Original Research Article

Microbiological profile and its resistance pattern in cases of Ventilation Associated Pneumonias- A retrospective study

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Abstract

Introduction: According to the WHO, respiratory infections are the first leading cause of death in low income countries and third leading cause of deaths worldwide. Ventilator associated pneumonia (VAP), an important form of hospital acquired pneumonia specially refers to pneumonia developing in mechanically ventilated patients more than 48 hours after tracheal intubation ortracheostomy.**Objectives: 1.**To study the microbiological profile among clinically and radiologicaly diagnosed VAPcases.2.To study the bacterial profile in these cases.3.To study the antibiotic susceptibility pattern of bacteria associated with VAP.**Material and methods:**Endotracheal aspirate of 120 clinically and radiologically suspected patients were collected and was subjected to microscopy, culture and antimicrobial susceptibility testing. **Results:**Maximum number of cases of VAP were found on day 5 i.e late onset cases were more prevalent in our study(61.66%). Pathogens were 75.8%, colonisers were 16.93% and sterile samples were 7.25%. Monomicrobial flora was more common in both pathogenic(75.5%) and coloniser group(66.66%).*Klebsiella* was most common in pathogenic monomicrobial(44.68%) group while *E. Coli* was more common in coloniser monomicrobial group(23.8%). Good sensitivity was found for imipenem but resistance was common for tetracycline, trimethoprim-sulfamethoxazole and cephalosporins. Methacillin resistance *Staphylococcus aureus* was found in 75% cases. **Conclusion:**Gram negative isolates were more common than Gram positive. Significant resistance was noted for tetracycline, trimethoprim-sulfamethoxazole and cephalosporins. As VAP is leading cause of mortality and morbidity,cases should be diagnosed and treated as soon as possible.

Keywords:*Klebsiella*,late onset, monomicrobial, MRSA, VAP

Introduction

Ventilation Associated Pneumonias(VAP) are the second most common cause of infection, among hospitalized patients, urinary tract infections being the first[1]. In intensive care units (ICUs), ventilator-associated pneumonia is the commonest[2]. Intensive care unit acquired pneumonia (occurring after first 48 hours of admission to the ICU) and ventilator associated pneumonia occurring after the first 48 hours of starting mechanical ventilation)are also included in the broader term 'nosocomial pneumonia'. Detection of causative organism is crucial for management of VAP.Microbiological investigation consists of samples(bronchoscopic/ nonbronchoscopic) obtained from the lower respiratory tract are cultured quantitatively or semiquantitatively[3].VAP continues to complicate the course of 8-28% cases receiving mechanical ventilation[4].

Material and methods

Type of study- Prospective

Sample size- 120

Inclusion criteria-

1)Beon ventilator for more than 48 hours.

2)Clinically diagnosedas VAP.

3)Radiological evidence of infiltration suggestive of pneumonia.

Collection of endotracheal aspirate- Suction catheter was gently introduced through the endotracheal tube, gentle aspiration was then performed and the catheter was withdrawn from the endotracheal tube.The sample collected was immediately transported to Microbiology Department.

Bacteriological processing-

1.Direct microscopic examination.

2.Inoculation of sample into culture media

3.Identification

4.Antibiotic susceptibility

5.ESBL, AmpC, MBL detection.

a)ESBL producers showed:

i)Zone diameters for aztreonam <27mm, cefotaxime <27mm, ceftazidime < 22 mm, Ceftriaxone < 25 mm.

ii)Susceptible to cefoxitin

iii)Increase in zone size with addition of an inhibitorby 5mm (ceftazidime+ clavulanic acid > ceftazidime)

b)Inducible AmpC producers showed:

i)Blunting of zone of any cephalosporin towards imipenem.

ii)No increase in zone size with addition of an inhibitor

iii)Susceptible to cefepime

c)Depressed mutants showed:

i)Resistance to cefoxitin and cefotaxime

ii)No increase in zone size with addition of an inhibitor

d)Multiple mechanisms might be present if the isolate showed:

i)Resistance to cefoxitin

ii)Blunting of zone towards inducer

iii)Increase in zone size with addition of an inhibitor by >5mm

Results

A total of 120 clinically and radiologicaly diagnosed VAP patients were enrolled for the study who fulfilled our study's predefined criteria.

