Use of Antibiotics and Presence of Germs in The Intensive Care Unit of a Second Level Spanish Hospital: An Observational Study

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ABSTRACT

Rationale: Antibiotic treatment is common practice within the ICUs. Up to 30-60% of antibiotics used in ICUs are considered unnecessary, inappropriate or suboptimal.

Objectives: Describe the use of antibiotics in patients from our ICU, including medical, post-surgical and polytrauma patients; describe the presented infections and multi-resistant (MR) germs; and assess the influence of this pattern of antibiotic treatment in the presence of MR germs in our unit.

Findings: From January to October 2019, 489 patients were admitted to the ICU, with a median age of 69.4 years. 46 patients died during their stay in the ICU (16%) and 57 patients died during all their hospital stay (19.8%). The scheduled postsurgical patients had the lowest hospital mortality (5%), followed by urgent postsurgical (19.5%), traumatological (25%) and medical patients (27%). There were 134 patients with ICU infections: community and nosocomial pneumonia (31.3%), intra-abdominal infections (29.9%), urinary infections (11.2%), and associated and not associated with mechanical ventilation tracheobronchitis (9.7% each other). There were MR germs in 46 patients. Patients with infection had a higher mortality (21.64 vs. 11.49%) and longer hospital stay -13 vs. 9 days-. There are elevated percentages of empirical (50%) and by surgical prophylaxis (36.1%) at initial antibiotic use. The most used antibiotics were amoxicillin/clavulanic, piperacillin/tazobactam, levofloxacin and ceftriaxone. The indications of beta-lactams exceeded 50% of the total prescriptions. The number of total days without antibiotic treatment related to total hospital days of patients with antibiotic treatment was 0.085. 34% of antibiotic treatment were adequate, 18.9% inadequate, 32% had negative cultures and in 15.1% no cultures were extracted.

Conclusion: There are several items related to antibiotic use in our ICU that must be improved.

Keywords

Antibiotic use, Intensive Care Unit, Multi-resistant germs.

Introduction

Antibiotic treatment is common practice within the Intensive Care Units (ICUs) [1]. The goal of this treatment can be multiple: treatment of infections, both empirically and directed; surgical

prophylaxis for patients undergoing scheduled surgical procedures; and another type of prophylaxis (pre-oro-tracheal intubation, the debatable antibiotic prophylaxis of severe acute pancreatitis, etc.). But up to 30-60% of antibiotics used in ICUs are considered unnecessary, inappropriate or suboptimal [2].

A high percentage of these treatment indications are for the

treatment of infections. Infections associated with health care in ICU rooms are one of the most frequent complications that involve critically ill patients. Many of them are infections acquired outside the ICU whose severity motivates their admission into ICU. In other cases, the infection arises intra-ICU, which implies an added severity. Invasive devices and procedures compromise the defense mechanisms of the host, especially if the patient has a serious situation and a previous alteration of the immune response.

The Spanish Society of Intensive Medicine SEMICYUC, and specifically the Working Group of Infectious Diseases and Sepsis (GTEIS) has promulgated recommendations on various aspects related to the infectious patient and with antibiotic treatment [3]. Specifically, it recommends establishing leadership in infection control and in the optimization of the use of antibiotics with the use of registries, the development of infection prevention programs and counseling on the prescription of antibiotics [4]; preventing infections related to devices with the implementation of the Bacteremia Zero, Pneumonia Zero and ITU-Zero programs [5-7]; following a program of control of multi-resistant (MR) microorganisms based on the recommendations of the Zero Resistance project [8] with the evaluation of antibiotic treatment according to internal protocols and local epidemiology, the use of broad-spectrum antibiotics only when necessary, the control of cross-transmission of MR germs, the correct identification of patients with MR and the correct disinfection of the critical patient's environment [9]; carrying out a fast and efficient control of the infectious process in the critical patient, with the early starting of antibiotic treatment, extracting appropriate microbiological samples if it does not involve an excessive delay in the administration of the antibiotic, and promoting measures to control the infectious focus if possible [10,11]; and early and adequate managing of patients with septic shock [12].

Another characteristic of the critically ill patient is the presence of MR germs. In the emergence and diffusion of antibiotic resistance, several fundamental factors converge: infection control measures, selective antimicrobial pressure [13], and other elements such as the high instrumentation to which our patients are subjected, and to deficient strategies of infection control (isolation measures, hand washing, etc.).

The comprehensive approach of our patients, and the obligation of continuous improvement in their management, encourages us, as intensive care team, to optimize all aspects related to the presence of germs, both in the form of colonization and in the form of infection, and antibiotic treatment.

In this area, the collection of infection data acquired in the ICU in the National Nosocomial Infection Surveillance Study (ENVIN) has been carried out for the last 25 years and beyond [14]. That wish to measure infections acquired in the ICU has radically changed the way we proceed with our current or potential infectious patients.

The ICU of the hospital de Sagunto is a small (9-bed) and polyvalent service, because it assumes the admission of medical,

post-surgical and some post-traumatic patients, located in a 2nd level hospital. Our unit participates in the development of ENVIN since its starting, collecting data for the study in the 3 months from April to June each year. But there is concern / desire to extend this collection to the full year.

The objective of this work is purely descriptive: to collect information about the use of antibiotics in our patients, including medical, post-surgical and polytrauma patients; describe the presented infections, and the existence of colonization / infection by MR germs; and finally, assess the influence of this pattern of antibiotic treatment in the presence of MR germs in our unit.

