

## POLA KEPEKAAN ANTIBIOTIK ORAL PADA INFEKSI SALURAN KEMIH KOMUNITAS PADA PASIEN PEDIATRIK RS X TAHUN 2022

Nicolas Layanto<sup>1\*</sup>, Ade Dharmawan<sup>1</sup>, Wani Devita Gunardi<sup>1</sup>, Veronica Rina<sup>2</sup>

<sup>1-3</sup>Departemen Mikrobiologi FKIK UKRIDA

<sup>2</sup>Medical Education Unit FKIK UKRIDA.

Program Studi Pendidikan Dokter

e-mail: nicolas.layanto@ukrida.ac.id

### ABSTRACT

Some pediatric urinary tract infection show unspecific symptoms and can be treated as an outpatient by choosing right oral antibiotic that can prevent those infection become more severe. Oral antibiotic available are amoxicillin, amoxicillin clavulanate, cefixime, fosfomycin and cotrimoxazole. In this study, all urin sample from pediatric patient without history of antibiotic before, were collected. Positive urin culture in 2022 that tested with amoxicillin, amoxicillin clavulanate, cefixime, fosfomycin and cotrimoxazole were collected. Pediatric patient were classified by age. From 0-1 year group dan 1-3 years old group, *Proteus mirabilis*, *Eschericia coli* and *Enterococcus sp.* are the most common bacteria found while oral antibiotic with highest sensitivity are cotrimoxazole and fosfomycin. Most MDR bacteria found in this study were from 0-1 year old group. The number of ESBL and gram positive bacteria have influence the less sensitivity of cefixime, amoxicillin, and amoxicillin clavulanate while have low impact on cotrimoxazole and fosfomycin.

**Keywords :** urinary tract infection., pediatric., oral antibiotic

### INTRODUCTION

Urinary tract infection (UTI) can be diagnosed with positive culture with acceptable count.<sup>1</sup> Urinary tract is the most common source infection in pediatric population with significant morbidity and mortality.<sup>2</sup> Not all UTI cases in pediatric have specific symptom, some often found with asymptomatic or non-specific symptoms with probably no indication to treat as inpatient patient and can be treat with oral antibiotic. Some studies shows that there is no significant different result from patient that were treat with oral antibiotic compare with treat with intravena antibiotic that followed by oral antibiotic.<sup>1,3</sup>

The most common pathogen for UTI in pediatric population *Eschericia coli*.<sup>1,4-6</sup> Some oral antibiotics also included in UTI guideline for pediatric such as *amoxicillin*, *amoxicillin-clavulanat*, *cefixime*, *cotrimoxazole* and *fosfomycin*.<sup>7-10</sup> No studi found that give specific information about sensitivity those oral antibiotics. Clinical decision for using oral antibiotics also affected by prevalence of MDR bacteria (*Multi Drug Resistant*) that found from pediatric patient. Some MDR bacteria with special precaution are *Eschericia coli* dan *Klebsiella sp. Extended Spectrum Beta Lactamase* (ESBL), *Methicillin Resistance Staphylococcus aureus* (MRSA), *Carbapenem resistant Pseudomonas aeruginosa*, *Carbapenem resistant Acinetobacter baumannii* resisten *Carbapenem*.<sup>11</sup>

### METHOD

All sample collected from medical record data that include age, sex, diagnose, and positive urine culture from microbiology laboratory. Positive urin culture taken must have bacteria with colony count, and sensitivity for *amoxicillin*, *amoxicillin-clavulanat*, third generation *cephalosporin*, *cotrimoxazole*, dan *fosfomycin*. *Cefixime* result is extrapolated from third generation *cephalosporin*. All patient data from January 1<sup>st</sup>, 2022 until December 31<sup>th</sup>, 2022 were included in this study.

