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Drug-related problems (DRPs) on antibiotic therapy in pediatric patients: a review

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ABSTRACT

Drug-related problems (DRPs) is event that can interfere with the outcome of therapy. It can occur in various patient populations and ages. The DRPs in pediatric patients is found to be significantly frequent due to their vulnerable features. Many factors such as age, weight, body surface area should be considered during drug therapy in pediatric patients. The organs development continues for many years and the organs responsible for drug metabolism and elimination have not yet full capacity in pediatric patients. Antibiotics are often prescribed to pediatric patients. Several studies concerning DRPs on antibiotic therapy have been conducted in some countries. This review summarizes types, factors and impacts to the occurrence of DRPs on antibiotic therapy in pediatric patients.

ABSTRAK

Drug-related problems (DRPs) atau masalah terkait obat adalah kejadian yang dapat mempengaruhi keberhasilan terapi. DRPs dapat terjadi pada berbagai kelompok umur dan populasi pasien. DRPs pada pasien anak ditemukan sering terjadi karena kondisi yang rentan pada anak. Banyak faktor seperti umur, berat dan luas permukaan tubuh harus dipertimbangkan selama terapi obat pada pasien anak. Perkembangan organ pada anak terus berlanjut pada beberapa tahun berikutnya dan organ yang bertanggung jawab terhadap metabolisme dan eliminasi belum mencapai kapasitas penuh. Antibiotik sering diresepkan pada pasien anak. Beberapa penelitian tentang DRPs pada terapi antibiotic telah dilakukan di beberapa negara. Pada telaah pustaka ini dirangkum tipe, faktor dan dampak terhadap kejadian DRPs pada terapi antibiotik pada pasien anak.

INTRODUCTION

Drug-related problems (DRPs) are unwanted or unexpected events by patients that involve drug therapy and actually or potentially interferes with therapeutic outcomes and requires professional judgment to resolve these problems.[1,2] In the United States, DRPs are the second most common problem that causes very expensive medical costs. Pediatrics is included in the 6th largest among 16 specialties that often experience DRPs.[3] Problems related to drug therapy include choosing unnecessary therapy, needing additional therapy, ineffective therapy, too low a dose, too high a dose, adverse treatment (drug interactions and drug side effects), and non-adherence.[4] Failure in the treatment process has the potential to cause harm to patients, including prescribing errors; dispensing errors; medication preparation errors; administrative errors, and monitoring errors. The DRPs can cause death and the morbidity due to DRPs increases more than twofold. The estimated median cost of treatment failure was $977 and the cost of drug-related morbidity and mortality was $177.4 billion in 2000 in the United States.[5]

Pediatric patients are the main population requiring special attention in treatment. The vulnerability of

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children is caused by pharmacodynamic, pharmacokinetic, and toxicological changes in patients of various ages and developmental stages. Pharmacokinetics and pharmacodynamics of drugs in children will affect drug choice, dosage, dosage form, and dosing interval.[6] Pediatric prescribing requires dose adjustments related to dose calculations.[7] Decision-making on therapeutic action in children requires information regarding dose, patient age, and patient weight.[8] Antibiotics are one of the most frequently prescribed therapies in pediatrics. Improvements in health care, lack of uniformity in drug prescribing, and antibiotic resistance occur as a result of abuse.[9,10] The use of aminoglycoside antibiotics has potential side effects such as hearing loss.[11] Caution in the use of antibiotics is necessary when prescribing antibiotics in children because of the risk of causing allergic reactions and potential antibiotic resistance. Different dosage forms of the same active ingredient, it is necessary to select the right dosage and dosage form for each child to achieve bioavailability and avoid inappropriate dosing.[12] The review was conducted to explore drug-related problems of antibiotic therapy that can occur in pediatric patients.

DISCUSSION

Criteria of DRPs

According to the Pharmaceutical Care Network Europe (PCNE), DRPs are situations involving drug treatment that will actually or probably or manifest affect the desired treatment outcome.[2] Detected DRPs are classified as actual if the problems occurred immediately while the patient is taking the drug and potential if they have the prospect of causing harm to the patient regardless of whether a hazard is actually observed, and manifest if they have caused harm to the patient. The DRPs could be identified as inappropriate diagnosis, inappropriate patients, drug dose to low (underdose), drug dose to high (overdose), dose timing relative to meals, drug interactions and drug compliance (TABLE 1).

