Clinical Characteristics of Bacterial Spectrum and Antimicrobial Resistance in Urine and Stone Cultures From Patients With Kidney Stone Disease

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Abstract

Background

It is important to understand the clinical characteristics of bacterial spectrum and antibiotic resistance of urine and stone pathogens for the prevention and treatment of urolithiasis and perioperative infection.

Methods

Consecutive patients with kidney stones treated by percutaneous nephrolithotomy (PCNL) from September 2016 to September 2018 were included. The bacterial species and antibiotic sensitivity test of the germs cultured from clean middle-stream urine and from stones intraoperatively were evaluated.

Results

In 1055 patients, the rate of positive bacterial test was higher in stones than in urine (337, 31.0% vs. 221, 20.9%, *p=0.016*). 167(15.8%) patients had both positive urine culture (UC) and stone culture (SC), of which 137 (82.0%) had identical bacteria in both cultures. In infection stone patients, the positive rate of bacteria was 34.7% (91/262) in urine and 52.3% (137/262) in stone, and in non-infection stone patients, was 16.4% (130/793) and 25.2% (200/793). The positive rate of SC in patients with different types of stones were higher than that of UC. *E. coli* was the most common organism not only in both UC (54.3% ,120/221) and SC (43.9%,148/337) but also in urine and stones from patients with infection stones (44.0%,32.8%) or non-infection stones (61.5%,51.8%). Furthermore, the pathogens isolated from urine and stones showed high resistance to fluoroquinolones, ceftriaxone, cefazolin, cefuroxime, β-lactamases and sulfonamides (all resistance>20%).

Conclusions

The bacterial spectra demonstrated in stones and urine samples were significantly different. Positive SC was more commonly encountered than positive UC. Compared with non-infection stones, infection stones were accompanied by higher rates of positive tests in both cultures. The antibiotic resistance was comparable between bacteria in the two cultures. A combination of antibiotic sensitivity results in urine and stones might be a useful guide for selection of effective and appropriate treatment aiming at reduced problems with bacterial antibiotic resistance.

1. Introduction

Urolithiasis is one of the most common global diseases in urology and the incidence is gradually increasing [1, 2]. The presence of urinary stones is often accompanied by urinary tract infections (UTI)

and commonly associated with urine flow obstruction[3].This combination might promote the further development of stones [4, 5].

Stones can be divided into infectious stones and non-infectious stones by aetiology. According to the latest EAU guidelines, the ingredients of infectious stones include magnesium ammonium phosphate, highly-carbonated apatite and ammonium urate. Previous Chinese studies have shown that the most common pathogen in stone-related UTI is *Escherichia coli*, for which multiple drug-resistant subgroups account for a proportion as high as 80%[6]. Consequently, these infections are very difficult to treat. Percutaneous nephrolithotomy (PCNL) is the most common method for surgical removal of kidney stones with diameters >2cm[7, 8].Serious postoperative complications may follow PCNL which, if not treated in time may develop into urosepsis and life-threatening septic shock[9,10]. Perioperative infection complications might occur despite intensive preoperative antibiotic therapy based on microbiological analyses of urine [11].

Previous studies showed that results of mid-stream urine cultures from patients treated with PCNL were not sufficiently reliable in reflecting bacteria in renal pelvic urine or stones [12,13], especially in the presence of urinary tract obstruction. Moreover, both urine cultures (UC) and stone cultures (SC) were independent risk factors for urosepsis in patients with complex urinary stones. The simultaneous positive occurrence of bacteria in urine and stones was associated with an increased risk of postoperative infections compared with the situation when only a single positive culture was recorded [14].

In several studies it was only shown that the results of UC and SC were not always the same, Nevertheless, a comparison and analysis of the specific differences between the bacterial spectrum in stones and urines were not carried out. But it is necessary to understand the characteristics of urine and stone bacteriology and the degree of antibiotic sensitivity for adequate treatment of patients with urinary stones. In the current study, we retrospectively determined the bacterial spectrum and antibiotic sensitivity of SC and UC in patients with kidney stones. In addition, the positive results of SC and UC between infection stones and non-infection stones were compared to provide a scientific basis for a clinically rational selection of perioperative antibiotics.

