Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/20609
DOI URL: http://dx.doi.org/10.21474/IJAR01/20609

RESEARCH ARTICLE

"THE DURATION OF ANTIBIOTIC THERAPY IN INTENSIVE CARE (PROSPECTIVE STUDY)"

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Manuscript Info

Manuscript History
Received: 14 January 2025
Final Accepted: 17 February 2025
Published: March 2025

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-termsideeffects in some patients. Inappropriate or excessive use of antimicrobialspromotes the spread of antibiotic-resistantbacteriastrains, leading to superbugsthat are resistant to mostavailableantibiotics. To fightantibioticresistance, antibioticstewardship has been implemented to preserve the effectiveness of currenttherapies. However, itsimplementationischallenging in ICUs due to the complexity of antibiotic prescriptions in ICUs.

ICU-admitted patients'sufferfrompotentially life-threateningillness, oftencoupledwithseverecomorbidities and impairedphysiologicalreserves. Boththeircriticalillnesses and interventions used can also alter antibioticmetabolism, suchthat plasma levels are discordant. ICU settings also face infection frommultidrug-resistantorganisms. Due to the

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urgency of the case, antibiotic prescriptions in the ICU are oftenprobabilistic, broad-spectrum, and high-dose, whichcontributes to antibioticresistance.

Reduction of the antibiotictreatment duration aims to limit the dangers of long duration and high dose therapy, hold in check the emergence of resistantstrains, limitsideeffects and financialcosts, withoutprovokingsignificanttherapeuticfailures in the ICU. Our studyaims to evaluatequantitatively the duration of antibiotictreatment in the surgical emergency ICU of CHU Ibn Rochd of Casablanca, takingintoaccountalsoothercriteriasuch as empiricaltreatments, dosages, routes of administration, and the resistance profiles of bacteria in the unit.

Material and Methods:

This is a prospective descriptive studyconducted in the surgical emergency ICU "P33" of the Ibn Rochd University Hospital of Casablanca over a period of one year, fromJanuary 2022 to December 2022. The studyincluded all patients admitted to this unit during the year 2022 and whopresentedwith an infectious syndrome and weretreatedwithantibiotics. Patients treatedwithantibiotics for a duration of lessthan 72 hourswere not included in the study. Demographic, clinical, and laboratory data werecollectedfrom the patients' medical records. The evolution and outcome of the patient werefollowedfrom the admission register or the department to which the patient wastransferred. For each patient, data wererecordedusing a pre-establishedform. Data entry was made with Excel software. The results of the descriptive analysiswereexpressed in percentage.

Results:

Among the 477 patients whowereadmitted to the surgical emergency intensive care unit "P33" in 2022, 226 (46%) of themreceived the benefit of antibiotictherapy for 72 hours or more. The averageage of the patients was 44 years, with a predominance of the age group "20-39 years" (41%). The agevariedbetween 15 years and 88 years. The sex ratio (male/female) was 2.57. Among the 226 patients kept in the study, 49% of themhad one or more underlyingchronic pathologies. The mostfrequentchronic pathologies seenwerearterial hypertension (28%), diabetes (22%), and heartdiseases (16%). At the level of toxic habits, 35% of the patients werechronicsmokers. It must alsobenotedthat 29% of the patients had no knownpathologicalhistory or comorbidity. Cerebrallesionswerepresent in 38% of the patients on admission, with 31% of themhavingcranial trauma, 4% havinginfectiouslesions (meningitis, meningoencephalitis), 2% havingstrokes (ischemic and hemorrhagic), and 1% havingcerebraltumorlesions. In thisseries of cases, 28% of the patients hadundergone abdominal surgery, 13% hadlimb and thoracic trauma, 6% hadsepticshockuponarrival in the intensive care unit, and 13% weretaken in for other indications such as pulmonaryembolism, pyelonephritis, infection of osteosynthesismaterial, or diabeticketoacidosis. The infectious syndrome wasexpressed by generalsignsrepresented by fever (78% of the patients), tachycardia (68% of the patients), tachypnea (26% of the patients), and arterial hypotension (10% of the patients). Suppurative lesionswerepresent in 35% of the patients, while purulent bronchorrheawasseen in 25% and pyuria in 5%. The completeblood count revealedneutrophilicleukocytosis in 91% of the patients, lymphopenia in 74%, and anemia in 59%. The CRP waselevated in 96% of the patients, with an average of 110-210 mg/L in half of the patients. The procalcitoninwas positive in all the patients whoweretested (>2µg/L), with a mean of 7.49 µg/L. Hypoalbuminemiawaspresent in 90% of the patients, withmostrangingbetween 35 to 25 g/L. Pulmonary infections accounted for 29% of the cases, followed by intra-abdominal infections (21%) and bacteremia (19%). Gram-negativebacteriawere more common (79%) compared to Gram-positive bacteria (21%), with Acinetobacter baumannii (21%) and Klebsiella pneumoniae (15%) being the mostfrequent. The respiratory infections weremostly due to Acinetobacter baumannii (32%) and Klebsiella pneumoniae (20%), while intra-abdominal infections wereoverwhelmingly due to Escherichia coli (29%). Urinary tract infections weremostly due to Escherichia coli (34%), followed by Acinetobacter baumannii (21%).

