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Factors That Influence Prognosis in Nosocomial Acinetobacter Infections

KEYWORDS: Hospital acquired infections,Acinetobacter, Mortality

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ABSTRACT Background-Nosocomial infections have steadily increased in incidence in recent years and contribute to significant morbidity and mortality in hospitalised patients. Aim- This study was done to evaluate the clinical, microbiological characteristics contributing to mortality in patients with nosocomial Acinetobacter infection. Methods- All patients who were admitted to the intensive care unit of Sri Ramachandra Medical College and Research Institute, Chennai, India between September 2012 to February 2014 and who acquired nosocomial Acinetobacter infections were followed up prospectively. Data pertaining to the patients was collected and they were followed up till death or discharge from the hospital. Statistics- All the variables were analysed using SPSS 16.0 software and factors that affected outcomes were determined by univariate analysis.Results- 92 patients developed Acinetobacter infections during the period of study. Elderly, immunosuppressed, diabetics, those who developed multidrug resistant organisms or had severe infection as manifested by a worsening APACHE II score had a higher mortality rate.

INTRODUCTION

Acinetobacter species were first recognized in the late 1970s as a hospital acquired pathogen and since then have steadily increased in incidence over-the years and are now recognized as a commonly occurring nosocomial pathogen responsible for increasing mortality rates and contributing to longer hospital stay[1]. They account for 10-50% of nosocomial infections especially in Intensive care units(ICU)[2] .The most common of these is A.baumanii which is responsible for 80% of all Acinetobacter infections[3].These organisms are pleomorphic gram negative bacilli that preferentially colonize aquatic environments. They tend to primarily affect respiratory tract and other organ systems such as peritoneum, urinary tract and blood stream. They have been implicated as the cause of death with an attributable mortality rate of 19-35% in the critically ill[3]. Data from India has been chiefly in the form of retrospective case series and often from a micro-biological point of view emphasising on reasons for and patterns of resistance including analysis on metallo beta lactamases[4,5,6,7,8].Prospective studies from a clinical perspective focussing on differentiating between colonisation and infection and esti-mation of factors that determine outcomes are lacking and hence this study was conducted to address this lacunae.

METHODOLOGY

This was a prospective study of patients who were admit-ted to one of the 3 intensive care units of a tertiary care hospital located at Chennai, India between September 2012 to February 2014 and developed Acinetobacter infection af-ter a duration of 48 hours of hospital stay. The study was approved by the Institutional Ethics Committee. The subjects were >18 years of age.

Data Collection

Patients were examined daily in the ICU and followed up till their death or discharge from hospital. All discharged patients were contacted via tel-ephone on day 28 to ascertain their medical status.

The following information was recorded: age, gender, medical co morbidities, use of immunosuppressive medication, invasive procedures during hospitalisation, prior antibiotic usage, antibiotic susceptibility pattern , drug administered after diagnosis of Acinetobacter infection, duration of hospital stay prior to and after developing the infection.

The Acute Physiology And Chronic Health Evaluation II (APACHE) score was calculated twice-first at the time of admission and again at the time when nosocomial infection was suspected and appropriate cultures sent. The difference between the 2 values was calculated and used for analysis. This was based on a pilot sample evaluation which revealed that