2. Patients And Methods

2.1 General information

We included 1055 patients with kidney stones who consecutively had been subject to stone removal with PCNL in the first affiliated Hospital of Guangzhou Medical University from September 2016 to September 2018. Ethics Committee approval was obtained from the First Affiliated Hospital of Guangzhou Medical University. Informed consent was obtained from each patient.

2.2 Collection method of the urine

A clean mid-stream urine sample of about 10 mL was collected in a sterile test tube, and the samples were either cultured within 1 hour after collection, or stored at 4 °C and treated within 8 hours.

2.3 Collection method of stones

All patients were treated with pneumatic or ultrasonic lithotripsy during PCNL. After the core of the stone was removed with stone forceps, it was immediately immersed in sterile saline. Following elimination of impurities on the stone surface by washing 3 times, 10 mL of saline was added and the stone ground. The solution containing the ground stone was added to the nutritious broth and placed in the 37 °C incubator for enrichment and culture. The process strictly followed aseptic principles.

2.4 Bacterial culture and identification of strain

The strains found in positive mid-stream urine cultures and stone cultures were identified by VITEK®2 automatic bacteria identification instrument. The bacterial antibiotic sensitivity test was performed with the KirbyBauer (Kmurb) method, and the results were interpreted according to the standards established by guidelines from the Clinical and Laboratory Standards Institute (CLSI).

VITEK®2 automatic microbiological identification instrument was purchased from French BioMérieux company. Antibacterial antibiotic sensitivity papers were purchased from British Oxoid company. Blood Agar and antibiotic sensitivity test medium Agar were purchased from Jiangmen Kailin Trading Co, Ltd.

2.5 Statistical methods

SPSS25.0 software was used for statistical analysis. The Chi-square test or Fisher´s exact probability test was performed to detect differences between categorical variables. Significance was assumed at the 0.05 level.

3. Results

3.1 The bacterial spectrum of urine and stones

In the 1055 patients, positive stone cultures were recorded in 337 (31.9%) compared with only 221 positive urine cultures (20.9%). Table 1 shows the number and relative occurrence of common microorganisms in urine samples and stones. Emphasis was placed on the four most common types of kidney stones encountered in patients (Figure1a). Four of these stones were dominated by calcium oxalate, uric acid, cystine and infection components. The detection rate of bacteria in the stones was significantly higher than that in urines (Figure1b).

There were also statistically significant differences in the proportional pattern of antimicrobial spectra between UC and SC (Table 1). The most common microorganism observed in both cultures was *E. coli*, but its relative occurrence was significantly higher in UC than in SC (54.3% vs 43.9%; *p=0.016*). Other frequently isolated pathogens in urine were *Proteus mirabilis* in 17 samples (7.7%), *Enterococcus faecalis* in 15 samples (6.8%) and *Pseudomonas aeruginosa* in 13 samples (5.9%). The other common pathogens

in stones were *Proteus mirabilis* in 41 (12.2%), *Pseudomonas aeruginosa* in 18 (5.3%) and *Staphylococcus epidermidis* in 14 (,4.2%). The occurrence of *Staphylococcus epidermidis* in stones was higher than that in urine (0.9% vs 4.2%; *p =0.024*), but *Enterococcus faecalis* was more common in urine (6.8% vs 3.0%; *p =0.033*).

In addition, 167 patients (15.8%) had both positive urine and stone cultures (UC+ and SC+), of which the bacterial strains were identical in 137. Of these cultures 76 were found for infection stones, 18 of which (23.7%) presented with different cultures between stone and urine. In the 91 patients with non-infection stones, the number of the patients with calcium oxalate stones, uric acid stones and cystine stones were 63, 25, and 3, respectively. Twelve of these patients (13.2%) had inconsistent UC and SC results.