All urin sample for culture collected before patients take antibiotics. Urinary tract infection were diagnosed based on physician decision written in medica record. Urine sample inoculated to Blood Sheep Sgar (BSA) 7% and McConkey Agar using sterile ose 10 uL using quantitative streak method before 2 hours after collected or keep in 4<sup>0</sup>C prior inoculated (maximum 24 hours). Both agar incubated in incubator 35<sup>0</sup>C for 18-24 hours. Positive culture if bacteria count are >100.000 CFU/uL. If colony count less than 100.000 CFU/uL, will be confirmed as positive if the physician write UTI as working diagnose or with specific UTI symptoms written.<sup>12</sup>

Age classification based on *National Institutes of Health*, which consist of *neonatus* (birth - 1 month), *infant* (1 month - 1 year), *toddler* (1-3 years), *preschool* (3-6 years), *school age child* (6-12 years), *adolescent* (12-18 years). From each group, most bacteria found will be analysed with antibiotic sensitivity test. If the total bacteria

found are less than 30, than the group will be combined with other group.

## RESULT

**Table 1** Pediatric Patient Age Distribution

| Age              | Boy (%)           | Girl (%)          | Jumlah    |
|------------------|-------------------|-------------------|-----------|
| 0-1 month        | 0                 | 1 (100)           | 1         |
| 1 month - 1 year | 26 (62)           | 16 (38)           | 42        |
| 1 - 3 year       | 17 (57)           | 13 (43)           | 30        |
| 3-6 year         | 2 (29)            | 5 (71)            | 7         |
| 6-12 year        | 0                 | 5 (100)           | 5         |
| 12-18 year       | 0                 | 4 (100)           | 4         |
| <b>TOTAL</b>     | <b>45 (50,6%)</b> | <b>44 (49,4%)</b> | <b>89</b> |

**Table 2** Antibiotic Sensitivity Pattern for UTI in Pediatric Patient (0-1 years)

| Pathogen                    | N         | Amx  | Amc  | Cfx  | Fos  | Sxt  |
|-----------------------------|-----------|------|------|------|------|------|
| <i>Proteus mirabilis</i>    | 9         | 55.5 | 77.7 | 88.8 | 100  | 66.7 |
| <i>Eschericia coli</i>      | 8         | 75   | 75   | 75   | 87.5 | 87.5 |
| <i>Enterococcus sp</i>      | 7         | 28.5 | 57.1 | 0    | 100  | 57.1 |
| <i>Klebsiella sp</i>        | 5         | 0    | 40   | 40   | 100  | 60   |
| <i>Morgagnella morganii</i> | 5         | 40   | 80   | 80   | 40   | 100  |
| <i>COnS</i>                 | 5         | 60   | 80   | 0    | 60   | 100  |
| <i>Citrobacter koseri</i>   | 2         | 100  | 100  | 100  | 100  | 100  |
| <i>Enterobacter cloacae</i> | 2         | 100  | 100  | 50   | 100  | 100  |
| <b>Total</b>                | <b>43</b> |      |      |      |      |      |

*COnS* : Coagulase Negative Staphylococcus, *Amx* : Amoxicillin, *Amc* : Amoxicillin – clavulanate, *Cfx* : Cefixime, *Fos* : Fosfomycin, *Sxt* : Cotrimoxazole

**Tabel 3** Antibiotic Sensitivity Pattern for UTI in Pediatric Patient (1-3 years)

| Pathogen                          | N  | Amc  | Amx  | Cfx  | Fos  | Sxt |
|-----------------------------------|----|------|------|------|------|-----|
| <i>Eschericia coli</i>            | 7  | 28.5 | 57.1 | 57.1 | 42.8 | 100 |
| <i>Proteus mirabilis</i>          | 6  | 66.7 | 66.7 | 66.7 | 66.7 | 50  |
| <i>Enterococcus sp</i>            | 4  | 50   | 75   | 0    | 75   | 100 |
| <i>COnS</i>                       | 4  | 50   | 50   | 50   | 75   | 50  |
| <i>Acinetobacter sp</i>           | 2  | 0    | 50   | 0    | 100  | 100 |
| <i>Pseudomonas aeruginosa</i>     | 2  | 0    | 0    | 0    | 50   | 50  |
| <i>Klebsiella sp</i>              | 1  | 100  | 100  | 100  | 100  | 0   |
| <i>Citrobacter koseri</i>         | 1  | 0    | 100  | 100  | 100  | 100 |
| <i>Streptococcus agalactiae</i>   | 1  | 0    | 0    | 100  | 100  | 100 |
| <i>Streptococcus gallolyticus</i> | 1  | 0    | 0    | 0    | 100  | 100 |
| <i>Lactococcus garvieae</i>       | 1  | 100  | 100  | 100  | 100  | 100 |
| Total                             | 30 |      |      |      |      |     |

