IDENTIFICATION OF DRUG-RELATED PROBLEMS ON BETA LACTAM ANTIBIOTICS USED FOR PEDIATRIC AT A SECONDARY-CARE HOSPITAL IN CIMAHI, INDONESIA

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ABSTRACT

World Health Organization (WHO) estimated that >50% of medicines are used inappropriately. One that posess highest risk due to inappropriate use is beta-lactam antibiotic, espescially in pediatric patient since the organ function in pediatric patient has not completely developed as in adult yet. This cross-sectional study was performed to retrospectively identify drug-related problems (DRPs) occurred during beta-lactam therapy in pediatric hospitalized in a secondary-care hospital in Cimahi. Amedication-use criteria based on the current literatures was created as an assessment standard tools. Furthermore, identification of DRPs based on The Pharmaceutical Care Network Europe (PCNE) v6.2 classification was carried out to 351 patients hospitalized from January to March 2015. As many as 458 potential DRPs were found in those patients including 22 cases inappropriate drugs (category C1.1), 127 cases no indication for drug (C1.2), 42 cases inappropriate combination of drugs, or drugs and food (C1.3), 1 case of too many drugs prescibed for indication (C1.6), 137 cases drug dose too low (C3.1), 89 cases drug dose too high (C3.2), 39 cases duration of treatment too short (C4.1) and 1 case of duration of treatment too long (C4.2). The potential DRPs was estimated to be occured for approximately 1-2 DRPs per patient.

Keywords: drug-related problems; beta-lactam antibiotic; pediatric; pharmaceutical care

IDENTIFIKASI PERMASALAHAN TERKAIT OBAT (DRUG-RELATED PROBLEMS) ANTIBIOTIK BETA LAKTAM PADA PASIEN ANAK SUATU RUMAH SAKIT DI KOTA CIMAHI, INDONESIA

ABSTRAK

World Health Organization (WHO) memperkirakan >50% obat di dunia digunakan tidak sesuai dengan rekomendasi. Salah satu obat yang memiliki resiko tinggi bila digunakan secara tidak rasional yaitu antibiotik beta laktam terutama apabila digunakan pada pasien pediatrik karena fungsi organ yang belum sempurna seperti orang dewasa. Studi potong lintang ini dilakukan untuk mengidentifikasi permasalahan terkait obat (*drug-related problems*/DRPs) antibiotik beta laktam secara retrospektif pada pasien anak rawat inap di suatu rumah sakit rujukan pelayanan sekunder di Cimahi. Selanjutnya dibuat kriteria penggunaan obat sebagai standar untuk menilai ketepatan penggunaan obat disusun berdasarkan pustaka mutakhir. Kemudian dilakukan identifikasi DRPs pada 351 pasien yang dirawat pada bulan Januari hingga Maret 2015 berdasarkan klasifikasi *The Pharmaceutical Care Network Europe* (PCNE) v6.2). Ditemukan 458 jenis potensi ketidaktepatan penggunaan antibiotik beta-laktam (DRP) terdiri dari 22 kasus obat tidak tepat (kode C1.1), 127 kasus obat tanpa indikasi (C1.2), 42 kasus ketidaktepatan kombinasi obat-obat / obat makanan (C1.3), 1 kasus terlalu banyak obat untuk 1 indikasi (C1.6), 137 kasus dosis terlalu rendah (C3.1), 89 kasus dosis terlalu tinggi (C3.2), 39 kasus durasi terapi kurang (C4.1), dan 1 kasus durasi terapi lebih (C4.2). Potensi terjadinya DRP diperkirakan sekitar 1-2 kasus DRP per pasien.

Kata kunci: drug-related problems; masalah penggunaan obat; antibiotik beta laktam; pediatrik; asuhan kefarmasian

Introduction

Drug-related problems (DRPs) has become a growing threat for patients beside the disease itself. The Pharmaceutical Care Network Europe (PCNE) defines DRPs as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (PCNE 2010). Drug-related problemss was known to affect not only deteriorate the health outcome, but also increase the healthcare utilization and cost (Heider et al. 2017). There were general concern that the potential harm caused by DRPs is even more higher in several special populations e.g. renal impairment, liver disease, pregnant women, geriatric and pediatric than the average population due to their unique physiological characteristics (Zakharov et al. 2012). (reference?)

Previous study investigated the occurrence of DRPs in pediatric patients in different diseases and settings. A multicenter study in a pediatric cardiac and intensive care unit reported that inappropriate administration technique (29 %), untreated indication (25 %) and supra-therapeutic dose (11 %) were among the most common DRPs (Prot-Labarthe et al. 2013). A study in United Kingdom and Saudi Arabia also showed that overall DRP incidence was 45.2% (95% CI, 41.5–48.8) where dosing problems were the most frequently reported DRPs (54%). However, 80.3% of them were preventable (Rashed et al. 2012). A study in Hong Kong also reported similar results although the overall incidence of DRPs was lower (21.0%; (95% CI, 16.7–25.8%) (Rashed et al. 2014).