We also found that 169 patients (16.0%) with negative urine cultures had positive stone cultures (UC-, SC+), the bacteria were mainly *E. coli*, *Proteus mirabilis*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa.* Moreover, the bacteria cultured from the 54 (5.1%) of the patients with positive urine cultures but negative stone cultures (UC+, SC-), comprised *E. coli*, *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*.

We further separately analyzed the bacterial spectra in urine and stones from patients with infection and non-infection stones. These results are summarized in Tables 2 and 3. The most common bacteria was *E. coli* in infection stones and non-infection stones. Whether in urine or stone, *Proteus mirabilis* and *Pseudomonas aeruginosa* were significantly more common in patients with infection stones than in non-infection stones (p<0.05). Among the 206 patients with infection stones, 34.7% had positive urine cultures, and 52.3 % positive stone cultures. For 793 patients with non-infection stones, bacteria were detected in the urine of 130 patients (16.4%) and in the stone of 200 patients (25.2%) (Figure 2).

3.2 The antimicrobial sensitivity of common bacteria in urine and stones

3.2.1 E. coli

The drug resistance was almost the same for *E. coli* cultured from stones and urine (Figure 3a). Whether *E. coli* was isolated from stones or urine, entrains had high sensitivity for tigecycline, imipenem, meropenem, ertapenem, piperacillin/tazobactam, latamoxef, amikacin and nitrofurantoin.

The drug resistance for ampicillin was the highest (84.5%,80.9%), followed by Cefuroxime sodium (57.1%,63.2%) and Cefuroxime axetil (57.1%,63.2%). Among cephalosporins, resistance to the third and fourth generation of cephalosporins such as ceftazidime (29.4%,22.9%) and cefepime (20.9%,23.0%) were significantly lower than that of the first and second generations of cephalosporins, such as cefazolin (64.8%,56.1%) and cefuroxime (61.0%,54.4%).

3.2.2 Proteus mirabilis

Proteus mirabilis in urine and stones showed high sensitivity to carbapenem. Regarding beta-lactamase inhibitors, *Proteus mirabilis* was sensitive to cefoperazone / sulbactam, piperacillin / tazobactam and latamoxef. It was of note that *Proteus mirabilis* had high resistance patterns for nitrofurantoin (100.0%,97.0%) and tigecycline (84.6%,72.2%; Figure 3b). They were resistant to some cephalosporins, such as cefazolin (50.0%,32.4%), cefuroxime sodium (60.0%,28.6%), cefuroxime axetil (60.0%,28.6%), ceftriaxone (35.7%,21.6%) and cefotaxime (35.7%,21.6%). In addition, they also had resistance to ampicillin (44.4%,40.0%), sulfamethoxazole (57.1%,35.1%) and ciprofloxacin (22.2%,26.7%).

3.2.3 Pseudomonas aeruginosa

Pseudomonas aeruginosa in urine and stones was resistant to most commonly used antibiotics, such as cefazolin, ceftriaxone, cefuroxime sodium, cefuroxime axetil and nitrofurantoin, ampicillin, sulfamethoxazole. These strains were completely sensitive to ceftazidime, cefepime, aztreonam, and polymyxin B. *Pseudomonas aeruginosa* in urine was more sensitive to beta-lactamase inhibitors such as piperacillin/tazobactam, cefoperazone/sulbactam and aztreonam (resistance <20%). These strains were more resistant to carbapenem and instance meropenem (27.3%,14.3%) than to aminoglycoside antibiotics such as tobramycin (10.0%,14.3%) gentamicin (0.0%,7.7%) and amikacin (18.2%,14.3%; Figure3c).