Methods

This study is observational retrospective, and data have been collected for 10 months, between January and October 2019. All patients who for any reason undergo antibiotic treatment have been included.

Several variables have been defined in several moments: baseline situation, evolution during the stay in ICU and hospital ward, antibiotic use and presence of infection / colonization / MR germs. Infections have been defined according to ENVIN and EPINE study criteria [14,15].

The variables can be discrete categorical:

- sex;
- admission box (numbered from 151 to 159);
- reason for admission (defined generically as medical, scheduled surgical, urgent surgical or polytrauma);
- presence of risk factors (use of invasive devices: mechanical ventilation -MV-, bladder catheter, catheters, etc.);
- comorbidities that influence the presence of infectious complications;
- origin of the patient (hospital service, primary care center or another hospital in which he/she has been assessed before admission to the ICU);
- presence of infection (yes/no);
- before vs intra-ICU infection;
- indication of antibiotic treatment (surgical prophylaxis, other prophylaxis, empirical or directed);
- isolation of MR germs (defined as yes/no);
- colonization / infection of these MR germs;
- origin of these MR germs (before ICU vs intra ICU);
- the presence of complications and mortality of the patient, both in the ICU and during his subsequent stay in the hospital.

Continuous numerical variables have been also described: age, ICU stay and hospital stay (calculated from birth date, hospital and ICU admission dates, and ICU and hospital discharge dates), number of antibiotics used in each patient and duration of antibiotic treatment. Indicators of antibiotic use were made analogously to what was done in the ENVIN [14].

The distribution of these numerical variables is sometimes adjusted to normal distribution, but in many others it is not. To

maintain the same criteria, these distributions are described with the median and with the interquartile range (IQR), with Tukey hinges). The description of categorical variables is done with proportions and percentages. The comparison of a numerical variable with a dichotomous one is made with the Student's t-test since the sample size is adequate ($n > 30$). The comparison of 2 categorical variables is carried out with the JI AL SQUARE test under the same assumption. An exploratory correlation analysis between 2 continuous numerical variables is attempted. Box, bar and sector charts are made. A survival analysis is applied to the temporal variables with the Kaplan - Meier method. There are several figures -identified with letters, from A to AC- and tables included in the Appendix.

To describe the hospital stay, the fortnights during which each patient was admitted have been counted. The first fortnight of the month covers from day 1 to 15, both inclusive. The second fortnight of the 16th to the last day of the month, also both inclusive.

For example, a patient with an admission to the hospital from March 28th to April 16th is admitted during 3 fortnights -2nd fortnight of March and the 2 fortnights of April-. To simplify mathematical management, antibiotic treatments are not attributed to the interval of administration, but to the number of fortnights in which the patient is admitted.

The calculations are made with the statistical package SPSS v.15.

Results

Baseline and risk factors results

From January to October 2019, 489 patients with 1691 stays were admitted to the ICU, with an average ICU stay of 3.46 days. Of these, 288 patients took antibiotic treatment anytime during their hospital admission (58.9%), with 1580 associated ICU stays, a median ICU stay of 3 (IQR 2-5) and a median hospital stay is 11 days (IQR 6 - 17.5). The pre-ICU stay was variable (1 to 34 days, median 1 day). 94 patients were women (32.6%). There were 10 readmissions (3.5%) and 16 patients who moved to another hospital at the time of discharge from the ICU (5.6%). The patients had a median age of 69.4 years (IQR 57.1-78.5). The severity indicators during the first 24 hours were: APACHE-III median 59 (IQR 40-82); SAPS-II 36 (IQR 26-48).

46 patients died during their stay in the ICU (16%) -compared with 56 cases in all the patients admitted to the ICU (11.5% of the total) -. 57 patients died during all their hospital stay (19,8%).

The origin of these patients was varied (Figure 1), with a predominance of 3 sources: Emergency (38.2%), Internal Medicine (21.2%) and Surgery (23.6%). The reason for admission to the ICU was multiple: 23,3% surgical interventions scheduled for neoplasms (14,2% motivated by digestive tract pathologies, 7,6% colon neoplasms); community pneumonia (12.2%), peritonitis (8%) (most involve urgent surgery), and significant bradycardia. who justified definitive pacemaker implantation (5.2%).

Figure 1: Origin of patients.

The reason for admission of these patients was medical (56.6%), scheduled surgical (27.8%), urgent surgical (14.2%) and traumatological (1.4%) (Figure A). The age distribution of the groups was similar between groups, with a median of 70 years, except in the trauma group, clearly younger (Figure 2).

Figure 2: Differences of age distributions of patients admitted to the ICU with reason for admission.

The reasons for admission of these patients was described in table 1. The distribution of the 5 most frequent diagnoses per fortnight was detailed in Figure B. Community pneumonia occurred within the 10 months, although with a higher prevalence in the months of January and February, while COPD exacerbations occurred throughout the 10 months period.

The reasons why the patient was admitted to the ICU conditioned their evolution and hospital mortality. The scheduled postsurgical patients had the lowest mortality (5%), followed by urgent postsurgical (19.5%), traumatological (25%) and medical patients (27%) ($p = 0.001$) (Figure 3).

Regarding the risk factors for the acquisition of infections in the ICU, the patients carried devices in an appreciable percentage (central venous catheter 88.5%, artificial airway 56.3%, bladder

catheter 91 %), 17.3% underwent urgent surgery during their stay in the ICU and 7.3% received renal replacement therapies. The patients had a certain baseline risk profile of infection at admission: 17.4% were diabetic, 9.7% had chronic renal failure, 23.3% had a neoplasm, 24% had a previous pulmonary pathology, etc.

