Etiological Agents and Antimicrobial Susceptibility in Hospitalized Children with Acute Pyelonephritis

Agentes Etiológicos e Suscetibilidade aos Antimicrobianos em Crianças Internadas por Pielonefrite Aguda

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ABSTRACT

Introduction: Antibiotic resistance driven by antibiotic use remains a major public health and professional concern. Our aim was to know the local prevalence of uropathogens and their antimicrobial susceptibility profile in acute pyelonephritis.

Material and Methods: A prospective study of patients admitted in a level III Pediatric Department ward with acute pyelonephritis from 1994 to 2012 was performed in Northern Portugal. Etiological agents and their antimicrobial sensitivity profile were evaluated in four timed periods (G1: 1994-97; G2: 2002; G3: 2007; G4: 2012).

Results: We evaluated 581 patients, 66% female with median age 22 months. *Escherichia coli* was the leading uropathogen and its prevalence remained stable during the last 18 years. It showed an increased sensitivity to amoxicillin-clavulanate from 71% in G1 to 81.5% in G4 (p = 0.001) and a decreased resistance rate from 8.7% in G1 to 2.8% in G4 (p = 0.008). Its sensitivity to 2nd and 3rd generation cephalosporin was more than 90% (p = ns) and more than 95% to nitrofurantoin (p = ns). Resistance rate of cotrimoxazole increased from 22% to 26% (p = 0.008).

Discussion: *Escherichia coli* remains the main uropathogen responsible for acute pyelonephritis, reason why its antimicrobial sensitivity profile will determine the empirical therapeutic choice.

Conclusions: Amoxicillin-clavulanate remains a good first-line choice for empirical treatment of acute pyelonephritis in our inpatient health care.

Keywords: Anti-Bacterial Agents; Child; Drug Resistance, Bacterial; Pyelonephritis.

RESUMO

Introdução: A resistência aos antimicrobianos, provocada pela utilização de antibióticos continua a ser um importante problema de saúde pública e uma preocupação para os profissionais de saúde. O nosso objetivo foi conhecer a prevalência local dos uropatógenos e o seu perfil de suscetibilidade aos antimicrobiannos na pielonefrite aguda.

Material e Métodos: Estudo prospetivo nas crianças internadas por pielonefrite aguda no internamento de Pediatria de um hospital do norte de Portugal entre 1994-2012. Os agentes etiológicos e o seu perfil de sensibilidade aos antimicrobianos foram avaliados em quatro períodos de tempo (G1: 1994-1997, G2: 2002; G3: 2007; G4: 2012).

Resultados: Avaliámos 581 doentes, 66% do sexo feminino, com idade mediana de 22 meses. A *Escherichia coli* foi o principal uropatógeno e a sua prevalência manteve-se estável durante os últimos 18 anos. Verificou-se um aumento da sensibilidade à amoxicilina/ácido clavulânico de 71% no G1 para 81,5% no G4 (p = 0,001) e uma diminuição da taxa de resistência de 8,7% no G1 para 2,8% G4 (p = 0,008). A sua sensibilidade às cefalosporinas de segunda e terceira geração e nitrofurantoína foi superior a 90% (p = ns). A taxa de resistência ao cotrimoxazol aumentou de 22 % para 26 % (p = 0,008).

Discussão: A *Escherichia coli* continua a ser o uropatogénio mais frequente responsável por pielonefrite aguda, motivo pelo qual o seu perfil de sensibilidade aos antimicrobianos determina a escolha da antibioticoterapia empírica.

Conclusões: A amoxicilina/ácido clavulânico mantém-se como escolha de primeira linha para o tratamento empírico da pielonefrite aguda em regime de internamento.

Palavras-Chave: Pielonefrite; Antibacterianos; Crianças; Farmacorresistência Bacteriana.

