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Achromobacter denitrificans blood stream infection in adult patients: Clinical and microbiological features from a tertiary care centre in North India

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Abstract

Introduction and objective: *Genus Achromobacter* is ubiquitous, opportunistic pathogen. Treating Achromobacter infections are a challenge as the bacterium is intrinsically resistant to several empirically used antibiotics. There is a dearth of data on this organism so; the present prospective study was undertaken to understand various aspects of this uncommon organism.

Methods: This single centre prospective study of adult admitted patients diagnosed as cases of *Achromobacter denitrificans* septicaemia in a 714 bedded tertiary care super speciality hospital in North India between January 2022 and June 2022.

Results: We identified 10 patients with *A. denitrificans* bacteraemia with overall prevalence of <0.1 cases per 1,000 hospital admissions. Diabetes mellitus in 40% and bronchial asthma 30% of cases were common comorbidities. Prior systemic antibiotic therapy (30 days) (70%) and recent ICU admission (30 days) in 70% cases were predisposing factors. All the episodes (10) were health care associated. Cefaperazone salbactum and Tigecycline were the agents with the best *in vitro* activity. While resistance pattern for cotrimoxazole, amikacin and gentamicin was common. 30% isolates were Multi drug resistant phenotypes. For the source investigation of all cases intensive, "Surveillance of unusual pathogens" was carried out by infection control team as per our institutional policy.

Conclusion: In conclusion, bacteraemia due to *A. dentrificans* can be a serious complication among hospitalized patients, mainly those with immunosuppression. The importance of source control and infection control practices still continue to be the biggest armour against the infection.

Introduction

Genus Achromobacter of the order *Burkholderiales* are an obligate aerobe, gram negative, non-lactose fermentative bacilli. They are often misdetected as other common lactose non fermenting Gram-negative bacilli like *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia* complex, *Acinetobacter* spp etc by conventional methods of detection and hence misdiagnosed and under reported [1,2].

They are found ubiquitously in nature especially in pelagic environment and mainly associated with Health Care Associated Infections (HCAI) [1,2]. They were first identified in purulent ear discharge of chronic otitis media patients by Yabuuchi and Ohyama in 1971 [3]. Presently, fifteen (15) pathogenic species have been isolated from clinical specimens, including the most common species *Achromobacter xylosoxidans* and second most common *Achromobacter denitrificans* [1,4]. *Achromobacter species* is an opportunistic pathogen which is usually associ-

ated with underlying various risk factors and immunosuppression. Primary bacteraemia/ septicaemia is the commonest clinical presentation [5] whereas other infections like pneumonia, peritonitis, urinary tract infections, meningitis, encepahlitis, osteomyelitis, abscesses, corneal ulcers, pros¬thetic valve endocarditis have also been reported [5] Poor clinical prognosis and varied case mortality rates ranging from 3% for catheter related and primary septicaemia to 80% for neonatal case infections makes the organism even more alarming and appalling [6,7].

Treating *Achromobacter* infections are a challenge as the bacterium is intrinsically resistant to several empirically used antimicrobials often vesting in a phenotype of Multidrug Resistance (MDR) status [8]. There is a dearth of data on this uncommon organism as majority of past studies are restricted to case reports or small case series. So, the present prospective study was undertaken in our tertiary care super speciality centre to understand the clinical features, risk factor, therapeutic options and outcome of *Achromobacter denitrificans* in our institute over a period of 6 months.

Material and methods

This single centre prospective study include data of 10 adult admitted patients diagnosed as cases of *Achromobacter denitrificans* septicaemia in a 714 bedded tertiary care super speciality hospital in North India between January 2022 and June 2022.

All episodes of bacteraemia due to *A. denitrificans*, detected in January 2022 until June 2022 were evaluated prospectively. Paediatrics and neonate and patients where *Achromobacter denitrificans* could not be isolated on consecutive samples were excluded (environmental contamination). A case of *A. denitrificans* bacteraemia was defined as minimum of two or more consecutive blood cultures positive for *A. denitrificans* with clinical and laboratory evidence of sepsis [9]. Aseptically collected blood culture samples were incubated into automated system Bactec 9240 system (Becton Dickinson, USA) for up to five days [9]. A sample from the blood culture bottle with positive beep was inoculated into 5% sheep blood agar and Mac Conkey agar (HiMedia Laboratories, India) and incubated at 36.5°C for 18-20 hours. Direct grams stain was done for preliminary diagnosis as per standard protocol [10]. Gram negative bacilli with positive oxidase reaction were identified and antimicrobial susceptibility testing done by Vitek 2 Compact (Biomerieux, USA) using AST-N 280 and AST-N 281 cards. CLSI M 100 S 24 (2020) antibiotic sensitivity was utilised to denote sensitive, intermediate, and resistant strains [11]. The MDR phenotype was defined by demonstrated resistance to ≥3 different types of antimicrobial agents [12].

