Brief report

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Is it possible to extrapolate the rates of resistance of *Escherichia coli* from asymptomatic bacteriuria in pregnant women to those of *E. coli* in uncomplicated community-acquired UTI?

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ABSTRACT

Objective. Treatment of uncomplicated urinary tract infections in primary care is generally empirical without requesting urine culture and based on biased resistance data collected from selected patients, most of them having risk factors for the isolation of resistant microorganisms. In order to overcome the lack of information on the real resistance rates in uncomplicated UTI, we compared antimicrobial phenotype and genotype of *Escherichia coli* isolated from pregnant women with asymptomatic bacteriuria (culture always performed) with those from women with uncomplicated acute cystitis (culture rarely performed) of different age groups.

Material and methods. Between September 2017 and March 2018, 103 urines were randomly collected from pregnant women aged between 16 and 47 with asymptomatic bacteriuria (AB) (n=42), not hospitalized women in the same age range with uncomplicated acute cystitis (UAC) (n=31) and women older than 47 not hospitalized with UAC (n=30). Bacteria identification was performed using mass spectrometry and the antibiogram by broth microdilution. Genetic typification was carried out by pulsed-field gel electrophoresis.

Results. There are no significant differences between the groups of patients in the antibiotic susceptibility. Likewise, as expected, a wide genetic diversity is observed among the strains of *E. coli* studied without significant differences between the three groups.

Conclusions. We propose a simple model that could provide better guidance for selection of empirical antimicrobial therapy for non-pregnant women with UAC than do generic hospital antibiogram data based on reliably extrapolating the susceptibility data of strains isolated from pregnant women with AB as representation of women with community-acquired UAC.

Keywords: uncomplicated UTI, antibiotic resistance, asymptomatic bacteriuria, pregnant women

¿Es posible extrapolar las tasas de resistencia de *Escherichia coli* de bacteriurias asintomáticas en gestantes a las de *E. coli* en ITU no complicada adquirida en la comunidad?

RESUMEN

Objetivos. El tratamiento en atención primaria de las infecciones del tracto urinario no complicadas es generalmente empírico sin solicitar urocultivo y basado en datos de resistencia sesgados procedentes de pacientes seleccionados, muchos de ellos con factores de riesgo de aislamiento de microorganismos resistentes. Con el fin de solventar el déficit de información sobre las tasas de resistencia reales en ITU no complicada, comparamos el fenotipo antimicrobiano y genotipo de aislados de *Escherichia coli* procedentes de mujeres embarazadas con bacteriuria asintomática (cultivo siempre realizado) con aquellos procedentes de mujeres con cistitis aguda no complicada (cultivo raramente realizado) de diferentes grupos de edad.

Material y métodos. Entre septiembre de 2017 y marzo de 2018 se recogieron aleatoriamente 103 orinas de mujeres embarazadas con edades entre 16 y 47 años con bacteriuria asintomática (BA) (n=42), mujeres no hospitalizadas en el mismo rango de edad con cistitis aguda no complicada (CANC) (n=31) y mujeres mayores de 47 años no hospitalizadas con CANC (n=30). La identificación bacteriana se realizó por espectrometría de masas y el antibiograma por microdilución en caldo. La tipificación genética se llevo a cabo por electroforesis en gel por campo pulsado.

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Resultados. No hay diferencias significativas en la sensibilidad antibiótica entre los grupos de pacientes. De igual forma, y según lo esperado, se observó una amplia diversidad genética entre las cepas de *E. coli* estudiadas sin diferencias significativas entre los diferentes grupos.

Conclusiones. Proponemos un modelo sencillo que podría orientar mejor que los datos generales del hospital en la selección del tratamiento antimicrobiano empírico de mujeres no embarazadas con CANC, basado en extrapolar los datos de sensibilidad de cepas aisladas de mujeres embarazadas con BA como representación de mujeres con CANC adquirida en la comunidad.

Palabras clave: ITU no complicada, Resistencia antimicrobiana, bacteriuria asintomática, mujer embarazada

INTRODUCTION

Uncomplicated urinary tract infections (UTIs), mainly cystitis, are a frequent cause of primary care consultation. *Escherichia coli* is the microorganism most frequently involved [1]. Treatment is generally empirical and based on local susceptibility data without requesting urine culture [2-4].