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Table 1:Duration of mechanical ventilation on which VAP was clinically and radiologicaly diagnosed

Day of development of VAP					
Days	**Day 3**	**Day 4**	**Day 5**	**Day 7**	**Day 10**
No. of cases	8	38	52	20	2

Table 2:Classification of VAP

VAP	Early (< 5 days)	Late(≥ 5 days)	Total
Number	46	74	120
Percentage	38.33	61.66	100

Table 3:Distribution of pathogens and colonisers

Tracheal Isolate	Number	Percentage	Classified as
$>10^5$ CFU/ml	94	75.8	Pathogens
$<10^5$ CFU/ml	21	16.93	Colonisers
No growth	9	7.25	Sterile
Total	**124**		

Out of 124 isolates 21 had $<10^5$ CFU/ml which was taken as colonisers and 9 samples showed no growth which was considered sterile, and 94 isolates showed $>10^5$ CFU/ml which were considered as pathogen

Table 4:Total pathogenic isolates

Sr. No.	Bacterial Isolates	Number	Percentage
1	*Klebsiella pneumonia*	42	44.68
2	*Pseudomonas aeruginosa*	29	30.85
3	*Acinetobacter spp.*	9	9.57
4	*E.coli*	3	3.19
5	*Citrobacter spp.*	3	3.19
6	*Proteus vulgaris*	2	2.12
7	*Morganella morgagni*	1	1.06
8	*Providencia rettgeri*	1	1.06
9	*MRSA*	4	4.25
Total		**94**	

Klebsiella pneumoniae (44.68%) were the predominant organism isolated followed by pseudomonas(30.85%) and acinetobacter(9.57%)

Table 5:Total colonizer isolates.

Colonisers	Number	Percentage
Klebsiella spp.	4	19.04
P. aeruginosa	3	14.28
E.coli	5	23.8
Acinetobacter spp.	4	19.04
Citrobacter spp.	5	23.8
Total	**21**	

Table 6:Bacterial Pattern In Case Of Pathogens In Pneumonia.

Bacterial type	Number	Percentage
Monomicrobial	71	75.5
Polymicrobial	23	24.4
Total	**94**	**100**

Monomicrobial isolates were predominant(75.5%)

Table 7: Spilt up of polymicrobial pathogenic organisms

Sr. No.	Organisms	Number	Percentage
1	*Klebsiella + Pseudomonas*	8	34.7
2	*MRSA + Pseudomonas*	1	4.34
3	*Pseudomonas + Citrobacter*	1	4.34
4	*Klebsiella + Citrobacter*	1	4.34
5	*Klebsiella + P. vulgaris*	1	4.34
6	*Klebsiella + E. coli*	2	8.69
7	*Acinetobacter + Pseudomonas*	3	13
8	*Klebsiella + Acinetobacter*	3	13
9	*Klebsiella + MRSA*	2	8.69
10	*Klebsiella + P. rettgeri*	1	4.34
Total		**23**	**100**

Klebsiella with pseudomonas were the predominant combination isolated (34.7%).

Table 8: Bacterial pattern in case of colonisers in pneumonia

Bacterial type	Number	Percentage
Monomicrobial	14	66.66
Polymicrobial	7	33.33
Total	**21**	

Monomicrobial isolates predominated among the colonisers(66.66%).

Table 9:Spilt up of polymicrobial colonisers

Sr. No.	Organisms	Number	Percentage
1	*K. pneumoniae + Citrobacter*	1	14.28
2	*P. aeruginosa + Citrobacter*	1	14.28
3	*E. coli + Acinetobacter*	2	28.57
4	*K. pneumoniae + E.coli*	1	14.28
5	*E. coli + Citrobacter*	1	14.28
6	*K. pneumoniae + Acinetobacter*	1	14.28
Total		**7**	

Most common combination isolated among colonisers were E. *coli* with acinetobacter (28.57%)

Table 10:Antibiotic sensitivity pattern of pathogenic gram negative isolates.