3.2.4 Enterococcus faecalis

Enterococcus faecalis were completely resistant to sulfamethoxazole, clindamycin and quinupstin/dafopristin. Interestingly, *Enterococcus faecalis* in stones was more resistant to erythromycin than urine (75.0% vs 10.0%; *P=0.013*). Whether *Enterococcus faecalis* in urine or stones, they all had high resistance to quinolones (Figure 3d).

4. Discussion

In this study, the proportion of calcium oxalate stones (55.2%) was much lower than that reported in Zhang's article (77.5%) [15], and the patients with uric acid stones were significantly more common. The explanation might be different dietary habits. It is possible that the patients in our study had eaten more foods with a high content urate/uric acid or urate precursors. Guangdong is a coastal area of South China and it was demonstrated that the composition of stones also was affected by geographical location, age and gender [16,17]. Interestingly, *E. coli* was the most common bacteria in both cultures. However, in the study by Paonessa [12], *Staphylococcus* was the most common pathogen in stones and urine. These findings may be attributed to differences in the distribution of urinary pathogens in various countries and regions. Consistent with the results of Walton and De Lorenzis et al [18,19], the rate of positive stone cultures (31.9%) in our study was significantly higher than that of urine (20.9%).

It needs to be mentioned that in the comparative analysis of antimicrobial spectra in stones and urine there were significant differences in the detection rate of *E. coli*, *Enterococcus faecalis*, and *Staphylococcus epidermidis* (*p* < 0.01). In 167 patients with both positive UC and SC, the non-coincidence

rate between the two cultures was 18.0% (30 of 167). This was like previously reported findings [20]. Accordingly, the culture results of bacteria in urine did not fully reflect the findings in stones.

In mid-stream urine, the detection rate of *Enterococcus faecalis* was as high as 6.8%, second only to the *Proteus mirabilis* (7.7%). The increased number of invasive treatment modalities for stone removal such as the mini-percutaneous surgery, the extensive use of immunosuppressants, and the long-term and irregular use of antibiotics, have resulted in continuously increased antibiotic resistance for *Enterococcus faecalis* [21]. Furthermore, *Enterococci* usually have high biofilm-forming ability and strong adaptability to the environment, which makes them more and more difficult to eradicate [22,23].

The spectrum of isolated uropathogens showed obvious differences between infection stones and non-infection stones. In urine, the antimicrobial spectrum of *E. coli*, the most commonly encountered bacteria in patients with infection and non-infection stones, was consistent with reports in the literature [24,25]. Moreover, we found that the frequency of *E. coli* was higher in patients with non-infection stones (*p =0.010*), and also that the antimicrobial spectra were the same in stones *(p=0.001)*. *Proteus mirabilis* and *Pseudomonas aeruginosa* were significantly more common in infection stones than in non-infection stones, whether isolated from UC or SC (*p<0.01*). This observation can be explained by the fact that infection stones mainly are caused by infection with urease-producing microorganisms. *Proteus mirabilis* is the main urease-producing microorganism [26].

Infection stones account for 10–20% of all human kidney stones, and their presence is associated with greater risk of renal tissue damage than is the case with non-infection stones. Infection stones also have a high recurrence rate [27]. Therefore, we also compared the antimicrobial bacterial spectra between patients with infection and non-infection stones. This was helpful for fully understanding the distribution of antimicrobial spectra in the different stone components and accordingly for the treatment strategy. Overall, the detection rate of bacteria in patients with infection stones was higher than that in patients with non-infection stones, irrespective of from which source the bacteria were isolated (*p < 0.01*, Figure 2). This observation proved that infection stones were caused by and associated with urinary tract infections. Non-infection stones were more related to the metabolism of oxalate and calcium. We have explained above that the choice of perioperative antibiotic regimen should be based not only on findings in mid-stream urine cultures, but also on the bacteriology in stone cultures.

