

## Aminoglycosides as An Alternative Antibiotic Therapy Against Urinary Tract Infection in Children due to Extended-Spectrum B-Lactamase (ESBL) Producing *Escherichia Coli* in Carbapenem Trends

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### ABSTRACT

**Background:** Extended-spectrum  $\beta$ -lactamase (ESBL) is an enzyme produced by certain *Escherichia coli* and *Klebsiella pneumoniae*. ESBL can induce the antibiotic resistance for betalactam antibiotics such as penicillin, cephalosporin, etc. Frequent utilization of carbapenem may induce the risk for carbapenem resistant against ESBLs producing microorganisms. This study aimed to communicate Aminoglycosides as an alternative antibiotic therapy against urinary tract infection in children.

**Case Presentation:** We present a case of 4 years child who was admitted to the state hospital of Madiun with main complaint of 10 days high fever accompanied by phimosis appearance. Laboratory results based on urine culture show the ESBL positive *Escherichia coli*.

**Results:** We have used aminoglycoside for treating the patient. Clinical presentation in this

patient start showing an improved clinical response and negative bacteriuria in the second urine test after the aminoglycoside therapy.

**Conclusion:** Aminoglycosides such as gentamicin can be considered to be one of the best options for treating an ESBL infection beside carbapenem in order to reduce the carbapenem trend. In clinical setting of the urinary tract infection caused by ESBL *Escherichia coli*.

**Keywords:** Aminoglycosides, Carbapenem, Extended-spectrum  $\beta$ -lactamase, Gentamicin, urinary tract infection

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### BACKGROUND

Extended-Spectrum  $\beta$ -Lactamases (ESBLs) are defined as capabilities of bacterial resistance to the beta-lactam ring of antibiotics such as penicillins, cephalosporins, and aztreonam by hydrolysis of these antibiotics, and which are inhibited by  $\beta$ -lactamase inhibitors such as clavulanic acid. ESBL is a resistance mechanism from the specific bacteria to inactivate the antibiotic.

Some of  $\beta$ -lactamases derived enzymes that is well-known are TEM-1, TEM-2, and SHV-1. TEM-1 is the most common plasmid-mediated  $\beta$ -lactamase of ampicillin resistant enteric gram-negative bacilli (for example, *Escherichia coli*), while SHV-1 is majorly produced by *Klebsiella pneumoniae*. TEM-2 is a less common member of the same group with identical biochemical properties to TEM-1. The ESBLs

derived from TEM-1, TEM-2, or SHV-1 differ from their progenitors by as few as one amino acid (Paterson and Bonomo, 2005).

National surveys reported the presence of ESBLs *Escherichia coli* in 12 to 24% isolates from Thailand, Taiwan, the Philippines, and Indonesia meanwhile 5 to 8% isolates from Korea, Japan, Malaysia and Singapore. The presence of ESBLs *Klebsiella pneumoniae* have been reported as low as 20 to 50% elsewhere in Asia (Paterson and Bonomo, 2005). Extended-spectrum beta-lactamase- (ESBL-) producing Enterobacteriaceae infections are increasingly identified with subsequent hospitalization. *E coli* genitourinary tract infections are known as risk factor for uncomplicated cystitis, but some can ascend, affecting the kidneys and—at worst—causing overflow bacteraemia. ESBL-E coli predominantly are widespread in sewage, pets, meat, and food animals based on the definitive confirmation by whole-genome sequencing isolates. The ESBL-E coli infection in genitourinary tract reported to be the most important origin of pathogenic widespread through bloodstream lead to the sepsis and bacteremia.

Minimum inhibitory concentrations (MICs) are described as the minimum concentration of an antimicrobial that will inhibit the growth of a bacterium or bacteria after overnight incubation. MICs are commonly used to diagnose and confirm resistance of antibiotic, but also can be used as a research tool to determine the in vitro activity of new antimicrobials (Andrews, 2001). MICs of  $\beta$ -lactamase-producing Enterobacteriaceae is reported as high but are still in the susceptible range. Literature determined the correlation between clinical outcomes of infection caused by ESBL microorganisms and MICs. These studies showed that a low value of MIC is positively

correlated with better clinical outcomes compared to the higher MIC (Walker, Lee and Klar, 2018). Recent literature on a MIC-based approach in settings where ESBL producers are endemic showed that cefepime and levofloxacin can both favorably achieve pharmacodynamic targets against isolates of fully susceptible Enterobacteriaceae at lowered MIC susceptibilities. There have been underlying issues with studies regarding the lack of clinical experience using these medications, as well as the conflicting reports of clinical outcomes in the literature when studying treatments for ESBL-producing *Escherichia coli* infection.

