"The duration of antibiotic therapy in intensive care (Prospective study)"

ABSTRACT :

Antibiotics are frequently prescribed medications, but their abuse is hazardous. They can promote the emergence of multi-resistant bacteria, have adverse effects on patients, and impose additional expenses on healthcare facilities. In the context of rationalizing antibiotic prescription, research and monitoring of treatment durations are needed to minimize risks of their abuse. A prospective study of one year duration analyzed the duration of antibiotic therapy in 226 patients with respiratory infections, bacteremia, intra-abdominal, and urinary tract infections. The median durations of treatment ranged from 5 to 10 days based on the type of infection. Mortality was 31% and differed based on the type of infection. Different strategies are recommended, such as the use of empirical antibiotic therapy while awaiting bacteriological results or the "Wait and Watch" strategy. The choice of empirical antibiotic treatment remains crucial and is based on the local bacterial ecology of each unit. Biomarkers such as procalcitonin can be used to guide discontinuation of treatment and reduce the duration of antibiotic therapy. Short treatment durations have been shown to have similar outcomes compared to longer treatment durations, and it is reasonable to individualize the duration of antibiotic treatment based on each patient's need. Overall, there is growing evidence for the use of shorter durations of antibiotic therapy with similar clinical outcomes to longer durations. The goal is to provide the right dose of antibiotics needed for each patient's treatment.

INTRODUCTION:

Antibiotics, as a breakthrough in 20th-century medical science, can cause short-term side effects in some patients. Inappropriate or excessive use of antimicrobials promotes the spread of antibiotic-resistant bacteria strains, leading to superbugs that are resistant to most available antibiotics. To fight antibiotic resistance, antibiotic stewardship has been implemented to preserve the effectiveness of current therapies. However, its implementation is challenging in ICUs due to the complexity of antibiotic prescriptions in ICUs.

ICU-admitted patients suffer from potentially life-threatening illness, often coupled with severe comorbidities and impaired physiological reserves. Both their critical illnesses and interventions used can also alter antibiotic metabolism, such that plasma levels are discordant. ICU settings also face infection from multidrug-resistant organisms. Due to the urgency of the case, antibiotic prescriptions in the ICU are often probabilistic, broad-spectrum, and high-dose, which contributes to antibiotic resistance.

Reduction of the antibiotic treatment duration aims to limit the dangers of long duration and high dose therapy, hold in check the emergence of resistant strains, limit side effects and financial costs, without provoking significant therapeutic failures in the ICU. Our study aims to evaluate quantitatively the duration of antibiotic treatment in the surgical emergency ICU of CHU Ibn Rochd of Casablanca, taking into account also other criteria such as empirical treatments, dosages, routes of administration, and the resistance profiles of bacteria in the unit.

MATERIAL AND METHODS:

This is a prospective descriptive study conducted in the surgical emergency ICU "P33" of the Ibn Rochd University Hospital of Casablanca over a period of one year, from January 2022 to

December 2022. The study included all patients admitted to this unit during the year 2022 and who presented with an infectious syndrome and were treated with antibiotics. Patients treated with antibiotics for a duration of less than 72 hours were not included in the study. Demographic, clinical, and laboratory data were collected from the patients' medical records. The evolution and outcome of the patient were followed from the admission register or the department to which the patient was transferred. For each patient, data were recorded using a pre-established form. Data entry was made with Excel software. The results of the descriptive analysis were expressed in percentage.

RESULTS:

