



## Original Research Article

# Correlation of surgical site infection with empirical antibiotic therapy in children with perforated appendicitis

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## ABSTRACT

**Background:** Surgical site infection (SSI) is one of the possible complications after the surgery of perforated appendicitis (PA) in children. This problem could occur due to the use of inappropriate empirical antibiotics. Evaluating the correlation between empirical antibiotics and surgical site infection could benefit patient care.

**Materials and Methods:** This was an observational analytic study. We included patients aged less than 18 years old who were diagnosed with PA and treated at Dr. Soetomo General Hospital, Surabaya, from March to July 2020. The patients were given cefuroxime and metronidazole as empirical antibiotics. Appendix tissue and pus samples were taken during the surgery and submitted for microbiology tests. Patients were observed for 30 days post-surgery to examine the occurrence of SSI. Data were taken from the medical records and the correlations with the incidence of SSI were analyzed with Pearson or Spearman correlation tests.

**Results:** Thirty patients were included in this study. Four patients developed superficial incisional SSI and two patients developed organ SSI. No significant relationship between empirical antibiotic therapy with the incidence of SSI was found ( $p = 0.129$ ). Further analysis also found no significant relationship between sex ( $p = 0.680$ ), age ( $p = 0.713$ ), nutritional status ( $p = 0.645$ ), culture result ( $p = 0.384$ ), or surgery waiting time ( $p = 0.13$ ) with the incidence of SSI. However, we found a significant relationship between surgery duration and the incidence of SSI ( $p = 0.004$ ). Patients with surgery duration  $> 120$  minutes had a 19-fold risk of developing SSI (OR = 19).

**Conclusion:** There was no correlation between the empirical antibiotic type and the incidence of SSI. On the other hand, surgery duration was significantly related to the incidence of SSI.

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## 1. Introduction

Perforated appendicitis (PA) is a common pediatric surgery case at Dr. Soetomo General Hospital, Surabaya, with 26 new cases in 2018. The therapy consists of laparotomy appendectomy and antibiotics, but surgical site infection (SSI) could still happen.<sup>1</sup> In 2018, the incidence of such complication at Dr. Soetomo Hospital were 2 cases.

Currently, intraoperative tissue sampling is routine management in the Pediatric Surgery Division of

Dr. Soetomo Hospital. The results of the culture will aid in determining the definitive antibiotic therapy. While waiting for the culture results, empirical therapy is given based on local susceptibility patterns. SSI could occur due to the use of empirical antibiotics that no longer suit the local susceptibility pattern or influenced by other factors.<sup>2</sup> Therefore, evaluating the correlation between empirical antibiotic therapy and SSI in children with PA could benefit patient care at Dr. Soetomo Hospital.

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## 2. Materials and Methods

### 2.1. Study design

This study was conducted with an observational analytic design. We included patients aged less than 18 years old who were diagnosed with PA and treated at Dr. Soetomo General Hospital, Surabaya, from March to July 2020. The diagnosis was obtained from clinical examination, laboratory results, and intraoperative findings. The intraoperative findings included a gangrenous or perforated appendix with a mix of pus and peritoneal fluid. As the empirical antibiotics, the subjects were given cefuroxime 100-150 mg/kg/day, twice daily with intravenous drips for 3-5 days, and metronidazole 10 mg/kg (maximum 500 mg) every 8 hours. Appendix tissue sample was taken during the surgery and put into a sterile container. Pus was taken in with a swab. All procedures were conducted in a sterile manner. The specimens were immediately submitted to the Clinical Microbiology Department for aerobic-anaerobic tests and antibiotic sensitivity tests according to standard procedures. After the results were available, the type of antibiotics was adjusted. Patients were observed for 30 days after surgery to examine the occurrence of SSI. The SSI was divided into superficial incisional, deep incisional, and organ SSI according to the CDC criteria.<sup>3</sup>

### 2.2. Data collection and analysis

Samples were collected using total sampling. Data were taken from the medical records in the Pediatric Surgery Department, Microbiology Department, and Emergency Department. The data collected included name, age at surgery, sex, lactate examination results, culture examination results, and antibiotic therapy. Pearson correlation tests were performed on normally distributed data. Spearman correlation tests were performed on non-normally distributed data. All statistical analyses were processed using the SPSS 16.