Informed patients consent was taken. Patient characteristics included gender, age, date of onset of symptoms, underlying diseases and risk factors i.e. on patient on frank immunosuppression, prolonged ICU admission, history of antimicrobial intake in the past, history of organ or bone marrow transplant, history of any surgical intervention, in-situ intravascular catheters, presence of Ventriculo-Peritoneal Shunt (VP shunt), Total Parenteral Nutrition (TPN) , number of positive blood cultures and other concordant infective sites yielding same organism *A. denitrificans* [1]. Intravascular catheter-related bacteraemia was suspected when the criteria proposed by the Infectious Diseases Society of America were met [13] or in the presence of local signs of infection (erythema, swelling, tenderness or purulent discharge) at the site of insertion or along the subcutaneous tunnel tract and no alternative source detected [13]. Secondary sources such as urinary tract infection or Skin and Soft-Tissue Infection (SSTI) were considered in the presence of relevant clinical suspicion along with laboratory and radiological findings. Primary bacteraemia was referred to as cases with no identifiable other source of infection [13]. Neutropenia referred to a count less than 1.5×10^9/L cells/mm^3 and thrombocytopenia as platelet count of less than 150 × 10(3) per µL [14,15]. Infections presenting with more than 72 h after hospitalisation were defined as Hospital Acquired Infections (HAI) and or else Community Acquired Infection (CAI) [16]. The severity of illness at time of bacteraemia was assesed with Pitt score [17].

For the source investigation of all cases, "Surveillance of unusual pathogens" was carried out by infection control team as per our institutional policy. Environmental samples were taken for bacteriological cultures including various intravenous solutions like saline, glucose, chlorhexidine etc, wash basins, incubator surfaces, liquid soaps, faucets, nebulizers, tap water, patient's beds and railings, side box. Health care workers were sampled for their hands by direct fingerprinting in Petri dishes [16]. All the collected samples were inoculated in Brain Heart Infusion Broth (BHIB) and after 24 hours subculture on 5% sheep blood agar (HI media, India). Plates were re-incubated for 24 h at 36°C. Environmental cultures were taken for all the cases over the span of 6 months [18]. Contact precautions recommended with the use of glove and gown while inside a room with patients infected with *A. denitrificans* was encouraged.

Results

In our study period, we identified 10 patients with *A. denitrificans* bacteraemia and their clinical characteristics are hereby described in Table 1. The overall incidence rates of *A. denitrificans* infection across the months encompassed by the study period were overall very low (<0.1 cases per 1000 hospital admissions) and no clear seasonal trend could be identified.

The susceptibility profile of *A. denitrificans* isolates is shown in Table 2. Cefaperazone salbactum and Tigecycline were the agents having best in vitro activity (100% [10/10] of isolates were susceptible), followed by ciprofloxacin, imepenem, meropenem and piperacillin/tazobactam (90% [09/10] of isolates). While resistance pattern for aminogly¬cosides like amikacin and gentamicin was common (80% [08/10] for amikacin and 100 % [10/10] for gentamicin) also total resistance was seen in all isolates for Cotrimoxazole (100% [10/10]). The criteria for MDR phenotype [9] were attained in 30% (3/10) of isolates.

Empirically combination therapy was used in majority of the cases (80%) with Beta-lactam/beta-lactamase inhibitor antibiotic therapy in 30% cases. Beta lactam + colistin and Beta lactam + colistin + vancomycin in 20% each cases. Empirical therapy was inadequate in 80% *cases in comparison to in vitro* susceptibility tests and required further modification(step up or step down). The all-cause 30-day mortality rate was 40%, with the 4 observed deaths deemed attributable to infection due to multiple organ failure (Table 1).

Table 1: Demographic and Clinical details of patients included in the study (n=10).

