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Case Report

Kluyvera ascorbata infections in children: a case series

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Abstract

Kluyvera is a relatively newly described member of the Enterobacteriaceae family that rarely causes infections in humans. In the pediatric population, it is described in association with clinically significant infections ranging from urinary tract infections to sepsis with multiorgan failure. Our aim is to determine the clinical significance of K. ascorbata infections in the pediatric population at our institution. We retrospectively analyzed clinical microbiology data as from 2006 and identified four clinically significant isolates in this period. The isolates were from four cases who presented with sepsis, bacteremia associated with central venous catheter, pyelonephritis and intraabdominal collection. The ages of these patients ranged between seven months to 17 years. All patients received prompt antimicrobial treatment on the basis of susceptibility testing and good clinical response was obtained in all patients. Successful treatment options include third-generation cephalosporins, aminoglycosides, betalactams with beta-lactamase inhibitors and carbapenems. Clinicians should be aware of the spectrum of disease and increasing clinical importance associated with this pathogen.

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Keywords: Abdominal infection, bacteraemia, *Kluyvera ascorbata*, pyelonephritis, sepsis

Introduction

Kluyvera is a gram negative bacillus and was defined by Kluyver and van Niel for the first time in 1936 (1). This bacillus which was initially thought to be a benign pathogen which could be localized in the respiratory tract, gastrointestinal system and urinary tract has been observed to cause to clinically severe disease in various anatomic localizations in the last 30 years. It was shown to be a new member of the Enterobacteriaceae family using molecular methods and deoxyribonucleic acid (DNA) hybridization technique in 1981 (2). There are four Kluyvera species which have been defined until the present time including *K. ascorbata*, *K. cryocrescens*, *K. georgiana* and *K. cochleae* (3). *Kluyvera* is a small, peritrichous, mobile, oxidase negative, catalase positive gram negative bacillus and ferments glucose (1, 4, 5). It is differentiated from other organisms with similar characteristics with its ability to use citrate and malonate, decarboxylate lysine and ornithine and to produce excessive α-ketoglutaric acid during glucose fermantation (6). Validation tests such as usage of ascorbate glucose fermentation at 5°C can differentiation Kluyvera species (2). It has no specific virulance factor, but the lipopolysachharide layer and superficial antigens are responsible of virulance as with other bacteriae in the Enterobacteriaceae family (6). *Kluyvera* is found in water, plants and canalization wastes in the environment, hospital wash basins and animal-derived food (4). It can also be isolated from various human-derived samples (frequently sputum, urine, stool, throat and blood).

In this article, four patients in whom *Kluyvera ascorbata* was isolated between January 2006 and December 2012 in Hacettepe University Medical Faculty İhsan Doğramacı Children's Hospital and accepted to be responsible of the clinical picture of severe infection are presented.

Case 1

A seven-month old male patient followed up with a diagnosis of double-outlet right ventricle, large ventricular

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septal defect, atrial septal defect, pulmonary hypertension and interrrupted arcus aorta was internalized for operation. Right paracardiac consolidation was observed on chest x-ray which was ordered because of the complaint of cough which had been lasting for three days. Cefepime was inititated by evaluating the undelying clinical picture. On the 10th day of treatment, the clinical findings worsened and the body temperature increased again (38,8°C). His laboratory findings were as follows: hemoglogin 9.6 g/dL, leukocytes: 20 500/mm^3, platelets: 294 000/mm^3 and C-reactive protein: 13.6 mg/dL. Since the findings on the chest x-ray improved, cefepime was discontinued after obtaining blood culture meropenem, vancomycin and amikacin treatments were started considering the hospitalization of the patient. Fever was controlled on the second day of treatment and *K. ascorbata* growth was found in blood culture. In the antibiotic sensitivity test, the isolate was found to be resistant to ampicillin, cephazolin and cefoxitin and sensitive to ampicillin-sulbactam, amikacin, aztreonam, ceftriaxon, ceftazidim, cefepime, ciprofloxacin, imipenem, meropenem and piperacillin-tazobactam. Vancomycin was discontinued on the seventh day. Meropenem and amikacin treatment was completed to 14 days and the patient was discharged with a good general status to be operated on a future date.

