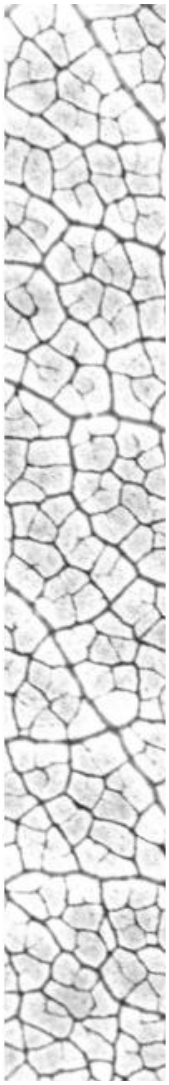

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Management in diarrhea patient caused by *E. coli* produce Esbl

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Abstract

Background: A 55 years old, Javanese man suffered diarrhea more than 8 times since 7 days before and complained a fever, feeling a pain and stiffness in the abdomen. His feces was watery, sometimes with mucus and blood. Previously he had suffered Diabetes Mellitus since 5 years ago and had been doing a regular treatment at local health facilities. **Result**: Random Blood Glucose test was 136 mg/dl, so the early diagnosis was a regulated DM and acute diarrhea caused by suspected Shigella infection. The initial treatment was intravenous Ciprofloxacin 400mg injection, but the patient's condition did not get any improvement. After 5 days of treatment, the Feces culture showed ESBL producing E. coli and resistant to Ciprofloxacin but sensitive to Meropenem. So the drug choice of antibiotics was replaced into Meropenem. Six days later, the patient's clinical and laboratory parameters were improved. The feces re-culture results showed there was no growth of E. coli. Then, the antibiotic was changed to Meropenem. **Conclusions:** The patient had succeeded according to standard procedures for ESBL and became better condition and had a good prognosis. Thus, the special treatment for patient who experience ESBL was a treatment which according to standard procedures and the selection of appropriate antibiotics.

Keywords: diarrhea, E. Coli, ESBL

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INTRODUCTION

Major issues in Asia about antimicrobial resistant in nosocomial pathogens were mostly health treatment effects that associated with infections, caused by *MDRO (Multi Drug Resistant Organism) / PDR (Pan Drug Resistant) / XDR (Extreme Drug Resistant) Organisms*. Preliminary data from *ANSORP (Asian Network Surveillance on Resistant Pathogens),* the study of 2008-2009 showed that Asia as a center of *MRSA (Methicillin Resistant Staphilococcus Aureus)* & *ESBL (Extended-Spectrum Beta-Lactamase)*, in which in some countries such as Korea, China, Japan, Taiwan, Hongkong, India and Singapore, the prevalence rate was more than 50 % of nosocomial pathogens. The rate of *ESBL* itself in Indonesia was 40 % in which *K.pneumoniae* is the most predominant factor, followed by *E.coli. ESBLs* constitute a growing class of plasmid-mediated ß-lactamases which confer resistance to broad spectrum beta-lactam antibiotics. The emergence of *ESBLs* creates a real challenge for both clinical microbiology laboratories and clinicians because of their dynamic evolution and epidemiology, wide substrate specificity with its therapeutic implications, their significant diagnostic challenges and their prevention and infection control issues (Al Jasser, 2006. Buntaran, 2009).

The problem to human health that caused by antimicrobial resistance of bacteria become a problem that increases continuously in the worldwide. The increasing number of antimicrobials use in humans, animals, and agriculture has resulted in many cases of microbes developing resistance to these powerful drugs. Many cases of infectious diseases which are difficult to be treated because of antimicrobial-resistant organism. Other fact shows in the United States in the period 1983-2007, the total number of new antibacterial agents that recognized was decreased significantly. To improve the antimicrobials use, the program of management antimicrobials use consisting two core strategies and supplemental strategies, can be implemented in health care facilities (Buntaran, 2009. Coque, Baquero, & Canton, 2008. Hadi, 2009; Shiberu, et al, 2014). Thus, this paper will discuss about management in diarrhea patient caused by *E. coli* causing *ESBL.*

