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*RESEARCH ARTICLE*

# THERAPEUTIC FAILURE OF ANTIBIOTICS ININTENSIVE CARE UNIT: TOWARD BETTER RISK MANAGEMENT AND OPTIMIZED PATIENT CARE (PROSPECTIVE DESCRIPTIVE AND ANALYTICAL STUDY OF 100 CASES)

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## *Abstract*

Infections in intensive care represent a critical situation where failure of anti-infective therapy, closely linked to high mortality rates, demands rapid detection and appropriate management by intensivists. Early intervention to identify and address treatment failure is therefore essential.This study aimed to determine the incidence of therapeutic failure, identify associated risk factors, and evaluate its prognostic consequences. We conducted a prospective, descriptive, and analytical study over nine months in the medical ICU of CUH Ibn Rochd in Casablanca. All patients receiving antibiotics for suspected or confirmed infections were included, with regular microbiological follow-up.Out of 100 patients, 58 experienced therapeutic failure. The causes were definitively identified in 53.5% of cases, probable in 34.4%, and undetermined in 12.1%. Infectious causes accounted for 41.4%, while non-infectious causes represented 12.1%. Key risk factors included severity at admission, nosocomial infections, atypical pathogens, irregular antibiotic administration, and anemia. A change in antibiotics was found to be an independent protective factor. Mortality was significantly higher in cases of failure (RR=32.977).Our findings indicate that better management of therapeutic failures could reduce associated mortality. Further research on a larger sample is needed to refine these conclusions and enhance clinical practices.



## Introduction:-

The discovery of anti-infective agents has radically transformed the management of infections. Despite advances in antibiotic therapy, infections remain a major cause of global mortality[1]. In intensive care units, infections are associated with significantly increased mortality, even in the presence of antibiotics[2]. Early and effective antibiotic therapy is essential to prevent the worsening of infections. This therapy is often administered as broad-spectrum treatment during the first 72 hours, followed by adjustments based on microbiological results to target the responsible bacteria and prevent resistance. However, between 4% and 14% of patients exhibit insufficient response to treatment, constituting therapeutic failure[3],[4].

Antibioticfailure can be categorized into two types: clinical failure, defined by the persistence or worsening of infection symptoms, and microbiological failure, characterized by the continued isolation of initially identified

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bacteria, regardless of resistance variations. Few studies have investigated the general factors influencing this failure in intensive care settings, although elements such as the frequency of resistant bacteria and the severity of patients are critical considerations.

The overall objective of this study is to determine the incidence of antibiotic failure in intensive care. Additionally, it aims to identify the different etiologies behind therapeutic failure, analyze the factors associated with this failure, and assess its prognostic implications. Finally, the study seeks to propose recommendations for improving antibiotic prescriptions in intensive care settings.

## Materials And Methods:-

This is a prospective, single-center, descriptive, and analytical study conducted over nine months in the medical intensive care unit of Ibn Rochd University Hospital in Casablanca. It included adult patients with confirmed or suspected bacterial infections who received antibiotics after initial bacteriological samples were collected. A reassessment was performed after 72 hours of treatment or in cases of suspected failure. Data were recorded and analyzed using EXCEL and SPSS software. Statistical tests, such as the Student's t-test for continuous variables and the Chi-square test for nominal variables, were employed to analyze the results and identify the risk factors for antibiotic failure and mortality.

## Results:-

During the study period, among the 100 patients hospitalized and treated for bacterial infections, we identified 58 cases of antibiotic treatment failure, corresponding to an incidence rate of 58%. Among them, 68.96% had persistent infection, while 31.03% had progressive infection. The average age of the patients was 44.14 years, with a standard deviation of 17.82. Male patients predominated, representing 55% of the cases, with a male-to-female ratio of 1.23. The patients were relatively severe, as indicated by a mean SOFA score of 4.8. The average length of stay was 21.14 days, with a standard deviation of 17.38. The combination of two comorbidities was present in 18.96% of cases. Diabetes was the most common comorbidity, found in 27.58% of cases.