Organisms	3rd gen Cephalosporin		Gentamicin		amikacin		ciprofloxacin		Trimothoprim-sulfamethoxazole		Tetracycine		Imipenem	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Klebsiella spp.(n=42)	5	11.9	11	26.19	28	66.6	14	33.3	5	11.9	3	7.14	42	100
P. *aeruginosa*(n=29)	6	20.6	10	34.4	19	65.5	8	27.5	-	-	-	-	27	93.1
Acinetobacter(n=9)	2	22.2	3	33.3	5	55.5	3	33.3	-	-	1	11.1	6	66.6
E. *coli* (n=3)	0	0	0	0	1	33.3	0	0	0	0	0	0	2	66.6
P.*vulgaris*(n=2)	1	50	1	50	2	100	1	50	1	50	1	50	2	100
Morganella *morgagni* (n=1)	1	100	1	100	1	100	1	100	1	100	1	100	1	100
Providencia *rettgeri* (n=1)	0	0	0	0	1	100	0	0	0	0	0	0	1	100
Citrobacter(n=3)	1	33.3	1	33.3	2	66.6	1	33.3	0	0	1	33.3	3	100
TOTAL														
N = 90	**16**	**17.7**	**27**	**30**	**59**	**65.5**	**28**	**31.1**	**7**	**7.7**	**7**	**7.7**	**84**	**93.3**

Bacterial isolates were most commonly sensitive to imipenem (93.3%) and amikacin (65.5%) and were most commonly resistant to tetracycline and trimothoprim-sulfamethoxazole(7.7%) each.

Table 11: Antibiotic susceptibility pattern of colonisers

Organisms	3rd gen Cephalosporin		Gentamicin		amikacin		ciprofloxacin		Trimothoprim-sulfamethoxazole		Tetracycine		Imipenem	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Kleb. (n=4)	1	25	1	25	4	100	3	75	2	50	1	25	4	100
P.*aeruginosa* (n=3)	1	33.3	2	66.6	3	100	3	100	1	33.3	1	33.3	3	100
E. *coli* (n=5)	2	40	2	40	5	100	4	80	2	40	1	20	5	100
Acinetobacter (n=4)	1	25	1	25	4	100	3	75	1	25	1	25	4	100
Citrobacter(n=5)	2	40	1	20	5	100	4	80	2	40	2	40	5	100
Total (21)	7	**33.3**	7	**33.3**	21	**100**	17	**80.9**	8	**38.09**	6	**28.57**	21	**100**

All the colonisers were 100% susceptible to imipenem and amikacin and resistant to tetracycline (28.57%) and 3rd gen cephalosporin(33.3%)

Table 12: Antibiotic sensitivity pattern of gram positive isolates

Organisms	penicillin		Cefoxitin		gentamicin		ciprofloxacin		Trimethoprim-sulfamethoxazole		tetracycline		linezolid	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Staph. aureus(n=4)	1	25	1	25	1	25	2	50	1	25	1	25	4	100
Total n=4	**1**	**25**	**1**	**25**	**1**	**25**	**2**	**50**	**1**	**25**	**1**	**25**	**4**	**100**

75% of strains of staphylococcus aureus were MRSA. All the strains were sensitive to linezolid.

Table 13:Sensitivity pattern of pathogenic bacterial isolates.