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CASE REPORT

Clinical Case

A male patient, Mr. L, 55 years old, Javanese. His occupation is spiritual teacher. He lived in Keputih, Surabaya. He reffered to dr. Soetomo Hospital on October 7th, 2009 with a major complaint of diarrhea. He suffered diarrhea more than 8 times since 7 days before. His feces was a little, watery, accompanied by a mucus, blood-red with brownish. He also complained a pain, stiffness in the lower abdomen, nausea and high fever. He told that he ate some fermented shrimp before got sick. He had been already treated by the local health facilities and got some drugs, one of which was ciprofloxacin. However, the patient took the drugs only once to twice a day for 3 days. He stopped consuming the drugs because the diarrhea was still continuous and decided to go to dr. Soetomo hospital. He did not have any complaint about urinate. He never had any history of a severe diarrhea like this before. He had a drug consumption history of antibiotics drugs from drugstore when he was sick without any doctor's prescription.

He suffered diabetes mellitus for >5 years and consumed glibenclamid regularly from a local health facilities. He had been hospitalized 3 times in the last one year because of his diabetic complications. He visited dr. Soetomo Hospital regularly for 3 weeks due to his high blood glucose levels and leg ulcer about 2 month ago. He did not have any history of food allergies, medication, previous gastrointestinal diseases, malignant disease, and thyroid disease.

The general condition was weak, weight was 58 kg, awareness was compos mentis, blood pressure was 120/70 mmHg, pulse was 110x/min regular, axillary temperature was 38.0^{o}C, respiratory rate was 20x/min. The head and neck examination results showed there were no anemia, jaundice, cyanosis, nor dyspnea. There was no white pitches in the oral cavity, enlargement of lymph nodes nor increased jugular venous pressure. Chest examination of cardiac was single S1 and S2, there were no murmur nor gallop. Pulmo examination were symmetrically, vesicular sound both right and left. There were no wheezing and rhonchi on both side. There was not found spider nevi. Abdominal examination were flat, not distended, there was no intra-abdominal mass. There were increased bowel sounds. Extremities examination were no edema nor hemorrhoids. The result of Chest X-ray was Cor and pulmo within normal limit and the result of ECG was Sinus Tachycardia 110x/m, normal axis. He also took laboratory examination. The result of his laboratory examination was shown by **Table 1**.

Table 1. The Result of Laboratory Examination

Parameter	Result
Hb	11.9 g/dl
WBC	*11,200/mm3*
Plt	378,000/mm3
Hct	37.7 %
ESR	*80 mm/hour*
Random Blood Glucose	*159 mg/dl*
BUN	18 mg/dl
Creatinin Serum	1.2 mg/dl
AST	29 U/L
ALT	27 U/L
Albumin	*3.1 mg/dl*
Total bilirubin	0.9 mg/dl
Direct bilirubin	0.6 mg/dl
Sodium	130 mEq/L
Potasium	3.7 mEq/L
Uric acid	3.3 mg/dl
Urine :	
- Bacteria	(-)
- Glucose	(-)
- Ketone	(-)
- Protein	(-)

Diagnose and Therapy

He was diagnosed of Regulated DM and Acute Diarrhea without dehydration, caused by suspected Shigellosis. The planning of this case were a feces examination, Feces culture + antibiotic sensitivity test, Random Blood Glucose/2hPP, HbA1C. The patient got a diet therapy of B1 2100 kcal/day, Inf. RL 1000cc/day, Inj, Actrapid 4 unit t.i.d subcutan, 15 minute before meal, Inj, Ciprofloxacin 400 mg b.i.d and paracetamol 500 mg t.i.d.

Progress Note

At 5th day care, the patient still had diarrhea, > 8x/day, accompanied pain in stomach. His condition was weak. His BP was 110/70 mmHg, pulse rate was 110x /min, respiratory rate was 22x /m, axillary temperature was 38.3^{o}C.