These susceptibility data are based on the urine cultures submitted to laboratories but a high percentage of uncomplicated UTIs are treated empirically without performing a urine culture. In addition, many of these urine samples are from selected patients (with complicated UTI or with previous failed treatments), most of them having risk factors for the isolation of resistant microorganisms [5]. Therefore, the empirical treatment prescribed for uncomplicated cystitis is based on biased resistance data, which are in most cases from strains that cause complicated or recurrent UTIs that have been shown to be more resistant [6]. Real and representative data are required.

The guidelines for the management of pregnant women recommend to screen with urine culture for asymptomatic bacteriuria at the end of the first trimester or beginning of the second trimester [7]. This enables us to have reliable susceptibility results of *E. coli* isolated in this population, which could be representative of the population with uncomplicated UTI of similar or higher age.

The objective of the study, in order to overcome the lack of information on the real resistance rates in uncomplicated UTI, was to validate the hypothesis that there is no difference in population or susceptibility between *E. coli* isolated from urine cultures of pregnant women with asymptomatic bacteriuria and those isolated from women with uncomplicated acute cystitis of different age groups. If so, a susceptibility pattern of *E. coli* causing uncomplicated cystitis could be obtained easily and inexpensively.

MATERIALS AND METHODS

Between September 2017 and March 2018, 103 urines submitted to the microbiology laboratory were randomly collected. The samples were from women which, after reviewing their clinical history, met the inclusion criteria:

– Pregnant women aged between 16 and 47 at the end of the first trimester or beginning of the second trimester with asymptomatic bacteriuria (AB), considering this term when >10^5 UFC/ml of *E. coli* were isolated.

– Not hospitalized in the same age range with uncomplicated acute cystitis (UAC) and the isolation of >10^3 UFC/ml of *E. coli*.

– Older than 47 not hospitalized with UAC and the isolation of >10^3 UFC/ml of *E. coli*.

From the first group, 42 strains of *E. coli* were collected, from the second, 31 and from the third, 30.

Bacteria identification was performed using mass spectrometry (MALDITOF) and the antibiogram by broth microdilution (MicroScan panels). Genetic typification was carried out by pulsed-field gel electrophoresis (PFGE) following digestion with the restriction endonuclease XbaI with the purpose of measuring the genetic variation between the strains of the different patient groups.

In addition, cumulative susceptibility data of adults from primary care with significant isolation of *E. coli* in urine cultures during 2017 were obtained from our laboratory computer system.

Data were introduced in a database created for the study. The results of PFGE were analyzed with InfoQuestFP, using a cut-off point of 85% similarity, and the diversity index was calculated [8].

To test the statistically significant differences in the susceptibility and genetic variability of the strains among the 3 study groups, either the chi-square test or Fisher's exact test was performed. When the p-value was inferior to the alpha error (5%), a statistical significance was considered.

The project was approved by the Ethics Committee (CEIm 18/19)

RESULTS

The strains studied showed high susceptibility rates to all the antimicrobials tested except to ampicillin with no significant differences between the different groups (table 1).

Interestingly, when the susceptibility data of the total UAC strains of the study (n=103) are compared with the 2017 cumulative laboratory data (n=2,328), significant differences were observed in the susceptibility of *E. coli* to ampicillin (p = 0.008), cefotaxime (p=0.03), cotrimoxazole (p = 0.002), nalidixic acid (p = 0.01), ciprofloxacin (p = 0.001) and to gentamicin (p = 0.008) (table 2).

