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ANTIMICROBIAL RESISTANCE PATTERN OF AEROBIC BACTERIAL ISOLATES OF LOWER RESPIRATORY TRACT INFECTIONS IN ICU PATIENTS OF A TERTIARY CARE HOSPITAL

Microbiology

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ABSTRACT

Background: Ventilator associated pneumonia is one of the common cause of morbidity and mortality in ICU. Microorganism profile and their resistance pattern varies from place to place .To prevent the spread of AMR formulation of rational empirical therapy followed by de-escalation of the antibiotic local microbiological profile and resistance pattern is essential

Aims & Objective : The aim of the study was to assess the incidence of LRTI in ICU, their microbiological profile with reference to resistance pattern and formulate initial emperical antibiotic regimen for patient with suspected VAE in ICU.

Materials And Methods: This prospective study was carried out over the period of 1 year (April 2015 to March 2016) in department of Microbiology of R.G.Kar Medical College,Kolkata on 60 samples collected from patients admitted in ICU and requiring mechanical ventilation for more than 48 hours and suspected of having LRTI . Semi quantative culture of Deep tracheal aspirate (DTA)was processed . Resistance pattern was further confirmed by double disk synergy test and Modified Hodge test.

Results: In the present study total 60 respiratory samples in the form tracheal aspirate -50(83%) showed growth and 10 (17%) showed no growth .14 (28%)sample yielded growth of 2 organisms.. In the study 98% isolates were gram negative bacilli and Acinetobacter spp was the commonest. There was no gender preponderance in culture positive infection .Common co-morbidity includes Cerebrovascular accident, puerperal sepsis, trauma, diabetic coma, anaphylaxis and neurosurgery post operative complication. Duration of ventilationand hospital stay and history of previous antibiotic use emerged as significant risk factors in development of LRTI in ICU in the study.

Conclusion: LRTI occurs frequently in ICU and is associated with significant morbidity and mortality not only due to VAP but the underlying critical illness in the patients. Microbiological data should be used for formulating empirical antibiotic therapy and not be restricted only to diagnosis. The pitfall in using empiric antibiotics for suspicion of VAP is the potential for antibiotic overuse, emergence of resistance, unnecessary adverse effects and potential toxicity.

KEYWORDS

INTRODUCTION

Lower respiratory tract infections are some of the most common bacterial infections among patients admitted in intensive care units (ICUs) being associated with high mortality, ranging from 22% to 71%(1). Nosocomial pneumonia are inflammatory conditions of the lung parenchyma caused by an infectious agent, not present or incubating at the time of admission and developed after 48–72 h of admission to the hospital. Despite the advancements in antimicrobial regimes, VAP continues to be an important cause of morbidity and mortality. VAP requires a rapid diagnosis and initiation of appropriate antibiotic treatment, as there is adverse effect of inadequate antibiotic treatment on patients' prognosis and the emergence of multidrug-resistant (MDR) pathogens.(2)Ventilator-associated pneumonia (VAP) is common in the intensive care unit (ICU), affecting 8 to 20% of ICU patients and up to 27% of mechanically ventilated patients .(3) Quantitative analysis of TA(tracheal aspirate) has been recommended as a simple and useful procedure in the diagnosis of VAP and has the added advantages of being a noninvasive and more inexpensive technique.(4) Microbial aetiology of intensive care unit (ICU)-acquired pneumonia (ICUAP) determines antibiotic treatment and outcomes. (5) ATS/IDSA Guideline Committee members recognized that currently, many patients with HAP, VAP, or HCAP are infected with multidrug-resistant (MDR) bacterial pathogens that threaten the adequacy of initial empiric antibiotic therapy.(3)

OBJECTIVES

Present study was conducted among the patients developing signs and symptoms of lower respiratory tract infection (LRTI) after admission in the adult Critical Care Units (CCU) of R. G. Kar Medical College & Hospital.

Samples containing lower respiratory tract secretion namely deep tracheal secretion were collected and studied for bacteriological profile and their antibiogram .

1. To identify the bacteriological profile by microscopy and culture of respiratory secretion collected by a Deep Tracheal Aspiration(DTA).

3. To determine antimicrobial susceptibility and resistance pattern of the aerobic bacterial isolate

VAP to “ventilator associated events” (VAEs), conditions, and complications, for which worsening physiologic parameters, such as oxygenation, are key metrics.(7)

MATERIALS AND METHODS

The study was carried out in Department of Microbiology collaboration of R.G.Kar Medical College and Hospital- Department of Microbiology, Department of Critical Care Medicine after getting ethical committee clearance from April 2015 to March 2016.

