Extended spectrum beta lactamase (ESBL)-producing Klebsiella pneumoniae clinical isolates and its susceptibility pattern to antibiotics at Dr. Soeradji Tirtonegoro General Hospital Klaten, Central Java

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ABSTRACT

Globally, the prevalence of Klebsiella pneumoniae (K. pneumonia) producing extended spectrum beta lactamase (ESBL) has been increasing steadily. The susceptibility patterns of ESBL-producing K. pneumonia varies considerably among countries. Therefore, the investigation of ESBL-producing K. pneumonia in clinical isolates and their susceptibility are warranted. This research aimed to determine the proportion of ESBL-producing K. pneumonia and the antibiotic susceptibility patterns of clinical isolates from Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java. Identification of K. pneumonia was performed by analyzing colony morphology, microscopic examination, and biochemical testing using Microbact. Both antibiotic susceptibility testing and ESBL screening (using ceftazidime, cefotaxime, and ceftriaxone discs) were conducted using disc diffusion method according to CLSI. The positive results were confirmed with modified double disk synergy (MDDST) using amoxicillin-clavulanate, ceftazidime, cefotaxime, and cefepime discs. From 962 clinical bacterial isolates, 168 (17.46%) isolates were identified as K. pneumoniae, during June 2017-May 2018. K. pneumoniae was mainly isolated from the Intensive Care Units (ICU) (29.17%) and with sputum being the most common specimen (45.24%). Overall ESBL producers were 52.98%, with the majority from ICU (41.57%) and isolated from sputum specimens (40.45%). ESBL-producing K. pneumoniae showed high resistance to many antibiotics. The sensitivity of ESBL-producing K. pneumoniae isolated from respiratory tract samples against piperacillin-tazobactam, amikacin, and meropenem was more than 80%. In conclusion, among all K. pneumoniae isolates, ESBL K. pneumoniae was 52.98%. ESBL K. pneumoniae from respiratory tract specimens had a sensitivity of more than 80% against piperacillin-tazobactam, amikacin, and meropenem.

ABSTRAK

**Keywords:** Klebsiella pneumonia; extended spectrum beta lactamase; modified double disk synergy; antibiotic resistance; susceptibility testing.

**INTRODUCTION**

*K. pneumoniae* is one of the bacteria with a high level of antibiotic resistance and often causes nosocomial infections in hospitals.²,³ Klebsiella pneumoniae is known to cause pneumonia, urinary tract infection (UTI), bacteremia, liver abscess, wound infection, intravascular infection, bile duct infection, peritonitis, rhinoscleroma meningitis, ozaena, sinusitis, otitis, enteritis, appendicitis, cholecystitis, pyogenic brain abscess, and endophthalmitis.²-⁵ It is often isolated from ICUs and associated with outbreaks in hospitals.⁶

Extended spectrum beta-lactamase (ESBL) is a mutated β lactamase enzyme capable of hydrolyzing penicillin, first, second, third and fourth generation cephalosporin, and monobactam but cannot hydrolyze cephamycins or carbapenem.⁷ ESBL encoding genes are frequently found on the same plasmids that encode resistance to aminoglycosides, sulfonamides, and fluoroquinolones, so that ESBL-producing bacteria are commonly multidrug-resistant (MDR) bacteria.⁸

Various studies have shown an increased prevalence of ESBL-producing *K. pneumoniae* worldwide. Data from the tigecycline evaluation and surveillance trial (TEST) during January 2004 to August 2006 showed ESBL-producing *K. pneumoniae* in Latin America (44%), Asia (22.4%), Europe (13.3%), and North America (7.5%) respectively.⁹ In China, ESBL-producing *K. pneumoniae* was reported 31.8% of *K. pneumoniae* during August 2010-2011.¹⁰ Meanwhile the prevalence of ESBL-producing *K. pneumoniae* in Iran was 43% of *K. pneumoniae* during 2007-2008¹¹ and in Tanzania it was 63.73% of *K. pneumoniae*.¹²