We observed 90 unique PFGE-profiles (34 from *E. coli* isolates of the AB group, 29 from the strains of patients with UAC aged between 16 and 47, and 27 from strains of the group older than 47 with UAC). The diversity index of the set of *E. coli* isolates was 87.38%. In table 3 the unique PFGE-pro-

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Table 1	Percentage of susceptibility of the 103 grouped strains studied and comparison between groups				
Antimicrobial agent	AB (n=42)	UAC (16-46 years) (n=31)	UAC (>47 years) (n=30)	p AB vs UAC (16-46 years)	p AB vs UAC (>47 years)
Ampicillin	54.14%	67.74%	53.33%	0.36	0.75
Amoxicillin clavulanate	93.02%	93.55%	90.00%	0.91	0.67
Cefotaxime	100.00%	100.00%	100.00%	1	1
Fosfomycin	100.00%	96.77%	100.00%	0.42	1
Cotrimoxazol	83.72%	83.87%	90.00%	0.83	0.59
Nalidixic acid	86.05%	77.42%	76.67%	0.22	0.20
Ciprofloxacin	95.35%	96.77%	86.67%	0.83	0.07
Gentamicin	93.02%	100.00%	100.00%	0.26	0.26

AB: asymptomatic bacteriuria; UAC: uncomplicated acute cystitis

files found are reported separately by the different groups of patients studied. There were no significant differences in the number of profiles.

DISCUSSION

Tan TY et al. provide evidence that laboratory antibiotic susceptibility reporting has a direct influence on antibiotic prescribing [9, 10]. Previous studies have shown that the susceptibility data of uropathogens provided by laboratories are not representative of those of uncomplicated UTI, leading to an overestimation of local resistance rates and the consequent inappropriate use of antibiotics in empirical treatment [11-13].

In our experience, we also observed significant differences after comparing the results obtained in this study with the cumulative laboratory UTI susceptibility data.

Following our local patterns and according to the guidelines recommendation not to use an antibiotic as empirical treatment in uncomplicated cystitis when the resistance is greater than 20%, ciprofloxacin (73.75% of susceptibility), cotrimoxazole (68.38% of susceptibility) or ampicillin (43.77% of susceptibility) could not be used as empirical treatment of UAC. However, taking into account the results of this research, the options for empirical treatment in women with uncomplicated UTI would be extended since all antibiotics could be used with the exception of ampicillin.

There are no significant differences between the groups of patients in the antibiotic susceptibility tested. Likewise, a wide genetic diversity is observed among the strains of *E. coli* studied without significant differences between isolates from women with AB and those from women with UAC acquired in the community regardless of patient's age. The genetic diversity found in most of the strains studied after performing the pulsed field is the expected in community-acquired UTI [14].

Table 2	Cumulative susceptibility data of significant isolates of *E. coli* in adults during 2017 in comparison with those of UAC.		
Antimicrobial agent	% susceptiblity (n=2,328)	UAC (n=61)	p
Ampicillin	43.77%	60.66%	0.008
Amoxicillin clavulanate	85.09%	91.8%	0.14
Cefotaxime	93.40%	100%	0.03
Fosfomycin	97.42%	98.36%	0.65
Cotrimoxazol	68.38%	86.88%	0.002
Nalidixic acid	61.68%	77.05%	0.01
Ciprofloxacin	73.75%	91.8%	0.001
Gentamicin	91.67%	100%	0.008

UAC: uncomplicated acute cystitis

A potential limitation of the study is the small sample size, but it takes long time to recover strains of *E. coli* from pregnant women with ABU.

We conclude that strains of *E. coli* from pregnant women with AB are similar in both genetic diversity and antimicrobial phenotype to those of women with UAC regardless of age. Given that *E. coli* urine isolates from all pregnant women with AB are generated routinely, we propose a reasonable, economical and simple model that could provide better guidance for selection of empirical antimicrobial therapy for non-pregnant women with UAC than do generic hospital antibiogram data. This model is based on reliably extrapolating the susceptibility data of strains isolated from pregnant women with AB as representation of women with community-acquired UAC.

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Table 3	Unique genetic profiles found in the 103 grouped strains studied and comparison between groups.				
	AB (n=42)	UAC (16-46 years) (n=31)	UAC (>47 years) (n=32)	p AB vs UAC (16-46 years)	p AB vs UAC (>47 years)
Unique profiles (n)	34	29	27	0.12	0.70
Diversity index	80.95%	93.55%	90.00%	-	-

AB: asymptomatic bacteriuria; UAC: uncomplicated acute cystitis

FUNDING

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest

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