Laboratory result showed that his Hb was 12.1 g/dl. His *WBC* was *17,000/mm3*. His Plt was 362,000/mm3. His Hct was 35.7 %. His Fasting Blood Glucose was 99 mg/dl. His 2hPP was 120 mg/dl. His BUN was 8.7mg/dl. His Creatinin Serum was 0.8 mg/dl. His AST was 29 U/L. His ALT was 27 U/L. His albumin was 3.2 mg/dl. His sodium was 125 mEq/L. His potasium was 3.8 mEq/L. The result of his feces examination showed that his erytrosit was 0-1. His leukocytes were in a large number, egg (-), larva (-), amoeba (-), *E. coli (+),* mucus (-), blood (-). His blood culture showed that there was no any organism. His urine culture showed that there was no any organism. His feces culture showed that there was *E. coli* pathogen serotype 1-11*, ESBL (+), >10^{5}* with antibiotics sensitivity test were sensitive to Amikacin, Piperacillin-Tazobactam, Cefoperazone-Sulbactam, and Meropenem. Resistant to Ceftazidim, Cefotaxim, Cotrimoxazole, and Ciprofloxacin. Patient was referred to Infection Control Committee.

They gave an advice to implement isolation cohort, contact precaution, and perform perianal swab to evaluate the progression of therapy. Patient was diagnosed as regulated DM and acute diarrhea caused by *E. coli* causing ESBL + sepsis. Inj. Ciprofloxacin was stopped and changed to Inj. Meropenem 1 g t.i.d (day^{0}1), other medications were continued.

At 9th day care, the patient condition was improved, the diarrhea frequencies became 3-4x/day. The consistency was already hard. His Hb was 12.5 g/dl. His *WBC* was *15,000/mm3*. His Plt was 272,000/mm3. His Hct was 32.7 %. His RPG was 142 mg/dl. His BUN was 8.7mg/dl. His CS was 0.8 mg/dl. His SGOT was 29 U/L. His SGPT 27 U/L. His albumin was 3.2 mg/dl. His sodium was 135 mEq/L. His Potasium was 3.8 mEq/L. He got diet B1 2100 kcal/day, inj. Actrapid 4 unit t.i.d, inf. RL 1000cc/day, Inj. Meropenem 1 g t.i.d (day^{0}4).

At 12th day care, the defecation was normal. His Hb was 11,=.5 g/dl. His *WBC 9,000/mm3*. His Plt was 291,000/mm3. His Hct was 32.7 %. His RPG was 133 mg/dl. His feces re-culture after therapy showed that there was no any organism. Inj. Meropenem was stopped (day^{0}7). Finally, at 13th day care, the patient was discharged and advised to control in outpatient department.

DISCUSSION

Diarrhea was defined as a defecation with feces weight more than 200 grams/day. However, the definition is less valuable because it measures the amount of clinical feces only done in research. Practical definition that often used is a defecation with watery feces as much as ≥ 3 times /day. Based on etiology, diarrhea can divided into 3 categories, such as acute, persistent, and chronic diarrhea. Acute diarrhea is diarrhea that lasted ≤ 14 days. Diarrhea that persist until >14 days is called persistent diarrhea, whereas when settled > 30 days is called chronic diarrhea. The cause of diarrhea can be infectious or non-infectious. Infectious diarrhea will cause symptoms of nausea, vomiting, and fever accompanied by abdominal pain, tenesmus, liquid feces with mucus and blood. *Shigella spp* is the most common bacterial cause of diarrhea classic. Other bacteria are *Salmonella, Campylobacter*, and *E coli* (Putri, 2018. Setiawan, 2006).

This patient suffered from diarrhea since 7 days accompanied by pain and stiffness in the abdomen, and fever. His feces was watery, sometimes accompanied by mucus and blood. Previously he had suffered from Diabetes Mellitus since 5 years ago and treated regularly at local health facilitates. Random Blood Glucose when he admitted was 136 mg/dl, so the early diagnosis was regulated DM and acute diarrhea caused by suspected Shigella infection.

