

## Original Article

# *Kluyvera ascorbata* as a Pathogen in Adults and Children: Clinical Features and Antibiotic Susceptibilities in a Single Center Study

Jaehyeon Lee<sup>1,4,5</sup>, Joo-Hee Hwang<sup>2,4,5</sup>, Dae Sun Jo<sup>3,4,5</sup>, Hye Soo Lee<sup>1,4,5</sup>, and Jeong-Hwan Hwang<sup>2,4,5\*</sup>

<sup>1</sup>Department of Laboratory Medicine, <sup>2</sup>Department of Internal Medicine, and <sup>3</sup>Department of Pediatrics, Chonbuk National University Hospital, Jeonju; <sup>4</sup>Research Institute of Clinical Medicine of Chonbuk National University, Jeonju; and <sup>5</sup>Biomedical Research Institute of Chonbuk National University Hospital, Jeonbuk, Republic of Korea

**SUMMARY:** To assess the clinical characteristics of the rare *Kluyvera ascorbata* infection, we reviewed the medical records of patients from whom *K. ascorbata* was isolated from 2010 to 2016, and conducted a systematic review of the English and Spanish literature in PubMed for reports of *K. ascorbata* infection in humans from 1971 to 2018. A total of 43 cases (24 adults and 19 children) were enrolled: 3 at our hospital and 40 from the literature review. The urinary tract was the most common site of infection (44.2%, 19/43), followed by the bloodstream (27.9%, 12/43). There was no significant difference in the frequency of urinary tract infections (50% vs 36.8%;  $P = 0.388$ ) and bloodstream infections (25% vs 31.6%;  $P = 0.633$ ) in adults and children. Seventeen (60.7%, present in 28 of 43 cases) had nosocomial or healthcare-associated infections: 72.7% among children and 60% among adults. Superinfection developed in 20% (6 in 30 cases). The overall mortality was 12.1%. The antimicrobial agents mainly used in these 43 cases were third-generation cephalosporin, cefepime, piperacillin-tazobactam, ciprofloxacin, amikacin, and carbapenem. Most strains were resistant to ampicillin and first- and second-generation cephalosporins. *K. ascorbata* is a rare but significant clinical pathogen in adults and children.

## INTRODUCTION

*Kluyvera*, a small, flagellated, motile-negative bacillus, was initially described by *Kluyvera* et al. in 1936 (1). Farmer et al. redefined *Kluyvera* as a separate genus based on DNA-DNA hybridization and biochemical reaction in 1981 (2). *Kluyvera* is present in the environment as a free-living organism in water, soil, sewage, hospital sinks, and some animals (3). In humans, *Kluyvera* has been recognized as a benign saprophyte of the normal flora of the human gastrointestinal tract, respiratory tract, and urinary tract (4). Currently, the genus has 4 species: *Kluyvera ascorbata*, *K. cryocrescens*, *K. georgiana*, and *K. cochlea* (5). All of these except *K. cochlea* have been reported to cause human infections, and *K. ascorbata* is the most common species to cause infection in humans (4,6). *Kluyvera* infection is rare but has been reported more frequently in recent years (3). However, surveys on *Kluyvera* infection in humans have been limited mainly to case reports, and studies of the clinical characteristics and pathogenic role of *Kluyvera* species are sparse. Therefore, this study aimed to conduct a systematic review of *K. ascorbata* infection in adults and children using PubMed Medline, and perform a retrospective review of *K. ascorbata* infections in our hospital over a

period of 7 years.

## MATERIALS AND METHODS

**Microbiology methods:** We reviewed the microbiologic reports from clinical specimens at the Chonbuk National University Hospital from January 2010 to December 2016. Chonbuk National University Hospital is a 1,200-bed university-affiliated teaching hospital and the largest referral center in Jeollabuk-do, a province of Korea. All bacteria were initially identified using VITEK® 2 (bioMérieux Inc., Hazelwood, MO, USA). All *K. ascorbata* isolates were confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Vitek-MS, bioMérieux Inc., Marcy l'Etoile, France) and 16S rRNA sequencing. Antimicrobial susceptibility tests were performed with VITEK® 2 AST-211 Cards (bioMérieux Inc., Hazelwood, MO, USA) and E-test (bioMérieux Inc., Marcy l'Etoile, France) per the manufacturer's instructions. The results were interpreted according to the protocol of the Clinical and Laboratory Standards Institute M100 S18:2018 (7).

**Literature search and data extraction:** We examined relevant literature published between 1971 and 2018 that discussed *K. ascorbata*; literature was found using the keywords "*Kluyvera*" or "*Kluyvera ascorbata*" in a PubMed Medline search. The results were limited to human studies published in English and Spanish. The clinical information of our patients was collected from electronic medical records in the hospital. Data collected from each study subject were age, sex, underlying condition, clinical symptoms and signs, type of infection (nosocomial, or healthcare-associated [HCA], or community acquired [CA]), superinfection, specimen,

Received September 6, 2018. Accepted November 6, 2018.

