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Impact of urinary selective antibiogram in primary care

Impacto do antibiograma seletivo nas uroculturas em cuidados primários

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ABSTRACT

Introduction: Selective reporting of antibiotic susceptibility test results (selective antibiogram), is increasingly recognized as one of the key strategies of antibiotic stewardship programs. The objective of this study is to determine the impact of selective susceptibility reporting on ciprofloxacin utilization and *Escherichia coli* susceptibility to ciprofloxacin in the outpatient setting. **Material and methods:** A selective reporting policy was created and implemented in 2011. The policy involves the non-reporting of ciprofloxacin susceptibility to *Enterobacteriaceae* isolated in a urine sample when there was susceptibility to other agents with narrow spectrum. The outcomes evaluated were outpatient ciprofloxacin utilization and *E. coli* susceptibility to ciprofloxacin between January 2011 and December 2018 **Results:** Between 2011 and 2018 we detected an increased susceptibility rate of *E. coli* to ciprofloxacin from 79% to 87% ($p < 0.001$) and a decreased incidence rate of *E. coli* resistant to ciprofloxacin from 2.52 to 0.87 ($p < 0.001$). The ciprofloxacin dropped from 0.75 defined daily doses (DHD) to 0.36 DHD and there was a compensatory increase in nitrofurantoin and fosfomycin utilization. **Discussion:** Our study showed that selective reporting can influence prescribing practice in a community level and encourages clinicians to select more narrow-spectrum and cost-effective antimicrobial agents in UTIs. **Conclusion:** Our results suggest that selective antibiogram should be considered an effective prevention strategy to reduce targeted antimicrobial utilization.

Key words: antimicrobial stewardship; *Escherichia coli*; ciprofloxacin.

RESUMO

Introdução: *A notificação seletiva dos resultados do teste de suscetibilidade aos antimicrobianos (antibiograma seletivo) é conhecida como uma das estratégias-chave dos programas de apoio à prescrição de antibióticos. O objetivo deste estudo foi determinar o impacto do antibiograma seletivo no consumo de ciprofloxacino e a suscetibilidade da bactéria* Escherichia coli *ao ciprofloxacino nos cuidados primários.* ***Material e métodos:*** *A política de notificação seletiva foi criada e implementada em 2011 e envolveu a não transmissão, no antibiograma, da suscetibilidade da família* Enterobacteriaceae *ao ciprofloxacino em amostras urinárias quando existia suscetibilidade a outros agentes com menor espectro. Os desfechos avaliados foram consumo de ciprofloxacino e evolução da suscetibilidade de* E. coli *ao ciprofloxacino entre janeiro de 2011 e dezembro de 2018.* ***Resultados:*** *Nesse período, um aumento foi detectado na taxa de suscetibilidade de* E. coli *ao ciprofloxacino, de 79% a 87% (*p *< 0,001). A taxa de incidência de* E. coli *resistente ao ciprofloxacino diminuiu de 2,52 para 0,87 (*p *< 0,001). O consumo de ciprofloxacino teve uma queda de 0,75 doses diárias definidas (DHD) para 0,36 DHD. Simultaneamente, um aumento compensatório foi observado no consumo de nitrofurantoína e fosfomicina.* ***Discussão:*** *Nosso estudo demonstrou que a utilização do antibiograma seletivo influenciou a prática de prescrição dos antimicrobianos e incentivou os clínicos gerais a selecionar antimicrobianos de espectro de ação mais reduzido e com melhor relação custo-benefício.* ***Conclusão:*** *Nossos resultados sugerem que a utilização de antibiogramas seletivos deve ser considerada uma estratégia eficaz na redução do consumo de determinados antimicrobianos.*

Unitermos: *programas de apoio à prescrição de antibióticos;* Escherichia coli*; ciprofloxacino.*

