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ORIGINAL ARTICLE

A Quantitative Survey on Antibiotic Prescribing Pattern in Three Indonesian Hospitals Using Digital Antimicrobial Stewardship

Survei Pola Kuantitas Peresepan Antibiotik di Tiga Rumah Sakit di Indonesia dengan Penatagunaan Antimikroba Digital

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ABSTRACT

Background

Antimicrobial Stewardship Program (ASP) is very essential. There are three categories of antimicrobial agents as recommended by WHO: Access, Watch and Reserve. e-RASPRO, a digital ASP model, may alter antibiotic prescribing patterns by prioritizing Access category antibiotic prescribing.

Methods

Our manuscript presented a quantitative survey on antibiotic prescribing patterns within 3 months and 9 months before and after implementing digital electronic-RASPRO (e-RASPRO) in three Indonesian hospitals, utilizing retrospective inpatient data. This analysis included the appropriateness of empirical antibiotic prescribing and the quantity of antibiotic prescribing based on each category.

Results

In the first 3 months, we found that 90.16%, 83.98%, and 81.15% of patients were included in Type 1 Risk Stratification. The appropriateness of initial empirical antibiotic prescribing with the digital guideline on antimicrobial use of e-RASPRO in three hospitals was 81.59%, 76.09% and 24.48%, respectively. Within 9 months after implementing e-RASPRO in Hospital A and B and within 3 months in Hospital C, there was a trend of reduced quantity of Watch category antibiotic prescribing of 54.93% (-58.86% per inpatient), 21.11% (-9.97% per inpatient), and 8.59% (-4.15% per inpatient), respectively. There was a 12.42% (+2.61 % per inpatient) and 223.17% (+268.83% per inpatient) increase in the quantity of Access category antibiotic prescribing in Hospitals A and B,

while in Hospital C, the quantity decreased by 6.81% (-2.29% per inpatient).

Conclusions
There are changes in antibiotic prescribing patterns, particularly in the antibiotics included in the Watch and Access categories following the implementation of e-RASPRO. The relationship between digital antimicrobial stewardship use and the results still needs further research.

Keywords: Access; Digital Antimicrobial Stewardship; Quantity; Survey; Watch.

ABSTRAK

Latar Belakang
Penatagunaan antimikroba (PGA) merupakan hal yang urgen dilakukan. World Health Organization (WHO) telah mengkategori antimikroba ke dalam 3 golongan yaitu: Access, Watch, dan Reserve. Perangkat PGA digital e-RASPRO diharapkan dapat merubah pola peresepan antibiotik dengan mengedepankan peresepan antibiotik kategori Access.

Metode
Artikel ini merupakan survei pola kuantitas peresepan antibiotik 3 bulan dan 9 bulan sebelum dan sesudah terapan perangkat digital elektronik-RASPRO (e-RASPRO) dengan data retrospektif pada rawat inap di 3 rumah sakit di Indonesia, mencakup kesesuaian peresepan antibiotik empirik, dan kuantitas peresepan antibiotik berdasarkan masing-masing kategori.

Hasil
Dalam 3 bulan pertama, didapatkan 90.16%, 83.98% dan 81.15% dari pasien yang diberikan antibiotik termasuk dalam Stratifikasi Risiko Tipe 1. Kesesuaian peresepan antibiotik empirik inisiasi dengan panduan penggunaan antimikroba digital perangkat e-RASPRO pada ketiga rumah sakit masing-masing mencapai 81.59%, 76.09%, dan 24.48%. 9 bulan sesudah terapan perangkat e-RASPRO di Rumah Sakit A dan B dan 3 bulan sesudah terapan perangkat e-RASPRO di Rumah Sakit C terdapat tren penurunan kuantitas peresepan antibiotik kategori Watch masing-masing sebesar 54.93% (-58.86% per pasien rawat inap), 21.11% (-9.97% per pasien rawat inap) dan 8.59% (-4.15% per pasien rawat inap). Kuantitas peresepan antibiotik kategori Access di Rumah Sakit A dan B meningkat 12.42% (+ 2.61% per pasien rawat inap) and 223.17% (+268.83% per pasien rawat inap), sementara itu di Rumah Sakit C menurun 6.81% (-2.29% per pasien rawat inap).

Kesimpulan
Terdapat perubahan pola peresepan antibiotik kategori Watch dan Access paska terapan perangkat e-RASPRO. Analisis hubungan antara penggunaan perangkat PGA digital dengan hasil yang ada masih membutuhkan penelitian lebih lanjut.

Kata Kunci: Access; Penatagunaan Antimikroba Digital; Kuantitas; Survei; Watch.

INTRODUCTION

The implementation of the Antimicrobial Stewardship Program (ASP) has been planned globally with the aim of promoting the prudent use of antimicrobial agents and reducing the risk of antimicrobial resistance development.[1] The World Health Organization (WHO) has categorized antibiotics into three categories: Access, Watch, and Reserve (AWARE).[2] Antibiotics included in Access category are antibiotics that have potency of lower incidence on resistance; while those in Watch category are types of antibiotics that have greater potency on resistance and antibiotics in Reserve category are types of antibiotics that are used only when there is an infection caused by suspected Multi-Drug Resistant (MDR) bacteria; these antibiotics should not be used carelessly, particularly in large quantity.

