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1 **What antibiotics for what pathogens? The sensitivity spectrum of isolated strains in an**
2 **intensive care unit**

3 Dana Carmen Zaha¹, Simona Bungau², Sélim Aleya³, Delia Mirela Tit², Cosmin Mihai Vesa¹,
4 Amarin Remus Popa⁴, Carmen Pantis⁵, Octavian Adrian Maghiar⁵, Ovidiu Gabriel Bratu⁶,
5 Cristian Furau⁷, Radu Dumitru Moleriu⁸, Izabella Petre⁹, Lotfi Aleya^{9*}

6

7 ¹ Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of
8 Oradea, Oradea, Romania

9 ² Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea,
10 Romania

11 ^{3,10} Faculty of Medicine, Besançon, Chrono-Environnement Laboratory, UMR CNRS 6249.

12 ⁴ Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea,
13 Oradea, Romania

14 ⁵ Department of Surgical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea,
15 Oradea, Romania;

16 ⁶ Clinical Department 3, University of Medicine and Pharmacy “Carol Davila”, Bucharest,
17 Romania

18 ⁷ Life Sciences Department, Western University “Vasile Goldis” of Arad, Arad, Romania

19 ⁸ Department of Mathematics, Faculty of Mathematics and Computer Science, West University
20 of Timisoara, Romania

21 ⁹ Department XII of Obstetrics and Gynecology, “Victor Babes” University of Medicine and
22 Pharmacy, Timisoara, Romania

23 ¹⁰ Laboratoire Chrono-environnement, UMR CNRS 6249, Université de Franche-Comté,
24 Besançon, France

25 *Author for correspondence: lotfi.aleya@univ-fcomte.fr

Abstract

Antibiotic sensitivity spectrum of isolated strains differs according to hospital departments, the hospitals themselves, and countries. Discrepancies also exist in terms of antibiotic use and dosage. The aim of the present study is to compare the antibacterial agents, the types of infections, the number and type of pathogens, and the sensitivity to antibiotics used in the Intensive Care Unit (ICU) of the Emergency Clinical County Hospital of Oradea, Romania. Over a one-year period, data were gathered from the pharmacy computer system and medical records of inpatients. WHO Anatomical Therapeutic Chemical (ATC) / defined daily doses (DDD) methodology was used to assess drug administration data, and antibiotic use was expressed as DDD/1000 PD (patient days). The antibiotic susceptibility of isolated strains was expressed through the cumulative antibiogram. The overall consumption of antimicrobial agents was 1247.47 DDD/1000 PD. The most common drugs used were cephalosporins and fluoroquinolones (52.97% of the total). Ceftriaxone was the most commonly used, followed by levofloxacin. Infections of the respiratory and urinary tract were the most frequently diagnosed infections. The most commonly isolated bacteria type was *Acinetobacter baumannii* (22.12% overall), isolated especially from the respiratory tract and resistant to all the β -lactam antibiotics including carbapenems. Antimicrobials intake at the ICU is much higher compared to medical and surgical wards. After we tested the existence of a possible connection between antibiotic consumption and antibiotic resistance of bacteria, it was revealed that on our sample exists a poor positive association.

Key words: antibiotic; defined daily dose; infection; intensive care unit; bacteria; susceptibility.

47

48

49 **1. Introduction**

50 Antimicrobial resistance is one of the major problems in global public health, and the main cause
51 behind the increasing presence of resistant pathogens is the inappropriate and widespread use of
52 antimicrobial agents. The outcome is increased morbidity and mortality, and rise in healthcare
53 costs (Prestinaci et al., 2015).

54 The European Centre for Disease Prevention and Control (ECDC) (2017) has confirmed that
55 many countries in Europe, including Romania, present high antimicrobial resistance rates.
56 However, the report does not include all hospitals. While the resistance of gram-positive bacteria
57 has remained almost the same (ECDC, 2017), there has been an upward trend in the resistance
58 of gram-negative species. This increase has been shown to be related above all to third-
59 generation cephalosporins, fluoroquinolones, carbapenems and aminoglycosides for *Klebsiella*
60 *pneumoniae* and to ceftazidime, piperacillin tazobactam and fluoroquinolones for *Pseudomonas*
61 *aeruginosa*. For instance, in 2017, rates of resistance of *K. pneumoniae* were reported to be
62 22.5% for carbapenems and 64.1% for third generation cephalosporins and fluoroquinolones
63 (ECDC, 2017). *Acinetobacter* spp., which has fewer therapeutic options (Lin and Lan, 2014),
64 presented a combined resistance rate of 81.3%.

65 Production and marketing of new antimicrobial agents directed against new bacterial targets or
66 receptors seem unable to keep up with the development of antibiotic resistance (Fair and Tor,
67 2014) Experimental findings suggest that some vegetable extracts can exert some protection
68 against bacterial infections, but they are not yet in use (Abdel-Daim et al., 2018).

69 Several studies have demonstrated a higher presence of antimicrobial resistance in ICUs than in
70 general patient-care departments (Brusselaers et al., 2011; Meyer et al., 2010). Other surveys
71 have additionally shown that monitoring of hospital data can change prescriptions in specific

72 patient-care areas (Lai et al., 2016; Owens et al., 2004). One of the primary goals of these studies
73 was to understand the connection between antimicrobial use and the increasing resistance of
74 pathogens, as well as to define their relationship with individual patient-care areas.

75 Antimicrobial consumption in Romania is complex and still largely unexplored, and data from
76 different studies are fragmented. Published or unpublished reports on antibiotic consumption
77 have shown use that has greatly increased (is proportionally high) and excessive (Cioca and
78 Munteanu, 2019). Increased consumption leads to dissemination of antibiotics in the
79 environment, from excretion from the human body and through inappropriate disposal of
80 medicinal waste (Bungau et al., 2015, Bungau et al., 2016).

81 Significant environmental and health impacts, difficult to control, occur due to urban waste
82 streams with high concentrations in pharmaceutical products such as antibiotics. These
83 compounds are not completely removed in wastewater treatment plants, and their residues may
84 be released through effluents into the aquatic environment (Turkdogan and Yetilmezsoy, 2009).
85 Because they pollute soil and water, they have negative effects on organisms in the environment,
86 and they also generate negative effects on human health, one of the most serious being the
87 increase in antibiotic resistance and interference with the hormonal system. Increasing
88 concentrations in active substances are the cause of the increase of the negative effects (Bungau
89 et al., 2018).

90 Recent data on use in hospitals or the primary-care sector show that the variation in resistance to
91 different antibiotics between different departments can be explained by the variation of selective
92 pressure on resistance to this type of drug (Oz et al., 2014). In Romania, data on antibiotic use or
93 susceptibility of isolated strains are not very well characterized, due to few studies or reports
94 having evaluated the subject. The aim of this study was to evaluate the antibiotic consumption

95 for one year and the variability in the present pathogens, to compare the antimicrobial
96 prescriptions with the pathogen sensitivity spectrum, and to suggest possible future interventions.

97

98 **2. Methods**

99 This study was carried out using data available at the ICU of the Emergency Clinical County
100 Hospital of Oradea, Romania. It is a clinical university hospital, with 917 acute-care beds, 6.5%
101 belonging to the ICU. For this study, data were collected over the period between January 1 and
102 December 31, 2017. The information used was selected from the medical records of the patients,
103 InfoWorld and the WHONET database on the number and type of pathogens, respecting each
104 patient's privacy.