Among the 477 patients who were admitted to the surgical emergency intensive care unit "P33" in 2022, 226 (46%) of them received the benefit of antibiotic therapy for 72 hours or more. The average age of the patients was 44 years, with a predominance of the age group "20-39 years" (41%). The age varied between 15 years and 88 years. The sex ratio (male/female) was 2.57. Among the 226 patients kept in the study, 49% of them had one or more underlying chronic pathologies. The most frequent chronic pathologies seen were arterial hypertension (28%), diabetes (22%), and heart diseases (16%). At the level of toxic habits, 35% of the patients were chronic smokers. It must also be noted that 29% of the patients had no known pathological history or comorbidity. Cerebral lesions were present in 38% of the patients on admission, with 31% of them having cranial trauma, 4% having infectious lesions (meningitis, meningoencephalitis), 2% having strokes (ischemic and hemorrhagic), and 1% having cerebral tumor lesions. In this series of cases, 28% of the patients had undergone abdominal surgery, 13% had limb and thoracic trauma, 6% had septic shock upon arrival in the intensive care unit, and 13% were taken in for other indications such as pulmonary embolism, pyelonephritis, infection of osteosynthesis material, or diabetic ketoacidosis. The infectious syndrome was expressed by general signs represented by fever (78% of the patients), tachycardia (68% of the patients), tachypnea (26% of the patients), and arterial hypotension (10% of the patients). Suppurative lesions were present in 35% of the patients, while purulent bronchorrhea was seen in 25% and pyuria in 5%.

The complete blood count revealed neutrophilic leukocytosis in 91% of the patients, lymphopenia in 74%, and anemia in 59%. The CRP was elevated in 96% of the patients, with an average of 110-210 mg/L in half of the patients. The procalcitonin was positive in all the patients who were tested (>2µg/L), with a mean of 7.49 µg/L. Hypoalbuminemia was present in 90% of the patients, with most ranging between 35 to 25 g/L. Pulmonary infections accounted for 29% of the cases, followed by intra-abdominal infections (21%) and bacteremia (19%). Gram-negative bacteria were more common (79%) compared to Gram-positive bacteria (21%), with Acinetobacter baumannii (21%) and Klebsiella pneumoniae (15%) being the most frequent. The respiratory infections were mostly due to Acinetobacter baumannii (32%) and Klebsiella pneumoniae (20%), while intra-abdominal infections were overwhelmingly due to Escherichia coli (29%). Urinary tract infections were mostly due to Escherichia coli (34%), followed by Acinetobacter baumannii (21%).

The Acinetobacter baumannii strains that were isolated showed 80% to 89% resistance to carbapenem, and also high rates of resistance to Amikacin (86%), Gentamicin (76%), Ciprofloxacin (89%), and the combination of Piperacillin-tazobactam (100%). They were, however, largely susceptible to Ceftazidime (24%), Doxycycline (19%), and Tigecycline (22%).

For patients with ventilator-associated pneumonia (VAP), 96% of the Acinetobacter

baumannii strains were resistant to Imipenem. The Klebsiella pneumoniae strains that were isolated were largely susceptible to Amikacin (94%), the combination of Amoxicillin-Clavulanic acid (76%), and Gentamicin (89%), while the highest rates of resistance were to the combination of Trimethoprim-sulfamethoxazole (50%) and Ciprofloxacin (40%). The Pseudomonas aeruginosa strains were resistant to Imipenem in 62% of cases, to the combination of Piperacillin-tazobactam in 50% of cases, to Ceftazidime in 56% of cases, and to Ceftazidime in 60% of cases. The highest rates of resistance for Escherichia coli were to the combination of Amoxicillin-Clavulanic acid (73%) and the combination of Trimethoprim-sulfamethoxazole (73%), while resistance to Gentamicin and Ceftriaxone was lower at 18%. Antibiotic prescriptions were mostly triple therapies (41%), followed by monotherapy (32%), dual therapy (25%), and quadruple therapy (2%). The most frequent combinations were the combination of Ceftriaxone, Gentamicin, and Metronidazole (10% of prescriptions), Imipenem, Amikacin, and Doxycycline (8% of prescriptions), and Ceftriaxone, Metronidazole, and Ciprofloxacin (6% of prescriptions). Amoxicillin-Clavulanic acid accounted for 22% of prescriptions. Beta-lactams were the most prescribed first-line therapy antibiotics (94%), followed by aminoglycosides (43%), metronidazole (29%), and tetracyclines (15%)(**FIGURE 1)**. The average duration of antibiotic prescription was 6.4 days, and the median was 6 days. Dual therapy was used in 32% of patients with VAP, and triple therapy in 68% of them. Imipenem was the most prescribed antibiotic in VAP (35%), followed by colistin (21%). Gentamicin was the most prescribed aminoglycoside with a mean duration of prescription of 4 days at a dose of 160 mg/day. Doxycycline was prescribed for a median of 6 days at a dose of 400 mg/day, in association with colistin, imipenem, or an aminoglycoside. The longest treatment durations were for VAP caused by Pseudomonas aeruginosa, with a median treatment duration of 9 days. Respiratory infections requiring treatment for a duration of more than 6 days were mostly caused by Acinetobacter baumannii (48%), followed by Klebsiella pneumoniae (20%) and Pseudomonas aeruginosa (13%)(**FIGURE 2**). For bloodstream infections, the median treatment duration was 7 days. Arterial and venous catheter-related bloodstream infections in patients accounted for 41% of documented bloodstream infections, with a median treatment duration of 7 days. Septic shock patients received Ceftriaxone, Gentamicin, and Metronidazole in combination for a median duration of 5 days. In urinary tract infections, median duration of treatment was 5 days for all types of infections. In lower urinary tract infections, Amoxicillin/clavulanic acid combination was used frequently, with or without Gentamicin. The main pathogen responsible for failure of initial treatment and necessitating a broadening of antibiotic spectrum in 11% of the patients was Acinetobacter baumannii (**TABLE 1**).

