity of all gram-negative organisms was also analysed. The sensitivity of commonly used combinations *i.e*. betalactams and a FQ or an AG were analysed. Sensitivity to either of the antibiotic in the combination was considered as sensitive for the combination. The sensitivity pattern of different antibiotics and combinations were analysed individually for isolates of *Acinetobacter baumanni*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

The frequency of sensitive and resistant strains was calculated as percentages with 95% confidence interval using the WHONET software. This was a retrospective review of electronic records and all care was taken to maintain the confidentiality of the patient details.

3. Results and Discussion

Out of the 269 isolates (Wards-155, ICU-114), the most common organism was *Pseudomonas aeruginosa* (125, 46%) followed by *Acinetobacter baumanni* (74, 27%), *Klebsiella pneumoniae* (50, 19%), *Escherichia coli* (10, 4%), *Enterobacter spp*. (5, 2%), *Burkholderia cepacia* (3, 1%) and *Staphylococcus aureus* (2, 1%). Cefoperazone-sulbactam (43%) was the antibiotic with the best overall sensitivity (Table 1). The antibiotic combination with the best sensitivity overall was found to be cefoperazone-sulbactam plus amikacin (56%) (Table 1). The antibiotic (individual) and antibiotic combination with the best sensitivity for *Acinetobacter baumanni* were cefoperazone sulbactam (50%) and cefoperazone sulbactam plus ciprofloxacin (54%) respectively (Table 2). The best sensitivity for *Klebsiella pneumoniae* was seen with imipenem (44%) while the best combination was imipenem plus amikacin (50%) (Table 2). The best sensitivity for *Pseudomonas aeruginosa* was seen with amikacin (59%) followed by meropenem (51%) while the best combination was meropenem plus amikacin (72%) (Table 2).

Table 1. Sensitivity pattern of all isolates of nosocomial pneumonia

Antibiotic name	%R	%S	%R, 95% CI
Piperacillin/Tazobactam	65.2	34.8	59.1 - 70.9
Amikacin	64	36	57.9 - 69.7
Cefoperazone/Sulbactam	57.2	42.8	51.0 - 63.2
Ciprofloxacin	74.6	25.4	68.8 - 79.6
Meropenem	64.8	35.2	58.7 - 70.5
Imipenem	60.6	39.4	54.4 - 66.5
Amoxicillin/Clavulanic acid	97.7	2.3	94.8 - 99.1
Cefotaxime	96.2	3.8	92.9 - 98.1
Ceftazidime	70.1	29.9	64.1 - 75.5
Cefoperazone/Sulbactam + Amikacin	43.6	56.4	37.6 - 49.8
Cefoperazone/Sulbactam + Ciprofloxacin	51.5	48.5	45.3 - 57.6
Imepenem + Ciprofloxacin	49.6	50.4	43.4 - 55.8
Imipenem + Amikacin	46.6	53.4	40.5 - 52.8
Meropenem + Ciprofloxacin	62.5	37.5	56.3 - 68.3
Meropenem + Amikacin	52.7	47.3	46.5 - 58.8
Piperacillin/Tazobactam + Amikacin	51.1	48.9	44.9 - 57.3
Piperacillin/Tazobactam + Ciprofloxacin	61	39	54.8 - 66.9

%R, percentage of resistant isolates. %S, percentage of sensitive isolates. CI, confidence interval.

The epidemiology of Indian critical care settings are different compared to western settings where gram positive organisms are the major concern (*7*). In a study by Gupta *et al*., it was found that gram negative organisms were more frequently associated with VAP while *Staphylococcus aureus* was associated with VAP in only 1.5% of cases (*8*). The most common organisms were *Acinetobacter spp*. followed by *Pseudomonas spp*. and *Escherichia coli* (*8*). In our study, almost all isolates were gram negative organisms with the commonest being *Pseudomanas aeruginosa* and *Acinetobacter baumanni*. There is an increasing trend of resistance in most isolates from ICU. In a recent study on VAP by Chaudhury *et al*., carbapenem resistance in non-fermenters was found to be as high as 33% (*4*). In a study done by Sharan *et al*., meropenem resistance in non-fermenters isolated from hospital acquired infections was found to be as high as 55% (*5*). The resistance in this study was higher compared to other Indian studies as

