



***Ochrobactrum anthropi* - An Unusual Cause of Line Related Sepsis. Current Knowledge of the Epidemiology and Clinical Features of This Pathogen**

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Authors' contributions

This work was carried out in collaboration between both authors. Authors SA and GJ designed the study, wrote the protocol, wrote the first draft of the manuscript, managed the literature searches and analyses of the study. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Onchrobactrum anthropi is a rare gram negative pathogen that is not usually associated with human infection. When it does occur, it tends to cause severe sepsis related to central venous devices. The susceptibility patterns vary and removal of the device and treatment using a suitable antimicrobial usually results in a cure. We present such a case in an immunocompetent patient and review the available.

Keywords: *Onchrobactrum anthropi*; bacteremia; line sepsis; diagnosis; treatment.

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1. CASE REPORT

This is a 40-year-old white male with a history of osteomyelitis of the right femur with an infected total knee arthroplasty (TKA) with *Klebsiella pneumoniae* and cirrhosis of the liver (Child-Pugh2) secondary to alcohol. He was not diabetic. Despite prolonged courses of intravenous antibiotics and repeated debridement and revision of the arthroplasty he did not improve and continued to have *Klebsiella* bacteremia and clinical evidence of active TKA infection. He therefore underwent an above knee amputation of the right leg. He then remained well for several months but then presented with several episodes of bacteremia with different pathogens including *Enterococcus faecalis*, *Klebsiella oxytoca*, *Stenotropomonas maltophilia*, and *Candida albicans*. The time interval between these episodes of bacteremia was 2-4 weeks. On each occasion he was treated with intravenous antibiotics based on the susceptibility reports. These included piperacillin-tazobactam, cefepime and imipenem. The primary sources of these bacteremia and fungi incidences were never discovered despite extensive work up including echocardiograms, imaging studies and even WBC labeled scans. Immunological work up looking for IgG and IgA deficiency and CD4 lymphopenia were also unremarkable.

On this occasion, the patient was admitted to the hospital with an abscess to the left hand that he said developed spontaneously. The cultures from the wound eventually grew gram-negative pathogens resembling *Brucella* and were sent for confirmation. He was placed on intravenous ceftriaxone, to which the infectious agent was susceptible to, and discharged home. He was readmitted 4 days later with fever and chills and a temperature up to 103.4F with hypotension. Following normal saline administration and cefepime he improved. Blood cultures (4 sets) that were drawn from the peripherally inserted central venous catheter (PICC) line grew a gram-negative bacillus that was identified as *O. anthropi*. The susceptibilities are mentioned in Table 2. The blood and pus samples were inoculated on blood agar media and then incubated at 28 C. The colonies that grew were pale yellow and had a popcorn like smell. Confirmation was done by a reference lab (LABCORP) using 16s rRNA sequencing.

Vital signs included a temperature of 102. 4F, blood pressure of 98/ 70 mm Hg and a pulse of 120 beats per minute. Physical examination was

unremarkable except for an above knee amputation of the right leg, which had healed well. The abscess of the palmar aspect of the left hand was small and mildly tender. Cultures from the abscess as well as the blood grew the same pathogen later identified as *O. anthropi*. The PICC line was removed and he was treated with oral levofloxacin (MIC< 0.25) for 14 days with resolution of the bacteremia and complete healing of the wound. It was suspected that these repeated infections were self-induced but this could not be proven.

2. DISCUSSION

2.1 Epidemiology

Hospital acquired sepsis is common, with over 250,000 estimated cases in the United States each year [1]. The sepsis may be primary or secondary depending on the etiology of the infection. Some primary infections are idiopathic but many have been known to be associated with intravascular catheterization such as with central venous catheters [2,3]. Since the 1980s, gram positive aerobes and *Candida* species have become more frequent causes of line-related sepsis, with coagulase-negative *Staphylococcus* species and *S. aureus* causing approximately 50% of line related sepsis cases [4]. Evidently patients who are more critically ill and/or require long-term catheterization are more at risk for developing line sepsis. A study by H. Shah and colleagues showed that percutaneous tunneled long-term central venous catheters (CVCs) had the highest incidence rate, at 3.6% incidence of infection per catheter placed, as opposed to peripheral venous catheters (PVCs), which had the lowest at 0.1% [5]. Wisplinghoff and colleagues stated that between 1995 and 2002, the majority of sepsis cases occurred in the ICU in patients with intravascular catheters [4]. The risk factors for line sepsis are dependent on the site of the insertion, skill and conditions of the insertion, and care of the catheterization site [6]. The increased risk for infection based on duration of the catheterization varies from catheter to catheter. For PVCs and Swan-Ganz catheters, the risk increases after three to four days, as opposed to CVCs and arterial catheters with an increased risk after six days [7-9]. The risk of infection can also be reduced depending on the material of the catheter. Teflon and polyurethane PVCs, anti-microbial-coated and silver-coated catheters, and catheters made with heparin-bonded components all confer a lowered risk of infection [7,10-12].