105 Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) was used for the
106 identification of isolates (Clark et al., 2013); it is a three-step process, as follows: 1. mixture of a
107 portion of a colony (the sample) with a matrix material and applying to a target plate; 2. pulsed
108 laser irradiation of the sample, causing the ablation and the desorption of the matrix material and
109 the sample; 3. finally, ionization of the molecules of the analyte (by protonation / deprotonation
110 in the hot plume of ablated gases); then, they can be accelerated into whichever mass
111 spectrometer. The mass spectra are generated and analyzed by a special software, being
112 compared with the stored profiles providing a faster species diagnosis.

113 The VITEK 2 system and Kirby–Bauer disk diffusion method were used for the antibiotic
114 susceptibility testing. Suspensions were prepared by emulsifying the bacterial isolates in 0.45 %
115 saline to the equivalent of a 0.5 McFarland turbidity standard. The isolate was classified as
116 susceptible, intermediate, or resistant based on the Clinical Laboratory Standards Institute
117 (CLSI) criteria (2018).

118 *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC
119 29212 were used as quality control strains to check the quality of culture media, and
120 antimicrobial cards and disks. The pharmacy has a computerized record of each antibiotic
121 prescribed, and antimicrobial data were extracted from the system.

122 Evaluation of the prescribed antimicrobials was carried out using the DDD methodology, which
123 was derived from the ATC/DDD Index 2018 made by the WHO Collaborating Centre for Drug
124 Statistics Methodology (2018), the reference standard for drug utilization methodology. WHO
125 promotes the use of the DDD methodology for each drug and route of administration. The
126 methodology defines the DDD as the assumed average maintenance adult dose per day for the
127 main direction of use of the agent and the maintains updates. The WHO DDD has also been used
128 to demonstrate a quantitative, ecological relationship between antimicrobial use and resistance in
129 hospitals (Muller et al., 2003; 2004; Westh et al., 2004; Kern et al, 2005).

130 Hospital consumption of antimicrobials was calculated by adding the total number of grams of
131 each antimicrobial used during the period of interest (one year). The result is divided by the
132 WHO-assigned DDD resulting number of DDD (DDDs). To control the population number, the
133 antimicrobial use density was determined, expressed as DDD / 1000 PD, for each antibiotic and
134 route of administration. The annual number of PD was provided by the hospital's admission
135 department.

136 In this research, antibiotics were defined as antibacterial for systemic use or group J01 of the
137 WHO ATC classification system. The antibiotics excluded from this study were: antibacterial
138 against tuberculosis (rifampicin), as this pathology is not treated in our institution; rifaximin used
139 in diarrheal disorders without a specific etiology; topical antibiotics (parenterally administered
140 prevalent); oral colistin and vancomycin (not used); metronidazole and antifungals (used without

141 having a sensitivity test); those not present in this study hospital (fosfomicin, ticarcillin,
142 ticarcillin + tazobactam, tobramycin).

143 The analyzed classes of antibiotics were cephalosporins, fluoroquinolones, aminoglycosides and
144 carbapenems prescribed in therapy and prophylaxis of hospital infections produced by gram-
145 negative and gram-positive bacteria. Almost all antibiotics were administered parenterally. The
146 positive pathological samples were sputum, fluids (pleura, peritoneal, pericardial), trachea-
147 bronchi aspirates, secretions of lesions, wounds, catheters, urine and blood. Antibiotic sensitivity
148 analysis was performed using a cumulative antibiogram, and only the percentage of strains
149 considered susceptible was reported. Descriptive analysis was performed. Values are expressed
150 as numbers with percentages; WHO DDD/1000 PD are calculated as described above.

151 To seek potential connection between antibiotic consumption and antibiotic resistance of
152 bacteria, we performed a correlation analysis using the SPSSv19 software and for the Scatter
153 Plot – the Microsoft Excel 2013 software. The Pearson coefficient, the determination coefficient
154 and the p value (obtained from the correlation model and considering $\alpha=0.05$ as the confidence
155 level) were also calculated.

156

157 **3. Results**

158 The overall consumption of antimicrobial agents (expressed as the total number of DDD of
159 antibiotics – ATC group J01, antibacterial for systemic use) was 114,269, and the overall DDD
160 per 1000 PD was 2180.4 in 2017. **Table 1** summarizes the antibiotic use for the whole hospital
161 as well as by department. Most of these were used in the ICU, followed by the surgical and
162 medical wards.

163 The parenteral administration of antibiotics represented almost 94.54%, while oral forms
164 represented only 5.46% of total antibiotic intake. Dividing antibiotic use by surgical/medical
165 wards and ICU, it was found that more than a half of the total antimicrobials were consumed in
166 the latter.

167 General use for the prescribed antibiotics classes is presented in **Table 2**. The most prescribed
168 antibiotics were cephalosporins in all departments (51.55% of the total), followed by
169 fluoroquinolones (10.91%), aminoglycosides (7.46%), penicillin and beta-lactamase inhibitor
170 combinations (6.36%), carbapenems (5.66%), penicillin (3.84%) and cefoperazone + sulbactam
171 (3.71%) (Table 2). Less frequently prescribed were linezolid, macrolides and tetracyclines.

172 The total consumption of antimicrobials in the ICU was 1247.4 DDD/1000 PD in 2017 (**Table**
173 **1**). Distribution of the top ten antibiotics was: ceftriaxone (J01DD04, 39.65%), levofloxacin
174 (J01MA12, 7.02%), cefuroxime (J01DC02, 6.30%), cefoperazone + sulbactam (J01DD62,
175 4.98%), meropenem (J01DH02, 4.79%), colistin (J01XB01, 4.43%), amikacin (J01GB06,
176 4.13%), piperacillin + tazobactam (J01CR05, 3.43%), ertapenem (J01DH03, 3.04%),
177 ciprofloxacin (J01MA02, 2.37%).

178 Less frequently prescribed were the following antibiotics: oxacillin (J01CF04), ampicillin +
179 sulbactam (J01CR01), doxycycline (J01AA02), ceftaroline fosamil (J01DI02), cefixime
180 (J01DD08), clarithromycin (J01FA09), azithromycin (J01FA10), benzylpenicillin (J01CE01),
181 ampicillin (J01CA01), cefaclor (J01DC04).

182 The total number of isolated pathogens in the hospital was 2750, and the most diagnosed
183 infections were those of the urinary tract (1031), followed by wounds (947) and respiratory
184 infections (651). Urinary and respiratory tract infections thus dominate (78.61%), followed by
185 wounds (8.99%) (**Table 4**).

186 The most commonly isolated pathogen was *Escherichia coli* (26.07%), which is responsible for
187 most of the urinary tract infections in the entire hospital (**Table 5**). This strain showed good
188 sensitivity rates to all antibiotics tested, except for ampicillin (**Figure 1A**).

189 The second most frequently isolated pathogen was *Staphylococcus aureus* (13.85%), which was
190 the common cause of wound and respiratory tract infections; its antibiotic sensitivity patterns is
191 presented in **Figure 1B**. *Enterobacter* spp. was the third most frequently isolated pathogen from
192 respiratory and urinary tract infections. *Enterobacter* spp. showed lower sensitivity rates
193 especially to fluoroquinolones and Gentamycin. Its resistance rates were higher : 77.4% for
194 ceftriaxone, 74.6% for ceftazidime, and 65.62 % for cefoperazone (**Figure 1C**).