Case 2

A 13-year old girl with a history of preterm delivery, distonic brain palsy, recurrent pulmonary infection and epilepsy presented with complaints of respiratory distress, fever and cough. Intravenous ampicillin-sulbactam was initiated in the patient who was found to have rales on physical examination, an oxygen saturation of 89% and consolidation on chest x-ray. The body temperature decreased and oxygen saturation increased. On the 8th day of the follow-up, her general status deteriorated, tachypnea increased and respiratory acidosis developed. An increase in infiltration was observed on lung graphy. The patient was intubated and internalized in the intensive care unit. Ampicillin-sulbactam treatment was discontinued. Meropenem, amikacin and linezolid treatments were started, because the patient had vancomycin allergy. Transient central venous catheter was placed because of difficulty experienced in achieving intravenous access. The antibiotics were completed to 14 days and discontinued. However, tracheostomy was performed on the 20th day, because the patient could not tolerate extubation. The patient could not be discharged, because antiepileptic treatment had to be adjusted. In the follow-up, fever with chills (39.4°C) and increase in oxygen requirement occured in the period when antimicrobial treatment was not administered. The laboratory findings were as follows: hemoglobin: 10,7 g/dL, leukocytes: 10 900/mm^3, platelets: 313 000/mm^3 and C-reactive protein 4,9 mg/dL. After obtaining catheter and blood culture, cefepime and amikacin treatment was started empirically. On the third day of treatment, fever was controlled and *K.ascorbata* was grown in the catheter culture. In the antibiotic sensitivity test, the isolate was found to be resistant to ampicillin, cefazolin, cefoxitin and sensitive to ampicillin-sulbactam, amikacin, aztreonam, ceftriaxon, ceftazidim, cefepime, ciprofloxacin, imipenem, meropenem and piperacillin-tazobactam. The antibiotic treatment was completed to 14 days and discontined. The patient is still being followed up in our ward.

Case 3

A six-year old girl had a non-vehicle traffic accident 10 months before presentation. Correction operation was performed in the patient who developed bladder rupture and vesicovaginal fistula after the accident. The patient who developed wound tissue and extention limitation in the arm was hospitalized in our hospital to perform free patch operation. The wound tissue was revised and patch operation was realized. 2 days after the operation the patient's body temperature increased (38.4°C) and her laboratory findings were as follows: hemoblobin: 13.8 g/dL, leukocytes: 12 000/mm^3, platelets: 240 000/mm^3 and C-reactive protein: 2.4 mg/dL. On urinary analysis, 20 leukocytes and 5 eryhtrocytes were observed and ceftriaxon treatment was initiated with a prediagnosis of urinary tract infection. On the third day of treatment, it was learned that *K.ascorbata* was grown in urinary culture. In the antibiotic sensitivity test, the isolate was found to be resistant to ampicillin, amoxycillin-clavunate, cefazolin, cefoxitin and trimetorprim-sulphametoxasol and sensitive to amikacin, aztreonam, cefuraxim, ceftriaxon, ceftazidim, cefepime, ciprofloxacin, imipenem, meropenem and piperacillin-tazobactam. The patient responded well to antibiotic treatment which was completed to 10 days and was discharged.

Case 4

A 17-year old male patient presented to our hospital with complaints of abdominal pain, diarrhea and weight loss before 1.5 months. On abdominal tomography, wall thickenning was observed in the terminal ileum. On colonoscopic examination, ulcerative lesions with spontaneous bleeding foci were found in the terminal ileum and cecum and the biospy result was compatible with chronic ileocolitis. Meselazin and budesonid treatment was given to the patient who was diagnosed with Crohn disease and he was followed up. On the 10th

day of treatment, the patient presented to another center because of abdominal pain and fever. Air-fluid levels were observed on direct graphy and pericecal collection was observed in the right lower quadrant on tomography. Therefore, the patient was referred to our hospital. His laboratory findings were as follows: hemoglobin: 11,1 g/dL, WBC: 11 500/mm^3, platelets: 338 000/mm^3 and C-reactive protein: 3.2 mg/dL. A drainage tube was placed for collection and ampicillin-sulbactam, amikacin and ornidazole treatment was initiated. *K. ascorbata* was grown in the drainage fluid and present antibiotic treatment was not changed. In the antibiotic sensitivity test, the isolate was found to be resistant to ampicillin, moderately sensitive to cefazolin and cefoxitin and sensitive to amikacin, amoxycillin-clavunate, aztreonam, cefotaxim, ceftriaxon, ceftazidim, ciprofloxacin, imipenem, meropenem, trimethoprim-sulphametoxazole, piperacillin-tazobactam and levofloxacin. The collection disappeared and the patient's drainage tube was removed on the 8th day. Antibiotic treatment was completed to 14 days and the patient was discharged.