Table 2. Proportion of the resistant isolates for the commonest organisms

Antibiotic name	Aba	95% CI	Kp	95% CI	Pae	95% CI
Piperacillin/Tazobactam	79.7	68.4 - 87.8	74	59.4 - 84.9	52	42.9 - 61.0
Amikacin	91.9	82.6 - 96.7	82	68.1 - 91.0	40.8	32.2 - 50.0
Meropenem + Amikacin	86.5	76.1 - 93.0	70	55.2 - 81.7	28	20.5 - 36.9
Amoxicillin/Clavulanic acid	97.3	89.7 - 99.5	94	82.5 - 98.4	100	96.3 - 100
Cefotaxime	94.6	86.0 - 98.3	96	85.1 - 99.3	100	96.3 - 100
Ceftazidime	91.9	82.6 - 96.7	86	72.6 - 93.7	50.4	41.4 - 59.4
Cefoperazone/Sulbactam	50	38.3 - 61.7	74	59.4 - 84.9	54.4	45.3 - 63.3
Ciprofloxacin	91.9	82.6 - 96.7	86	72.6 - 93.7	57.6	48.4 - 66.3
Meropenem	89.2	79.3 - 94.9	74	59.4 - 84.9	48.8	39.8 - 57.9
Imipenem	79.7	68.4 - 87.8	56	41.3 - 69.7	53.6	44.5 - 62.5
Piperacillin/Tazobactam + Amikacin	75.7	64.1 - 84.6	70	55.2 - 81.7	29.6	21.9 - 38.5
Piperacillin/Tazobactam + Ciprofloxacin	77	65.5 - 85.7	74	59.4 - 84.9	45.6	36.7 - 54.7
Cefoperazone/Sulbactam + Amikacin	47.3	35.7 - 59.2	70	55.2 - 81.7	31.2	23.4 - 40.2
Cefoperazone/Sulbactam + Ciprofloxacin	45.9	34.4 - 57.8	74	59.4 - 84.9	46.4	37.5 - 55.5
Imepenem + Ciprofloxacin	75.7	64.1 - 84.6	54	39.5 - 67.9	34.4	26.3 - 43.5
Imipenem + Amikacin	77	65.5 - 85.7	50	35.7 - 64.3	28.8	21.2 - 37.7
Meropenem + Ciprofloxacin	87.8	77.6 - 93.9	74	59.4 - 84.9	44.8	36.0 - 53.9

Aba, *Acinetobacter baumanni.* Kp, *Klebsiella pneumoniae,* Pae, *Pseudomonas aeruginosa*.

the study was conducted in an apex referral centre which receives critically ill with history of receipt of multiple antibiotics. The resistance to carbapenems in our study was as high as 60%. The single antibiotic with the best activity against the organisms implicated for nosocomial pneumonia was cefoperazone-sulbactam. But the meagre 43% sensitivity of CS is no match to the high standards of 95% set by the clinical practice guidelines. The sensitivity of combination of antibiotics from two different classes (betalactam plus FQ/AG) was also a mere 56%. Therefore, adding a FQ or AG to betalactam gave an advantage of only 13% in our study. It has been noticed in previous studies, that indiscriminate use of FQs or AGs for other indications in tuberculosis endemic areas have led to high prevalence of FQ/AG resistant tuberculosis (*9*). In a country like India, where there is widespread fluoroquinolone and aminoglycoside resistance in tuberculosis, a risk-benefit analysis should be done before empirically prescribing FQ or AG as a part of combination therapy. In a study reported from Mumbai, fluoroquinolone and aminoglycoside resistance in tuberculosis increased from 39% and 4% respectively pre-2010 to 94% and 19% respectively post 2010 (*10*).

In a recent study, it was found that early effective empirical antibiotic therapy was associated with better outcomes in patients with carbapenem resistant *Acinetobacter baumanni* pneumonia (*11*). In a setting with high prevalence of resistance to betalactams, choosing an empiric regimen that will prove effective becomes difficult. Polymyxin resistance is reported from our country, mostly in form of case reports (*12*). The available literature suggests polymyxins as the most effective drug in these isolates. Colistin sensitivity is not done routinely in our setting as it requires micro-broth dilution testing for sensitivity reporting (*13*). Guidelines suggest avoiding polymyxins if alternative agents with adequate gram negative activity are available. With increasing resistance to betalactams, the clinicians in our setting are left with a difficult decision to ensure early appropriate antibiotic coverage and avoid superfluous treatment at the same time.

4. Conclusion

The commonly implicated organisms like *Pseudomonas* spp. and *Acinetobacter* spp. have high resistance to beta-lactam/beta-lactam inhibitor combinations and carbapenems. The sensitivity of empiric antibiotics is low in our settings. Urgent measures like Antimicrobial stewardship programmes and development of new drugs are needed to address the issue and save the polymyxins from becoming an empiric drug of choice.

Limitation

This was only a review of retrospective isolates including possible colonisers and contaminants. Further studies with clinically significant isolates are required to understand the complexity of the problem.

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