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Case report

A case of acute focal bacterial nephritis caused by methicillin-resistant *Staphylococcus saprophyticus* in a 13-year-old adolescent girl treated with daptomycin

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ABSTRACT

Staphylococcus saprophyticus is a gram-positive, coagulase-negative member of the *Staphylococcus* genus and is second only to *Escherichia coli* as a cause of urinary tract infections in the young female population. *S. saprophyticus* usually has good susceptibility to drugs commonly used to treat urinary tract infections, but it is often methicillin-resistant. Here we report a case of acute focal bacterial nephritis in a 13-year-old female patient caused by methicillin-resistant *S. saprophyticus* and treated with daptomycin (DAP). The patient had a history of unilateral hearing loss and presented to her previous physician with a 3-day history of fever, right-sided abdominal pain, and diarrhea. Cefotaxime antimicrobial chemotherapy was initiated as an empiric therapy targeting *E. coli,* the most frequent cause of community-onset pyelonephritis. Vancomycin (VCM) was started for acute focal bacterial nephritis caused by methicillin-resistant *S. saprophyticus* but was stopped due to allergy and replaced with DAP. After 13 days of treatment with DAP, the patient received 17 days of treatment with sulfamethoxazole-trimethoprim combination therapy. The patient experienced no adverse events and did not relapse. DAP is a relatively new anti-methicillin-resistant *Staphylococcus aureus* drug used to treat gram-positive cocci infections. It is primarily excreted by the kidneys, which may be desirable in treating urinary tract infections. For children who cannot receive VCM for any reason, DAP may be a viable alternative.

Introduction

Staphylococcus saprophyticus is a gram-positive, coagulase-negative member of the *Staphylococcus* genus and is second only to *Escherichia coli* as a cause of urinary tract infection in the young female population [1]. In a European survey, *S. saprophyticus* had a low resistance rate to antimicrobial agents normally used to treat urinary tract infections [2], but methicillin-resistant strains are often isolated. Because vancomycin (VCM) is generally used to treat coagulase-negative staphylococci when it is methicillin-resistant, there is little experience with using daptomycin (DAP) to treat methicillin-resistant *S. saprophyticus* (MRSS). In addition, although data on the use of DAP in children are gradually accumulating, experience with its use is very limited in cases of urinary tract infections in children, as most experience is for skin and soft tissue, musculoskeletal, and bloodstream infections [3–6].

This report describes a 13-year-old adolescent girl with acute focal bacterial nephritis (AFBN) caused by MRSS, who was treated with DAP and had a good therapeutic response without experiencing any adverse effects.

Case

A 13-year-old female patient with a history of unilateral hearing loss presented to her previous physician with a 3-day history of fever, right-sided abdominal pain, and diarrhea. The patient was referred to our pediatric department for a thorough examination of the cause and treatment, and was admitted to the hospital. At the time of admission (day X), the patient continued to experience fever and abdominal pain, and diarrhea had also appeared. On admission, the patient's temperature was 38.8 °C, pulse rate was 120/min, blood pressure was 90/52

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mmHg, white blood cell count was 13,700/μL, the neutrophil proportion was 82.5 %, and C-reactive protein level was 8.93 mg/dL. Microscopic urine examination revealed numerous leukocytes 3+ (50–99/HPF), right costovertebral angle tap pain, and pyuria, leading to the suspicion of urinary tract infection such as appendicitis or pyelonephritis.

Cefotaxime (CTX, 3 g/day) antimicrobial chemotherapy was started as an empiric therapy targeting *E. coli*, the most frequent cause of community-onset pyelonephritis. On the day after admission (X + 1), abdominal echocardiography was negative for appendicitis, with no evidence of colon wall thickening, fluid retention, or enlarged mesenteric lymph nodes. There was also no perirenal fluid accumulation or hydronephrosis. Blood culture was negative, but urine culture revealed *S. saprophyticus* 10^7 CFU/mL, and contrast-enhanced computed tomography (CT) showed multiple and extensive wedge-shaped areas of contrast failure in the right kidney, leading to the diagnosis of AFBN (Fig. 1). No bacteria other than *S. saprophyticus* were detected in the urine culture, and contrast-enhanced CT did not reveal any obvious signs of abscess formation or urinary tract malformation.

