Int.J.Curr.Microbiol.App.Sci (2016) *5*(4): 741-749

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 5 Number 4 (2016) pp. 741-749**
Journal homepage: http://www.ijcmas.com

Original Research Article http://dx.doi.org/10.20546/ijcmas.2016.504.085

Infectious Etiology of Acute Respiratory Distress Syndrome (ARDS) with Thrombocytopenia in Adults and their Antimicrobial Sensitivity Pattern

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Keywords

Acute Respiratory Distress Syndrome (ARDS) with thrombocytopenia; Infectious etiology; Antimicrobial susceptibility (ABS) pattern.

Article Info

Accepted:
22 March 2016
Available Online:
10 April 2016

A B S T R A C T

Acute respiratory distress syndrome (ARDS) manifests as rapidly progressive dyspnea, tachypnea and hypoxemia. Diagnostic criteria include acute onset, profound hypoxemia, bilateral pulmonary infiltrates, and the absence of left atrial hypertension. To study the infective organisms and their antimicrobial susceptibility pattern among organisms isolated from Endo-tracheal (ET) aspirates in adult patients admitted to this hospital with ARDS and having thrombocytopenia. In this prospective study, 100 patients above 18 years, admitted in Intensive care Units and on ventilator in a tertiary care hospital were enrolled. Endotracheal secretion culture & blood culture were performed in all these patients. Out of total 100 patients, Endotracheal secretion culture positive was 76% and 35% was blood culture positive. In ET aspirates, *Acinetobacter species* was commonest (43.37%), followed by *Klebsiella pneumoniae* (18.07%) and *Pseudomonas aeruginosa* (16.86%). Overall susceptibility to amikacin was 24.4% and to cephalosporins was <2%. Susceptibility to imipenem was 89.3%. Overall carbapenem resistance was 10.7%. The need for diagnostic testing to determine the etiology of ARDS is essential so that management of patients with ARDS can be instituted promptly.

Introduction

ARDS, the most severe form of acute lung injury (ALI), is caused several direct injuries like Community Acquired Pneumonia (CAP), aspiration and indirect injuries to the lungs like sepsis, tropical illnesses etc. ARDS usually requires mechanical ventilation and admission to an intensive care unit (ICU). ARDS is also a major cause of ICU morbidity and mortality worldwide (Wang *et al.*, 2014). Infectious etiology of ARDS is Gram-negative bacteria like *Acinetobacter* species, *Klebsiella pneumoniae* are commoly isolated, followed by *Pseudomonas aeruginosa,Escherichia coli,Enterobacter cloacae,* Gram-positive bacteria like Methicillin Resistant *Staphylococcus aureus* (Bauer *et al.*, 2006).

Since recognition of ARDS in 1967, a lot of clinical studies and trials have been conducted in the field of ARDS (Bernard *et al.*, 2005). There are studies on incidence, outcome, etiology, treatment and ventilator strategies of ARDS but there is no

documented study on ARDS patients with thrombocytopenia. This study attempts to find out the infective organisms and their antimicrobial susceptibility pattern isolated from Endotracheal (ET) aspirates of adult ARDS patients with thrombocytopenia admitted in Intensive Care Units (ICU) of this hospital.

Materials and Methods

This is a prospective study enrolling 100 consecutive cases of ARDS with thrombocytopenia admitted to Medical Intensive Care Unit (MICU) and Intensive Respiratory Care Unit (IRCU) of a tertiary care hospital over a period of one year in 2013. Institutional Ethical Committee approval was obtained prior to commencement of the study.

Patients with ARDS were identified through a prospective daily ICU surveillance, based on the American-European Consensus Conference (AECC) criteria:

Acute onset

Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2 /FiO_2) of 200 or less, regardless of positive end-expiratory pressure

Bilateral infiltrates seen on frontal chest radiograph and pulmonary artery wedge pressure of 18 mm Hg or less when measured, or no clinical evidence of left atrial hypertension (Saguil *et al*., 2012)

All adult patients with ARDS with thrombocytopenia admitted in ICUs were included in this study and patients with chronic obstructive pulmonary disease, HIV seropositive, with cardiac failure and age below 12 years were excluded.