In this case, the RASPRO Indonesia Study Group has attempted to develop a system, known as the RASPRO system, that can guide clinicians in antibiotic prescribing based on local guidelines.[1] The RASPRO system was made by using risk stratification of patients, and it directs clinicians in initial prescribing of empirical antibiotics, as well as a guideline in changing antibiotics and providing definitive antibiotic treatment, including filling out compulsory specialized forms when there is any prolonged use of antibiotics.[1]

Our survey is a continuation of a previous survey conducted in a hospital in Central Java, Indonesia. The hospital has implemented a manual RASPRO system to carry out the ASP. The survey, conducted before and after the manual system had been implemented for three months, revealed a decrease in antibiotic prescribing from 64,799 ampules/vials to 51,661 ampules/vials, with a reduced mean percentage of antibiotic use within three months of implementation reaching 14.44%.[1] The previous RASPRO system, which used manual guideline forms, was then converted into an electronic form of RASPRO (e-RASPRO); therefore, e-RASPRO has become a digital tool in Indonesia designed to facilitate ASP in hospitals. Through e-RASPRO, a local antimicrobial guideline is developed digitally by completing RASPRO forms, which are also created digitally and comprise electronic forms for empirical antibiotics and definitive antibiotics. A previous survey of e-RASPRO implementation showed a 49.01% decrease in Watch category antibiotics Define Daily Dose (DDD) within 9 months of implementation, but still showed an increase in Watch category antibiotics DDD by 20.18% within 3 months of implementation.[3]

Clinical pharmacies can also perform direct verification on the appropriateness of indications, time limitations of antibiotic use, and the appropriateness of using empirical antibiotics by utilizing the digital guidelines on antimicrobial use that are applicable in hospitals where e-RASPRO has been implemented. By utilizing e-RASPRO, it is expected that there will be an altered pattern of antibiotic prescribing, i.e., prioritizing the use of Access category antibiotics to suppress the risk of widespread antibiotic resistance, particularly against wide-spectrum antibiotics. The aim of this study is to show the comparison of antibiotic prescription patterns among 9 months and 3 months of implementation of e-RASPRO in 3 hospitals.

METHODS

A survey was conducted at three hospitals in Indonesia: Hospital A, Hospital B, and Hospital C. All hospitals are located in West Java and were selected based on their service level category. One of them is a primary hospital (Hospital A), and the other two hospitals are secondary hospitals (Hospital B and C). Previously, various socialization on implementing digital antimicrobial stewardship program using e-RASPRO has been performed that includes socialization on digital prescribing of empirical antibiotics as well as definitive antibiotics, socialization on patient grouping based on the Risk Stratification in order to perform empirical antibiotics prescribing using digital tool and socialization on the digital guideline on using empirical antimicrobial agents, and socialization on prolonged antibiotic use in digital tools.

Socialization on Digital Prescribing of Empirical Antibiotics in e-RASPRO

Socialization was conducted on the implementation of e-RASPRO in three hospitals to guide the prescription of empirical antibiotics. When prescribing empirical antibiotics, clinicians were advised to determine the risk stratification of hospitalized patients based on their immune status, severity of infection, and medical history, such as previous antibiotic use, prior hospitalizations, and history of medical instrument usage.

Socialization also covered the guidelines and procedures for filling out forms for escalating and stepping down empirical antibiotics, aligning with the digital guideline on antimicrobial agent use in e-RASPRO. When empirical antibiotic prescribing did not follow the digital guideline, clinical

pharmacy would confirm with clinicians and the ASP team in the hospital to decide if the antibiotic could be used. The socialization was conducted by the investigators for the Antimicrobial Resistance Control Program Committee of the three hospitals and continued for clinicians at each hospital. It was held both online and offline.

Socialization on Patient Grouping based on Risk Stratification for Empirical Antibiotics Prescribing in e-RASPRO

Socialization was conducted on patient grouping based on their risk stratification in e-RASPRO. The socialization was carried out by the investigators for the Antimicrobial Resistance Control Program Committee of the three hospitals and was continued with the clinicians at each hospital. The socialization was performed both online and offline.

The administration of initial empirical antibiotics in hospitalized patients should be based on patients' risk stratification, as recommended by the digital guideline on the use of antimicrobial agents, which has been incorporated into e-RASPRO. The e-RASPRO categorized patients into three groups for risk stratification in initial empirical antibiotic treatment.[1,3]

The Group of Patients with Type 1 Risk Stratification was a group of patients who could receive empirical antibiotics covering multidrug-resistant microorganisms. This group included immunocompetent patients and immunocompromised patients with a non-threatening severity of bacterial infection or without a risk of MDR, as classified by Non-Type 2 and/or Type 3 Risk Stratification.

