

# The Association between Medical History-based Risks and Sepsis Events in Immunocompromised Patients according to Type III Stratification of the Indonesian Regulation on the Prospective Antimicrobial System (*Regulasi Antimikroba Sistem Prospektif / RASPRO*)

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## ABSTRACT

**Background:** The Indonesian Regulation on the Prospective Antimicrobial System (*Regulasi Antimikroba Sistem Prospektif/ RASPRO*) is a novel program. Its role has been reinforced by the Indonesian Ministry of Law and Human Rights Stipulation, which may predict the risk of sepsis events. Our study aimed to evaluate whether the risk factors listed in the *RASPRO* consensus have actual effects on sepsis events.

**Method:** The study was a retrospective cohort using secondary data with 98 subjects. The subjects were categorized into two groups, i.e., the *RASPRO* group with type III stratification (*RASPRO* Group) and Non-type III stratification *RASPRO* group (Non-*RASPRO* Group). Subjects with infection but with conditions other than the abovementioned criteria were categorized into the Non-*RASPRO* group.

**Results:** We found that among subjects in the *RASPRO* group, a history of antibiotic use over the past <30 days (OR 3.42; 95%CI 1.32–8.85; p=0.011) and a history of having procedure using medical instruments within the last <30 days (OR 2.62; 95%CI 1.06–6.45; p=0.037) seemed to be greatest risk factors for sepsis events.

**Conclusion:** The *RASPRO* group has a higher risk for sepsis events than the non-*RASPRO* with a history of antibiotic undergoing a procedure using a medical instrument within the last <30 days possessed the greatest risk factors for sepsis events.

**Keywords:** *RASPRO*, stratification, risks, sepsis.

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## INTRODUCTION

Sepsis is a condition in response to infection accompanied by multiorgan dysfunction.<sup>1,2</sup> Sepsis has severe consequences both for patients and the health system worldwide.<sup>1</sup> Since 2016, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) have introduced a new definition of sepsis, a condition of life-threatening organ dysfunction caused by a dysregulated host response to infection.

The definition used nowadays has shifted the old paradigm of sepsis, which was based on the SIRS (Systemic

Inflammatory Response Syndrome) criteria. In contrast, the new one is based on the Sequential Organ Failure Assessment (SOFA) criteria.<sup>2</sup> Mortality rate of sepsis patients with Sequential Organ Failure Assessment (SOFA) score of > 2 is greater than 10%.<sup>3</sup> Furthermore, the in-hospital mortality rate caused by septic shock may reach >40%.<sup>3</sup> Moreover, the Surviving Sepsis Campaign 2012 stated that the mortality rate due to sepsis in Europe reached 41%, while in the United States of America, it was about 28.3%.<sup>4</sup> The annual mortality rate may reach 6 million deaths out of 31 million cases worldwide.<sup>4</sup>

Numerous studies have demonstrated

that various immunocompromised conditions are possible factors for sepsis events.<sup>5,6</sup> A study in South Korea which involved 2286 subjects in 2011 suggested that subjects who had procedures using medical instruments such as urinary catheters and with various other immunocompromised conditions such as renal failure, neutropenia, liver disease, use of corticosteroids, etc were at risk for sepsis events with septic shock as a significant condition of their cause of deaths. (OR 3.34; 95%CI 2.35-4.74).<sup>6</sup> Moreover, a history of antibiotic use and hospitalization can be risk factors of developing an infection by resistant

microorganisms.<sup>7,8</sup> A study conveyed by Aliberti et al. in 2012 reported that a history of hospitalization within the last 90 days might serve as an independent factor for infection by resistant microorganisms (OR = 4.87; 95%CI 1.90–12.4; p = 001).<sup>7</sup> Gomila et al. in 2018 suggested that history of using a urinary catheter (OR, 1.44; 95%CI, 0.99–2.10) and antibiotic use (OR, 1.68; 95%CI, 1.13–2.50) may become risk factors for developing urinary tract infection by resistant microorganism.<sup>8</sup> Infection by resistant microorganisms, which is unpredicted in immunocompromised patients, certainly can be a risk factor for developing a severe infection or even sepsis.