195 *Enterococcus faecalis* and *Proteus* spp. were isolated from urinary tract infections and wounds at
196 almost the same ratio (8.18% and 8.58% respectively). Isolated *Proteus* spp. strains also showed
197 high resistance rates, and they represented 8.53% overall, but therapeutic options were more
198 varied and included aminoglycosides, cefoperazone + sulbactam, piperacillin + tazobactam, and
199 carbapenems. Isolated strains showed low sensitivity rates to cephalosporins and
200 fluoroquinolones despite their frequent prescription, as represented in **Figure 1D**.

201 Over the same period, a total of 868 strains of pathogens were isolated in the ICU. The most
202 common was *Acinetobacter baumannii* (22.12%), especially from the respiratory tract. This
203 multidrug-resistant pathogen showed sensitivity to colistin (99.03%), ampicillin + sulbactam
204 (62%), and cefoperazone + sulbactam (41.7%), as presented in **Figure 1E**. *E. coli* and
205 *Enterobacter* spp. were isolated at equal proportions (14.41%). Those two strains were the
206 second-most frequently isolated in the ICU, followed by *Proteus* spp. (8.53%), *Pseudomonas*
207 *aeruginosa* (7.72%), *Klebsiella* spp. (5.30%) and *Serratia* spp. (5.18%). *Morganella* spp.,

208 *Citrobacter* spp., *Providencia stuartii*, *Burkholderia complex* and *Stenotrophomonas maltophilia*
209 were isolated in small numbers (less than 1% for each).

210 The fourth etiological agent of the infectious disease in the ICU was *Pseudomonas aeruginosa*,
211 which showed increased resistance to the tested antibiotics. In this case, the therapeutic options
212 were colistin, cefoperazone-sulbactam, and piperacillin + tazobactam (**Figure 1F**). Half of the
213 tested strains were resistant to ceftazidime and 62.8% to cefepime, but both antibiotics were
214 relatively rarely administered.

215 A total of 128 *Klebsiella* spp. strains were isolated in the evaluated period in the ICU,
216 representing 5.30%; these strains exhibited low rates of sensitivity to the cephalosporins (26% in
217 the case of ceftriaxone) and fluoroquinolones (**Figure 1G**), which were frequently prescribed.

218 Gram-positive microorganisms were susceptible to linezolid (100%), teicoplanin (97.01%), and
219 vancomycin (96.81%), in descending order. The slight reduction in susceptibility to vancomycin
220 was found only for *Enterococcus* spp. Among these antimicrobials, the most prescribed was
221 teicoplanin, followed by vancomycin. Antibiotic susceptibility to gram positive strains can be
222 observed in **Figure 2**.

223 By analyzing the cumulative antibiogram results for both gram positive and negative
224 microorganisms, the best sensitivity rates were for linezolid (J01XX08, 100%), colistin
225 (J01XB01, 99.03%), teicoplanin (J01XA02, 97.01%), and vancomycin (J01XA01, 96.81%),
226 followed by amoxicillin + clavulanic acid (J01CR02, 67.18%), ertapenem (J01DH03, 66.26%),
227 tetracycline (J01AA07, 63.85%), cefoperazone + sulbactam (J01DD62, 63.76%), piperacillin +
228 tazobactam (J01CR05, 59.75%), amikacin (J01GB06, 56.8%), meropenem (J01DH02, 55.16%),
229 trimethoprim + sulfamethoxazole (J01EE01, 52.83%), and ampicillin + sulbactam (J01CR01,

230 50.85%). The sensitivity rates of the tested antibiotics (according to the cumulative antibiogram)
231 are presented in **Table 6**.

232 For the correlation model, the data presented in Table 3 and Table 6 were used. As Table 3
233 contains 32 entries and Table 6 contains 33 entries, we analyzed only the 27 common entries
234 (**Table 7** which presents values obtained from calculating the percentage of antibiotic use and the
235 sensitivity values of the tested antibiotics). For these two variables, a correlation model was run
236 and a positive insignificant correlation (the Pearson coefficient $r=0.21$; determination coefficient
237 $R^2=0.04$; p value returned from the correlation model $p=0.28$) was obtained. Our sample thus
238 shows a poor association between the variables, but this relation can't be generalized for the
239 whole population. In order to have a better image of this relation, the association was plotted
240 using a Scatter Plot chart, and a line chart as well – in order to highlight the dynamics of our data
241 (**Figure 3** and **4**).

242

243 4. Discussion

244 Antimicrobials used in hospitals vary widely, a fact that can be explained by differences in
245 patient and hospital characteristics, antibiotic policies, physician education, and healthcare
246 systems. There is also great variability in the antibiotic sensitivity spectrum of isolated strains
247 (Leekha et al., 2011).

248 The present study highlights the combination of antibiogram reports with antibacterial
249 consumption in the ICU, which provides potential measures for lowering morbidity and
250 mortality. The prescribed daily dose for most of the antibiotics corresponded to the WHO
251 defined daily dose, reflecting adherence to international recommendations. Antimicrobials intake
252 at the ICU is much higher than that at the medical and surgical wards, and they are prescribed

253 mainly for respiratory and urinary tract infections in a manner similar to other data reported in
254 literature, in accordance with the type of patient population and the geographical location studied
255 (Bitterman et al., 2016; Gianino et al, 2019). Antimicrobial consumption, sensitivity rates and
256 spectrum of pathogens isolated in the ICU and medical/surgical departments showed disputable
257 differences.

258 The most frequently prescribed antibacterial was ceftriaxone (39.65%), a third-generation
259 cephalosporin that is active on *Enterobacterales*, except *Enterobacter* spp. In the present study,
260 *E. coli*, *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp. and *Serratia* spp. were isolated in 33.53%
261 of cases, but annual sensitivity rates to ceftriaxone were low (28.35%), except for *E. coli*. The
262 high consumption of ceftriaxone despite the limited sensitivity of isolated strains could be
263 explained by its use in empirical therapy, and it could be a reasonable therapeutic option because
264 the most commonly isolated pathogen is *Escherichia coli* from urinary tract infections (which
265 demonstrate good sensitivity rates to all antibiotics tested, except for ampicillin). This contrasts
266 with other studies, which showed an increase in the prevalence of extended-spectrum β -
267 lactamase – producing *Escherichia coli* (ESBL – producing *E. coli*) worldwide (Alqasim et al.,
268 2018).

269 As mentioned previously, *Enterobacter* spp. has lower sensitivity rates to fluoroquinolones and
270 gentamycin. According to the ECDPC (2016), resistance to third-generation cephalosporins was
271 reported in 44% of cases of *Enterobacter* spp. isolates. In this study, the resistance rates were
272 higher: 77.4% for ceftriaxone, 74.6% for ceftazidime, and 65.62 % for cefoperazone.

273 Levofloxacin and cefuroxime, the second- and third-most used in the ICU (7.02% and 6.3%
274 respectively), can be used for both gram-negative and positive strains, showing sensitivity rates
275 of 33.8% and 45% respectively. Their consumption could be justified, as *E. coli* was the second

276 greatest etiological agent of infections in ICU and has good sensitivity to levofloxacin and
277 cefuroxime, which furthermore are used in treating half the cases of *Staphylococcus aureus* (the
278 fourth etiological agent in the ICU). For *Enterococcus faecalis* strains, 71.42% were sensitive to
279 Levofloxacin, but they represent only 2.53% of all strains. Sensitivity rates to Cefuroxime, the
280 second etiological agent of infections, were 53.1% for *Staphylococcus aureus* strains and 62.5%
281 for *E. coli* strains.