Study Population

Patients developing clinical signs and symptoms of lower respiratory infection after admission in the adult CCUs of R.G.Kar Medical College and Hospital in the above period.

Study Variables:

Independent Variables

- Age
- Sex
- History of predisposing factor s like COPD, Bronchiectasis, exposure ventilator
- Previous antibiotic therapy
- Any co-morbid illness like DM, CKD, any Immunosuppression .

Dependant Variables

- Aerobic bacterial from lower respiratory secretions like Deep Tracheal Aspirate .
- Drug sensitivity and resistance pattern of aerobic bacteria

Inclusion Criteria

- CCU patients undergoing Broncho alveolar lavage and Deep Tracheal aspiration on suspicion of LRTI.

Exclusion Criteria

- Patients or relatives who do not give consent for the procedure .

Sample Size

The sample size (ss) for the study

$$ss = \frac{Z\alpha^2 * (p) * (100 - p)}{L^2} = 60$$

where Zα value =1.96 for 95% confidence level and p(proportion) taken as 97.3%.(8)

L(error) taken as 4

Methods Of Data Collection

A case record form (pre-tested, semi-structured) with informed consent will be used for data collection. Relevant history will be taken and important clinical finding will be noted. Sample will be collected and processed following standard protocol (as mentioned in Mackie & McCartney. (9)

Microbiological Methods

Deep Tracheal aspiarate(DTA) samples were also processed through semiquantitative method on blood agar,chocolate agar , MacConkey agar, nutrient agar and colony count of 10^4bacterial colonies per ml of BAL fluid and 10^5CFU/ mL for DTA were considered significant except for the sample collected from patient who was on previous antibiotic .Aerobic isolates were identified Gram stain, routine biochemical tests as per standard protocol(9).

ANTIBACTERIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility of isolates was tested by modified Kirby Bauer disk diffusion method as per the recommendations of Clinical and Laboratory Standards Institute (CLSI). Mueller—Hinton agar was used as media, it was inoculated with a suspension of organism equivalent to 0.5 McFarland turbidity standard & discs were applied. Inhibition zones were interpreted according to CLSI guidelines.(10)

RESULT AND ANALYSIS

The study was carried out in the Department of Microbiology in collaboration with the Department of Critical Care Unit,R.G. Kar Medical College and Hospital, Kolkata.

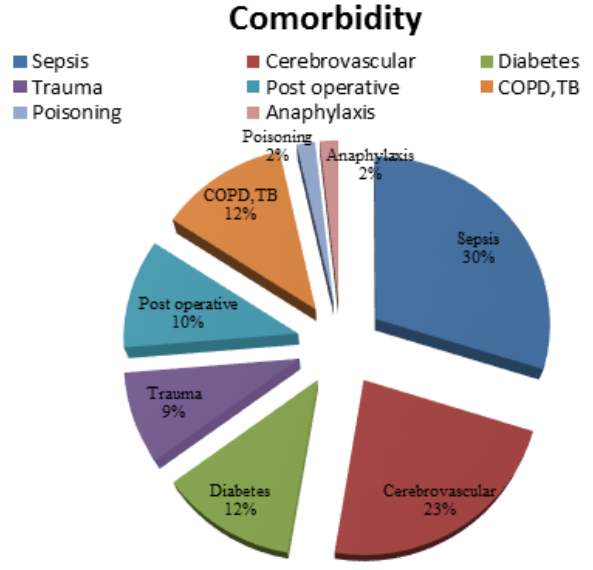
Total 60 respiratory samples from patients admitted in CCU were processed in the laboratory. Out of the total 60 samples from patients having sign and/ symptoms of infection, 50(83%) showed culture to be positive and 10(17%) samples showed no growth.

Table 1: Showing Age And Sex Wise Distribution Of Cases

Age	Total	Male	Female
<20 years	9	2	7
20-39 years	29	10	19
40-59 years	13	7	6
>60 years	9	6	3
Total	60	25	35

Chi square =5.12, df=3 ,p=0.163

There was no significant statistical correlation in gender.



The comorbidities most commonly associated with were generalized sepsis(n=17,30%) ,followed by Cerebrovascular disease(n=13.23%), Diabetes(n=7.12%),Trauma(n=5.9%).Trauma patients were mostly from Neurosurgery department requiring ventilaory support.

