Official Title of the study: Predictive Model for Multidrug Resistance in Patients Admitted to the Emergency Department with Sepsis

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Table of Contents

I. List of Abbreviations

Abbreviation	**Meaning**
ABA	*Acinetobacter baumannii*
AMR	Antimicrobial Resistance
ESBL	Extended Spectrum Beta-Lactamase-producing Enterobacterales
ESKAPE	Acronym summarizing the main clinically relevant resistant germs currently, each letter represents the initial of the scientific name of the bacterium: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.
EPC	Enterobacterales productores de carbapenemasas
GNB	Gram-Negative Bacilli
GPC	Gram-Positive Cocci
KPC	Carbapenem-resistant *Klebsiella pneumoniae*
MBL	Metallo-beta-lactamase
MDR	Multidrug-resistant
MOR	Multidrug-resistant Organisms
MRSA	Methicillin-resistant Staphylococcus aureus
OXA	Oxacillinase-type Carbapenemase
PAE MR	Multidrug-resistant *Pseudomonas aeruginosa*
PDR	Pan-resistant
SOFA	Sepsis-related Organ Failure Assessment
SSC	Surviving Sepsis Campaign
VRE	Vancomycin-resistant Enterococci
XDR	Extremely resistant

II. Abstract

Introduction: Early and accurate antibiotic administration in emergency department sepsis and septic shock patients is critical, given mortality rates of 20% and exceeding 40%, respectively, making sepsis a leading cause of in-hospital death. In settings with high antimicrobial resistance (AMR), effective empirical antibiotic selection is particularly challenging, balancing treatment efficacy with the need to prevent multidrug-resistant organism (MDRO) emergence. A predictive model for AMR probability could be a valuable tool for optimizing antibiotic use, improving patient outcomes, and mitigating AMR. While risk factors exist, a single, validated predictive model for multidrug resistance in sepsis is lacking. Accurate treatment prediction necessitates integrating patient characteristics and history, the causative microorganism and its resistance profile, the infection source, and antibiotic properties. **Objectives:** To estimate the prevalence of AMR in adult patients presenting to an adult emergency department with sepsis or septic shock We aim to develop and validate a clinically useful predictive model for estimating the probability of AMR and the likelihood of specific pathogens in patients. To evaluate the performance of a stepwise, three-phase model to: (1) predict culture positivity, (2) intermediate predict the likelihood of certain pathogens, and (3) predict AMR. Furthermore, to describe and evaluate individual-level statistics for deterministic and unpredictable patients based on the best-performing models... **Methods**: A cross-sectional study will be conducted in individuals presenting with sepsis or septic shock to the adult Emergency Department at Hospital Italiano over a total study period of 70 months, from January 1, 2017 to March 20, 2020, and from May 1, 2022 to August 10, 2025, excluding the COVID-19 pandemic period. The study will assess three primary outcomes: culture positivity; bacterial species; MDRO prevalence. For frequency analyses, numerators will comprise positive cultures, specific bacterial species, and resistance classifications (MDRO, MDR, XDR, PDR) including mechanisms (e.g., non-enzymatic, MRSA, ESBL, KPC, MBL, OXA). Denominators will be total sepsis patients (including culture-negatives) and, separately, culture-positive patients. 95% confidence intervals will be estimated using normal approximation for sufficiently large proportions. Multivariate logistic regression with backward stepwise selection will model predictors and interactions. A predictive model for multidrug resistance will be developed based on the hierarchical relationship between culture positivity, pathogen identification, and resistance profiles.

Keywords: Antimicrobial resistance, sepsis, septic shock, predictive models.

1. Introduction

Antimicrobial resistance (AMR) is one of the main challenges in the treatment of sepsis. On the one hand, early initiation of broad-spectrum antibiotics to cover potentially involved pathogens is directly associated with therapeutic success [1]. On the other hand, avoiding antibiotic overprescription, both in quantity and overly broad spectrum, is one of the key measures to combat the global rise in AMR [2–4]. Balancing the need for rapid initiation of appropriate antibiotics with the imperative of rational use without overextending antimicrobial coverage represents a major challenge when making decisions to determine optimal empirical antibiotic therapy [5].

1.1 Sepsis and AMR

1.1.1 Definition of Sepsis and AMR

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [6]. This description was the first to highlight the vital role of both innate and adaptive immune responses in the early stages of disease. Septic shock is its most severe form, characterized by a drop in blood pressure that reduces tissue perfusion pressure, causing the characteristic hypoxia of shock [7]. Patients with septic shock can be clinically identified by the requirement for vasopressors to maintain a mean arterial pressure of ≥65 mm Hg and a serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia. Among patients with sepsis, 4–7.4% will progress to septic shock regardless of management [8].