Carbapenem class antibiotics is admitted to be the empiric treatment of choice for ESBL-producing Enterobacteriaceae infections. Frequent carbapenem utilization in treated against ESBL producing organism which will build the carbapenem trend in clinical setting. Carbapenem trend impact to the multidrug resistance increases the risk that empirical treatment will fail, doubling the 17–18% mortality that is typical for E coli bacteraemia caused by EDL producing E coli (Day et al., 2019). Other report also showed that carbapenem use when MIC is  $\geq 4$  mg/liter contributed for the worse mortality outcomes compared to patients whose microbiological isolate MICs were lower than 4mg.liter, demonstrating awareness and limitation of carbapenem therapy in clinical setting. The emerging incidence of community-acquired ESBL-identified infections has demonstrated a positive association to the carbapenem resistance which can illustrate the need for alternative therapies against ESBL-producing organisms. Though prospective study demonstrating effectiveness of other therapies has been limited, there is emerging retrospective evidence in support of the use of non-carbapenem antibiotics, such as cefe-

pime, fluoroquinolones, and piperacillin/tazobactam several clinical occasions (Walker, Lee, and Klar, 2018). Carbapenems with their excellent in vitro activity are reserved for children with severe clinical presentation or nosocomial infection. Carbapenem-containing combination regimens are associated with more favorable outcomes in cases with relatively low MIC (<8 mg/L) and meropenem given as a prolonged Infusion (Bitsori and Galanakis, 2019). Carbapenem trend prevention should be done by the application of non-carbapenem antibiotics, such as fourth-generation cephalosporin which was considered as most considerable alternative to eradicate ESBL-producing organisms in in the clinical setting.

Gentamicin is an aminoglycoside antibiotic that is considered for children with an upper UTI. It is used intravenously and negligible in oral use. Gentamicin is a bactericidal antibiotic that works by binding to the bacterial ribosomes which will affect the protein synthesis. It is effective against all aerobic gram-negative rods including *Pseudomonas* and *Proteus*, and is also effective against staphylococci. Gentamicin is eliminated by glomerular filtration. The dose of gentamicin is weight related and should be calculated on the child ideal weight to avoid major adverse reactions such as ototoxicity and nephrotoxicity. Gentamicin can damage to the sensory cells of the ear and lead to hearing loss, balance problems, and tinnitus. Nephrotoxicity effect of gentamicin is occurred by the cells damage in the proximal tubule, which causes acute tubular necrosis and subsequent kidney injury. Renal function should be measured regularly, and if there is renal impairment, the interval between doses should be increased or the dose should be decreased. It is contraindicated

in children with myasthenia gravis (Ramlakhan et al., 2014).

This case report will show the clinical and microbiological responses to aminoglycoside antibiotic, gentamicin in treating the febrile UTI caused by ESBL *Escherichia coli* in order to find the alternative antibiotic therapy and emphasize previous studies on avoiding carbapenem trends era.

### CASE REPORT

A 4-year-old child presented with a ten days history of fever and frequent urination. The urination complaint was also followed by dysuria. The other complaints are nausea and loss of appetite. Patient demonstrated axillary temperature at 38.5 degrees Celsius. In addition to that, the other vital signs remain stable. Anthropometric measurement was examined during the first arrival at hospital to estimate drug doses and body fluid requirement purpose. From physical examination, patient demonstrated suprapubic pain meanwhile palpable mass in suprapubic area was not found. On the further flank examination, tenderness on costovertebral angle was not appeared. Upon further examination in genital area, the patient presented with a sign of phimosis with inability to pull back patient prepuce. Patient nutritional status is categorized as normal based on the analysis using water low criteria (90%) and the CDC curve plot (body height= 103cm, weight= 14.5 kg, ideal body weight= 16kg).

We already ensured that the patient family consent had completely agreed to give the information related to their relative and let their relative identity to be hidden in publication.

Blood test was performed to rule out the aetiology of fever. The laboratory finding showed the blood cells remain in normal range (hemoglobin 13.2 g/dL, leukocytes 23,390/mm<sup>3</sup>, platelets 299,000

/mm<sup>3</sup>). Urine analysis result showed an elevated white blood cells (4-5 cell), negative erythrocytes (0-1 cell), ketonuria (+3), bacteriuria (+), and a slight decrease of urine acidity (Ph 6.0). Based on the previous clinical findings and laboratory results, the patient was diagnosed as febrile urinary tract infection. 400 mg ampicillin was administered per 6 hours intravenous as an antibiotic therapy for 3 days. The patient fluid requirement was supplied by intravenous fluid using D5 1/4 NS 18 drop per minute based on the daily patient requirement (1225 cc/24 hours), another supportive treatment was also considered such as the use of paracetamol 500 mg in febrile condition (axillary temperature  $\geq 38.5^{\circ}\text{C}$ ) and domperidone for treating the vomiting and nausea. After 3 days ampicillin therapy, the patient had not shown any clinical response.

Urine culture was performed in next day after the ampicillin therapy was done to determine the suspect pathogen and sensitive antibiotic. The result of urine culture showed that ESBL phenotype was detected in the selected *E. coli* which became the responsible pathogen.

## RESULTS

Gentamicin was selected as the second antibiotic therapy replacing ampicillin in treating the patient. Gentamicin was intravenously administered per 12 hours as 35mg doses for 7 days. After the administration of antibiotic and supportive treatment in 7 days, the patient condition had shown an improved clinical response and did not appear a febrile condition in more than 24 hours. Subsequent urine analysis revealed the condition of negative bacteriuria and decreased urine leucocytes (1-2 cell). Patient was discharged from hospital once the gentamicin therapy has completed in 7 days followed by an arrangement for

circumcision procedure in next three days to minimize the risk of recurrent urinary tract infection in the future.