INTRODUCTION

Urinary tract infection (UTI), including cystitis and pyelonephritis, remains one of the most common bacterial infection in childhood[1] and its cumulative incidence in children by 6 years of age is 3-7% in girls and 1-2% in boys.[2] It can be associated with long-term renal scarring, which may cause hypertension, proteinuria, pregnancy-related complications, or even progressive renal failure.[2-4] Antibiotic resistance and multi-drug resistant infection, driven by antibiotic use, remain a major public health and professional concern.[5] Annual losses stemming from antimicrobial resistance are estimated to range from 21000 million to 34000 million dollars in the United States of America[6] and about 1500 million euros in Europe.[7] Due to geographic variation of uropathogens, their mechanisms of resistance and recent changes in antimicrobial resistance, it is crucial to know the prevalence of local microbial agents and their antimicrobial susceptibility profile to adjust the initial empirical treatment of UTI.[3-4] During the last decades there is concern in treating acute pyelonephritis (APN) at lowest cost and with maximum effectiveness. The aim

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of this study was to evaluate the etiological agents and antimicrobial susceptibility profile of urinary pathogens in hospitalized children with APN in our center.

MATERIAL AND METHODS

A prospective study from 1994 to 2012 was performed. All children with more than 29 days of life and adolescents admitted in level III Pediatric Department ward in Northern Portugal with the diagnosis of APN were included. Until 2010 the maximum age allowed at admission was 16 years-old and less than 18 years thereafter, when National Policies changed in Pediatric Health Care. Demographic and clinical data were recorded and etiological agents and their antimicrobial sensitivity profile were evaluated in four timed periods during the last 18 years (G1: 1994-1997; G2: 2002; G3: 2007; G4: 2012). Non-selective differential media (C.L.E.D., bioMérieux, Marcy l'Etoile, France) and selective differential media (MacConkey Agar, bioMérieux, Marcy l'Etoile, France) were used in the urine samples. Another non-selective media (Blood Agar, bioMérieux, Marcy l'Etoile, France) was used when a subculture was needed. Identification and susceptibility were determined using the Vitek1 system between 1994 and 2004 and the Vitek2 system between 2005 and 2012 (both from bioMérieux, Marcy l'Etoile, France). Therapeutic protocols used during the study period were the same, and regular updates were performed according to the 'state of the art'. The study was approved by the institutional research ethics board.

Analyzed data included demographic (age and gender), clinical (known nephro-urologic malformation, previous urinary tract infection, current antibiotic prophylaxis) and microbial data (etiological agent, antimicrobial susceptibility). Diagnosis and management of APN were performed according to the protocol, in use since 1994. The criteria to hospitalization and intravenous empirical antibiotic therapy are summarized in Table 1. Antibiotic therapy was replaced according to the clinical evolution and the results of previous antibiograms were taken into account in those cases of recurrent APN due to atypical agents. Antimicrobial therapeutic failure was considered in those cases with persistent fever or positive bacteriological urine examination at 48-72 hours of therapy.[8]

Statistical analysis was performed by SPSS® (IBM, USA) program v.20. Continuous variables were characterized by mean (± standard deviation) and median (medium-maximum) if they had symmetric or asymmetric distribution, respectively. Categorical variable were characterized by absolute and relative frequencies. To compare continuous variables with asymmetric distribution we used Kruskal-Wallis test and to compare categorical variables we used Chi-Squared and Fisher's exact test. *P* value less than 0.05 was considered statistically significant.

RESULTS

During the last 18 years, 581 patients were evaluated. There was prevalence of female children along the period study in all groups ($p < 0.0001$) with progressive decrease of median age at admission ($p < 0.0001$). There was an increase of nephro-urologic malformations and in the prevalence of first episode of APN in G3 and G4 ($p < 0.0001$). There were no differences in the prevalence of APN under prophylaxis and cases of antibiotic failure. Demographic and clinical characteristics are summarized in table 2.

Escherichia coli was the leading uropathogen and its prevalence remained stable during the last 18 years. There was significant decrease in the prevalence of *Klebsiella spp*. ($p = 0.001$) and *Enterococcus spp*. ($p = 0.046$) during the period study. Uropathogens causing APN during the last 18 years are summarized in Fig. 1.