282 According to our results, the most commonly isolated pathogen in ICU was *Acinetobacter*
283 *baumannii*, which has sensitivity to colistin, ampicillin + sulbactam, and cefoperazone +
284 sulbactam. All three of these antimicrobials were relatively rarely prescribed, although they can
285 eradicate the infection, usually respiratory infections, especially in combination with
286 carbapenems (Lenhard et al., 2017; Altun, et al., 2014). *Acinetobacter baumannii* was the only
287 pathogen that was consistently isolated in the ICU (22.12% of total pathogens) in a way similar
288 to other studies. All the *Acinetobacter baumannii* isolates were resistant to all the β -lactam
289 antibiotics, including the carbapenems, as other studies have described (Handal et al., 2017).

290 According to ECDPC (2016), the most frequently isolated microorganism was *Pseudomonas*
291 *aeruginosa* in ICU-acquired pneumonia episodes. Moreover, the same study indicated that rates
292 of resistance of *Klebsiella* spp. isolates were 38% to third generation cephalosporins and 11% to
293 carbapenem. In contrast, isolated *Klebsiella* spp strains showed good sensitivity to Amikacin
294 (88.6%), as demonstrated by other studies as well (Baicus et al., 2018).

295 Fluoroquinolones were the second therapeutic option, in both hospitals and ICUs: ciprofloxacin,
296 although quite commonly used, and moxifloxacin (less often prescribed) showed annual
297 sensitivity of only 38.17% and 12.76% respectively to the strains tested. In the same situation,

298 the following were also prescribed quite often but with relatively low sensitivity: clindamycin,
299 ceftazidime, cefoperazone and cefepime.

300 In the case of carbapenems, the most prescribed was meropenem, which showed a sensitivity rate
301 of 55.16%. ertapenem, which is prescribed less often than meropenem, presented better
302 sensitivity in 66.26% of the tested strains. Both are useful in the treatment of pneumonia,
303 complicated urinary tract infections (including pyelonephritis), complicated intra-abdominal
304 infections, and complicated skin infections. This difference in sensitivity rate was clinically
305 significant and indicated underutilization of ertapenem and overutilization of meropenem.
306 Imipenem, although less, used showed sensitivity in 42.3% of the tested gram-negative strains.

307 As for aminoglycosides, 56.8% of the strains tested were sensitive to amikacin, which was
308 predominantly prescribed. This figure was 43.29% for gentamycin, which was prescribed less
309 often.

310 Combinations (cefoperazone + sulbactam, ampicillin + sulbactam, amoxicillin + clavulanate,
311 piperacillin + tazobactam) showed good annual sensitivity rates. Cefoperazone + sulbactam and
312 piperacillin + tazobactam were more frequently prescribed than amoxicillin + clavulanate.

313 For the *Staphylococcus* spp. strains, 35% were methicillin sensitive. As a result, they should have
314 been treated with oxacillin, but this antibiotic has not been prescribed to the same extent. The
315 most frequently isolated microorganisms were coagulase-negative staphylococci in ICU-acquired
316 bloodstream or catheter infections.

317 Some of the isolated strains were tested for susceptibility to tetracycline and trimethoprim +
318 sulfamethoxazole and showed good sensitivity rates (63.85% and 52.83% respectively).
319 Doxycycline was rarely administered to patients included in our study, and trimethoprim +
320 sulfamethoxazole was not administered.

321 According to the data available in Romania, statistics on antibiotic use or susceptibility of
322 isolated strains are not very clear or well centralized; only very few research studies evaluated
323 and presented valuable conclusions on these subjects. Even under these circumstances, published
324 reports show increased antibiotic resistance in diverse healthcare settings (Bedreag et al., Penes
325 et al., 2017; Timofte et al., 2016).

326 The analysis of antimicrobial consumption is an important component of medical audits for
327 monitoring, evaluation, and making the necessary changes in physicians' prescribing patterns in
328 order to achieve rational and cost-effective medical care. Yet, antibiotic resistance is a major
329 worldwide concern, and selective use of antimicrobial drugs is by far the most important driving
330 force behind the development of resistance. As a result, stewardship initiatives should direct
331 educational efforts to shortening durations of antimicrobial exposure and review the current
332 approach to empirical prescribing (Davey et al., 2017). Antimicrobial stewardship programs
333 should be implemented to control microbe resistance in inpatients, and surveillance of
334 antimicrobial use with observation of bacterial resistance rates can help control resistance in
335 general. Each hospital must enact priority measures to control the emergence of antibiotic-
336 resistant bacteria, including control of overuse (Doron and Davidson, 2011).

337 Optimal management of antimicrobial use implies that physicians should prescribe patients the
338 least harmful treatment, using the cheapest antibiotic, for the shortest possible time needed to
339 cure or prevent an infection. Literature data recommend four possible strategies to ensure that
340 this goal is achieved: rational use of all antimicrobials; selective control and restriction of
341 antimicrobial agents; cyclic or rotational antimicrobial use; and the use of combined
342 antimicrobial therapy, where appropriate, to prevent the emergence of resistance (Shales et al.,
343 1997).

344 Considerable efforts have been made in recent years and should be continued and intensified, to
345 educate physicians, pharmacists, and the population about the importance of minimizing the
346 unnecessary use of antimicrobials and the inappropriate disposal of waste in the form of expired
347 or unused medicinal products, in order to reduce negative impact on the health of the population
348 and the environment (Bungau et al., 2018; Tit et al., 2016). Romania is among the top four
349 countries of Europe in terms of the total amount of antibiotics used (ECDPC, 2017). This is due
350 to insufficient information on the effect of antibiotics and insufficient education on their role and
351 effects. The consequences of abusive use of antibiotics are precisely increases in antibiotic
352 resistance and the amount of antibiotic-derived waste (Bungau et al., 2018).

353 It is increasingly recognized and affirmed the role of the environment in the global spread of
354 antibiotic clinical resistance (Singer et al., 2016). Also, bacterial resistance to antibiotics is a
355 natural phenomenon found in various and numerous locations in the environment, apparently
356 without antibiotics (Pallecchi et al., 2007) or with trace/low levels of antibiotics of natural
357 synthetic origin (Raaijmakers and Mazzola). Although antibiotic concentrations found in the
358 environment are not very high, in the order of μg or ng/L , due to the cumulative effect of the
359 intensified synthesis of new antibiotics and their continuous release into ecosystems, the new
360 mechanisms of resistance to these antibiotics have adapted and grown; therefore, bacteria have
361 developed resistance to numerous antibiotics (Ding and He, 2010). Research has shown that
362 antibiotic resistance genes (ARGs) have ecological origins, but the release and accumulation of
363 additional antimicrobials in the environment facilitated their spread (Baquero et al., 2008).
364 Consequently, ARGs are found in all environments and are currently considered becoming
365 visible pollutants (Pruden et al, 2006).

366 There are few studies in Romania that quantify the existence of antibiotics in an ARB or ARG
367 environment. The presence of antibiotics in the classes of penicillin, cephalosporin and
368 tetracycline has been investigated by Opris et al. (2013) in wastewater and effluent samples
369 collected at a waste water treatment plant. The results indicated the presence of ceftriaxone 334
370 $\mu\text{g/L}$, tetracycline 146 $\mu\text{g/L}$ and doxycycline 110 $\mu\text{g/L}$ in residual water; these antibiotics were
371 not detected in water samples taken from effluents. Ceftriaxone was determined in the largest
372 amount, correlated with the results of our study showing that ceftriaxone is the most commonly
373 prescribed antibacterial agent.