The lack of the diagnostic methods that are accurate and rapid causes the diagnosis making of enteric pathogens to antibiotics is often established empirically. So there are only clinical indications, such as: patients with fever, bloody feces/mucoid, there are vague or leukocyte blood in the feces, patients with bowel frequency > 8x/day, dehydration, symptoms > 1week, which requires treatment. The diarrhea that due to suspected by Shigella infections can be treated with antibiotics such as cotrimoxazol, ampicillin, or quinolone. However few literature recently reported that many strains of microbial that now resistant to cotrimoxazol and ampicillin (Putri, 2018. Keusch, Kopecko, 2009. Thielman, & Guerrant, 2004).

He received empirical antibiotic therapy such as inj. Ciprofloxacin 400mg b.i.d while waiting complete feces examination and feces culture result.

ESBLs are known as extended-spectrum ß-lactamase because they are able to hydrolyze a broad spectrum of ß-lactam antibiotics than the simple parent ß-lactamases from which they are derived. They are acquired plasmid-mediated ß-lactamases. They have the ability to inactivate ß- lactam antibiotics containing an oxyimino-group such as oxyimino-cephalosporins as well as oxyimino-monobactam. They are not active against cephamycins and carbapenems. ESBLs have been found in a wide range of Gram-negative rods. However, the vast majority of strains expressing these enzymes belong to the family Enterobacteriaceae. *Klebsiella pneumoniae* seems to remain the major ESBL cause. Another organism that have an important role of ESBL is *Escherichia coli*(Al Jasser, 2006)

Infections due to ESBL-caused by organisms present a major therapeutic dilemma, because the choice of antibiotics becomes extremely limited. Due to the broad-spectrum of the beta lactamases produced by these organisms, ESBL producing Enterobacteriaceae are typically resistant to beta-lactam antibiotics including broad-spectrum cephalosporins, aztreonam, and extended-spectrum penicillins. Furthermore antibiotics such as trimethoprim-sulfamethoxazole and aminoglycosides especially gentamicin are often co-transferred on a resistance plasmid, resulting in multiple drug resistance. However, ß-lactam / ß-lactamase inhibitors are not regarded as suitable first line therapy for serious infections caused by ESBL producer. The carbapenems class of drugs should be regarded as the drugs of choice based on in vitro susceptibility studies and clinical experience. This class are highly stable to beta lactamase hydrolysis. Clinical observational studies have shown that the mortality rates in patients with ESBL-producing bacteremia treated with the carbapenems are lower than if treated with other antibiotic combinations. However, widespread use of carbapenem may lead to emergence of carbapenem-resistant. For non-life threatening infections with ESBL-producers, therapy should be streamlined based on the initial treatment response and the sensitivity results (Sabra, et al. 2009. Parasakthi, et al. 2001).

Feces examination was found E. coli (+) and feces cultures was found E. colli pathogenic serotypes 1-11, that produce ESBL, >10^5,with an antibiotic sensitivity test was sensitive to Amikacin, Piperacillin-Tazobactam, Cefoperazone-sulbactam, and Meropenem. Resistant to Ceftazidim, Cefotaxim, Cotrimoxazole, and Ciprofloxacin. Initially, he got Inj. Ciprofloxacin but there

were no any clinical improvement. The antibiotic was changed to Meropenem based on culture results, literature, and clinical progress.

Infection and colonization by ESBL producing organisms is usually hospital-acquired especially in intensive care units (ICUs). Initially ESBL-producing organisms were only seen to cause nosocomial infections. Later on they were shown to cause a long-term carriage in the community. Recently there have been several reports of true community-acquired infections with ESBL producing E. coli. It was found that diabetes mellitus, prior quinolone use, recurrent urinary tract infections, prior hospital admission and older age were independent risk factors. ESBLs-producing organisms cause a wide spectrum of clinical diseases ranging from colonization to serious infections(Al Jasser, 2006).