Indonesia has a high morbidity of infection disease in paediatric population. Based on Basic Health Research 2013 (Riset Kesehatan Dasar/Riskesdas tahun 2013), the period prevalence of acute repiratory tract infection was 15.4-25.8%, which was the highest group compared with other age group (Balitbangkes-Kemenkes 2013). The prevalence of tuberculosis in children was also high (0.2-0.4%) (Balitbangkes-Kemenkes 2013). This situation potentially increase antibiotics use in this population group. An extensive database study showed that there was an increase in antibiotics prescribed to children after the year of 2000 (Schneider-Lindner et al. 2011) although recent study in the US showed that antibiotic dispensing for children is relatively consistant during 2000s (Vaz et al. 2014). This potentially includes beta lactam antibiotics group since the majority of beta lactams were approved for pediatric use. However, to our knowledge, no research focusing on beta lactam antibiotic-related DRPs in Indonesian hospitalized children with various diagnosis ever carried out except only one study using Gyssens method (Febiana 2012). The aims of this study were to identify drug-related problems on beta lactam antibiotics prescribed for pediatric inpatients.

Methods

Study design and setting

This cross-sectional study was performed at pediatric ward of a secondary-care hospital at Cimahi, West Java, Indonesia to the patients hospitalized from January to March 2015. We retrospectively assess the medical record of each included patients.

Study sample

Patients hospitalized in pediatric ward was aged <16 years. From a total of 770 patients hospitalized in pediatric ward within January-March 2015, 513 were treated with beta lactams.. The minimum sample size calculated with Isaac-Michael method with 1% sampling error was 301. Thus, we randomly select the medical records of 351 patients aged <16 years old who received beta lactam antibiotics during study period.

DRPs Identification and Classification

DRPs were identified by analyzing patients' medical record and medication order from pediatrician. Following data were extracted from those records: 1) demographic data (age, gender, weight, anamnesis, diagnosis); 2) medication data (name, strength, dosage, pharmaceutical dosage form) and laboratorium data provided.

DRPs was classified based on The Pharmaceutical Care Network Europe classification v6.2 (PCNE 2010). The basic classification provided 4 primary

domains for problems, 8 primary domains for causes, and 5 primary domains for Interventions. Due to our retrospective design and limited information in the medical records, we only assessed "causes"domain, particularly drug selection (code C1), dose selection (C3), and treatment duration (C4). The definition of DRPs domain for causes used in this study can be found in Table 1.

Table 1. Several items of PCNE Classification scheme for DRPs v6.2 from domain Causes that have been assessed in this study.

Primary Domain	Code	Cause
Drug selection The cause of the DRP is related to the selection of the drug	C1.1	Inappropriate drug (incl. contra-indicated)
	C1.2	No indication for drug
	C1.3	Inappropriate combination of drugs, or drugs and food
	C1.4	Inappropriate duplication of therapeutic group or active ingredient
	C1.5	Indication for drug-treatment not noticed
	C1.6	Too many drugs prescribed for indication
Dose selection The cause of the DRP is related to the selection of the dosage schedule	C3.1	Drug dose too low
	C3.2	Drug dose too high
	C3.3	Dosage regimen not frequent enough
	C3.4	Dosage regimen too frequent
Treatment duration The cause of the DRP is related to the duration of therapy	C4.1	Duration of treatment too short
	C4.2	Duration of treatment too long

A medication use standard was created as a standard to investigate if a drug-related problem occurred. This criteria was made based on relevant and up-to-date literature e.g. AHFS Drug Information Essentials 2011 (ASHP 2011), Drug Information Handbook 17th ed (Lacy et al. 2008), British National Formulary for Children 2011-2012 (Committee 2011), Guideline on Pediatric Healthcare for Secondary-care Hospital (Pedoman Pelayanan Kesehatan Anak di Rumah Sakit Rujukan Tingkat Pertama di Kabupaten/Kota) (WHO/MoH/IDAI 2009), Handbook on Injectable Drugs 15th ed (Trissel 2009) and Handbook of Food-Drug Interactions (McCabe et al. 2003). It consists of name of the drug, indication, dosage, pharmaceutical dosage form, administration, side effects, contraindication, warning, stability and incompatibility.

Data analysis

Descriptive statistics was used for data analysis.