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APACHE II score taken at the time when patient developed the nosocomial infection and
the difference between the admission and nosocomial infection values was more predictive of
adverse outcomes. CPIS-Clinical Pulmonary Infection Score-was calculated for patients with
pulmonary infection.
Patients were diagnosed to have Acinetobacter infections based on growth of the organism in
blood, bronchoalveolar lavage(BAL) fluid, non BAL culture, urine, catheter tip cultures after
48 hours of admission to the hospital. The drug susceptibility was done by disc diffusion
method .Isolates were labelled as susceptible, intermediate level sensitivity and resistant
based on inhibition zones as per standard guidelines. Acinetobacter blood stream infection
was diagnosed if patient had >2 Systemic Inflammatory Response Syndrome(SIRS)Criteria
with a blood culture growth or if two concomitant blood cultures were positive. Nosocomial
pneumonia was diagnosed if patient had fever, cough with purulent exudates, new
radiological shadow(atleast 2) with bronchoalveolar lavage growth of Acinetobacter. If non
BAL culture was used, CPIS score of greater than 6 was used as a cutoff [9].
Nosocomial urinary tract infection was diagnosed by urine culture growth of Acinetobacter
$>10^5$ colony forming units/ml with atleast 2 SIRS criteria. Patients who had been on a
longterm indwelling catheter or were catheterised outside were not included. Based on the
antibiotic susceptibility , organisms that were resistant to atleast 3 groups of antibiotics were
classified as multidrug resistant Acinetobacter.
Based on the outcomes , patients were classified into 2 groups. All patients who died during
the hospitalisation or within 28 days of discharge were nonsurvivor group and those who
were alive at day 28 were survivor group.
Statistical Analysis
Statistical analysis was performed using the SPSS software for Windows version SPSS 16.0.
Continuous variables were expressed as mean+_ standard deviation and discrete values as
number %.Association between Acinetobacter related mortality and patient factors(age> 65
years, prior medical comorbidities, prior antibiotic use, APACHE 2 variation, invasive
procedures, antibiotic susceptibility of the organism) were analysed by univariate analysis.

RESULTS

During the study period, a total of 118 patients had Acinetobacter growth. 16 participants (12
positive for urine culture and 4 nonBAL culture) did not fulfil criteria of SIRS/ had low
CPIS score and were excluded as possible colonizers.92 patients satisfied the study criteria
and were included in the analysis.
Baseline and laboratory characteristics of both nonsurvivor and survivor groups are shown in
table 1. 69 patients were above age 65 years. The prior medical comorbidities present in 52
patients included diabetes mellitus(41), systemic hypertension(41), Chronic Obstructive
Pulmonary Disease(COPD in 6 patients), Chronic Kidney Disease(CKD in 13
patients),Coronary Artery Disease(CAD in 12), malignancy(3), Human Immunodeficiency
Virus infection(3).
32 patients had 1-2 comorbid illnesses, 19 had 3-4 comorbidities and 1 had five. 3 patients
were on immunosuppressive drugs(steroids and chemotherapeutic agents).
A person was considered to have had prior antibiotics if they had received atleast 24 hours of
antibiotic within 2 weeks prior to growth of Acinetobacter. Acinetobacter infection was least
when no prior antibiotics were used(3) and highest when Ceftriaxone(28) or Piperacillin –
Tazobactum(26) were given . 61.5% of patients who received Piperacillin- Tazobactum as the
initial antibiotic did not survive.
The average number of invasive procedures undergone by a patient in both groups was 3.
Majority of the patients developed nosocomial pneumonia and BAL and/or nonBAL culture
growth was seen in 70 patients. There was urinary tract infection in 10 patients , 9 of whom
had a good outcome.80 patients had growth in a single culture while 12 had growth from 2 or
more sites. There was polymicrobial growth in 10 patients with Klebsiella, Pseudomonas
being some of the other pathogens grown.
Variation in the APACHE II score of >6 was associated with a very poor outcome and 92.9%
of patients in this subset succumbed to their illness as opposed to 21.2% in the group where
APACHE II remained the same or decreased by upto 3.
CPIS score was used to differentiate nonBAL colonisation and infection with a cutoff value
of 6 . However higher CPIS scores were not statistically associated with a poor outcome.
Table 2 lists the antibiotic susceptibility pattern. 82.5% of the organisms were resistant to at
least 4 groups of antibiotics. 2 isolates were pan resistant(including Polymyxin and
Tigecycline)and both the patients did not survive. Among the isolates, most were sensitive to
Polymyxin(97.5%) and Tigecycline was the next(73%).The incidence of carbapenem
resistance was 93%. Of the 85 isolates that were tested for meropenem resistance, only 6
were sensitive.
Table 3 lists the antibiotic that was used to treat the infection after the culture results were
obtained. Most patients received between 7 to 10 days of sensitive antibiotic .
Of the 17.5% of patients who were sensitive to all groups of antibiotics, 2 each were treated
with Levofloxacin and Aminoglycosides (Amikacin). All the 4 survived. Those with drug
resistant organisms were treated predominantly with polymyxin. 49% of patients did not
survive even after initiation of culture sensitive antibiotic.
Some published studies have shown benefit on addition of Sulbactum as a second antibiotic
probably due to inoculum effect.[10] Hence nearly 40 patients were started on Sulbactum.
There was variation on initiation of this drug based on individual treating physicians
perspectives. There was no appreciable change in the outcomes between those on additional
Sulbactum versus those who received a single sensitive antibiotic.