The prevalence of ESBL-producing *K. pneumoniae* in Indonesia was reported differently. At Dr. Soetomo General Hospital, Surabaya, the prevalence of ESBL-producing *K. pneumoniae* was reported 35.35% during January 2005-April 2005¹³; 23% during January-June 2010; 50.28% during January-November 2011; 58% during July-December 2012, and 38.5% during October 2014-May 2015.¹⁴,¹⁵ Meanwhile the prevalence of ESBL-producing *K. pneumoniae* was reported 66.2% at Dr. Arifin Achmad General Hospital, Pekanbaru during January-December 2015.¹⁶

ESBL-producing bacteria are a major concern because they are associated with MDR microbes, which cause limited choices of antibiotics for the treatment of infections leading to increased morbidity, mortality and hospital costs.¹⁷ Thus, the detection of ESBL-producing *K. pneumoniae* is important for optimal patient therapy choices and outcomes.

Screening of ESBL-producing *K. pneumoniae* can be done by disk diffusion using ceftazidime, cefotaxime, and ceftriaxone discs in accordance with the clinical laboratory standards institute (CLSI) M100 28th Edition.¹⁸ This should be followed by a confirmation test with the modified double disk synergy test (MDDST) using ceftazidime, cefotaxime,
The globally increasing prevalence of ESBL-producing *K. pneumoniae* infections, the increasing incidence of antibiotic resistance, and the increasing morbidity and mortality due to MDR bacterial infections in hospitals, prompt researchers to investigate ESBL-producing *K. pneumoniae* clinical isolates and their antibiotic sensitivity pattern. This research aimed to determine the proportion of ESBL-producing *K. pneumoniae* and the antibiotic susceptibility patterns of clinical isolates from Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java.

**MATERIALS AND METHODS**

**Study design and data collection**

This was a cross-sectional descriptive study using secondary data from the archive of culture and susceptibility testing results at the Clinical Microbiology Laboratory Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java during June 2017-May 2018. Screening and confirmation of ESBL-producing *K. pneumoniae* was conducted in the Microbiology Laboratory of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. The research protocol was approved by The Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with number KE/FK/0784/EC/2018.

**Subjects**

The subjects of the study were *K. pneumoniae* samples isolated from various clinical specimens of patients at Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java during June 2017-May 2018.

**Isolation, identification, and antibiotic susceptibility test (AST)**

Clinical specimens were inoculated on blood agar and Mac Conkey agar (Oxoid, UK). All incubations were conducted aerobically at 37°C for 18-24 hours. Identification of *K. pneumoniae* isolates was based on the morphology of colonies on blood agar and Mac Conkey, microscopic examination with gram stain and biochemical test using Microbact™ GNB 24E (Oxoid, UK). Biochemical tests were conducted according to company instructions.

*K. pneumoniae* isolates were tested for their AST by the disc diffusion method in accordance to CLSI guideline. The following antibiotic discs from Oxoid, United Kingdom were used accordingly: cephazolin (30µg), gentamicin (10µg), tobramycin (10µg), amikacin (30µg), amoxicillin-clavulanate (20/10µg), piperacillin-tazobactam (100/10µg), cefuroxime (30µg), cefepime (30µg), ceftriaxone (30µg), ciprofloxacin (5µg), levofloxacin (5µg), meropenem (10µg), nitrofurantoin (100µg), trimethoprim-sulfamethoxazole (25µg), cefotaxime (30µg), and ceftazidime (30µg). Sensitive or resistant determination was based on CLSI references (18). Antibiotics were used according to the panel of agreement from the Indonesian Society for Clinical Microbiologist of 2015 based on CLSI references.

**Screening and confirmation of ESBL-producing *K. pneumoniae***

ESBL-producing *K. pneumoniae* screening was done with ceftriaxone, cefotaxime, and ceftazidime discs (Oxoid, UK) based on CLSI references. The confirmation test of ESBL-producing *K. pneumoniae* was done using amoxicillin-clavulanate (20/10 µg) disc along with ceftazidime 30 µg, cefotaxime 30 µg, and cefepime 30 µg discs (Oxoid, UK). A lawn culture of the organisms was made...
on a Mueller Hinton (MH) agar plate, as recommended by CLSI. Amoxicillin-clavulanate (20/10 µg) disc was placed in the center of the plate. The discs of ceftazidime 30 µg, cefotaxime 30 µg, and cefepime 30 µg were placed center to center to amoxicillin-clavulanate disc 20 mm apart. Then MH agar was incubated for 18-24 hours at 37°C. Any distortion or increase in the zone towards the disc of amoxicillin-clavulanate was considered as positive for the ESBL production.\textsuperscript{19,20}