AMR is the phenomenon by which bacteria develop the ability to resist or evade antibiotics or antiseptics designed to kill them, allowing them to continue growing and spreading [9,10]. While the impact of AMR in sepsis remains a matter of controversy, and its effect on sepsis mortality is debated, several studies have reported unfavorable outcomes such as prolonged hospital stays or rehospitalizations [11], mainly due to delays in administering an effective antibiotic.

1.2 Sepsis as a Public Health Problem

The incidence and mortality of sepsis vary considerably across regions, with the highest burden in low- and middle-income countries [12,13]. The age-standardized incidence rate of sepsis worldwide is 677.5 cases per 100,000 people [12]. In North America, the incidence ranges from 500 to 1,000 cases per 100,000 people [14], and in Europe, between 400 and 800 cases per 100,000 people [15]. It is more common in low- and middle-income countries, with rates exceeding 1,500 cases per 100,000 people [16,17]. In 2017, approximately 48.9 million incident cases of sepsis were recorded globally, with 11 million sepsis-related deaths reported, representing 19.7% of all global deaths [12].

Sepsis has an approximate mortality rate of 20% [18], and septic shock can exceed 40% [19,20]. It is the leading cause of in-hospital mortality [21]. Mortality rates also vary significantly between geographic areas, from 15–25% in high-income countries to 30–40% in middle-income countries [19], and significantly higher in low-income countries, frequently exceeding 40% in sepsis and 50% in septic shock [22,23]. Sepsis mortality rates have

improved over time, especially in high-income countries; for example, in the U.S., sepsis mortality rates have decreased from over 35% in the early 2000s to 15–20% [24,25]. In middle- and low-income countries, rates have remained high over time, indicating the need for better access to healthcare resources and implementation of evidence-based treatment practices [26,27]. Notable differences exist in the prevalence of sepsis and septic shock between industrialized and low-income countries. Sepsis is less frequent in high-income countries, but the overall burden remains significant due to aging populations and rising rates of chronic comorbidities [13].

Mortality is directly linked to delays in appropriate management [1]. A critical point is patient detection. For early recognition and management, several clinical scores (such as NEWS, SOFA, or qSOFA) are used to identify patients with sepsis and at risk of mortality. The diagnosis of sepsis involves the detection of organ dysfunction and infection. The SOFA score (Sequential Organ Failure Assessment) was designed to detect organ failure and predict the risk of mortality associated with sepsis or septic shock [28]. This scale assesses the function of organ systems using objective parameters: respiratory, coagulation, hepatic, cardiovascular, renal, and central nervous systems.

The consequences of sepsis extend beyond the acute event in survivors. Post-sepsis syndrome involves deficits in multiple systems: immune, cognitive, psychiatric, cardiovascular, and renal. Collectively, these adverse outcomes lead to rehospitalizations, poorer quality of life, and increased long-term mortality [29]. In a retrospective cohort study evaluating various 30-day outcomes in patients after discharge, surviving sepsis was associated with a tripled risk of subsequent infections ($p=0.0006$), rehospitalization for infection within the year following the initial hospitalization ($p=0.0009$), and post-discharge mortality ($p=0.003$) [30].

In high-income countries, the cost of care for sepsis patients is estimated between USD 20,000 and USD 50,000 per patient episode [31,32]. In the United States, sepsis is among the most expensive conditions treated in hospitals, accounting for over USD 20 billion in annual healthcare costs [13]. Similarly high costs have been reported in Europe, with sepsis-related expenses ranging from €7,500 to €27,000 per patient [33]. In low- and middle-income countries, the direct costs of sepsis care are generally lower than in high-income countries but still represent a significant burden on healthcare systems and patients [21]. In Latin America, the best available estimate comes from a Brazilian study, which estimated that the average cost of sepsis treatment is approximately USD 10,000 per patient [34].

The Surviving Sepsis Campaign (SSC) is a global collaboration aiming to reduce sepsis mortality [35]. Since its first publication in 2004, the SSC and the Institute for Healthcare Improvement (IHI) have partnered to achieve a 25% reduction in sepsis mortality by 2009, producing high-quality, evidence-based clinical practice guidelines, with subsequent updates in 2016 and 2021 [1].

1.2.3. Antimicrobial resistance as a global and local issue

In the past, antimicrobial resistance (AMR) was a phenomenon confined mainly to nosocomial infections. However, it has now become a public health problem at the community level as well. Several factors contribute to this situation, including the extensive

and often indiscriminate use of antibiotics, the excessive use of broad-spectrum drugs, and the limited availability of narrow-spectrum antimicrobials [36]. Meanwhile, the incidence of multidrug-resistant organisms (MDROs) continues to rise, while the availability of effective antimicrobials becomes increasingly limited. Additionally, the development of resistance is occurring at an accelerating pace, narrowing the gap in the “arms race” between the emergence of new antimicrobials and the appearance of new resistance mechanisms [37].