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RESUMEN

Introducción: *La notificación selectiva de resultados de la prueba de susceptibilidad bacteriana (antibiograma selectivo) es conocida como una de las estrategias clave de los programas de optimización de antimicrobianos. El objetivo de este estudio fue determinar el impacto del antibiograma selectivo en el consumo de ciprofloxacino y la sensibilidad de la bacteria* Escherichia coli *al ciprofloxacino en la atención básica.* ***Material y métodos:*** *La política de informe selectivo fue creada e implementada en 2011 e incluyó la no trasmisión, en el antibiograma, de sensibilidad de* Enterobacteriaceae *al ciprofloxacino en muestras urinarias cuando había sensibilidad a otros agentes de espectro reducido. Los desenlaces evaluados fueron el consumo de ciprofloxacino y la evolución de sensibilidad de* E. coli *al ciprofloxacino entre enero de 2011 y diciembre de 2018.* ***Resultados:*** *En esse período, se detectó un aumento en la tasa de sensibilidad de* E. coli *al ciprofloxacino, del 79% al 87% (*$p < 0,001$*). La tasa de incidencia de* E. coli *resistente al ciprofloxacino descendió de 2,52 a 0,87 (*$p < 0,001$*). El consumo de ciprofloxacino tuvo un descenso de 0,75 doses por mil habitantes día (DHD) a 0,36 DHD. Al mismo tiempo, un aumento compensatorio se observó en el consumo de nitrofurantoína y fosfomicina.* ***Discusión:*** *Nuestro estudio demostró que el uso del antibiograma selectivo influyó en la práctica de prescripción de antimicrobianos y animó a los médicos generales a elegir antimicrobianos de espectro más reducido y con mejor relación de costo-beneficio.* ***Conclusión:*** *Nuestros resultados sugieren que la utilización de antibiogramas selectivos debe ser considerada una estrategia efectiva en la reducción del consumo de determinados antimicrobianos.*

Palabras clave: *programas de optimización del uso de antimicrobianos;* Escherichia coli*; ciprofloxacino.*

INTRODUCTION

Antimicrobial stewardship is a bundle of integrated interventions employed to optimize the use of antimicrobials in health care settings[1].

The benefits of antibiotic stewardship covers improved patient outcomes, reduced adverse events including *Clostridium difficile* infection, improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care[2].

Selective reporting of antibiotic susceptibility test (AST) results is increasingly recognized as one of the key strategies of antibiotic stewardship programs and has been included in the list of interventions recommended by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), even though the level of evidence supporting this measure is quite low[3].

Cascading microbiology laboratory reporting, as defined by the Clinical and Laboratory Standards Institute (CLSI), is a "strategy of reporting antimicrobial susceptibility test results in which secondary (e.g., broader-spectrum, more costly) agents may only be reported if an organism is resistant to primary agents within a particular drug class" (cascade reporting is one type of selective reporting)[4].

The ultimate goal is to reduce antimicrobial consumption, particularly the use of broad-spectrum agents, in order to minimize the resistance potential. Selective reporting helps prescribers choose the most appropriate antimicrobial agent based on a susceptibility pattern[5].

Antibiotic stewardship programs aim not only to limit antibiotic therapy to proven or strongly suspected non-self-limiting bacterial infections but also to reduce the use of broad-spectrum antibiotics, such as third generation cephalosporins and fluoroquinolones. So, two goals are pursued: to avoid unnecessary antibiotic use and to limit inappropriate antibiotic prescribing[6].

The objective of this study is to determine the impact of selective susceptibility reporting on ciprofloxacin utilization and *Escherichia coli* susceptibility to ciprofloxacin in the outpatient setting.

MATERIAL AND METHODS

Setting

The Matosinhos Local Unit of Health (ULSM) encompasses Hospital Pedro Hispano, with 348 beds, and 15 Primary Care Centers, and provides care to the municipality of Matosinhos, with approximately 180 thousand inhabitants.

Study design

Prior to the intervention, for adult patients, the microbiology laboratory practice was to report ciprofloxacin susceptibility for

all *E. coli* regardless of susceptibility to other agents. A selective reporting policy was created and implemented by the microbiology laboratory in late 2011, after an articulated verbal and written communication about selective antibiograms between the microbiology laboratory and the clinician regarding the content of selective reporting of AST for urinary samples. This policy involves the introduction of fosfomycin susceptibility in urinary AST and the simultaneous non-reporting the ciprofloxacin susceptibility of *Enterobacteriaceae* isolated in a urine sample, when there is susceptibility to narrow-spectrum agents (amoxicillin, nitrofurantoin and fosfomycin). The selective reporting policy was automated. Our microbiology lab always reports in AST all the resistance to antimicrobials likely to be used in urinary tract infection and the resistance mechanisms [extended-spectrum beta-lactamase (**ESBL**)-producing *Enterobacteriaceae* and carbapenemase-producing *Enterobacteriaceae*].

Outcomes

The primary outcome was outpatient ciprofloxacin utilization as measured in defined daily doses per thousand inhabitants/day (DHD), tabulated on a year basis between January 2011 and December 2018. Total of medical prescriptions in primary care centers was the source of the drug utilization data.