## 3. Results

### 3.1. Basic characteristics of study subjects

The study subjects consisted of 30 patients with 22 males (73.3%) and 8 females (26.7%). The average age was  $6.4 \pm 2.60$  years. After given cefuroxime and metronidazole as the empirical antibiotics, 6 patients (20%) developed SSI. According to the CDC criteria,<sup>3</sup> 4 patients (66.7%) had superficial incisional SSI while the other 2 patients had organ SSI. Pus culture results showed that *E. coli* grew on 15 samples (50%). *E. coli* also grew on 18 tissue cultures (60%).

### 3.2. Statistical analysis results

Four males and two females developed SSI. Using the contingency coefficient, no significant relationship was found between sex and the incidence of SSI ( $p = 0.680$ ). Three patients under 5 years old and three patients over 5 years old developed SSI. Using the contingency coefficient, no significant relationship was found between the age group and the incidence of SSI ( $p = 0.713$ ).

Patients were divided into nutritional status groups according to the WHO growth chart for children under 5 years old and the CDC growth chart for children over 5 years old. There were 2 SSI incidences among underweight children ( $< 90^{th}$  percentile), 3 incidences among normal-weight children ( $90^{th}$ - $100^{th}$  percentile), and 1 incidence among overweight children ( $100^{th}$ - $110^{th}$  percentile). Using the contingency coefficient, no significant relationship was found between nutritional status and the incidence of SSI ( $p = 0.645$ ).

From 4 patients who later developed superficial incisional SSI, 3 tissue samples grew *E. coli* and the other sample grew ESBL (Extended Spectrum Beta-Lactamase) *E. coli*. From 2 patients who later developed organ SSI, 1 sample grew *E. coli* and the other sample had no growth. Using the linear regression test, no significant relationship was found between the culture results and the incidence of SSI ( $p = 0.384$ ).

Among 22 patients with surgery waiting time  $< 8$  hours, 2 patients developed SSI. On the other hand, 4 developed SSI among those with waiting time  $> 8$  hours. Using the contingency coefficient, no significant relationship was found between surgery waiting time and the incidence of SSI ( $p = 0.13$ ).

One patient with surgery duration  $< 120$  minutes developed SSI, while 5 patients with surgery duration  $> 120$  minutes developed SSI. Using the contingency coefficient, we found a significant relationship between surgery duration and the incidence of SSI ( $p = 0.004$ ). Patients with surgery duration  $> 120$  minutes had a 19-fold risk of developing SSI (OR = 19).

All subjects in this study were given cefuroxime and metronidazole as empirical antibiotics. Six patients developed SSI during the 30-days post-surgery observation. For comparison, we gathered medical records of 30 patients that matched the criteria for this study but were treated with ceftriaxone and metronidazole as the empirical antibiotics. A correlation test using the contingency coefficient showed that there was no significant relationship between empirical antibiotic therapy and the incidence of SSI ( $p = 0.129$ ). A comparison test was performed using the Fisher exact test. No significant difference was found between the administration of Ceftriaxone-Metronidazole and Cefuroxime-Metronidazole ( $p = 0.127$ ).

**Table 1:** Characteristics of study subjects

Characteristics		Frequency (n=30)	Percentage (%)
Sex	Female	8	26.7
	Male	22	73.3
Age	< 5 years	13	43.3
	> 5 years	17	56.7
Nutritional status	Underweight	6	20.0
	Normal	19	63.3
	Overweight	5	16.7
	Obese	0	0.0
Tissue culture results	No growth	4	13.3
	Escherichia coli	18	60.0
	ESBL Escherichia coli	4	13.3
	Klebsiella pneumoniae	1	3.3
	Enterococcus avium	1	3.3
Surgery waiting time	Bacteroides uniformis	1	3.3
	Streptococcus agalactiae	1	3.3
Surgery duration	< 8 hours	22	73.3
	> 8 hours	8	26.7
Surgery duration	< 120 minutes	20	66.7
	> 120 minutes	10	33.3

Note: ESBL; Extended Spectrum Beta-Lactamase.

#### 4. Discussion

Typically, broad-spectrum antibiotics are chosen as empirical therapy. The choice of antibiotics is based on the site of infection, pathogens that are present in the patient, and local susceptibility pattern.<sup>4</sup> In the antibiotics guideline book of Dr. Soetomo Hospital, there was no recommendation on empirical antibiotics for PA in children. Antibiotics were categorized into first-line (unrestricted), second-line (restricted), and third-line (reserved). Cefuroxime was categorized as the first line, while ceftriaxone was the second line. Cefuroxime was used as one of the empirical antibiotics in this study. Cefuroxime is a broad-spectrum antibiotic, recommended by the British Pharmacological Society to prevent SSI. Cefuroxime could prevent the occurrence of second-line antibiotic resistance.