TABLE 1. Criteria for DRPs identification

Drug-related problems	Definition
Inappropriate diagnosis	Drug is not consistently prescribed with the drug indications and not intended to treat the disease.
Inappropriate patients	Drug is absolutely contraindicated in patients with specific age or\disease. The drug is not contraindicated, but its safety and efficacy for children have not been established, and the dosage range is not recommended. However, it is still prescribed while there are other available and optimal active ingredients for the patient.
Drug dose to low (underdose)	The dosage form is unsuitable for children since it is not possibly or accurately divided into smaller doses.
Drug dose to high (overdose)	The drug is prescribed with high single dose and/or excessive number of times taking medicine daily, resulting in a 24-h dose that is higher than the maximum recommended dose.
Dose timing relative to meals	The drug is prescribed with low single dose and/or excessive number of times taking medicine daily, resulting in a 24-h dose that is lower than the minimum recommended dose.
Drug interactions	The drug is recommended to be used before meals, during meals or after meals, but the prescription is insufficiently or incorrectly instructed.
Drug compliance	Severe drug-drug interactions are contraindicated or advised to avoid combination.

Incidence of DRPs in pediatric patients

Drug-related problems that often occurs in children related to antibiotic therapy is underdose, overdose, adverse reaction, indications without therapy, and compliance.

Underdose

Administration of drugs with doses that are too low will result in ineffectiveness in achieving the desired therapeutic effect. Dosage calculations based on body surface area can potentially cause an overdose in children under five if the calculations are not appropriate.[13,14] Hannesdóttir[15] and Truter *et al.*[16] reported that the problem of inappropriateness in antibiotic therapy in children is the highest DRP, which is more than 30%. Underdose is more common than overdose. Zazuli *et al.*[17] reported that the highest incidence of DRP is a mismatch of therapeutic doses where 30% of patients with diarrhea received doses of antibiotics that are smaller than those that should be recommended for therapy. A study concerning the use of antibiotics in pediatric patients in District General Hospital, Semarang reported that among 28% of patients experiencing DRPs in the form of underdose.[18] Whereas a study in Brazil concerning the use of antibiotics in children in general hospitals found that 12% of the incidence of DRP underdose. If the use of the drug is below the dose and the effect does not achieve the best results, the patient will be dissatisfied and stop taking the drug.

Overdose

The overdose of therapy in pediatrics can result in side effect, even toxicity. Dosage calculations based on body surface area can lead to an overdose in children under five if the calculations are not appropriate.[13,14] Abrogoua *et al.*[20] reported that the incidence of overdose at a pediatric unit in Cote d'Ivoire is 21.1%, whereas at Jimma University Medical Center in Southwest Ethiopia is 10.9%.[21] Another study conducted in the Children's Department at the Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia reported the incidence of overdose is 7.5%.[13] EmyInumaru *et al.*[19] reported that the incidence of overdose in children less than 18 years of age in General Hospital in Sourthen Brazil is 14.6%. A study conducted in the Distric Hospital, Semarang, Central Java reported that the incidence of overdose in pediatric patients is 8.97%, whereas in the neonatal care unit and pediatric wards at a tertiary academic hospital in Gauteng, South Africa is 34%. The problem of dose in the use of antibiotics is something that needs to be considered and monitoring related to antibiotic treatment in pediatrics.

Drug interactions

Drug interactions is defined as the interference of a drug in the action of another drug or the interference of food or nutrient in the action of drugs.[22] Pediatrics patients require special attention from medical doctor of health professionals concerning the drug interactions as they response to drugs differently from adult patients. The body of pediatrics patients that are responsible for drug metabolism or elimination processes are not fully mature, resulting in extended half-life of drugs.[23] Drug interactions may lead an increase in the adverse effects or a decrease in the effectiveness of given drugs or antibiotics. Therefore, the medical doctor or the health professionals should avoid complex prescription regimens (polypharmacy), provide simple and clear instruction, monitor the patient.

