The Role of Colistin in Urinary Tract Infections in the Neurologic Patient

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Urinary tract infections represent a frequent, infectious casuistry of the neurologic patient, often recurrent, with the significant involvement of multidrug-resistant bacteria (MDRs). A retrospective study, during the period 01.01.2018-31.12.2018, in the Clinical Neurology Hospital in Craiova, on a group of 334 Px with urinary tract infections and proven microbial etiology (positive urocultures), for whom antibiograms were performed using KIRBY-BAUER disk diffusion test. The duplicates and samples considered contaminated were excluded from the study. Urinary tract infections are frequently encountered in the neurologic patient, the major etiology being represented by E. coli; the risk of multidrug-resistance is not to be neglected, Klebsiella pn being the most common in such a situation.

Keywords: urinary tract infections, Colistin, multidrug-resistant strains, neurological pathology

Urinary tract infections represent a frequent, infectious casuistry of the neurologic patient, often recurrent, with the significant involvement of multidrug-resistant bacteria (MDRs). Colistin is a *rescue* therapy in such critical situations, with proven efficacy and safety profile [1], alone or in combination with other antibiotics [2].

Objectives: Bacteriological and therapeutical analysis of urinary tract infections (UTI) in the neurologic patient (Px).

Experimental part

Material and method: A retrospective study, during the period 01.01.2018-31.12.2018, in the Clinical Neurology Hospital in Craiova, on a group of 334 Px with urinary tract infections and proven microbial etiology (positive urocultures), for whom antibiograms were performed using KIRBY-BAUER disk diffusion test. The duplicates and samples considered contaminated were excluded from the study.

Antibiotic sensitivity was defined as: very high: 90-100%, high: 80-89.99%, medium: 50-79.99%, low <50%. Multidrug resistant strains were those that showed resistance to at least 3 classes of antibiotics.

The dose of colistin was adjusted according to the creatinine clearance, calculated according to the Cockcroft-Gault equation [3].

Antibiotic therapy was carried out according to the local hospital protocol (which includes as well the list of *reserve* antibiotics), the antibiogram results and the patient profile.

The statistical analysis used EpiInfo programme, the p threshold being considered statistically significant at a value of <0.05.

Results and discussions

During the study, there were 6135 Px admitted, of whom 872 (14.21%) presented urinary tract infections, with a proven bacterial etiology in 334 cases (38.31%) (fig. 1).

The etiology of urinary tract infections was mainly represented by *Escherichia coli* (81 strains - 63.75%),

Fig. 1. Urinary tract infections with proven etiology

followed, at a distance, by *Klebsiella pneumoniae* (48 strains - 14.51%) (fig. 2).

Multidrug resistant strains were highlighted in 22 cases (6.59%), as follows: 3 strains of *E. coli*, 8 strains of *Klebsiella pn*, 3 strains of *Enterobacter spp.*, 2 strains of *Proteus mirabilis*, 6 strains of *Pseudomonas aeruginosa*.

For multidrug-resistant bacteria, antibiograms have shown a sensitivity to colistin of 68.19% (15 strains), to meropenem of 54.55% (12 strains), to amikacin of 27.27% (6 strains), to fosfomycin of 18.18% (4 strains), to aztreonam of 13.64% (3 strains), to levofloxacin of 13.64% (3 strains), to cephalosporin: cefazolin 4.54% (1 strain), cefepime 4.54% (1 strain), to amoxicillin-clavulanate of 4.54% (1 strain), to ampicillin, amoxicillin and co-trimoxazole of 0%; a number of 6 strains (27.27%) were sensitive only to colistin.

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Fig. 2. Etiology of urinary tract infections

By analyzing the sensitivity phenotype of multidrug-resistant bacteria to Colistin, the following data were obtained: all 3 strains of *E. coli* were sensitive, in the case of *Enterobacter spp.*, 2 strains were sensitive, 1 strain sensitive to *Proteus mirabilis*, of 6 strains of *Ps. aeruginosa* 4 were sensitive and for *Klebsiella pn.*, we registered 5 sensitive strains (fig.3).

Strains resistant to all classes of tested antibiotics were as follows: 1 case of *Ps. aeruginosa* and 1 case of *Proteus*

Chart Title

Fig. 3. Colistin sensitivity of multidrug resistant strains

mirabilis, both situations being noted in patients with long-term urinary catheter.

We performed a comparative analysis of colistin sensitivity and meropenem sensitivity of multidrug-resistant uropathogens and there was not obtained any statistically significant difference ($p = 1,000$) (table 1).

