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Multidrug Resistant *Acinetobacter species*: A significant cause of sepsis in an Intensive care unit in a regional hospital, Durban

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Abstract:

Introduction: *Acinetobacter species (A.species*) are common hospital environmental bacteria that have gained importance during the past few decades as important nosocomial pathogens in critically ill patients. This problem has been compounded by the worldwide increase in carbapenem-resistant Acinetobacter infections. In South Africa also, multidrug resistant, including carbapenem resistant *A. species* causing significant sepsis has recently increased. *Acinetobacter baumannii* remains an important and difficult-to-treat pathogen whose resistance patterns result in significant challenges for the clinician. The study was conducted to determine the prevalence of MDR-*A. species*, and to differentiate between significant infection and colonization by correlation with clinical data .

Method: All patients identified with *A. species* isolates after 48hrs in the intensive care unit (ICU) were included in the study over a year period. Data was recorded prospectively including any underlying chronic disease, type of specimens, antibiogram, antibiotic usage in the unit and outcome during daily ward rounds. Analyses were done retrospectively.

Results: During the study period, there were 187 isolates from different specimens of 86 patients. Significant sepsis was identified in 30/86 (35%), colonization in 51/86 (59%) and bacteraemia in 5/86 (6%) patients with *A. species* respectively. Lack of appropriate treatment resulted in the death of 18/86 (21%) patients. *A. species* was isolated mainly from endotracheal aspirates 67/187 (36%), and the others were from the various types of specimens. Isolates were multidrug resistant including carbapenem.

Conclusion: MDR- *A. species* was identified as a significant cause of sepsis and high mortality rate ($p < 0.001$) among the patients in surgical ICU. Our findings highlight the impact of antibiotic stewardship in the treatment of patients in whom *A. species* is isolated and the urgent need for the development of standardised guidelines for management of patients with *A. species* sepsis.

Key words: Multidrug Resistant, *Acinetobacter species*, colonization, sepsis, intensive care unit

INTRODUCTION

The prevalence of *Acinetobacter baumannii (A. baumannii)* infection in hospitals is increasing worldwide [1] with a concomitant significant increase in mortality associated with bacteraemia (19 to 54%) compared to other bacterial infections [2, 3]. It is now well recognized that in addition to colonization, *A.species* play a significant role in community as well as hospital acquired infections [4]. Although it is difficult to differentiate between colonization and sepsis, community acquired *Acinetobacter* pathogens are relatively sensitive to antibiotics and the resistant isolates are almost exclusively present in hospitals and high risk areas [5].

A.species had also been reported as the cause of serious infectious diseases such as ventilator associated pneumonia, bacteraemia, urinary tract infections, burn wound infections, endocarditis, secondary meningitis, and septicaemia, involving mostly patients with impaired host defences, especially in intensive care units (ICUs) [6, 7]. *A.species* have emerged as particularly important organisms causing late-onset ventilator associated pneumonia which may have been related to the increasingly invasive diagnostic and therapeutic procedures used in hospital ICUs in recent years [8].

A.species have acquired resistance to almost all currently available antimicrobial agents, including the aminoglycosides, quinolones, and broad-spectrum beta-lactams. The spectrum of antibiotic resistance of these organisms, together with their survival capabilities, makes them a threat in hospital environments, as documented by recurring outbreaks both in highly developed countries and elsewhere [9]. Most strains are resistant to cephalosporins, while resistance to carbapenems is being reported increasingly [9].

There has been a worldwide increase in infections caused by multidrug resistant *A. baumanni* (MDRAB) [10]. In South Africa also, an increase in Carbapenem resistant *A. species* has been recently reported [11, 12].

The challenges of treating multidrug-resistant bacteria continue to be at the forefront of the clinician's practice in caring for hospitalized patients. *A. baumannii* has proven to be an increasingly important and challenging species in health care–associated infections. The drug-resistant nature of the pathogen, its unusual and unpredictable susceptibility patterns and poor clinical understanding of significant sepsis, make empirical and therapeutic decisions even more difficult [13].

During our routine standard of care, we have observed that a significant proportion of nosocomial isolates include MDR *A. species* in the ICU at a regional hospital in Durban. The clinical significance of this has yet to be elucidated. In this retrospective study, we determined the proportion of MDR *A.species* in an adult surgical ICU, differentiated significant infection from colonization and clinical outcomes of

treatment. Outcomes of both significant and colonisation were recorded Our findings highlight the impact of antibiotic stewardship in the treatment of patients in whom *A. species* is isolated in order to develop guidelines for treatment and management of *A.species* infection.

METHOD

Study setting:

The regional hospital accommodates 950 beds and includes multi-discipline speciality wards. There is one ICU (13 bed ward) for the management of mainly surgical adult patients.