Variables	
Age, years [mean ± SD]	62 ± 14
Gender (male) [n (%)]	6 (60%)
Pitt bacteraemia score [median (IQR)]	3(0- 9)
Comorbidities [n (%)]	
Solid organ malignancy	2(20%)
Heart failure/ pacemaker in situ	2 (20%)
Bronchial asthma	3(30%)
Diabetes mellitus	4(40%)
Chronic liver disease	2(20%)
Hydrocepahalous	2(20%)
Neurological malignancy	1(10%)
Predisposing conditions [n (%)]	
Prior systemic antibiotic therapy (30 days)	7(70%)
Recent surgery (30 days)	5(50%)
On Chemotherapy	3(30%)
Total parenteral nutrition (TPN)	3(30%)
Recent ICU admission (30 days)	7(70%)
CVC in place at diagnosis	5 (50%)
Duration of CVC placement [median days (IQR)]	12(1- 12)
Source of bacteraemia [n (%)]	
Primary	4(40%)
Catheter-related	3(30%)
Intra abdominal infection	1(10%)
Pneumonia	1(10%)
Urinary tract infection	1(10%)
Polymicrobial bacteraemia [n (%)]	3(30%)
Empirical antibiotic therapy [n (%)]	
Monotherapy	2(20%)
Combination therapy	8(80%)
Regimen containing	
Carbapenems	1(10%)
Third-generation cephalosporin	1(10%)
Beta-lactam/beta-lactamase inhibitor	3(30%)
Beta lactam / vancomycin	1(10%)
Beta lactam + colistin	2(20%)
Beta lactam+ vancomycin + colistin	2(20%)
30-day all-cause mortality [n (%)]	4(40%)

Table 2: In vitro susceptibility profile of 10 Achromobacter dentrificans isolates to antimicrobial agents.

Antimicrobial agents			
	Susceptible (%)	**Intermediate (%)**	**Resistant (%)**
Trimethoprim/ Sulfamethoxazole (Cotrimoxazole)			100
Amikacin		20	80
Meropenem	90	10	
Imipenem	90	10	
Pipericillin tazobactum	90	10	
Ciprofloxacin	90	10	
Cefepime		20	80
Ceftriaxone		20	80
Cefaperazone Salbactum	100		
Gentamicin			100
Tigecycline	100		

Epidemiologic investigation

Following the index case, four additional cases were diagnosed within the next two months. For the source investigation of all cases intensive, "Surveillance of unusual pathogens" was carried out by infection control team as per our institutional policy. Cohorting and contact precautions with gown and glove use on entry to rooms of patients infected with *A. dentificans* and enhanced environmental cleaning was instituted. An investigation for determination of source of infection for each patient was started Environmental vectors were suspected and extensive bacteriological cultures of environmental samples were taken but the source could not be identified.

Discussion

A. dentrificans bacteraemia is an emerging nosocomial infection specially in immunosuppressed population [1]. It represents as massive as 12.5% of total Gram negative non-fermenting bacilli isolated during SENTRY program (1997-2002) of latin american medical centres [19]. Bacteremia caused as a result of *A. dentrificans* is usually nosocomial in origin, related to intravascular catheters and frequently associated with immunosuppressive conditions [1].

In a Spanish study of 54 cases over wide duration of 10 years, the patients had a mean age of 26.6 years [20] and 96% episodes were health care associated bacteraemia, whereas the mean age in a recent Spanish study of 2018 was 52.1 ± 32 and majority cases (12/13) were nosocomial in origin too [10]. Similar results were seen in our study, with elderly age group of (62 ± 14) years majorly affected and 100% cases were nosocomial in nature.

Studies report *Achromobacter* species bacteraemia as polymicrobial in their patients (15 episodes, 28%) [20], similarly we too report polymicrobial infection in 30% vases with co-infection of Staphylococcus aureus (2/3) and *Pseudomonas aeruginosa* in (1/3) in our patients. Whereas certain other studies report comparatively lesser prevalence of polymicrobial infections (2/13 15.3%) [10,21].

Shie et al. in Taiwan reported *A. xyloxidans* bacteremia and found that oncology patients, those having central venous catheter implants and having undergone major surgery were demonstrated to be at maximum underlying risk [22]. A 2018 retrospective study in spain found 13 bacteraemia isolates over a period of 10 years and evaluated that malignancy of solid organs and heart failure were the most common comorbidities (4 cases each [30.7%]) [10]. Major risk factors were consumption of antibiotic therapy in the last 30 days (7 [53.8%]) and presence of Central Venous Catheter (CVC) in (6 [46.1%]) patients. Exposure to chemotherapy and patients with recent surgery were also common risk factors [10]. Present study shows similar results in 10 patients with major risk factors as prior systemic antibiotic therapy (30 days) (70%) and recent ICU admission (30 days) in 70% cases. Indwelling Central Venous Catheter (CVC) in situ at the time of diagnosis and recent history of surgery in past 30 days were also common predisposing conditions seen in our tertiary care centre.