Hence, various risk factors contributing to the development of sepsis must be recognized by clinicians in their daily practice. Patients who have risks for developing sepsis must be managed accordingly. The Indonesian Regulation on the Prospective Antimicrobial System (*Regulasi Antimikroba Sistem Prospektif/RASPRO*) Study Group has issued a consensus derived from various literature reviews to predict the severity of infection, including the risk of sepsis.<sup>9</sup> The consensus has been approved for copyright by the Stipulation of the Indonesian Ministry of Law and Human Rights Number 000121541. The system used in the RASPRO consensus has utilized risk stratification, and it evaluates the risk factors of the hosts and their medical history associated with sepsis events.

Regarding the risk of developing sepsis, the RASPRO consensus has categorized patients into three types of stratifications: type I, II, and III.<sup>9</sup> Subjects with type III RASPRO stratification may tend to have a greater risk for sepsis compared to subjects without type III stratification (non-RASPRO group). Our study evaluated the effects of risk factors for sepsis events in subjects with type III RASPRO stratification (RASPRO group) and compared them with the non-RASPRO subjects. Moreover, our study also evaluated risk factors that have the greatest effects on sepsis events in subjects of the RASPRO group.

## METHOD

The design used in our study was a retrospective cohort. The study was conducted at a type B private hospital in the Depok area. Samples were collected between June and July 2020 in the form of secondary data retrieved from the patients' medical records documented between 2017 and 2020. Subjects were all adult patients aged > 18 years with infectious diseases with sepsis and non-sepsis conditions, including immunocompetent subjects and subjects with various immunocompromised conditions such as geriatric patients, patients with uncontrolled diabetes mellitus or with comorbidity of chronic illness. Moreover, the exclusion criteria were adult patients without diagnosis of infection and/or incomplete data in their medical records.

There were three types of stratifications in RASPRO, i.e., the type I, II and III stratification.<sup>9</sup> Based on a literature review performed by the Indonesian RASPRO Study Group, a consensus has been developed for subjects with type III RASPRO stratification. They were subjects considered to have a high risk for sepsis events. Subjects who were included in the type III RASPRO stratification (RASPRO Group) were those with infectious disease and immunocompromised conditions (elderly patients AND/OR uncontrolled DM AND/OR chronic illness) plus (medical history of antibiotic use AND/OR medical history of hospitalization AND/OR history of having procedure using the medical instrument, all of them were within the past <30 days).<sup>9</sup>

Subjects who were included in the type II RASPRO stratification were those with infectious disease and immunocompromised conditions (elderly patients AND/OR uncontrolled DM AND/OR chronic illness) plus (medical history of antibiotic use AND/OR medical history of hospitalization AND/OR history of having procedure using the medical instrument, all of them were within the past <90 days).<sup>9</sup> Meanwhile, subjects in the type I RASPRO stratification did not fulfill the type II and type III stratification categories.

Our study analyzed risk factors between subjects in the RASPRO group and the non-RASPRO group (type I and type II stratification) against sepsis events using bivariate analysis. Afterward, it was continued with multivariate analysis to determine which medical history factors in the RASPRO group have the most effect on sepsis events.

Secondary data were retrieved from patients' medical records documented between 2017 and 2020. The sample size was determined using a sampling formula of two proportion differences between subjects in the RASPRO group and non-RASPRO group on risk factors. Subjects were categorized into two groups, i.e., the type III RASPRO stratification group and the non-type III RASPRO group (RASPRO and non-RASPRO groups). Afterward, a bivariate analysis was performed using Chi-square analysis to provide a general evaluation of both groups and determine which group had a greater tendency for experiencing sepsis. A multivariate analysis was then carried out to evaluate which medical history factor in the type III stratification RASPRO group has the greatest risk of developing sepsis. Data processing of our study was done using a computer software program of SPSS version 20.0.