Study design and patient population:

In this analytical, descriptive cross sectional study, all patients identified with *A.species* after 48hrs in ICU was included over a year study period.

Ethical consideration:

The study was approved by the Biomedical Research Ethics Committee, University of KwaZulu-Natal and National Health Laboratory Service (Ref: BE 283/12)

Data collection:

The data collection included the total number of *A.species* isolated, total number of patients with *A. species*, specimen type, antibiogram, antibiotic usage in the unit and clinical outcomes of the patients from whom *A.species* was isolated. The data was prospectively recorded during routine daily ward rounds during one year study period. The clinical & laboratory data were analyzed retrospectively.

Case definitions:

Diagnosis of *Acinetobacter* pneumonia was based on results of endotracheal aspirates together with clinical manifestations and identification of new infiltrates on CXR.

Acinetobacter bacteraemia was diagnosed on at least one positive blood culture. Significant *A. species* sepsis was based on both positive blood culture and repeated isolation from multiple sites.

Colonization was defined as *A. species* isolated from a single specimen of a clinically stable, patient on whom a sepsis screen was performed.

Data analysis:

Frequency distributions were calculated for the number of *A. species* isolated from the specimen types, antibiograms and stratification of patients with clinical symptoms or colonisation. Pearson chi^{2}was used to calculate statistical significance, which was set at $P \leq 0.05$.

RESULTS

During the study period, isolates of *A. species* were cultured from 187different specimens of 86 patients (Figure 1). The most predominant specimen obtained was endotracheal aspirates 67/187(36%) followed by blood, CVP tips, peritoneal fluid, arterial line tip, pus and catheter urine 24/187- 11/187 (13-6%) respectively. Abdominal drains, tissue, pleural fluid and others were less commonly sampled 3/187 (2% and less).

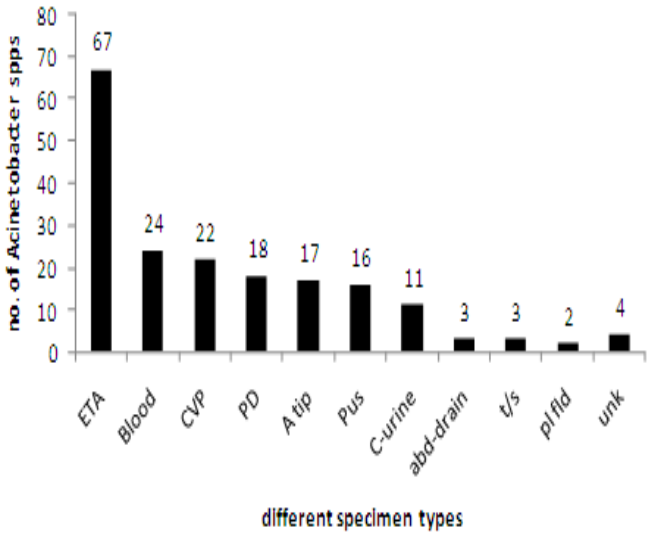

Figure 1. The number of *A. species* isolated from different specimen types in 86 patients from the surgical ICU over a year study period. The commonest specimen was ETA.

ETA(Endotracheal aspirate); CVP(Central venous pressure tip); PD(Peritoneal fluid);

A tip(arterial line tip); C-urine(catheterised urine) ; abd drain (specimen from abdominal drain);t/s (Tissue); pl fluid(pleural fluid); unk(unknown specimen)

Colonisation was observed in the majority 51/86 (59%) of the 86 patients. Significant clinical sepsis was observed in 30/86 (35%) of patients, whilst 5/86(6%) were diagnosed with bacteraemia (Figure 2).

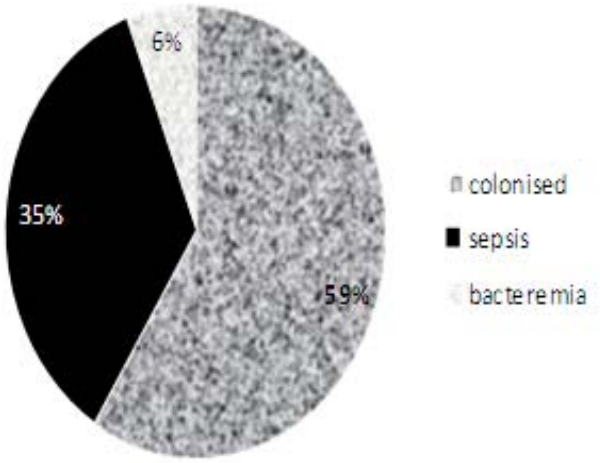

Figure 2. Stratification of patients with significant clinical symptoms or colonisation. Patients with bacteraemia comprised 6% and significant clinical sepsis, 35%.

The majority of patients (59%) were colonised.