Table 1 – Hospitalization criteria and empirical antibiotic therapy according to the National Protocol[8]

Hospitalization criteria	
Age ≤ 3 months Poor clinical conditions: dehydration, bad perfusion, sepsis Oral intolerance Bad social conditions or difficulties to maintain follow-up Impossibility of re-evaluation in 48-72 hours Lack of response and/or clinical worsening in children under oral antibiotic Recurrent acute pyelonephritis due to atypical agents Nephro-urologic malformation with renal failure	
Intravenous empirical antibiotic therapy	
From 1st to 3rd month of life	Cefotaxime* 75-100 mg/kg/day, q8/8h OR Ceftriaxone* 50-75 mg/kg/day, q24/24h *Add ampicilin 100 mg/kg/day, q6/6h if there is clinical and analytical suspicion of sepsis
More than 3 month of life	Amoxicillin/clavulanate 75-100 mg/kg/day of amoxicillin, q8/8h (max 3 g) OR Cefuroxime 75-150 mg/kg/day, q12/12h (max 1 g)

Table 2 – Demographic and clinical characteristics of hospitalized children with APN (n = 581)

	G1[24] (n = 196)	G2[25] (n = 119)	G3 (n = 141)	G4 (n = 125)	p
Gender, n (%)					
Female	147 (75)	68 (57.1)	99 (70.2)	68 (54.4)	< 0.0001*
Male	49 (25)	51 (42.9)	42 (29.8)	57 (45.6)	
Median age, months (min-max)	42.6 (29 days-13 years)	15.1 (29 days-13 years)	19.4 (3 months-13 years)	7 (1 month-17 years)	< 0.0001¥
Nephro-urologic malformation, n (%)	16 (8.2)	-	82 (58.2)	71 (56.8)	< 0.0001*
First APN episode, n (%)	107 (54.6)	-	121(85.6)	100 (80.0)	< 0.0001*
APN under prophylaxis, n (%)	-	20 (16.8)	16 (11.3)	18 (14.4)	ns*
Empirical therapeutic failure, n (%)	8 (4.1)	3 (2.5)	5 (3.5)	4 (3.2)	ns*

*Chi-square test, ¥ Kruskal-Wallis test, APN – acute pyelonephritis, ns – non significant.