The next day (X + 2 days), the *S. saprophyticus* was found to be resistant to methicillin (Table 1). Since the patient still had a persistent high fever in the 39 °C range and was suffering from AFBN, aggressive treatment with injectable drugs was deemed necessary, and CTX was switched to VCM. VCM was administered for 90 min, but after the first dose, itching occurred at the intravenous injection puncture site and throughout the body. After the first dose, the patient was suspected of having had an allergic reaction rather than a VCM infusion reaction, and the drug was discontinued.

Because of a history of unilateral hearing loss and as fluoroquinolone is contraindicated in pediatric patients according to the Japanese package insert, the use of aminoglycoside or fluoroquinolone was avoided. DAP was selected as an alternative. After initiating treatment with DAP 300 mg/day (6.5 mg/kg), the patient's fever rapidly resolved, and DAP was continued for 13 days without the patient experiencing any adverse effects such as elevated creatine phosphokinase, eosinophilic pneumonia, or severe diarrhea. After 13 days of DAP therapy, she had a C-reactive protein level of 0.12 mg/dL, a white blood cell count of 9000/μL, and her neutrophil % had decreased to 66.7 %. The patient was switched to oral sulfamethoxazole-trimethoprim (ST, 320 mg/day as trimethoprim) and discharged from the hospital. The ST was used for 17 days, and AFBN did not recur.

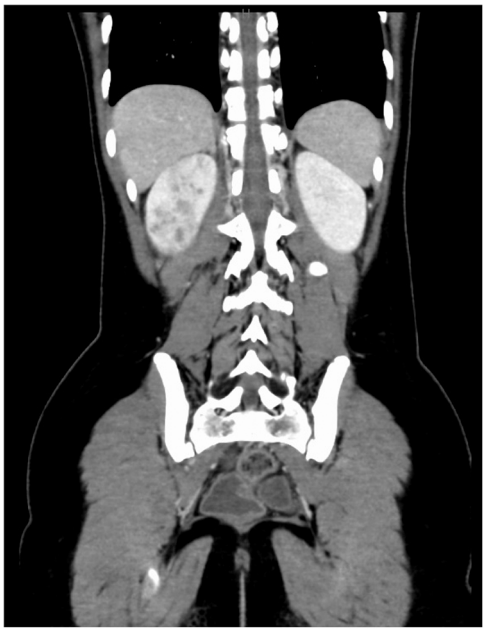

Fig. 1. Computed tomography image. Contrast computed tomography image on day X + 1. Multiple wedge-shaped areas of contrast ineffectiveness are seen in the right kidney.

Table 1
Drug susceptibility of Staphylococcus saprophyticus (Drug susceptibility was based on Clinical and Laboratory Standards Institute M100 Ed 28).

	Drug	MIC μg/mL	
SBT/ABPC	Sulbactam/Ampicillin	≤ 2	R
MPIPC	Oxacillin	0.5	R
CEZ	Cefazolin	≤ 2	R
CTM	Cefotiam	1	R
CMZ	Cefmetazole	≤ 1	R
CDTR-PI	Cefditoren pivoxil	1	R
LMOX	Latamoxef	8	R
IPM/CS	Imipenem/Cilastatin	≤ 0.5	R
MEPM	Meropenem	≤ 0.5	R
AMPC/CVA	Amoxicillin/Clavulanic acid	≤ 2	R
GM	Gentamicin	≤ 2	S
ST	Sulfamethoxazole/Trimethoprim	≤ 20	S
LVFX	Levofloxacin	≤ 1	S
CPFX	Ciprofloxacin	≤ 1	S
LZD	Linezolid	2	S
DAP	Daptomycin	≤ 0.5	S
VCM	Vancomycin	1	S
TEIC	Teicoplanin	2	S
CFX	Cefoxitin	≤ 2	R

MIC, minimum inhibitory concentration.

One month after discharge, voiding cystography showed no vesicoureteral reflux. Dimercaptosuccinic acid scintigraphy five months after discharge showed no scar formation.

