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A NARRATIVE REVIEW OF ANTIBIOTICS USED IN UPPER RESPIRATORY TRACT INFECTION AMONG PEDIATRIC PATIENTS IN INDONESIA

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Abstract: **Upper respiratory tract infection (URTI) is one of the leading causes of infectious disease and disease mortality in the world. Mortality is very high among infants, children and elderly, especially in low- and middle-income countries. Irrational administration of antibiotics related to the indication, type of drug, dose, and duration of antibiotics can lead to microbial resistance leading to morbidity and mortality of children.**

Objective: to assess the characteristics of antibiotic used in URTI infection among pediatric patients.

Methods: narrative review with inclusion criteria, namely the literature from 2010-2020 which uses a pediatric population of 0-12 years, uses interventions in the form of antibiotics, compares antibiotic administration, evaluates outcomes in the form of rationality drug use and exclusion criteria, namely literature that uses a population> 12 years and does not contain rationality drug use. Through search engines in the form of Garuda Portal, Lembaga Ilmu Pengetahuan Indonesia, and Google Scholar with the keywords antibiotic, upper respiratory tract infection (URTI), pediatrics, and Indonesia obtained 338 journals that are ready to be reviewed. A total of 9 journals are suitable as references in writing this review. The data obtained are in the form of qualitative and quantitative data which are then arranged systematically according to each topic discussed so that a conclusion is obtained that represents the entire content of the review.

Discussion: Characteristic of antibiotics used in URTI among pediatric patients are diagnosed with pharyngitis. The types of antibiotics that most widely used is amoxicillin with based on parameters of the rational use by Ministry of Health of the Republic of Indonesia 2012, most of the antibiotics were given in the precise indication

Conclusion: The most types of antibiotics used was amoxicillin which most of them were given in the right indication

Keywords: **Antibiotics, Upper Respiratory Infection (URTI), Pediatrics.**

1. INTRODUCTION

Upper respiratory tract infection (URTI) is one of the main causes of morbidity and mortality of infectious diseases in the world. In general, URTI is caused by polymicrobials. Pathogens that cause URTI can be transmitted through several ways, including aerosols, droplets, and direct contact with pathogens. The incubation period between one pathogen and another is different. Symptoms of URTI that appear, such as erythema, edema, mucous secretions, and fever are the result of the work of the host immune system against pathogens and from toxins produced by pathogens.[1] The mortality rate is very high in infants, children, and the elderly, especially in countries with low and middle income per capital.[2]

Child mortality cases due to URTI in developing countries are 2-6 times higher than in developed countries. The prevalence of URTI in Indonesia in 2013 was 25% with the highest incidence occurring in the 1-4 year age group at 25.8% and followed by the <1 year age group at 22%.[3] URTI in children usually causes mild symptoms so it is often considered trivial and does not get special attention. These mild symptoms usually also do not hinder children's activities, making it easier for transmission to occur. The ease of transmission has been studied in relation to the imperfect adaptive immune system, nutritional status of children, immunization status, and not getting exclusive breastfeeding.[4] The average Indonesian child can suffer from ISPA 6-8 times per year, even 10-15% of children experience 12 infections each year. The geographic influence of Indonesia as a tropical country which is a good place for an infection to develop has to an increases in URTI cases in Indonesia.[5]

The high prevalence of URTI has resulted in the high use of antibiotics which in clinical practice their use is often considered excessive. The management of URTI should not always use antibiotics because some cases can be caused by viruses.[6] Management of URTI in children primarily precedes supportive therapy and can improve within a week or two without antibiotics. Antibiotics that are often used in pediatric patients suffering from URTI include amoxicillin, cotrimoxazole and cefotaxime.[7] In Indonesia in 2013, the level of antibiotic use in non-specific URTI and non-pneumonia was a relatively high figure, namely 47.8%. Based on these data, children as the age group with the highest incidence are also the age group most at risk of irrational antibiotic use.[8] Rational use of drugs is when patients receive medication according to their clinical needs, in doses according to their needs, in an appropriate time period and at a cost affordable to most people. Especially for pediatric patients, the ideal treatment should be based on the child's age, psychological condition, and weight. The formation of organs that is still imperfect in children causes different responses to drugs.[9]

