Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 14 (63) No. 1 – 2021
https://doi.org/10.31926/but.ms.2021.63.14.1.5

PROVIDENCIA SPECIES – INVOLVEMENT IN PATHOLOGY AND MULTIDRUG RESISTANCE IN A ROMANIAN COUNTY HOSPITAL

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Abstract: *The aim of the study was to evaluate the distribution on hospital wards, the spectrum of infections and the pattern of antimicrobial resistance of Providencia strains identified between 01.01.2018-31.12.2020 in the samples of the patients hospitalized in the Clinical County Emergency Hospital of Brasov. 380 strains of Providencia species were identified in the medical and surgical wards, especially in ICU (76.84%), Internal medicine ward (5.79%) and General surgery (3.95%). More frequently, Providencia spp. were isolated from tracheobronchial secretions (35.79%), pus (22.89%) and urine (19.74%). The levels of antimicrobial resistance of Providencia strains were very high for all the tested antimicrobials.*

Key words: *Providencia species, infections, antimicrobial resistance*

1. Introduction

The first species of the genus was isolated by Retgger in 1904 as an agent of epidemic bird diarrhea. In 1918, it was studied by Hadley et al and called Bacterium rettgerii. In 1951, Kauffmann and Edwards used the name Providencia for a group of bacteria studied by Stuart from Brown University in Providence, Rhode Island, USA. Until 1983, P. rettgeri, P. stuartii, P. alcalifaciens and P. rustigianii were included in the genus, all being isolated from humans. In 1986, the species P. heimbachae was included in the genus. Taxonomically, the Providencia genus is in the family Enterobacteriaceae, order Enterobacteria, class Proteobacteria and kingdom Bacteria [1], [2], [3].

Microorganisms of the Providencia genus are gram-negative bacilli, unencapsulated, usually mobile, non-sporogenic and

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aerobes facultative anaerobes bacteria. In laboratory practice, this genus must be differentiated from the genera Proteus and Morganella, which also include fermentative glucose, non-fermentative lactose, phenylalanine de- aminase positive and mobile microorganisms. The differentiation is based on the production of hydrogen sulphide (visible in Proteus spp.) and the use of citrate as a carbon source by germs (Morganella spp. does not have this biochemical capacity) [1], [4].

Providencia spp. are ubiquitous germs being present in water, soil and animal reservoirs but also an opportunistic pathogens affecting especially hospitalized patients [2], [5].

These germs are currently emerging (rate 4 per 100,000 hospital admissions) and are important in that they are biofilm-forming pathogens and often multidrug resistant with very limited options of infection treatment and significant impact on patients' mortality (around 30% in hospitals) [6], [7], [8].

The main Providencia species involved in human pathology are P. stuartii and P. rettgeri which can produce urinary tract infections, pneumonia, meningitis, wound infections, endocarditis, osteomyelitis, intraabdominal and bloodstream infections in hospitalized patients [1], [2], [9], [10], [11], [12].

These germs are isolated more frequent from the people with long-term indwelling urinary catheters who were hospitalized or resided in the elderly nursing homes [13]. Providencia spp. are involved in ventilator-associated pneumonia making therapy very difficult due to pandrug resistance [14].

Risk factors for selection of carbapenem-resistant Providencia and for outbreaks in hospitals are the prolonged hospitalization, especially in ICU (Intensive Care Unit) and burn wound units, intensive use of antibiotics for other infections (eg use of colistin or tigecycline for infections with Pseudomonas aeruginosa or Acinetobacter baumannii), catheterization or the use of different medical equipments (dialysis machines, ventilators). Immunocompromised are more susceptible [1].

Providencia spp. are commonly susceptible to second and third-generation cephalospo-rins, carbapenems (imipenem, meropenem) amikacin, ciprofloxacin, trimethoprim-sulfa-metoxazole, aztreonam and resistant to the aminopenicillins, first-generation cephalo-sporins, gentamicin, tobramycin. They also have intrinsic resistance to colistin and to tigecycline [10].

The mechanisms of resistance to β-lactams are the production of inducible AmpC β-lactamases but especially the production of extended-spectrum β-lactamases (ESBL) and metallo β-lactamases. New Delhi metallo β-lactamase 1 (NDM-1) but also KPC-2, OXA 48, IPM-1, VIM-1 and VIM-19 β-lactamases were most often involved in the carbapenem resistance of Providencia stuartii. OXA-72 carbapemenase was detected in P. rettgeri. [1], [15], [16], [17]

Resistance to these antibiotics may also be due to non-carbapenemase mechanisms consisting of changes in penicillin-binding proteins or in outer membrane proteins or activation of efflux-pumps [1], [13], [18].