The secondary outcome was *E. coli* susceptibility to ciprofloxacin. This analysis was carried out after the elimination of duplicates according to CLSI Standard M39-A4.

Data analysis

For each active pharmaceutical ingredient, DHD was calculated using the formula: number of Anatomical Therapeutic Chemical (ATC)/defined daily doses (DDD) × total tablets/(total inhabitants/thousand inhabitants × 365 days). The World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology was the source of number of ATC/DDD for each antimicrobial.

To assess the effectiveness of implementation of our selective reporting we present the susceptibility rate of ciprofloxacin in *E. coli* (number of *E. coli* susceptible to ciprofloxacin/total number of *E. coli*) and the incidence rate (number of *E. coli* per total inhabitants each year). To test hypotheses about the independence of categorical variables, the Chi-squared test of independence was applied.

To determine the risk of infection each year, odds ratios (OR) and their 95% confidence intervals (CI) through logistic regression were determined. The analysis was carried out using the Statistical Package for the Social Sciences (SPSS®) statistical analysis program v. 21.0.

RESULTS

E. coli (n = 7,515) was responsible for 80% of all urinary infections (n = 9,328) during the time analysis. Between 2011 and 2018 we detected an increase in the susceptibility rate to ciprofloxacin in *E. coli* from 79% to 87% ($p < 0.001$).

The ciprofloxacin utilization dropped from 0.75 DHD to 0.36 DHD after the implementation of selective reporting. In the time series analysis post-intervention, there was an immediate and sustained reduction in ciprofloxacin utilization in 2013 ($p < 0.001$). Additionally, there was a steeper decline in the trend of utilization ($p = 0.002$) after the intervention. There was a significant rise in nitrofurantoin utilization from 0.56 DHD to 0.62 DHD between 2011 and 2018. In the time series analysis, there was a maximum utilization in 2014 (0.68 DHD).

Post-intervention analysis showed an increased use of fosfomycin. Mean fosfomycin utilization prior to intervention was 0.08 DHD/thousand inhabitants, whereas after the intervention it increased to 0.13 DHD (**Figure 1**).

We found a statistically significant reduction on the incidence rate of *E. coli* resistant to ciprofloxacin from 2.52 to 0.87 ($p < 0.001$), as presented in **Figure 2**.

The risk of contracting an *E. coli* resistant to ciprofloxacin is also much lower in 2018 and progressively declined relatively to 2011, as shown in **Table**.

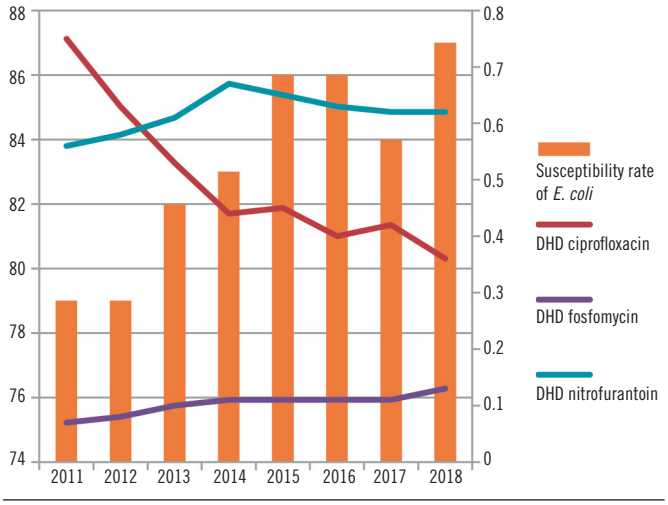

FIGURE 1 – *Susceptibility rate of* Escherichia coli *and DHD per thousand inhabitants/year DHD: defined daily doses.*

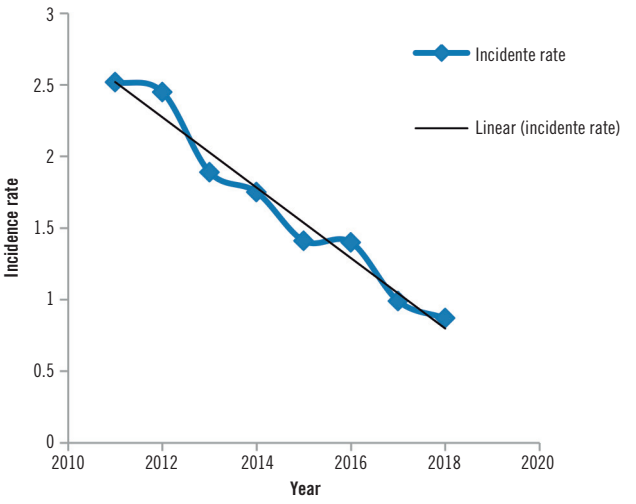

FIGURE 2 – *Incidence rate of* E. coli *resistant to ciprofloxacin between 2011 and 2019*