In some published literature on this rare organism, *A. xylosoxidans* bacteraemia has been isolated from patients having haematological malignancy [10]. Aisenberg et al. studied 52 episodes diagnosed during a 14-year period in 46 patients with

Table 3: Various studies showing bloodstream infection caused by Achromobacter species.

S.No	Authors	Place of study, Year	Species isolated	Underlying medical conditions	Type of study	Number of isolates	Treatment given	Response to treatment
1.	Arjun R et al[27]	Kerla, 2021	1.*Achromobacter dentrificans*(9) 2.*Achromobacter xylosoxidans*(5)	1.Medical/Cardiac ICU admission(11/12) 2. Interventional procedure(6/12) 3. Haemodialysis(5/12) 4. CVC/arterial line(6/12)	Outbreak investigation	14 in 12 patients	Majority cases Pipericillin tazobactum	4 of 12 died due to underlying heart failure
2	Singh S et al[28]	Ludhiana, 2020	*Achromobacter xylosoxidans*	B acute lymphoblastic leukaemia on steroids	Case report	1	Levofloxacin + doxycycline added to meropenem + teicoplanin and voriconazole	Died (cardiac arrest)
3	Janarthanan M et al[29]	Chennai, 2019	*Achromobacter xylosoxidans*	X linked agammaglobulinaemia on immunosuppression	Case report	1	Pipericillin tazobactum continued and oral cotrimoxazole added	Survived
4.	Raghuman K et al[6]	New Delhi, 2015	*Achromobacter xylosoxidans*	HCC on chemotherapy	Case report	1	Amoxicillin clavulanate	Survived

cancer as a major underlying immunosuppression [23]. As demonstrated in Spanish single-centre study, *A. xylosoxidans* bacteraemia was found in 39% of cases among patients with cancer. Furthermore, in 35% and 30% of those cases, patients had received chemotherapy and developed neutropenia respectively [20]. We too report malignancy in 40% cases (solid organ and neurological) whereas untreated/partially treated diabetes mellitus (40%) and bronchial asthma patents on steroids (30%) ruled the charts of most common underlying comorbidities.

Most of our isolates demonstrated *in vitro* sensitivity to cefaperazone sulbactum, carbapenems and piperacillin/tazobactum as described by various authors [5,10,24]. However, as a unique finding, we also describe a significant rate of resistance to aminoglyocosides, trimethoprim/sulfamethoxazole, ceftriaxone which is in concordance to many other studies over time [10,20,23]. However we report high sensitivity pattern for flouroquinolones (80%) whereas many studies report them as resistant in nature [20,21,25]. Reportedly, such infor¬mation holds a paramount importance while making empirical therapeutic decisions, es¬pecially in a unique subgroup of patients i.e. immunocompromised and critically ill, principally due to emergence of MDR strains [1]. From this perspective, it is highlighted that the present study has demonstrated almost 30% of MDR phenotypes.

We report "All cause 30 day mortality" to be 40% in our series and most of them were caused due to sepsis. This figure is somewhat higher than previously reported, ranging from 0.0% to 15.0% to 23.1% [10,20,26]. The increase in the mortality rate probably indicates the increase in virulence potential of the organism.

In a case series of oncology patients, a positive finding of sepsis and high APACHE II scores at the time of infection onset were independent predictors of 30-day mortality [23]. In our study, we could not identify significant differences in outcome across different subgroups of patients using Pitt bacteraemia score. The source of contamination in our study could not be traced even after extensive workup but *Achromobacter* infection has been previously linked to be found in contaminated drinking water and intravenous infusions, such as diagnostic contrast solutions and haemodialysis systems [1,4]. Various other bacteraemia cases reported in India are hereby described in Table 3.

Conclusion

In conclusion, *A. dentrificans* bacteraemia can lead to morbid complications among hospitalized patients, chiefly in immunosuppressed patients. Empirical antibiotic therapy with a carbapenem agent appears to be appropriate in majority of cases, although *in vitro* susceptibility testing is recommended for further adjustments. Nevertheless, this uncommon entity must be evaluated in future studies for potential impact on the outcome of different sources of infection, underlying conditions and appropriateness of initial therapy. The importance of source control and infection control practices still continue to be the biggest armour against the infection.

Declarations

Ethical disclosures: Protection of human and animal subjects: This research do not used animals.

Confidentiality of data: The authors declare to have followed the reccomendations of its institution to keep the confiden¬ciality of patient´s data.

Right to privacy and informed consent: No data that permit to identify identity of patients is published, the authors have obtained the informed consent from patients

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Conflict of Interest: The author declare no conflict of interest.

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