Figure 3: Mortality of patients according to their reason for admission.

There were complications in 33% patients: 21.2% septic shock or hemodynamic instability in general; 25.3% respiratory failure; 13.2% renal failure; 4.9% neurological deterioration (encephalopathy, critical patient myoneuropathy, etc). The presence of these complications caused longer hospital stays and a higher mortality (Figure C).

Survival curves (Figure D) showed certain trends: urgent post-surgical patients died within the first 20 days of ICU stay, while medical patients died in a sustained manner throughout their stay in the ICU.

Outcomes on global infections, and colonization / infection by MR germs

There were 134 patients with ICU infections, 46.5% of patients treated with antibiotics. Most infections were of 5 types: community and nosocomial pneumonia (31.3%), intra-abdominal infections (29.9%), urinary infections (11.2%), and associated and not associated with MV tracheobronchitis (9.7% of each type) (Figure 4).

Figure 4: Types of infection of patients included in our study.

Patients with infection had a higher mortality (21.64 vs. 11.49%) ($p = 0.002$) and longer hospital stay -13 days (IQR 8-24) vs. 9 days (IQR 6-13) than those who had no infection- (Figures 5 and E). In addition, the hospital stay before admission to the ICU was greater in patients who develop infection in the ICU (median 13 days, IQR 8-24.25 days) compared to those without infection (median 9, IQR 5.75 - 13.25 days) with a statistically significant difference ($p = 0.032$).

Figure 5: Survival graph of the groups of patients with and without ICU infection.

Mortality of patients with acquired pre-ICU and intra-ICU infection were similar (28 and 26.7%). Also, the mortality of the most frequent infectious syndromes was similar (pneumonia 26.2%, tracheobronchitis 30.8%, urinary infection 26.7%) (Figure F).

The most frequent microbiological isolates in patients with ICU infection were (Figure G): *pneumococcus*, *E coli*, H1N1 influenza A virus and *Klebsiella pneumoniae*. In 4 patients, “mixed flora” was described in an intra-abdominal sample (varied germs, with no clear predominance). In 38 patients (28.4%) negative cultures were described, and in 16 (11.9%) no samples were extracted for microbiological culture.

There were MR germs in 46 patients. Of these, 31 were colonizations (67.4%) and the remaining 15 (32.6%) were infections. Most of these germs were already present upon arrival at the ICU (27, 58.7%), and the remaining 19 were acquired intra-ICU (41.3%). The most common germ was *E coli* (18, 39.1%), followed by *Klebsiella pneumoniae* and SAMR (10 each, 26.3%). There are no isolates of *Acinetobacter baumannii*. The relative frequency of colonization / infection by these germs was described in Figure H. The presence of MR germs seemed to be associated with a higher mortality (30.4 vs 17.8%, $p = 0.048$) (Figure I) with overlapping survival curves and apparently higher mortality as hospital stay lengthened (Figure J). The hospital mortality of patients colonized and infected by MR germs was similar (29 and 33.3%), although infected patients

died somewhat earlier and those colonized later (Figure K).

Antibiotic use

There were elevated percentages of empirical (50%) and by surgical prophylaxis (36.1%) at initial antibiotic use. Very few patients received a targeted treatment of entry (2.1%). Mortality was different in each group: low in the surgical prophylaxis group (3.8%) and targeted treatment (16.7%), and significantly higher in the remaining two groups (28.5% mortality in the empirical treatment group and 32.4% in the other prophylaxis group) (Figure L). Survival curves confirmed these findings, with higher and earlier mortality from the group of other prophylaxis and empirical treatment (Figure M).

The number of antibiotics, used at an initial time and throughout their ICU stay, was very variable, from 1 to 10 (median 1, mean 1.83 days). The number of antibiotics was somewhat higher in patients who die (Figure N), although the difference was not statistically significant ($p = 0.13$).

Antibiotic treatment duration was also variable, from 1 to 57 days (median 3 days, IQR 2-5), and with different duration according to the reason for admission (longer treatment durations for urgent surgery and medical patients, median of 4 days, versus trauma patients, median 3 days, and scheduled surgical, median 2 days) (Figure O).

The number of started treatments of each antibiotic and the sum of days of treatment of each antibiotic were shown in table 2. The number of therapies indicated therapies for each antibiotic, ordered by families, was shown in Figure 6.

Figure 6: Number of indications of antibiotic treatment ordered by antibiotic families.

Among the 4 most used antibiotics, there were 3 beta-lactams (amoxicillin/clavulanic 111, piperacillin/tazobactam 46 and ceftriaxone 34) and 1 fluorquinolone (levofloxacin 37). The indications of beta-lactams exceeded 50% of the total prescriptions (Figure P).

The number of total days without antibiotic treatment related to total hospital days of patients with antibiotic treatment was 0.085.

The mean duration of treatments with each antibiotic was variable (figure Q). Several treatments of special surveillance, such as antifungals (echinocandins, fluconazole and voriconazole), antiviral (oseltamivir) and broad-spectrum antibiotics such as ceftolozane / tazobactam and tigecycline were the most prolonged (more than 10 days).

The distribution of total stays with each antibiotic was quite similar the treatment prescription: amoxicillin/clavulanic (362, 15.36% of the total), piperacillin/tazobactam (248, 10.52%), levofloxacin (179, 7, 59 %), meropenem (157, 6.66%), linezolid (154, 6.53%) and ceftriaxone (143, 6.07%) (Figure R).