Results And Discussion

Subject characteristics

Table 2 showed the demographic and clinical data of the patients. The majority of study participants were male (n=199; 57%) and aged between 0-5 years old. Most of the patients is covered by health insurance during hospital admission (n=187; 53.28%) but the patients without health insurance were also have high proportions (n=164; 46.72%). As many as 56.31% of the patients were diagnosed with one disease. As many as 84.06% patients were diagnosed with infection (ICD-X code A00 - B99) which potentially increase the exposure of antibiotics. Although the majority of patients diagnosed with one disease, most of them received 4-6 (51.85%) medications during hospitalization period. Since the occurrence of DRPs strongly correlated with the number of medications received by patients, this situation potentially also increased the risk of DRPs (Rashed et al. 2012, Rashed et al. 2014, Zazuli et al. 2017). Another study which was created a predictive score for detecting DRPs also reported that number of drugs during hospitalization increased the risk of having DRPs (OR=3.335; CI95% 2.956–3.763; p<0.001) (Urbina et al. 2014). Most of the patients hospitalized for 4-6 days (51.85%) and discharged from hospital with improved medical condition (89.74%).

Table 2. Participant demography and clinical characteristics.

Characteristics	n	%
Gender		
Male	199	57
Female	152	43
Age (years)		
0-5	251	71,51
6-11	92	26,21
12–16	8	2,28
Type of insurance		
State-owned insurance	160	45.58
Private insurance	27	7,69
Out-of-pocket	164	46,72
No. of diseases diagnosed		
1	197	56,13
2	109	31,05
3	29	8,26
4	8	2,28
5	4	1,14
>5	4	1,14
No. of drugs received		
1 – 3	51	14,53
4 – 6	181	51,85
7 – 9	93	26,78
≥ 10	26	6,84
Hospital discharge status		
Dead	3	0,85
Improved	315	89,74
Discharge against medical advice	30	8,55
Referred	3	0,85
Length of stay (days)		
1-3	43	12,25
4-6	204	58,12
7-9	77	21,94
10-12	12	3,42
13-15	7	1,99
16-18	3	0,85
19-21	3	0,85
22-24	1	0,28
25-27	1	0,28
Total	**351**	**100**

Antibiotic usage profile

Antibiotics were ordered 771 times. Most of them (n=604) were beta lactams derivate (Table 3). Third generation cephalosporins were preferred by the pediatrician consists of cefixime (22,02%) followed by ceftriaxone (21,19%) and cefotaxime (18.05%). Most of the antibiotics administered in injection form (75.52%). All antibiotics were used empirically since there was no facility to conduct microbial culture and antibiotic sensitivity test.

Table 3. Beta lactams usage within study participants.

Characteristics	n	%*
Beta lactams (n=604)		
Amoxicillin	59	9,77
Ampicilin	44	7,28
Ampicilin-sulbactam	103	17,05
Dicloxacilin	11	1,82
Meropenem	10	1,66
Cefixime	133	22,02
Cefotaxime	109	18,05
Ceftazidime	5	0,83
Ceftizoxime	2	0,33
Ceftriaxone	128	21,19
Pharmaceutical dosage forms (n=604)		
Liquid	148	24,50
Injection	438	72,52
Solid (tablet, capsule)	18	2,98

n = times beta lactams prescribed
*percentage based on times beta lactams prescribed

This data were not in accordance with data from other published studies. A Korean study reported that third generation cephalosporin is less frequent prescribed to children than second generation cephalosporins and penicillin derivates (Song et al. 2017). A Danish study also showed that penicillin derivatives were the most pescribed antibiotics while cephalosporins were rarely prescribed (Pottegard et al. 2015). This differences might be caused by different infectious disease pattern and different pathogens since the studies were from different country. Regardless that difference, in such limited facilities, pediatrician should choose the empirical antibiotics carefully, particularly in reserving the newer antibiotics for more difficult cases. Overuse of antibiotics may lead to rapid rate of antibiotic

resistance (Shallcross dan Davies 2014). The main reason why pediatrician preferred to prescribe injection form was because most of beta lactams only available as injection e.g. ampicilin, ampicillin-sulbactam, dicloxacilin, meropenem, cefotaxime, ceftazidime, ceftizoxime dan ceftriaxone). This dosage forms also ensure the antibiotics immediately reach its minimum inhibitory concentration.

DRPs pattern

We found 458 DRPs which were divided in three category of causes (Table 4) as following:

Table 4. Prevalence of DRPs identified based on selected PCNE v6.2 classification.