E. coli and *Proteus mirabilis* were highly sensitive to carbapenem, followed by amikacin in aminoglycoside antibiotics. This observation was roughly consistent with the description in the China Antimicrobial Resistance Surveillance System (CARSS). But the disadvantage is the high cost of carbapenem antibiotics. Because of the wide antibacterial spectrum, strong antibacterial activity, and high stability to a variety of β-lactamases, carbapenem was rarely used for treatment of mild infections or for infection prevention. This antimicrobial agent is accordingly more suitable for severe infection in critically ill patients.

Pseudomonas aeruginosa was highly sensitive to polymyxin B, ceftazidime and cefepime, an observation that differed from that presented in the China Antimicrobial Resistance Surveillance System (CARSS).

The reported sensitivity of *Pseudomonas aeruginosa* to the aminoglycoside antibiotics tobramycin, gentamicin and amikacin was 91.6%, 86.4% and 94.0%, respectively, which was higher than that detected in stones analyzed in our study. Thus, urologists are requested not to underestimate the antimicrobial resistance of *Pseudomonas aeruginosa*. However, when using it as an empirical treatment for patients with urinary stones and systemic symptoms, it should be noted that amikacin has nephrotoxicity, ototoxicity, and other serious side effects.

It was worth mentioning that our study showed the drug resistance of *Enterococcus faecalis* to erythromycin in stones was significantly higher than that in urine, which to a certain extent explained that even if the use of antibiotics before operation could make urine culture negative, it was still difficult for us to treat the bacteria in stones. Extensive attention needs to be paid to bacteria isolated from stones because they may get directly into the blood circulation during lithotripsy and trigger postoperative infections [28]. Moreover, patients with positive cultures in both stones and urine were more likely to have fever [29].

Previous studies showed that UC and SC were independent risk factors for postoperative infection [14]. As mentioned above, we still found a high percentage of patients with positive stone culture despite negative urine culture. The reason may be that the use of antibiotics has not been so strict in China, and many patients can easily obtain antibiotics in pharmacies and hospitals. Before seeking medical advice, they may have carried out antibacterial treatment on their own. This situation may result in false negative urine cultures. Therefore, we suggest that in addition to routine urine culture before operation and antibacterial treatment according to the result, intraoperative stone culture always should be carried out. Similarly, we recommend doctors to fully realize and understand the history of antibiotic usage before stone treatment, it also is necessary to educate patients so that they correctly understand the dual nature of antibiotics and always to avoid the abuse of antibiotics.

The advantage of our study was that we not only described the characteristics of antimicrobial spectra of bacteria in urine and stones, but also emphasized the differences in UC and SC between infection stones and non-infection stones. These findings have not been observed in recent studies. Moreover, we analyzed the antimicrobial sensitivity of bacteria in urine and stones. These findings will be of great importance for the future perioperative antibacterial treatment of patients with urinary stones. We have emphasized that urologists never should underestimate the antimicrobial resistance of *Pseudomonas aeruginosa* and *Enterococcus faecalis*. The limitation of our report was that it only was a single-center study within a certain restricted region and our data mainly focused on patients with kidney stones. In the future, we also need to establish more antibiotic sensitivity data on common pathogens in urine and stones.

Conclusion

The antimicrobial spectra isolated in bacteria from stones and urine were significantly different. The occurrence of positive of SC was higher than that of positive UC. Patients with infection stones were

much more likely to have positive cultures in both urine and stones than had patients with non-infection stones. The drug resistance was similar between bacteria in urine and stones. Combining the observations on drug resistance of bacteria in urine and stones should guide the use of effective and appropriate treatment regimens in association with active stone-removal.

Abbreviations

UC
urine culture
SC
stone culture
PCNL
percutaneous nephrolithotomy

Declarations

Author contributions:

ML: wrote the first draft of the manuscript. ZJ: analyzed the data. PX, LYA and ZLC: modified figures and tables. All authors contributed in collecting the data. YYZ, SKZ, TZ and SJL revised the manuscript. WQW, GHZ and Hans-Göran Tiselius assisted in reviewing and revising the manuscript. All authors read and approved the final manuscript.