Risk Factors

Ventilator Use

Risk factors	Culture positive	Culture positive (%)	Culture negative	Culture negative (%)	Total
On Ventilator support	49		8		57
Not on ventilator support	1		2		13
	50		10		60

X^2=5.68,df=1,p=.017

Ventilatory support has statistically significant association with development of LRTI(VAE) in CCU.

Previous Antibiotic Use

	Culture positive(n)	%	Culture negative(n)	%
H/o previous antimicrobial	50	86.3%	8	13.7%
No h/o Previous antimicrobial	0	0%	2	100%

X^2=10.3 df=1 p=0.001

Association of culture positivity was significantly associated with previous use of Antimicrobial (p<0.0005)

Out of 50 culture positive samples 13 samples(26%) showed more than one bacterial isolate .Generalized sepsis was commonest(49%) associated co-morbidity in patients with polymicrobial infection.

Isolates

Acinetobacter (43%) was the commonest isolate recovered from respiratory secretion samples followed by Klebsiella(24%)and Pseudomonas(22%). Only Polymixin B showed 100 % sensitivity against all these isolates.

Resistance Pattern Of Gram Negative Bacilli

Organism	Polymixin B N(%)	Carbapenem N(%)	Pieracillin-Tazobactum N(%)	3rd generation Cephalosporin N(%)	Aminoglycoside N(%)	Quinolone N(%)
Acinetobacter(29)	0(0%)	22 (76%)	27 (93%)	29(100%)	28(97%)	28 (97%)
Klebsiella (16)	0(0%)	11 (65%)	13 (76%)	16(94%)	14(82%)	17 (100%)
Pseudomonas(15)	0(0%)	8(53%)	7(47%)	14(93%)	12(80%)	13 (86%)
Escherichia coli (3)	0(0%)	1(33%)	1(33%)	3(100%)	1(33%)	3 (100%)

Isolates of *Acinetobacter spp.* were highly resistant to Ciprofloxacin, Chloramphenicol, 3rd generation Cephalosporins with resistance rate being 100% each. Even Aminoglycoside , Doxycycline, Levofloxacin, showed high degree of resistance of 97% each. Cotrimoxazole and Carbapenems and Piperacillin-Tazobactum combination showed only 10%,24% and 7% sensitivity against the isolates respectively. Only Polymixin –B has more than 100 % sensitivity against Acinetobacter. (Diagram 1)

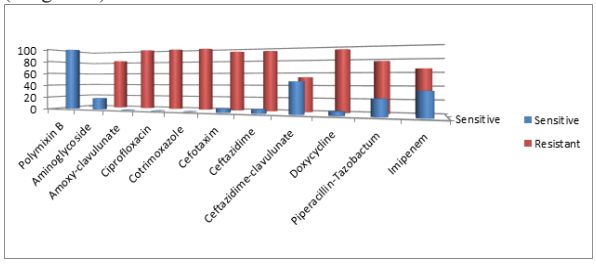


Diagram 1: Clustered cylinder showing sensitivity and resistant pattern of Acinetobacter

Klebsiella pneumoniae showed high degree of resistance to Aminoglycosides(81%). Levofloxacin, resistance rate being 94%, each.. Ciprofloxacin, Amoxycillin-clavulanate , 3rd generation Cephalosporins were practically of no use against these isolates with

100% resistance rate..Carbapenems like Imipenem was only 35% sensitive. Piperacillin-Tazobactum combination was 75% resistant.(Diagram 2)

Pseudomonas aeruginosa causing pneumonia in ICU showed high level resistance to Aminoglycoside, Meropenam and3rd generation Cephalosporin, with resistance rate being 80%,53%,86% respectively. All the isolates (100%) were resistant to Quinolones.

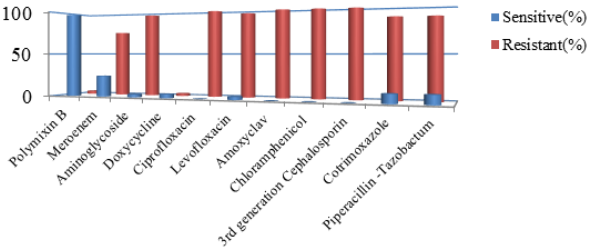


Diagram 2: Clustered Cylinder Showing Sensitivity And Resistant Pattern Of Klebsiella

Only one gram positive isolate was detected –Methicillin resistant *Staphylococcus aureus* isolated from respiratory samples, which(100%) was sensitive to Vancomycin and Linezolid whereas 100% resistant to Ciprofloxacin, Amoxycillin-clavulanate, Chloramphenicol and Cephalosporins.