374 The impact and presence of waste resulting from or generated by antibiotics were investigated as
375 well (Szekeres et al., 2017). This research also evaluated the diversity of numerous antibiotic
376 resistance genes (ARGs) along with the composition of the bacterial community that can be
377 found in the wastewater effluents discharged from different Romanian hospitals. The results
378 pointed to increased concentrations of certain β -lactam antibiotics including trimethoprim and
379 glycopeptides. Moreover, ARGs collected from contaminated effluents were diverse, exhibiting
380 an increased relative abundance concomitantly to the dominance of the genera *Acinetobacter*,
381 *Enterococcus*, *Pseudomonas* and members of the Enterobacteriaceae family. The community
382 structure of these potential sources of resistance genes as demonstrated in our survey (Szekeres
383 et al., 2017) varied from one hospital to another.

384 It is noteworthy that the treatment of wastewater installed by authorities removed only partially
385 these pollutants (Szekeres et al., 2017), which thus infers that residual waters in hospitals are
386 important contributing factor in the dissemination of resistant bacteria and resistance genes. This
387 is also supported by other recent findings evidencing the presence of isolated bacterial species in
388 the environment (Hrenovic et al., 2014, Khan et al., 2018, Marinescu et al., 2015).

389 The present study on antimicrobials provides many important characteristics of antibacterial
390 prescription. The antibiotic classes prescribed in more than 50% of cases were cephalosporins,
391 fluoroquinolones, aminoglycosides, and beta lactam/beta lactamase inhibitors. Cephalosporins
392 continued to be a main prescription of antibiotic therapy in the hospital because of their broad
393 spectrum of activity and clinical efficiency. The most commonly prescribed agent was
394 Ceftriaxone, the utilization pattern being similar to the one described by Anand et al (2016). The
395 preference of fluoroquinolones over aminoglycosides points towards a trend of using less toxic
396 antimicrobial classes and the broader spectrum of action including both gram-positive and
397 negative. Many studies in this field demonstrated that the antibiotic resistance proportion of
398 bacterial strains presents large variations in different countries, most probably due to the
399 differences between the consumption of antibiotics and hospital infection control. Proper and
400 effective implementation of prevention and control programs regarding antimicrobial resistance
401 is imperative at every hospital and pharmacy level (Davey et al., 2017; Lee et al., 2013).

402 Testing in our research the possible connection between antibiotic consumption and antibiotic
403 resistance of bacteria, pointed out a weak positive association $r=0.21$; thus, it can be admitted
404 that if the sensitivity of an antibiotic is increasing, the use of that antibiotic is increasing as well.
405 Because of this poor association, medicine uses a wide variety of different types of antibiotics
406 because there is no particular drug / treatment that works every time in every patient, which is
407 easy to understand given the complexity of the human body.

408 Limitations of this study can be considered to be the collection of data from only one ICU, in a
409 single hospital, and the short observation period. In addition, it was not possible to differentiate
410 every patient and their comorbidities. The majority of the patients whose data were registered in
411 the hospital were elderly, suffering chronic diseases (such as diabetes and hypertension). Another

412 (potential) limit of the study is that it may underestimate year-over-year changes in
413 susceptibility.

414

415 **Conclusions**

416 This research shows differences between antibacterial use and the sensitivity spectrum of
417 isolated strains. Among the isolated pathogens, the preponderance of gram-negative bacteria
418 *Acinetobacter* spp. strains stands out, which can mean insufficient measures to control
419 nosocomial infections.

420 Based on the record data, priority measures should be implemented to control the resistance of
421 microbes in inpatients and the surveillance of antimicrobial use, in particular by controlling over-
422 use. Future studies should be undertaken to verify these findings in different settings and among
423 diverse inpatient populations.

424

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596 **List of figures**

597 **Figure 1.** Antibiotic sensitivity patterns of: **A.** *E. coli* isolates; **B.** *Staphylococcus aureus*; **C.**
598 *Enterobacter* spp.; **D.** *Proteus* spp.; **E.** *Acinetobacter baumannii*; **F.** *Pseudomonas aeruginosa*;
599 **G.** *Klebsiella* spp.

600 **Legend for figures 1.A.-G.:** AK – Amikacin; AMC – Amoxicillin + Clavulanate; ; AM –
601 Ampicillin; CAZ – Ceftazidime; CES – Cefoperazone + Sulbactam; CFM – Cefixime; CFP –
602 Cefoperazone; CIP – Ciprofloxacin; CLR – Clarithromycin; CN – Gentamycin; CRO –
603 Ceftriaxone; CT – Colistin; CXM – Cefuroxime; DA – Clindamycin; E – Erythromycin; ETP –
604 Ertapenem; FEP – Cefepime; IPM – Imipenem; LEV – Levofloxacin; LNZ – Linezolid; MEM
605 – Meropenem; MXF – Moxifloxacin; OFX – Ofloxacin; OX – Oxacillin; P – Benzylpenicillin;
606 SAM – Ampicillin + Sulbactam; SXT – Trimethoprim + Sulfamethoxazole; TE – Tetracycline;
607 TEC – Teicoplanin; TZP – Piperacillin + Tazobactam; VA – Vancomycin.

608 **Figure 2.** Antibiotic sensitivity patterns of gram-positive strains

609 **Figure 3.** The association between the antibiotic use values and the sensitivity values

610 **Figure 4.** The dynamics between the antibiotic use values and the sensitivity values