He had some risk factors such as diabetes, antibiotics abuse, history of admission in hospital, and older age. Infection of ESBL producing E. coli in this patient come from outside the hospital (community-acquired infections with ESBL producing E. coli).

If ESBL gram-negative bacteria are isolated from any sample, the ward should be informed promptly. Known ESBL cases at the time of readmission are identified via ESBL labels or a 'flag' be put in the facility's computer database that is accessible. Screening of patient in high risk units (ICUs and oncology wards) is optional after discussion with the microbiologist (CDC. Management of Multidrug-Resistant Organism in Healthcare Settings. 2006.

(Kola, et al. 2007).Room's supervisor, all nurses, workers and infection control committee were informed about the ESBL case when the diagnosis was established.

The accurate detection of ESBL production in clinical isolates is crucial. The concern for this is twofold: first is the therapeutic implications and second is the epidemiological and infection control aspects (Al Jasser, 2006. Jitsurong, & Yodsawat, 2006).

Successful control of MDROs (Multi Drug Resistant Organism) has been documented in the United States and abroad using a variety of combined interventions. The various types of interventions used to control or eradicate MDROs may be grouped into seven categories. These include administrative support, judicious use of antimicrobials, surveillance (routine and enhanced), Standard and Contact Precautions, environmental measures, education and decolonization. These interventions provide the basis for the recommendations for control of MDROs in healthcare settings(CDC. Management of Multidrug-Resistant Organism in Healthcare Settings. 2006. Siegel, et al. 2007). In several reports, administrative support and involvement were important for the successful control of the target MDRO and authorities in infection control have strongly recommended such support. Other interventions that require administrative support include: 1) implementing system changes to ensure prompt and effective communications e.g., computer alerts to identify patient previously known to be colonized/infected with MDROs; 2) providing the necessary number and appropriate placement of hand washing sinks and alcohol-containing hand rub dispensers in the facility; 3) maintaining staffing levels appropriate to the intensity of care required, and 4) enforcing adherence to recommended infection control practices (e.g., hand hygiene, Standard and Contact Precautions) for MDRO control (Patel, et al. 2008.CDC. Management of Multidrug-Resistant Organism in Healthcare Settings. 2006. Patient's medical record book was marked / written as ESBL. There were special places to wash hands with liquid chlorhexidine gluconate 4%.

While a comprehensive review of antimicrobial stewardship is beyond the scope of this guideline, recommendations for control of MDROs must include attention to judicious antimicrobial use. The CDC Campaign to Prevent Antimicrobial Resistance was launched in 2002. This effort targets all healthcare settings and focuses on effective antimicrobial treatment of infections, use of narrow spectrum agents, treatment of infections and not contaminants, avoiding excessive duration of therapy, and restricting use of broad-spectrum or more potent antimicrobials to treatment of serious infections when the pathogen is not known or when other effective agents are unavailable. Achieving these objectives would likely diminish the selective pressure that favors proliferation of MDROs. Strategies for influencing antimicrobial prescribing patterns within healthcare facilities include education; formulary restriction; prior-approval programs, including pre-approved indications; automatic stop orders; academic interventions to counteract pharmaceutical influences on prescribing patterns; antimicrobial cycling provides evidence-based principles for judicious use of antimicrobials and tools for implementation computer-assisted management programs and active efforts to remove redundant antimicrobial combinations (Patel, Srinivasan, & Perz, 2008. Patel, et al. 2008).

Initially, he diagnosed as acute diarrhea caused by suspicious Shigella infection. After 5 days of treatment, the feces culture showed ESBL producing E. coli and resistant to Ciprofloxacin and sensitive to Meropenem. So the antibiotics replaced with Meropenem. Six days later, the patient's clinical and laboratory parameters were improved. Feces re-culture results showed no growth of E. coli.

Surveillance is a critically important component of any MDRO control program, allowing detection of newly emerging pathogens, monitoring epidemiologic trends, and measuring the effectiveness of interventions. Multiple MDRO surveillance strategies have been employed, ranging from surveillance of clinical

microbiology laboratory results obtained as part of routine clinical care (Patel, et al. 2008. Tacconelli, 2009).