J-STAGE Advance Publication November 30, 2018.

DOI: 10.7883/yoken.JJID.2018.375

\*Corresponding author: Mailing address: Department of Internal Medicine, Chonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju-si, Jeollabuk-do 54907, Republic of Korea. Tel: +82-63-250-2362, Fax: +82-63-254-1609, E-mail: smilehwang77@hanmail.net

infection site, period of antibiotic use, the result of susceptibility to antimicrobial agents, and outcome (recovery or death).

**Ethical approval:** This study was approved and conducted according to the guidelines of the Institutional Review Board of Chonbuk National University Hospital (IRB no.: CUH 2018-01-022).

**Definition:** HCA infection was defined as *K. ascorbata* infection that developed within 48 h of hospital admission in patients who had a history of hospitalization for 2 or more days in the preceding 90 days, receipt of intravenous medication or home wound care in the previous 30 days, receipt of hemodialysis, or residence in a nursing home or long-term care facility (8,9). CA infection was defined as infection in patients with no risk factors for HCA infection for whom the first positive culture for *K. ascorbata* was identified within 48 h of admission. Hospital-acquired (HA) infection was defined as a positive culture for *K. ascorbata* over 48 h after admission or in patients who had been discharged from an acute care hospital within the past 10 days (9). Superinfection was defined as *K. ascorbata* infection that developed either during initial empirical therapy or within about 2 weeks of discontinuation of initial therapy (10). The cut-off age for adulthood was 19 years.

**Statistical methods:** Descriptive statistics were expressed as number and percentage and as median and range. Categorical variables such as the source of infection and case fatality rate were compared using the chi-square test unless > 20% of cells had a count < 5, in which case Fisher's exact test was used. A *p* value < 0.05 was considered statistically significant. SPSS version 19.0 (IBM Corp., Chicago, IL, USA) was used for all statistical analyses.

## RESULTS

**Selected articles:** A total of 40 patients with *K. ascorbata* infection were reported on PubMed from 1971 through 2018. We discovered 303 references from PubMed Medline and screened the titles, abstracts, and full texts of these publications. Reasons for exclusion of cases were no case report form, no human study, involvement of other pathogens besides *K. ascorbata*, and duplication. We included 26 articles and excluded 277 (Fig. 1). A total of 40 cases were collected from the 26 articles, as shown in Tables 1 and 2.

**Clinical findings:** In the review of our hospital records, *Kluyvera* isolates in 20 patients (19 adults and 1 child) were identified in Chonbuk National University Hospital from 2010 to 2016. Among the 20 isolates, 6 were classified as *K. ascorbata*, 12 as *K. cryocrescens*, and 2 as *K. intermedia*. All 6 *K. ascorbata* strains showed more than 99% similarity to *K. ascorbata* strain ATCC 33433 (NR\_028677.1). Sources of the 20 isolates were wound culture, blood, urine, and sputum, and *K. ascorbata* was isolated from wounds (*n* = 3), blood (*n* = 1), urine (*n* = 1), and sputum (*n* = 1). Three (2 wound specimens and 1 sputum specimen) isolates were identified as colonizers, and the remaining 3 were confirmed as clinical pathogens (Fig. 1). One of the 12 *K. cryocrescens* isolates was identified as a pathogen from blood culture. All *K. intermedia* isolates were colonizers. The clinical characteristics of our 3 patients infected with *K. ascorbata* are described in Table 2. The 40 cases of infection with *K. ascorbata* were found from the literature search in PubMed Medline, and included 21 adults and 19 children (Fig. 1).

The ages of the 19 children (10 males and 9 females) ranged from 1 day to 18 years. Ages of adults (10 males and 14 females), including the 3 patients from our