Outcome

Mortality rate for VAP patients varies from 24-50% and can reach 76% in some specific settings.

In present study out of 50 patients 29 patients improved,21 patients(42%) succumbed to their illness .But out of 21, 17 patients were having any three comorbidities like Diabetes with metabolic abnormality ,generalized sepsis, neurological diseases.

DISCUSSION

ICU associated lower respiratory infection and antimicrobial resistance is considered a serious problem worldwide and it is associated with significant increase in morbidity, mortality and healthcare costs . (11)(12)The present study was undertaken to determine the bacterial profile and the pattern of drug sensitivity and resistance of the bacterial isolates from various samples from patients suspected of having lower respiratory infections after admission in the adult CCU of R.G.Kar Medical College & Hospital, a tertiary care centre in Kolkata. The rate of development of VAP in ICU of our set-up was 31% Out of 156 patients 48 developed VAP(30.7%).

Ventilator associated respiratory infections continue to be a frequent and fatal complication in critically ill patients with mortality ranging from 40% to 80%.(13)

Pneumonia is a frequent complication in patients admitted to the ICU. It is frequently polymicrobial with predominently multi drug resistant GNB, such as *Acinetobacter, Pseudomonas, Klebsiella, E.coli* .(14–16).In our study 98% isolates were gram negative bacilli and *Acinetobacter spp* was the commonest isolate which is similar to study by Rajasekhar et al(17) and Dey et al(18)and Ranjan et al.(19)

In the present study total 60 respiratory samples in the form of BAL fluid and deep tracheal secretions were collected and processed in our Microbiology laboratory. Out of the total 60samples 50(83%) showed growth and 10 (17%) showed no growth.

14 (28%)sample yielded growth of 2 organisms, so total 64 isolates were processed and their results were analysed.Ferrer, Miquel et al found about 14%polymicrobial isolates from respiratory samples of ICU pneumonia patient. (5) In Indian scenario Goel et al had found similar rate of polymicrobial infection in her study In a four year study from Kashmir.(20)

Age of the study subjects were evaluated as a factor for association with infection. The lowest age of patient was 8 years and highest age was 82 years in this study. Mean age was 37.33years which is similar to study by Gadani et al.(21)

In the present study subjects were distributed according to gender . 80% of males and 85.7% of females showed culture positive infection among whom the samples were collected. But this association was not statistically significant.

Disease profile of patients who developed ventilator associated pneumonia:

Out of 49 patients who developed VAP – 8 cases of cerebrovascular accident(16%),4 cases with previous respiratory disease(8%),2 cases of Guillen Barre syndrome,8 cases of pregnancy induced complication(16%)-puerperal sepsis or eclampsia ,7 post operative cases including 3 neurosurgery cases (14%) 6 cases diabetes with metabolic or other complication and 1 case each of poisoning,drug anaphylaxis and connective tissue disorder . Study by Dey et al also revealed similar disease profile.(18)This findings are also similar to study by Vora et al (2015) .(22)

Comorbidities associated with VAP

In our study comorbidities associated with development of pneumonia in ICU were mainly generalized Sepsis (30%).Other comorbidities include CNS diseases(23%) like Encephalopathy, Strokes, comatose patients ,Trauma (9%) like road traffic accident, neck trauma etc,post operative complication. Diabetes mellitus with or without metabolic complication and COPD,TB and other compromised respiratory function were the other two common comorbidity 12% each.Association of these comorbidities were similar to other studies by Dey et al(23)and Sujatha et al(24)

Risk Factors

Mechanical ventilator,duration of stay in Hospital,history of previous antibiotic use emerged as significant risk factors in development of LRTI in ICU in our study.

Previous use of antibiotic has also statistical significant association with development of LRTI caused multi drug resistant isolates in our study (p value<.001),prolonged antibiotic administration to ICU patients for primary infection is thought to favour selection and subsequent colonization with resistant pathogens responsible for super infection. A sentinel study of VAP in a French ICU noted that prior antimicrobial therapy markedly increased the rate of VAP caused by *P. aeruginosa* and *Acinetobacter* spp.(25)

Microbial Etiology

Acinetobacter spp.(43.75%) was found to be the most common bacteria causing pneumonia in our CCU set-up. Other organisms causing pneumonia were *Klebsiella pneumoniae* (25%),*Pseudomonas aeruginosa* (23.4%), *Escherichia coli* (4.6%) and *Staphylococcus aureus* (1.5%) The finding of Acinetobacter as commonest isolate is similar to other recent studies.