Statistical analysis was performed using computer based program SPSS version 15. Student *t*-test was performed for continuous variables. *P* value < 0.05 was considered to be statistically significant.

Patients were sedated with midazolam or fentanyl and oxygen saturation was monitored during the procedure of collection of ET secretion. A tracheal aspiration (TA) tube was inserted approximately 24 cm into the trachea and the sample fluid (ET secretion) was aspirated into a polypropylene tube and collected in a sterile container. If there was no fluid production during the procedure, 5 mL of saline solution was injected and rapidly aspirated (Kirtland *et al.*, 1997).

Gram stain was done, followed by plating on blood agar, chocolate agar and MacConkey agar and all the plates were incubated at 37°C for 24 hours. Chocolate agar was kept in candle jar. Next day, growth of even single colony was processed and organisms were identified by standard biochemical tests. Antibiotic susceptibility testing was done on Muller Hinton agar by Kirby Bauer Disc Diffusion Method (KBDDM), according to CLSI guidelines (Paimer *et al.*, 1995) (Slagle *et al.*, 1989).

For collection of blood culture sample, a tourniquet was applied and a suitable vein was selected. The venepuncture site was cleansed with 70% alcohol, followed by 2% tincture of iodine/ chlorhexidine. Disinfectant was allowed to dry before blood was aspirated. Minimum of 10 ml blood was collected and inoculated into blood culture bottle containing tryptic soy broth. The bottles were incubated at 37°C for 7 days. Each bottle was examined daily for macroscopic evidence of microbial growth. Total three subcultures were done on blood agar and MacConkey agar plates,

i.e. on 2nd day, 4th day and 7th day. Any growth from one of the subcultures was identified by standard biochemical tests.If no growth was seen up to third subculture, the bottle was finally discarded (Ntusi N *et al.,* 2010).

Results and Discussion

The incidence of ARDS with thrombocytopenia in ICUs during the study period of one year was 10.26%. ARDS was more common in patients who were aged >60 years (32%) and in males (60%).The mortality rate was high among them.

Maximum ET secretions were purulent (71%) followed by mucoid (17%) and mucopurulent (12%). In Gram stain of ET secretion culture,66% showed pus cells and Gram negative bacilli/ coccobacilli; 3% showed pus cells and Gram positive cocci; 2% showed pus cells, Gram negative bacilli Gram negative coccobacilli; whereas 29% showed pus cells and no organisms.

Out of 100ET secretions, culture was positive in 76%, of which 96.06% were Gram negative bacilli and 03.94% were gram positive cocci. Organisms isolated from ET secretions shown in Table 1. Commonest organism isolated was *Acinetobacter species* (43.37%), followed by *Klebsiella pneumoniae* (18.07%) and *Pseudomonas aeruginosa* (16.86%).

Maximum ET secretions showed single growth (90.78%).

Comparison of ARDS patients with growth and no growth in ET secretions was done.

Age and platelet count were significantly lower in patients showing no growth in ET secretions, whereas PaO_2/FiO_2 was significantly lower in patients showing growth in ET secretion (Table 2).

In blood cultures of these 100 patients, 35% showed growth, of which 91.43% were Gram negative bacilli and 08.57% were Gram positive cocci. The organisms isolated from blood cultures are shown in Table 3. Commonest organism isolated was also *Acinetobacter species* (34.28%). All blood culture samples showed single growth.

On comparison of growth of bacteria in blood cultures and ET secretion cultures in 100 cases, in 34% cases, both ET and blood cultures were positive, whereas in 42% of cases only ET culture was positive (Barr Diagram1).

In isolates from ET secretions, overall susceptibility to amikacin was 24.4% and to cephalosporins was <2%. Susceptibility to imipenem was 89.3%, followed by 51.5% susceptibility to netilmycin. Overall carbapenem resistance was 10.7%. Other Gram negative bacilli showed less than 17% susceptibility to all first line antibiotics (Tables 4 & 5). Five carbapenem resistant *Acinetobacter spp*. were susceptible to tigecycline, colistin and two carbapenem resistant *Enterobacter spp*. was susceptible to tigecycline. None of the isolates were Extended Spectrum Beta-lactamase (ESBL) producers.