Different genetic studies reveal that multi-drug resistance in P. stuartii and P. rettgeri were predominantly due to resistance genes from class 1 and 2 integrons. These species express different genes related to the cellular transport systems and to energy metabolism which gives them a stronger ability to adapt to

various environments and also diversity in pathogenicity [19].

The choice of treatment schema is made depending on the sensitivity to antibiotics and the origin of the strain and the patient's comorbidities [2]. In case of pandrug resistant Providencia strains in vitro, use of a high dose antibiotic combinations (eg meropenem 1 g every 12 hours, intravenous amikacin 1.5 mg every 48 hours and nebulised amikacin 250 mg every 6 hours) could be an option because, according to published studies or cases, it could lead to clinical improvement and bacterial eradication. [1], [14].

Phage therapy is one of the most promising solutions but the number of available phages targeting Providencia species is very limited. However, phages can be used mainly for the treatment of urinary tract infections [7].

2. Material and Methods

The study was retrospective-descriptive and its aim was to evaluate the pathogenic role, distribution on wards and pattern of antimicrobial resistance of the strains (380) of Providencia species identified between 01.01.2018 and 31.12.2020 in the samples of the patients admitted to Clinical County Emergency Hospital of Brasov.

For the identification of the genus, bio-chemical tests (TSI, Urea, Citrat) and VITEK 2 COMPACT automated system have been used. Antibiograms for Providencia strains were made using Kirby-Bauer difusimetric method according to C.L.S.I. (Clinical and Laboratory Standard Institute) 2018-2020.

The processed data has been obtained from the WHO-net database of the bacteriological department from the clinical laboratory of the hospital, their analysis being made from a microbiological perspective.

3. Results and Discussions

The variation of the number of Providencia spp. strains from one study year to another was initially analysed, as shown in Figure 1.

There is an increase in the number of strains of Providencia spp. in 2020 compared to previous years, this aspect being due to the casuistry but also due to the improved methods for detecting and reporting these germs. Figure 1 also shows the distribution in relation to the profile of hospital wards – medical/surgical - in the 3 years of the study.

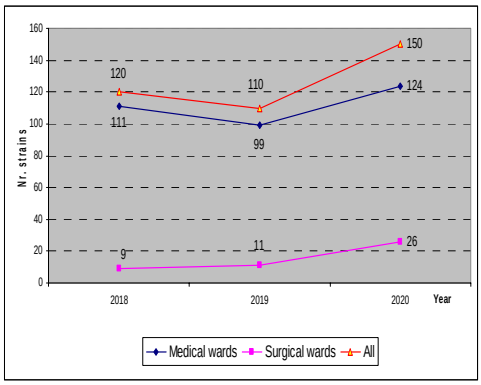

Fig.1. *The dynamics of the number of Providencia spp. strains between 2018-2020*

We can notice a higher number of strains of Providencia spp. in patients from medical wards compared to surgical wards, this result being influenced by the fact that this category also includes ICU where most of the isolated strains came from (76.84%).

Table 1

The distribution of Providencia strains on medical wards

Medical wards	**2018**	**2019**	**2020**
ICU	103	82	107
Dermatology	2	0	1
Nephrology	1	7	1
Internal medicine	4	7	11
Hematology	1	0	1
Neurology	0	3	3
Total:	**111**	**99**	**124**

Table 2

The distribution of Providencia strains on surgical wards

Surgical wards	**2018**	**2019**	**2020**
Plastic surgery	2	3	4
General surgery	4	2	9
Orthopedic surgery	3	2	2
Vascular surgery	0	1	1
Thoracic surgery	0	0	1
Urology	0	3	6
Neurosurgery	0	0	3
Total:	**9**	**11**	**26**

Table 3

The distribution of Providencia strains on the pathological products

Pathological products	**2018**	**2019**	**2020**
Blood	2	7	7
Ear secretions	1	0	0
Wound secretions	15	10	15
Pus	52	27	8
Urine	3	28	44
Respiratory secretions	44	36	56
Varicose ulcers	2	0	1
Catheters	1	1	14
Urethral secretions	0	1	3
Abdominal fluid	0	0	2
Total:	**120**	**110**	**150**