MDROs also have a remarkable capacity for adaptation and can acquire and transmit resistance genes through mechanisms such as horizontal plasmid transfer, which amplifies their spread beyond the individual, impacting both the ecosystem and the broader community [38].

The One Health approach considers humans as part of an interdependent ecological system, constantly interacting with microorganisms, animals, plants, and the environment. Under this framework, the health of people, animals, plants, and ecosystems are closely interconnected. One of the main drivers of AMR is the excessive and inappropriate use of antimicrobials, not only in human healthcare but also in livestock, agriculture, and the food chain [39].

AMR has been called a “new pandemic,” and it is projected to become the leading cause of death worldwide by 2050, a process that has been accelerated by the COVID-19 pandemic [40]. Multidrug-resistant organisms have been recognized by the World Health Organization (WHO) as a critical threat to global health security [41]. In 2011 [42], consensus definitions were established to classify microorganisms based on their resistance profiles: multidrug-resistant (MDR, resistant to at least three tested antimicrobial groups), extensively drug-resistant (XDR, resistant to all but one or two groups), and pandrug-resistant (PDR, resistant to all available antibiotics for that bacterial family) [43].

Antimicrobial exposure is directly related to the development of AMR; therefore, efforts to reduce both the number of administered antibiotics and their spectrum of activity are crucial strategies in patients with sepsis and septic shock [44].

Excessive antibiotic prescribing is associated with multiple adverse consequences, including an increased risk of side effects, more frequent relapses, unnecessary medicalization of self-limiting diseases, and the emergence of resistance. This issue is particularly problematic in primary care, where most infections are viral. Approximately 90% of antibiotic prescriptions are written by general practitioners, particularly in emergency departments or outpatient clinics [2]. In patients with sepsis, following the Surviving Sepsis Campaign (SSC) guidelines has promoted a “treat first, ask questions later” culture, which tends to drive overprescribing [45].

Other relevant aspects include treatment duration (the “less is more” principle) [46] and the failure to de-escalate antibiotic therapy [47]. De-escalation, which consists of narrowing the spectrum based on microbiological findings, has been shown to be safe in septic patients, with additional benefits such as cost savings, reduced toxicity and side effects, and decreased emergence of multidrug resistance [48].

The pressure to initiate immediate treatment, prescribe unnecessary antibiotics, prolong therapy, or use excessively broad-spectrum agents can lead to overtreatment and related

harms. At the individual level, antibiotics disrupt the microbiota, causing imbalances and promoting colonization by resistant organisms [49]. At the ecosystem level, they foster the emergence and transfer of bacteria and resistance genes among humans, animals, and the environment [50,51]. These harms include drug adverse reactions, acute kidney injury, *Clostridioides difficile* infections, antibiotic resistance, superinfections, and even potentially increased mortality [52].

In the context of sepsis, correctly identifying patients is crucial to avoid overprescription, and three levels of optimization of antimicrobial treatment can be distinguished:

- **Appropriate:** This has a double meaning: on the one hand, that the treatment covers the presumed pathogen according to in vitro susceptibility; on the other, that it aligns with published guidelines and consensus regarding agent selection and duration [53]. It may also include adherence to local or institutional clinical practice guidelines.
- **Adequate:** In addition to being appropriate, the treatment is considered adequate if pharmacokinetic and pharmacodynamic strategies are applied, such as shorter dosing intervals, consideration of physicochemical properties when targeting specific infection sites, therapeutic drug monitoring, and prevention of drug interactions [54,55].
- **Optimal:** Beyond being appropriate and adequate, optimal therapy involves administering a dose that achieves effective concentrations at the site of infection to ensure eradication. Examples include prolonged infusions of beta-lactam antibiotics [56,57] or early adjustment of doses according to renal function in septic patients [58,59].

1.3. Types of AMR

Among the so-called “superbugs,” current concerns focus mainly on resistant Gram-negative bacilli (GNB), along with some problematic Gram-positive cocci (GPC), grouped under the acronym **ESKAPE**: vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant Enterobacterales (CRE), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*

Bacteria exhibit various AMR mechanisms, including efflux pumps, reduced permeability to antibiotics, enzymatic inactivation, target site protection or modification, and biofilm formation. Some enzymatic mechanisms are potentially transmissible and can be shared across bacterial species via plasmids, facilitating the spread of resistance to beta-lactam antibiotics, which are the most commonly used antimicrobial group in clinical practice. This group includes penicillins, cephalosporins, carbapenems, and monobactams. Among GNB, ESBL- and CRE-producing strains are of particular concern due to their increasing prevalence [60], limited treatment options, the faster emergence of resistance compared to the development of new antimicrobials, healthcare costs, length of hospital stays [61], and associated mortality [62]. The WHO has included these pathogens in its 2024 update of critical priority pathogens [63].