Information about the distribution of patients undergoing each antibiotic treatment in different fortnights, the frequency of total and initial use, reason for use and confirmation of the indication of the different antibiotics, the performance of antibiotic change and the reason for that change, the administration of an antibiotic at the beginning of admission, and the indications for treatment (surgical prophylaxis, other prophylaxis, empirical or directed) were detailed in Tables 3 to 8. Figure S showed the number of therapies, how many antibiotics are scheduled at start of antibiotic therapy, and the reason why they are prescribed, referring to the most frequently prescribed antibiotics.

The adequacy of antibiotic treatment was described in Figure T. Assessing the 297 antibiotic treatments used, 34% was adequate, 18.9% inadequate, in 95 32% the cultures were negative, and in 15.1% no cultures were extracted.

The reasons why the antibiotic treatment was modified were explained in Tables 7 and 8, and Figure U. The most frequent reasons were the reduction of the spectrum (32.2%), bad evolution of the patient (20%) and not covered germ by the previous treatment (18.9%).

The description of the change in antibiotic, and the reason for that change, in important groups of antibiotics, were described in figure V. The percentages of change by spectrum reduction were higher than other reasons, although they are variable depending on the antibiotic group valued.

The relationship between taking fluoroquinolones and the presence of extended spectrum beta-lactamases (ESBL)-producing germs 4

months later in the ICU was described in Figures W and X. The first figure had pairs of columns: the first shows the number of patients treated with quinolones in a fortnight, and the second the number of patients with ESBL producing germs identified in the ICU 4 weeks (8 fortnights) later. Visually there seemed no relationship. The scatter plot with the same data showed the absence of a relationship between both variables.

The relationship between administration of “high impact antibiotics” and the appearance of MR germs was analyzed in the following graphs. Carbapenemic antibiotics, new antipseudomonic drugs (ceftolozane/tazobactam and ceftazidime/avibactam), linezolid, daptomycin, colistin and new antifungals (anidulafungin, caspofungin and voriconazole) were included in this group. Figure Z represented in pairs of columns the number of patients with MR germs in each fortnight and the taking of special surveillance antibiotics in that same fortnight.

Visually there seemed something more concordant than in the previous analysis, with fortnights with little isolates of MR germs and low intake of these antibiotics, and other fortnights with more numerous isolates and higher intake of high-impact antibiotics. Figure 7 showed a positive correlation between both variables ($R^2 = 0.473$) with moderate signification.

Figure 7: Scatter plot of the relation between the number of patients with MR germs and antibiotic treatments of special surveillance in the same fortnight.

Several ICU boxes may have a higher risk of having MR germs than others, maybe in relation with a greater or lesser occupation by patients of these boxes. The median stays in each bed were analogous, but beds number 151 and 152 had patients with somewhat longer stays (Figure Z). Figure AA showed the number of admissions in each ICU box, the number of patients with MR germs isolated in that box, and the median stay of the box. There seemed no graphical relationship between the number of MR germs and the average stay of the patients in each box (Figure AB).

Discussion

The results of our study cannot go beyond the simple objective of describing the reality of our ICU, a polyvalent unit of a 2nd grade hospital.

Most of the patients admitted come from the Emergency Department and from Internal Medicine service (in many of them which their admission to ICU was not considered adequate, but the subsequent evolution does determine their subsequent admission). The high frequency of programmed postoperative patients, where theoretically patients in good condition are selected and patients with certain comorbidity are ruled out, can influence their better prognosis. Patients from our study many risk factors, and are polyinstrumented (with central venous catheter, artificial airway and bladder catheter rates clearly above 50%). Also, the presence of complications during admission increases the mortality of these patients.

The proportion of patients with active infections among patients who received antibiotics was close to 50%. Patients with infection had a longer hospital stay and higher mortality than those without. The information administered by Microbiology had its limitations (28% of patients with confirmed infection had negative cultures). The doctors also had aspects to improve, with 12% of patients with infection without having extracted any microbiological cultures.

The number of total days without antibiotic treatment was 0.85, less than the value of the ENVIN study (0.21) [14]. This bad outcome may be due to the profile of patients (many scheduled postsurgical), but it should draw attention to the convenience of shortening antibiotic therapies.

The use of antibiotics was empirical in 50% of cases, and as surgical prophylaxis in 36.1%. The reason for antibiotic treatment also conditioned subsequent evolution and mortality, possibly due to the different reason for ICU admission. Beta-lactam treatments account for more than 50% of the total. A very used antibiotic in outpatients as amoxicillin / clavulanic is the most used in our ICU (38.5%) as in the ENVIN study ($> 11\%$) [14]. The most frequent uses are as surgical prophylaxis (56.4%) or prophylaxis for another reason (23.6%), although there are also 17.3% of empirical treatments with this antibiotic. The use clearly greater use of this antibiotic than that found at national level [14] may be related to the high percentage of post-surgical patients in our ICU.

The antibiotics with which we treat a greater number of patients, approximately, accumulated more days of treatment. Adequate antibiotic treatment of an infection only accounted for 34% of the total antibiotic regimens. This data is also analogous to those collected in the recent report of the ENVIN study (31,4%) [14].

In an very complex environment as ICU, with continuous interactions with other spheres - Primary Care, Emergencies, etc. - there was no clear numerical relationship between treatment with fluorquinolones and the appearance of ESBL producing germs, contrary to what was found in other works from different points

of view [16-18], which is probably related to the fact that these extra ICU factors have not been taken into account. On the other side, there seemed to be a certain association between treatment with special surveillance antibiotics and the greater occurrence of MR germs, although the existence of this association cannot be categorically confirmed (although R2 provides an estimate of the strength of the relationship between these variables in a lineal regression model, it does not prove this relationship).