Regarding the changes in antibiotic therapy, approximately 31% of the patients required a new protocol of treatment. In 21% of the cases, a broadening of spectrum or a change in antibiotic was necessary, while in 10% of the cases, therapeutic de-escalation was preferred. The reason for the change in treatment was primarily acute renal failure and hematological toxicity.

Discontinuation of antibiotic therapy was mainly based on the normalization of clinical and paraclinical parameters. The decision was aided by the absence of fever in 98% of the patients, normalization of heart rate in 85%, respiratory rate in 96%, oxygen saturation in 95%, and blood pressure in 94%. Besides clinical criteria, biological criteria for discontinuation of antibiotic therapy included normalization of the leukocyte count in 61% of the patients, normalization of the CRP level in 43% and its decrease in 96%, and normalization of PCT values in 93% of the patients in whom it was initially measured. In the

first 48 hours after discontinuation of antibiotic therapy, 94% of the patients were afebrile, while 6% remained febrile. A new infectious episode occurred in 11% of the patients. The intensive care unit stay was ≤7 days in 44% of the patients, and 20% of patients had a stay longer than 20 days. The majority of patients had a hospital stay of less than 14 days (54%). Four patients were readmitted to the intensive care unit after being transferred to other departments. In our series, 71 deaths were observed, representing 31% of the patients. The leading causes of death were infections (61%), followed by neurological (15%), respiratory (14%), and cardiovascular causes (3%). Among deaths associated with infections, 61% were caused by septic shock due to pulmonary infections, 13% by intra-abdominal infections, 8% by bacteremia, 7% by urinary tract infections, 3% by meningitis and meningoencephalitis, and 1% had an undetermined cause. The mortality was 47% for lower respiratory tract infections, 28% for bacteremia, 25% for intra-abdominal infections, 25% for meningitis, and 24% for urinary tract infections.

FIGURE 1 : Distribution of families of antibiotics used.

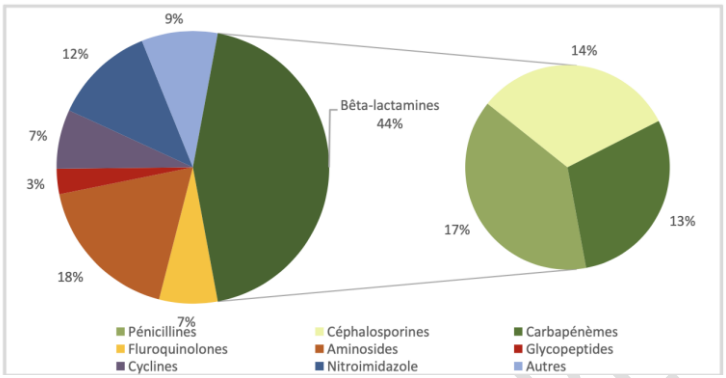

FIGURE 2 : Distribution of germs found in respiratory infections.