The Group of Patients with Type 2 Risk Stratification was a group of (immunocompromised patients and/or uncontrolled diabetes mellitus with unthreatening severity of bacterial infection) PLUS (a history of receiving antibiotic treatment within 90 days ago (31-90 days in the system) and/or a history of having treatment at a healthcare facility of ≥48 days within 90 days ago (31-90 days in the system), and/or a history of using medical instrumentation within 90 days ago (31-90 days in the system)). This group was at risk of having a multidrug-resistant (MDR) Extended-Spectrum Beta-Lactamase (ESBL) infection.[1,3–8]

The Group of Patients with Type 3 Risk Stratification was a group of (patients with threatening infection, and/or immunocompromised individuals and/or individuals with uncontrolled diabetes mellitus) PLUS (a history of receiving antibiotic treatment within 30 days ago and/or having treatment at a healthcare facility ≥48 hours within 30 days ago, and/or a history of using medical instrument within 30 days ago). This group was a group with high severity of infection or a group that was at risk of having ESBL infection and infection caused by other Multi-Drug Resistant (MDR) microorganisms, including MDR *Pseudomonas sp.*[1,6,9–14] A group of patients with Healthcare-Associated Infections (HAIs) was also included in the group with Type 3 Risk Stratification. The group with the HAI category was a group with a period of infection of ≥48 hours of treatment at a healthcare facility, even within 90 days following a surgery.[15–18]

Socialization on the Digital Guideline of Using Empirical Antimicrobial Agents in e-RASPRO

Socialization was conducted on the implementation of e-RASPRO, which included the digital guideline on the use of antimicrobial agents in three Indonesian hospitals. The socialization was carried out by the investigators for the Antimicrobial Resistance Control Program Committee of each hospital and was continued for clinicians at each facility.

A digital guideline on the use of antimicrobial agents was developed, incorporating antibiotic categories based on the AWARE category proposed by the World Health Organization (WHO) in 2021. The guideline was then mutually agreed upon by the hospital management and the Antimicrobial Resistance Control Program Committee, which was subsequently incorporated into

e-RASPRO. The three hospitals used similar digital guidelines on using antimicrobial agents, which were developed by the RASPRO Indonesia Study Group by considering the WHO AWARE category as follows:

Empirical Antibiotic Choice for Patients with Type 1 Risk Stratification in e-RASPRO Digital Guidelines on the Use of Antimicrobial Agents

Most of empirical antibiotic choice included in the digital guideline on antimicrobial use for patients with type-1 risk stratification were the Access category antibiotics such as: Ampicillin, Ampicillin Sulbactam, Amoxycillin Clavulanate, Amikacin and Gentamicin; with the exception of Hospital B, in accordance with and on consideration of the continuity of drug availability as well as based on the agreement made by the Antimicrobial Resistance Control Program Committee, Cefuroxime (second generation of Cephalosporin) was included as the Access category antibiotic. Whenever necessary, most empirical antibiotic choices for the Type 1 Risk Stratification patient group could include antibiotics in the Watch category, i.e., third-generation cephalosporins such as Cefotaxime and Ceftizoxime.

Empirical Antibiotic Choice for Patients with Type 2 Risk Stratification in e-RASPRO Digital Guidelines on the Use of Antimicrobial Agents

For the group of patients with Type 2 Risk Stratification in e-RASPRO, the empirical antibiotic options included anti-ESBL antibiotics. Most of the antibiotic choices fell into either the Access category, such as Ampicillin-Sulbactam / Amoxicillin-Clavulanate combined with Amikacin / Gentamicin, or the Watch category, as outlined in the digital guidelines for antimicrobial use, which include Piperacillin-Tazobactam or the single use of Ertapenem.

Empirical Antibiotic Choice for Patients with Type 3 Risk Stratification in e-RASPRO Digital Guidelines on the Use of Antimicrobial Agents

Patients included in the Type 3 Risk Stratification group of the e-RASPRO system were a group of patients at risk of having sepsis. Therefore, for this group, the empirical antibiotic choice was an antibiotic capable of eradicating ESBL-producing bacteria and other MDR bacteria, with the majority of antibiotic selection following the digital guidelines on antimicrobial agents. These guidelines include categories such as Watch to Reserve, which encompasses antibiotics like Meropenem and Imipenem, with or without combination with Access category antibiotics, including Amikacin or Gentamicin, or with the use of Polymyxin or Tigecycline.

The e-RASPRO system with digital guidelines also guide clinicians if they need to step down or escalate the antibiotic empirically while the culture result still in progress.[1,3]

Socialization on Prescribing Definitive Antibiotics in e-RASPRO

Socialization was performed by implementing e-RASPRO in three hospitals to prescribe definitive antibiotics. In e-RASPRO, a digital form was used to administer definitive antibiotics, which clinicians were required to fill out when prescribing antibiotics in accordance with culture findings.[1,3] The socialization was conducted by the investigators for the Antimicrobial Resistance Control Program Committee of the three hospitals, and it was subsequently continued for clinicians at each hospital. The socialization was performed online and offline.

Socialization on Prolonged Antibiotic Use in e-RASPRO

Socialization was performed by implementing e-RASPRO in three hospitals. When there is a prolonged antibiotic prescribing, a clinician must describe the indication for prolonged antibiotic use through a digital form in e-RASPRO.[1,3] It would then be verified by the clinical pharmacy, and the results would be reported to the ASP team in the hospital.