The presence of MR germs is a serious public health problem [19] that implies high hospital costs and loss of productivity [20]. The fight against MR germs has been carried out in recent years in Spanish ICUs within the Zero Resistance project [8]. This intervention promotes several aspects: an adequate antibiotic policy to reduce antibiotic pressure as much as possible [21], obtaining the most appropriate sample and the correct form of infected tissues before starting antibiotic treatment [22], starting an empirical antibiotic treatment wide spectrum to cover the most likely germ and then adjusting/de-escalating after knowing the germ and the initial clinical evolution [23], assessing the tissue penetration, dose and dosage of the antibiotic treatment in patients with poor evolution [24], assessing the possibility to shorten the duration of antibiotic treatment depending on the focus, germ and clinical and microbiological response [25], and using active antibiotics against MR germs only in infections with severe systemic response compatible with sepsis or septic shock and high suspicion of MR germs and not in MR germs colonizations [26], among others. All these actions are integrated in the daily effort to rationalize as far as possible the different indications of antibiotic treatment of our patients [27]. With all these items, the number of patients who acquire a MR bacterial infection in Spanish ICUs has been reduced by about 20 percent [28].

Our study has its limitations. When considering as a retrospective work, we may have an information bias, with poor classification of certain variables due to insufficient information written in history, (for example, the reason for antibiotic changes). And the high numbers of inadequate microbiological information (with negative cultures, or without culture samples) are also very improvable.

But it also has positive aspects. These are consecutive cases, without losses, which makes it a very adequate reflection of the epidemiological situation of the unit. The non-short follow-up (10 months) seems adequate to appreciate dynamics of MR germs. However, there is no doubt that it is not a closed system, and that there are continuous influences from Emergency Service and from hospital services, for example, in terms of added antibiotic pressure not reflected in our work.

Conclusion

Antibiotic treatment is very common in patients admitted to our ICU. The presence of infection during admission, or the presence of MR germs both in the form of colonization and infection, relate to an increased mortality. Most used antibiotics are beta-lactams (amoxicillin / clavulanic, piperacillin / tazobactam, meropenem) and levofloxacin. In only 34% of empirical antibiotic treatments it

is adequate. There are several items related to antibiotic use in our ICU that must be improved.

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APPENDIX

Diagnosis at admission	N (=288)	%
Abdominal abscesses	2	0.7
Acute meningoencephalitis	4	1.4
Atrioventricular block	15	5.2
Biliary sepsis	12	4.2
Bladder neoplasia	10	3.5
Bricker (neobladder) perforation	1	0.3
Cardiac arrest	8	2.8
Cardiac failure	10	3.5
Caustic intake	2	0.7
Cerebral haemorrhage	3	1
Colon neoplasia	22	7.6
Coma	7	2.4
Community pneumonia	35	12.2
Crohn disease	1	0.3
Definitive pacemaker electrocatheter dislocation	1	0.3
Digestive haemorrhage	6	2.1
Diabetic ketoacidosis	1	0.3
Esophageal neoplasia	5	1.7
Ethylene glycol poisoning	1	0.3
Febrile neutropenia	2	0.7
Hemoptisis	2	0.7
Hemorrhagic shock -prostate adenoma	1	0.3
Hepatic failure	1	0.3
Hip fracture	1	0.3
Hip prosthesis infection	1	0.3
Intestinal ischemia	1	0.3
Intestinal occlusion	2	0.7
Larynx neoplasia	3	1
Liver cysts	1	0.3
Lumbar osteoarthritis	3	1
Metabolic acidosis	1	0.3
Morbid obesity	1	0.3
Near drowning	1	0.3
Nosocomial pneumonia	3	1
Pancreas neoplasia	6	2.1
Pancreatitis	4	1.4
Pericardial effusion	2	0.7
Perirenal hematoma	1	0.3
Pneumomediastinum	1	0.3
Polytrauma	5	1.7
Preeclampsia	1	0.3
Prostate neoplasia	7	2.4
Renal neoplasia	4	1.4
Respiratory failure - other	4	1.4
Respiratory failure - COPD	20	6.9
Seizures	5	1.7
Sepsis without focus	1	0.3
Skin and soft tissue infection	6	2.1
Stomach neoplasia	8	2.8
Tetanus	1	0.3
Thoracic pain	1	0.3

Tumor mass in gastric wall	1	0.3
Uretral stenosis	1	0.3
Urinary sepsis	11	3.8
Uro-digestive fistula	2	0.7
Uterine neoplasia	2	0.7
Ventricular arrhythmia	1	0.3

Table 1: Main diagnosis on admission on ICU.