TABLE – OR for *E. coli* resistant to ciprofloxacin

Year	OR	CI 95%
2011	1*	
2012	0.97	0.834-1.129
2013	0.747	0.636-0.877
2014	0.693	0.588-0.815
2015	0.588	0.469-0.662
2016	0.555	0.468-0.656
2017	0.393	0.322-0.469
2018	0.395	0.309-0.429

*OR: odds ratio; CI: confidence interval; *2011: reference year [before the full implementation of fosfomycin in urinary antibiotic susceptibility test (AST) and selective reporting].*

DISCUSSION

Over recent years, the use (or abuse) of empirical treatment for urinary tract infections (UTIs) by general practitioners and specialists has contributed to a significant increase in bacterial resistance worldwide. This is especially relevant for the most important uropathogens: *E. coli* and *Klebsiella pneumonia*[7].

Selective susceptibility reporting has been shown to alter prescribing decisions on an individual patient level[8]. However, selective reporting of AST results is largely underused and shows great variability among individual microbiology laboratories in Europe and Israel[3].

There are a number of studies that showed a relationship between the selective reporting of AST and alterations of prescription by clinicians[9].

A study conducted in 2013 demonstrated an association between laboratory susceptibility reporting practices and the prescription of specific antibiotics for the treatment of UTIs. Reporting of quinolone or cephalosporin susceptibilities by a microbiology laboratory was associated with a 50% increase in prescribing of each antibiotic by the general practitioners surveyed in this study, whereas the difference for nitrofurantoin prescribing was substantially larger[9].

A study conducted in Spain describes the trends in prescribing antibiotics and analyzes its possible relationship with the evolution of antimicrobial sensitivity of respiratory pathogens isolated in the health area of Zamora, Spain. A recovery of sensitivity to antibiotics was seen in respiratory pathogens parallel to a progressive decrease in prescription of those antibiotics[10].

A study conducted by Langford *et al.* (2016)[8] found a decrease in inpatient ciprofloxacin utilization after the microbiology laboratory started to routinely suppress ciprofloxacin susceptibility of *Enterobacteriaceae* when there was lack of resistance to other antibiotics on the Gram-negative panel.

More recently, Binda F. *et al.* (2018)[6] conducted a study in a French outpatient setting, targeting UTIs caused by *E. coli*. It was the first interventional prospective controlled study to evaluate the effectiveness of selective reporting of AST results to reduce the prescription of broad-spectrum antibiotics. Data were collected for each AST performed on *E. coli*-positive urine cultures in 2017 (before period) and 2019 (after period) in all laboratories. Still, no preliminary data has been published.

Our study is the first, to our knowledge, to show an impact of selective AST on prescription of antibiotics in UTIs at a community level. An increase in the susceptibility rate to ciprofloxacin in *E. coli* was associated with an immediate and sustained reduction of ciprofloxacin utilization. As ciprofloxacin usage declined, there appeared to be a compensatory increase in utilization of nitrofurantoin and fosfomycin.

Communication, including seminars about selective antibiograms in primary care centers, and telephone advice between the microbiology lab and general practitioners, was determinant to the success of this protocol implementation.

There are several limitations to this study: 1. it is not the aim of this study evaluating the appropriateness of antibiotic prescriptions; 2. some clinicians may only submit urine samples for the treatment of complicated UTIs, which may require different empirical antibiotic treatment, a limitation that Tan *et al.* (2003)[9] also found; 3. although the selective

reporting policy was automated, there were some situations in which ciprofloxacin was reported to the clinicians, which might have led to the prescription of this medication, thus tampering the results; 4. the data about antimicrobial agents prescription was obtained from the online prescription platform of National Health Service (SNS), not including, therefore, information about self-medication or hand prescription, from which we might assume greater antimicrobial agents consumption than that obtained; 5. our selective reporting policy was complemented with other interventions of antimicrobial stewardship. Hence, it is difficult to determine with certainty if selective reporting was the sole cause for the reduction of ciprofloxacin utilization.

CONCLUSION

Our results suggest that selective reporting of AST should be considered an effective prevention strategy to reduce targeted antimicrobial utilization as part of a broader antimicrobial stewardship program.

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