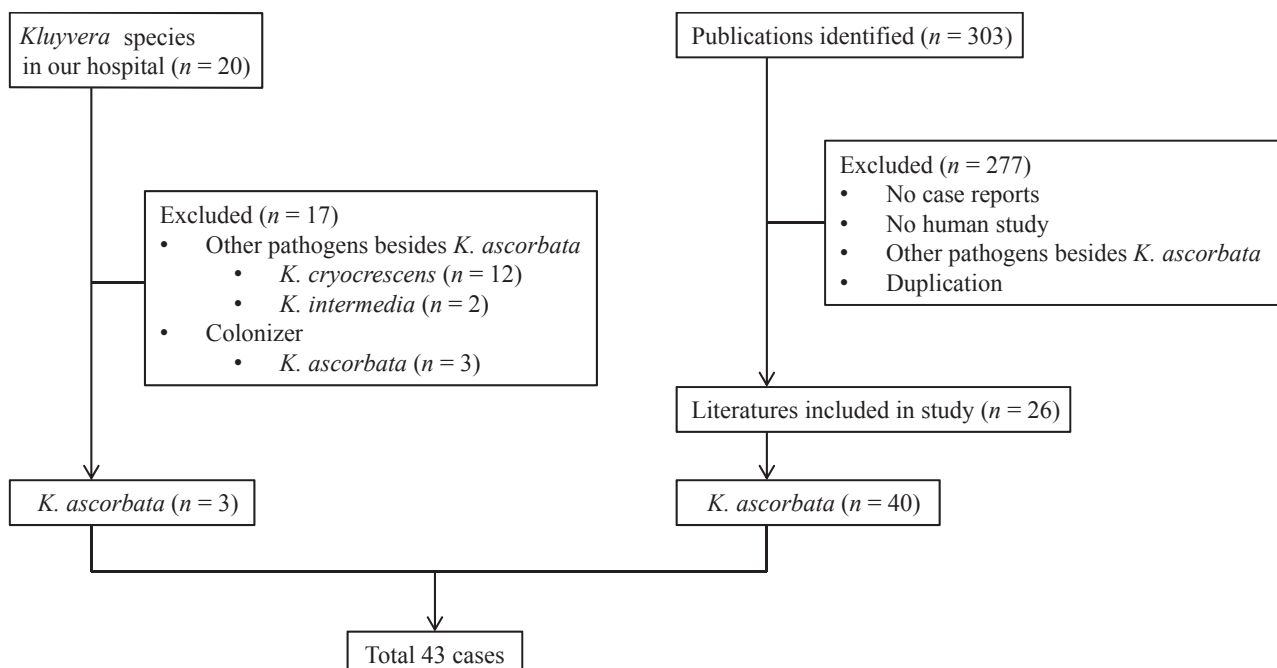


Fig. 1. Flow diagram of eligible article selection and patient enrollment.

Table 1. Pediatric cases infected with *Kluyvera ascorbata* reported in literature reviews

Reference	Age /sex	Underlying condition	Type of infection	Super-infection	Specimen	Symptom or sign /clinical impression	Antibiotic	Duration (days)	Outcome
6	7 m/M	Congenital heart diseases	Nosocomial	Yes	Blood	Fever/sepsis	Meropenem, amikacin	14	Recovery
6	13 y/F	Preterm delivery, Distonic brain palsy, epilepsy, recurrent pulmomary infection	Nosocomial	Yes	Blood	Fever, chills /catheter infection with sepsis	Cefepime, amikacin	14	Recovery
6	6 y/F	Bladder rupture, vesicovaginal fistula	Nosocomial	No	Urine	Fever/UTI	Ceftriaxone	10	Recovery
6	17 y/M	Crohn's disease	Health care associated	No	Pericecal fluid	Abdominal pain, diarrhea, weight loss / IAI	Ampicillin-sulbactam, amikacin, ornidazole	14	Recovery
15	1 d/M	Extremely low birth weight, preterm delivery	Nosocomial	No	Blood	SIRS/sepsis	Piperacillin-tazobactam, meropenem	5	Death
22	16 y/M	None	Community	No	Blood	Fever, chills /septic shock	Meropenem, amikacin	> 15	Recovery
3	3 m/M	None	Community	No	Urine	Fever/UTI	Ceftriaxone, cefdinir, cefaclor	7, 14, 30	Recovery
23	4 m/M	N.A	N.A	N.A	Gastrostomy tube site fluid	N.A /sepsis, soft tissue infection	N.A	N.A	Recovery
24	3 m/F	None	Community	No	Urine	Fever, lethargy/ UTI	Ceftriaxone, ceftibuten	6, 8	Recovery
25	1 d/M	Ventriculoperitoneal shunt, myelomeningocele, dilated cerebral ventricles	Nosocomial	No	CSF	Fever, irritable crying, poor appetite /meningitis	Meropenem	28	Recovery
26	19 m/F	None	Community	No	Urine	Fever, lethargy, abdominal pain/ UTI	Cefuroxime, cephalixin	4 , 10	Recovery
11	4 y/M	N.A	N.A	N.A	Blood	N.A /sepsis, necrotizing enterocolitis	N.A	N.A	N.A
11	11 y/M	N.A	N.A	N.A	Peritoneal fluid	N.A /peritonitis, acute appendicitis	N.A	N.A	N.A
11	2 m/F	N.A	N.A	N.A	Blood	N.A/sepsis	N.A	N.A	N.A
4	16 y/F	Pregnancy	N.A	N.A	Urine	N.A/UTI	Nitrofurantoin	7	Recovery
27	18 y/M	Ureteral rupture, urethrorectal fistula	N.A	No	Pus from fistula	Colostomy prolapse /purulent drainage from urethrorectal fistula	N.A	N.A	N.A
13	13 y/F	Heart failure after cardiac asystole, peritoneal dialysis for azotemia,	Nosocomial	No	Peritoneal fluid, intra-abdominal abscess, urine, lung tissue	N.A /IAI, pneumonia, UTI	Gentamicin, moxalactam	9	Death
18	13 y/F	Left third hepatectomy due to hepatoblastoma	Health care associated	No	Perihepatic fluid	Fever, jaundice /IAI	Meropenem, levofloxacin	N.A	N.A
37	19 d/F	None	Community	No	Urine	Fever, lethargy /UTI, sepsis	Cefotaxime	10	Recovery