The most frequent reason for admission was feverless consciousness disturbances in 35% of cases, followed by febrile consciousness disturbances in 24%, respiratory distress in 19%, and septic shock in 12%. 79.3% of our patients had either fever or hypothermia. The average APACHE II score of our patients increased from 14.71 (standard deviation: 1.767) on admission to 17.02 (standard deviation: 2.51) on the day of failure. 64% of the patients who failed treatment were intubated and ventilated at admission.

Leukocytosis was found in 69% of the patients. CRP was positive in 41% of cases. Chest X-ray showed an infectious focus in 13.79% of cases.

Urine culture (ECBU) was the most frequently performed test, conducted in 81% of cases, with a yield of 11.90%. The highest yield was obtained with PBDP (43.75% positive samples), followed by blood cultures on Sabouraud agar (17.2%). (Table 1)

| Prélèvements | n | %(patients) | Positifs n (% prélèvements positifs) |
|---|---|---|---|
| ECBU | 47 | 81 | 5 (10,63) |
| PBDP | 32 | 55,2 | 14 (43,75) |
| Hémoculture aérobie | 34 | 56,8 | 5 (14,70) |
| Ponction lombaire | 28 | 48,3 | 1 (1/28) |
| Hémoculture anaérobie | 32 | 55,2 | 0 (0) |
| Hémoculture Sabouraud | 10 | 17,2 | 4(4/10) |
| PCR Tuberculose dans le LCR | 2 | 3,44 | 1 (1/2) |
| Examen de bout de KTC | 8 | 13,8 | 1 (1/8) |
| Ecouvillonnage nasopharyngé | 3 | 5,17 | 1 (1/ 3) |

**Table1:-**Initialmicrobiologicalinvestigations.

**Documented infection was identified in 25 patients, representing 43.10%, with 12 pathogens identified.** Acinetobacter baumannii **was the most frequently isolated pathogen, found in 25.58% of the positive samples, followed by** Candida albicans **in 13.95%, and** Methicillin-resistant Staphylococcus aureus **(MRSA), which was isolated in 13.95% of cases (Figure 1).**