2.2 Microbiology and Clinical Presentation

Ochrobactrum anthropi is an unusual and rare causal organism of line sepsis. *O. anthropi* is a gram negative (Fig. 1), urease positive bacillus that produces oxidase and does not ferment lactose [13]. This pathogen was previously classified under the CDC group Achromobacter Vd [13]. The bacteria share the same family as *Brucella spp.*, *Brucellaceae*, but are more commonly found in soil [14,15]. It also oxidizes glucose and is motile by virtue of a peritrichous flagella [13]. The clinical presentation of *O. anthropi* is not well documented due to its rarity and morphological and metabolic similarities to other organisms. Hagiya and colleagues followed an 85 year old man with *O. anthropi* sepsis acquired from a transcatheter arterial chemoembolization. They reported the patient as having non-specific symptoms such as fevers, chills, and rigors [15]. When the organism was isolated and cultured from the patient, it produced pale yellow colonies with a popcorn-like odor [15]. The bacteria's 16s rRNA was analyzed and revealed homology with the rRNA of *Brucella spp.* [15]. For this reason, *O. anthropi* bacteremia has been known to be misdiagnosed as Brucellosis [16]. There even a case of Brucellosis being misidentified as an *O. anthropi* infection [17]. However, proper identification of the organism is essential for the treatment of line sepsis caused by *O. anthropi*. For example, *O. anthropi* has an outer membrane that is not permeable to hydrophobic substances as opposed to *Brucella spp.* [16]. Its membrane composition makes it susceptible to polymyxin antibiotics with the exception of colistin [16]. Recall that *O. anthropi* is also motile as opposed to *Brucella spp.*

Despite these characteristics *O. anthropi* has a low pathogenicity. Zakariya-Yousef and colleagues, in a case study of a patient who developed line sepsis from *O. anthropi*, emphasized its tendency to infect immunocompromised patients. They stated that the bacteria is often an etiological agent of hospital-acquired infections and that the frequency of infections by the organism is increasing [18]. Menezes et al. [19] noted the characteristics of the bacteria when they documented a case of an *O. anthropi* infection in an infant with Cystic Fibrosis. These authors also claim that that this organism has an ability to adhere to silicone via multiple surface proteins,

which may explain its association with catheter-related infections.

Overall, it can be said that the clinical presentation of line sepsis related to *O. anthropi* presents with fevers, chills, and gram-negative bacteremia with a resolution of symptoms on removal of the catheter and appropriate antibiotic administration.

2.3 Treatment Regimen

The ideal treatment for *O. anthropi*- related bacteremia has yet to be determined. Treatment regimens varied with each case and were dependent on the strain of *O. anthropi* causing the infection. However, we found that according to the case reports discussed in this paper, the majority of patients responded well to treatment with gentamicin or imipenem. For example, in 1992, Gransden and Eykyn reported the results of treatment for seven patients with *O. anthropi* line sepsis. Four of the seven patients were treated with Gentamicin. All but the fourth patient recovered; she died due to causes unrelated to the infection [20]. One of their patients was treated with imipenem, which also showed promising results [20]. Alnor and Colleagues also used gentamicin to treat one of their patients infected by *O. anthropi* [21]. Another case report by Shrishrimal treated their patient with a six-week regimen of gentamicin, with an addition of ciprofloxacin during the last four weeks [22]. On the other hand, Kern and colleagues discussed four cases that were not treated with gentamicin. Two of their patients recovered with combinations of drugs. The other two were treated with imipenem [23]. A more recent case by Siti Rohani and colleagues stated that their patient was also treated with imipenem [24]. Another case treated by using a combination of Gentamicin and Trimethoprim-sulfamethoxazole was documented by Kish and colleagues [25]. Our patient ultimately recovered with cefepime administration. We cannot state that there was a significant difference between the successes of treatment using monotherapy versus that of multidrug therapy based on the cases we discuss here.

In general, the specifics of course length for antibiotic treatment in the aforementioned cases are vague. Evidently, the amount of time required to administer antibiotic therapy may vary on a case-by-case basis or have to be adjusted depending on whether or not the indwelling catheter is removed. For example, the first

patient mentioned by Kern and Colleagues was treated with a fourteen-day course of ceftizadime/ netilmicin with the catheter left in place. However, the bacterial infection in the second patient was treated with piperacillin/ netilmicin for ten days. A third patient received two intervals of imipenem for five days each, due to a relapse of the infection, until the catheter was removed [23]. It would seem prudent to treat the bacteremia for a 2-week period.

It appears that recovery was predominantly dependent on the removal of the catheter. Of the fourteen cases in this series, 12 had their catheters removed. Of these twelve, ten survived. Table 1 summarizes the information mentioned above. Gransden and Eyken explained that removing the catheter facilitated the management of the infection to the extent of avoiding antimicrobial therapy [20]. This may be true for the two patients in their study that received no drug therapy but did have their catheter removed. However, further data is necessary to confirm this method of treatment. However, when the line cannot be removed then treatment with the above mentioned antibiotics should be implemented with surveillance cultures done after therapy.