Isolation method

For isolation of *Kluyvera* urinary and drainage fluid samples were planted in blood agar by way of qualitative method by placing 10 **µ**L urine/fluid in the middle of the plaque and by zigzagging with a loop on the whole plaque. Planting on MacConkey agar was performed by way of single colony method by placing 10 **µ**L urine/fluid in the edge of the plaque and by diluting with the help of a loop. The blood culture sample was placed in Becton Dickenson's (BD) Peds Plus™/F culure bottles and put in Bactec 9240 device. The cultures which gave positive alarm were planted in blood, Mac Conkey and chochlate agars. Gram staining was performed for the colonies which were thought to be gram negative macroscopically and gram negative bacillus was defined. All strains were planted in Columbia

Table 1. Pediatric cases Kluyvera infection reported in the literature

Reference	Age	Gender	Clinical finding	Infection region	Kluyvera types	Outcome
Aevaliotis[9] (1985)	3 weeks	Female	İshal	Stool	*K.ascorbata*	Recovery
Wong[10] (1987)	17 months	Male	Kateter enfeksiyonu, sepsis	Blood	*K.cryocrescens*	Exitus
Tristram[11] (1988)	11 months	Female	Pyelonephritis, sepsis	Urine, blood	*Kluyvera*, tiplendirilmemiş	Recovery
Yogev[12] (1990)	13 years	Female	Peritonitis, pneumonia, sepsis, urinary tract infection	Peritoneal fluid, lung tissue, urine	*K.ascorbata*	Exitus
Dollberg[13] (1990)	5 years	Female	Pyelonephritis	Urine	*Kluyvera*, undifferentiated	Recovery
Ortega[14] (1999)	10 years	Female	Pyelonephritis, proteinuria	Urine	*K.cryocrescens*	Recovery
Sarria[15] (2001)	16 years	Female	Urinary tract infection	Urine	*K.ascorbata*	Recovery
Brooks[4] (2003)	17 years	Female	Catheter infection	Blood	*Kluyvera*, undifferentiated	Recovery
Eisenhut[16] (2005)	2 years	Female	Emphysematous gastritis	Stomach, spleen	*Kluyvera*, undifferentiated	Exitus
Carter[3] (2005)	2 months	Female	Sepsis	Blood	*K.ascorbata*	Recovery
	4 years	Male	Growth retardation	Blood	*K.ascorbata*	Recovery
	11 years	Male	Acute appendicitis, peritonitis	Periton sıvısı	*K.ascorbata*	Recovery
Narchi[5] (2005)	19 months	Female	Pyelonephritis	Urine	*K.ascorbata*	Recovery
Darling[17] (2005)	15 years	Male	Cellulitis in association with abscess	Wound in the foot	*Kluyvera*, undifferentiated	Recovery
Rosso[18] (2007)	Yenidoğan	Male	Meningitis	Cerebrospinal fluid	*K.ascorbata*	Recovery
Carter[8] (2008)	4 months	Male	Cellulitis, sepsis	The area around the gastrostomy tube	*K.ascorbata*	Recovery
Ruffini[19] (2008)	3 months	Female	Urinary tract infection	Urine	*K.ascorbata*	Recovery
Toprak[20] (2008)	2 years	Male	Catheter infection	Blood	*K.cryocrescens*	Recovery
İsozaki[21] (2010)	3 months	Male	Urinary tract infection	Urine	*K.ascorbata*	Recovery
Olgularımız	7 months	Male	Sepsis	Blood	*K.ascorbata*	Recovery
	13 years	Female	Catheter infection	Blood	*K.ascorbata*	Recovery
	6 years	Female	Pyelonephritis	Urine	*K.ascorbata*	Recovery
	17 years	Male	Intraabdominal collection	Intraabdominal collection fluid	*K.ascorbata*	Recovery

agar (BD) and the strains isolated form the urinary/fluid sample were evaluated in the UNMID/ID-83 urine panel of BD Phonix™ 100 device. The strains which were isolated from the blood culture were evaluated in the NMIC/ID-99 enteric panel. These strains were defined to be *Kluyvera ascorbata* 18-24 hours later. With the objective of validation, the reactions in malonate, esculin and citrate media and growth in Müeller Hinton medium which did not include blood were evaluated. It was observed that these strains were malonate, esculin and citrate positive and formed purple-dark colonies in the Müeller Hinton (7).

Discussion

Kluyvera which was known as enteric group 8 and API group 1 previously has been defined molecularly in the last 25 years and its types have been demonstrated. It has been reported that three (*K. ascorbata, K. cryocrescens, K.georgiana*) of the four types demonstrated until the present time cause infection in humans and the most common among these is *K. ascorbata* as in our patient series (8). While *K. ascorbata* was isolated in 11 of 19 pediatric patients in the literature and *K. cryocrescens* was isolated in three, typing could not be done in five (3-5, 8-21). In Table 1, all pediatric cases in which *Kluyvera* infection was reported is summarized.