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DISCUSSION

Nosocomial infections have increased in incidence in intensive care settings world over and studies have shown a prevalence of 14.7% in developing countries.[11]Acinetobacter has gained importance as etiological agent responsible for 13.2-34.5% of nosocomial infections in India[8,12].

In our hospital, there were 0 .3 episodes of Acinetobacter infection in the hospital for every 1000 adult patients who were admitted during the period of study. We observed a mortality rate of 45.62% among the 92 patients who developed the infection. Most of the patients developed the illness between day 11 and 13 of hospital stay suggesting that the longer duration of stay in the ICU played a role in acquiring these pathogens. Elderly patients> 65 years and those with multiple comorbidities (diabetes mellitus, COPD, malignancy and HIV infections) had a poorer outcome (table 4).

Previous studies have also linked prolonged ventilator use and number of invasive procedures to have an adverse effect[3,7].However we found no difference between the 2 groups.

The majority of infections were respiratory as seen by the number of BAL and nonBAL growths. A point of interest was the high number of patients with a urine culture growth who had a good survival. Despite only including patients who had atleast 2 markers of SIRS,90% of patients did well raising suspicion as to whether it was a coloniser.

Analysis of APACHE 2 scores also revealed that those who had a significant deterioration in clinical parameters with increase in APACHE score at the time of developing nosocomial infection did worse and 93% of people with a change in values of >-6 succumbed to the ailment. Baseline APACHE II scores had no influence on the outcome. This probably reflects the acute decompensation and the severity of the hospital acquired infection.

Prior broad spectrum antibiotic use put patients at a disadvantage. This has been seen in multiple studies and Carbapenem resistance has been linked to prior use of Imipenem or Meropenem. [12]In fact, the small subgroup of patients who had not received antibiotics had the best outcome.

The sensitivity pattern which showed a high percentage of multidrug resistant organisms including panresistance in 2 cases was alarming. Previous data in complicated urinary tract infections have shown a pandrug resistance rate of 3.5%.[6] Multi drug resistant organisms accounted for 82.5% of all isolates and Carbapenem resistance was seen in 93% of patients.

In recent years there has been a global increase in the incidence of carbapenem resistant Acinetobacter and Colistin , Tigecycline are the drugs that have been used for treatment.

However in our patients, prior Imipenem use was present only in 14 patients and yet carbapenem resistance very high .Mortality rates were 49% in patients who were treated with polymxin.

The strengths of our study was that it was a prospective study that followed up patients who developed the infection during their stay in the hospital and hence could look at infections versus colonisers. A detailed analysis of the drugs used and pattern of resistance of could be obtained and factors that influence outcomes could be determined. The limitations were the smaller numbers of patients .We were unable to perform a logistic regression analysis to determine the effect of individual variables on mortality in view of the small numbers.

Conclusions

Acinetobacter infections have increased in number. Elderly, diabetics, immunosuppressed patients with a long ICU stay who develop multidrug resistant organisms or have severe disease as manifested by worsening APACHE II scores are at risk of succumbing to the disease. Larger prospective studies are needed to estimate the effect of different variables which may help to formulate control plans.