	N=526	Sum=2357
Amoxicillin/clavulanic	111	362
Meropenem	29	157
Piperacillin/tazobactam	46	248
Ceftriaxone	34	143
Aztreonam	3	13
Cefazoline	21	32
Cefotaxime	15	40
Cefoxitine	1	2
Ceftolozane/tazobactam	3	14
Ceftazidime/avibactam	2	38
Cefepime	2	9
Cefuroxime	2	4
Ceftazidime	2	21
Ceftaroline	4	15
Ampicillin	7	27
Cloxacillin	3	22
Penicillin G	4	15
Imipenem	15	54
Ertapenem	5	17
Ciprofloxacin	24	112
Levofloxacin	37	179
Clarithromycin	15	88
Azithromycin	1	2
Amikacin	16	66
Tobramycin	13	35
Tigecycline	3	43
Clindamycin	3	11
Metronidazole	22	75
Vancomycin	6	34
Linezolid	29	154
Daptomycin	11	71
Colistin	1	3
Phosphomicin	1	3
Fluconazole	11	80
Voriconazole	1	15
Anidulafungin	2	17
Caspofungin	1	8
Amphotericin B	1	1
Aciclovir	4	26
Oseltamivir	13	96
Albendazole	2	5

Table 2: Number of started treatment of each antibiotic (N) and sum of days of treatment of each antibiotic (Sum).

	q11	q12	q21	q22	q31	q32	q41	q42	q51	q52	q61	q62	q71	q72	q81	q82	q91	q92	q101	q102
Patients in a fortnight	13	26	29	26	19	18	20	20	22	21	12	24	18	17	16	17	13	13	9	17
number of antibiotics used in every fortnight	23	72	87	69	62	34	34	35	30	54	39	51	48	29	32	33	24	24	22	31
Amoxicillin/clavulanic	9	9	11	7	5	9	9	6	10	11	6	11	9	9	5	2	8	4	4	7
Meropenem	1	3	3	2	2	1	2	1	1	5	4	6	2	1	1	4	3	2	3	1
Piperacillin/tazobactam	2	7	5	4	7	3	2	3	4	3	3	1	2	3	6	4	2	4	2	4
Ceftriaxone	1	5	6	6	2	3	4	6	2	1	0	1	4	4	0	2	2	2	1	0
Aztreonam	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0
Cefazoline	1	1	1	1	1	4	2	1	1	0	1	3	0	0	2	0	0	2	1	1
Cefotaxime	0	2	4	1	2	1	0	0	1	1	1	1	0	0	0	0	0	2	0	1
Cefoxitine	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ceftolozane/tazobactam	0	1	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1
Ceftazidime/avibactam	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1
Cefepime	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Cefuroxime	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Ceftazidime	0	1	1	1	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Ceftaroline	0	0	1	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0
Ampicillin	0	1	2	3	1	0	0	0	0	2	2	2	2	0	1	0	0	0	0	0
Cloxacillin	0	1	1	1	1	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0
Penicillin G	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Imipenem	0	0	0	0	1	0	2	1	1	1	0	3	2	0	1	1	1	1	1	2
Ertapenem	0	2	1	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0	0

Table 3: Use of beta-lactam antibiotics in successive fortnights. Legends: q11 1st half of January, q12 2nd half of January, q21 1st half of February, q22 2nd half of February, q101 1st half of October, q102 2nd half of October.

	q11	q12	q21	q22	q31	q32	q41	q42	q51	q52	q61	q62	q71	q72	q81	q82	q91	q92	q101	q102
Patients in a fortnight	13	26	29	26	19	18	20	20	22	21	12	24	18	17	16	17	13	13	9	17
number of antibiotics used in every fortnight	23	72	87	69	62	34	34	35	30	54	39	51	48	29	32	33	24	24	22	31
Amikacin	2	3	3	3	3	1	2	2	0	2	3	1	0	1	1	1	0	0	1	2
Tobramycin	0	3	2	2	2	0	2	0	1	3	2	3	2	0	0	0	0	0	0	0
Ciprofloxacin	0	1	1	3	1	1	2	1	3	4	1	3	1	2	2	4	1	1	1	3
Levofloxacin	2	3	4	4	2	1	2	6	3	2	2	0	4	5	4	3	2	1	1	0
Clarithromycin	0	5	9	5	1	2	1	2	0	0	0	0	1	0	0	0	0	0	0	0
Azithromycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Vancomycin	0	0	1	3	3	2	1	1	0	0	0	1	1	0	0	0	0	0	0	0
Linezolid	1	3	4	3	6	2	1	1	0	5	2	2	2	0	2	3	3	2	3	2
Daptomycin	0	1	1	2	0	0	0	0	0	2	1	1	1	1	2	3	1	1	1	2
Clindamycin	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Metronidazole	1	3	7	3	5	2	1	0	1	3	1	2	0	0	0	1	0	0	0	1
Tigecycline	1	1	1	2	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0
Colistin	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Phosphomycin	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Fluconazole	1	4	4	3	3	1	0	0	0	3	3	2	2	1	1	1	0	0	0	1
Voriconazole	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0
Anidulafungin	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0
Caspofungin	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0
Amphotericin B	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Aciclovir	0	1	0	1	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0
Oseltamivir	0	7	9	4	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Albendazole	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0

Table 4: Use of non-beta-lactam antibiotics in successive fortnights.