IAI, intra-abdominal infection; N.A, not available; UTI, urinary tract infection.

# *Kluyvera ascorbata* as a Clinical Pathogen

Table 2. Adult cases infected with *Kluyvera ascorbata* reported in literature reviews

Reference	Age /sex	Underlying condition	Type of infection	Super-infection	Specimen	Symptom or sign /clinical impression	Antibiotic	Duration (days)	Outcome
28	64 y/F	Left nephrectomy	Community	No	Blood	Fever, jaundice, RUQ pain/sepsis, acute cholangitis	Piperacillin-tazobactam, ceftriaxone	N.A	Recovery
29	64 y/M	DM, prostate cancer, neurogenic bladder	Nosocomial	Yes	Blood	Fever, low BP/sepsis	Meropenem	13	Recovery
30	22 y/F	ESRD, Kidney transplantation, immunosuppressant	Health care associated	No	Urine	Fever, abdominal pain /UTI	Ciprofloxacin, TMP-SMX	N.A	Recovery
12	78 y/M	Prostate cancer, DM, anoxic ischemic encephalopathy	Community	No	Urine	Fever, weakness, confusion/UTI	Ceftriaxone, cefixime	6, 5	Recovery
11	40 y/F	N.A	N.A	N.A	Wound	N.A /soft tissue infection in right hand	N.A	N.A	N.A
11	24 y/F	N.A	N.A	N.A	Urine	N.A/UTI	N.A	N.A	N.A
11	55 y/F	N.A	N.A	N.A	Urine	N.A/UTI	N.A	N.A	N.A
11	73 y/F	N.A	N.A	N.A	Urine	N.A/UTI	N.A	N.A	N.A
31	85 y/M	COPD, aortic stenosis	Nosocomial	Yes	Sputum	Fever, dyspnea, purulent respiratory secretion /respiratory tract infection	Imipenem	N.A	Recovery
32	48 y/M	HIV, ESRD with PD	Nosocomial	Yes	Peritoneal fluid	Abdominal pain, discharge at the exit site of PD catheter/peritonitis	Levofloxacin, tobramycin	14	Recovery
33	67 y/F	None	Community	No	Bile	Abdominal pain, vomiting /acute cholecystitis	Cefoxitin, netilmicin	N.A	Recovery
34	29 y/M	Ileovesical fistula	Nosocomial	Yes	Urine	Urinary symptom, poor general condition/UTI	Cefuroxime	10	Recovery
4	78 y/F	DM	N.A	N.A	Urine	N.A/UTI	Ciprofloxacin	7	Recovery
4	28 y/F	None	N.A	N.A	Urine	N.A/UTI	TMP-SMX	5	Recovery
4	72 y/F	Urinary incontinence, pulmonary fibrosis, steroid therapy	N.A	N.A	Urine	N.A/UTI	Ciprofloxacin	7	Recovery
4	70 y/M	None	N.A	N.A	Abscess	N.A /soft tissue infection in finger	Ampicillin-sulbactam, amoxicillin-clavulanic acid	5, 10	Recovery
14	57 y/F	Colon cancer, chemotherapy, colostomy state	Nosocomial	No	Blood	Fever, diarrhea, vomiting/septic shock, enteritis	Ceftazidime, amikacin	N.A	Death
35	23 y/M	Liver cirrhosis, HBV	Community	No	Blood	Fever, abdominal pain, vomiting, nausea /sepsis, acute cholecystitis	Ceftriaxone	7	Recovery
36	72 y/M	Liver cirrhosis, HCV, HCC, chronic alcoholic abuse	Community	No	Blood	Fever/sepsis	Cefotaxime	N.A	Recovery
27	36 y/M	None	N.A	No	Urine	Fever, dysuria/UTI	N.A	N.A	N.A
16	73 y/F	Lung cancer, left femoral artery occlusion	Community	No	Urine	Dysphagia, weight loss/ UTI, sepsis	Ceftriaxone	N.A	Death
PR	37 y/F	Thyrotoxicosis	Nosocomial	No	Urine	Fever/UTI	Cefepime	10	Recovery
PR	63 y/F	Lymphoma, chemotherapy	Health care associated	No	Blood	Fever/sepsis	Cefepime	14	Recovery
PR	67 y/M	Gastric cancer with gastrectomy, DM chemotherapy	Nosocomial	No	Pus	Fever, swelling and tenderness at the exit site of Hemovac drainage tube/soft tissue infection	Piperacillin-tazobactam	5	Recovery

BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; N.A, not available; PD, peritoneal dialysis; RUQ, right upper quadrant; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; PR, present case.

hospital and 21 cases from literature review, ranged from 22 to 85 years. Among the 43 subjects, identification of underlying conditions was available in 35 cases. Twenty-six patients (16 adults and 10 children) had underlying conditions.

All 43 patients had an identified source of infection. The most common associated infection site was the urinary tract ( $n=19$ , 44.2%), followed by the bloodstream ( $n=12$ , 27.9%). Other infectious sites were as follows: intra-abdominal ( $n=10$ , 23.3%), soft tissue ( $n=4$ , 9.3%), respiratory tract ( $n=2$ , 4.7%), meninges ( $n=1$ , 2.3%), and pus discharge from rectourethral fistula ( $n=1$ , 2.3%). Two adults had the organism isolated from 2 sites, 1 child had the organism isolated from 2 sites and 1 child had the organism isolated from 3 sites. Bloodstream and urinary tract infections accounted for 68.4% of infections in children and 75% of infection in adults. There was no significant difference in the frequency of bloodstream infections (25% vs. 31.6%;  $P=0.633$ ) and urinary tract infections (50% vs. 36.8%;  $P=0.388$ ) between adults and children.

Twenty-eight of the 43 cases described the type of infection. Seventeen (60.7%) had nosocomial or HCA infections (72.7% among children and 60% among

adults). Eight (80%) of 10 children with underlying conditions presented with nosocomial or HCA infections, and 5 pediatric cases without underlying conditions had CA infections. In adults, among the 16 with underlying conditions, 9 (60%) showed nosocomial or HCA infections, and 5 (31.3%) had CA infections. Superinfection information was available in 30 of 43 (14 children and 16 adults). Six (20%: 2 children and 4 adults) presented with superinfection.

The antimicrobial susceptibility test results of our 6 patients are summarized in Table 3. All strains isolated in the 6 cases were resistant to ampicillin and cefazolin but susceptible to ampicillin-sulbactam and amoxicillin-clavulanic acid. The antimicrobial agents most commonly used in the 43 cases in this study were third-generation cephalosporins, cefepime, piperacillin-tazobactam, ciprofloxacin, amikacin, and carbapenem, and most patients recovered (Tables 1 and 2). Mortality data for 33 of the 43 cases were available; 4 patients (12.1%) died before the infection was cured. The mortality rates in adults and children were not significantly different (10.5% in adults and 14.3% in children;  $P=1.000$ ).

Table 3. Antibiotics susceptibility profile of the 6 *Kluyvera ascorbata* strains isolated from our hospital

Antimicrobial agent	Method	Case 1 <sup>1)</sup>		Case 2 <sup>1)</sup>		Case 3 <sup>1)</sup>		Case 4 <sup>2)</sup>		Case 5 <sup>2)</sup>		Case 6 <sup>2)</sup>	
		MIC	Result	MIC	Result	MIC	Result	MIC	Result	MIC	Result	MIC	Result
Amikacin	E-test	2	S	1	S	4	S	4	S	2	S	2	S
Amoxicillin-clavulanic acid		2	S	2	S	2	S	2	S	2	S	2	S
Cefepime		0.063	S	0.125	S	0.125	S	0.125	S	0.25	S	0.063	S
Ceftazidime		0.125	S	0.25	S	0.25	S	1	S	0.5	S	1	S
Ceftriaxone		0.5	S	1	S	1	S	0.5	S	1	S	0.25	S
Ertapenem		0.016	S	0.004	S	0.004	S	0.004	S	0.008	S	0.004	S
Gentamicin		0.5	S	1	S	1	S	1	S	0.5	S	0.5	S
Imipenem		0.25	S	0.5	S	0.25	S	0.25	S	0.25	S	0.5	S
Levofloxacin		1	S	1	S	1	S	1	S	0.063	S	0.5	S
Meropenem		0.5	S	0.25	S	0.031	S	0.5	S	0.063	S	0.5	S
Ofloxacin	Vitek2	0.125	S	0.25	S	0.25	S	0.125	S	0.25	S	1	S
TMP-SMX		0.063	S	1	S	0.125	S	0.063	S	0.125	S	0.5	S
Ampicillin		16	I	16	I	16	I	≥ 32	R	≥ 32	R	≥ 32	R
Ampicillin-sulbactam		≤ 2	S	≤ 2	S	≤ 2	S	≤ 2	S	4	S	4	S
Aztreonam		≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S
Piperacillin-tazobactam		≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S	≤ 4	S
Cefotaxime		≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S
Cefazolin		≥ 64	R	≥ 64	R	≥ 64	R	≥ 64	R	≥ 64	R	≤ 4	R
Cefoxitin		≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S	≤ 1	S
Tigecycline		≤ 0.5	S	1	S	≤ 0.5	S	≤ 0.5	S	≤ 0.5	S	≤ 0.5	S