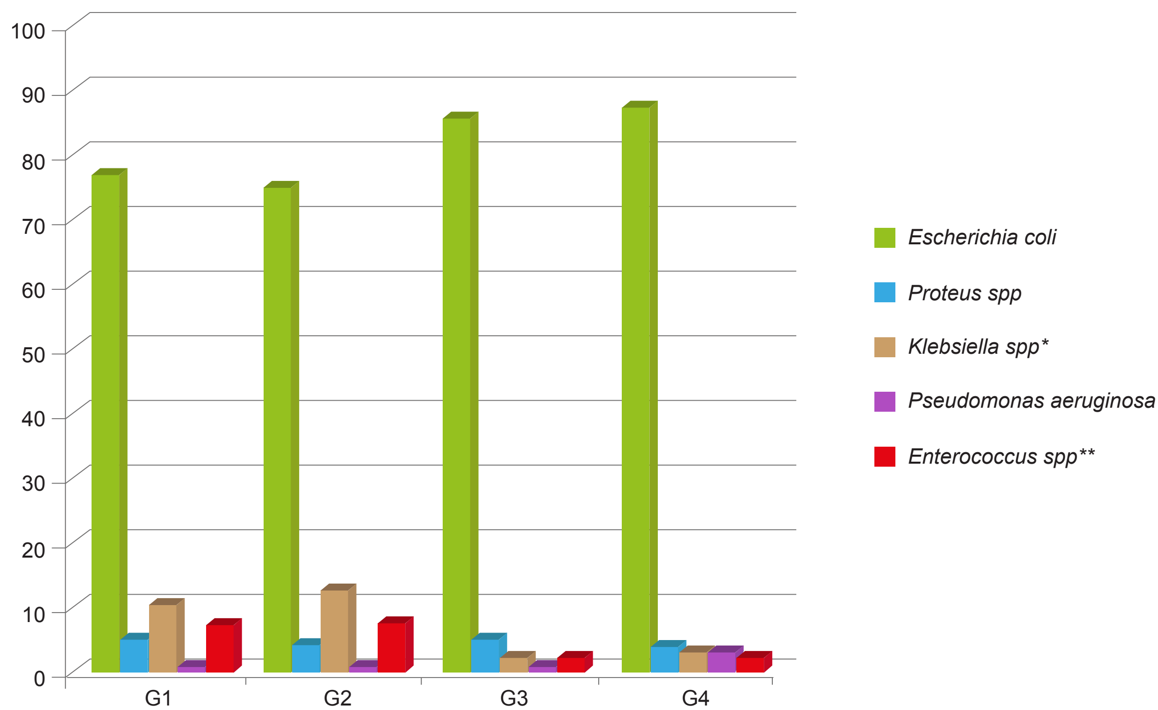

Figure 1 - Uropathogens causing APN in hospitalized children during the last 18 years.
p = 0.001 (Fisher's exact test); ***p* = 0.046 (Fisher's exact test)

Escherichia coli showed an increased sensitivity to amoxicillin-clavulanate over the years from 71% in G1 to 81.5% in G4 ($p = 0.001$), an increased intermediate sensitivity from 16% in G2 to 20% in G4 ($p = 0.002$), and a decreased resistance rate from 8.7% in G1 to 2.8% in G4 ($p = 0.008$). Its sensitivity to 2nd and 3rd generation cephalosporin was more than 90% (p = ns) and more than 95% to nitrofurantoin (p = ns) over the study period. Regarding cotrimoxazole, its sensitivity decreased from 90% in G1 to 74% in G4 ($p < 0.0001$) with resistance rate from 22% to 26% ($p = 0.008$).

The sensitivity of *Proteus spp*. to amoxicillin-clavulanate was 50% in G1, 100% in G2 and G3 and 67% in G4 ($p = 0.008$). There were no resistant cases to amoxicillin-clavulanate during the study period.

The sensitivity of *Klebsiella spp*. to amoxicillin-clavulanate was 67% in G1, 56% in G2 and 100% in G3 and G4 (p = ns). The resistance rate to amoxicillin-clavulanate was 17% in G1 and any resistant case was registered in G2-4. Antimicrobial susceptibility profile of the most frequent uropathogens in APN is summarized in Fig.s 2-4.

DISCUSSION

Escherichia coli is responsible for 60-90% of community-acquired UTIs in childhood.[1,2,4] Other common gram negative organisms include *Klebsiella, Proteus, Enterobacter*, and occasionally *Pseudomonas*. Fungal infections are much less common and are usually to those who are immune-compromised or diabetic, are on long-term antibiotics, or have long-term indwelling catheter.[2]

Escherichia coli remains the main uropathogen responsible for APN, reason why it antimicrobial sensitivity profile will determine the empirical therapeutic choice. In Portuguese pediatric population, *Escherichia coli* is the main etiological agent with variable prevalence according to the different centers (53-81%). Its resistance to ampicillin is 44.8-54.9%, 5.7-21.7% to amoxicillin-clavulanate, 1.2-4% to cephuroxim, 1-4.7% to nitrofurantoin and 19-31.3% to cotrimoxazole.[8] There is high rates of resistance of this agent to cotrimoxazole, already described in other studies[3,9] probably as consequence of indiscriminate use of this drug in the past. Uropathogens other than *Escherichia coli* were more prevalent in children and adolescents with uropathy and there were no differences between those under prophylaxis.