Both MRSA isolated was susceptible to vancomycin and linezolid.Single MSSA isolated was susceptible to co-trimoxazole and ciprofloxacin. No Vancomycin Intermediate *Staphylococcus aureus* (VISA), Vancomycin Resistant *Staphylococcus aureus* (VRSA) or Vancomycin Resistant *Enterococci* (VRE) was detected.

A total of 100 patients were enrolled in this study. The incidence of ARDS with thrombocytopenia in ICUs during the study

period of one year was 10.26% (100/974). A study from India showed incidence of ARDS in ICUs as 10%, which is almost similar to the present study (Sachdev SPS *et al.*, 2014). Maximum number of cases of ARDS was seen in the age group of > 60 years (32%). Studies from America and Washington and have stressed that incidence of ARDS increases with age (http://emedicine.medscape.com/article/165 139-overview#showall) (Rubenfeld GD *et al.*, 2005).

In ARDS patients, ET secretion culture is indicated, as it is a lower respiratory tract sample and therefore, is less likely to be contaminated by oropharyngeal colonizers (Mandell LA *et al.* 2007)In this study, 76% of ET secretions showed growth and 24% showed no growth in culture. Study by Shanmuga *et al.* (2014) showed growth in 73% and Anushan *et al.* (2014) showed growth in 75% of ET secretion cultures, which are almost similar to the present study. In this study, gram negative bacilli (96.06%) were most commonly isolated from ET secretions. Study by Shanmuga *et al.* (2014) and Anushan *et al.* (2014) also showed predominance of gram negative bacilli in 92% and 94.2% respectively.

Commonest organisms isolated from ET cultures in the present study were *Acinetobacter spp*. (43.37%), followed by *Klebsiella pneumoniae* (18.07%) (Table1). Study by George *et al* (2010) and Abdollahi *et al* (2013) also showed *Acinetobacter sp.* (37.5% and 24.2% respectively) as the commonest organism from ET secretions. In a study by Vigg *et al.* (2003) from hederabad, commonest organisms isolated from ET culture in ARDS patients was *Pseudomonas aeruginosa,* followed by *Klebsiella species*. Studies from India by Shanmuga *et al.* (2014) and Anushan *et al.* (2014), showed that most common organism isolated from ET cultures to be *Klebsiella pneumoniae* (36% and 38.5% respectively).

In the present study, 35% of blood culture samples showed growth and 91.43% of them were gram negative bacilli. Blood cultures are optional for all hospitalized patients with ARDS, though yield of blood cultures is relatively low (Mandell LA *et al.*, 2007). Commonest organisms isolated from blood cultures were *Acinetobacter spp*. (34.28%), followed by *Klebsiella pneumoniae* (20%) (Table 3). Study by Vigg *et al.*, (2003) showed *Pseudomonas aeruginosa* to be the commonest (42%), followed by *Klebsiella species* (28%), isolated from blood cultures in ARDS patients.

In this study, 34% of patients showed growth, both in ET secretions and blood cultures and 42% of patients showed growth only in ET culture. Growth in ET secretion was mostly seen in direct causes and in some cases of acute febrile illness, whereas growth in both ET secretion and blood culture was seen mostly in indirect causes. One patient had growth in blood culture but not in ET secretion. This was a case of urinary tract infection (UTI) and *Escherichia coli* was grown both from blood culture and urine culture (Bar Diagram 1). Study from Gujarat ET secretion positive in 85% and blood culture in 38% of patients (Modi P *et al.*, 2011).