**RESULTS**

During June 2017-May 2018, 168 (17.46\%) of *K. pneumoniae* isolates were isolated from 962 total clinical bacterial isolates at Dr. Soeradji Tirtonegoro General Hospital Klaten, Central Java. The *K. pneumoniae* isolates were mainly obtained from patients treated in the intensive care unit (29.17\%) (TABLE 1), and isolated from sputum specimens (45.24\%) (TABLE 2).

**TABLE 1. Specimen locations [n (%)] of *K. pneumoniae* isolates at Dr. Soeradji Tirtonegoro General Hospital, Klaten during June 2017-May 2018**

<table>
<thead>
<tr>
<th>Specimen locations</th>
<th><em>K. pneumoniae</em> isolates (n=168)</th>
<th>ESBL producing <em>K. pneumoniae</em> isolates (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensives Care Unit</td>
<td>49 (29.17)</td>
<td>37 (41.57)</td>
</tr>
<tr>
<td>• Adults</td>
<td>27 (16.07)</td>
<td>16 (17.98)</td>
</tr>
<tr>
<td>• Children and Neonates</td>
<td>22 (13.10)</td>
<td>21 (23.60)</td>
</tr>
<tr>
<td>Non-Surgery ward</td>
<td>37 (22.02)</td>
<td>10 (11.24)</td>
</tr>
<tr>
<td>Pulmonary ward</td>
<td>24 (14.29)</td>
<td>9 (10.11)</td>
</tr>
<tr>
<td>Surgery ward</td>
<td>23 (13.69)</td>
<td>11(12.36)</td>
</tr>
<tr>
<td>Pediatric ward</td>
<td>16 (9.52)</td>
<td>11 (12.36)</td>
</tr>
<tr>
<td>Perinatology ward</td>
<td>11 (6.55)</td>
<td>6 (6.74)</td>
</tr>
<tr>
<td>Clinic</td>
<td>7 (4.17)</td>
<td>5 (5.62)</td>
</tr>
<tr>
<td>Obstetrics and Gynecology ward</td>
<td>1 (0.60)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**TABLE 2. Distribution of specimen types [n (%)] for isolating *K. pneumoniae* at Dr Soeradji Tirtonegoro General Hospital Klaten during June 2017-May 2018**

<table>
<thead>
<tr>
<th>Types of specimen</th>
<th>ESBL-producing <em>K. pneumoniae</em> isolates (n=89)</th>
<th><em>K. pneumoniae</em> isolates (n=168)</th>
<th>Proportion ESBL-producing <em>K. pneumoniae</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>36 (40.45)</td>
<td>76 (45.24)</td>
<td>36/76 (47.36)</td>
</tr>
<tr>
<td>Pus</td>
<td>12 (13.48)</td>
<td>27 (16.07)</td>
<td>12/27 (44.44)</td>
</tr>
<tr>
<td>Blood</td>
<td>18 (20.22)</td>
<td>20 (11.90)</td>
<td>18/20 (90)</td>
</tr>
<tr>
<td>Urine</td>
<td>8 (8.99)</td>
<td>12 (7.14)</td>
<td>8/12 (66.67)</td>
</tr>
<tr>
<td>Bronchial washings</td>
<td>1 (1.12)</td>
<td>9 (5.36)</td>
<td>1/9 (11.11)</td>
</tr>
<tr>
<td>Feces</td>
<td>5 (5.62)</td>
<td>6 (3.57)</td>
<td>5/6 (83.33)</td>
</tr>
<tr>
<td>Wound swab</td>
<td>3 (3.37)</td>
<td>5 (2.98)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Sterile site</td>
<td>2 (2.25)</td>
<td>7 (4.17)</td>
<td>2/7 (28.57)</td>
</tr>
<tr>
<td>Others*</td>
<td>4 (4.49)</td>
<td>6 (3.57)</td>
<td>4/6 (66.67)</td>
</tr>
</tbody>
</table>
Out of 168 isolates of *K. pneumoniae*, 104 isolates were possible ESBL producers (61.90%), with 85.58% (89/104) confirmed as ESBL producers using the MDDST method (FIGURE 1). The proportion of *K. pneumoniae* confirmed as ESBL producers was 52.98% (89/168) of the total isolates of *K. pneumoniae*. ESBL-producing *K. pneumoniae* were mostly obtained from patients treated in the ICU (41.57%) (TABLE 1).