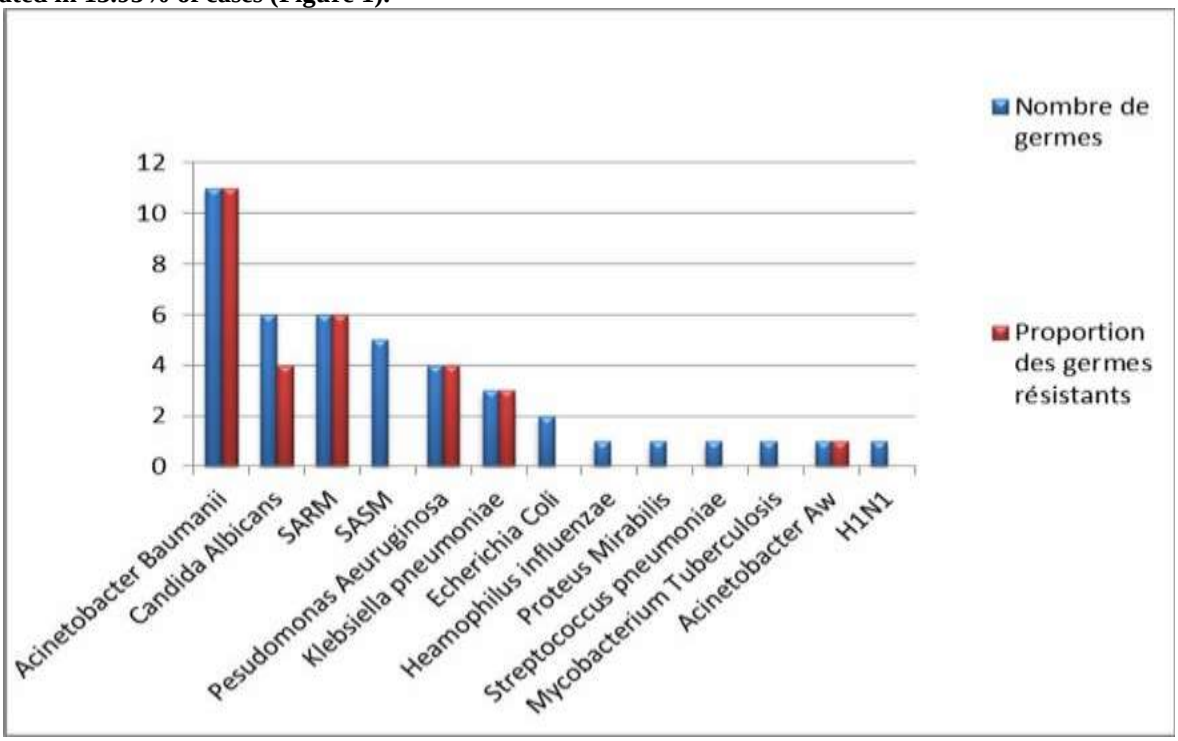


**Figure1:-**Proportionsofresistantgerms.

MRSA:methicillin-resistantstaphylococcusaureus;MSSA:methicillin-susceptiblestaphylococcus aureus; H1N1: influenzae virus A subtype H1N1

Thenotionofhavingtakenanantibioticduringthe2monthspriortoadmissionwasfoundin24patients (41.4%). All initial anti-infective prescriptions were probabilistic. Dual therapy was prescribedas first-line treatment in 53% of cases, monotherapy in 26% and triple therapy in 21%. Ceftriaxone was the molecule most frequently prescribed as monotherapy, in 66.7% of our patients.Combination therapy was dominated by Ceftriaxone+Levofloxacin, accounting for 15.51% of cases. The combination Imipenem+Teicoplanin+Amikacin was the most prescribed triple therapy in 8.62% of cases. Seven patients were treated with the antifungal :fluconazole for a confirmed mycotic infection. Five patients were treated with Acyclovir for viral infections, one of which was confirmed. Antibiotic therapy was modified in 27% of prescriptions, with an average delay of 6 days (standard deviation=3.18).12%weredé-escalationsand15%weretherapeuticescalations.Noprescriptionwere made after a therapeutic window.

Theoutcomeofourpatientsrevealedamortalityrateof.Ofthese,72.4%hadfailedantibiotic therapy, compared with 14.28% of those who had receivedeffectiveantibiotic treatment. Allcasesof treatmentfailurewereassociatedwithpersistentinfections.

All patients with antibiotic failure due to nosocomial infection died.»Adetailedanalysisofourresultsenabled us to identify factors predictive of failure, as well as elements associated with a poor prognosis.

Analysisofthefactorspredictiveantibiotictherapyfailureinourserieshighlightedseveraldecisive elements. Among patient-related factors, severity on admission stood out,includingaGlasgowscorebelow9/15(p=0.012)andahighSOFAscore,associatedwithasignificantrisk(p<0.0001).Alow hematocrit(p=0.046)wasalsoaimportant predictive factor.».Mechanicalventilation,whetherinstitutedadmission(p=0.011),atthebeginningofthe antibiotic treatment (p= 0.004) or after 72 hours (p= 0.000), as well as central line placement on admission (p = 0.008), are also correlated with treatment failure. Furthermore, ahypoalbuminemia(p=0.025)issignificantlyassociatedfailure.

With regard to antibiotic therapy factors, irregular antibiotic use (p = 0.000) and failure to modify anti-infectivetreatment(p=0.010)increasetheriskfailure.Finally,amonggerm-relatedfactors,nosocomial infection (p = 0.024) was significantly associated with failure, although antibiotic resistance showed no correlation.

We also analyzed factors predictive of poor prognosis. Host included the presence of apyretic consciousness (p=0.024). Death was significantly associated with antibiotic failure. (p<0.0001), septic shock (p=0.000)andthedevelopmentofhypoalbuminemia(p=0.039).Otherfactors,suchascriticalcondition requiring mechanical ventilation, central line , irregularity of anti-infectives and infectionarealsocorrelatedwithapoorprognosis.Intermsofgerm-relatedfactors,infectionwithatypicalgerms (p=0.001) was an unfavorable factor. Conversely, persistent infection (p=0.012) seems paradoxically to be a protective factor against death.