Primary domains	PCNE Code	Cause	No. of cases	%
Drug selection	C1.1	Inappropriate drug (incl. contra-indicated)	22	4,80
	C1.2	No indication for drug	127	27,73
	C1.3	Inappropriate combination of drugs, or drugs and food	42	9,17
	C1.4	Inappropriate duplication of therapeutic group or active ingredient	0	0
	C1.5	Indication for drug-treatment not noticed	0	0
	C1.6	Too many drugs prescribed for indication	1	0,22
Dose selection	C3.1	Drug dose too low	137	29,91
	C3.2	Drug dose too high	89	19,43
	C3.3	Dosage regimen not frequent enough	0	0
	C3.4	Dosage regimen too frequent	0	0
Treatment duration	C4.1	Duration of treatment too short	39	8,52
	C4.2	Duration of treatment too long	1	0,22
Total			458	100

1) Drug selection which the cause of the DRP is related to the selection of the drug (C1), 2) Dose selection which the cause of the DRP is related to the selection of the dosage schedule (C3) and 3) treatment duration which the cause of the DRP is related to the duration of therapy (C4). Overall, the potential DRPs was estimated to be occured for approximately 1-2 DRPs per patient. Dosing problems has the highest rate of DRPs (n=226; 49.34%). This confirms the results of previous study in the UK, Saudi Arabia, Ethiopia and Hong Kong (Birarra et al. 2017, Rashed et al. 2012, Rashed et al. 2014) although those studies did not limited the drugs to antibiotic. Second most frequent causes was improper drug selection (n=192; 41.92%) which is supported also by a study in Hong Kong (Rashed et al. 2014). Interestingly, another study on hospitalized children in Indonesia reported that improper drug selection (e.g. antibiotics not indicated, more effective , less toxic, and less costly alternative available) is the main causes of DRPs (32.97%) followed by dosing problems (11.9%) (Febiana 2012). Differences in methods might result in inconsistent findings since the study was conducted based on Gyssens algorithm instead PCNE classification.

The most cause of inappropriate drug (C1.1) was prescribing ceftazidime or ceftriaxone for treating pneumonia instead using cotrimoxazole or amoxicillin/ampicillin (n=10).

The usage of amoxicilin, ampicilin, ampicilin-sulbactam, dicloxacilin, cefixime, cefotaxime, ceftizoxime and ceftriaxone in degue hemorrhagic fever (DHF) patients contribute to most causes of no indication for drug (C1.2) (n=55) followed by amoxicilin, ampicilin, ampicillin-sulbactam, cefixim, cefotaxim, ceftazidime, ceftriaxone use for non-infectious diagnosis e.g. perinatal asphyxia, asthma, cerebral palsy, colic, dehydration, thalassemia, suspect epileptic, unspecified febrile etc (n=27) . Inapproriate combination (C1.3) such as combining cefotaxime, ceftazidime or ceftriaxone with aminoglikosida (amikacin, gentamicin) may increase the risk of nephrotoxicity (n=24). We also identify the combination of ampicillin-sulbactam, cefixime, and cefotaxime for treating bronchiolitis in one patient (C1.6). Instead of using such inappropriate

combination, patient can be treated with cotromoxazole or singe agent amoxicillin or ampicillin or with combination with chloramphenicol if the infection became severe, or ceftriaxone as single agent. Dose too low (C3.1) mostly related with cefotaxime to treat bronchopneumonia (n=58) and dose too high (C3.2) mostly caused by ampicillin-sulbactam in bronchopneumonia (n=30). Duration of treatment too short had vary causes while duration of treatment too long caused by the use of ampicillin in sepsis. Four subdomains of causes (C1.4 Inappropriate duplication of therapeutic group or active ingredient, C1.5 Indication for drug-treatment not noticed, C3.3 Dosage regimen not frequent enough, and C3.4 Dosage regimen too frequent) were not detected in this study.

This study possess some strengths. Our study focus on pediatric with various infectious diseases and on a group of drugs which is highly used in such population (beta lactams).We put more focus on the type medication (beta lactams) rather than the diseases. Most of published studies in Indonesia focusing on specific diseases in children e.g. respiratory diseases or typhoid fever which potentially limiting the result generalizability. We also focus on inpatient setting since patients tend to have various medications in which potentially increase the risk of experiencing DPRs. However, several limitations also addressed from this research. We assume that the DRPs might be higher than our current findings since it was difficult to identify several DRPs in other Causes domain within PCNE classification such the cause of the DRP is related to drug form (C2), drug use process (C5), logistics (C6), and patient (C7) due to incomplete medical record. We also could not distinguished which DRPs was actually happened. This mainly caused by the nature of retrospective method. We suggest to do prospective research in order to minimize the potential bias due to incomplete data.

Conclusion

The majority of the DRPs was related with dosage selection (n=226; 49.34%) followed by drug selection (n=192; 41.92%) and treatment duration (n=40; 8.74%). The potential DRPs was estimated to be occured for approximately 1-2 DRPs per patient. We recommend more active role of clinical pharmacist in pediatric ward to improve interdiscliplinary patient-centered care among the healthcare team. We also call for institutional-based surveilance system to increase the appropriateness of antibiotics usage.

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