![FIGURE 1. A positive MDDST for cephalosporin discs; A) A positive MDDST with an increased inhibition zone for ceftazidime, cefotaxime and cefepime towards amoxicillin clavulanate; B) A positive MDDST with increased inhibition zone for cefotaxime and cefepime; C) A positive MDDST with increased inhibition zone only for cefepime. AMC=amoxicillin clavulanate; CAZ=ceftazidime; CTX=cefotaxime; FEP=cefepime; CN=gentamicin](image)

Based on the distribution of specimen types, ESBL-producing *K. pneumoniae* was mostly isolated from sputum (40.45%) (TABLE 2). Whereas if based on the proportion of ESBL producers, these isolates were often found in all specimens except those originating from bronchial washings. The proportion of ESBL-producing *K. pneumoniae* in sputum, pus, blood, and urine was 47.36%, 44.44%, 90% and 66.67%, respectively (TABLE 2).

TABLE 3 shows the percentage susceptibility of ESBL-producing *K. pneumoniae* clinical isolates to various origin specimens using antibiotic panels according to the Indonesian Society for Clinical Microbiologist. In this study, 38 isolates of *K. pneumoniae* were derived from respiratory tract specimens, namely sputum, bronchial washings, and tracheal aspiration. ESBL-producing *K. pneumoniae* from respiratory tract specimens had a sensitivity of more than 80% to piperacillin-tazobactam (88.89%), amikacin (97.37%), and meropenem (100%). Sensitivity to cefepime and ceftriaxone were 0% in each.
TABLE 3. Percentage of susceptibility (%) of ESBL-producing *K. pneumoniae* isolates to antibiotics based on the origin of specimens at Dr. Soeradj Tirtonegoro General Hospital Klaten during June 2017-May 2018

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Respiratory tracts (n=38)</th>
<th>Blood (n=18)</th>
<th>Wound (n=17)</th>
<th>Urine (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephazolin</td>
<td>0</td>
<td>-</td>
<td>11.76</td>
<td>0</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>34.21</td>
<td>11.11</td>
<td>64.71</td>
<td>37.5</td>
</tr>
<tr>
<td>Tobramycin*</td>
<td>26.32</td>
<td>16.67</td>
<td>35.29</td>
<td>37.5</td>
</tr>
<tr>
<td>Amikacin*</td>
<td>97.37</td>
<td>100</td>
<td>82.35</td>
<td>87.50</td>
</tr>
<tr>
<td>Amoxicillin-Clavulanate</td>
<td>28.95</td>
<td>-</td>
<td>58.82</td>
<td>12.50</td>
</tr>
<tr>
<td>Piperacillin-Tazobactam*</td>
<td>88.89</td>
<td>75</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2.63</td>
<td>0</td>
<td>5.88</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0</td>
<td>0</td>
<td>5.88</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-</td>
<td>66.67</td>
<td>17.65</td>
<td>62.50</td>
</tr>
<tr>
<td>Levofoxacin*</td>
<td>71.05</td>
<td>83.33</td>
<td>29.41</td>
<td>75</td>
</tr>
<tr>
<td>Meropenem*</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>18.42</td>
<td>-</td>
<td>11.76</td>
<td>25</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75</td>
</tr>
</tbody>
</table>

*Not all ESBL-producing *K. pneumoniae* isolates were tested with piperacillin-tazobactam discs. The number of ESBL-producing *K. pneumoniae* isolates tested with piperacillin-tazobactam in the respiratory tract = 9, blood = 4, wounds = 4, urine = 1; #Antibiotics with restricted use based on Indonesian Society for Clinical Microbiologist.