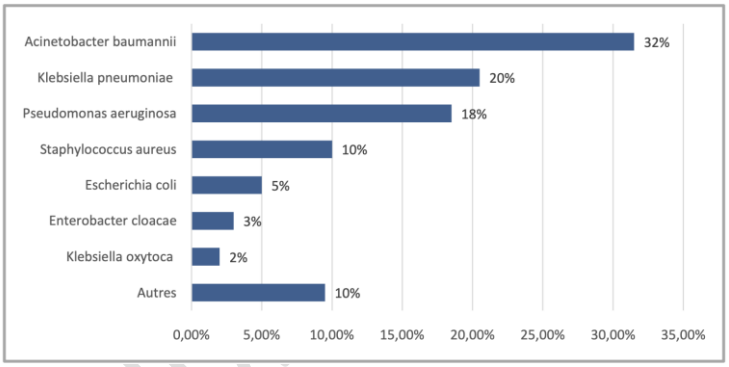

TABLE 1 : The antibiotic resistance profile of the germ Acinetobacter baumannii in our patients.

Antibiotics	Susceptible	Susceptible (high dose)	Resistant	Not Tested
Imipenem	11 %	-	89 %	-
Meropenem	20 %	-	80 %	-
Amikacin	14 %	-	86 %	-
Cefepime	24 %	16 %	60 %	-
Ceftazidime	5 %	-	89 %	6 %
Tigecycline	22 %	-	2 %	76 %
Doxycycline	19 %	-	21 %	60 %
Gentamicin	14 %	-	76 %	10 %

Ciprofloxacin	-	-	89 %	11 %
Piperacillin-tazobactam	0 %	-	100 %	-

DISCUSSION :

Antibiotic optimization is the foundation of Antibiotic Stewardship and is based on five main pillars: right drug, right dose, right route of administration, adequate duration, and timely de-escalation to targeted therapy.

ICUs are among the priority areas due to the widespread use of broad-spectrum antibiotics, which increases the risk of multidrug-resistant organisms. Antibiotic choice therefore must be based on suspected pathogens, resistance patterns, and the patient's clinical condition. Timely initiation of antibiotic therapy is crucial—delays significantly increase mortality in septic patients, as demonstrated in multiple studies. Administering appropriate antibiotics within the first hour can improve clinical outcomes.

Empiric treatment was started in 80% of cases in the study. While this allows for rapid action, it also increases the risk of resistance and unjustified broad-spectrum use. Both local resistance patterns and patient history are required for streamlining treatment.

In terms of treatment regimens, triple therapy was the most frequent, followed by monotherapy and dual therapy. For critical cases, combination therapy is usually preferred, whereas for less severe cases with no risks of resistance, monotherapy can be used.

Biomarkers like procalcitonin (PCT) are useful to direct the treatment duration and reduce unnecessary antibiotic exposure. Evidence shows that PCT-guided treatment leads to shorter treatment duration, reduced side effects, and lower mortality.

Therapeutic de-escalation, or the reduction in the scope or number of antibiotics once microbiological results are available, is employed to limit resistance without being fatal. It is currently supported and promoted by clinical guidelines on a broad basis.

Early re-evaluation of antibiotic treatment within 48–72 hours is necessary to alter or discontinue treatment based on clinical and microbiological results. However, clinical and microbiological determinants like initial inappropriate treatment or lack of documentation can be obstacles to de-escalation.

CONCLUSION:

Over the past two decades, considerable efforts have been made to determine the optimal duration of antibiotic treatments by comparing "short-course" therapies to traditional (longer) treatments. Data from randomized controlled studies have been gathered for specific conditions such as respiratory infections, urinary tract infections, bacteremia, and intra-abdominal infections. In numerous studies, it has been observed that short-course treatments were equally effective as longer treatments and were associated with fewer side effects. Given the lack of definitive and generalizable data regarding the optimal duration of antibiotic treatment, it is not surprising that practices vary significantly. Ideally, the duration of antibiotic therapy should be individualized, taking into account the patient's condition, underlying comorbidities, and the bacterial ecology of the infection, which could be facilitated by the use of biomarkers and new rapid tests currently under development.