The severity of clinically important infections which can be observed in all age groups varies. The relation of the host's immune status with the severity of infection has not been shown definetely (18). In the literature, there are five patients who were lost due to *Kluyvera* infection and related complications and three of these patients were in the childhood age group (10, 12, 16). A 17-year patient who was followed with a diagnosis of Fallot tetralogy by Wong (10) was lost because of catheter-related sepsis despite 10-day ampicillin and gentamycin treatment. In a 13-year old patient who was followed up by Yogev et al. (12) with a diagnosis of Friedreich ataxia and dilated cardiomyopathy, peritonitis secondary to ileum perforation and pneumonia developed. The patient was lost despite 2-day moxolactam and 9-day gentamycin treatment. On postmortem examination, *K. ascorbata* was isolated in the lung tissue, peritoneal fluid and in the abscess found in the subdiaphragmatic region. The third patient was a 2-year old female patient with many medical problems who presented with vomiting and tachycardia and was lost in 6 hours (16). On autopsy, endocarditis and emphysematous gastritis were demonstrated and *Kluyvera* species were isolated in postmortem gastric and spleen cultures. The mutual characteristic of these patients was presence of underlying diseases. Mortality was not observed in any of our patients, although an underlying disease was present in all of them. This was thought to be related with early initiation of empirical antibiotics when the findings of clinical infection developed in our patients.

The distribution of the regions where infection is isolated in children is similar to adults. Infection has no specific localization; it may be observed in the urinary tract, gastrointestinal system, soft tissue, central nervous system and blood (6, 18). The first patient reported was a newborn who presented with diarrhea which had been lasting for three weeks and completely recovered after 7-day symptomatic treatment (9). Since *Kluyvera* species are a part of the gastrointestinal system flora, demonstration of the agent in stool is an expected condition. Isolation of this agent in patients with diarrhea does not show that diarrhea is directly related to this microorganism. In addition, diarrhea related to *Kluyvera* has not been reported in the last 20 years in the literature. *K.cryocrescens*-related catheter infection was demonstrated for the first time in 1987 in a 17-month patient reported by Wong (10) and the patient was lost because of sepsis. In subsequent years, the agent was isolated most frequently in the urinary tranct both in the pediatric and adulthood age groups. Urinary tract infection was found in eight of the pediatric cases in the literature; findings of pyelonephritis were present

Table 2. Antibiotic resistance test results

	Number of the Kluyvera species (%)		
Antibiotic	Sensitive	Moderate-sensitive	Resistant
Amikacin	4 (100)	-	-
Ampicillin	-	-	4 (100)
Ampicillin-sulbactam	3 (75)	-	1 (25)
Amoxycillin-clavunate	3 (75)	-	1 (25)
Aztreonam	4 (100)	-	-
Cefazolin	-	1 (25)	3 (75)
Cefoxitin	-	1 (25)	3 (75)
Ceftriaxon	4 (100)	-	-
Ceftazidim	4 (100)	-	-
Cefepime	4 (100)	-	-
Ciprofloxacin	4 (100)	-	-
Imipenem	4 (100)	-	-
Meropenem	4 (100)	-	-
Piperacillin-tazobactam	4 (100)	-	-
Trimethoprim-sulphametoxasole	3 (75)	-	1 (25)

in four of these patients (5, 11, 13, 14), while findings compatible with lower urinary tract infection were observed in the other four patients (12, 15, 19, 21). Resistant proteinuria was found in a patient with growth of *K. cryocrescens* who was reported by Ortega et al. (14). Proteinuria was not observed in our patient in whom *K.ascorbata* was isolated in urine in our series. This is thought to be related with the difference in the types isolated.

Another region in which *Kluyvera* species are isolated frequently is blood. The agent was demonstrated in the blood in five of the pediatric cases reported (3, 4, 10, 11). Sepsis secondary to catheter infection was observed in two of these patients (4, 10) and primary bloodstream infection was observed in three (3, 11). In addition, cellulitis (8), pyelonephritis (11) and sepsis secondary to peritonitis (12) have been reported in pediatric cases. Bloodstream infection was observed in two patients in our case series and *K.ascorbata* was isolated in one of these patients in relation with catheter.

Our information about in vitro antibiotic sensitivities of *Kluyvera* species and treatment time are limited. However, third generation cefalosporins, fluoroquinolone, aminoglycosides, teracycline, aztreonam and cabapenems are the most efficient antibiotics which are used in treatment (3, 13). The resistance rate for ampicillin and first and second generation cephalosporins is about 50% (3). This rate was found to be 75% in our patients (Table 2). It was demonstrated that treatment efficiency increased with addition of clavunate (22). However, resistance to amoxycillin-clavunate was observed in one of our patients (25%). In the literature, no antibiotic has been defined as the first-line treatment (3). It has been recommended that treatment should be preferred depending on antibiotic sensitivity results, the clinical status and infection region. While single antibiotic treatment is sufficient in cutaneous and and lower urinary tract infections, multiple antibiotic regimes should be preferred for treatment of life-threatening infections including bloodstream infections. It should be kept in mind that *Kluyvera* which is a rare microorganism and which may lead to severe infections can cause to various clinical findings in humans and appropriate antibiotics should be initiated in the early period.

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