We should also note that these patients were not all infected by the same strain of *O. anthropi*. In

other words, susceptibility and resistance of the microbe to certain drug classes may not be the same across every case. Susceptibility and resistance of the infectious agent was determined, for most cases, in vitro using MIC data collected from each case. In the cases reviewed by Gransden et al. [20] the causal organism was susceptible to Gentamicin, tobramycin, amikacin, ciprofloxacin, imipenem, Trimethoprim-sulfamethoxazole. They reported that the strains isolated from their patients were resistant to certain penicillin and cephalosporin drugs, as well as trimethoprim [20]. Kern and colleagues reported similar findings with the addition of imipenem and amikacin but also stated that their cases were resistant to most other beta-lactams [23]. Alnor and colleagues determined that their strains of *O. anthropi* were susceptible to tobramycin, some but not all cephalosporins, and imipenem but resistant to most beta-lactams including ampicillin, aztreonam, and piperacillin [21]. Given the relative morbidity of line sepsis, therapy must be administered prior to the results of the susceptibility studies to prevent further deterioration of the patient's condition. For example, Kish and colleagues stated that their patient had also responded well with tobramycin therapy without removal of the catheter despite the fact that their culture had shown resistance to it [25].



Fig. 1. Gram stain showing the gram negative rods resembling *O. anthropi*

Table 1. Diagnosis of patients diagnosed with and treated for *O. anthropi* line sepsis

Author	Year	Sex/Age	Underlying Illness	Catheter site	Treatment	Outcome
M. A. Kish et al.	1984	F/16	Hodgkin's disease	CVC	Gentamicin, Trimethoprim-sulfamethoxazole	Recovered
W. R. Gransden, S. J. Eykyn	1992	F/13	Rhabdomyosarcoma	*CVC	None	Recovered
		F/33	Thymoma	*CVC	None	Recovered
		F/70	Focal peritonitis	*CVC	Gentamicin	Recovered
		M/43	pancreatitis	*CVC	Gentamicin	Recovered
		F/28	Acute RF after C-sec	*CVC	Gentamicin	Recovered
		F/71	Post-cardiac surgery	*CVC	Gentamicin	**died
W. V. Kern et al.	1993	M/65	Post-thoracic surgery	*CVC	Ciprofloxacin, imipenem	**died
		F/67	Acute leukemia	CVC	Ceftazidime/netilmicin	Recovered
		F/59	Acute leukemia	*CVC	Piperacillin/netilmicin	Recovered
		F/19	Acute leukemia	*CVC	imipenem	Recovered
D. Alnor et al.	1994	F/2	ALL	CVC	Imipenem; amikacin	Recovered
		F/33	Crohn's disease	*CVC	----	Recovered
A. H. Siti Rohani	2013	F/56	Gastric ulcer	Subclavian venous catheter	Piperacillin; gentamicin	Recovered
		M/60	Type II DM, HTN, IHD, ESRF, small vessel disease	*permacath, *Triple lumen catheter, peripheral vein catheter	Imipenem	Recovered
K. Shrishrimal	2012	M/78	Type II DM, ESRF	*Tunneled hemodialysis catheter	Gentamicin, ciprofloxacin	Recovered

Summary of each case report and treatment. The list of antibiotics is not comprehensive and does not include every drug used by the authors to treat each patient. It is meant to represent the drug they noted to be the most effective against the infection. Legend: (* Catheter removed; ** Death unrelated to infection; CVC = Central Venous Catheter; HTN = Hypertension, DM = Diabetes Mellitus, ESRF = End Stage Renal Failure; IHD = Ischemic Heart Disease)

Table 2. Susceptibility studies of *O. anthropi*

Antibiotics	Susceptibilities	MIC
Amikacin	S	<16
AMP/Sulbactam	R	>16/8
Cefepeme	R	>16
Aztreonam	R	>16
Cefotaxime	R	>32
Ceftazidime	R	>16
Ceftriaxone	R	>32

3. CONCLUSION

This case series illustrates several important points about the characteristics of the patient infected by this unusual pathogen and is intended to provide a guide on how to best treat line sepsis caused by it. First and foremost, it is an opportunistic pathogen that tends to occur in immunocompromised patients and rarely in immunocompetent patients. Although *O. anthropi* bacteremia is not exclusively acquired via catheterization, several studies show that this is the most usual case. Secondly, the symptoms of the infection are non-specific and therefore one must rely on cultures and rRNA PCR for the proper identification of the organism. Once the proper strain has been identified, empiric treatment must be adjusted according to what that strain is susceptible to and may need to be further adjusted based on how the patient responds to treatment. Lastly, removal of the catheter seems to be the cornerstone of treatment and rapid recovery.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images'.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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