Polypharmacy and comorbidities in pediatric patients have the potential for drug interactions. Birarra *et al.*[13] reported that the incidence of drug interaction in pediatric ward of Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia is 38.6%. Whereas a study in District General Hospital in Semarang, Central Java, it was reported as much as 42.32%[18] and another study conducted in District General Hospital and Muhammadiyah Private Hospital in Yogyakarta was 56.4%.[3]

Therapy without indication

Therapy without indication is the administration of drugs that are not in accordance with the indications or diagnosis in the patient. Administration of drugs without indications can cause harm to the patient with the appearance of unnecessary effects. This can be caused by patients using drugs that are not in accordance with the indications of the disease at this time.[1] The use of antibiotics that are not properly indicated can have the effect of increasing resistance and poor health outcomes.[24]

Timur *et al.*[18] reported that there are 5 (6.4%) events of antibiotic therapy without indication in the study conducted in the District General Hospital, Semarang. Pediatric patients with a diagnosis of fever received cefotaxime or ceftriaxone without clear indications. Birarra *et al.*[13] reported that the incidence of antibiotic therapy without indication in pediatric ward of Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia is 7.3%. Another study conducted at Jimma University Medical Center in Southwest Ethiopia reported that the antibiotic therapy without indication is 7.3%.[21] Whereas a study in in a Secondary Care Hospital in Cimahi, West Java reported that the antibiotic therapy without indication is 27.73%.[17]

Majority antibiotics were empirically prescribed without microbial culture and antibiotic sensitivity test. The antibiotics were prescribed mostly for fever or symptoms associated with the upper respiratory tract infections which commonly caused by viral infections.[25] A study conducted in a Secondary Care Hospital in Cimahi, West Java reported that amoxicilin, ampicilin, ampicillin-sulbactam, dicloxacilin, cefixime, cefotaxime, ceftizoxime and ceftriaxone were prescribed in dengue hemorrhagic fever (DHF) patients which they no indication treated by these antibiotics. Furthermore, amoxicillin, ampicillin, ampicillin-sulbactam, cefixime, cefotaxime, ceftazidime, ceftriaxone were prescribed for non-infectious diagnosis such as perinatal asphyxia, asthma, cerebral palsy, colic, dehydration, thalassemia, suspected epilepsy, unspecified febrile.[17]

Adherence

Adherence is the patient unable or unwilling to take medication decisions as instructed.[1] Antibiotic adherence is an important issue in pediatric infection management.[26] Several factors influence doctors in the selection of antibiotics such as adherence or patient compliance, cause, sensitivity and location as well as extent of infection. Furthermore, several factors influence the adherence of patients such as age, allergies, route of drug administration, formulation, penetration rate, side effects, and toxicology. In addition, the taste of antibiotics also affects clinical outcomes and improves adherence.[27]

Non-compliance with the use of antibiotics in caregivers is one of the factors causing cases of antibiotic resistance. Antibiotic resistance results in an increase in mortality, long hospital stays, and health services.[28,29] There were 27 (71.05%) of 35 caregivers showing non-adherence to treatment. Factors causing non-adherence include belief in unexpected drug reactions, false hopes of healing, wrong knowledge about antibiotics, routine or busy caregivers, phenomena of various drugs, and types of preparations given to patients.[28]

The adherence of the antibiotic use among pediatric patients ranges from 1.28-28.65%. Mechessa *et al.*[21] reported that there is a non-compliance of 28.65% among pediatric patients with infectious diseases admitted to Jimma University Medical Center, Southwest Ethiopia. Abrogoua *et al.*[20] reported that the non-compliance at a pediatric unit in Cote d'Ivoire is 24.1%. Whereas, studies conducted by Arfania *et al.*[3] and Timur *et al.*[18] found that non-compliance of antibiotic use among pediatric patients are 1.28 and 9.88%, respectively.

Factors influencing DRPs

The factors influencing DRPs of antibiotic therapy in pediatric patients are complex including cultural, cognitive, educational, and socio-economic factors integrated at the level of patients or parents, physicians and pharmaceutical industries.[30] Parent's pressure is the main factor that influence antibiotics prescription by physicians. Due to misperception regarding antibiotic prescription, most parents expect physicians to prescribe non-indicated antibiotics.[31] Although physicians might feel uncomfortable to prescribe antibiotics to children, they may be forced to make irrational prescription in order to foster good relationship with the parents.[30] On the other hand, physicians generally overestimate parental expectations. They prescribe non-indicated antibiotics, even the parents do not expect.