DISCUSSION

In this study, the proportion of *K. pneumoniae* isolates was 17.46% of total clinical bacterial isolates during June 2017-May 2018. This finding should be a major concern because *K. pneumoniae* is often associated with high levels of antibiotic resistance, nosocomial infections, and outbreaks in hospital.6

The ESBL-producing *K. pneumoniae* was mostly isolated from sputum. This is in line since *K. pneumoniae* often causes pneumonia, septicemia, UTI and wound infections.22 The same results were also reported from Dr. Arifin Achmad General Hospital Pekanbaru,15 whereas research at Bugando Medical Center Tanzania reported that the pathogen originated mostly from urine.12

The majority of infections caused by *K. pneumoniae* are associated with hospitalization, especially in ICUs.6 In this study, ESBL-producing *K. pneumoniae* was mostly isolated from patients treated in the ICU. Similar results were also reported at Dr. Arifin Achmad General Hospital Pekanbaru,16 and Imam Reza Hospital of Mashhad Iran,11 ESBL-producing *K. pneumoniae* are mainly obtained from ICUs for adults, neonates and premature infants.12
Accordingly, ICU is one of the risk factors of ESBL infection, because patients in intensive care unit are often given long-term broad-spectrum antibiotics, invasive procedures, and long-term catheter placements. Other risk factors are pressure sores, poor nutritional status, and travel history to Asia, Greece, Turkey, and the United States.\textsuperscript{11,23-26}

In this study, the ESBL confirmation test was done with MDDST, which is a modification of the Double Disc Synergy Test (DDST) to increase sensitivity to bacteria that co-produce AmpC and ESBL enzymes. Many of \textit{K. pneumoniae} isolates are able to produce both of those enzymes.\textsuperscript{27} AmpC β-lactamase hydrolyzes penicillins, cephalosporins, cephemycins, and monobactams but does not inhibit clavulanate.\textsuperscript{28} Clavulanate induces high levels of AmpC expression in bacteria with AmpC and ESBL co-production, thereby hydrolyzing third generation cephalosporins. AmpC expression covers the synergy of third generation cephalosporins with amoxicillin-clavulanate.\textsuperscript{23}

High level AmpC expression has minimal effect on cefepime, so that an increase in the inhibition zone between amoxicillin-clavulanate and cefepime discs can still be observed. If the synergy effect is only positive for cefepime but has a negative effect on third generation cephalosporins, isolates are suspected of co-production of AmpC and ESBL (20). MDDST using ceftazidime 30 μg, cefotaxime 30 μg, and cefepime 30 μg, has a sensitivity of 100% and specificity of 93%.\textsuperscript{19}

After confirmation testing, most of the \textit{K. pneumoniae} isolates were identified as ESBL producers with ceftazidime, cefotaxime, and cefepime discs. Only a small number of isolates were confirmed as ESBL producers with cefotaxime or cefepime discs, because the optimal substrate profile varied among the ESBL enzymes.\textsuperscript{29}

In this study, the proportion of ESBL-producing \textit{K. pneumoniae} isolates was 52.98%. The proportion of ESBL-producing bacteria is important to know because it correlates with an increase in antibiotic resistance. This causes limited choice of antibiotics. Sensitivity patterns of ESBL producing bacteria can help clinicians determine the right antibiotic for therapy. Similar results were reported from Dr. Soetomo General Hospital, Surabaya in 2011 (50.28%) and in 2012 (58%).\textsuperscript{14} While higher yields were reported from Dr. Arifin Achmad General Hospital, Pekanbaru in 2015 (66.2%).\textsuperscript{16} The difference in this study findings might be due to differences in ESBL detection methods, sampling techniques, study population, patient characteristics, guidelines for antibiotic use and infection control strategies.\textsuperscript{11,13,15}

The number of ESBL producing bacteria is one indicator for the observation of outbreaks of MDR bacteria.\textsuperscript{30} The high number of ESBL-producing \textit{K. pneumoniae} among various hospitals in Indonesia, shows the large role of ESBL bacteria in antibiotic resistance. Evaluation of antibiotic usage and surveillance of MDR bacteria must be routinely done and reported periodically by the local Antimicrobial Stewardship Team in the relevant hospital.\textsuperscript{30} Regulations are needed related to compliance with prudent antibiotic usage, especially cephalosporins.\textsuperscript{31} In addition, compliance with the principle of standard precautions must be increased to prevent the spread of resistant bacteria through plasmids.\textsuperscript{32}