## Discussion:-

The management of anti-infective agents in the ICU remains a major challenge despite its frequency, due to the many factors influencing the infectious process: the germ, the site of infection, host characteristicsandchoiceofanti-infectiveagent.treatmentfailureconsiderationofbacterialresistance, accesstotheinfectedsite,immunedefensesandadjustmentofthetherapeuticprotocol.Thisdefinition is complex, as it involves identifying the symptomsanddeterminewhentheirpersistencebecomesabnormal.

Sincethe1980s,failurehavebeenestablishedforsimplecontexts,butbyresuscitation,thesecriteriaareofteninadequate,leavin gmuchtotheclinicaljudgmentoftheresuscitator.

**Definingantibiotictherapyfailure:**

No consensus definition of treatment failure has yet been published [22]. Detection of failure is based primarily on clinical criteria, such as persistence or worsening of local and/or general signs of infection despite appropriate antibiotic treatment. Prolonged use of catecholamines may also indicate failure. Timetoregressionofclinicalsignsvariesaccordingtothepathology:3to6daysforventilator-associated pneumonia (VAP) and 5 to 6 days for meningitis[6,7]. Radiological infiltrates disappear on average after 10 days in cases of community-acquired pneumonia[8].

Biochemicalandmicrobiologicalcriteriasuchaspersistentisolationoftheoriginalbacteriaindiagnostic samples (with or without modification of the resistance phenotype), can also signal failure.
ProcalcitoninisavaluablemarkerforassessingthesesituationsintheICU[5].