Health education is an important factor influencing to the DRPs in pediatric patients. Patient's or parent's lack knowledge in antibiotic therapy and the harmful effect due to inappropriate antibiotic use is contributing factor to antibiotic related problems.[32] Parent's misconception regarding appropriate indication for antibiotics use leads to an increase consumption of antibiotics in pediatric patients. The majority of parents have a false notion that viral infections in children would not cure on its own and antibiotics are needed to treat the symptoms.[33] It is believed that educating parents concerning antibiotics use and their implications would reduce antibiotic related problems.[34]

Socio-economic status is considered as an important factor also in the incidence of DRPs in pediatric patients. Inappropriate antibiotics consumption is associated to low socio-economic status of patients, which might be associated to low education levels.[35,36] However, another study reported that patients with high socio-economic status are more likely to request antibiotics, because the parents believe that antibiotics treat viral infection faster. Moreover, they are more likely to consume antibiotics due to their better access to health care facilities.[37]

Self medication is more common in under develop and developing countries due to availability of antibiotics without prescription, unrestricted access to antibiotics, lack of national regulation, prescribing and dispensing antibiotics without indication.[30] Antibiotic self-medication may cause several DRPs to the child including antibiotics misuse and drug interactions.

Impacts of DRPs

Although antibiotics have a significant contribution in the reduction of morbidity and mortality rates of infectious diseases worldwide, their inappropriate antibiotic use may cause DRPs and lead several impacts such as antimicrobial resistance, increase of health services cost and side effects, even morbidity and mortality. Inappropriate antibiotic consumption (*underdose*) causes to the development of microbial resistance which is likely to lead to reduction in the effectiveness of many antibiotics.[38-40] The microbial resistance has been reported worldwide that varies by geographic region with highest level in Asia-Pacific countries. In Europe, 30% of pediatric patients experienced resistant bacteria infections, in Middle East, 90% of newborns with sepsis experienced resistant bacteria infection, in South East Asia, 83% of children experienced *E. coli* resistant to first line antibiotics, in Sub-Sahara Africa, 66% of neonatal sepsis and meningitis were caused by bacteria resistant to antibiotics, and in USA, 20% of pediatric patients receiving colistin to treat already MDR Gram negative bacteria developed resistance.[41,42]

Infections caused by resistant bacteria are difficult to treat and result in higher health service cost due to prolonged hospital stays and increased morbidity and mortality. The health services cost significantly increases due to the problem of inappropriate antibiotic

use.[43] In US, almost $ 100 million are spent annually to treat pediatric patients with resistant bacterial infections.[44] It was estimated that the cost of drug-related morbidity and mortality was $177.4 billion in 2000 in USA. Hospital admissions accounted for nearly 70% ($121.5 billion) of total costs, followed by long-term-care admissions, which accounted for 18% ($32.8 billion).[5] In Saudi Arabia, the total estimated average cost of related problems annually was $122 billion including the cost of non-compliance was $36 billion, the cost of adverse reaction $31 billion, and the cost of indication without medications problems was $24 billion.[45]

Antimicrobial resistance due to antibiotic misuse is one of the most important public health problems worldwide. In 2016, World Health Organization estimated that infection caused by multidrug resistant bacteria result in 700,000 deaths across all ages, of which about 200,000 are newborns.[46] Recent data reported among 4.95 million death globally in 2019, 1.27 million deaths occurred directly due to multidrug resistant bacteria infections. The highest death burden was reported in Sub-Saharan Africa and South Asia.[47]

CONCLUSION

Drug-related problems on antibiotic therapy has become a growing threat for pediatric patients beside the disease itself. The majority of the DRPs is related with underdose, overdose, drug interactions, therapy without indications, and drug compliance. The factors associated with the DRPs are complex including cultural, cognitive, educational, and socio-economic factors integrated at the level of patients or parents, physicians and pharmaceutical industries. Furthermore, the DRPs lead several impacts such as antimicrobial resistance, increase of health services cost and side effects, even morbidity and mortality. The role of clinical pharmacists, physicians and other health workers in education of patients or their parents is needed in order to minimize the DRPs incidence.

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