*COnS* = Coagulase Negative Staphylococcus, *Amx* = Amoxicillin, *Amc* = Amoxicillin – clavulanate, *Cfx* = Cefixime, *Fos* = Fosfomycin, *Sxt* = Cotrimoxazole

**Tabel 4** Antibiotic Sensitivity Pattern for UTI in Pediatric Patient (3-18 years)

| Pathogen                         | N | Amx | Amc | Cfx | Fos | Sxt |
|----------------------------------|---|-----|-----|-----|-----|-----|
| <i>CONS</i>                      | 3 | 33  | 67  | 0   | 33  | 67  |
| <i>Enterococcus faecalis</i>     | 2 | 100 | 100 | 0   | 100 | 100 |
| <i>Proteus mirabilis</i>         | 2 | 100 | 100 | 50  | 50  | 100 |
| <i>Acinetobacter baumannii</i>   | 1 | 100 | 100 | 0   | 100 | 100 |
| <i>Burkholderia cepacian</i>     | 1 | 0   | 0   | 0   | 0   | 100 |
| <i>Escherichia coli</i>          | 1 | 0   | 0   | 100 | 100 | 100 |
| <i>Klebsiella sp</i>             | 1 | 0   | 100 | 100 | 100 | 0   |
| <i>Kocuria kristinae</i>         | 1 | 0   | 100 | 0   | 100 | 100 |
| <i>Leuconostoc mesenteroides</i> | 1 | 100 | 100 | 0   | 0   | 100 |
| <i>Streptococcus agalactiae</i>  | 1 | 100 | 100 | 0   | 100 | 0   |
| <i>Streptococcus anginosus</i>   | 1 | 100 | 100 | 100 | 100 | 100 |
| <i>Candida albicans</i>          | 1 |     |     |     |     |     |

Total 16

COnS = Coagulase Negative Staphylococcus, Amx = Amoxicillin, Amc = Amoxicillin – clavulanate, Cfx = Cefixime, Fos = Fosfomycin, Sxt = Cotrimoxazole

**Table 5. Multi Drug Resistant Bacteria**

| Age group  | Spesies                | MDR | Non MDR | Total |
|------------|------------------------|-----|---------|-------|
| 0-1 year   | <i>Eschericia coli</i> | 2   | 6       | 8     |
|            | <i>Klebsiella sp</i>   | 3   | 2       | 5     |
|            | <i>Enterococcus sp</i> | 0   | 2       | 2     |
| 1-3 years  | <i>Eschericia coli</i> | 3   | 4       | 7     |
|            | <i>Klebsiella sp</i>   | 0   | 1       | 1     |
|            | <i>Enterococcus sp</i> | 0   | 4       | 4     |
| 3-18 years | <i>Eschericia coli</i> | 0   | 1       | 1     |
|            | <i>Klebsiella sp</i>   | 0   | 1       | 1     |
|            | <i>Enterococcus sp</i> | 0   | 2       | 2     |

## DISCUSSION

Table 1 shows prevalens of UTI in pediatric patient that is similar between boys and girls. In the other hand, Sonkar et al (India, 2018-2019) and Miron et al (Rumania, 2017-2019) found that UTI in pediatric patient were dominated by girl. But others studi, Bajpai et al (India, 2022), Woo et al (Korea, 2019), Agus Tusino and Niken (Central Java, 2017) shows dominated patient were boys. From the same study by Bajpai et al, that compare UTI prevalence from different countries from 2010 untul 2017, found sthat UTI cases in pediatric not always dominated by certain gender. Both gender have different risk factor such as circumcision in boys and anatomical structure in girls.<sup>2,6,13-16</sup>

In this study, for 1-3 years group, from 26 children, 25 children are under 2 years old, and it is 75,4% from all patient in this study that have positive urin culture is less than 2 years old. Similar result from Miron et al, that found 52,7% cases come from children under 1 year old.<sup>15</sup> Robinson et al (2014) from Canadian Pediatric Society, recommend pediatric patient that diagnosed UTI with fever should undergo future test to exclude kidney disorder.<sup>3</sup> However, this study didn't include data about fever, so it cant conclude amount of children that shoud have undergo follow-up test.