Ethical approval: none.

Consent for publication: not applicable

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Tables

Table 1: Analysis of bacterial spectrum of urine and stones (All patients, N=1055)

Bacterial classification	Urine N =221 (%)	Stone N =337 (%)	P
Escherichia coli	120 (54.3)	148 (43.9)	0.016*
Proteus mirabilis	17 (7.7)	41 (12.2)	0.090
Pseudomonas aeruginosa	13 (5.9)	18 (5.3)	0.785
Klebsiella pneumoniae	13 (5.9)	10 (3.0)	0.090
Enterococcus faecalis	15 (6.8)	10 (3.0)	0.033*
Enterococcus faecium	5 (2.3)	7 (2.1)	1.000
Staphylococcus epidermidis	2 (0.9)	14 (4.2)	0.024*
Streptococcus agalactiae	9 (4.1)	5 (1.5)	0.056
Other bacteria	24 (10.9)	79 (23.4)	<0.001***

Table 2: Comparison of bacterial spectrum in urine between infectious and non-infectious stones

Bacterial classification	Infection stones N=91 (%)	non-infection stones N=130 (%)	P
Escherichia coli	40 (44.0)	80 (61.5)	0.010*
Proteus mirabilis	16 (17.6)	1 (0.8)	<0.001***
Pseudomonas aeruginosa	10 (11.0)	3 (2.3)	0.007**
Klebsiella pneumoniae	7 (7.7)	6 (4.6)	0.339
Streptococcus agalactiae	5 (5.5)	4 (3.1)	0.493
Enterococcus faecalis	3 (3.3)	12 (9.2)	0.084
Enterococcus faecium	1 (1.1)	4 (3.1)	0.651
Other bacteria	9 (9.9)	26 (19.3)	0.043*

Table 3: Comparison of bacterial spectrum in stones between infectious and non-infectious stones

Bacterial classification	Infection stones N=137 (%)	non-infection stones N=200 (%)	P
Escherichia coli	45 (32.8)	103 (51.8)	0.001***
Proteus mirabilis	37 (27.0)	3 (1.5)	<0.001***
Pseudomonas aeruginosa	14 (10.2)	4 (2.0)	0.001***
Klebsiella pneumoniae	7 (5.1)	3 (1.5)	0.097
Staphylococcus epidermidis	3 (2.2)	11 (5.5)	0.135
Streptococcus agalactiae	3 (2.2)	2 (1.0)	0.400
Enterococcus faecalis	4 (2.9)	6 (3.0)	1.000
Enterococcus faecium	2 (1.5)	5 (2.5)	0.705
Other bacteria	22 (16.1)	63 (31.0)	0.001**

* Statistically significant based on chi- square test (P < 0.05).