Of 16 Px with multidrug-resistant uropathogens to colistin, the treatment with colistin was indicated only for 12 Px (75%), in all cases it was established depending on the antibiotic results (6 strains were sensitive to colistin

Table 1

COLISTIN SENSITIVITY VERSUS MEROPENEM SENSITIVITY IN CASE OF MULTIDRUG-RESISTANT STRAINS

	Tx sensitive to Meropenem-no. (%)	Tx resistant to Meropenem-no. (%)
Tx sensitive to Colistin-no.(%)	8 (36.37%)	7 (31.81%)
Tx resistant to Colistin-no.(%)	4 (18.19%)	3 (13.63%)

alone, 1 strain to colistin and cefepime, 2 strains to aztreonam, amikacin and colistin, 3 strains were sensitive only to amikacin and colistin).

The characteristics of Px treated with colistin were as follows: the average age of Px was 68.12 years, the gender distribution was in favour of the male gender (9 Px-75%), and the residence environment showed the presence of 7 Px (58.33%) in rural areas. They presented the following comorbidities: 9 Px with ischemic stroke, 3 Px with stroke, 11 Px with diabetes, 9 Px with ischemic cardiomyopathy, 8 Px with acute pneumonia, 7 Px with chronic obstructive bronchopneumonia, 4 Px with neoplasia, 3 Px with chronic liver disease.

Colistin was intravenously administered as follows: the loading dose of 9 million IU (3 million IU every 8 hours) on the first day, afterwards 3-6 million IU / day, with a total duration of 10-14 days. In these Px, Colistin was not used in combination with other antibiotics.

Patients suffering of mild, functional kidney failure (3 cases) were given the dose of colistin, depending on the results of creatinine clearance, with creatinine monitoring at 2-3 days and appropriate hydration, as well as nephrology examinations, without registering the worsening of renal function.

No adverse reactions were reported in any of the cases of colistin administration, Px being strictly monitored for: nephrotoxicity, neurotoxicity and hypersensitivity reactions.

Px evolution was favourable, with clinical healing (the disappearance of signs and symptoms of urinary tract infection), biological healing (normalization of white blood cell counts and inflammatory markers) and proven bacteriological healing (negative urocultures 72 h after treatment interruption) without registering any recurrence in the next 30 days; there were no deaths registered.

Urinary tract infections are a frequent pathology in neurologic Px, the choice of antibiotic therapy representing a serious test for the clinician, due to the increasing antibiotic resistance, drug interactions, adverse reactions, as well as the Px profile with multiple comorbidities. Colistin is an etiological topical therapy, practically a *re-emergence* of antibiotic therapy, due to the change in the sensitivity phenotype, after a period in which it had almost been discontinued.

In our study, the sensitivity of multidrug-resistant microbes to colistin was average (68.19%), but higher compared to the sensitivity to meropenem (54.55%), without though a correlation between these antibiotics; the appearance is different from the results of another study in which the risk of colistin resistance is increased in meropenem-resistant strains [5].

The most frequent multidrug-resistant uropathogen in this study was *Klebsiella pn.* The increase of *Klebsiella pn* resistance. to carbapenems has been reported in the last years, particularly in Europe, Romania being on the list of these countries, as of 2013 [4]. The acquired colistin-resistance of *Klebsiella pn.* is rare, but it begins to become frequent in Italy [4].

The most frequently encountered adverse reactions to colistin are: nephrotoxicity and hypersensitivity reactions [6]. In our study, there was no registering of adverse event, unlike other studies [7; 8], in which the only adverse reaction noted was nephrotoxicity in 25% -36.3% of Px, or even higher of 53.5% [9], but the reaction was reversible after the treatment interruption. This difference can also be explained by the small number of Px in our group receiving colistin as their treatment.

The effectiveness of colistin in the treatment of urinary tract infections caused by multidrug-resistant bacteria proved to be excellent, in this study, clinical and

bacteriological healing was proven in all cases treated with colistin, a similar aspect to other studies [7, 10-28].

Colistin resistance of multidrug-resistant bacteria is associated with the increase of mortality [4]; in the paper presented, Px evolution was favourable, which was possibly due to the preserved colistin sensitivity of uropathogens.

Our study is limited by: the discontinuities in antibiotic testing, reduced number of multi-drug resistant strains included, the short period of analysis and the reduced number of Px who received Colistin.

Conclusions

Urinary tract infections are frequently encountered in the neurologic patient, the major etiology being represented by *E. coli*; the risk of multidrug-resistance is not to be neglected, *Klebsiella pn* being the most common in such a situation.

Colistin was the *rescue* therapy, with the best sensitivity in case of multidrug-resistant strains, a fact that recommends it in the future, as a backup antibiotic, but with strict monitoring of adverse reactions.

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