	Total antibiotic use	Initial use of antibiotic	Reason for use				Treatment confirmation			
			Surgical prophylaxis	Another prophylaxis	Empiric	Targeted	Adequate	Inadequate	Negatives cultures	No cultures
Amoxicillin/clavulanic	111	105 (94,6%)	63 (56,8%)	26 (23,4%)	19 (17,1%)	3 (2,7%)	6 (20)	5 (16,7)	10 (33,3)	19 (30)
Meropenem	29	17 (58,6)	0	1 (3,4)	24 (82,8)	4 (13,8)	6 (26,1)	4 (17,4)	10 (43,5)	3 (13)
Piperacillin/tazobactam	46	36 (78,3)	0	2 (4,3)	42 (91,3)	2 (4,3)	21 (47,7)	8 (18,2)	13 (29,5)	2 (45)
Ceftriaxone	34	32 (94,1)	1 (2,9)	3 (8,8)	25 (73,5)	5 (14,7)	9 (33,3)	2 (7,4)	11 (40,7)	5 (18,5)
Aztreonam	3	3	0	0	3	0	1	1	1	0
Cefazoline	21	21 (100)	20 (95,2)	0	1 (4,8)	0	0	0	0	1
Cefotaxime	15	13 (86,7)	10 (66,7)	0	3 (20)	2 (13,3)	1	1	0	1
Cefoxitine	1	1	1	0	0	0	0	0	0	0
Ceftolozane/tazobactam	3	0	0	0	1	2	0	0	1	0
Ceftazidime/avibactam	2	1	1	0	0	1	1	0	0	0
Cefepime	2	0	0	0	1	1	0	0	1	0
Cefuroxime	2	1	1	0	0	1	0	0	0	0
Ceftazidime	2	0	0	0	0	2	0	0	0	0
Ceftaroline	4	1	0	0	1	3	0	1	0	0
Ampicillin	7	5	1	0	5	1	1	3	1	0
Cloxacillin	3	2	1	0	0	2	0	0	0	0
Penicillin G	4	0	0	0	0	4	0	0	0	0
Imipenem	15	15 (100)	3 (20)	1 (6,7)	11 (73,3)	0	7 (58,3)	1 (8,3)	1 (8,3)	3 (25)
Ertapenem	5	4	0	1	2	2	1	0	1	0

Table 5: Total use -number of patients in which the antibiotic is used-, number of patients in which the antibiotic is placed initially, reason for use and confirmation of the adequacy of the treatment in relation to cultures extracted, for beta-lactam antibiotics.

	Total antibiotic use	Initial use of antibiotic	Reason for use				Treatment confirmation			
			Surgical prophylaxis	Another profilaxis	Empiric	Targeted	Adequate	Inadequate	Negatives cultures	No cultures
Ciprofloxacin	24	17 (70,8%)	11 (45,8%)	1 (4,2%)	7 (29,2%)	5 (20,8%)	2	1	4	1
Levofloxacin	37	33 (89,2)	0	1 (2,7)	34 (91,9)	2 (5,4)	13	3	13	5
Clarithromycin	15	14 (93,3)	0	2 (13,3)	11 (73,3)	2 (13,3)	2	6	3	0
Azithromycin	1	0	0	0	0	1	0	0	0	0
Amikacin	16	11 (68,8)	0	0	14 (87,5)	2 (12,5)	5	4	4	1
Tobramycin	13	10 (69,2)	9 (69,2)	0	1 (7,7)	3 (23,1)	1	0	1	0
Tigecycline	3	2	0	0	2	1	2	0	0	0
Clindamycin	3	1	1	0	1	0	0	1	0	0
Metronidazole	23	20 (87)	12 (52,2)	0	11 (47,8)	0	2	5	2	2
Vancomycin	6	2	0	0	1	5	0	0	1	0
Linezolid	29	16 (55,2)	0	0	23 (79,3)	6 (20,7)	8	7	7	1
Daptomycin	11	6 (54,5)	1 (9,1)	0	6 (54,5)	4 (36,4)	3	0	2	1
Colistin	1	0	0	0	0	1	0	0	0	0
Phosphomicin	1	0	0	0	0	1	0	0	0	0
Fluconazole	11	0	0	0	4 (36,4)	7 (63,6)	0	1	3	0
Voriconazole	1	0	0	0	0	1	1	0	0	0
Anidulafungin	2	1	0	0	1	1	1	0	0	0
Caspofungin	1	0	0	0	1	0	0	0	1	0
Amphotericin B	1	0	0	0	0	1	0	0	0	0
Acyclovir	4	3	0	0	4	0	1	1	2	0
Oseltamivir	13	9 (69,2)	0	0	9 (69,2)	4 (30,8)	7	1	1	0
Albendazole	2	2	1	0	1	0	0	0	1	0

Table 6: Total use, number of patients in which the antibiotic is placed initially, reason for use and confirmation of the adequacy of treatment in relation to cultures extracted, for non-beta-lactam antibiotics.

	Antibiotic change			Reason for the change							
	no	yes	Early stop	Not covert	Spectrum reduction	Resistance to treatment	Bad evolution	toxicity	other	No infection	unknown
Amoxicillin/clavulanic	24	4	8	2	0	0	5	0	1	4	0
Meropenem	23	3	2	0	0	0	3	0	0	3	0
Piperacillin/tazobactam	29	10	6	4	6	1	3	0	0	2	0
Ceftriaxone	21	5	6	3	5	1	0	0	1	1	0
Aztreonam	2	0	1	0	1	0	0	0	0	0	0
Cefazoline	0	1	1	0	0	0	1	0	1	0	0
Cefotaxime	4	0	1	0	0	0	0	0	0	1	0
Cefoxitin	0	0	0	0	0	0	0	0	0	0	0
Ceftolozane/tazobactam	1	0	2	0	2	0	0	0	0	0	0
Ceftazidime/avibactam	2	0	0	0	0	0	0	0	0	0	0
Cefepime	2	0	0	0	0	0	0	0	0	0	0
Cefuroxime	1	0	0	0	0	0	0	0	0	0	0
Ceftazidime	2	0	0	0	0	0	0	0	0	0	0
Ceftaroline	3	0	1	0	0	0	0	0	0	1	0
Ampicillin	2	1	3	2	0	0	2	0	0	0	0
Cloxacillin	2	0	0	0	0	0	0	0	0	0	0
Penicillin G	3	0	1	0	0	0	0	0	0	0	1
Imipenem	11	1	0	0	1	0	0	0	0	0	0
Ertapenem	4	0	0	0	0	0	0	0	0	0	0

Table 7: Antibiotic change and reason for the change for beta-lactam antibiotics.