The Acinetobacter baumanniistrainsthatwereisolatedshowed 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%). Theywere, however, largely susceptible to Ceftazidime (24%), Doxycycline (19%), and Tigecycline (22%). For patients withventilator-associatedpneumonia (VAP), 96% of the Acinetobacter baumanniistrainswereresistant to Imipenem. The Klebsiella pneumoniaestrainsthatwereisolatedwerelargely susceptible to Amikacin (94%), the combination of Amoxicillin-Clavulanicacid (76%), and Gentamicin (89%), while the highest rates of resistancewere to the combination of Trimethoprim-sulfamethoxazole (50%) and Ciprofloxacin (40%). The Pseudomonas aeruginosastrainswereresistant 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-Clavulanicacid (73%) and the combination of Trimethoprim-sulfamethoxazole (73%), whileresistance to Gentamicin and Ceftriaxone waslower at 18%.

Antibiotic prescriptions weremostly triple therapies (41%), followed by monotherapy (32%), dual therapy (25%), and quadruple therapy (2%). The mostfrequent 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-Clavulanicacidaccounted for 22% of prescriptions. Beta-lactamswere the mostprescribed first-line therapyantibiotics (94%), followed by aminoglycosides (43%), metronidazole (29%), and tetracyclines (15%)(**FIGURE1)**. The average duration of antibiotic prescription was 6.4 days, and the medianwas 6 days. Dual therapywasused in 32% of patients with VAP, and triple therapy in 68% of them. Imipenemwas the mostprescribedantibiotic in VAP (35%), followed by colistin (21%). Gentamicinwas the mostprescribed aminoglycoside with a mean duration of prescription of 4 days at a dose of 160 mg/day. Doxycycline wasprescribed for a median of 6 days at a dose of 400 mg/day, in association withcolistin, imipenem, or an aminoglycoside. The longesttreatment durations were for VAP caused by Pseudomonas aeruginosa, with a mediantreatment duration of 9 days. Respiratory infections requiringtreatment for a duration of more than 6 daysweremostlycaused by Acinetobacter baumannii (48%), followed by Klebsiella pneumoniae (20%) and Pseudomonas aeruginosa (13%)(**FIGURE 2**). For bloodstream infections, the mediantreatment duration was 7 days. Arterial and venouscatheter-relatedbloodstream infections in patients accounted for 41% of documentedbloodstream infections, with a mediantreatment duration of 7 days. Septicshock patients received Ceftriaxone, Gentamicin, and Metronidazole in combination for a median duration of 5 days. In urinary tract infections, median duration of treatmentwas 5 days for all types of infections. In lowerurinary tract infections, Amoxicillin/clavulanicacid combination wasusedfrequently, with or withoutGentamicin. The main pathogenresponsible for failure of initial treatment and necessitating a broadening of antibioticspectrum in 11% of the patients was Acinetobacter baumannii (**TABLE 1**).

Regarding the changes in antibiotictherapy, approximately 31% of the patients required a new protocol of treatment. In 21% of the cases, a broadening of spectrum or a change in antibioticwasnecessary, while in 10% of the cases, therapeutic de-escalationwaspreferred. The reason for the change in treatmentwasprimarily acute renalfailure and hematologicaltoxicity.

