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ORIGINAL ARTICLE

# *Kocuria kristinae*: A true pathogen in pediatric patients

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**KEYWORDS**
Catheter-related bacteremia;
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*Kocuria kristinae*

*Background: Kocuria kristinae* is a Gram-positive microorganism, which has rarely been reported as a pathogen that causes infection in humans. Recently, a few studies had concluded that this pathogen can indeed cause infection in immunocompromised hosts. However, the number of reports on *K. kristinae* infection in pediatric patients is still relatively limited.
*Methods:* Clinical data on pediatric patients who had *K. kristinae* cells isolated from their blood specimens during the period from January 2008 to May 2012 in a tertiary-care hospital in northern Taiwan were gathered and analyzed.
*Results:* Among 12 patients with *K. kristinae* cells isolated from their blood specimens, laboratory test results confirmed seven to have *K. kristinae* bloodstream infection. Six of them were premature babies, and one had acute leukemia. The infections were all healthcare associated. All the six premature babies had clinical presentation of sepsis and were inserted with percutaneous central venous catheters. One patient had two sets of blood culture positive for *K. kristinae* infection, and two premature patients had two sets of *K. kristinae* isolated, one from blood culture and the other from catheter tip culture, both of which were done at the same time. The leukemic child was inserted with a Broviac catheter and had *K. kristinae* isolated from both blood specimen and Broviac catheter. In the remaining five patients, *K. kristinae* infection was considered to be contaminant because they had only one set of positive blood culture and had other recognized infections.
*Conclusion: K. kristinae* can cause infections in premature babies and immunocompromised pediatric patients using long-term intravenous catheters. Therefore, *K. kristinae* should be

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considered as a true pathogen and proper treatment should be provided to all susceptible pediatric patients.


## Introduction

*Kocuria kristinae* is a Gram-positive microorganism found on human skin and mucosa. Previously, they were classified under the genus *Micrococcus*, and regarded as a harmless normal skin microorganism. However, they have now been reclassified under the new genus *Kocuria*.[1] There are some reports of *K. kristinae*-associated infections in patients, especially those with malignancies or other immunosuppressed states.[2–9] The number of documented cases of infections is rare and the clinical pathogenic potency of *K. kristinae* is still doubtful. In addition, the number of reported patients in the pediatric group is even more limited. Therefore, we performed this study in order to better understand the clinical characteristics of *K. kristinae* bacteremia in pediatric patients.

## Materials and methods

### Patients' information

Data on all patients in the pediatric group with *K. kristinae* cells isolated from their blood culture during the period from January 2008 to May 2012 were retrieved from the microbiology laboratory database. We collected their clinical information from related medical records, including age, sex, underlying disease, comorbidity, clinical presentation, invasive procedure, infection source, laboratory data, management, and outcome. This study was approved by the Institutional Review Board of the Mackay Memorial Hospital (12MMNIS162).

### Definition

Bloodstream infection is confirmed in the laboratory tests if a recognized pathogen could be cultured from one or more blood cultures and the organism cultured from blood samples was not related to an infection at another site. An episode of bacteremia was defined as the condition of having more than one blood culture positive for *K. kristinae* that contributed to clinical sepsis. If there was only one positive blood culture, another positive culture should be obtained directly from an intravenous catheter or the clinical significance was otherwise evident.[10] The clinical significance of neonatal sepsis was defined as follows: (1) at least one of the following clinical signs or symptoms with no other recognized cause: fever, hypothermia, apnea, or bradycardia; (2) no apparent infection at another site; and (3) receiving treatment for sepsis.[11,12] Episodes associated with contaminants were defined as the isolation of *K. kristinae* from a single blood culture and where criteria for laboratory-confirmed bloodstream infection were not met.

The criteria for confirming catheter-related bacteremia were: (1) isolation of the same microorganism from blood and exudates from the catheter's exit site or specimens from the catheter lumen with signs of inflammation; and (2) isolation of the same microorganism from blood and the catheter tip upon removal of the catheter.[13]

Healthcare-associated infection was a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or its toxin. There must be no evidence that the infection was present or that the bacteria were incubating at the time of admission to the acute-care setting.[10]

### Microbiology

One set of blood culture was obtained from most of the patients. A catheter tip culture might be done simultaneously if the catheter was removed immediately. Approximately 0.5–3 mL of blood was drawn after sterilizing the skin. The blood samples were then added into BD BACTEC Peds Plus culture vials (Becton Dickinson Company, Benex Limited, Shannon, Ireland). Blood culture specimens were processed by the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France) with VITEK 2 Gram-positive identification card used to confirm Gram-positive bacterial identification.