## DISCUSSION

The patient in this case was diagnosed as febrile urinary tract infection. Urinary tract infection (UTI) is a condition of significant growth of bacteria in the urine accompanying the symptoms. After a single UTI, 15–41% of children are in risk to develop long-term complications of kidney disease, proteinuria, hypertension, and renal dysfunction in later life (Ramlakhan et al, 2014). Ampicillin was selected as the primary antibiotic therapy for treating the UTI in this case. Persistence of the febrile condition after 3 days therapy strengthens a suspicion of inadequate antibiotic therapy. Urine culture was performed to detect the ESBL producing *E. coli* and the sensitive antibiotic. Studies reported that possibilities of increased bacterial resistance to ampicillin is related to widespread use for childhood infections because it has a low side-effect profile (Ramlakhan et al., 2014).

Presence of ESBL producing organism in an infection disease results in a high rate of inadequate antibiotic therapy, hence the patients with ESBL-producing organisms need to receive adequate antibiotic therapy immediately in 24 hours after the blood culture result revealed. Immuno-incompetent patients will be in risk for the negative impact of delayed antibiotic therapy (Puvanendran et al., 2019). In this case, the ESBL producing *E. coli* was resistant to Cephazolin, Ceftazidime, Ceftriaxone, Aztreonam, Ciprofloxacin, and Trimethoprim-Sulfamethoxazole. However, it was sensitive to gentamicin, nitrofurantoin, amikacin, meropenem, and ertapenem. Some studies reported that aminoglycoside antibiotic susceptibility such as gentamicin and

amikacin is still high against the ESBL producing *E. coli* (Kumar et al., 2014).

Zohar et al. (2020) study compared aminoglycoside and carbapenem piperacillin/ tazobactam declared that aminoglycoside is more superior in reducing the 30 day mortality rate (13%) than carbapenem or piperacillin/tazobactam (21.2%), although it is still inferior in reducing the recurrence of bacteriuria within 90 days and acute kidney injury in bloodstream infection caused by ESBL-producing Enterobacteriaceae (Zohar et al., 2020). Gentamicin was selected to be the antibiotic therapy in this case combined with ampicillin. Antimicrobial susceptibility in this case showed that gentamicin was the antibiotic with the lowest MIC compared to the other sensitive antibiotics, such as amikacin and nitrofurantoin. Another study of the antimicrobial susceptibility profile revealed that gentamicin has a quite higher sensitivity than nitrofurantoin (Kumar et al., 2014). The combination of ampicillin and gentamicin becomes the empiric antibiotics for childhood UTI. The amino group side-chain of ampicillin induce the penetration in outer membrane of some gram-negative bacteria accounting for its broader spectrum of activity. Ampicillin will inhibits cell-wall synthesis by the binding mechanism of the antibiotic to penicillin-binding proteins in the bacterial cell wall.

Patient in this case will be arranged for a circumcision in the outpatient setting of which purpose is to reduce the risk of another UTI in the future. Circumcision procedure during childhood is practiced in >80% in Islamic countries, South Korea, and the Philippines, but the procedure is not commonly adapted in the majority of the other Asian countries, including China, India, Japan, and Taiwan. In the countries where circumcision is commonly performed, also considered the procedure as a

choice of treatment for male infants with urinary tract infection (UTI). Hence, the setting of appropriate age for circumcision remain as a question (Kanematsu, 2016). Colonization of bacteria in the inner prepuce can be modified by circumcision procedure which will reduce the potential source of bacteria causing UTI (Singh-Grewal et al., 2005). Circumcision effect on reducing the preputial colonization of bacteria has been reported in several countries. There have been several non-randomized studies reporting a decreased rate of UTI in circumcised boys compared with non-circumcised boys (Kanematsu, 2016).

Many reports and studies have shown the effectiveness of aminoglycoside antibiotics, such as gentamicin and amikacin in treating UTI patient. Even though aminoglycoside is not more superior than carbapenem as antibiotic therapy, it still show the good efficacy as an alternative antibiotic treatment in carbapenem trends. Based on our report, we recommend aminoglycoside, such as gentamicin and amikacin as an alternative for treating patient with UTI caused by ESBL *Escherichia coli*.

#### **AUTHOR CONTRIBUTION**

Muhammad Pradhika designed the study, analyzed data, and drafted the manuscript. Muhammad Ramadhan collected clinical data and wrote the paper. Muhammad Pradhika collected sequence data and revised the manuscript. Mega Apriska Sutowo Putri interpreted data and substantially revised the manuscript. All authors read and approved the final version of the manuscript.

#### **CONSENT FOR PUBLICATION**

The parents of the patient provided written informed consents to publish their child's personal or clinical details along with any

identifying images. A copy of written consent is available for review by editor-in-chief of this journal.

#### CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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