The majority of isolates were multidrug-resistant, including resistance to carbapenems (Figure 3). Amikacin sensitive *A. species* was isolated from 39/86 (45%) of the 86 patients. The other patients were infected with isolates sensitive to TZP (piperacillin and tazobactam) 4/86[5%], ceftazidime 4/86[5%], ciprofloxacin 9/86[10%] and meropenem 10/86[12%].

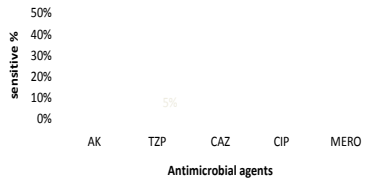

Figure 3.Antibiogram of *A. species* isolated from sepsis patients (n=86) surgical –ICU Over a year study period. AK(Amikacin);TZP(Tazocin);CAZ(Ceftazidime);CIP(Ciprofloxacin); MERO (Meropenem)

The majority of patients ;68/86(79%) recovered and were discharged in a stable condition, whilst 18/86 (21%) died. *Acinetobacter* was significantly associated with sepsis in 30 patients. Of these, 18/30 (60%) died and 12/30 (40%) recovered (p= <0.001) (Table)

Table: Clinical outcomes of patients following treatment in surgical ICU during study period Number of patient

	Sepsis	**colonised**	Total	P
Recovered	12	56	68	
Died	18	0	18	<0.001
Total	30	56	86	

DISCUSSION

A. species are aerobic Gram-negative cocco-bacilli that are ubiquitous, commonly found in hospital environments and easily colonize skin and mucous membranes. In the past, *A. species* were considered to be of little clinical significance, but the appearance of drug resistant *Acinetobacter* infections have increased worldwide frequently [14].

This study showed that *A. species* was more commonly a colonizer, especially from endotracheal aspirates of patients in ICU. Although it is difficult to differentiate between colonization and sepsis with *A. species*, the former increases the risk of the latter.
Therefore, appropriate infection control and good oral hygiene practices are of paramount importance during the collection of ETA and management of patients.

Although the proportion of colonisation was higher, clinical sepsis was identified in a large proportion of patients (35%) with multiple sites being culture positive.

The majority of isolates in this study was MDR, including resistance to carbapenem. *A. species* was regarded as colonisers in general and therefore, not directly targeted for therapy in surgical ICUs and other clinical units. The patients in ICU during that study period were treated for hospital acquired infections with tazocin (pip +tazobactum) and followed by carbapenam empirically according to the local antimicrobial therapy protocols. Despite an exponential rise in *A. baumanii* infections over the past decade, the treatment regimen remains controversial and many questions remain unanswered on the issue of appropriate therapy.

Difference between case patients and control subjects in most previous studies did not show statistical significance , however the higher mortality was observed consistently among the case patients [13]. Although the lack of statistical support consistently, it is evident that *A. baumannii* is also important as other common pathogens. To combine local antibiogram with the agent effectively is the challenge for clinicians. The prescription of combination therapy, for both empirical and directed, has not proved yet but hopefully future studies would demonstrate practically.

The in-hospital mortality attributable to *A. species* sepsis reported in other studies was between 8%–23%, while in the intensive care unit, was found 10%–43% [13]. Until now, clinical outcomes of patients with *A. species* infections were not documented in our local settings. Our study documented for the first time significant mortality rates (60%) associated with patients diagnosed with sepsis compared to those who were colonised
(p= <0.001)(Table).

The 12 (40%) patients who recovered from sepsis were treated with tazocin, which is used to treat the common known pathogens empirically. Tazocin is chosen for both empirical and direct therapy of common pathogens as second line therapy in the current treatment guideline in the study hospital.

Community and nosocomial infections caused by *A. species* have become a serious public health concern in many countries [15]. In a regional hospital in KwaZulu Natal (KZN) province in South Africa, we have shown that MDR-*A. species* contributes significantly to nosocomial isolates causing sepsis. This problem is compounded by the lack of an information of clinical significance and policy recommended guideline for *A. species* infection.

In conclusion**,** MDR- *A. species* is a significant cause of sepsis in surgical ICU. This highlights the impact of antibiotic stewardship in the treatment of patients in whom *A. species* is isolated and the urgent need for the development of standardised guideline for management of patients with *A. species* sepsis.

There is a need for surveillance studies that conduct the spread of antibiotic-resistance genes of *A. species* in local clinical settings. Further research should include the determination of genetic relatedness based on circulating *A. species* which is isolated to study transmission dynamics. In addition, the comparisons of phenotypic and molecular antibiotic resistance patterns should be studied in the research. This would serve to identify the sources of these strains and introduce intervention strategies to interrupt the transmission chains.

In addition, genotyping would ascertain relatedness if any of the strains associated with clinical sepsis and colonisation.

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