In this study, the relationship between empirical antibiotics and the incidence of SSI was tested using the contingency coefficient, but no significant relationship was found ( $p = 0.129$ ). Similar to this study, Gravilovska (2017) also found no correlation between empirical antibiotic administration and the incidence of SSI and treatment duration in cranial and spinal surgeries. Bo Ohlin et al. compared the use of piperacillin-tazobactam with cefuroxime and metronidazole. Similarly, they found no difference in the incidence of abscesses after surgery.<sup>5</sup>

Gravilovska stated that endogenous and exogenous factors influenced the incidence of infection. Patient characteristics, such as age, sex, weight, nutritional status, immunological status, comorbidities, and etiology were endogenous factors. Medical care such as surgery procedure variation and duration were the exogenous factors. Surgical

wound care was said to be more significant than the antibiotics used. Most of the SSIs were localized and systemic antibiotics weren't effective to reach those tissues.

Moving from those findings, we analyzed the endogenous and exogenous factors of the study subjects. The endogenous factors analyzed were age, sex, nutritional status, and etiology. The patients' immunology status was homogenous and none of them has any comorbidities. The exogenous factors analyzed were surgery waiting time and duration.

There was no correlation between sex and the incidence of SSI. Aghdassi et al. (2019) found that sex generally correlated with SSI, but this statement was not entirely accurate, especially considering the surgery procedure.<sup>6</sup>

We did not find any significant correlation between age and the incidence of SSI. Kayee et.al found a strong correlation between age and the incidence of infection, but the mechanism was complex and influenced by many variables. The correlation was seen after adjusted for the National Nosocomial Infections Surveillance (NNIS) risk index, procedure type, and hospital type.<sup>7</sup>

No correlation between nutritional status and the incidence of SSI was found. This is similar to a study by Porrás-Hernández et al. which was conducted in Mexico. They reported no relationship between nutritional status and SSI, but the accuracy of the procedure and the interaction of surgeons during the surgery were correlated with the incidence of SSI.

Most intra-abdominal infections were caused by multiple pathogens. Escherichia coli is the most common pathogen in PA. More than one pathogen could grow on tissue specimens from patients with PA.<sup>8</sup> In this study, E. coli

is the most common bacteria grew on cultures followed by ESBL *E. coli*, but analysis showed that the species of pathogen did not significantly correlate with the incidence of SSI. Kokoska (1999) found that there were no positive implications from intra-operative culture examination on the outcome of PA patients. This could be because the culture results obtained did not reflect the pathogen that caused PA in the patient. It was recommended to continue giving empiric antibiotics as a therapy for PA.<sup>9</sup>

As one of the exogenous factors analyzed, surgery waiting time was not significantly correlated with the incidence of SSI. Eight hours was chosen as the cut off time based on the half-lives of metronidazole and cefuroxime.<sup>10</sup>

There was a significant correlation between the duration of surgery with the incidence of SSI. This was similar to a study by Cheng et al. (2017) who performed combined analysis for colorectal surgery. In their study, surgery duration was significantly associated with SSI, and increased duration could increase the risk of developing SSI by 30% ( $p < 0.0001$ ). Leong et al. (2006) suggested that the cut-off duration of surgery should be on the 75th percentile. Exceeding this cut-off point was identified as a risk factor for SSI. On the other hand, longer surgery duration could reflect the complexity of the case, surgical technique, longer exposure to pathogens in the surgery environment, and decreased antibiotic efficacy<sup>11</sup>. Casanova et al. in a large 4-years cohort study found that surgery that was performed  $\geq 2$  hours decreased the time to develop SSI by 1.6 times ( $p = 0.003$ ).

## 5. Conclusion

There was no correlation between the empirical antibiotic type and the incidence of SSI. Among other factors that might influence the incidence of infection, we found a significant correlation between surgery duration and the incidence of SSI. For further similar research, more homogeneous data are needed.

## 6. List of Abbreviations

SSI: Surgical Site Infection

PA: Perforated Appendicitis

ESBL: Extended Spectrum Beta-Lactamase

## 7. Conflicts of Interest

All contributing authors declare no conflicts of interest.

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None.

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