## RESULTS

### Subject Characteristics

Table 1 showed a total sample size of 98 subjects, with 48 subjects in the non-RASPRO group and 50 subjects in the RASPRO group. Demographic characteristics of subjects in the non-RASPRO group were dominated by subjects aged <65 years (68.7%) with predominant female subjects. Among subjects in the RASPRO group, we found that the number of subjects aged ≥65 years and <65 years was comparable. In this group, we found 58% of subjects were male. Moreover, 52% of subjects in the RASPRO group had uncontrolled diabetes mellitus as their comorbidity, while only 20.8% of subjects with uncontrolled DM were found in the non-RASPRO group. About 40% of subjects in the RASPRO

group had chronic illness; while it was only found in 14.2% of the non-RASPRO group. Regarding medical history, among the subjects of the RASPRO group, 56% of subjects had a history of antibiotic use, 34% of subjects had a history of hospitalization, and 64% of subjects had a history of having procedures using medical instruments within the past < 30 days.

### Comparing Sepsis Events

According to Table 2, subjects in the RASPRO group were more likely to experience sepsis than subjects in the non-RASPRO group. (OR = 3.59; 95%CI 1.56-8.28; p=0.004).

### Risk Factors with the Greatest Effect on Sepsis Events in the RASPRO group

On further analysis, we found that the variable of chronic illness had been independently become a risk factor for sepsis events; however, the findings were not significant with p value of > 0.20. Therefore, it was not included in the subsequent multivariate regression analysis (Table 3).

On multivariate analysis of subjects in the RASPRO group, we found that the history of antibiotic use within the past < 30 days (OR 3.42; 95%CI 1.32 – 8.85; p = 0.011) and history of having procedures using medical instruments (OR 2.62; 95%CI 1.06 – 6.45; p = 0.037) were significant risk factors for sepsis events. At the same time, medical history

of hospitalization does not correlate with sepsis events (Table 4).

### DISCUSSION

Our study found that subjects in the RASPRO group were more likely to experience sepsis than the subjects in the non-RASPRO group. Subjects in the RASPRO group were immunocompromised conditions, which were later considered, i.e., elderly age, uncontrolled DM that serve as risk factors of the hosts for sepsis events before we consider another factor, i.e., medical history. Moreover, subjects with chronic illness were not considered a factor for sepsis events.

Wang et al. has demonstrated that

**Table 1. Demographic Characteristics of Subjects in Non-RASPRO and RASPRO group.**

		Non-RASPRO group	RASPRO group
		Description (n = 48)	Description (n = 50)
Age	≥65 years	15 (31.3)	25 (50.0)
	<65 years	33 (68.7)	25 (50.0)
Sex	Male	23 (47.9)	29 (58.0)
	Female	25 (52.1)	21 (42.0)
Comorbidity			
Uncontrolled DM	Yes	10 (20.8)	26 (52.0)
	No	38 (79.2)	24 (48.0)
Chronic illness	Yes	7 (14.6)	20 (40.0)
	No	41 (85.4)	30 (60.0)
Medical History			
Antibiotic use within the past < 30 days	Yes		28 (56.0)
	No		22 (44.0)
Hospitalization within the past <30 days	Yes		17 (34.0)
	No		33 (66.0)
History of having procedure using medical instruments within the past < 30 days	Yes		32 (64.0)
	No		18 (36.0)

**Table 2. Effects of Risk Factors on Sepsis Events among subjects in RASPRO and Non-RASPRO group.**

		Sepsis		P value	OR	95%CI
		Positive	Negative			
RASPRO	Type III	31 (62.0)	19 (38.0)	0.004	3.59	1.56 - 8.28
	Non Type III	15 (31.3)	33 (68.8)			

elderly age can indeed become one of the risk factors for sepsis ( $p < 0.001$ ).<sup>10</sup> Furthermore, DM is a phenomenon that may become a risk factor for sepsis development.<sup>11,12</sup> A meta-analysis conducted by Wang et al. from 2000 to 2016 showed that DM could be an independent risk factor for sepsis events (RR = 0.97; 95%CI: 0.96-0.98 ;  $p < 0.00001$ ).<sup>11</sup> Furthermore, Frydrych et al. have suggested that from the pathogenesis point of view, patients with DM have a poor prognosis for infection and sepsis. However, they have received optimal care, including the use of wide-spectrum antibiotics.<sup>12</sup>