On comparing the two categories of "growth" and "no growth" in 100 cases of ARDS, mean age and mean platelet count was significantly lower in patients with no growth (39.33 years and 42.75 thousand /cu.mm respectively) in ET secretions as compared to growth (48.72 years and 64.99 thousand /cu.mm respectively) (Table 2). Possible explanation is that ARDS caused due to tropical illnesses like malaria, dengue, leptospirosis, etc., which is very prevalent in Indian scenario, will have very low platelet count due to the tropical illness

and might not show any growth in ET secretion culture. Mean PaO_2/FiO_2 ratio was significantly low in growth (147.09), than no growth (165.88). This can be explained as most patients showing growth in ET secretions were suffering from direct causes like Community Acquired Pneumonia (CAP), aspiration, etc. All the other parameters were not significant.

Table.1 Organisms Grown from ET Secretion Cultures in 76 Cases

Bacteria	No.	%
Acinetobacter species	36	43.37
Klebsiella pneumoniae	15	18.07
Pseudomonas aeruginosa	14	16.86
Escherichia coli	09	10.84
Enterobacter species	06	07.22
Methicillin resistant *Staphylococcus aureus* (MRSA)	02	02.40
Methicillin sensitive *Staphylococcus aureus* (MSSA)	01	01.20
Total	**83**	**100**

Table.2 Comparison of ARDS Patients with Growth and No Growth in ET Secretions

Parameters	Growth (76) Mean (± SD)	No growth (24) Mean (± SD)	P value	Significance
Age (years)	48.72 (±16.868)	39.33(±16.521)	0.019	**Significant**
Hb (gm/dl)	7.82 (±1.186)	7.92(±1.157)	0.719	NS
Platelet (/cu.mm in thousands)	64.99 (±24.968)	42.75(±27.235)	0.000	**Significant**
PCO_2 (mmHg)	51.51 (±12.618)	49.63(± 12.479)	0.523	NS
PaO_2 (mmHg)	84.61 (±48.756)	85.00(±12.148)	0.906	NS
PaO_2/FiO_2	147.09 (±34.273)	165.88(±34.893)	0.022	**Significant**
Hospital stay (days)	15.47 (±6.094)	14.88(±3.904)	0.652	NS

NS = Not significant

Table.3 Organisms Grown from Blood Cultures in 35 Cases

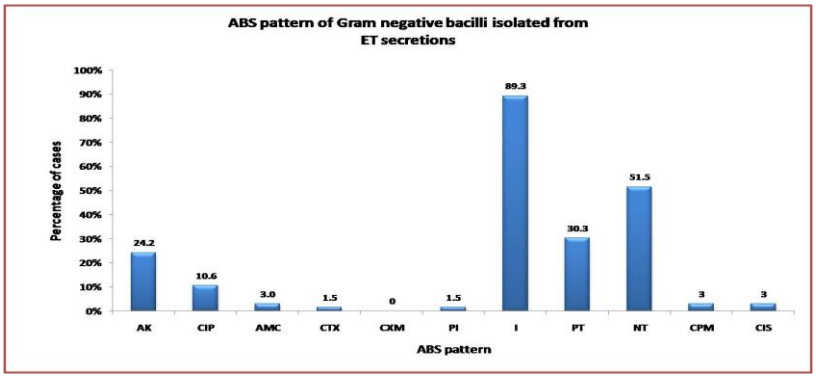
Organism	No.	%
Acinobacter species	12	34.28
Klebsiella pneumonae	07	20.00
Pseudomonas aeruginosa	04	11.42
Escherichia coli	07	20.00
Enterobacter species	03	08.57
Methicillin resistant *Staphylococcus aureus* (MRSA)	02	05.71
Methicillin sensitive *Staphylococcus aureus* (MSSA)	01	02.85
Total	**35**	**100**

Table.4 Antimicrobial Susceptibility (ABS) Pattern of Gram Negative Bacilli Isolated from ET Secretions