When prolonged antibiotic use occurred without a completed electronic form in e-RASPRO regarding the concerned issue or without clear indication, the clinical pharmacy, in accordance with the consent issued by the Hospital ASP team, could perform an Automatic Stop Order (ASO). Socialization was conducted by the investigators for the Antimicrobial Resistance Control Program Committee of the three hospitals, and it was also continued for clinicians at each hospital. The socialization was performed online and offline.

Survey Setting and Time Period of Data Collection

The retrieved data were secondary, univariate analyses obtained from reports on the use of injected antibiotics in the hospital wards of the three hospitals. Data was taken from January 2021 – June 2022 in Hospital A, March 2021 – August 2022 in Hospital B and August 2021 – January 2022 in Hospital C. Through implementation of e-RASPRO, initial data collection was performed within the first three-month, which included percentage of patients in each risk stratification group based on the digital e-RASPRO forms as well as appropriateness of initial empirical antibiotic prescribing with the digital guidelines on the use of antimicrobial agents.

The survey was followed by collecting all quantitative data on empirical antibiotic prescribing, as well as definitive antibiotic prescribing, for hospitalized patients within 9 months before and after the implementation of e-RASPRO in two hospitals (Hospital A and B), and within 3 months before and after utilizing e-RASPRO in another hospital (Hospital C). When the data was retrieved, Hospital C had just implemented e-RASPRO for 3 months. Interviews and discussions with the Antimicrobial Resistance Control Program Committee of the three hospitals were conducted during the initial implementation of e-RASPRO, as well as when the survey data were retrieved.

RESULTS

The following was data obtained from the survey conducted within the first 3 months of implementing e-RASPRO at 3 hospitals in Indonesia:

Table 1. Demographic Characteristics of 3 Surveyed Hospitals

Demographic Characteristics of Hospitals	Hospital		
	A	B	C
Number of Doctors			
General Physicians	14	14	25
Dentists	5	15	8
Specialist Doctors	37	98	102
Total	56	127	135
Number of Pharmacists	9	26	39
Number of Nurses	115	74	368
Number of Beds			
Wards	124	168	259
ICU + HCU + ICCU + NICU + PICU	10	17	26
Total	134	185	285
Ratio on numbers of specialist doctors : beds	1 : 3.62	1 : 1.89	1 : 2.79
Ratio on numbers of pharmacists : beds	1 : 14.89	1 : 7.12	1 : 7.31
Ratio on numbers of nurses : beds	1 : 1.17	1 : 2.50	1 : 0.77
The extent of the Buildings	7,247.35	8,120.00	31,099.94

Data: sirs.kemkes.go.id

Table 1. Actual demographic data of the three surveyed hospitals, which was collected from sirs.kemkes.go.id, Ministry of Health, Republic of Indonesia, was as follows: Hospital A, B, and C had 134 beds, 185 beds, and 254 beds, respectively; with a ratio of specialist doctors per bed of each hospital was 1 per 3.62 beds, 1 per 1.89 beds, and 1 per 2.79 beds.

Table 2. Initial Risk Stratification of Patients Receiving Antibiotics that Had Been Filled Out in the Digital Forms within 3 Months Following the Implementation of e-RASPRO in Three Hospitals

Risk Stratification	Hospital A 3 Months Oct – Dec 2021		Hospital B 3 Months Dec 2021 – Feb 2022		Hospital C 3 Months Nov 2022 – Jan 2023	
	Number	%	Number	%	Number	%
Type 1	284	90.16%	692	83.98%	1,472	81.15%
Type 2	31	9.84%	15	1.82%	84	4.63%
Type 3	-	0.00%	117	14.20%	258	14.22%
Total	315	100.00%	824	100.00%	1,814	100.00%

Table 2. In the digital e-RASPRO form, which was completed within 3 months during the initial utilization of e-RASPRO, the majority of patients were in the Type 1 Risk Stratification category, with percentages of 90.16%, 83.98%, and 81.15% in Hospitals A, B, and C, respectively.

Table 3. Appropriateness of Initial Empirical Antibiotic Prescribing with the Digital Guideline on the Use of Antimicrobial Agents within 3 Months Following the Implementation of e-RASPRO in Three Hospitals

	Hospital A 3 Months Oct – Dec 2021		Hospital B 3 Months Dec 2021 – Feb 2022		Hospital C 3 Months Nov 2022 – Jan 2023	
	Number	%	Number	%	Number	%
Empirical antibiotic prescribing is consistent with the digital guideline of antimicrobial use in e-RASPRO	257	81.59%	627	76.09%	444	24.48%
Empirical antibiotic prescribing is not consistent with the digital guideline of antimicrobial use in e-RASPRO	57	18.09%	197	23.91%	1,022	56.34%
Empirical antibiotic prescribing has unidentified consistency in e-RASPRO	1	0.32%	-	0.00%	348	19.18%
Total of forms had been filled out	315	100.00%	824	100.00%	1,814	100.00%

Table 3. The appropriateness of empirical antibiotic prescribing, as documented in Hospitals A, B, and C, using the digital guideline on the use of antimicrobial agents contained in e-RASPRO, reached 81.59%, 76.09%, and 24.48%, respectively, within 3 months before and after the implementation of e-RASPRO. Empirical antibiotic prescribing with non-identified appropriateness, which was documented in the digital forms, was defined as antibiotic prescribing using e-RASPRO with vague appropriateness, for example combined antibiotics prescribing in which one of the antibiotic was appropriate; while the other was not consistent with the digital guideline of antimicrobial agents or other variant condition, in which the appropriateness could not be concluded during data collection. Such a condition was documented in as many as 19.18% of cases at Hospital C.