From positive culture, 82% sample come from children under 3 years old. Different with study from Bajpai et al that only 37% children are under 3 years old. This different

result cause by different positive criteria. Bajpat et al only use urine colony count  $\geq 10^5$  CFU/uL. Sonkar et al also have similar result with Bajpat et al, with 31,15% using same positive criteria but include children up to 5 years old.<sup>2,14</sup>

In this study from group 0-1 year old, most pediatric patients are boys (60%) and switch to dominated by girls by the age of 3 (71%). Woo et al (2019) also found that most pediatric patient under 1 year old with UTI were dominated by boys, but they found that the patient dominated by girls soon after 1 year old.<sup>6</sup> Meta analysis study by Marjo Renko et al, found that in the first 2 years of life, UTI were not dominated by certain gender, but after 6 years old, most UTI cases dominated by girl.<sup>17</sup>

Most pathogen found in this study (table 2) from 0-1 year old group are *Proteus mirabilis* (20,9%), followed by *Eschericia coli* (18,6%) and *Enterococcus sp* (16,3%). All these three bacteria are normal flora from human gut. Schweta et all only found 3 isolate from this group but they also found *Candida sp.* that is not found in this study.<sup>2</sup>

The most sensitive oral antibiotic in this study for 0-1 year old group is fosfomycin (86,04%), followed cotrimoxazole (79,06%), amoxicillin clavulanat (72,01%), cefixime (53,48%) and amoxicillin (51.16%). Based on PAMKI (Persatuan Ahli Mikrobiologi Klinik Indonesia) recommendation, oral antibiotic that can be used alone for empiric therapy are fosfomycin and cotrimoxazole because both antibiotic have sensitivity more than 75%.<sup>11</sup> These are affected by ESBL bacteria ( 2 *E.coli* and 3 *Klebsiella sp.*)

and *Enterococcus sp* (8 isolate) found in this study that are resistant to amoxicillin, amoxicillin clavulanate, and cefixime. In table 3, from age 1-3 years old group, positive urin culture are dominated by *Eschericia coli* (23,33%) and *Proteus mirabilis* (20%). In this group, *Enterococcus sp* were far more less than dibandingkan *Eschericia coli* dan *Proteus mirabilis*. Although these 3 spesies are also normal flora in human gut.<sup>17</sup> *Coagulase Negative Staphylococcus* are also found in this group with same number with *Enterococcus sp* (13.3%). Schweta et al only found 6 isolates from this group, and also dominated by *Klebsiella sp* which is also normal flora of human gut.<sup>2</sup>

Oral antibiotic for 1-3 years old group with sensitivity more than 75% is cotrimoxazole (76,7%). Fosfomycin sensitivity in this group is 70%, much lower than previous group. The others three oral antibiotics are less than 60% (amoxicillin clavulanate 60%, cefixime and amoxicillin are 40%). Pathogen found in this group such as *E. coli* ESBL, *Enterococcus sp*, and *CoNS* are directly affect the sensitivity of betalactam antibiotics, in particular cefixime.<sup>17, 18</sup> Isolate bacteria from 3 until 18 years old are combined into 1 group to table 4, because isolates found are less than 30. For this group, no dominant bacteria found. Most isolate found are *CoNS* 18,8%, followed by *Enterococcus faecalis* (12,5%) and *Proteus mirabilis* (12,5%). The last two species are normal human gut flora.<sup>18</sup> Schweta et al found that *E. coli* is the most common pathogen for this group that reach 60%, although they use patient patient from 3-12 years old for this group.<sup>2</sup> Number of positive culture from this study are very influential to this difference. For antibiotic sensitivity in table 4, highest sensitivity are amoxicillin clavulanate and cotrimoxazole. Both antibiotics have sensitivity more than 80%. Fosfomycin sensitivity is 66,7%, amoxicillin 60%, while cefixime is only 26,7%. Different result with study from Madenovic et al, which found that cefixime sensitivity reach 100%. This due to different population and in Madenovic study, all pathogen were from *Enterobacteriaceae* family that have no intrinsic resistant to cefixime.<sup>9</sup> In table 5, specific focus on MDR bacteria with special highlight according to WHO. Most MDR bacteria found in this study are from 0-1 year old group. From 8 *E. coli* isolate, 25% detected as ESBL producer, and 60% of *Klebsiella sp* are also ESBL. No carbapenemase *Enterobacteriaceae* and vancomycin resistant *Enterococcus* (VRE) found in this study. From 1-3 years old group, only *E. coli* ESBL that meet MDR criteria but reach 42,9% from all *E. coli* in this group. No bacteria that meet MDR criteria with special highlight according to HWO in 3-18 years old group. Overall from this study, 31,3% *E. coli* found are ESBL while 42,9% *Klebsiella sp* are ESBL. From Asnakech et al (2020) in Etiopia, they found similar percentage of *E. coli* ESBL (37,5%) but much more higher rate of *Klebsiella sp* ESBL (62,1%). Miron et al in Romania also found 13% of *E. coli* and 41,2% of *Klebsiella sp* are ESBL producer. In Korea, study by Woo et al. found that *E. coli* ESBL are low