The behavioral impact of using irrational antibiotics leads to increased bacterial resistance and an increase in unwanted side effects. The problem of bacterial resistance to antibiotics is not a personal problem for a country but has become a worldwide health problem. One way to overcome this is by using antibiotics rationally, monitoring and evaluating the use of antibiotics systematically, standardized and regularly carried out in hospitals or in public health centers, and intervening to optimize the use of antibiotics.[8] Based on the high prevalence of URTI in children and the incidence of cases and the impact of inappropriate antibiotic use, the authors are interested in examining the use of antibiotics in children with URTI. In this narrative review based on a literature search completed from December 2020 until February 2021, researcher sought to review characteristic of antibiotics used in URTI among pediatric patients in Indonesia.

2. METHODS

Sources of information

Literature searches conducted during October-November 2020 against literature obtained from previous researchers in the form of national and international journals using the database such as Portal Garda Rujukan Digital (GARUDA), Lembaga Ilmu Pengetahuan Indonesia (LIPI), and Google Scholar

Search terms & delimiting

Literature search is carried out by keywords and using filters in the form of Medical Subject Headings (MeSH) and text words so that it can make it easier to find the literature to be used. The keyword filters used were: URTI, pediatric, antibiotic, and Indonesia.

Selection criteria employed

The strategy used in finding articles is the PICOS which consists of; 1) Population that is a study using a population of pediatric patients aged 0-12 years with URTI; 2) Intervention that is studies evaluating treatment interventions in the form of antibiotics; 3) Comparison that is the comparison intervention groups used were administration of antibiotics; 4) Outcome that is studies that describe the intervention given in the form suitability of use (precise of indication, kind, dosage, duration, and frequency). Publications eligibility criteria included those which published from 2010 to 2020 in national and international journals.

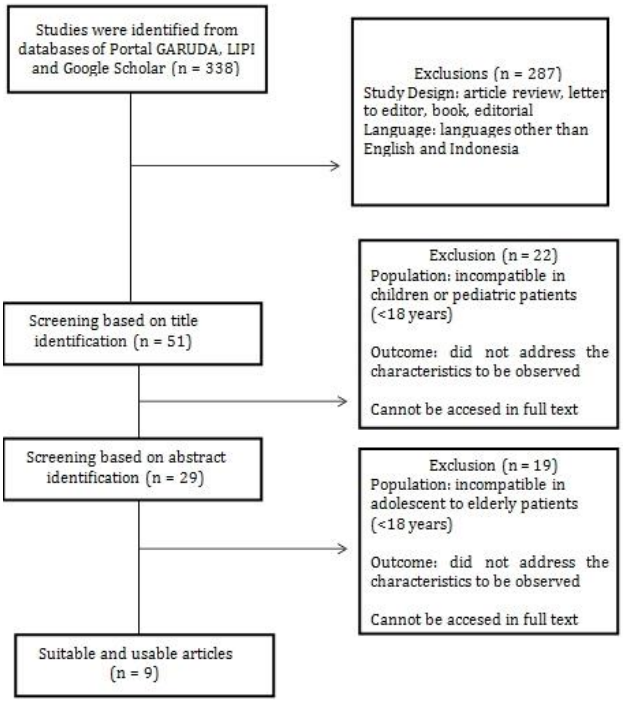

Figure 1. Literature Search Flow Diagram

Based on the results of a literature search through the database that was previously mentioned using keywords and filters (Figure 1), 338 articles were obtained. Furthermore, a selection was carried out in the form of screening based on the title and abstract so that there were 29 articles. A total of 29 articles were then analyzed thoroughly using inclusion and exclusion criteria so that there were 9 articles that could be used in this narrative review

3. RESULTS

Based on the table below (Table 1), the majority of the patients in the articles were diagnosed with pharyngitis. It was followed by tonsillitis, allergic rhinitis, sinusitis, and laryngitis. Pharyngitis is an inflammation of the pharyngeal mucosa and often extends to the surrounding tissue. Pharyngitis usually occurs together with tonsiiitis, rhinitis and laryngitis. Pharyngitis affects children aged 0-5 years in the region with warm climate.[10] Pharyngitis is also found in adults who still have school-age children or work at children's environment. The symptoms that arise in acute pharyngitis depend on the microorganisms that accompany it. Acute pharyngitis caused by bacteria having symptoms of severe headache, fever or chills, malaise, painful swallowing, vomiting and possibly coughing but rarely occurs. Pharyngitis caused by viruses usually has symptoms of a sore throat severe and may be accompanied by coughing, hoarseness and substernal pain. Then, symptoms in fungal pharyngitis is sore throat and swallowing pain. On examination, white plaques appear in the oropharynx and other pharyngeal hyperemic.[10]