Table 4. The Quantity of Intravenous Watch and Access Category Antibiotic Prescribing for Inpatient within 9 Months and 3 Months Before and After Implementing e-RASPRO

Antibiotics	Hospital A			Hospital B			Hospital C		
	Pre-implementation of e-RASPRO Jan – Sept 2021 Number of patients: 4,215	9 months post implementation of e-RASPRO Oct 2021 – June 2022 Number of patients: 4,618	Increase / Decrease	Pre-implementation of e-RASPRO Mar– Nov 2021 Number of patients: 7,754	9 months post implementation of e-RASPRO Dec 2021 – August 2022 Number of patients: 6,794	Increase / Decrease	Pre-implementation of e-RASPRO August – Oct 2022 Number of patients: 2,805	3 months post implementation of e-RASPRO Nov 2022 – Jan 2023 Number of patients: 2,675	Increase / Decrease
	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials
Ceftriaxone	15,514	5,753	-62.92%	11,602	6,894	-40.58%	4,513	4,014	-11.06%
1 g Cefotaxime	756	1,023	35.32%	950	4,189	>100%	1,360	1,237	-9.04%
0.5 g Cefotaxime	-	-	-	76	145	90.79%	-	-	-
Ceftazidime	-	-	-	866	359	-58.55%	724	774	6.91%
Cefoperazone	-	-	-	232	413	78.02%	-	-	-
Cefoperazone Sulbactam	-	-	-	-	-	-	-	146	100.00%
Ceftixozime	-	282	100.00%	527	596	13.09%	129	-	-100.00%
Cefepime	-	-	-	14	6	-57.14%	1,465	1,089	-25.67%
750 mg Levofloxacin	2,147	741	-65.49%	2,770	2,400	-13.36%	360	854	>100%
500 mg Levofloxacin	833	457	-45.14%	3,197	1,124	-64.84%	1,002	238	-76.25%
Ciprofloxacin	-	288	100.00%	136	1,258	>100%	-	234	100.00%
Moxifloxacin	-	-	-	487	221	-54.62%	-	-	-
1 g Meropenem	968	568	-41.32%	8,690	7,521	-13.45%	1,619	1,781	10.01%
0.5 g Meropenem	-	-	-	19	-	-100%	550	475	-13.64%
Imipenem + Cilastatin	-	-	-	133	43	-67.67%	-	-	-

Antibiotics	Hospital A			Hospital B			Hospital C		
	Pre-implementation of e-RASPRO Jan – Sept 2021 Number of patients: 4,215	9 months post implementation of e-RASPRO Oct 2021 – June 2022 Number of patients: 4,618	Increase / Decrease	Pre-implementation of e-RASPRO Mar– Nov 2021 Number of patients: 7,754	9 months post implementation of e-RASPRO Dec 2021 – August 2022 Number of patients: 6,794	Increase / Decrease	Pre-implementation of e-RASPRO August – Oct 2022 Number of patients: 2,805	3 months post implementation of e-RASPRO Nov 2022 – Jan 2023 Number of patients: 2,675	Increase / Decrease
	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials	Ampules/vials
Piperacillin Tazobactam	-	-	-	45	-	-100%	-	-	-
Azithromycin	-	-	-	2,662	179	-93.28%	-	-	-
0.5 Vancomycin	-	-	-	207	379	83.09%	356	198	-44.38%
Total Watch	**20,218**	**9,112**	**-54.93%**	**32,613**	**25,727**	**-21.11%**	**12,078**	**11,040**	**-8.59%**
Total Watch / In Patient	**4.7967**	**1.9731**	**-58.86%**	**4.2060**	**3.7867**	**-9.97%**	**4.3059**	**4.1271**	**-4.15%**
Ampicillin	-	947	100.00%	-	93	100%	-	-	-
1.5 g Ampicillin Sulbactam	-	-	-	214	484	>100%	207	466	>100%
0.75 g Ampicillin Sulbactam	-	-	-	746	6,291	>100%	296	164	-44.59%
Amoxycillin – Clavulanic	-	263	100.00%	-	-	-	-	-	-
Gentamicin	969	202	-79.15%	722	1,650	>100%	-	-	-
Amikacin	-	-	-	428	1,105	>100%	-	-	-
Metronidazole	1,180	1,004	-14.92%	1,731	2,424	40.03%	1,610	1,339	-16.83%
Cefuroxime	-	-	-	838	3,074	>100%	-	-	-
Total Access	**2,149**	**2,416**	**12.42%**	**4,679**	**15,121**	**223.17%**	**2,113**	**1,969**	**-6.81%**
Total Access / In Patient	**0.5098**	**0.5232**	**2.61%**	**0.6034**	**2.2256**	**268.83%**	**0.7533**	**0.7361**	**-2.29%**