** Statistically significant based on chi- square test (P < 0.01).

*** Statistically significant based on chi- square test (P < 0.001).
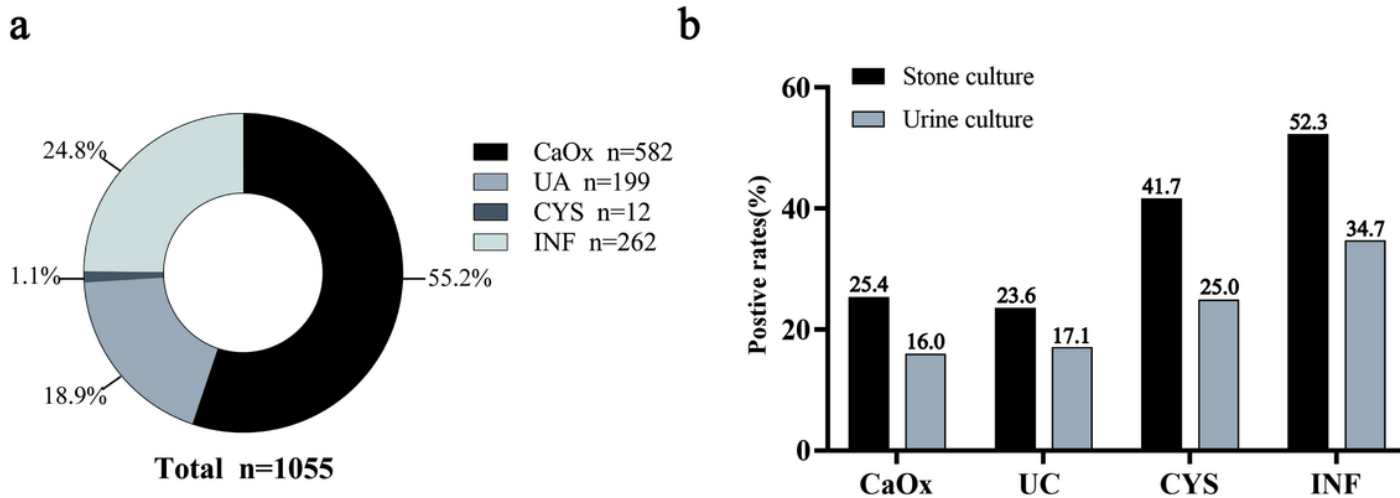
Figures

Figure 1

The proportion and positive rate of all stone types. (a) The proportion of four types of stones. CaOx: calcium oxalate stones UA: uric acid stones CYS: cystine stones INF: infectious stones (b) Bacteria detection rate in urine and stones of the four types of kidney stones.
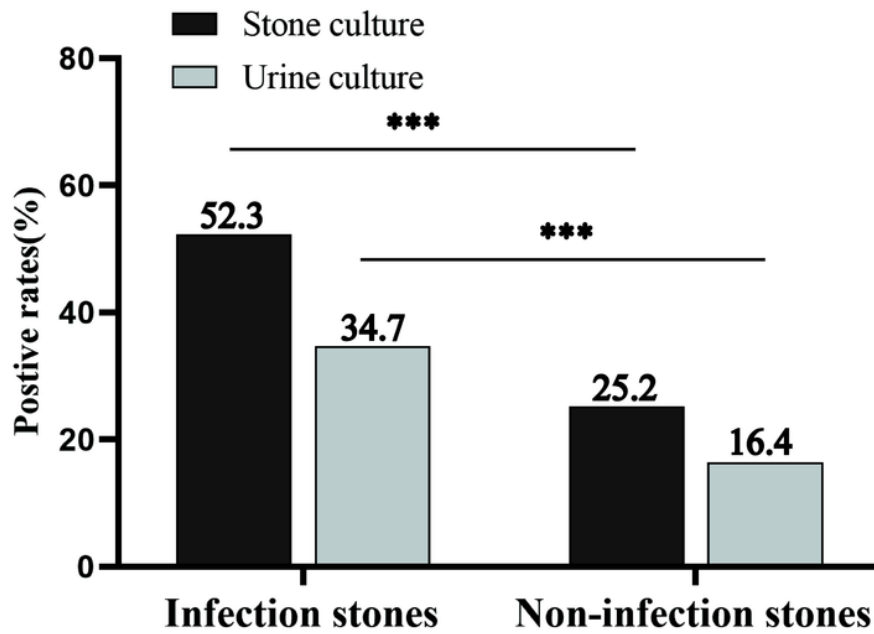
Figure 2

