

RECEIVING CONTINUOUS ANTIBIOTIC PROPHYLAXIS

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Keywords: vesicoureteral reflux, urinary tract infections, antibiotics

Abstract: Continuous antibiotic prophylaxis represents an initial management strategy for decreasing the risk of urinary tract infections in children with vesicoureteral reflux. A significant number of cases resolve spontaneously in time, reason for which continuous antibiotic prophylaxis is not required in every patient with this disorder. It is mandatory to select the patients who need continuous antibiotic prophylaxis according to their risk group. We do not have a lot of scientific evidences about what is better or not for these patients, but the main objective for the case management is to maintain the renal function, by minimizing the risk of pyelonephritis, renal scars and its consequences such as hypertension or renal failure. The selection of these patients who do not require continuous antibiotic prophylaxis is difficult, and the prophylaxis remains the safest method in most of the cases. To take the best decisions for our patients, it is important to consider the last published guidelines and studies.

INTRODUCTION

Continuous antibiotic prophylaxis represents an initial management strategy for decreasing the risk of retrograde urinary tract infections in children with primary vesicoureteral reflux, because a significant number of cases resolve spontaneously in time.(1,2)

The drugs that are most commonly prescribed among the pediatric population in both the hospital and pediatric clinics are antibiotics.(3) Often, antibiotics are unnecessarily recommended, many children receive antibiotic treatment for viral etiology infections.(4) Studies have shown that up to 50% of antibiotics prescriptions are prescribed without any justified reason.(5,6)

Due to inadequate prescribing of antibiotic treatment, it developed multi-drug resistant pathogenes, with an impact on the global public health, with the delay of the therapeutic response, prolonged hospitalization period and increasing the costs regarding the medical assistance.(7,10) The European Antimicrobial Resistance monitoring system has seen a significant increase in multidrug-resistant bacteria in the last years.(11)

However, there are conditions in which the specialized guidelines recommend the continuous administration of antibiotic therapy, especially in the vesicourethral reflux in order to prevent acute pyelonephritis.

Vesicourethral reflux is an anatomical and/or functional disorder, with potentially serious consequences, such as high blood pressure, renal scars, or renal failure.(12) This condition is a common cause of childhood hypertension.

Studies have shown that 10-20% of children with vesicoureteral reflux will develop high blood pressure or renal failure.(13)

Continuous prophylaxis with antibiotics is not required in every patient with this disorder. It is mandatory to select the

patients who need continuous antibiotic prophylaxis according to their risk group.(14-16)

MATERIALS AND METHODS

A performed analysis of PUBMED electronic database was searched for studies written in English published between January 2015 to January 2020 using the following search terms: urinary tract infections, vesicoureteral reflux, continuous antibiotic prophylaxis, antimicrobial prophylaxis, with importance of this pathology in children, up to the age of 18 years old.

There were included: original research articles, meta-analyses, randomized clinical trials, systematic reviews, describing antibiotic prophylaxis for urinary tract infections in children diagnosed with vesicoureteral reflux.

"Continuous antibiotic prophylaxis" was defined as daily antibiotic dosing for at least 6 months.

The data was correlated with the data presented in the Guidelines of the European Association of Urology-Pediatric Urology published in 2019.

RESULTS AND DISCUSSIONS

The recommendations of the Guidelines of the European Association of Urology-Pediatric Urology 2019

The scientific literature regarding the correct management of vesicoureteral reflux is limited. We do not have a lot of scientific evidence about what is better or not for these patients, but the main objective for the case management is to maintain the renal function, by minimizing the risk of pyelonephritis.(17)

The Guideline of the European Society of Urology - Pediatric Urology published in 2019 recommends that continuous antibiotic prophylaxis to be performed in both symptomatic and asymptomatic patients with a high grade of

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Article received on 15.01.2020 and accepted for publication on 24.02.2020

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reflux, if it associates vesicoureteral reflux with other lower urinary tract diseases or if the kidney presents an abnormal aspect.

It is not recommended for symptomatic or asymptomatic patients with a low grade of reflux, in which the kidneys have a normal aspect.(18)

Risk Group	Presentation	Initial treatment recommendation
High	Symptomatic male or female patients after toilet-training with: - high-grade reflux (grades IV-V) - abnormal kidneys - LUTD	- always for LUTD with CAP - intervention may be considered in cases of BT infections or persistent reflux
Moderate	Symptomatic male or female patients before toilet-training, with: - high-grade reflux - abnormal kidneys	- CAP - intervention may be considered in cases of BT infections or persistent reflux
Moderate	Asymptomatic patients with: - high-grade reflux - abnormal kidneys	- CAP - intervention may be considered in cases of BT, infections or persistent reflux
Moderate	Symptomatic male or female patients after toilet-training, with: - high-grade reflux - normal kidneys with LUTD	- always for LUTD with CAP - intervention may be considered in cases of BT infections or persistent reflux
Moderate	All symptomatic patients with: - normal kidneys - low- grade reflux - LUTD	- with or without CAP
Low	All symptomatic patients with: - normal kidneys - low-grade reflux - no LUTD	- no treatment or CAP
Low	All asymptomatic patients with: - normal kidneys - low-grade reflux	- no treatment or CAP in infants

Data published in the scientific literature

Numerous prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent urinary tract infections or renal scarring.