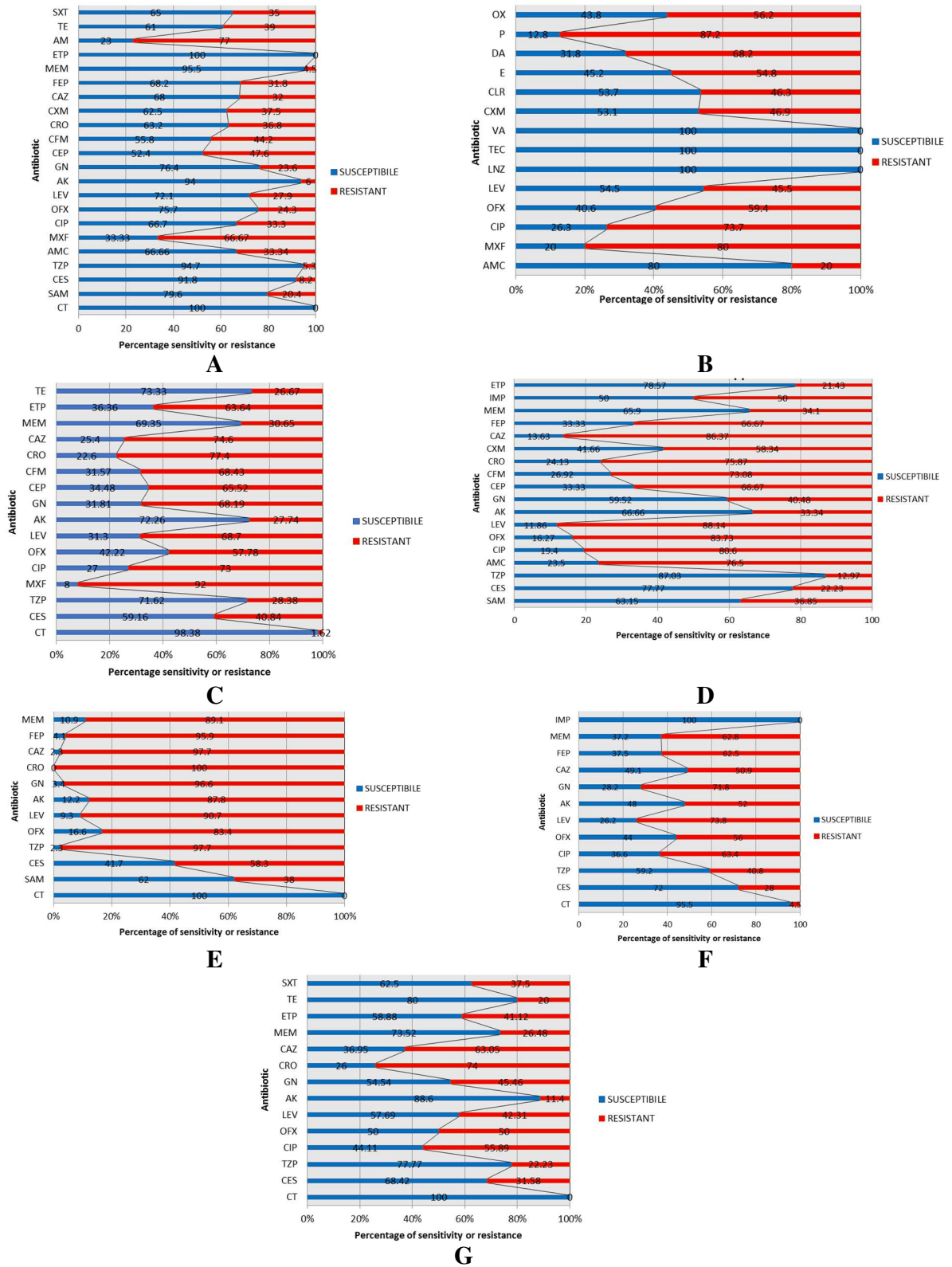


Figure 1.

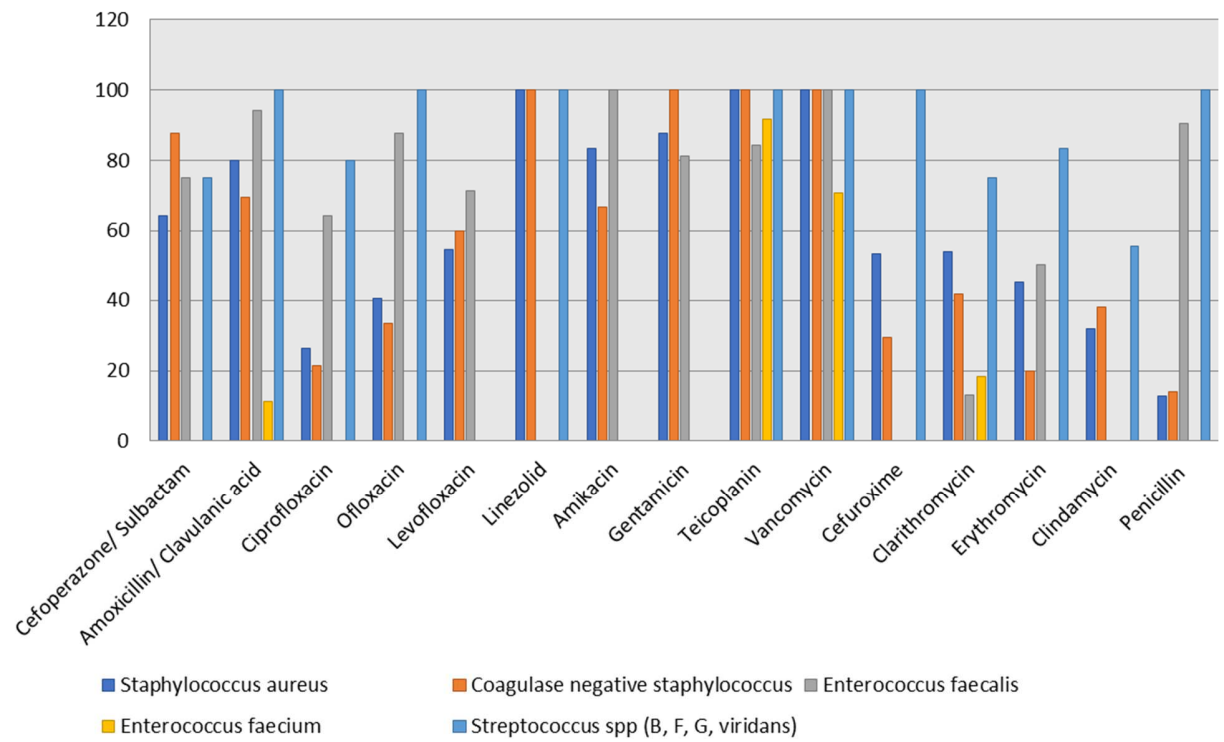


Figure 2.

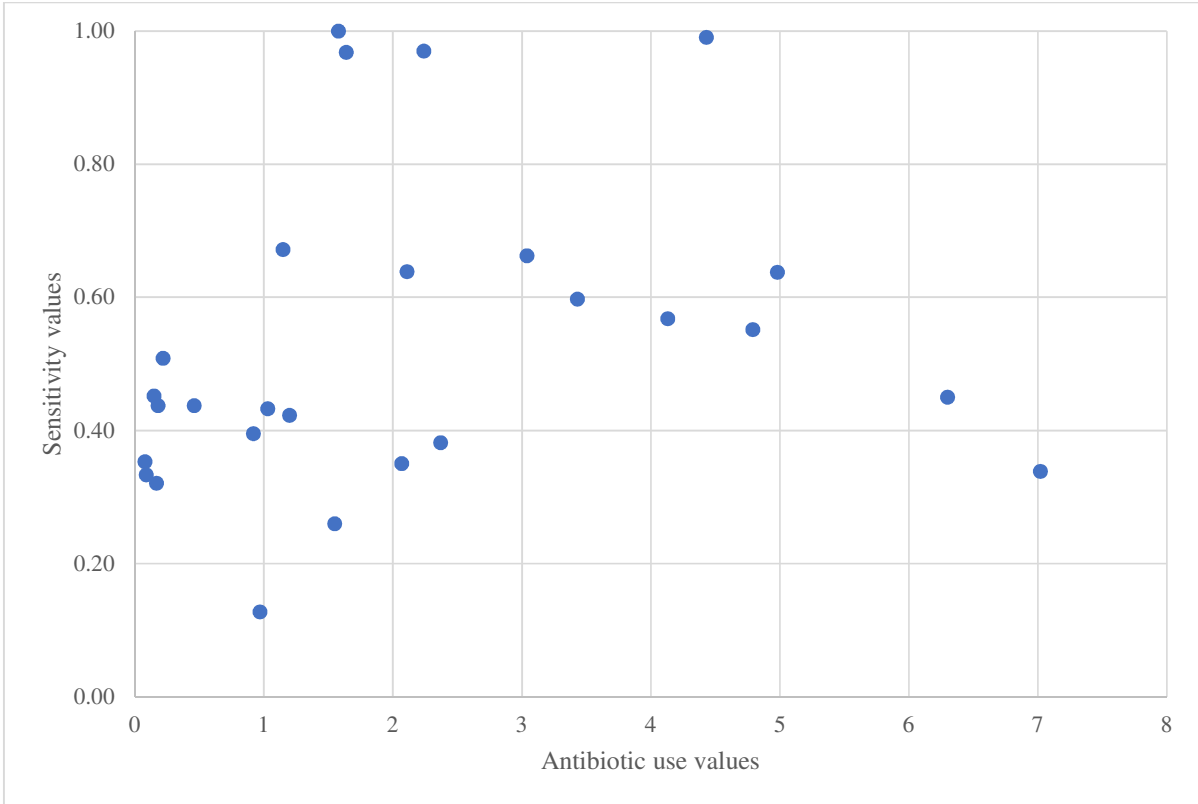


Figure 3.