	Antibiotic change			Reason for the change							
	no	yes	Early stop	Not covert	Spectrum reduction	Resistance to treatment	Bad evolution	Toxicity	Other	No infection	Unknown
Ciprofloxacin	10	1	1	0	1	0	0	1	0	0	0
Levofloxacin	29	3	4	1	4	0	1	0	0	1	0
Clarithromycin	11	1	1	2	0	0	0	0	0	0	0
Azithromycin	1	0	0	0	0	0	0	0	0	0	0
Amikacin	9	1	5	0	4	0	0	1	0	0	0
Tobramycin	3	2	0	0	1	0	1	0	1	0	0
Tigecycline	3	0	0	0	0	0	0	0	0	0	0
Clindamycin	2	0	0	0	0	0	0	0	0	0	0
Metronidazole	11	0	0	0	0	0	0	0	0	0	0
Vancomycin	5	0	1	0	0	0	0	0	0	1	0
Linezolid	24	1	2	1	1	0	0	1	0	0	0
Daptomycin	8	2	0	0	1	0	1	0	0	0	0
Colistin	0	1	0	0	1	0	0	0	0	0	0
Phosphomycin	0	0	0	0	0	0	0	0	0	0	0
Fluconazole	9	2	0	0	0	0	0	2	0	0	0
Voriconazole	1	0	0	0	0	0	0	0	0	0	0
Anidulafungin	2	0	0	0	0	0	0	0	0	0	0
Caspofungin	1	0	0	0	0	0	0	0	0	0	0
Amphotericin B	1	0	0	0	0	0	0	0	0	0	0
Acyclovir	2	0	2	1	0	0	1	0	0	0	0
Oseltamivir	8	1	2	2	1	0	0	0	0	0	0
Albendazole	1	0	0	0	0	0	0	0	0	0	0

Table 8: Antibiotic change and reason for the change for non-beta-lactam antibiotics.

Figure A: Reason for hospital admission.

Figure D: Survival curves of patient groups according to their reason for admission.

Figure B: Reasons for admission more frequent throughout the different fortnights.

Figure C: Survival curves of groups of patients with and without complications during their stay in the ICU.

Figure E: Description of the mortality of patients according to whether they have or have not an infection during their stay in the ICU.

Figure F: Mortality of the different infectious syndromes.

Figure G: Prevalence of germs in intra-UCI infections. The “other” section includes isolates of 1 germ on a single occasion: Herpes Simplex Virus, Aspergillus fumigatus, Moraxella catarrhalis, Bacteroides spp, Stenotrophomona maltophilia, Klebsiella oxytoca and an unidentified anaerobic Gram positive bacillus.

Figure H: Mortality of patients with and without MR germs.

Figure I: Survival graphs of patients with and without MR germs.

Figure J: Presence of MR germs in patients included in the work, with specific cases of infection.

Figure K: Survival curves of patients colonized and infected by MR germs.

Figure L: Mortality of patient groups according to the initiated type of antibiotic treatment.

Figure M: Survival curves of the groups of patients according to their initial antibiotic treatment.

Figure P: Number of indications of antibiotic treatment classified by families.

Figure N: Box plot of the number of antibiotics used in the groups of patients who die and not during their hospital stay.

Figure Q: Mean duration of therapies with each antibiotic. The number in the title means number of treatment prescriptions.

Figure O: Days of antibiotic treatment of patients according to their reason for admission.

Figure R: Percentage of the duration of antibiotic treatments with respect to total stays.

Figure S: Most prescribed antibiotics, with number of prescriptions, initial uses of the antibiotic and reason for use. The initial column (total antibiotic prescriptions) is equal to the sum of the 3rd to 6th columns (reasons for use). There are several models of distribution: amoxicillin/clavulanic and ciprofloxacin are more frequently used as surgical prophylaxis, while meropenem, piperacillin/tazobactam and ceftazidime have much empirical treatment indications.

Figure T: Overall description of how many initial treatments are adequate, inadequate, with negative cultures or without extracted cultures.

Figure V: Change of antibiotic and reason for that change in several groups of antibiotics of special importance. Special surveillance antibiotics are: linezolid, daptomycin, ceftazidime, ceftolozane/tazobactam, ceftazidime/avibactam, voriconazole, anidulafungin, caspofungin and colistin. New antifungal agents are anidulafungin, caspofungin and voriconazole. New anti Gram positive germs are linezolid and daptomycin.

Figure W: Relationship between the frequency of taking fluoroquinolones during a fortnight and the frequency of ESBL-producing germ isolates 4 months (8 fortnights) later.

Figure X: Scatter plot about the relationship between fluoroquinolones use and occurrence of ESBL-producing germs 4 months later.

Figure U: Reasons for modification of the initial antibiotic treatment.

Figure Y: Relationship between the number of patients taking special surveillance antibiotics and the number of patients colonized by MR germs in each fortnight.

Figure AA: Number of patients admitted, patients with MR germs and median stay in each bed of our service.

Figure Z: Box plot of ICU stays in each box of our ICU.

Figure AB: Scatter plot between the number of MR germs isolated in each bed and the average stay of their patients.