Saravu et al in 2013 (26) ,Dey et al(18) in 2007 and Manchanda V et al (27)in 2010 in Indian study and Meduri in 1991(28) in American study had similar kind of isolates.Ranjan N et al found (29) that the most common pathogens causing VAP were *Acinetobacter* spp. and *Pseudomonas aeruginosa*.

Most of the other studies had detected prevalence of gram negative isolates from respiratory samples collected in ICU similar to our study.Pseudomonas spp and Klebsiella were reported as commonest isolate in many Indian and International studies .(29–31)

Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to it.(32,33)

In the present study isolates of *Acinetobacter spp*. causing lower respiratory tract infections were highly resistant to Ciprofloxacin, 3rd generation Cephalosporins and even to Meropenem.

The only drug having a good in-vitro activity against *Acinetobacter* isolates were Polymyxin B with a sensitivity rate being 100%.

Klebsiella spp showed high level of resistance against Amoxycillin-clavulinicacid,Quinolones and cotrimoxazole being 100% each. The resistance of some GNB to aminoglycosides has been well-recognized in many hospitals. Klebsiella showed 81% resistance against Amikacin in our study. Carbapenems are frequently used as a last

choice in treating serious infections caused by GNB's. Our study Klebsiella showed 31.25% resistance towards carbapenem in accordance to observations made by other studies like Akhtar et al 2010(34)that showed 26.1% resistance and Fatima *et al2012(35).* that showed 24% resistance. This was in contrast to observations made by Gonlugur *et al*.(36) and Gladstone *et al*.2005(37) that comparatively showed lower rates of resistance toward carbapenems, whereas study done by Kucukates and Kocazeybek showed high sensitivity to carbapenem.(38)This finding suggests that carbapenem should be judiciously used in ventilated patients to prevent any further increase in resistance.

Pseudomonas in our study showed maximum resistance against 3rd generations Cepholosporins, Quinolones and Aminoglycoside 93%,86% and 80% respectively.Carbapenems like Imipenem and Meropenem and Piperacillin-Tazobactum combination were somewhat effective against Pseudomonas with sensitivity rate of 47% and 53% respectively. Only Polymixin B showed 100% sensitivity against all the isolates .Results was in accordance with other studies.(39,40).Another past study that evaluated the in vitro activity of colistin in isolates of Gram-negative bacteria using Clinical and Laboratory Standards Institute broth micro-dilution methods reported that all MDR *P.aeruginosa* isolates were susceptible to colistin. These data support a role for colistin in the treatment of infections caused by MDR *P. aeruginosa.(39)*

Until now, ceftazidime was held as the most effective antibiotic among the cephalosporin group for the treatment of pneumonia due to *P. aeruginosa* .

However, ceftazidime showed low activity against *Pseudomonas* in the present investigation similar to study done by Yayan et al 2015.(40) Colistin, or polymyxin E,/Polymixin B is an antibiotic originally isolated from *Bacillus colistinus* in 1950 (41,42) , with activity against many Gram-negative bacteria including *E coli*, *Klebsiella pneumoniae, P aeruginosa, Enterobacter* species and *Acinetobacter* species. There has been renewed interest in colistin despite concerns about its nephrotoxicity and neurotoxicity in light of the increasing numbers of infections caused by multi-drug-resistant (MDR) pathogens, particularly *P aeruginosa* and *Acinetobacter baumannii .(40,43,44)*

CONCLUSION

Acinetobacter spp has emerged as the most common bacteria causing serious infections in the ICUs. Most of the gram negative isolates specially *Acinetobacter spp* showed resistance to commonly prescribed antibiotics . Outcome in case LRTI in ICU depends not only on drug resistance pathogen but also on the presence comorbid conditions like sepsis ,CNS diseases and diabetes. Worrisome increase in the resistance to antibiotics with Polymixin-B as the only useful antimicrobial against most of the gram negative isolates from respiratory samples calls for urgent intervention to prevent their continued rise. It is recommended that hospital antibiotic policies be based on, and regularly reviewed in accordance with hospital antibiogram results by hospital infection control committee.

Therefore, we can conclude that for effective management of LRTI's, an ultimate and detailed bacteriological diagnosis and susceptible testing is required to overcome global problem of antibiotic resistance.

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