The second most common URTI identified in literature search was tonsillitis. Tonsillitis is an inflammation of the palatine tonsils that are a part of Waldeyer's ring. The Waldeyer ring consists of an arrangement of lymph glands found in the in the oral cavity, namely pharyngeal (adenoid) tonsils, palatine tonsils (faucial tonsils), lingual tonsils (tonsils base of the tongue), Eustachian tube tonsils (lateral pharyngeal wall band or Gerlach's tonsils). Acute tonsillitis usually caused by Streptococcus bacteria β hemolyticus, Streptococcus viridans and Streptococcus pyogenes, can also caused by a virus. The symptoms of viral tonsillitis are more like a commond cold with taste sore throat. Epstein Barr virus is the most common cause. Hemophilus influenzae is a cause of acute suppurative tonsillitis. While the symptoms of bacterial tonsillitis will cause an inflammatory reaction in the form of leucocytes polymorphonuclear to form detritus.[11]

The third common cases of URTI in this study was acute infectious rhinits. Acute infectious rhinitis is an acute inflammation of the nasal mucosa characterized by symptoms of rhinorrhea, nasal obstruction, sneezing and accompanied by general symptoms of malaise and body temperature rises. Rhinitis is caused by a viral infection (Rhinovirus, Myxovirus, Coxsakie virus and ECHO virus) or bacterial infection especially Haemophylus Influenza, Steptococcus, and so on. The initial symptoms of acute rhinitis in the prodromal staidum are indeed similar to allergic rhinitis but what distinguishes it include the presence of common symptoms (malaise, rise of body temperature) and secret which then turn

thick. Secret is initially watery, clear then turns thick and sticky (mucoid) in color yellow contains pus and bacteria (macopurulent).[12]

This study found that the most widely used antibiotic treatment were amoxicillin followed by cotrimoxasol, cefadroxsil, cefikxime, cefotaxim, azithromycin, erythromycin, and ceftriaxone from the most to the least frequency. The most widely used antibiotic class is the betalactam class antibiotic, derived from penicillin, namely amoxicillin especially in one of URTI type, pharyngitis Amoxicillin works by inhibiting the formation of bacterial cell walls. Amoxicillin which is a derivative of penicillin is free of toxic properties, most of the severe adverse effects occur due to hypersensitivity. This antibiotic is the first line antibiotic for URTI patients.[13] Giving a single amoxicillin with no combination can have benefits such as preventing the risk of drug interactions, reducing side effects and reducing costs so that therapy costs are cheaper. The amoxicillin dosage forms given to URTI patients are usually syrup and tablets. Syrup is the most widely used dosage form with the consideration that it is easier for the patient to take the medicine. This is because the patient is a toddler who will find it easier to take medicine if the medicine is in syrup.[13,14]

The second most widely used antibiotic based on the results of a literature search was cotrimoxazole. Cotrimoxazole is one class of sulfonamides, which is a combination of trimethoprim and sulfamethoxazole which is often used for the treatment of lung infections. Cotrimoxazole competing against bacteria by inhibiting the use of paraaminobenzoic acid during the synthesis of dihydrofolate by bacteria. This ability gives rise to a bacteriostatic mechanism. Cotrimoxazole also reversibly inhibit the enzyme dihydrofolate reductase, which is an enzyme that activates the metabolic pathway of folic acid by converting dihydrofolate to tetrahydrofolate. Cotrimoxazole is actually the first antibiotic of choice in the treatment of URTI, especially in developing countries. Cotrimoxazole is the first choice because this antibiotic is very effective, easy to administer, and inexpensive. The cotrimoxazole dosage forms given to URTI patients are usually syrup and tablets. Syrup is the most widely used dosage form with the consideration that it is easier for the patient to take the medicine.[13,14]