Sr.No.	Bacterial isolate		ESBL	ESBL+AmpC	AmpC	MBL	Other mechanism
1	Enterobacteriacea	*Klebsiella spp.* (n=42)	19(45.23%)	9(21.42%)	6(14.28%)	1(2.38%)	0
2		*E.coli* (n=3)	1(33.33%)	-	1(33.33%)	1(33.33%)	-
3		*P. vulgaris* (n=2)	1(50%)	-	-	-	-
4		*Morganella morgagni* (n=1)	-	-	-	-	-
5		*Providencia rettgeri* (n=1)	1(100%)	-	-	-	-
6		*Citrobacter* (n=3)	1(33.33%)	1(33.33%)	-	-	-
7	Non fermenter	*P. aeruginosa* (n=29)	13(44.82%)	3(10.34%)	5(17.24%)	1(3.44%)	2(6.89%)
8		*Acinetobacter* (n=9)	-	5(55.55%)	-	2(22.22%)	-
		Total 90	**36(40%)**	**18(20%)**	**12(13.3%)**	**5(5.55%)**	**2(2.22%)**

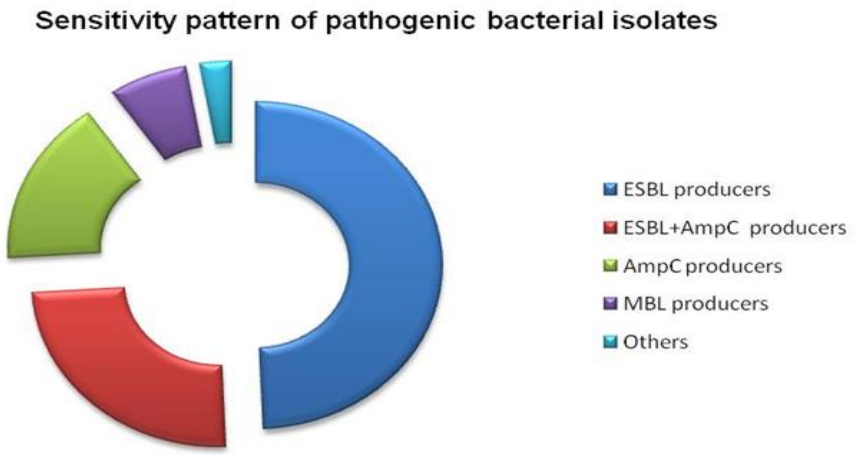

Fig 1: Sensitivity pattern of pathogenic bacterial isolates

ESBL producers	=	36 (40%)
ESBL+AmpCproducers	=	18 (20%)
AmpC producers	=	12 (13.3%)
MBL producers	=	5 (5.55%)
Others	=	2 (2.22%)

Discussion

A prospective study was done which included 120 clinically and radiologically diagnosed cases of VAP for microbiological profile. **Period of onset of VAP:**In the present study 38.3% patients had an earlyonset pneumonia (< 5 days of intubation) and 61.6% had late onset pneumonia (≥5 days).Similar findings were observed by Violan J et al with 34% of patients developing early onset and 65.8% developing late onset pneumonia[5].Similar findings were also noted by Abukhabar et al in their study showing predominance of late onset VAP (76.6%) in comparison to early onset VAP which was (23.3%) [6].Trouillet JL et al considered 7 days as the cut off between early and late onset VAP and observed that duration of intubation and antimicrobial treatment predicted the isolation of drug resistant bacteria[7].

Microbiology of VAP:The specific microbial causes of VAP are many and varied. The relative prevalence of specific pathogens vary considerably depending on the characteristics of the patient population, duration of hospitalization, mechanical ventilation prior to onset of pneumonia, prior exposure to antibiotic therapy and methods and criteria used for diagnosis.In the present study bacteria isolated from the Endotracheal aspirate of VAP cases were Acinetobacter species, Klebsiella species, Pseudomona species, Escherichia coli and Staphylococcus auerus. We observed <105cfu/ml in 21 cases which is categorized under colonisers group ,and 9 were sterile this categorization is similar to the study done by Heyland DK et al[8]The sterile cases could have been caused by viruses or by those bacteria whose cultures were not performed in the present study. These include legionella, anaerobes and viral causes. Further, the cases could have also been of a non-infective nature, such as chemical pneumonia. Similar observation was encountered in studies conducted by Muder RR et al[9]. Increased use of advanced diagnostic and interventional procedures in hospital ICU is responsible for the emergence of Acinetobacter species as an important nosocomial pathogen in the ICUs. They pose a great therapeutic problem for the clinician because of the resistance of these organisms to the major group ofantibiotics.The isolation of bacteria from clinical specimens may not necessarily mean infection but rather may result from colonization or may be a contaminant to some extent. This is reflected in our study where bacteria was isolated from the ETAof sterile and colonizing cases.Bacteria considered as high risk pathogens like Acinetobacter species, klebsiella species, pseudomonas species figure prominently in the cases of VAP in the present study. In the present study also multiple isolate growth pattern is appreciated similar to otherstudies.