Discussion

S. saprophyticus has a high affinity for urothelial cells due to uroadherence factor A *(UafA)*, and its high urease-producing capacity makes it a representative causative agent of urinary tract infections. It is second only to *E. coli* as a causative agent of urinary tract infections, especially in young women [1]. According to one Japanese report, the prevalence of *mecA* in *S. saprophyticus* is 7.9 % [7], and it is less likely to be methicillin-resistant. Although the resistance rate of *S. saprophyticus* to antimicrobial agents usually used to treat urinary tract infections has been reported to be low in European surveys [2], many methicillin-resistant strains have been reported in surveys in the United States [8], and the prevalence of MRSS may likely increase in Japan in the future.

DAP is a relatively new anti-methicillin-resistant *S. aureus* (MRSA) drug used to treat gram-positive cocci infections. It is excreted primarily through the kidneys, which may be a desirable property for treating urinary tract infections. DAP has also been found to have excellent activity against methicillin-resistant coagulase-negative staphylococci [8], suggesting that it may be a promising option for complicated urinary tract infections caused by gram-positive cocci in adults [9]. However, there is minimal experience using DAP for urinary tract infections in children.

In the present case, VCM had been administered for 90 min. However, the appearance of generalized erythema, pruritus, and a bulging rash led to suspicion of type I allergy rather than a VCM infusion reaction. Teicoplanin (TEIC), aminoglycoside, fluoroquinolone, and DAP were considered alternatives, but TEIC was avoided because of reports of cross-reactivity with VCM as glycopeptides [10]. Because of the patient's history of unilateral hearing loss and aminoglycoside effect on hearing, it was also avoided. Fluoroquinolones were not used because of concerns about joint damage in children.

Due to the increased clearance of DAP in children compared with adults, it is prescribed in higher doses in the pediatric population [11, 12]. Nevertheless, in children aged 12–17 years, its pharmacokinetics are comparable to those of adults [13]. In the present case, we chose a dose of 300 mg/day (6.5 mg/kg), almost equivalent to that of adults,

because the patient did not develop bacteremia, and DAP is well transferred to the urinary tract.

According to the European Committee on Antimicrobial Susceptibility Testing clinical breakpoint table v12.0 and Clinical and Laboratory Standards Institute 2022 M100 Ed32, DAP is considered effective when minimum inhibitory concentration (MIC) ≤ 1, and *S. saprophyticus*, the isolate in the present case, had a MIC ≤ 0.5 μg/mL in response to DAP treatment. DAP is generally a safe and well-tolerated drug, although myopathy and eosinophilic pneumonia have been reported as specific adverse events in adults. In previous clinical studies conducted on pediatric patients [3,11], the most frequently reported adverse effects were mild gastrointestinal disturbances, injection site reactions, and creatine phosphokinase elevation. No adverse effects were observed in this case. AFBN in children is associated with 4–10 % of patients hospitalized for urinary tract infection, although reports vary [12–15].

Subjective symptoms, such as flank or abdominal pain, are often nonspecific for urinary tract infections, and some patients have been reported to have no pyuria and negative urine cultures [16]. The appropriate duration of treatment for AFBN in children is unclear. However, at least one week of transvenous therapy and four weeks of treatment are recommended [17,18]. If not complicated by a renal abscess, a high rate of cure is achieved with antimicrobial therapy alone. In the present case, there was no complication of renal abscess, and treatment was completed only with DAP and ST for 30 days.

Asian guidelines for urinary tract infections in children [19] recommend using third-generation cephalosporins as empiric therapy, followed by a narrowing of the range according to the antimicrobial susceptibility of the causative organism. In young women, if gram-positive cocci clusters are detected by gram staining of urine, and there is no improvement with third-generation cephalosporins, the use of anti-MRSA drugs should be considered with MRSS in mind.

In the treatment of urinary tract infections caused by MRSS, DAP is likely to be an effective treatment in patients in whom VCM cannot be used for some reason, as in this case.

CRediT authorship contribution statement

Teruhisa Kinoshita, and Shoko Sahara: Writing – original draft. **Yuka Mihara, Yumiko Asai, Hiroko Sato, Takashi Sakakibara, and Norio Takimoto:** Writing – review & editing. **Keisuke Oka:** Supervision.

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Ethical approval

Not applicable.

Consent

Since the patient was a minor, written informed consent was obtained from the patient's mother.

Authorship statement

All authors have met the ICMJE authorship criteria and have given final approval for the submission of the final version.

Declarations of interest

None.

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