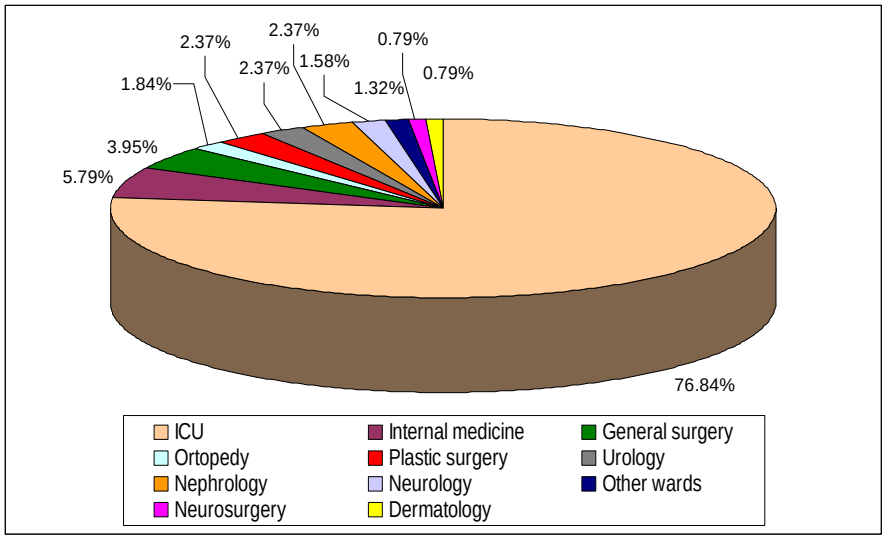

Fig. 2. *The distribution of Providencia strains on the hospital wards*

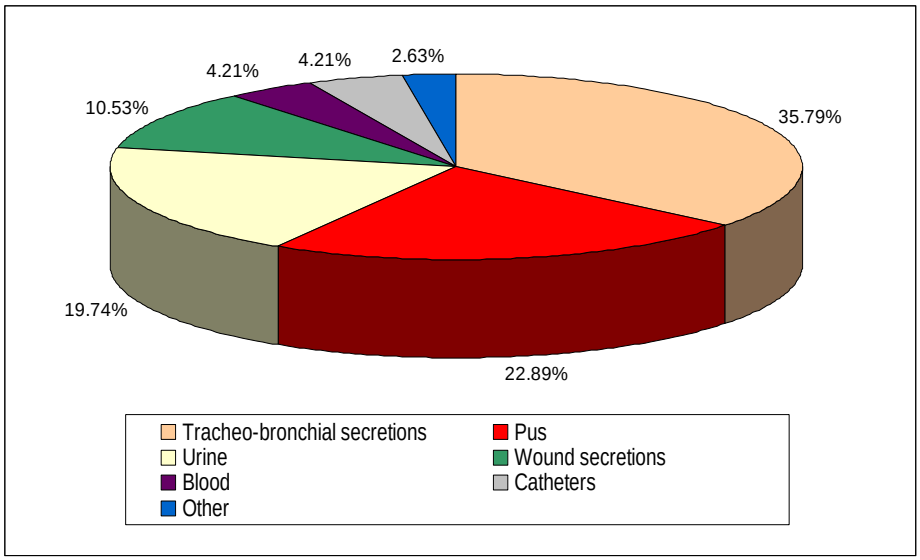

Fig. 3. *The distribution of Providencia strains on the pathological products*

Figure 2 illustrates the distribution on the hospital wards of the strains of Providencia spp. isolated during the studied period.

It can be notice the highest share of isolated strains in ICUs, followed by Internal medicine and General surgery.

Figure 3 illustrates the distribution of the Providencia strains on pathological products in the studied period. There is a higher share of strains in the tracheo-bronchial secretions, followed by pus and urine.

The study also aimed to analyze the patterns of antibiotic resistance of the Providencia species strains due to the known multidrug resistance character of these microorganisms. (Figures 4 to 7).