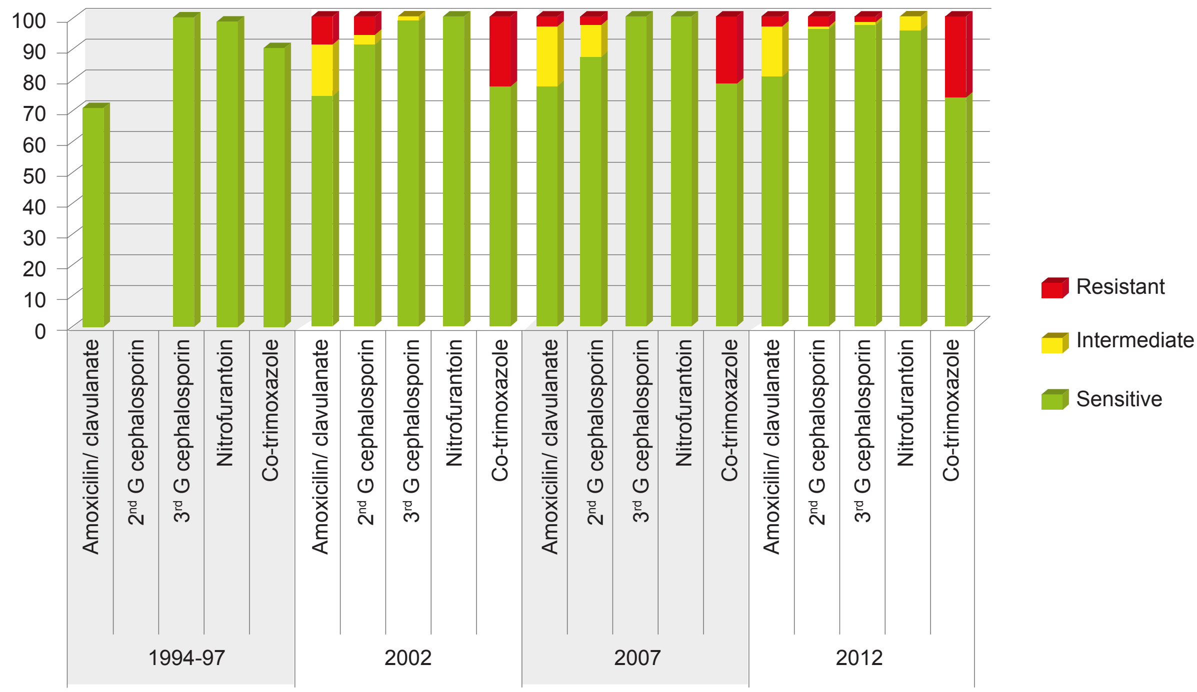

Figure 2 - *In vitro* antimicrobial susceptibility of *Escherichia coli* causing APN in hospitalized children

Figure 3 - *In vitro* antimicrobial susceptibility of *Proteus spp.* causing APN in hospitalized children