Controlling the spread of ESBL-producing bacteria is done by identifying and immediately isolating patients with suspected ESBL-producing bacteria colonization or infection, conducting molecular epidemiological analyzes on strains of colonized or infected patients,\textsuperscript{23} and also minimizing the length of treatment to reduce the likelihood of patients being a source of cross infection.\textsuperscript{31} The spread of pathogens...
and the risk of cross infection can be minimized by placing infected patients in isolation rooms. If the isolation room is not available, the patient should be placed in a cohorting way, which involves treating several patients with the same pattern of infection in one room.\textsuperscript{30}

Precautions should always be applied since the proportion of ESBL-producing \textit{K. pneumoniae} is high in sputum, pus, blood and urine. The principle of standard precautions must be done especially in hospitalized patients to avoid nosocomial infections. Lower respiratory tract infections should be of particular concern, especially in patients using endotracheal tubes.\textsuperscript{31} Likewise, the use of an intravenous catheter, arterial catheter and urinary catheter should also be a concern for septicemia and urinary tract infection.

The results of bacterial sensitivity testing for antibiotics can be arranged into an antibiogram for empirical therapy guidelines. Antibiogram contains isolate data according to the type of specimen and room location.\textsuperscript{30} The number of isolates needed to make the ideal antibiogram is at least 30.\textsuperscript{34} In this study, the data that can be used was ESBL-producing \textit{K. pneumoniae} isolates originating from the respiratory tract. Antibiotics that have a sensitivity of more than 80% can be used as empirical therapy.\textsuperscript{30}

ESBL-producing \textit{K. pneumoniae} isolates originating from the respiratory tract have a sensitivity of more than 80% against amikacin, piperacillin tazobactam, and meropenem. Although piperacillin-tazobactam has a sensitivity of more than 80%, not all isolates of \textit{K. pneumoniae} originating from the respiratory tract were tested for sensitivity to piperacillin-tazobactam. So, it needs special consideration for piperacillin-tazobactam to be used as empirical therapy.

ESBL-producing \textit{K. pneumoniae} isolates originating from other specimens are less than 30 isolates each. Therefore, the results of sensitivity must be interpreted with special consideration. The sensitivity data of less than 30 isolates may cause an unreliable and unrepresentative antibiogram.\textsuperscript{34}

The sensitivity of ESBL-producing \textit{K. pneumoniae} with more than 80% were obtained for ertapenem, meropenem, and amikacin at Dr. Arifin Achmad General Hospital, Pekanbaru in 2015.\textsuperscript{16} Whereas amikacin, cefoperazone-sulbactam, meropenem and phosphomycin were antibiotics which are reported to have a sensitivity of more than 80% in Dr. Soetomo Hospital Surabaya, Dr. Saiful Anwar General Hospital, Malang, and Dr. Kariadi General Hospital, Semarang in 2010.\textsuperscript{31} This means an antibiotic choice with good sensitivity, is limited to antibiotics which are restricted such as meropenem, piperacillin-tazobactam, and amikacin.

Carbapenem is the treatment of choice for severe infections caused by ESBL-producing \textit{K. pneumoniae}.\textsuperscript{35} However, the increasing incidence of infection with ESBL-producing bacteria throughout the world, has led to an increase in the use of carbapenem. The use of excessive carbapenem triggers selection pressure resulting in carbapenem resistant bacteria.\textsuperscript{2} Carbapenem resistance causes antibiotic resistance problems which are more difficult to overcome.

This study has limitations due to the scarcity of piperacillin-tazobactam discs. Not all \textit{K. pneumoniae} isolates were tested for antibiotic susceptibility with piperacillin-tazobactam so that representative sensitivity data were not available.

**CONCLUSION**

Proportion of ESBL-producing \textit{K. pneumoniae} clinical isolates is 52.98% of total \textit{K. pneumoniae} isolates at Dr. Soeradji Tirtonegoro General Hospital, Klaten.
Piperacillin-tazobactam, amikacin, and meropenem have a sensitivity of more than 80% in the respiratory tract sample isolates from patients at Dr. Soeradji Tirtonegoro General Hospital, Klaten.

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