Discontinuation of antibiotictherapywasmainlybased on the normalization of clinical and paraclinicalparameters. The decisionwasaided 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%. Besidesclinicalcriteria, biologicalcriteria for discontinuation of antibiotictherapyincludednormalization of the leukocyte count in 61% of the patients, normalization of the CRP level in 43% and itsdecrease in 96%, and normalization of PCT values in 93% of the patients in whomitwasinitiallymeasured. In the first 48 hoursafter discontinuation of antibiotictherapy, 94% of the patients wereafebrile, while 6% remainedfebrile. A new infectiousepisodeoccurred in 11% of the patients. The intensive care unit staywas ≤7 days in 44% of the patients, and 20% of patients had a stay longer than 20 days. The majority of patients had a hospitalstay of lessthan 14 days (54%). Four patients werereadmitted to the intensive care unit afterbeingtransferred to otherdepartments. In ourseries, 71 deathswereobserved, representing 31% of the patients. The leading causes of deathwere infections (61%), followed by neurological (15%), respiratory (14%), and cardiovascular causes (3%). Amongdeathsassociatedwith infections, 61% werecaused by septicshock 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 mortalitywas 47% for lowerrespiratory 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.

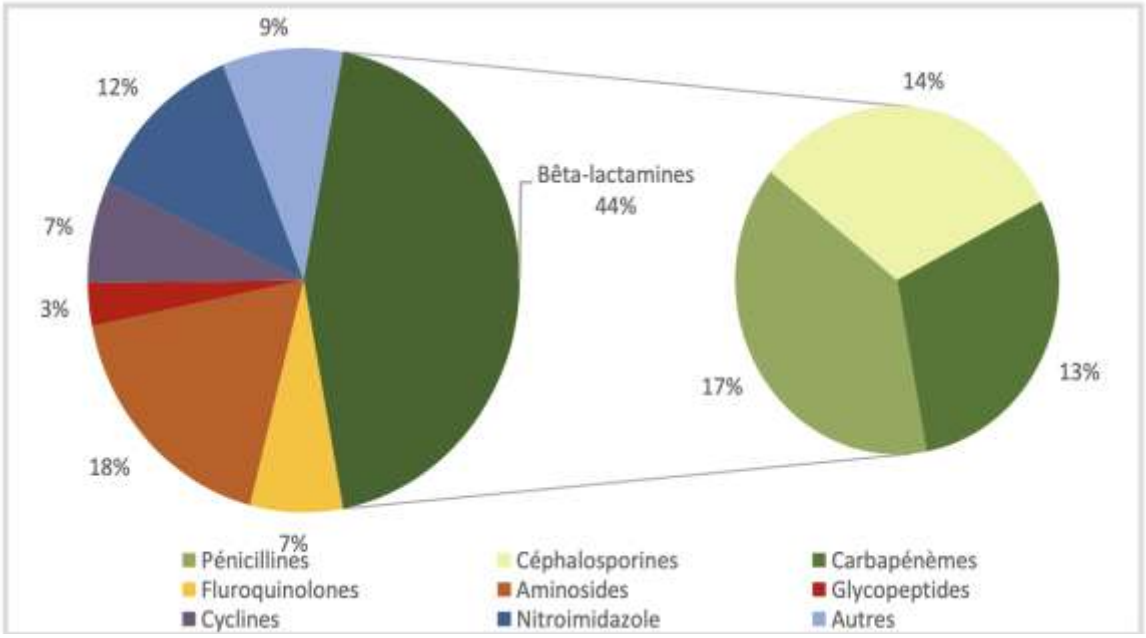

Figure 2: Distribution of germsfound in respiratory infections.