<sup>1)</sup>: Pathogen.

<sup>2)</sup>: Colonizer.

TMP-SMX, trimethoprim-sulfamethoxazole; S, susceptible; I, intermediate; R, resistant.



## DISCUSSION

The purpose of this study was to investigate the clinical characteristics of *K. ascorbata* infection in adults and children. The literature describing the *Kluyvera* species is mostly in the form of case reports in PubMed Medline. With few clinically significant cases reported, it is difficult to identify trends of *K. ascorbata* infection in the data. This study is the first to compare and report the clinical characteristics of infection in adults and children with *K. ascorbata*, which accounts for the majority of *Kluyvera* species infections.

In this study, *Kluyvera* species were isolated from 20 patients. *K. ascorbata* was isolated from 6 of the 20 and *K. cryocrescens* was isolated from 12 samples. This result was not in agreement with previous studies, which showed that *K. ascorbata* was most commonly isolated from clinical specimens (4,11). This result suggests that there is a difference in the frequency of the type of isolate at each hospital. These 20 isolates of *Kluyvera* species represented approximately 0.02% of the total number of Enterobacteriaceae isolated during the study period, which is lower than the 0.07% reported in another study (11). The small number of isolates of *Kluyvera* in clinical specimens may be because the organism is not present in sufficient numbers to facilitate routine detection (4).

Clinically significant infections with *K. ascorbata* were involved in all age groups, from neonates to the elderly, and all states of health from the healthy to those with a wide variety of underlying conditions. There was also a diversity of clinical outcomes from recovery with the response to antibiotics to fatal outcomes, and various type of infections, including nosocomial, HCA, CA, and superinfection, as shown in Tables 1 and 2.

*K. ascorbata* seems to present a variety of clinically significant manifestations in humans. Analysis of the 43 cases in this study showed that urinary tract and bloodstream infections were the most common diseases caused by *K. ascorbata*. Although they occurred at a relatively low frequency, intra-abdominal, soft tissue, respiratory tract, and central nervous system infections also occurred. There was no significant difference in the incidence of bloodstream infection and urinary tract infection between adults and children. The distribution of infectious diseases was similar in adults and children.

In terms of the type of infection, nosocomial infection and HCA infection were observed mostly in the presence of underlying diseases. In contrast, CA infections occurred in relatively healthy individuals. Superinfection developed from nosocomial infections. Despite being able to infect immunocompetent individuals, *K. ascorbata* is likely to be an opportunistic pathogen that causes disease in patients in an immunocompromised state with anatomical or functional problems (12). However, in this study, it was not possible to generalize the underlying medical conditions associated with *K. ascorbata* infection as some past reports have done.

The overall mortality was 12.1% in our study. Three patients died because of sepsis and multifocal abscess in the immunocompromised state despite appropriate antibiotic treatment with susceptibility in Tables 1 and 2 (13–16). However, most patients improved clinically and responded to antimicrobial agents, and clinical outcome

was likely to be good. The research materials on virulence factors related to severe infection or mortality have not been identified, and it is difficult to describe the association of severe infection or mortality with the virulence factors (11). Because the patients who died were immunocompromised and did not show clinical improvement despite antimicrobial treatment, the poor underlying conditions could have contributed more to mortality than did the pathogen itself.