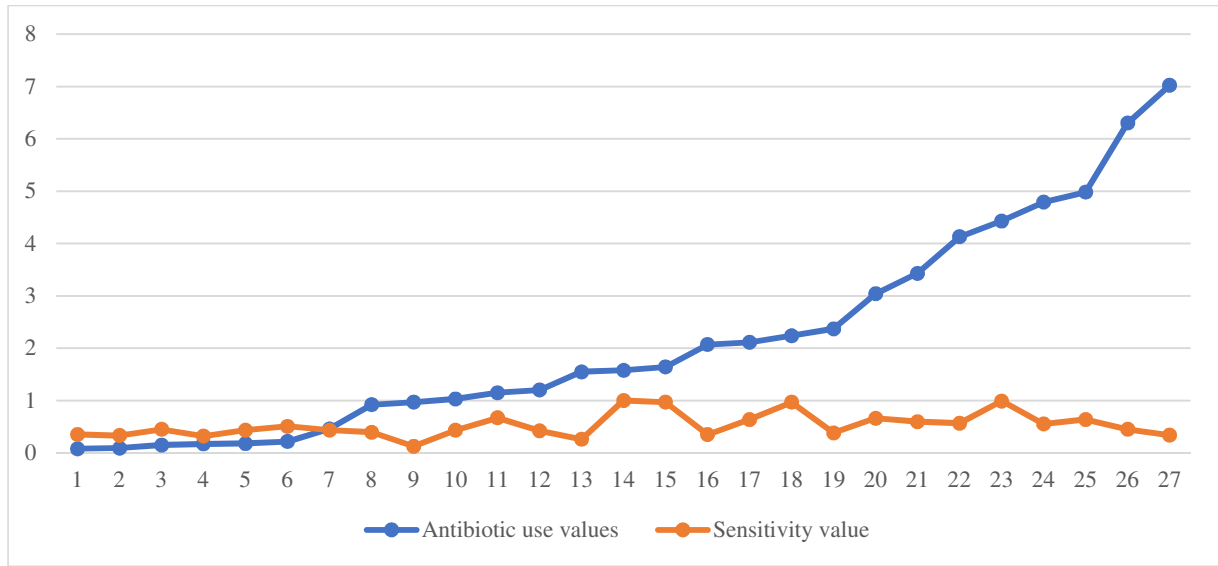


Figure 4.

Table 1. Overall antibiotic use

Department	No. of PD	No. of DDDs	DDD/1000 PD
Intensive Care Unit	17,053	21,272	1247.4
Surgical wards	110,530	53,387	483.0
Medical wards	87,859	39,610	450.8
TOTAL	215,442	114,269	2180.4

Table 2. General use for the prescribed antibiotics classes

Antibacterial	DDD/1000 PD				
	Surgical wards	Intensive care unit	Medical wards	Total	
				No. of doses	%
Cephalosporins	31	61.99	15.53	108.52	51.55
Fluoroquinolones	3.69	12.74	6.54	22.97	10.91
Aminoglycosides	2.79	6.331	6.581	15.70	7.46
Penicillins and beta-lactamase inhibitor	1.08	5.9	6.403	13.38	6.36
Carbapenems	0.62	11.1	0.19	11.91	5.66
Penicillins	5.6	0.96	1.524	8.084	3.84
Cefoperazone + sulbactam	0.29	6.12	1.4	7.81	3.71
Polymyxins (Colistin)	0.04	5.45	0.07	5.57	2.65
Lincosamide (Clindamycin)	2.42	2.54	0.46	5.42	2.57
Glycopeptides	0.11	4.78	0.041	4.93	2.34
Tigecycline	0.01	2.59	0.009	2.61	1.24
Linezolid	0.029	1.93	0.01	1.97	0.94
Macrolides	0.17	0.33	0.69	1.19	0.57
Tetracycline (Doxycycline)	0.01	0.22	0.17	0.41	0.20

Table 3. Antibiotic use expressed as DDD/1000 PD in the ICU

Antibacterial	ATC code	DDD/1000 PD	
		No.	%
Ceftriaxon	J01DD04	48.76	39.65
Levofloxacin	J01MA12	8.64	7.02
Cefuroxime	J01DC02	7.75	6.30
Cefoperazone + sulbactam	J01DD62	6.12	4.98
Meropenem	J01DH02	5.89	4.79
Colistin	J01XB01	5.45	4.43
Amikacin	J01GB06	5.07	4.13
Piperacillin + tazobactam	J01CR05	4.22	3.43
Ertapenem	J01DH03	3.74	3.04
Ciprofloxacin	J01MA02	2.91	2.37
Teicoplanin	J01XA02	2.76	2.24
Tigecycline	J01AA12	2.59	2.11
Clindamycin	J01FF01	2.54	2.07
Ceftazidime	J01DD02	2.04	1.66
Vancomycin	J01XA01	2.02	1.64
Linezolid	J01XX08	1.93	1.58
Cefepime	J01DE01	1.91	1.55
Imipenem cilastin	J01DH51	1.47	1.20
Amoxicillin + clavulanate	J01CR02	1.41	1.15
Gentamycin	J01GB03	1.26	1.03
Moxifloxacin	J01MA14	1.19	0.97
Cefoperazone	J01DD12	1.13	0.92
Oxacillin	J01CF04	0.57	0.46
Ampicillin + sulbactam	J01CR01	0.27	0.22
Ceftaroline fosamil	J01DI02	0.24	0.20
Doxycycline	J01AA02	0.22	0.18
Clarithromycin	J01FA09	0.22	0.18
Benzylpenicillin	J01CE01	0.21	0.17
Ampicillin	J01CA01	0.18	0.15
Azthromycin	J01FA10	0.11	0.09
Cefixime	J01DD08	0.1	0.08
Cefaclor	J01DC04	0.06	0.05

Table 4. Number and frequency (%) of infection types

Type of infection	Total (n = 2870)	Intensive care unit (n = 879, 100%)	
		No.	%
Respiratory tract	651	586	66.67
Urinary tract	1031	105	11.95
Wounds	947	79	8.99
Blood	58	38	4.32
Catheter	46	40	4.55
Fluids (pleural, pericardial, peritoneal)	137	31	3.53

Table 5. Number and frequency (%) of the pathogens isolated

Strains	Total (n = 2750)	Intensive care unit (n = 868, 100%)	
		No.	%
<i>Staphylococcus aureus</i>	381	65	7.49
<i>Coagulase negative staphylococcus</i>	119	47	5.41
<i>Enterococcus faecalis</i>	225	22	2.53
<i>Enterococcus faecium</i>	56	27	3.11
<i>Streptococcus pneumoniae</i>	2	1	0.12
<i>Streptococcus pyogenes</i>	3	0	0
<i>Streptococcus</i> spp. (<i>B, F, G, viridans</i>)	33	14	1.61
<i>Escherichia coli</i>	717	125	14.40
<i>Enterobacter</i> spp.	283	125	14.40
<i>Proteus</i> spp.	236	74	8.53
<i>Klebsiella</i> spp.	128	46	5.30
<i>Acinetobacter</i> spp.	240	192	22.12
<i>Pseudomonas aeruginosa</i>	195	67	7.72
<i>Serratia</i> spp.	80	45	5.18
<i>Morganella</i> spp.	32	4	0.46
<i>Citrobacter</i> spp.	5	1	0.12
<i>Providencia stuartii</i>	7	5	0.58
<i>Burkholderia complex</i>	7	7	0.81
<i>Stenotrophomonas maltophilia</i>	1	1	0.12