The third most widely used antibiotic based on the results of a literature search was cefadroxil. Cefadroxil is a broad spectrum antibiotic that is effective for infections caused by the Streptococcus pyogenes bacteria, which is a hemolytic Group A Streptocci. Streptococcus pyogenes is the most common bacteria causing pharyngitis. Cefadroxil binds and inactivates the penicillin-binding protein (PBP) located on the inside of the bacterial cell wall membrane. PBP is an enzyme that is involved in the terminal stage of bacterial cell formation and changes in the shape of the cell wall during growth and division of bacterial cells. PBP inactivation disrupts the cross-linking of the peptodiglycan chain which is needed to maintain cell wall strength and rigidity and result in cell lysis. The cefadroxil dosage forms given to URTI patients are usually syrup and tablets.[15]

4. DISCUSSION

Upper Respiratory Tract Infection

Acute upper respiratory tract infection (URTI) is an acute respiratory infection that attacks the throat, nose and lungs that lasts approximately 14 days. URTI affects the structure of the ducts above the larynx, but most of these diseases affect the upper and lower tracts stimulant or sequentially.[16] URTI is a disease that attacks one part and or more of the respiratory tract, starting from the nose to the alveoli including adnexal tissue such as the sinuses, middle ear cavity and pleura. According to WHO (2007) URTI is defined as an acute respiratory disease caused by an infectious agent that is transmitted human-to-human . The onset of symptoms is usually rapid, that is, within a few hours to several hours.[9]

URTI is still one of the major public health problems. This is due to the high morbidity and mortality rates for infants and toddlers due to URTI . URTI is more common in children. The immune system of children is very different from adults because the body's defense system is not yet strong. With the child's body condition that is still weak, the process of spreading the disease becomes faster. In a year, a child in the world on average can experience 6-8 times URTI disease. In developed countries, the incidence of URTI has reached 50% of all diseases suffered by children under 5 years of age and 30% of all diseases suffered by children aged 5-12 years.[17]

The etiology of URTI has more than 300 types of bacteria, viruses, and rickets. Bacteria that cause URTI include the genus Streptococcus, Staphylococcus, Pneumococcus, Hemophilus, Bordetella, and Corynebacterium. Viruses that cause URTI include the Mexovirus, Adenovirus, Coronavirus, Pikornavirus, Mycoplasma, Herpesvirus, and others. Apart from organic matter, inhaled dURTI pollution such as wood fuel which contains substances such as dry base, ash, carbon, hydrogen, sulfur, nitrogen and oxygen can also cause URTI.[18]

Clinical symptoms URTI is different depending on the etiology of infection Common clinical findings in URTI caused by viruses include: pharyngeal erythema, exudate of pharynx and tonsils, presence of superficial vesicles or ulcers on the palate, conjunctivitis, tonsillar hypertrophy, cough, diarrhea, fever. Frequent clinical findings of URTI caused by bacteria include: erythema, swelling, and the appearance of exudate on the pharynx and tonsils, temperature 38.3 degrees or higher, absence of conjunctivitis, cough, and rhinorea.[17]

In general, URTI therapy is symptomatic therapy to relieve symptoms, and causal therapy to eliminate causes with antibiotics. Most URTIs are diagnosed and treated at home, and go away without a prescription. Therefore, the patient should be educated for symptomatic treatment at home if there are signs and symptoms of URTI disease. It is also important to recognize the types of pathogens (both viruses and bacteria) that cause URTI to be done in order to choose the appropriate antiviral or antibacterial agent. Usually, paying attention to local trends regarding the prevalence of URTI -causing microorganisms and local resistance patterns, can be the key to selecting suitable therapies for the type of pathogen. URTI is very rarely cause permanent disability or death, however, they often interfere with a person's health activities. Usually URTI are diagnosed and treated at home, and can be cured without a prescription. However, if the infection occurs continuously, it can cause serious complications.[2]