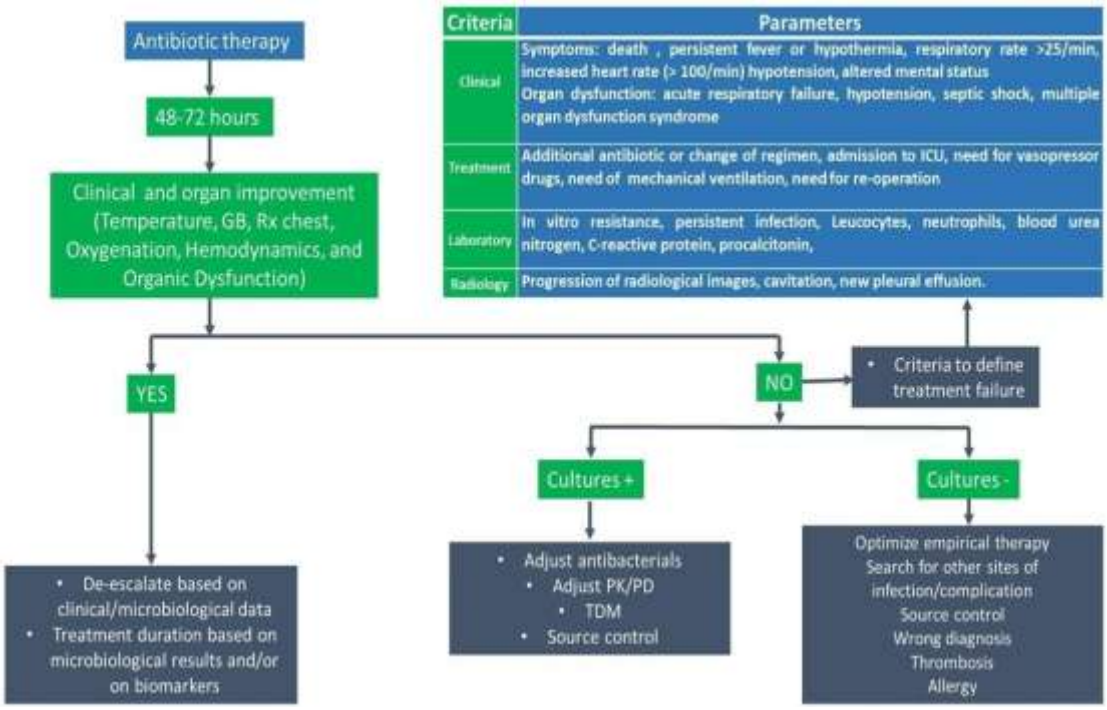


**Fig. 1:-** Algorithm for antibiotic failure and what to do in the event of failure22.

**Causesofantibiotictherapyfailure**

**Patient-relatedfailures**

In some situations, despite correct diagnosis and treatment, antibiotic therapy may fail, particularly in immunocompromisedpatients.Itisessentialtorememberthatantibioticssupporthostdefensesinthe eradication of pathogens. Neutropenia and lymphopenia are well-established risk factors for antibiotic failure[9,10].

**Failureduetodelay antibiotic**

Thelongerthedelay,theworsetheprognosis,asshowninthestudybyKumaretal:eachhour'sdelay administering the first dose of antibiotics increases mortality by around 7% [2].

**Antibiotic-relatedfailure:**

Antibioticfailurecanresultfromavarietyoffactors.

**Unsuitable choice of initial antibiotic:**

Unsuitable initial antibiotic therapy is a frequent cause of therapeutic delay, often associated with high mortality, irrespective of the site or severity of the infection[11]. In the ICU, this situation is exacerbated by the complexity of diagnoses, the diversity of clinicalpicturesandthewiderangeofresistance,whichcanleadtoanantibacterialspectrumthatis insufficient to cover the germs responsible. In addition, the failure to detect certain pathogens, particularly anaerobic bacteria in polymicrobial infections, induetoinadequatesampling,transportorculture,underlinestheimportanceofsystematicallyperforming anaerobic blood cultures [12].

**Pharmacodynamic parameters**:

The particularities of resuscitation, such as alterations in hepatic and renalfunction,modifythepharmacokineticparametersofantibiotics,reducingmaximumandminimum plasma concentrations and the area under the curve. These variations can lead to therapeutic failure if doses or administration are not adapted[13].

**Insufficient distribution**:

The effectiveness of treatments can also be limited by insufficient diffusion. insufficientuptakeoftheantibioticininfectedtissue,dependingonitsphysicochemicalproperties.By Forexample,macrolidesworkbestintracellularly,whilechloramphenicoleffectivelypenetratesthe central nervous system.

**Inactivation**:

Certaindruginteractions,suchastheformationofinactivecomplexesduringsimultaneous infusions, can also reduce antibiotic efficacy. Similarly, purulent media or hypoxia in abscesses diminish the activity of certain agents, such as aminoglycosides and polymyxins[14].

**Unsuitablerouteofadministration**:

Defectsinabsorptionareanotherfactorinfailure,particularlywith oral antibiotics administered in the presence of digestive disorders, or in interaction with substances such as antacids, calcium or iron, which reduce their bioavailability [15].

**Inappropriatedurationoftreatment**:

Finally,inappropriatedurationoftreatment,eithertooshortor poorly adhered to, is a well-known cause of failure, often leading to relapse [16].

**Bacterialfailures:**

**Pathogenmisidentification**

Failure of antibiotic therapy, which is often probabilistic, may be due to non-bacterial origin of the infection, particularly in pulmonary, central nervous system or systemic infections in intensive care. In immunocompromisedpatients,suchasthoseinfectedwithHIVorreturningfromtropicalzones,awide range of differential diagnoses must be considered in the event of antibiotic therapy failure[17].

Laboratory errors or misinterpretation of microbiological results can also explain failure. This occurs when the germ is difficult to culture, or when diagnostic tests are not sufficiently specific. It is therefore essentialtoreassesssignificanceofinitialmicrobiologicalexaminations,takingintoaccountfactorssuch as the type of

sample, its reliability in relation to the infected site, the number of positive samples (particularly for blood cultures), the bacterial count and the pathogenicity of the bacteria isolated. In addition, errorsinterpretationoftheantibiogram,orlackofprecisionconcerninginvitroandinvivosensitivity discrepancies, can also lead to therapeutic failures.