Table 6. Sensitivity rates of tested antibiotics (according to cumulative antibiogram)

Antibacterial name	ATC code	Sensitivity rates %
Linezolid	J01XX08	100
Colistin	J01XB01	99.03
Teicoplanin	J01XA02	97.01
Vancomycin	J01XA01	96.81
Amoxicillin + Clavulanic acid	J01CR02	67.18
Ertapenem	J01DH03	66.26
Tetracycline	J01AA07	63.85
Cefoperazone + Sulbactam	J01DD62	63.76
Piperacillin + Tazobactam	J01CR05	59.75
Amikacin	J01GB06	56.8
Meropenem	J01DH02	55.16
Trimethoprim + Sulfamethoxazole	J01EE01	52.83
Ampicillin + Sulbactam	J01CR01	50.85
Ampicillin	J01CA01	45.2
Cefuroxime	J01DC02	45
Clarithromycin	J01FA09	43.75
Oxacillin	J01CF04	43.75
Gentamicin	J01GB03	43.29
Imipenem	J01DH51	42.3
Erythromycin	J01FA01	41.37
Amoxicillin	J01CA04	40.62
Ofloxacin	J01MA01	39.57
Cefoperazone	J01DD12	39.53
Ciprofloxacin	J01MA02	38.17
Ceftazidime	J01DD02	37.03
Cefixime	J01DD08	35.32
Clindamycin	J01FF01	35.04
Levofloxacin	J01MA12	33.84
Azithromycin	J01FA10	33.33
Benzylpenicillin	J01CE01	32.08
Ceftriaxone	J01DD04	28.35
Cefepime	J01DE01	26
Moxifloxacin	J01MA14	12.76

Table 7. The relation between the antibiotic use expressed as DDD/1000 PD in the ICU and the sensitivity values of tested antibiotics (according to cumulative antibiogram)

Antibiotic	Antibiotic use	Sensitivity values
Cefixime	0.08	0.35
Azthromycin	0.09	0.33
Ampicillin	0.15	0.45
Benzylpenicillin	0.17	0.32
Clarithromycin	0.18	0.44
Ampicillin + sulbactam	0.22	0.51
Oxacillin	0.46	0.44
Cefoperazone	0.92	0.40
Moxifloxacin	0.97	0.13
Gentamycin	1.03	0.43
Amoxicillin + clavulanate	1.15	0.67
Imipenem cilastin	1.20	0.42
Cefepime	1.55	0.26
Linezolid	1.58	1.00
Vancomycin	1.64	0.97
Clindamycin	2.07	0.35
Tigecycline	2.11	0.64
Teicoplanin	2.24	0.97
Ciprofloxacin	2.37	0.38
Ertapenem	3.04	0.66
Piperacillin + tazobactam	3.43	0.60
Amikacin	4.13	0.57
Colistin	4.43	0.99
Meropenem	4.79	0.55
Cefoperazone + sulbactam	4.98	0.64
Cefuroxime	6.30	0.45
Levofloxacin	7.02	0.34

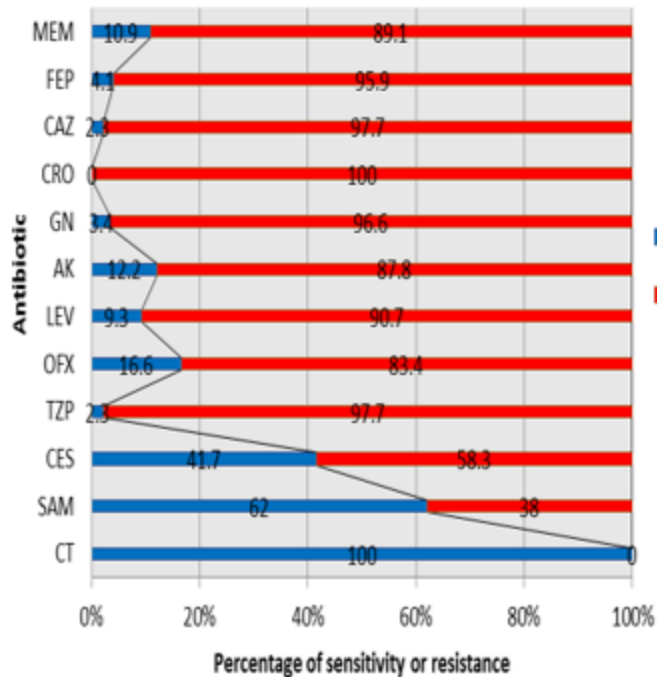


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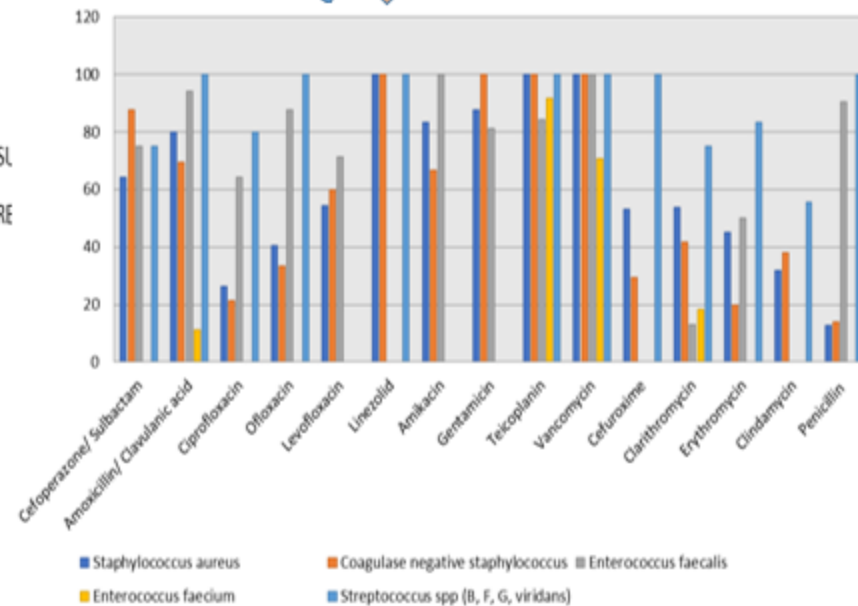
Analysis of the antibacterial agents, the types of infections, the number and type of pathogens, and the sensitivity to antibiotics.

Department	No. of PD	No. of DDDs	DDD /1000 PD
Intensive Care Unit	17 053	21 272	1247.4
Surgical wards	110 530	53 387	483.0
Medical wards	87859	39 610	450.8
TOTAL	215 442	114269	2180.4

Overall antibiotic use



Antibiotic sensitivity patterns of *Acinetobacter baumannii*



Antibiotic sensitivity patterns of gram-positive strains

Among the isolated pathogens, the preponderance of gram-negative bacteria and the statistically significant isolation of *Acinetobacter* spp. strains stand out, which can mean insufficient measures to control nosocomial infections.