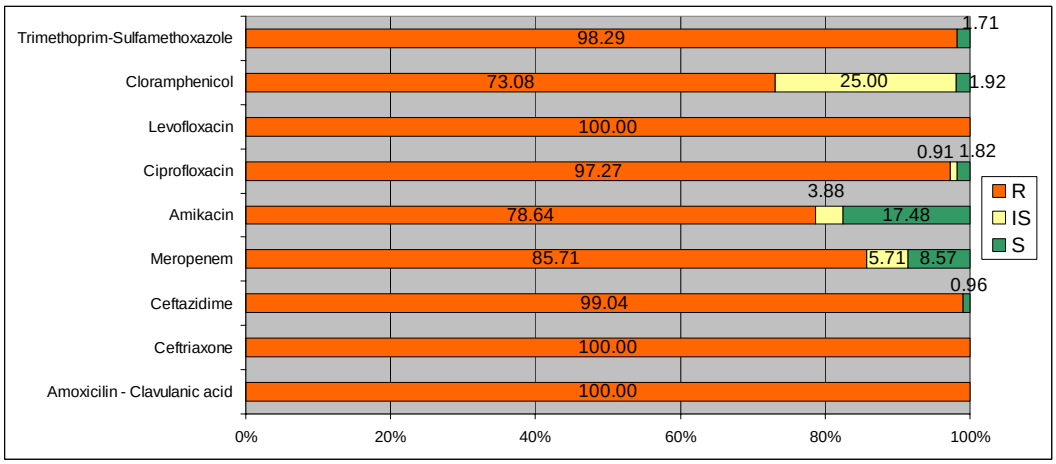

Fig. 4. *The resistance to antibiotics of Providencia spp. in 2018*

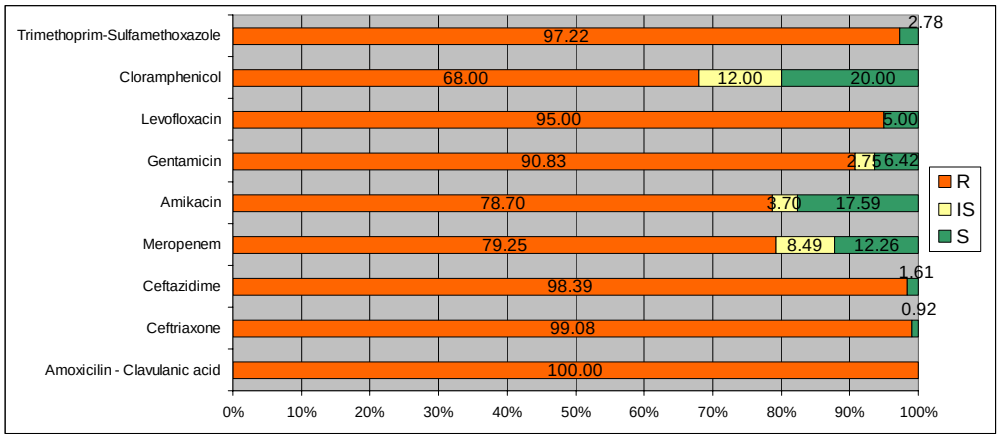

Fig. 5. *The resistance to antibiotics of Providencia spp. in 2019*

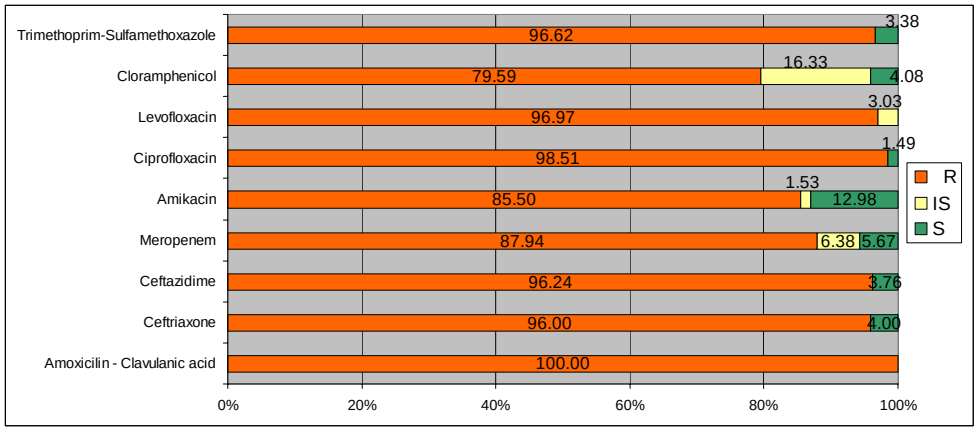

Fig. 6. *The resistance to antibiotics of Providencia spp. in 2018-2020*

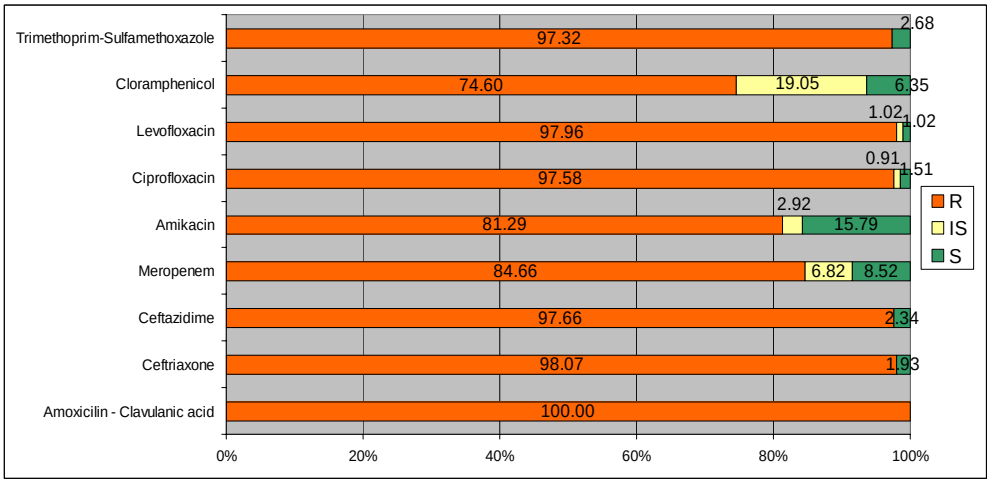

Fig. 7. *The resistance to antibiotics of Providencia spp. in 2018-2020*

It can be seen that the share of resistant strains is very high in all studied years for all tested antibiotics. In the current study the majority of strains were carbapenem-resistant Providencia spp. (84,66%), which, given the intrinsic resistance of these germs to colistin and to tigecycline, raises very big issues in case management and applied therapy. From this point of view, there are no noticeable differences from one year of study to another.

There are not many clinical studies on Providencia spp., for a long time this emerging pathogen being considered only a rare cause of nosocomial infection.

The obtained results are consistent with some studies and case reports that have also reported multiple drug resistance, including carbapenem resistance, especially in the ICU (92.1% -100%) [2], [20].

In the current study, the resistance to amikacin was 81.29%, close to that obtained in other studies on urinary catheterized patients (86%) [8], [21]; also, the higher weights of sensitive Providencia spp. were obtained for amikacin (15.79%) and meropenem (8.52%) which indicates a possible in vivo efficacy and recommends the use of these antibiotics for both empirical therapy and for pan drug resistant strains.