Our study has demonstrated that in the RASPRO group, medical history of antibiotic use within the last <30 days and a history of having procedures using medical instruments are significant risk factors for sepsis events among subjects. A study by Cilloniz et al., carried out among elderly subjects with community-acquired pneumonia (CAP), has demonstrated that male sex and chronic illness such as chronic kidney disease and DM are independent risk factors for developing sepsis. However, a history of prior antibiotic use has unexpectedly become a

protective factor for sepsis events.<sup>13</sup> On the other hand, Patola et al. have demonstrated that a history of antibiotic use within the past four weeks may become a risk factor for developing sepsis events caused by resistant microorganisms (OR = 3.3; 95%CI = 1.6–6.8;  $p = 0.001$ ).<sup>14</sup> Baggs et al. in their report have also demonstrated that history of antibiotic use within the past 90 days can be a risk factor for developing sepsis (OR=1.65; 95%CI = 1.59–1.70).<sup>15</sup> Meanwhile, the use of the medical instrument has been long identified as a risk factor for developing an infection. In individuals with immunocompromised conditions such as elderly age, diabetes mellitus or chronic illness, medical instruments will increase the risk of infection. Bennett et al. suggest that using the medical instrument is associated with the risk of developing sepsis (OR = 2.3; 95%CI = 1.12, 4.75;  $p = 0.024$ ).<sup>16</sup>

On the other hand, as have been explained, the sepsis events found in subjects with a history of prior antibiotic use and probably also the use of medical instruments are often associated with infections caused by a resistant microorganism, which are hard to treat. Various studies have shown that antibiotic

treatment is associated with the risk of developing resistant microorganisms.<sup>15,17</sup> Falcone et al. have indicated that the presence of one of the diagnostic criteria for hospital-acquired pneumonia (history of hospitalization within the past 90 days, history of antibiotic use within the last 30 days or history of living in a healthcare facility for a long time) is a risk factor for developing a respiratory infection caused by multi-resistant microorganisms (OR = 2.52 ; 95%CI = 1.57-4.09 ;  $p < 0.001$ ).<sup>17</sup>

While in the RASPRO group, as shown in our study, we found that history of hospitalization within the last < 30 days did not significantly serve as a risk factor for sepsis events. However, Marchaim et al. in a multicenter study, have demonstrated that actually history of hospitalization within the past three months is a risk factor for bacteremia (sepsis) caused by Extended Spectrum Beta Lactamases (ESBLs) microorganisms (OR = 1.5; 95%CI = 1.3–1.8;  $p = 0.001$ ).<sup>18</sup> The fact is then supported by Capsoni et al., who suggest that hospitalization within the past 90 days has indeed significantly affected sepsis events with ESBLs as the causative microorganism ( $p = 0.02$ ).<sup>19</sup>

**Table 3. Bivariate Analysis of Predictive Factors on Sepsis Events in the RASPRO group .**

		Sepsis		p-value	OR	95%CI
		Positive	Negative			
Age	≥65 yr	23 (57.5)	17 (42.5)	0.125	2.06	0.91 – 4.67
	<65 yr	23 (39.7)	35 (60.3)			
Uncontrolled DM	Yes	21 (58.3)	15 (41.7)	0.130	2.07	0.90 - 4.77
	No	25 (40.3)	37 (59.7)			
Chronic illness	Yes	13 (48.1)	14 (51.9)	1.000	1.07	0.44 - 2.60
	No	33 (46.5)	38 (53.5)			
Medical history of antibiotic use within the past <30 days	Yes	19 (67.9)	9 (32.1)	0.016	3.36	1.33 - 8.50
	No	27 (38.6)	43 (61.4)			
Medical history of hospitalization within the past <30 days	Yes	13 (76.5)	4 (23.5)	0.016	4.73	1.42 - 15.78
	No	33 (40.7)	48 (59.3)			
History of having procedures using medical instruments within the past <30 days	Yes	20 (62.5)	12 (37.5)	0.053	2.56	1.07 - 6.12
	No	26 (39.4)	40 (60.6)			