*Kluyvera* species were known to be the source of CTX-M type  $\beta$ -lactamases (17). In particular, genes encoding the CTX-M-1 and CTX-M-2 enzymes have been detected in strains of *K. ascorbata* (17). *Kluyvera* species have also been reported as carbapenemase-producing Enterobacteriaceae. Recently, KPC-2 producing *K. ascorbata* has been reported to cause human infection (18). In addition, GES-5 carbapenemase-producing *K. intermedia* was isolated in the hospital environment, and *K. georgiana* producing KPC-2 was isolated from the respiratory specimen of a patient with pneumonia (19,20). Nineteen of the 40 strains obtained from PubMed Medline had antimicrobial susceptibility data, and antimicrobial susceptibility results for third-generation cephalosporins in less than 10 strains were confirmed. Because the number of strains analyzed is small and reporting bias should be considered, it is difficult to discuss susceptibility results to third-generation cephalosporins in the present study. However, no resistance to third-generation cephalosporins was observed in our 6 cases. Stock reported the antimicrobial susceptibilities of 58 strains of *K. ascorbata*, and the results of susceptibility to third-generation cephalosporins, except cefpodoxime, were more than 90% (21). Other studies also reported the sensitivity of third-generation cephalosporins as 90 to 100% (6,11). Based on susceptibility results and clinical outcomes in our cases and other reported studies, the following agents might be effective treatment options: third-generation cephalosporins, cefepime, piperacillin-tazobactam, carbapenem, aztreonam, fluoroquinolones, and aminoglycosides.

In summary, *K. ascorbata* is emerging as an unusual but clinically significant pathogen with various forms of the disease, including bloodstream infection and urinary tract infection in adults and children. *K. ascorbata* should not be neglected when isolated in the clinical setting. *K. ascorbata* may be potentially life-threatening in immunocompromised patients despite the earlier report that it is a benign saprophyte. Clinicians should be aware of its potential pathogenic role and provide appropriate antimicrobial therapy. Further studies concerning the antimicrobial susceptibility patterns are required.

**Acknowledgments** This paper was supported by fund of Biomedical Research Institute, Chonbuk National University Hospital.

**Conflict of interest** None to declare.

## REFERENCES

1. Kluyver AJ, Van Niel CB. Prospects for a natural system of classification of bacteria. Zentralabl Bakteriell Parasitenkd Infektionskr Hygiene.1936;94:369-403.