Other studies have variable results indicating that carbapenems (meropenem), amikacin, extended-spectrum cephalosporin or ciprofloxacin can be used for the treatment of infections [19], [22]. Most commonly, Providencia spp. were isolated from tracheobronchial secretions, pus or urine samples of the hospitalized patients, same as in other published cases [1], [17], [20].

The vast majority of strains of Providencia spp. came from patients hospitalized in the Intensive Care Unit, a result also reported by other authors [1], [17], [20].

Worldwide, the number of infections with gram negative bacilli (Enterobacteriaceae, P. aeruginosa, A. baumanni) which acquired resistance to carbapenems have dramatically increased and represent a main concern.

4. Conclusions

1. The distribution of the Providencia spp. strains on hospital wards was wide, including various wards of medical and surgical profile.
2. The highest share of Providencia spp. strains was recorded in Intensive Care Unit (76,84%), followed by the Internal medicine ward (5,79%) and the General surgery ward (3,95%).
3. More frequently, Providencia spp. were isolated from traheo-bronchial secretions (35,79%), from pus (22,89%) and from urine (19,74%).
4. Antimicrobial resistance levels were very high in all antimicrobials tested, including carbapenems.
5. The results of the study support the need for monitoring these germs with high potential for pan-resistance with an eye to the judicious case management, based on the knowledge of local patterns of resistance but also on previous clinical experience or various studies reports.

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