## Results

During the study period, a total of 12 pediatric patients with blood cultures of *K. kristinae* were included for analysis. The demographic data and clinical characteristics of the patients are summarized in Tables 1 and 2. Seven patients (Case Numbers 1–7) were regarded as having laboratory-confirmed *K. kristinae* bloodstream infection, whereas *K. kristinae* infection was considered to be a contaminant in the remaining five patients (Case Numbers 8–12).

Among the laboratory-confirmed bloodstream infection group, six of them were premature babies (Case Numbers 1–6) and one patient had acute leukemia (Case Number 7). The six premature patients had risk factors for infection including small for gestation age, low birth weight, prolonged hospital stay, use of intravascular devices and respiratory support, and total parenteral nutrition. They all had a clinical presentation of sepsis, were inserted with percutaneous central venous catheters, and received antibiotic treatment. Three premature babies (Case Numbers 1–3) had *K. kristinae* cells isolated from their only set of blood culture, and a simultaneous catheter culture was not performed. One premature patient (Case Number 4) had two sets of blood culture, done in 2 successive days, positive for *K. kristinae*. Two premature patients (Case Numbers 5 and 6) had two sets of *K. kristinae* isolated, one from blood culture and the other from catheter tip culture,

**Table 1** Demographic data of 12 patients with *Kocuria kristinae* isolated from blood cultures

| | Case | Sex/ Age (mo) | Diagnosis at admission | Underlying disease | Concomitant disease | Isolation site | Intravascular devices | Healthcare-associated infection | Clinical presentation |
|---|---|---|---|---|---|---|---|---|---|
| Group 1 | 1 | M/1.4 | Prematurity, GA 26 + 3 wk | Prematurity | No | Blood | PCVC | Yes | Apnea, bradycardia |
| | 2 | M/0.6 | Prematurity, GA: 27 + 3 wk | Prematurity | No | Blood | PCVC | Yes | Apnea, bradycardia |
| | 3 | F/0.7 | Prematurity, GA: 28 + 1 wk | Prematurity | No | Blood | PCVC | Yes | Apnea, bradycardia |
| | 4 | F/1.1 | Prematurity, GA 25 + 4 wk | Prematurity | No | Blood × 2 | PCVC | Yes | Desaturation, thrombocytosis |
| | 5 | F/0.6 | Prematurity, GA 31 + 1 wk | Prematurity | No | Blood & catheter tip | PCVC | Yes | Apnea, bradycardia |
| | 6 | F/0.6 | Prematurity, GA 31 + 1 wk | Prematurity | No | Blood & catheter tip | PCVC | Yes | Apnea, bradycardia |
| | 7 | F/2.5 | Infantile acute leukemia | Leukemia | No | Blood & Broviac | Broviac | Yes | Neutropenic fever |
| Group 2 | 8 | F/4.4 | UTI | No | UTI: *E. coli* | Blood | Peripheral catheter | No | Fever to 40 °C for 3 d |
| | 9 | M/13.8 | UTI | No | UTI: *E. coli* | Blood | Peripheral catheter | No | Fever to 39 °C for 1 d |
| | 10 | F/33.9 | Bronchopneumonia | No | Pneumonia | Blood | Peripheral catheter | No | Fever to 39 °C for 4 d |
| | 11 | F/9.0 | Acute bronchiolitis | No | Febrile convulsion | Blood | Peripheral catheter | No | Fever to 40 °C for 3 d |
| | 12 | F/16.9 | Acute pharyngitis | No | Viral exanthem | Blood | Peripheral catheter | No | Fever to 40 °C for 4 d |

*E. coli* = *Escherichia coli*; F = female; GA = gestation age; M = male; PCVC = percutaneous central venous catheter; UTI = urinary tract infection.