This case had already cooperated with the Hospital's Infection Control Committee.

CDC has recommended the use of Standard and Contact Precautions for MDROs. Standard Precautions have an essential role in preventing MDRO transmission, even in facilities that use Contact Precautions for patient with an identified MDRO. Therefore, Standard Precautions must be used in order to prevent transmission from potentially colonized patient. Hand hygiene is an important component of Standard Precautions. Contact Precautions are intended to prevent transmission of infectious agents, including epidemiologically important microorganisms, which are transmitted by direct or indirect contact with the patient or the patient's environment. A single-patient room is preferred for patients who require Contact Precautions. When a single-patient room is not available, consultation with infection control is necessary to assess the various risks associated with other patient placement options (e.g., cohorting, keeping the patient with an existing roommate). Health Care Personal (HCP) caring for patients on Contact Precautions should wear a gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment. Gown and gloves upon room entry and discarding before exiting the patient room is done to contain pathogens, especially those that have been implicated in transmission through environmental contamination (Clock, et al. 2010. Stelfox, Bates, & Redelmeier, 2003).

This case had already applied standard and contact precautions, hand hygiene procedure, patient's cohort system, use of gloves and gowns when interacted with the patient, and cooperated with the Hospital Infection Control Committee.

The potential role of environmental reservoirs, such as surfaces and medical equipment, in the transmission of MDROs has been the subject of several reports. While environmental cultures are not routinely recommended, environmental cultures were used in several studies to document contamination, and led to interventions that included the use of dedicated noncritical medical equipment, assignment of dedicated cleaning personnel to the affected patient care unit, and increased cleaning and disinfection of frequently-touched surfaces (e.g., bedrails, charts, bedside commodes, doorknobs). Therefore, monitoring for adherence to recommended environmental cleaning practices is an important determinant for success in controlling transmission of MDROs and other pathogens in the environment(Al Jasser, 2006).

The focus of the interventions was to encourage a behaviorur change through improved understanding of the problem MDRO that the facility was trying to control. Educational campaigns to enhance adherence to hand hygiene practices in conjunction with other control measures have been associated temporally with decreases in MDRO transmission in various healthcare settings.

Patient, his families, and all personnel involved in the patient care were emphasized about the importance of handling the MDRO.

Decolonization entails treatment of person that colonized with a specific MDRO, to eradicate carriage of that organism. Decolonization regimens are not sufficiently effective to warrant routine use. Several factors limit the utility of this control measure on a widespread basis: 1)identification of candidates for decolonization requires surveillance cultures; 2)candidates receiving decolonization treatment must receive follow-up cultures to ensure eradication.

Environmental cultures and decolonization was not performed in handling this case because the procedure has not become a permanent in the ward.

ESBLs have become a widespread serious problem and several aspects of them are worrying. ESBLs occurrence and spread need to be controlled. The continued emergence of ESBLs presents diagnostic challenges to the clinical microbiology laboratories, who need to be more aware of the need for their detection. Appropriate antimicrobial selection, surveillance systems and effective infection control procedures are the key partners in their control(Al Jasser, 2006. Buntaran, 2009).

He was already handled according to standard procedure, including selection of antibiotics. At the 9th day of treatment, his condition was improved. At the 15th day of treatment, he was discharged and advised to control the outpatient department. The prognosis was good.

CONCLUSION

It has been reported a patient who suffered from diabetes mellitus, acute diarrhea infection caused by suspected Shigella and sepsis. Initially, he treated with intravenous Ciprofloxacin injection, but there was no clinical improvements. After 5th of treatment, Feces culture showed *ESBL* producing *E coli* and the antibiotic was changed to meropenem. *ESBL* is one of the *MDRO* that require special handling, such as the choice of antibiotics and infection control measures. This patient had already managed according to standard procedures for ESBL and getting better. The patient had a good prognosis.

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