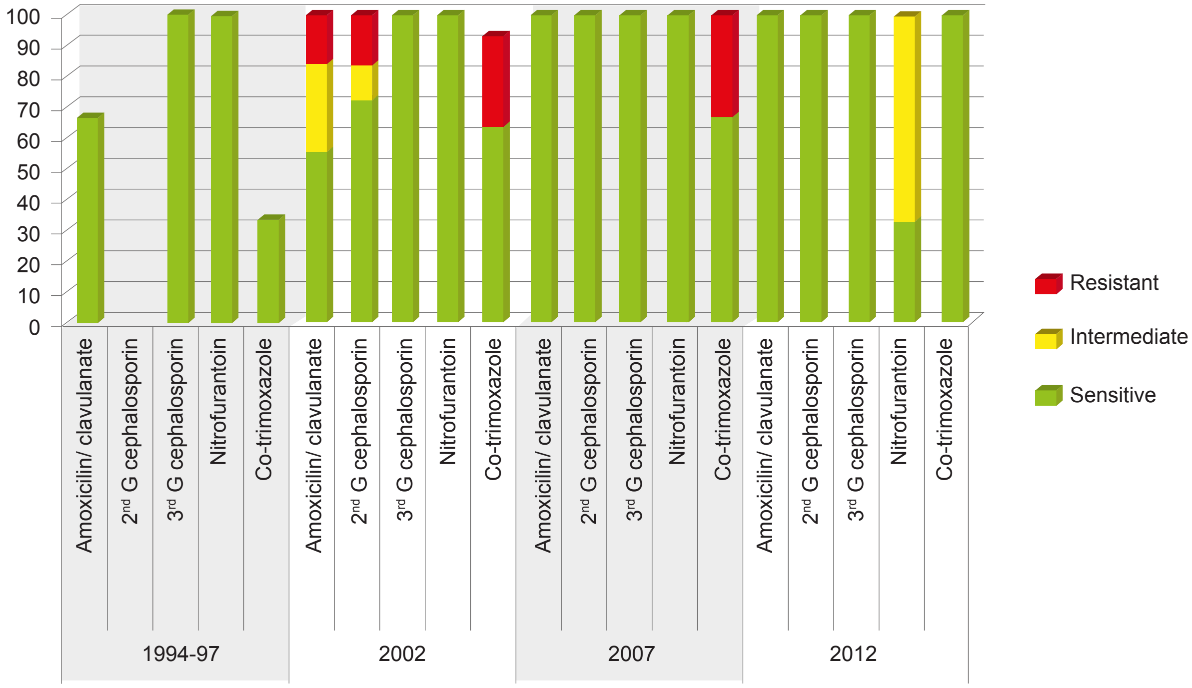

Figure 4 - *In vitro* antimicrobial susceptibility of *Klebsiella spp*. causing APN in hospitalized children

Empirical antibiotic therapy should be based on local antimicrobial sensitivity patterns, if available, and adjusted according to sensitivity testing of the isolated uropathogen.[10] Other factors that should be taken into account are the age, the presence of underling conditions, renal function, previous episode of UTI, current antibiotic prophylaxis and oral tolerance.[3] As frequent irrational use of antibiotics changes the intestinal flora, leading to bacterial resistance[1], antibiotic for APN treatment should be selected based on resistance percentage of the main etiological agents, preferably under 10-20%.[3] And because increasing rates of resistance among bacterial uropathogens has caused growing concern in both developed and developing countries[11] regular monitoring of resistance patterns is necessary to improve guidelines for empirical antibiotic therapy.[12] In our study, sensitivity of *Escherichia coli* to amoxicillin-clavulanate, including intermediate sensitivity *in vitro* was around 100% with very low percentage regarding resistance. There were no cases of resistance to amoxicillin-clavulanate regarding *Proteus spp.* during the study period and *Klebsiella spp* since 2002.

There is a positive correlation between antimicrobial resistance and the consumption of antibiotics.[13] In European countries, systemic antibiotics are prescribed in the greatest volumes to ambulatory patients, mostly for respiratory tract infections.[14] Increasing awareness of antimicrobial resistance and promoting the rational use of antibiotics among prescribers and the general public are the key to combating the unnecessary use of these drugs and various initiatives have been implemented throughout Europe to support the prudent use of antimicrobials, including the Antibiotic Stewardship International projects.[15-21]

In Portugal antibiotic management policies regarding resistance and costs have been changing during the last decades.[22] The higher use of antibiotics in respiratory infections in Primary Care changed during the last decade.[23] In clinical practice should be target that in line with policies of rational use of drugs, mainly antibiotics, treatments should be based on maximum efficiency and lowest cost strategies.

During the study period the protocol used was the same and regular updates were performed according to the 'state of the art'. Regarding the criteria age for hospitalization included in the protocol it decreased over the time, fact that justifies the decreasing of median age in hospitalized children in our center during the study period.

CONCLUSIONS

UTI is one of the most common diseases in children. Early diagnosis and treatment can significantly decrease late serious complications. Knowledge of the sensitivity and resistance pattern of uropathogens in specific geographical locations is an important factor for choosing suitable antibacterial treatment.

Our results show an improvement in the profiles of sensitivity and resistance of antimicrobial agents used in APN treatment during the last 18 years. Amoxicillin-clavulanate remains a good first-line choice for empirical treatment of APN in our inpatient care.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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