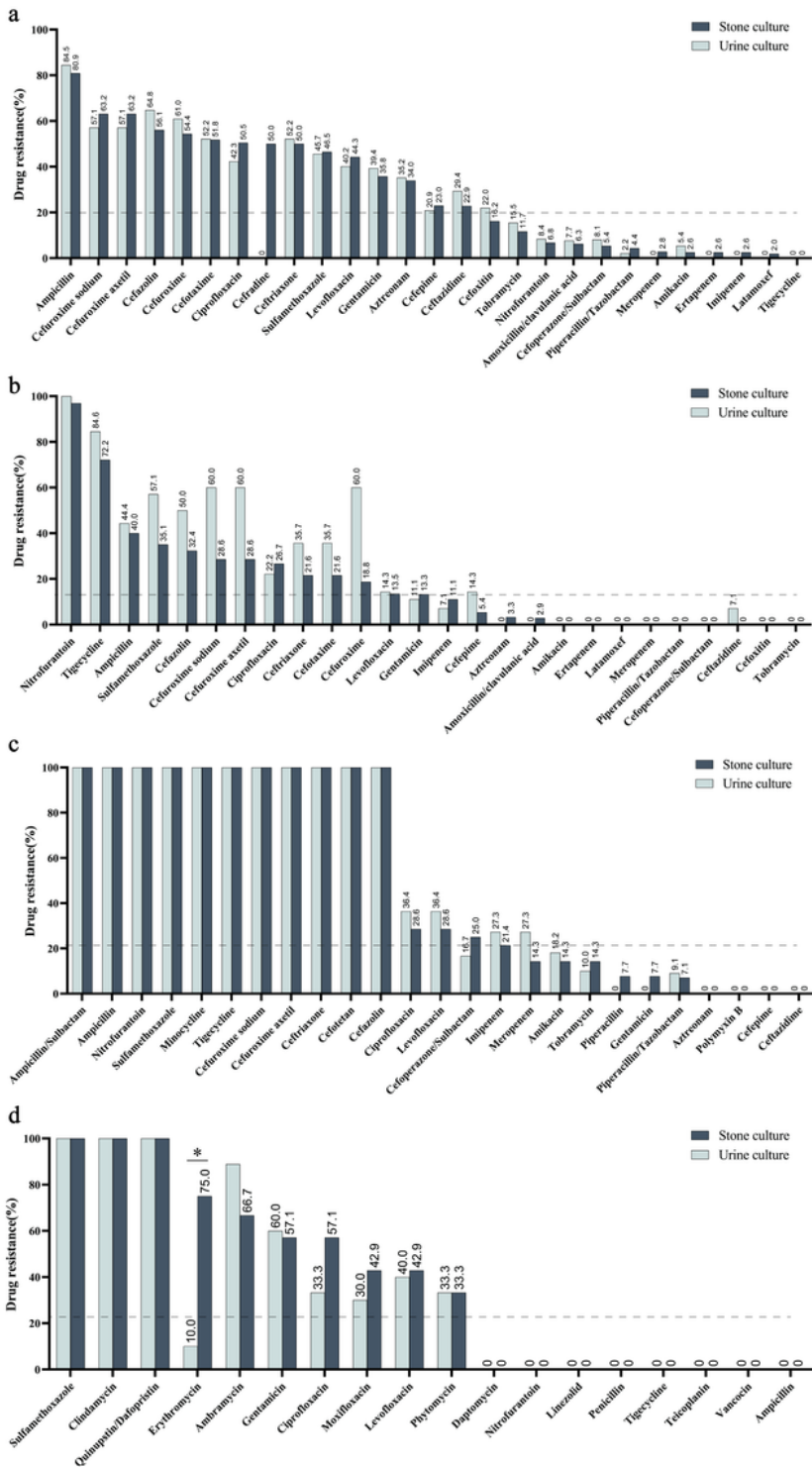Comparison of the rate of bacteria detection in urine and stones between infection and non-infection stones

Figure 3

(a): Comparison of antimicrobial resistance rates of E. coli in urine and stones (b): Comparison of antimicrobial resistance rates of Proteus mirabilis in urine and stones (c): Comparison of antimicrobial resistance rates of Pseudomonas aeruginosa in urine and stones (d): Comparison of antimicrobial resistance rates of Enterococcus faecalis in urine and stones *Statistically significant based on chi-square test ($P < 0.05$).