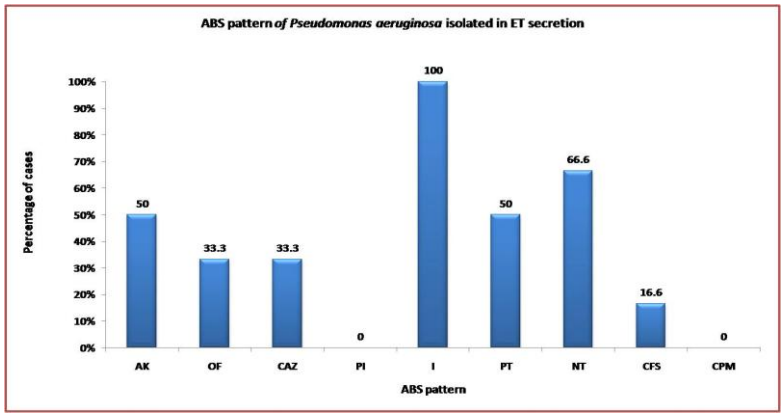
Gram negative bacilli (No.)	AK	CIP	AMC	CTX	CXM	PI	IPM	PIT	NET	CPM	CIS
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
***Acinetobacter* species(36)**	04 (11.1)	03 (8.3)	02 (5.5)	01 (2.7)	00 (00)	00 (00)	31 (86.1)	6 (16.6)	13 (36.1)	2 (5.5)	00 (00)
***Klebsiella pneumoniae*(15)**	10 (66.6)	03 (20)	00 (00)	00 (00)	00 (00)	01 (6.6)	15 (100)	4 (26.6)	13 (86.6)	00 (00)	02 (13.3)
***Escherichia coli* (09)**	05 (55.5)	01 (11.1)	00 (00)	00 (00)	00 (00)	00 (00)	9 (100)	7 (77.7)	6 (66.6)	00 (00)	00 (00)
***Enterobacter* species(6)**	01 (16.6)	00 (00)	00 (00)	00 (00)	00 (00)	00 (00)	4 (66.6)	3 (50)	2 (33.3)	00 (00)	00 (00)
Total (66)	16 (24.2)	07 (10.6)	02 (3.0)	01 (1.5)	00 (00)	01 (1.5)	59 (89.3)	20 (30.3)	34 (51.5)	02 (3.0)	02 (3.0)

AK - Amikacin; I – Imipenem; CIP- Ciprofloxacin; PT- Piperacillin-Tazobactam;
AMC - Amoxycillin-Clavulinic acid; NT- Netilmicin; CTX – Cefotaxime; CPM- Cefepime; CXM- Cefuroxime; CIS- Cefoperazone-Sulbactum; PI – Piperacillin.

Bar diagram.1 ABS Pattern of Gram Negative Bacilli Isolated from ET Secretions

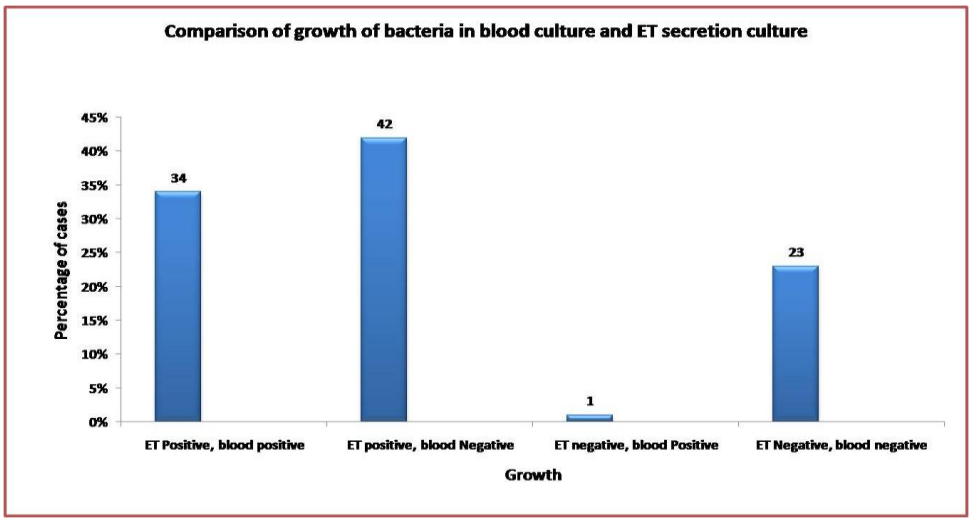


Bar diagram.2 ABS Pattern of *Pseudomonas aeruginosa* Isolated in ET Secretion



CFS- Cefoperazone sulbactum; *Pseudomonas aeruginosa* showed 100 % susceptibility to Imipenem