Types of URTI among pediatric in Indonesia

According to the Indonesian Ministry of Health in 2012, the classification of URTI can be differentiated based on the severity of the symptoms caused, namely the signs and symptoms mild (not pneumonia), moderate (moderate pneumonia / pneumonia), and severe (severe pneumonia). Colds such as rhinitis, pharyngitis, tonsillitis and other upper airway diseases are classified as not pneumonia.[2] Based on the classification most frequently used by clinicians, URTI is divided into several classifications according to clinical symptoms, namely: acute infectious rhinitis, pharyngitis and tonsillitis, otitis media, acute sinusitis, laryngitis, laryngotracheo-bronchitis, epiglottitis, acute bronchitis, acute bronchiolitis, and pneumonia. Until now, there have been no studies concluding URTI prevalence data among pediatric in Indonesia nationally. URTI among pediatric has a high cost to society, being responsible for absenteeism from school and unnecessary medical care, and sometimes is occasionally associated with serious sequelae.[19]

Table 1: Literatures Searched In This Study

Reference	Sample	Type URTI	Type Antibiotic	Right Indication	Right Drug	Right Dose	Right Duration
Sugiarti *et al.*, 2015	120 individuals, ages 0-5 years	URTI not pneumonia like influenza	Amoxicillin, Cotrimoxasol	24.2% had an accurate indication	100% had an accurate drug	The majority of the dose were over (91.1%)	NA
Dewi *et al.*, 2020	51 individuals, ages 0-5 years	Pharyngitis and tonsillitis, and sinusitis	Amoxicillin, Cotrimoxasol	100% had an accurate indication	NA	Correct dosage (100%)	Less duration (100%)
Albertin *et al.*, 2018	396 individuals, ages <12 years	Pharyngitis and tonsillitis	Cefadroxil, Cefixime, Azithromycin, Erythromycin	69.79% had an accurate indication	70.83% had an accurate drug	The majority of dose were less (85.37%)	The majority of the duration is less (92.68%)
Utami *et al.*, 2017	56 individuals, <12 years of age	Tonsillitis, pharyngitis, sinusitis and laryngitis	Cefotaxime, Ceftriaxone, Cefadroxil, Gentamicin, Ampicillin	75% had an accurate indication	62.5% had an accurate drug	The majority of the dose were over (89.58%)	NA
Maakh *et al.*, 2017	366 individuals, ages <5 years	Mild URTI /not pneumonia	Amoxicillin, Cotrimoxazole, Combination	NA	NA	Incorrect dose: more and less	The majority of the duration is more (100%)
Sugiharta *et al.*, 2018	223 individuals, ages 0-5 years	URTI not pneumonia like influenza	Amoxicillin, Cotrimoxazole	NA	NA	The majority of the dose were over (59.53%)	The majority of the duration is less (76.19%)

Umar, 2020	40 individuals, ages 0-12 years	influenza, sinusitis and pharyngitis	Ceftriaxone, Cefadroxil, Cefotaxime, Cefixime	100% had an accurate indication	100% had an accurate drug	NA	NA
Grassela *et al*., 2018	340 individuals, ages 0-12 years	Allergic rhinitis (with and without secondary infections), pharyngitis, tonsillitis, laryngitis, sinusitis	Cefixime, Erythromycin, Cefadroxil, Azithromycin, Erythromycin	91.72% had an accurate indication	72.94% had an accurate drug	Majority of correct dose (72.62%)	The majority of duration is correct (56.76%)
Pramita *et al*., 2019	24 individuals, ages 0-12 years	Pneumonia, sinusitis, pharyngitis, bronchitis	Amoxicillin, Cefotaxime, Cefadroxil, Cefixime, Ceftriaxone, Azithromycin	NA	NA	Majority of correct dose (91%)	NA

NA : not available

Antibiotics prescribing for URTI among pediatric

Antibiotic use in childhood URTIs remains contentious since more than 90% of the infections are of viral aetiology. The reasons cited for prescribing antibiotics include diagnostic uncertainty, socio-cultural and economic pressures, concern over malpractice litigation and parental expectations of an antibiotic. Research found giving antibiotics can accelerate the healing of URTI disease compared to only giving symptomatic drugs, besides that by giving antibiotics to prevent further infection from bacteria administration, the selection of antibiotics in this disease must be considered carefully so that there is no resistance to germs or materials in the future. Antibiotics are usually overprescribed for URTIs and promote antibiotic resistance. However, there is a role for defined indications, such as severe acute rhinosinusitis lasting more than ten days and severe acute otitis media. Fahey et al's quantitative systematic review of randomised controlled trials comparing antibiotics to placebo for paediatric URTIs concluded that antibiotic treatment did not alter clinical outcome or reduce complication rates. The authors do, however, make the point that the efficacy of antibiotic treatment may be greater in a subgroup with a higher baseline risk of developing complications.[20,21] In Indonesia, antibiotic therapy of choice the first commonly used to treat patients with URTI is cotrimoxazole (trimethoprim + sulfamethoxasol), and the second choice of antibiotic is amoxicillin.[2]