**Resistanceacquisitionduringtreatment:**
Theacquisitionofresistanceduringtreatmentisalsoakeyfactorinfailure.Thisresistancecanarisethrough several mechanisms, demonstrated by Livermore et al[17]. The

Resistanceismostcommoninmonotherapywithantibioticssuchaspenicillins,aminoglycosidesand fluoroquinolones, and is particularly notable in bacteria such as*Acinetobacterspp.*,*Pseudomonasaeruginosa*,*Serratiaspp.*andEnterobacteriaceae.Intensivecarepatients, especially those on mechanical ventilation, are more likely to resistance acquired during treatment [18].

**Insufficientbactericidalactivity**
Bactericidalfailuremayoccurmainlyinpatientswithsystemicorlocalimmunedeficiency.Inthecase ofthe**inoculumeffect**,failuremayoccuriftheantibioticdosageisinsufficienttoreachinfectiousfoci with a high microbial inoculum, such as inabdominalsuppurations.Apurulentcollectionmaycontainmorethan10⁹bacteria/mlofpus,well above the concentration used to determine the minimum inhibitory concentration (MIC) during antibiotic susceptibility testing ($10^5$), making the latter falsely underestimated.

**Quiescentbacteria**,whichhaveaslowmetabolismandcansurviveforyearsinsitesthataredifficultto access with antibiotics, are also a factor in failure. Thesebacteriaareinsensitivetothemajority ofantibiotics,whichactprimarilyontheactivemetabolisms.Thisisparticularlytrueforchronicosteomyelitis,chronicpyelone phritis,and endocarditis caused by bacteria of the HACEK group.

**Failuresrelatedtotheinfectedsite:**
**Undrained purulent retention** is a factor therapeutic failure, especially when the purulent focus measures more than 5 cm, whether initial or due a complication. If this type of focus is not managed surgically, it is associated with a poor outcome[19].

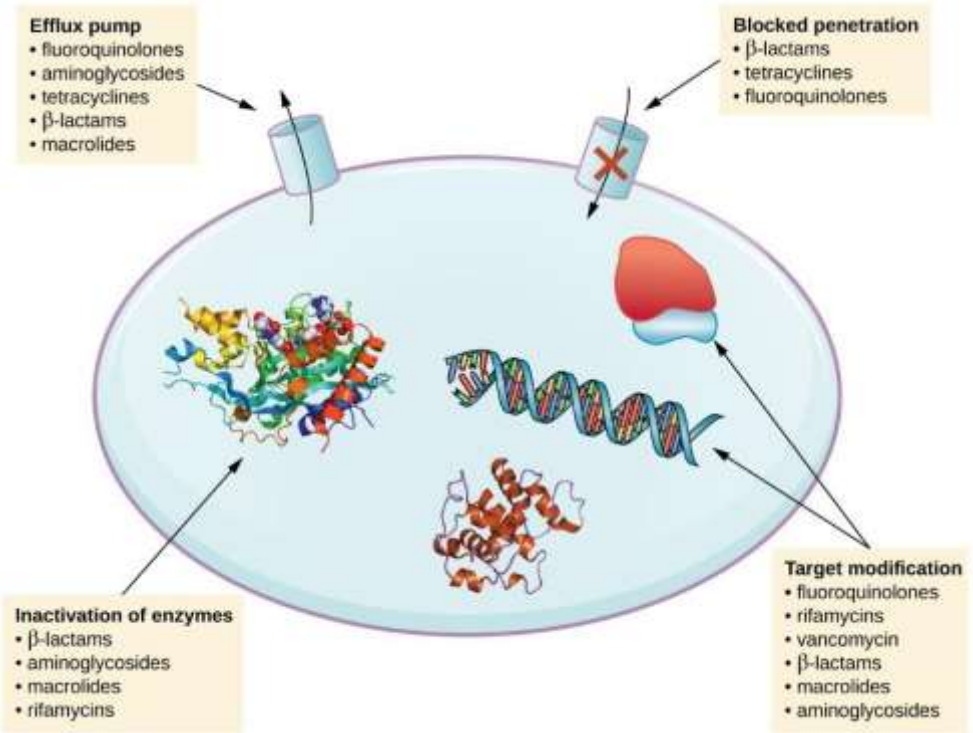


**Figure2:-**Therearemultiplestrategiesthatmicrobesusetodevelopresistancetoantimicrobial drugs[23].

The**presenceofforeignmaterial**,suchasavalveprosthesis,pacemaker,intravascularordialysis catheter, urinary catheter, or orthopedic material, increases the risk.failureantibiotictherapy.These devices promote germ adhesion and the formation of a protective polysaccharide biofilm., making infection more difficult to treat[20].