Table 1 : Baseline characteristics of study patients with Acinetobacter infections

Variable	Fair outcome(n=50) No.&% or Mean+/-SD	Poor outcome(n=42) No.&% or Mean+/-SD	Total(n=92)
Gender:			
Male	40(43.47)	32(34.78)	72(78.26)
Female	10(10.87)	10(10.87)	20(21.74)
Age (years) MEAN	42.7+/-17.34	54.64+/-14.49	
<65 years	41(44.56)	28(30.43)	69(75)
>65 years	9(9.78)	14(15.21)	23(25)
Medical comorbidities	24(26.08)	28(30.43)	52(56.52)
Diabetes Mellitus	17(18.47)	24(26.08)	41(44.56)
Hypertension	20(21.74)	21(22.82)	41(44.56)
CAD	4(4.34)	8(8.69)	12(13.04)
CKD	6(6.52)	7(7.60)	13(14.13)
Malignancy	0(0)	3(3.2)	3(3.2)
HIV	0(0)	3(3.2)	3(3.2)
Invasive procedures			
1-2	3(3.2)	2(2.17)	5(5.43)
3-4	35(38)	31(33.69)	64(69.56)
5-6	12(13.04)	9(9.78)	21(22.82)
APACHE II Variation			
3-6	8(8.69)	0	8(8.69)
0-3	26(28.2)	7(7.6)	33(35.87)
-3-0	12(13.04)	8(8.69)	20(21.73)
-4- -6	4(4.34)	27(29.34)	31(33.69)
Site of growth			
Blood	6(6.52)	6(6.52)	12(13.04)
BAL	13(14.13)	13(14.13)	26(28.26)
NonBAL	22(23.91)	22(23.91)	44(47.82)
Urine	9(9.78)	1(1.08)	10(10.87)
>1	9(9.78)	3(3.26)	12(13.04)
Duration of hospital stay before developing Acinetobacter(days)	13+/-9	11+/-7	
CPIS Score	6.85+/-.72	7.09+/-.68	
Prior antibiotic use[a]	47(51.08)	42(45.65)	89(96.73)
Multidrug resistant Acinetobacter	40(43.47)	42(45.65)	82(89.13)
Total duration of stay in hospital(days)	36+/-25	23+/-12	

[a] Prior antibiotics used included Ceftriaxone in 28 pa-

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tients, Cefaperazone with sulbactum in 16 patients, Piperacillin- Tazobactum in 26 patients, Imipenem in 14 patients.

Table 2: Acinetobacter sensitivity pattern

Antibiotic	subgroup	Isolates tested	% susceptible
Aminoglycosides	Amikacin	91	17.5%(16)
	Gentamicin	91	8.7%(8)
Cephalosporins	Cefaperazone +sulbactum	91	17.5%
	Cefepime	92	6.5%
	Ceftazidime	92	7.6%
	Ceftriaxone	90	5.5%
Carbapenems	Imipenem	84	8.3%
	Meropenem	85	7%
Cotrimoxazole		91	6.5%
Polymyxin		80	97.5%
Tigicycline		78	73%
Fluoroquinolones	Ciprofloxacin	92	10.8%
	Levofloxacin	92	13%

Table 3 : Antibiotics used after culture

Antibiotics	Fair Outcome	Poor Outcome
Polymyxin	26	25
Imipenem	6	4
Levofloxacin	2	0
Tigecycline	6	5
Cefaperazone+Sulbactum	4	5
Amikacin	2	0
Nil[a]	4	3

a In all cases, urine culture growth. Urinary catheter was removed and no specific antibiotic was started as the fever had resolved by the time the cultures were available(in fair outcome group) and death had occurred in the poor outcome group.

Table 4: Factors affecting outcome

Variables	P Value	OR of death(95% CI)
Age >65 years	.091	2.28(.87-5.98)
Medical Comorbidities	.071	
Diabetes Mellitus	.026	2.59(1.11-6.03)
COPD	.055	1.93(.78-7)
Immunocompromised	.055	2.28
APACHE II Variation>-4	.0005	20.7(6.23-68.79)
Site of Acinetobacter growth-urine	.005	.09(.01-.7)
Multi drug resistant Acinetobacter	.07	9.45(1.14-78.01)

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