Bar diagram.3 Comparison of Growth of Bacteria in Blood Culture and ET Secretion Culture



In the present study, antibiotic susceptibility of the organisms isolated from ET secretions were tested. Amikacin susceptibility of *Klebsiella pneumoniae* was66.6%, followed by *Escherichia coli* (55.5%) (Tables 4 & Bar diagram 3). Susceptibility of *Acinetobacter spp*. to ciprofloxacin, cefotaxime, imipenem, cefepime, netilmycin and piperacillin-tazobactam was 8.3%, 2.7%, 86.1%, 5.5%, 36.1% and 16.6% respectively(Table 4). A study by Abdollahi *et al* (2013) showed susceptibility of *Acinetobacter spp.* to ciprofloxacin, cefotaxime, imipenem and cefepime to be 12%, 2.6%, 92.6%% and 0% respectively in ET secretions. One Indian study reported *Acinetobacter spp*. susceptible to ciprofloxacin, cefotaxime, imipenem, netilmycin and piperacillin-tazobactam as 28%, 10%, 100%, 14% and 21% respectively in ET secretions (Modi PP 2012). Vadivoo NS *et al* (2014) also showed good susceptibility of *Acinetobacter spp*. to imipenem (94%).

In this study, *Klebsiella pneumonia* susceptibility to ciprofloxacin, cefotaxime, imipenem, netilmycin and piperacillin-tazobactam was 20%, 0%, 100%, 86.6% and 26.6% respectively (Table 4). One Indian study showed *Klebsiella pneumonia* susceptibility to the above 5 antibiotics to be 47%, 18%, 93%, 40% and 38% respectively (Modi PP *et al* 2012). A study by Abdollahi *et al* (2013) showed *Klebsiella pneumoniae* susceptibility to ciprofloxacin, cefotaxime, imipenem and cefepime as 76.66%, 14.3%, 98.2% and 25% respectively.

In this study, *Pseudomonas aeruginosa* susceptibility to amikacin, ofloxacin, ceftazidime, piperacillin, imipenem and piperacillin-tazobactam was 50%, 33.3%, 33.3%, 0%, 100% and 50% respectively(Bar diagram 3). A study by Modi *et al* (2012) showed susceptibility to all the above 6 antibiotics to be 78%, 43%, 43%, 43%, 86% and 43% respectively.

Overall carbapenem resistance in this study was 10.7% (Table 4).

ARDS is significantly associated with ESBL producing organisms (Graffunder EM *et al.*, 2005), though in the present study, none of the isolates were Extended spectrum beta-lactamase (ESBL) producer.

The use of appropriate antibiotics which are

directed towards the most prevalent organisms improves the cure rate and survival and also reduces the emergence of resistant strains. A local antibiogram for each hospital, based on bacteriological patterns and susceptibilities is essential to initiate empiric therapy, to prevent poor outcomes and help in framing the appropriate institutional antibiotic policy (Anusha N *et al.*, 2014).

In conclusion, all patients with ARDS should be investigated for specific pathogens that would significantly alter standard management decisions. The need for diagnostic testing to determine the etiology of ARDS is essential so that management of these patients can be instituted promptly.

Increased mortality and increased risk of clinical failure in ARDS patients are more common with inappropriate antibiotic therapy. De-escalation or narrowing of empirical antibiotic therapy on the basis of antibiotic susceptibility testing is likely to decrease an individual's risk of death and also decrease cost and antibiotic resistance pressure.

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How to cite this article:

Pritam J. Pardeshi, Anuradha S. De and Sujata M. Baveja. 2016. Infectious Etiology of Acute Respiratory Distress Syndrome (ARDS) with Thrombocytopenia in Adults and their Antimicrobial Sensitivity Pattern. *Int.J.Curr.Microbiol.App.Sci.*5(4): 741-749.
doi: http://dx.doi.org/10.20546/ijcmas.2016.504.085