**Secondarylocations**,suchassepticmetastases,mustbesystematicallyinvestigated.intheeventfailure,particularlyinthecas eofbacteremia.Theycomplicateupto30.3%of*Staphylococcus aureus* bacteremias[21].

**Analysisofourresults:**
FailureofantibiotictherapyintheICUisafrequentphenomenon,ashighlightedbyourstudy,whichwas conducted independently to ensure impartial results. Three pointsThemainfindingswere:highfrequencyoffailure,resistanceofgermstoinitialprobabilisticantibiotic therapy asthe main cause,andincreasedmortality in the event offailure. An in-depth analysisof the microbiological results was carried out.

Our study identified Acinetobacter baumannii as the most frequently isolated germ (25.), responsible forpersistentinfectionsintheICU,inlinewiththeliterature[24,25].Thisgermshowsmarkedresistanceto initial antibiotic therapy[26,27], underlining the importance of thorough microbiological evaluation to adjust treatment.Lesscommongerms,suchasmycoses(13.),tuberculosis(2.32%)andtheH1N1virus(2.32%),werealso present.%),werealsoidentifiedascausesofprimaryinfections.ThelowuseofbloodculturesonSabouraud medium (17.) and of viral tests (5.) could explain the low rates of infection.diagnosticdelaysandassociatedfailures.Thehighprevalenceoffungalinfectionsmaylinkedtothehigh proportion of diabetics in our population (27.6%)[28].

As for the etiologies of antibiotic failure, persistent infections predominated (55.18%), mainly due to resistance to initial probabilistic antibiotics [30]. Irregular use of antibiotics (58.62%) and their administrationpriortoadmission(41.)alsocontributedtothisfailure.Incontrastotherstudiesreporting a high incidence of nosocomial infections[29], our cohort showed a higher prevalence of persistent infections.

In terms of prognosis, overall mortality was 48%, with an alarming 72.4% in patients with treatment failure. This figure is higher than the rates reported by Orban et al[31]and Kyan et al[32], probably due to factorssuchasanemia(86%)andundernutrition(68.2%)[34].TheprevalenceofAcinetobacterbaumannii, implicated in 29.of bacteremia deaths[33], also contributes to these results.

A correlation has been observed between clinical severity on admission (high APACHE II score, anemia, mechanical ventilation, central line) and the risk of antibiotic failure. Furthermore, nosocomial infection remainsamajorriskfactor[35].Finally,failuretoadheretoantibioticadministrationschedulessignificantly increases the risk of failure (multiplied by 17.725), highlighting the importance of strict adherence to therapeutic protocols[36].

## Conclusion:-

Our study identified several risk factors for antibiotic treatment failure, including patient severity admission,lowhematocrit,nosocomialinfectionandirregularintakeanti-infectiveagents.Treatment failure is often associated with high mortality, requiring early identification and management. The detection resistant or unusual germs relies repeated microbiological investigations.

In developing countries, the regularity of anti-infective treatment plays a crucial role in optimizing clinical outcomes. In order to better manage antibiotic failures, it is essentialstrengthennosocomial infection prevention and improve microbiological diagnosis byusing advanced tools such as PCR tests and procalcitonin assays. Close collaboration with microbiology laboratories is essential to monitor microbial ecology and adapt therapeutic strategies accordingly. In addition, complementary measures in resuscitation,suchasnutritionmanagement,hygieneandregularaudits,arealsonecessarytoreduce mortality and improve clinical outcomes.

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