**Table 2** Treatment and outcomes of 12 patients with *Kocuria kristinae* isolated from blood cultures

| | Case | Hospital duration (d) | Isolation time after admission (d) | Antibiotic regimen | Antibiotic treatment course (d) | Respiratory support | Total parenteral nutrition | Empirical antibiotic indication | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Group 1 | 1 | 85 | 43 | Vancomycin, Ceftazidime | 10 | Yes | Yes | Clinical sepsis | Recovery |
| | 2 | 79 | 17 | Vancomycin | 10 | Yes | Yes | Clinical sepsis | Recovery |
| | 3 | 69 | 21 | Vancomycin, Ceftazidime | 10 | Yes | Yes | Clinical sepsis | Recovery |
| | 4 | 97 | 33 | Oxacillin, Vancomycin | 9 | Yes | Yes | Clinical sepsis | Recovery |
| | 5 | 66 | 18 | Vancomycin, Cefotaxime | 12 | Yes | Yes | Clinical sepsis | Recovery |
| | 6 | 46 | 20 | Vancomycin, Cefotaxime | 10 | Yes | Yes | Clinical sepsis | Recovery |
| | 7 | 88 | 19 | Vancomycin, Piperacillin/ Tazobactam | 10 | No | No | Neutropenic fever | Recovery |
| Group 2 | 8 | 8 | 0 | Cefazolin | 7 | No | No | UTI | Recovery |
| | 9 | 7 | 0 | Gentamicin, Cefazolin | 7 | No | No | UTI | Recovery |
| | 10 | 5 | 0 | Amoxicillin/Clavulanate | 9 | No | No | Pneumonia | Recovery |
| | 11 | 3 | 0 | No | 0 | No | No | No | Recovery |
| | 12 | 4 | 0 | No | 0 | No | No | No | Recovery |

UTI = urinary tract infection.

both of which were done at the same time. The leukemic patient had a prolonged hospital stay and was inserted with a Broviac catheter (C. R. Bard, Inc., New Jersey, USA). She developed a neutropenic fever and had *K. kristinae* isolated from her blood specimen, Broviac catheter, and urine specimen. All seven episodes were healthcare-associated infections; three were proved to be catheter-related bacteremia.

These seven patients developed *K. kristinae* bacteremia within 17—43 days (24.4 ± 9.8) after their admission. These patients had a mean white blood cell count of 7768 ± 4319/μL, C-reactive protein level of 2.65 ± 1.44 mg/dL, and platelet count of 143,000 ± 76,000/μL. The mean duration of use of intravascular devices was 18.7 ± 8.4 days. Six patients, except Case Number 7, received ventilator support (endotracheal tube and nasal continuous positive airway pressure) and the mean duration for the support was 24.6 ± 10.9 days. These episodes were mainly treated with vancomycin for 9—12 days (10.1 ± 0.9 days). Besides, their intravenous devices were all removed. The hospitalization courses were 46—97 days (75.7 ± 16.9 days). All the *K. kristinae* infections were successfully managed and there was no infection-related mortality.

The second group was thought to be a skin contaminant. All the five patients had associated comorbidity, including two urinary tract infections (Case Numbers 8 and 9), one pneumonia (Case Number 10), one acute bronchiolitis with febrile convulsion (Case Number 11), and one viral exanthema (Case Number 12). The two patients with urine culture positive for *Escherichia coli* infection and the one with pneumonia received antibiotic therapy for 7—9 days, and other two cases did not. Their second blood cultures were all negative for *K. kristinae*.

## Discussion

*K. kristinae* is a facultative anaerobic Gram-positive bacterium that occurs in tetrads and produces pale cream nonhemolytic colonies on blood agar.[7] This bacterium used to be a member of the *Micrococcus* family. They have been identified as common skin and oral flora in humans. According to the Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definition of healthcare-associated infections, *Micrococcus* spp. are thought to be common skin contaminants.[10] Recently, Stackebrandt et al[1] made a taxonomic revision of this class of microorganisms and some strains were reclassified under the new genus *Kocuria*. At present, *K. kristinae* can be identified by the new version of the VITEK 2 system.[14] Previously, there was a possible misidentification of coagulase-negative *Staphylococci* as *Kocuria* spp. when using the old version of the automated identification system in the hospital laboratory. However, this misidentification is avoidable when using the recent versions of this system.[7,14]

Only a few cases of *K. kristinae* infection were found in the related literature. Infection due to *K. kristinae* was first reported in an ovarian cancer patient with catheter-related bacteremia.[2] In addition, *K. kristinae* infection was also reported for acute cholecystitis,[3] brain abscess,[5] infective endocarditis,[6] central venous catheter-related bacteremia among immunocompromised hosts receiving total parenteral nutrition,[7] and dialysis-related peritonitis.[8,9] In our patients, the *K. kristinae* infections are mainly found in premature babies and patients with malignancy. They were all with percutaneous central venous catheters. This finding is similar to the previous reports that most *K. kristinae* infections are catheter related and in immunocompromised patients.[2—7]