Optimizing the Use of Antibiotic

The use of antibiotic is said to be rational according to WHO if the patient receives the right antibiotic for clinical needs, in doses that meet the needs for a sufficient period of time, and at affordable costs for both individuals and society. This concept applies from the first time the patient comes to the health worker, which includes the accuracy of the assessment of the patient's condition, the right diagnosis, the right indication, the right type of antibiotic, the right dose, the right method and duration of administration, the right information, paying attention to affordability, patient compliance, and vigilance. side effects. Optimizing the use of antibiotics is imperative to guarantee adequate treatment, avoid toxicity and the occurrence of antibiotic resistance, both on a patient level and on a population level.[22]

The use of antibiotics is said to be a right indication if the therapy for URTI patients with a diagnosis of cough, cold and fever is not given antibiotics. This happens because according to the standards of the Indonesian Ministry of Health 2012, patients are only given enough home treatment without being given antibiotics. Each antibiotic has a specific spectrum of therapy so that the administration of the antibiotic is said to be an accurate indication if the drug given is in accordance with the symptoms of the disease that arises so that the drug can give the best effect. Bacterial resistance to an antibiotic is one example of the inaccuracy of using antibiotics both from the selection and determination of the use dose.[2,23] Based on the results of a literature search, that the majority of patients have received the prescription with the appropriate indication

The use of antibiotics is said to be a right drug if in giving the antibiotic, various aspects have been considered such as patient complaints, previous treatment therapy programs from doctors, whether there is drug allergy, drug interactions, and drug side effects.[23] According to standards from Indonesia, namely Pharmaceutical Care for Respiratory Infectious Diseases of the Indonesian Ministry of Health in 2012 explained that cotrimoxazole, cefadroxil, and azythromycin are

among the recommended antibiotics for URTI, so that the right amount of medicine given based on the results of a literature search is passable.[2]

Despite from the result of literature search that administration antibiotics had been precised in term right indication and right drug, it also can be concluded that most of the antibiotics were not given in the right dose and duration. According to the standards used, amoxicilin, cotrimoxazole, and cefadroxil therapy for pharyngitis and tonsillitis in under-five patients is 3 × 125 mg, 2 × 240 mg, and 2 x 30 mg respectively. The difference in providing standard doses of antibiotic is due to the empiric administration of antibiotics by clinicians and depends on the pattern of bacterial resistance in each study location.[13-15]

Long inappropriate administration of antibiotics can result in bacteria becoming resistant to antibiotics, can lead to failure of therapy and can even produce effects dangerous or unwanted side. The duration of antibiotic use is generally at least 5 days, but due to the many problems regarding antibiotic resistance and the existence of several considerations such as in patients at high risk of developing URTI, the use of oral antibiotics is extended to an average of 10 days.[24]

LIMITATIONS TO THE OVERVIEW

Based on the research, the dominant cross sectional study has limitations on the limited research sample. It is difficult to find cause and effect because of taking risk and effect data are carried out at the same time. It is potential for prevalence bias or incidence bias due to effects a risk factor over a period of time, can misinterpreted as a disease effect. It is also takes a large number of subjects, especially if there are a lot of variable that is studied. This narrative review found the risk of bias as a limitation of various studies. The biases found from this study include selection bias and information bias. In addition, the risk of bias can also be found from the literature search due to the limited number of studies regarding the review of antibiotics used in URTI among pediatric patients.

5. CONCLUSION

Based on the results of a literature search found that one of the most common feature of URTI is pharyngitis, the types of antibiotics that most widely used is amoxicillin, with based on parameters of the rational use by Ministry of Health of the Republic of Indonesia 2012, most of the antibiotics were given in the right indication (precise indication). Characteristics of antibiotics used in URTI among pediatric patients were various.

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