**Table 4. Multivariate Analysis on Medical History as Risk Factors for Sepsis Events of Subjects in the RASPRO group.**

	B	SE.	P-value	OR	95%CI
Age $\geq 65$ years	0.60	0.45	0.181	1.83	0.75 - 4.44
Uncontrolled DM	0.31	0.48	0.523	1.36	0.53 - 3.51
Medical history of antibiotic use within the past < 30 days	0.80	0.57	0.156	2.23	0.74 - 6.77
Medical history of hospitalization within the past < 30 days	0.78	0.81	0.336	2.18	0.45 - 10.66
History of having procedure using medical instrument within the past < 30 days	0.59	0.58	0.312	1.80	0.58 - 6.61
Age ( $\geq 65$ years)	0.60	0.45	0.184	1.82	0.75 - 4.42
History of hospitalization within the past < 30 days	0.82	0.81	0.315	2.26	0.46 - 11.07
History of having procedure using medical instrument within the past < 30 days	0.60	0.58	0.301	1.82	0.58 - 5.69
Age ( $\geq 65$ years)	0.53	0.45	0.231	1.71	0.71 - 4.08
History of antibiotic use within the past < 30 days	1.12	0.49	0.023	3.07	1.17 - 8.07
History of having procedure using medical instrument within the past < 30 days	0.95	0.46	0.040	2.59	1.05 - 6.42
History of antibiotic use within the past < 30 days	1.23	0.48	0.011	3.42	1.32 - 8.85
History of having procedure using medical instrument within the past < 30 days	0.96	0.46	0.037	2.62	1.06 - 6.45

Logistic regression, Hosmer and Lemeshow test = 0.999; AUC = 0.679 (95%CI: 0.57 – 0.79)

Probability was calculated using the formula of:  $1/(1+\exp[-y])$ .

$y = -0.79 + 1.23 \times \text{history of antibiotic use} + 0.96 \times \text{history of having procedure using medical instrument}$

Meanwhile, Johnson SW suggests that history of antibiotic use within the past 90 days ( $p < 0.001$ ), history of the urinary catheter within the last 30 days ( $p < 0.001$ ) and history of hospitalization within the past one year can be considered as risk factors for developing ESBL infection.<sup>20</sup> It has been generally known that the development of resistant microorganisms as the causative agent of infection in immunocompromised subjects has become a distinctive complication and it may bring greater risk for sepsis to patients.

## CONCLUSION

The RASPRO group has a higher risk for sepsis events than the non RASPRO group. Medical history of antibiotic use within

the last <30 days and a history of having procedures using medical instruments are the biggest risk factors for sepsis events in the RASPRO group. Our study was conducted at a hospital, implying a very limited scope. More extensive studies are necessary to provide greater inputs on risk factors listed in type III stratification of the RASPRO program for sepsis events.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of our manuscript.

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We did not receive any specific grant from the government or any private sectors.

## ETHICAL CONSIDERATION

Our study has been approved by the Ethical Committee Trisakti School of Medicine, Jakarta Indonesia. All study procedures were carried out in accordance to the Helsinki Declaration of human rights.

## AUTHOR CONTRIBUTION

Ronald Irwanto Natadidjaja is a pioneer of RASPRO Indonesia Study Group and responsible for finding literatures, writing the original draft, and data interpretation. Armi Setia Kusuma and Gede Bangun Sudradjad are responsible for data collection and interpretation. Lies Nugrohawati is responsible for writing the original draft, project administration, and supervision. All authors have reviewed the final version of the manuscript.

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