RIUVUR, one of the largest multicentric trials, a randomized, double-blind, placebo-controlled study, in which 607 children were included, aged between 2-72 months diagnosed with vesicoureteral reflux (I-IV). This study demonstrated that continuous antibiotic prophylaxis reduced the risk of recurrence of urinary tract infections in 50% of cases, but did not have positive results in renal scarring and its consequences such as hypertension or renal failure, with the secondary effect, increasing the antimicrobial resistance. In patients with grade III or IV of vesicoureteral reflux, but in the absence of lower urinary tract disease, the antibiotic prophylaxis had no significant benefit.(19-22)

A three-year retrospective study, in which 81 children were included diagnosed with vesicoureteral reflux under the age of 2 years old, following a febrile or symptomatic urinary tract infection, with urine culture that confirmed the pathogens. Each child received trimethoprim-sulfamethoxazole (TMP-SMX) as antibiotic prophylaxis, regardless of the outcome of uroculture.

There were excluded from the study the children with a history of ectopic ureter, megaureter, urethral duplication,

ureterocele, neurological or structural abnormalities of the bladder, renal failure, or those who followed continuous antibiotic prophylaxis with a preparation other than TMP-SMX.

Of the 81 children with primary vesicoureteral reflux, the mean age at the diagnosis of the vesicoureteral reflux was 5.3 months, the boys-girls ratio was 67:14. The age of diagnosis in 64 patients were ≤ 6 months old, 11 patients were aged between 6–12 months, and 6 patients were older than 12 months. The vesicoureteral reflux grade at diagnosis was classified from 1 to 5. Bilateral vesicoureteral reflux was observed in 42 patients and renal scarring in 54 patients. The pathogens causing urinary tract infections were *Escherichia Coli* (58.0%), *Enterococcus* (18.5%), *Klebsiella* (8.6%), *Enterobacter* (7.4%), *Proteus* (5.0%) and *Pseudomonas* (2.5%). Based on the susceptibility to TMP-SMX, 51.9% children were classified into the susceptible group and 48.1% children in the resistant group. The resistant group was noted to have more frequent higher grade of vesicoureteral reflux and non-*Escherichia Coli* pathogens, compared with susceptible group. Age, sex and initial renal scarring were not significantly different between the groups.(23)

In the studies it was highlighted that the continuous antibiotic prophylaxis has no benefit or has a minimal benefit on the cases of low grade vesicoureteral reflux. To prevent recurrent urinary tract infections, continuous antibiotic prophylaxis is useful in patients with high grade reflux, respectively III or IV. Its usefulness in preventing the occurrence of other kidney disease has not been demonstrated. Continuous antibiotic prophylaxis has a greater benefit in children trained to use the toilet or those with lower urinary tract disorders.(24-29)

A study that used data from the RIVUR study revealed that there was no significant difference in the recurrence of urinary tract infections in children with continuous antibiotic prophylaxis who had resistance to TMP-SMX compared with those who were sensitive to TMP-SMX.(30)

A Japanese study that evaluated the optimal period of continuous antibiotic prophylaxis in children diagnosed with vesicoureteral reflux revealed that prophylaxis should be continued at least one year after the last urinary tract infection, and patients with a high grade of reflux have an increased risk of recurrent urinary tract infections.(31)

Despite the benefits of the continuous antibiotic prophylaxis in cases of vesicoureteral reflux, the main concern regarding antibiotic prophylaxis is the increasing number of multidrug-resistant pathogens.(32-34)

A Cochrane study on long-term antibiotic prophylaxis for preventing the recurrence of urinary tract infections included 16 studies in which 2036 children were included. Different situations were compared, cases where continuous antibiotic prophylaxis was opted, versus placebo, or cases where no treatment was given. It was concluded that antibiotic prophylaxis may reduce the risk of recurrent symptomatic urinary tract infections among children who have had in their medical history one or more urinary tract infections, but given the risk of increasing the antibiotic resistance, the benefit is quite small.(35)

A recent study in the United States, conducted by family physicians, which included children under the age of 12 months, concluded that continuous antibiotic prophylaxis is useful in preventing recurrent urinary tract infections in patients diagnosed with vesicoureteral reflux.(36)

CONCLUSIONS

The selection of the patients who do not require continuous antibiotic prophylaxis is difficult, which is why the use of prophylaxis is the safest method in most of the cases. The

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decision should also take into account the presence of risk factors for urinary tract infections, for example young age, female sex, high grade vesicoureteral reflux, associated lower urinary tract disorders, if the patient is circumcised or if he is trained to use the toilet.

Even if the scientific literature does not provide us with accurate information on the duration of continuous antibiotic prophylaxis in patients with vesicoureteral reflux, a practical approach would be antibiotic prophylaxis until the children is trained to use the toilet and be sure that there are no other diseases of lower urinary tract. If the vesicoureteral reflux is associated with other conditions of the lower urinary tract, continuous antibiotic prophylaxis becomes mandatory. After discontinuation of prophylaxis, active surveillance of urinary tract infections is required.

The follow-up of patients, the decision to carry out an anti-reflux procedure or the discontinuation of continuous antibiotic prophylaxis depends on the personal preferences, the attitude of the patients but also of their caregivers. It is important to discuss with the family, both the advantages and disadvantages.

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