but they also found that there is significant growth that reach 100% of *E. coli* ESBL in 2 consecutive period.<sup>6,15,20</sup>

Combined all group age in this study, oral antibiotic with highest sensitivity is cotrimoxazole (78,4%) followed by fosfomycin (77,3%). Other antibiotics that included in this study is less than 75%. Sensitivity for amoxicillin clavulanate, amoxicillin dan cefixime are 69,3, 48,9, and 44,3% respectively. Sensitivity result for cefixime in this study is in line with study by Woo et al that found decline of third generation cephalosporin in two consecutive period, from 91,7% to 75,5%. In the same study, no remarkable decline for ampicillin in the same period, although the sensitivity is already low (32,59-40,13%). This ampicillin sensitivity can be used to predict sensitivity for amoxicillin.<sup>6, 18</sup> Sonkar et al in India found that third generation cephalosporin (ceftriaxone and cefotaxime) sensitivity is 24% for *Enterobacteriaceae*. That percentage can be decreased if *Staphylococcus aureus* and *Enterococcus sp* that found in that study are included and used to measure sensitivity to cefixime, because both bacteria are intrinsic resistant to cefixime.<sup>14,18</sup> Asnakech Agegnehu et al from Ethiopia, found that prevalence on *Enterobacteriaceae* ESBL is 41,7%. This data also means that cefixime isn't usefull because ESBL bacteria are resistant to cefixime. Other antibiotics such as amoxicillin, amoxicillin clavulanate, and cotrimoxazole are also not recommended because the sensitivity are less than 15%. Fosfomycin was not included in that study.<sup>20</sup> High sensitivity for cefixime found on study by Victor Daniel et al in Rumania. In that study, cefixime sensitivity reach 83,4%. Low prevalence of ESBL bacteria influential in high cefixime sensitivity. Cotrimoxazole come in second with 70,8%, while amoxicillin and amoxicillin clavulanate are 28,9 and 40,9%.<sup>15</sup>

No study about Fosfomycin sensitivity for UTI in pediatric when this study was done, however with high rate of *E. coli* and *Klebsiella sp* that are ESBL producer found in this study and study by Agegnehu et al, also data shown by Woo et al about increase prevalence of ESBL, Fosfomycin can be useful to treat UTI in pediatric patient to prevent the infection become more serious and need to be treated as an inpatient. MDR bacteria especially *Enterobacteriaceae* ESBL have been spread to community and become global phenomenon that affect pediatric patient.<sup>10, 21, 22</sup>

## CONCLUSION

From this study, best oral antibiotic that can be used as empiric therapy are cotrimoxazole and Fosfomycin especially for patient less than 3 years old. Because not enough sample for patient older than 3 years old, it is recommended to culture urine because high rate of ESBL bacteria that already found in younger patient. This study didn't consider side effect of each antibiotics so that clinical aspect of the patient correlated to side effect from each antibiotics still have to be considered before choose empiric antibiotic for UTI in pediatric patient.



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