Bacterial isolates in different study

Table 14: Bacterial isolates in different study

Study	Place and study	Year	Organism isolated
K.H. Raghwendra et al[10]	Indra Gandhi Institute, Patna	2002	Pseudomonas species, Staphylococcus auerus, Klebsiella species, CONS
Rajshekar et al[11]	Nizams Institute, Hyderabad	2006	Acinetobacter species, Pseudomonas species,Klebsiella species
Arindam Dey et al[12]	Manipal	2006	Acinetobacter species,Pseudomonas species, Klebsiella species
Julio Medine MD et al [13]	Uruguay	2007	Acinetobacter species, Staphylococcus auerus, Pseudomonas species
Lee MS et al[14]	Community hospitals from Virginia, north & south Carolina, and Georgia.	2013	MRSA, Pseudomonas species and, Klebsiella species.
Present study	-	2013	Acinetobacter species,Klebsiella species, Pseudomonas species

The present study correlates with all the above studies where gram negative bacilli are the most common bacteria isolated. Another important feature of the microbiology of VAP is that in many instances it is a polymicrobial infection. This lends support to the fact that aspiration of oropharyngeal contents is an important cause of pneumonia[15].Polymicrobial etiology was seen in 24.4% cases while 75.5% of cases were monomicrobial in the present study, the outcome of the patients of monomicrobial and polymicrobial VAP did not differ significantly, which co related with a study conducted by Combes A et al[16]

Antibiotic susceptibility pattern : Antibiotic sensitivity pattern of most common organism are compared between different studies:

T. Rajasekhar et al study:Acinetobacter species were sensitive to cefoperazone-sulbactam (100%), imipenem (80%). Klebsiella species were sensitive to cefoperazone-sulbactam (100%), imipenem (100%). Pseudomonas species were sensitive to imipenem (25%). Staphylococcus aureus were sensitive to vancomycin (100%)[11]

Arindam Dey et al[12] study:Acinetobacter species were sensitive to cefoperazone-sulbactam(78.2%),imipenem(60.8%),amikacin(17.3%). Klebsiella species were sensitive to cefoperazone-sulbactam (100%), imipenem(100%), amikacin (66.6%). Pseudomonas species were sensitive to imipenem (50%) amikacin (16.6%). Escherichia coli were sensitive to amikacin(100%),imipenem (100%), cefoperazone-sulbactam(100%).

Chiranjay Mukhopadhyay et al[17] study: Acinetobacter species were sensitive to cefoperazone- sulbactam (51%), imipenem (24%),ciprofloxacin(14%). Klebsiella species were sensitive to amikacin (55%),co-trimoxazole (50%), gentamicin (28%), ciprofloxacin (27%). Pseudomonas species were sensitive to imipenem (70%), cefoperazone-sulbactam (60%), amikacin (40%), ciprofloxacin (40%), gentamicin (14%). Escherichia coli were sensitive to imipenem (100%), cefoperazone-sulbactam (100%), amikacin (50%), co-trimoxazole (50%), ciprofloxacin (25%). Staphylococcus aureus were sensitive to erythromycin (67%), ciprofloxacin (33%), gentamicin(33%).