Intravascular devices can be seen in most patients with primary bloodstream infections. Using intravascular devices in premature babies and in immunocompromised patients is the most powerful risk factor for bloodstream infection. Blood cultures are usually performed when clinical sepsis is suspected, but many culture results may be negative, especially in neonates. Stoll et al[15] reported that although the actual number of very low-birth-weight newborns with culture-proven infection was only 1.9%, 50% of the babies were prescribed antibiotics by clinicians on the basis of clinical and risk factors. This is because the behavior of the bacterium is not constant, and the sensitivity of the blood culture increases with the number of cultures drawn and the volume of the sample.[16] Neonates are at high risk of acquiring healthcare-associated infections because of impaired host-defense mechanisms, limited amounts of protective endogenous flora on skin at time of birth, reduced barrier function of their skin, and use of invasive procedures and devices.[17] Neonates with a gestational age less than 30 weeks, birth body weight less than 1500 g, and on respiratory support, with peripheral catheter, central-long catheter, total parenteral nutrition, and prolonged hospital stays have a greater risk of developing sepsis.[18] The risk factors for infection, except prematurity but including other underlying disorders, which impair host-defense mechanisms are neutropenia, end-stage renal disease, and the administration of certain drugs such as corticosteroids and other immune suppressants.[19] The *K. kristinae* infections generally occur during a long hospital course. Our patients developed the infection within 17—43 days after their admission and fulfilled the definition of healthcare-associated infections.[10,20] Even though some of our patients had only one set of positive culture for *K. kristinae*, we still think of it as a potentially infectious pathogen in these special groups.

Because of the limited number of reports available regarding this infection, there are no guidelines for managing it. In our patients, they were mainly treated with vancomycin due to the underlying diseases. The *K. kristinae* infections have been managed successfully with a number of different antimicrobial drugs according to previous reports.[7] In the literature, isolated *K. kristinae* may be sensitive to β-lactams, quinolones, lincosamides, cotrimoxazole, glycopeptides, streptogramins, fusidic acid, or linezolid so far, but may or may not be resistant to oxacillin/methicillin.[21] Treatment has been successful using monotherapy with oxacillin, vancomycin, piperacillin/tazobactam, and ciprofloxacin and combination therapy with teicoplanin and vancomycin, ciprofloxacin, and clindamycin as well as ceftriaxone and ofloxacin.[7] Previous reports have also suggested that the removal of the intravascular catheter is necessary due to catheter-related, healthcare-associated infection characteristics.[2,6,7] The infection course and outcome are usually good after antibiotic treatment and catheter removal.

Contamination of *K. kristinae* may occur in immunocompetent children; however, if the contamination rate is relatively high, unnecessary antibiotic usage and longer hospital stay with more hospital-care costs will increase.[22] Three of our *K. kristinae* contaminant patients only received antibiotic therapy for other bacterial infections. The other two did not receive prescribed antibiotic agents because they were considered to be viral infections. Physicians need to make a judgment on whether the isolated *K. kristinae* cells represent a true infection or not.

Our study has several limitations that are worth noting. First, although the number of children studied is larger than previous reports, it is still small and premature patients are the major part of this study. A larger patient number and broader spectrum of patients are needed for further evaluation. Second, it was difficult to distinguish between true *K. kristinae* infections and contaminant organisms. The gold standard for diagnosing an infection is to get two blood cultures from separate sites at sepsis evaluation. The Clinical and Laboratory Standards Institute guidelines recommend that a single set of cultures should never be drawn initially in patients with clinical suspicion of sepsis. Independently drawn venipuncture helps to distinguish between contaminant organisms.[22] However, usually only one set of blood culture was performed in the newborns. Adequate blood sampling volume is also an important factor for detecting a bloodstream organism.[22] This could be difficult in the pediatric group especially in premature babies. It is difficult to obtain adequate blood samples in this group and the average volume of blood placed in a blood culture bottle is $<$0.5 mL, making this test markedly less sensitive.[12] Third, we used only the VITEK 2 system to confirm the identity of bacteria and lack of molecular typing of this pathogen. In addition, we did not perform a drug-sensitivity test to provide guidance on antibiotic choice. The best identification method for *K. kristinae* and the best choice of antibiotics still need further studies.

In conclusion, we should not underestimate the possibility of *K. kristinae* infection when blood culture shows a positive result particularly in pediatric immunocompromised patients, including newborns, with intravenous catheter. Therefore, *K. kristinae* should be considered as a true pathogen and proper treatment should be provided to all susceptible pediatric patients.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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