

Utility of the study of antibiotic activity by bioassay in the management of urinary tract infection in pediatric patients

Utilidad del estudio de la actividad antibiótica mediante bioensayo en el manejo de la infección del tracto urinario en pacientes pediátricos

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Abstract

Urinary tract infection is the most frequent non-respiratory bacterial infection in pediatrics. The aim of this study was to determine the presence of antibiotic activity in urine samples and to evaluate its possible influence on the clinical management of pediatric patients. One hundred and thirty-eight patients with clinical suspicion of urinary tract infection were included. There was previous use of antibiotics in 30 urine samples, but only in 18 of these samples antibiotic activity was found by bioassay. This study shows a high percentage of pediatric patients with antibiotic use prior to urine collection. Biochemical parameters of the urine, such as the presence of more than 25 leukocytes per field or positive nitrites, should alert us to the possibility of bacterial infection. The evaluation of the antibiotic activity in the urine of pediatric patients in parallel with microbiological culture and biochemical parameters allows the optimization of the antibiotic treatment.

Keywords: antibiotic; infection; pediatric; urine.

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Resumen

La infección del tracto urinario es la infección bacteriana no respiratoria más frecuente en pediatría. El objetivo de este estudio fue determinar la presencia de actividad antibiótica en muestras de orina y evaluar su posible influencia en el manejo clínico de los pacientes pediátricos. Se incluyeron 138 pacientes con sospecha clínica de infección del tracto urinario. Hubo uso previo de antibióticos en 30 muestras de orina, pero sólo en 18 de estas muestras se encontró actividad antibiótica mediante bioensayo. Este estudio muestra un alto porcentaje de pacientes pediátricos con uso de antibióticos antes de la recolección de la orina. Los parámetros bioquímicos de la orina, como la presencia de más de 25 leucocitos por campo o nitritos positivos, deben alertarnos sobre la posibilidad de una infección bacteriana. La evaluación de la actividad antibiótica en la orina de pacientes pediátricos, junto con el cultivo microbiológico y los parámetros bioquímicos, permite optimizar el tratamiento antibiótico.

Palabras clave: antibiótico; infección; orina; pediátrico.

INTRODUCTION

Urinary tract infection is the most frequent non-respiratory bacterial infection in pediatrics and it represents a diagnostic challenge, since the only manifestation in this population is usually the presence of fever without an obvious focus. The American Academy of Pediatrics recommends that, in all children with fever without apparent focus, a urine culture be performed before the start of antibiotic treatment, in addition to a biochemical and microscopic study of the sample (Shaikh, *et al.*, 2008; Shaikh, *et al.*, 2014).

In Europe, 9% of all prescribed antibiotics are for the treatment of urinary tract infections in the pediatric population, leading to an increasing incidence of antibiotic resistant urinary tract infections. In addition, in some cases, the microbiological study of urine does not provide useful information in the management of these infections due to the prior use of antibiotics (Bengtsson-Palme, *et al.*, 2018; Vásquez, *et al.*, 2017).

The aim of this study was to determinate the presence of antibiotic activity in urine samples and to assess its possible influence on the clinical management of pediatric patients.

MATERIAL AND METHODS

This is a descriptive, prospective, and observational study carried out in an area hospital with 591 beds (Seville, Spain), and it adhered to the ethical recommendations of the Declaration of Helsinki (World Medical Association, 2013). Pediatric patients treated from September 2020 to February 2021 at the hospital were studied. The inclusion criteria used

were patients under 5 years of age with clinical suspicion of urinary tract infection with at least one of the following symptoms: fever, hematuria, and dysuria. The exclusion criteria were patients with other recent infections (less than 6 months). Included patients were classified into two groups according to the result of the antibiotic activity bioassay: positive or negative.

The medical records of pediatric patients who met all inclusion criteria and none of the exclusion criteria were reviewed. The following clinical data were collected: a) Demographic data: age and sex; b) Signs and symptoms: fever, hematuria, and dysuria; and c) Treatment: previous use of antibiotics in the last 7 days. Two researchers also reviewed data collection forms independently to verify the data collected.