When the data was collected, e-RASPRO had been implemented for 9 months in Hospitals A and B, but it had only been implemented for 3 months in Hospital C; the results were as follows:

Table 4. The use of antibiotics included in the Reserve category, such as Polymixin and Tetracycline, e was not found in this survey. There was a significant reduction in the quantity of Ceftriaxone prescribed in Hospitals A, B, and C, by 62.92%, 40.58%, and 11.06%, respectively. Nevertheless, there was a significant increase in Cefotaxime prescribing in Hospitals A and B, with increases of 35.32% and more than 100%, respectively. A significant increase also occurred for Ciprofloxacin prescribing in three hospitals. The quantity of 500 mg Levofloxacin prescribed in Hospitals A, B, and C decreased by 45.14%, 64.84%, and 76.25%, respectively. The quantity of 750 mg Levofloxacin was reduced in Hospitals A and B by 65.49% and 13.36%, respectively; however, it increased significantly by more than 100% in Hospital C. The quantity of prescribing 1 gram of Meropenem in Hospitals A and B decreased by 41.32% and 13.45%, respectively; however, it increased in Hospital C by 10.01%. The quantity of azithromycin prescribed also decreased significantly in Hospital B, by 93.28%. Piperacillin-Tazobactam seemed to be used very rarely. The minimum use was found in Hospital B i.e.

as many as 45 ampules/vials within 9 9-month period before the e-RASPRO tool was implemented. In general, the quantity of antibiotic use included in the Watch category at Hospitals A, B, and C was reduced by 54.93% (-58.86% per inpatient), 21.11% (-9.97% per inpatient), and 8.59% (-4.15% per inpatient), respectively. The quantity of Access category antibiotic prescribing in Hospitals A, B, and C was as follows: there was a 100% increase in Ampicillin and Amoxicillin-Clavulanate prescribing in Hospital A. While the prescribing of 1.5 g Ampicillin Sulbactam had also increased by>100% in Hospitals B and C.

Antibiotic prescribing of 0.75 g ampicillin-sulbactam increased by more than 100% in Hospital B; however, there was a decrease of 44.59% in Hospital C. The quantity of Gentamycin prescribing had a reduction of 79.15% in Hospital A; nevertheless, there was a significant increase up to >100% in Hospital B. Meanwhile, in Hospital C, Gentamycin had not been used before and after the implementation of e-RASPRO. Increased Cefuroxime prescribing was also found very significant in Hospital B, based on the agreement made by the Antimicrobial Resistance Control Program Committee, as well as continuity of drug availability in Hospital B, Cefuroxime was included in the Access category. In general, the quantity of Access category antibiotic prescribing in Hospitals A and B increased by 12.42% (+2.61 % per inpatient) and 223.17% (+268.83% per inpatient), respectively. Meanwhile, in Hospital C, it decreased by 6.81% (-2.29% per inpatient)

DISCUSSION

An integrated survey on Antimicrobial Resistance (AMR) and Antimicrobial Use (AMU) is very essential, and it should be carried out in order to evaluate the effectiveness of policy, evidence and the implementation of ASP.[21,22] This survey is a limited survey conducted at three hospitals in Indonesia, which have different characteristics as shown in Table 1.

In Table 1, it is evident that Hospital C has the greatest resources in terms of the number of physicians, pharmacists, and nurses compared to Hospitals A and B. It also has the largest building compared to the other two hospitals. The various human resources in the hospital, along with its large size, presented their own challenges in implementing the antimicrobial stewardship program, whether using manual or digital methods. In daily practice, unevenly distributed levels of socialization may affect the level of appropriateness of antibiotic use with the digital guideline on the use of antimicrobial agents contained in e-RASPRO.

In Table 2, we can see that most patients who would receive early empirical antibiotic prescribing at hospital admission are those who have a Type 1 Risk Stratification, as documented in e-RASPRO. These patients include a group of immunocompetent patients or

immunocompromised patients who had unthreatening bacterial infection or those who are not at risk of having infection caused by MDR microorganisms.[1] Prescribing wide-spectrum antibiotics should be avoided as much as possible in patients who were mostly included in the group with Type 1 Risk Stratification. It should be taken into consideration that using various types of antibiotics may increase the risk of developing resistance.[3,6,23] As the disease progresses, empirical antibiotic treatment certainly can be escalated in accordance with the patient's condition.

Table 3 describes the appropriateness of initial empirical antibiotic prescribing using the digital antimicrobial guideline as documented in Hospitals A, B, and C within 3 months of implementing e-RASPRO, which achieved rates of 81.59%, 76.09%, and 24.48%. It is categorized as "appropriate prescribing" when the empirical antibiotic is given in accordance with the digital guideline of antimicrobial use included in e-RASPRO that is compliant with the patient's risk stratification. There is a high percentage of patients in a group with Type 1 Risk Stratification. This result is expected to bring some changes in the quantitative pattern of antibiotic prescribing from the type of antibiotics included in the Watch category to those in the Access category.