2. Farmer JJ 3rd, Davis BR, Hickman-Brenner FW, et al. Biochemical identification of new species and biogroups of *Enterobacteriaceae* isolated from clinical specimens. *J Clin Microbiol.* 1985;21:46-76.
3. Isozaki A, Shirai K, Mimura S, et al. A case of urinary tract infection caused by *Kluyvera ascorbata* in an infant: case report and review of the literature. *J Infect Chemother.* 2010;16:436-8.
4. Sarria JC, Vidal AM, Kimbrough RC 3rd. Infections caused by *Kluyvera* species in humans. *Clin Infect Dis.* 2001;33:E69-74.
5. Muller HE, Brenner DJ, Fanning GR, et al. Emended description of *Buttiauxella agrestis* with recognition of six new species of *Buttiauxella* and two new species of *Kluyvera*: *Buttiauxella ferruginea* sp. nov., *Buttiauxella gaviniae* sp. nov., *Buttiauxella brennerae* sp. nov., *Buttiauxella izardii* sp. nov., *Buttiauxella noackiae* sp. nov., *Buttiauxella warmboldiae* sp. nov., *Kluyvera cochleae* sp. nov., and *Kluyvera georgiana* sp. nov. *Int J Syst Bacteriol.* 1996;46:50-63.
6. Karadağ Öncel E, Özsüreki Y, Akyön Y, et al. *Kluyvera ascorbata* infections in children: a case series. *Turk Pediatri Ars.* 2015;50:123-8.
7. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 28th supplement. Document M100. Wayne, PA: CLSI; 2018.
8. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Int Med.* 2002;137:791-7.
9. Son JS, Song JH, Ko KS, et al. Bloodstream infections and clinical significance of healthcare-associated bacteremia: a multicenter surveillance study in Korean hospitals. *J Korean Med Sci.* 2010;25:992-8.
10. Nucci M, Spector N, Bueno AP, et al. Risk factors and attributable mortality associated with superinfections in neutropenic patients with cancer. *Clin Infect Dis.* 1997;24:575-9.
11. Carter JE, Evans TN. Clinically significant *Kluyvera* infections: a report of seven cases. *Am J Clin Pathol.* 2005;123:334-8.
12. Torre D, Crespi E, Bernasconi M, et al. Urinary tract infection caused by *Kluyvera ascorbata* in an immunocompromised patient: case report and review. *Scand J Infect Dis.* 2005;37:375-8.
13. Yogev R, Kozłowski S. Peritonitis due to *Kluyvera ascorbata*: case report and review. *Rev Infect Dis.* 1990;12:399-402.
14. Linares P, Castañón C, Llano C, et al. Bacteremia by *Kluyvera ascorbata* in a patient with neutropenia and fever. *Enferm Infecc Microbiol Clin.* 2000;18:48-9. Spanish
15. Sharma D, Dasi T, Murki S, et al. *Kluyvera ascorbata* sepsis in an extremely low birth weight infant. *Indian J Med Microbiol.* 2015;33:437-9.
16. Alfreijat M. A case of urinary tract infection and severe sepsis caused by *Kluyvera ascorbata* in a 73-year-old female with a brief literature review. *Case Rep Infect Dis.* 2017;2017:3848963.
17. Rossolini GM, D'Andrea MM, Mugnaioli C. The spread of CTX-M-type extended-spectrum beta-lactamases. *Clin Microbiol Infect.* 2008;14 Suppl 1:33-41.
18. Wang L, Jing Y, Lai K, et al. A case of biliary tract infection caused by KPC-2-producing *Kluyvera ascorbata*. *Case Rep Infect Dis.* 2018;2018:5745708.
19. Ribeiro VB, Zavascki AP, Rozales FP, et al. Detection of *bla*<sub>GES-5</sub> in carbapenem-resistant *Kluyvera intermedia* isolates recovered from the hospital environment. *Antimicrob Agents Chemother.* 2014;58:622-3.
20. Ribeiro VB, Zavascki AP, Nodari CS, et al. Detection of *bla*<sub>KPC-2</sub> in a carbapenem-resistant *Kluyvera georgiana*. *J Antimicrob Chemother.* 2012;67:2776-7.
21. Stock I. Natural antimicrobial susceptibility patterns of *Kluyvera ascorbata* and *Kluyvera cryocrescens* strains and review of the clinical efficacy of antimicrobial agents used for the treatment of *Kluyvera* infections. *J Chemother.* 2005;17:143-60.
22. Carrillo Esper R, Peña Pérez C, Muciño Bermejo J, et al. Severe sepsis, septic shock and secondary multiple organ dysfunction in infection by *Kluyvera ascorbata*. *Gac Med Mex.* 2011;147:355-60. Spanish.
23. Carter JE, Laurini JA, Mizell KN. *Kluyvera* infections in the pediatric population. *Pediatr Infect Dis J.* 2008;27:839-41.
24. Ruffini E, Pace F, Carlucci M, et al. Urinary tract infection caused by *Kluyvera ascorbata* in a child: case report and review of the *Kluyvera* infections in children. *Minerva pediatrica.* 2008;60:1451-4.
25. Rosso M, Rojas P, Garcia E, et al. *Kluyvera* meningitis in a newborn. *Pediatr Infect Dis J.* 2007;26:1070-1.
26. Narchi H. *Kluyvera* urinary tract infection: case report and review of the literature. *Pediatr Infect Dis J.* 2005;24:570-2.
27. Sanchís Bayarri V, Sánchez Sánchez R, Marcaida Benito G, et al. *Kluyvera ascorbata* infections. Apropos 2 cases. *Rev Clin Esp.* 1992;190:187-8. Spanish.
28. López-Larramona G, Gómez-de-Oña E, Maestre-Muñoz MM, et al. *Kluyvera ascorbata* bacteremia in an adult patient. *Rev Esp Quimioter.* 2013;26:226-7. Spanish.
29. Moonah S, Deonarine K, Freeman C. Multidrug resistant *Kluyvera ascorbata* septicemia in an adult patient: a case report. *J Med Case Rep.* 2010;4:197.
30. Cheruvattath R, Balan V, Stewart R, et al. *Kluyvera* co-infection in two solid organ transplant recipients: an emerging pathogen or a colonizer bystander? *Transpl Infect Dis.* 2007;9:83-6.
31. Oteiza J, Tiberio G, Melendez A, et al. Respiratory infection by *Kluyvera* sp. cause or consequence? *An Med Interna.* 2005;22:45-6. Spanish.
32. Velusamy L, Mohanty MJ. *Moraxella* and *Kluyvera* peritonitis in a CAPD patient with human immunodeficiency virus. *Perit Dial Int.* 2003;23:611-2.
33. Batista N, Diez O, Moreno A, et al. Acute cholecystitis due to *Kluyvera ascorbata*. *Enferm Infecc Microbiol Clin.* 2002;20:370-1. Spanish.
34. Medina López RA, García Ramos JB, Congregado Ruíz B, et al. *Kluyvera ascorbata*. Case report of a patient with crohn's disease. *Actas Urol Esp.* 2001;25:69-70. Spanish.
35. Oteo J, Gómez-Garcés JL, Alós JI. Acute cholecystitis and bacteremia caused by *Kluyvera ascorbata* in a cirrhotic patient. *Clin Microbiol Infect.* 1998;4:113-5.
36. Padilla E, Tudela P, Giménez M, et al. *Kluyvera ascorbata* bacteremia. *Med Clin.* 1997;108:479. Spanish.
37. Ochi F, Tauchi H, Mizumoto M, et al. *Kluyvera ascorbata* infection in a neonate. *Pediatr Int.* 2017;59:640-1.