The biochemical study of the leukocytes and nitrites in urine samples was carried out using the Aution Eleven Analyzer (Menarini). For the microbiological study, samples were inoculated into biphasic blood culture vials (bioMerieux) as recommended by the American Society for Microbiology (Baron, *et al*, 2013).

The determination of antibiotic activity in urine samples was carried out by bioassay, according to the recommendations of The Pneumonia Etiology Research for Child Health Project (Levine, *et al*, 2012). At the time of sample collection, a 6 mm disk of sterile filter paper (Oxoid) was impregnated with 20 µl of urine and stored at -70 °C. The filter paper was placed on a Mueller-Hinton agar plate (Beckton Dickinson) inoculated with an antibiotic-sensitive strain of *Bacillus subtilis* (ATCC 6633). Growth inhibition around the disc was considered evidence of antimicrobial activity in urine samples. Each sample was studied in duplicate on separate plates and the diameters of the inhibition zone were expressed as the average of duplicate readings. Commercial ampicillin and vancomycin discs (Oxoid) were used as positive controls and discs inoculated with sterile saline as negative controls.

Data were processed using MedCalc 13.0 (MedCalc Software, Ostend, Belgium).

RESULTS

The study population consisted of 138 patients (73 males and 65 females) aged between 1 month and 5 years (median = 1.8 years).

Previous use of antibiotics was confirmed by reviewing medical records in 30 urine samples (21.7%). Only in 18 of these samples, antibiotic activity was found by bioassay; the median of the inhibition halos was 19 mm (range: 13-31 mm).

These 18 urine samples presented a negative result in bacteriological culture (Table 1). The antibiotic treatments indicated in these patients were amoxicillin, amoxicillin-clavulanate, mepifiline, phosphomycin, or cefixime.

Table 1.
Results of previous use of antibiotics, number of leukocytes, and bacteriological culture of the samples studied.

Bioassay	Previous use of antibiotics		Leukocytes on the test strip (μL)		Bacteriological culture	
	Yes	No	< 25	\geq 25	Positive	Negative
Positive (n=18)	18	0	3	15	0	18
Negative (n=120)	12	108	96	24	15	105

DISCUSSION

The results of this study show a high percentage (21.7%) of pediatric patients with antibiotic use prior to urine collection. This coincides with other works that demonstrate the use of antibiotherapy before taking the sample for the bacteriological study, which affects the clinical management of patients (Khennavong, *et al*, 2011; Rhodes, *et al*, 2010).

Biochemical parameters of the urine, such as the presence of more than 25 leukocytes per field or positive nitrites, should alert us to the possibility of bacterial infection and must be taken into account in the management of patients.

It would be interesting to consider the adequacy of the microbiological study of urine samples with a positive bioassay or where previous use of antibiotics is verified. The use of blood culture vials with resins capable of neutralizing the presence of the antibiotic or the use of molecular biology techniques could be very interesting alternatives in the microbiological study of these cases.

The absence of antibiotic activity in 12 of the urine of patients with previous antibiotic administration reveals the importance of considering their pharmacokinetics. This could be due to an antibiotic concentration below the detection limit of the bioassay, the absence of urinary excretion or its complete elimination at the time of sample collection.

The limitation of this study is that the concentration of antibiotic fluctuates in the dosing interval, decreasing the sensitivity of detection of antibiotic activity by bioassay, and this may affect the results.

In conclusion, the evaluation of the antibiotic activity in the urine of pediatric patients in parallel with microbiological culture and biochemical parameters allows the optimization of the antibiotic treatment. This fact would allow a much more effective approach to the laboratory study of urine samples.

Ethical aspects:

This work follows the ethical recommendations of the Declaration of Helsinki and was approved by the Seville Sur Clinical Research Ethics Committee.

Conflict of interest:

No conflicts of interest are declared by any of the authors.

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