The appropriateness of antibiotic prescribing in Hospital C, which is documented in digital e-RASPRO forms, is still relatively low. Through discussions and interviews with the investigators, it may be caused by the socialization associated with e-RASPRO implementation that has not been thoroughly conducted for the clinicians, or there might be other unidentified obstacles.

Table 4 is a table describing the quantity of antibiotic prescribing, both empirical and definitive antibiotics prescribed using e-RASPRO. The absence of Reserve category antibiotic prescribing in our survey may be due to difficulties in supplying those antibiotics in the three hospitals, or it may also be attributed to the extremely small number of cases associated with this issue in the three hospitals.

Table 4 describes the quantity of Watch category antibiotic prescribing within 9 months before and after implementing e-RASPRO in Hospital A and B as well as within 3 months before and after implementing the tool in Hospital C. There was a significant decrease of Ceftriaxone prescribing in Hospital A, B and C since those three hospitals had carried out some efforts to lower Ceftriaxone prescribing either as empirical or definitive antibiotics; therefore, in the digital guidelines on the antimicrobial use in e-RASPRO of the three hospitals, the use of Ceftriaxone could be minimized

In some group of patients with Type 1 Risk Stratification when the Third Generation of Cephalosporins should be administered, Cefotaxime becomes the appropriate choice as recommended by the digital antimicrobial guidelines in the three hospitals; therefore, although in most cases the empirical antibiotics used in patients with Type 1 Risk Stratification are those in the Access category, but there are some focal infection that can be treated with Cefotaxime as the empirical antimicrobial agent of choice. The Antimicrobial Resistance Control Program Committee of Hospitals A and B has obviously included Ceftizoxime as the Cephalosporin that has been commonly used, and it can be administered when necessary. This might explain the relatively significant increase in Cefotaxime and Ceftizoxime prescribing in Hospital A and B. Meanwhile, in Hospital C, Ceftizoxime had not been included in the digital antimicrobial guideline; therefore, Ceftizoxime had not been used within 3 months following the implementation of e-RASPRO.

The significant increase in Ciprofloxacin prescribing in three hospitals may occur because the prescribing was less consistent with the recommendation included in the digital antimicrobial guideline of e-RASPRO. Nevertheless, the guideline recommends that Ciprofloxacin may serve as a β-lactam antibiotic, which is optional for all types of risk stratifications when patients have a Penicillin allergy. Based on the digital guidelines for antimicrobial use in e-RASPRO, Ciprofloxacin has also been used as the antibiotic of choice for tropical infectious diseases in the three hospitals, such as typhoid fever, and many cases have been reported in Indonesia. For such

infections, according to the digital guideline of antimicrobial use in e-RASPRO, Ciprofloxacin is recommended as one of the antibiotics of choice. Moreover, increased prescribing of Cefotaxime and Ciprofloxacin may also be caused by clinicians who have prescribed definitive antimicrobial treatments using e-RASPRO. However, we still require additional data to confirm this event.

In general, there is a significant decrease in the quantity of Meropenem and Levofloxacin prescribing in hospitals A and B. This is consistent with the digital guideline on antimicrobial use included in e-RASPRO of the three hospitals, which minimizes the use of Levofloxacin for patients with Type 1 Risk Stratification, who are the majority in the three hospitals. Meanwhile, Meropenem can only be administered to patients with Type 3 Risk Stratification. The use of Meropenem cannot be separated from the possibility of escalating antibiotic treatment, which is in accordance with the digital guideline on antimicrobial use included in e-RASPRO.

The increased prescribing quantity of 750 mg Levofloxacin and 1 g Meropenem in Hospital C still persists. It is probably caused by a compliance issue or inconsistency with the digital guideline on antimicrobial use. In the first 3 months of survey conducted in Hospital C, the appropriateness level of antimicrobial prescribing with the digital guideline on the use of antimicrobial agents is still considered to be low; while the majority of patients actually are included in the Type 1 Risk Stratification group, in which most of their empirical antibiotic choices are those included in the Access category. Nevertheless, further review should be conducted to assess the situation that has occurred at Hospital C.

This survey has not found antimicrobial prescribing of Piperacillin-Tazobactam and Ertapenem for patients included in the Type 2 Risk Stratification group following the implementation of e-RASPRO. Through various discussions with those hospitals, we identified that it is difficult to provide antimicrobial agents of Piperacillin Tazobactam and Ertapenem; therefor antibiotics of Access category such as Ampicillin Sulbactam or Amoxycillin Clavulanate with or without combination of Aminoglycosides as the anti-ESBLs often serve as empirical antibiotic of choice to be given for patients who are included in the Type 2 Risk Stratification. Nevertheless, in reality, the initial 3-month survey on the implementation of e-RASPRO in three hospitals has shown that the number of patients included in the Type 2 Risk Stratification group was a minority. Overall, there is a reduction in the quantity of antibiotic prescribing in the Watch category at Hospitals A, B, and C, by 54.93% (-58.86% per inpatient), 21.11% (-9.97% per inpatient), and 8.59% (-4.15% per inpatient), respectively, following the implementation of e-RASPRO.