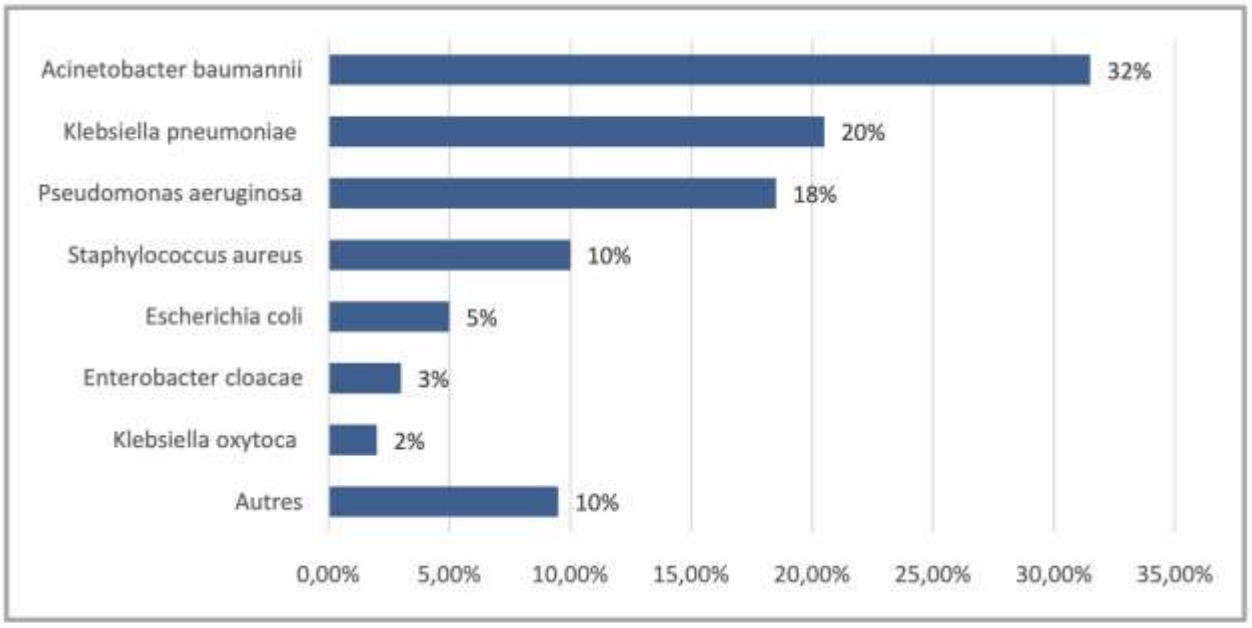

Table 1: The antibiotic resistance profile of the germAcinetobacter baumannii in our patients.

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:

Antibioticoptimizationis the foundation of AntibioticStewardship and isbased on five main pillars: right drug, right dose, right route of administration, adequate duration, and timely de-escalation to targetedtherapy. ICUs are among the priority areas due to the widespread use of broad-spectrumantibiotics, whichincreases the risk of multidrug-resistantorganisms. Antibioticchoicetherefore must bebased on suspectedpathogens, resistance patterns, and the patient'sclinical condition.

Timely initiation of antibiotictherapyis crucial—delayssignificantlyincreasemortality in septic patients, as demonstrated in multiple studies. Administeringappropriateantibioticswithin the first hour can improveclinicaloutcomes.

Empirictreatmentwasstarted in 80% of cases in the study. Whilethisallows for rapid action, italsoincreases the risk of resistance and unjustifiedbroad-spectrum use. Both local resistance patterns and patient history are required for streamliningtreatment.

In terms of treatmentregimens, triple therapywas the mostfrequent, followed by monotherapy and dual therapy. For critical cases, combination therapyisusuallypreferred, whereas for lesssevere cases with no risks of resistance, monotherapy can beused.

Biomarkers like procalcitonin (PCT) are useful to direct the treatment duration and reduceunnecessaryantibioticexposure. Evidence shows that PCT-guidedtreatment leads to shorter treatment duration, reducedsideeffects, and lowermortality.

Therapeutic de-escalation, or the reduction in the scope or number of antibiotics once microbiologicalresults are available, isemployed to limitresistancewithoutbeing fatal. It iscurrentlysupported and promoted by clinical guidelines on a broad basis.

Early re-evaluation of antibiotictreatmentwithin 48–72 hoursisnecessary to alter or discontinue treatmentbased on clinical and microbiologicalresults. However, clinical and microbiologicaldeterminants like initial inappropriatetreatment or lack of documentation can be obstacles to de-escalation.

Conclusion:

Over the pasttwodecades, considerable efforts have been made to determine the optimal duration of antibiotictreatments by comparing "short-course" therapies to traditional (longer) treatments. Data fromrandomizedcontrolledstudies have been gathered for specific conditions such as respiratory infections, urinary tract infections, bacteremia, and intra-abdominal infections. In numerousstudies, it has been observedthat short-course treatmentswereequally effective as longer treatments and wereassociatedwithfewersideeffects. Given the lack of definitive and generalizable data regarding the optimal duration of antibiotictreatment, itis not surprisingthat practices varysignificantly. Ideally, the duration of antibiotictherapyshouldbeindividualized, takingintoaccount the patient's condition, underlyingcomorbidities, and the bacterialecology of the infection, whichcouldbefacilitated by the use of biomarkers and new rapid tests currentlyunderdevelopment.