Present study:Klebsiella spp are sensitive to imipenem (100%) followed by amikacin (66.6%), (33.3%) are sensitive to ciprofloxacin and (26.1%) are sensitive to gentamicin, (11.9%) are sensitive to trimethoprim sulfamethoxazole and third generation cephalosporins each and (7.1%) are sensitive to tetracycline.Pseudomonas are (93.1%) sensitive to imipenem, (65.5%) are sensitive to amikacin, (34.4%) are sensitive to gentamicin, (27.5%) are sensitive to ciprofloxacin, while (20.6%) are sensitive to third generation cephalosporins. Acinetobacter are (66.6%) sensitive to imipenem, (55.5%) are sensitive to amikacin, (33.3%) are sensitive to ciprofloxacin and gentamicin each (22.2%) are sensitive to third generation cephalosporins and(11.1%) are sensitive to tetracycline.E. coli are sensitive to imipenem (66.6%) and (33.3%) sensitive to amikacin. Citrobacter are (100%) sensitive to imipenem (66.6%) sensitive to amikacin while(33.3%)are sensitive to gentamicin,third generation cephalosporins, ciprofloxacin and tetracycline each. Providentia rettgeri (100%) sensitive to imipenem and amikacin. Proteus vulgaris (100%) sensitive to imipenem and amikacin, while (50%) sensitive to third generation cephalosporins, gentamicin, ciprofloxacin,tetracycline each. Morganella morgagni(100%) sensitive to imipenem, amikacin, ciprofloxacin, gentamicin and third generation cephalosporins each.Pseudomonas spp, acinetobacter spp, and even enterobacteriace are quite often multidrug resistant due to production of extended spectrum beta lactamases(ESBL), Amp C beta lactamases (AmpC) and metallo beta lactamases (MBL) [18,19]Klebsiella spp are known to be intrinsically resistant to ampicillin and other aminopenicillins and can acquire resistance to cephalosporins and aztreonam by the production of extended spectrum beta lactamases.20 5- 10% oxyimino beta lactam resistant K.peumoniae do not produce an ESBL, but rather a plasmid mediated AmpC type enzyme[21]. In the present study 14% of K. peumoniae produced AmpC and 1 out of 3 (33.3%) E.coli produced AmpC similar findings were noted in a study conducted by Joseph NM et al 33.3% of enterobacteriaceae produced AmpC beta lactamase[22].In the present study AmpC beta lactamase produced by P.aeruginosa was 17.2% while in study done by joseph NM et al AmpC production in non- fermenters were 60.7%[22]In present study MBL was produced by 1 out of 29 P.aeruginosa(3.4%) and 2 out of 9 (22.2%) acinetobacter spp. Similarly In a study conducted by Joseph NM et al 2 out of 10(20%) P.aeruginosa produced MBL[22]Recently in a study conducted by Goel et al [14] (51.85%) isolates of Acinetobacter baumannii and 8(47.06%) isolates of Pseudomonas aeruginosa were plasmid-mediated metallo-beta lactamases enzyme producing strains detected[23]Klebsiella pneumoniae and E.coli producing extended spectrum beta lactamase were 19(45.23%) and 1(33.3%) respectively. Similar findings were noted in a study conducted by Lee MS et al.[14]Also in a study conducted by Joseph NM et al they found that ESBL was produced by 50% and 65% of E.coli and Klebsiella pneumoniae respectively[22]In a very recent study conducted by Krishnamurthy V et al 46.15% ESBL producers belonged to Enterobacteriaceae family in patients of VAP[24] In the present study, we found that prior antibiotic therapy and current hospitalization of five days or more were independent predictors of VAP caused by MDR pathogens. We observed that imipenem and amikacin were highly active against enterobacteriaceae as well asnon-fermenters.AmpC beta lactamase was produced by most of enterobacteriace while MBLwas produced by Acinetobacter and pseudomonas consistent with other studies[25,26]

Conclusion

Maximum number of cases of VAP were noted on day 5. Late onset pneumonia was more common. Pathogens were more than colonizers.Klebsiella was most common pathogenic bacteria isolated.Monomicrobial bacteria were more common than polymicrobials. As a significant degree of resistance was noted, it is very important to disgnose and treat paient of VAP as soon as possible.

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