In Table 4 a survey conducted for 9 months before and after the utilization of e-RASPRO in Hospital A and B and 3 months before and after implementing e-RASPRO in Hospital C has demonstrated a significant increase in the quantity of antibiotic prescribing of Ampicillin, Amoxycillin Clavulanate and 1.5 g Ampicillin Sulbactam, which are antibiotics included in Access category in the three hospitals. The survey conducted within the first 3 months of e-RASPRO utilization has demonstrated that the majority of patients are included in the Type 1 Risk Stratification group at those three hospitals (Table 2), in which the majority of empirical antibiotic choices are indeed antibiotics included in the Access category. Nevertheless, further surveys are certainly required to be carried out in Hospitals A and B in the following months.

The significant increase of 0.75 g Ampicillin Sulbactam prescribing may also still be associated with the continuity of 1.5 g Ampicillin Sulbactam availability in Hospital B. Some sources at Hospital B, through discussions with investigators, suggest that there is often a shortage of 1.5 Ampicillin-Sulbactam in the hospital. Therefore, considering this reasoning, the Antimicrobial Resistance Control Program Committee in Hospital B has included Cefuroxime in the Access category of its guideline on antimicrobial use. This condition explains the presence of an increased quantity of Cefuroxime prescribing, which is included in the Access category in Hospital B.

Based on the digital guideline on antimicrobial use in e-RASPRO of the three hospitals, Aminoglycosides have actually been used as combined antibiotics. It has not been identified clearly about the cause of reduced Gentamycin prescribing is in Hospital A, while in Hospital C, the use of Gentamycin and Amikacin has not been documented either before or after the implementation of e-RASPRO. Increased Gentamycin and Amikacin prescribing in Hospital B could occur because the digital guideline on antimicrobial use for those three hospitals recommends using aminoglycosides as combined empirical antibiotics for some focal infections in patients with Type 1 risk stratification and almost all focal infections in patients with Type 3 Risk Stratification. Overall, there is increased quantity of Access category antibiotic prescribing in Hospital A and B of 12.42% (+2.[illegible]% per inpatient) and 223.17% (+268.83% per inpatient), respectively. A survey conducted within 3 months before and after the implementation of e-RASPRO in Hospital C demonstrated a reduction in Access category antibiotic prescribing of 6.81% (-2.29% per inpatient).

In Table 4, regarding the number of patients before and after the implementation of e-RASPRO in those three hospitals, it can also be seen that the numbers were not significantly different. This survey has not correlated the quantity of prescribing with the duration of antibiotic use; furthermore, it has not calculated the percentage of escalating and stepping down empirical antibiotic treatment. However, in this survey, we observed a reduced percentage of Watch category antibiotic prescribing in three hospitals, as well as an increased percentage of Access category antibiotic prescribing in two hospitals (Hospital A and B) following the implementation of e-RASPRO. The increased quantity of Access category antibiotic prescribing, particularly in Hospital B, is extremely significant.

The altered quantity of Watch and Access category antibiotics prescribed, particularly in Hospitals A and B, is likely still influenced by the appropriateness of empirical antibiotic use, which is guided by the digital guideline on antimicrobial use included in e-RASPRO. However, it certainly requires further studies. Hospital characteristics, such as the number of hospital beds, the number of physicians, and other facilities, may also affect the pattern of antibiotic prescribing. A systematic review showed a decrease in the antimicrobial DDD range from -8.42% to -61.29% related to the use of a digital antimicrobial stewardship tool.[24]

Some studies have demonstrated that the utilization of digital tools to implement ASP can reduce the use of antimicrobial agents and also decrease the DDD.[24,25] In other previous study the duration of digital antimicrobial stewardship implementation may show a different antibiotic DDD result.[3] However, we still cannot conclude what type of digital intervention will certainly reduce the use of antimicrobial agents.[25] Our study is an initial survey on the utilization of e-RASPRO, one of the digital antimicrobial stewardship programs used in Indonesia. This study is a survey only and cannot yet describe the correlation between e-RASPRO use and antibiotic prescribing patterns. To achieve good results, the utilization of e-RASPRO should be carried out in conjunction with compulsory disciplines and with full support from the hospital management team. Demographic characteristics of the hospitals can also affect the effectiveness of e-RASPRO utilization. To provide a comprehensive explanation of this issue, more extensive studies with full support from the managerial team are required to further analyze the causal correlation between the utilization of e-RASPRO and the altered quantitative pattern in antibiotic prescribing.

CONCLUSION

The survey has not been able to describe the causal-effect correlation between e-RASPRO implementation and the quantity of antibiotic prescribing. However, in general, there is an altered quantitative pattern in the quantity of empirical antibiotic prescribing, particularly for those included in the Watch and Access categories, following the implementation of e-RASPRO. We

suggest a broader scope of research on digital antimicrobial stewardship tools to evaluate their effectiveness in implementing antimicrobial stewardship programs.

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AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: RIN; data collection: WL, RA, RM, HS, SM, DA, TSM, IIP, DD, GNL, ALR; analysis and interpretation of results: RIN, WL, AA, HA; draft manuscript preparation: RIN, WL, YY, JS, NH, HA, MAF, TFF, JVK, YY. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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