According to the Ambler classification, beta-lactamases, including carbapenemases, are divided into four classes [64].

Class A	Enzymes with predominant activity against penicillins. The main carbapenemase-producing strains (CPE) in this group are Klebsiella pneumoniae carbapenemase (KPC) producers [65].
Class B	Metalloenzymes with predominant activity against cephalosporins. Metallo-β-lactamases (MBLs) confer resistance to penicillins, cephalosporins, and carbapenems but retain susceptibility to aztreonam (a monobactam). There are three main types: NDM [66], VIM [67] and IMP [68].
Class C	Inducible chromosomal cephalosporinases (CCI) of Gram-negative bacteria, also known as AmpC β-lactamases. Some Enterobacterales species have genes encoding these enzymes, which confer resistance to penicillins and cephalosporins (except cefepime and aztreonam). High-risk species include Enterobacter cloacae complex, Citrobacter freundii, and Klebsiella aerogenes; lower-risk species include Serratia marcescens, Morganella morganii, and Providencia stuartii [69].
Class D	Enzymes that include oxacillinase-type (OXA-type) carbapenemases, such as OXA-11, OXA-13, OXA-15, and OXA-18 [65].

Some types of carbapenemase-producing Enterobacterales (CPE) are endemic in certain regions of the world. For instance, KPC is prevalent in the United States, Mexico, Portugal, Italy, Israel, and Greece [70], while MBLs are more common in Southeast Asia, the Mediterranean, Romania, Denmark, Poland, and the Pacific region of Asia, including Australia, China, Japan, and Turkey [71]. Latin America and the Caribbean experienced a significant increase in CPE during the COVID-19 pandemic [72], with Argentina currently presenting the highest rate of carbapenem resistance [73].

The RECAPT-AR study, conducted in Argentina in the post-COVID-19 era, is a prospective, multicenter study aiming to evaluate the prevalence of carbapenemase-producing Enterobacterales in infectious processes during the post-pandemic period. Among 821 CPE isolates, Klebsiella pneumoniae was the most frequently recovered species, accounting for 76% of the isolates. MBLs (42.0%) and KPC (39.8%) together represented 81.8% of carbapenemases; dual producers were found in 7.8% of isolates [74].

Another relevant pathogen is methicillin-resistant Staphylococcus aureus (MRSA), which is highly prevalent in skin and soft tissue infections, surgical site infections, and catheter-associated bloodstream infections. In skin and soft tissue infections from three tertiary care centers in Buenos Aires City, resistance rates among isolates ranged from 64% to 77% [75–77]. Additionally, the Whonet network for antimicrobial resistance surveillance reports that MRSA accounts for over 30% of isolates from blood cultures and nearly 45% from skin and soft tissue samples [78].

1.4. Factors Associated with Antimicrobial Resistance (AMR)

There is no single validated predictive model for multidrug resistance in patients with sepsis. However, several risk factors have been identified. Predicting appropriate treatment for a given scenario should include [79]:

- Physiological and pathophysiological characteristics of the patient.

- The causative bacterium and its resistance profile.
- Site of infection.
- The antibiotic and its pharmacological properties.

The main individual risk factors for AMR are: prior antibiotic exposure within the last 90 days, hospitalization within the past 3 months, current hospitalization lasting more than 5 days, presence of invasive devices, and prior colonization or infection by multidrug-resistant organisms (MDROs) [80]. Local epidemiology with high resistance rates to multiple antibiotics is an important risk factor that must be considered [81].

The severity of illness as a risk factor for multidrug resistance is controversial. However, the presence of septic shock is considered a risk factor for MDROs in hospital-acquired pneumonia according to both European and American guidelines [82]. In contrast, in critically ill patients with intra-abdominal infections, no differences were found in the incidence of MDROs between those with or without sepsis or septic shock [83].

The risk score by Tumbarello et al. [84], published in 2011, was developed to estimate the risk of infection with ESBL-producing organisms in patients presenting with urinary tract infections. Higher risk was associated with age ≥70 years, recent hospitalization, use of a urinary catheter, comorbidities (Charlson score ≥4), and prior antibiotic use—especially fluoroquinolones.

Most nosocomial infections are endogenous, originating from the mucosal microbiota. These endogenous infections result from the translocation of predominant aerobic microorganisms in the intestinal mucosa [85]. Patients colonized with CPE are at higher risk of developing infections caused by MDROs and have higher infection rates compared to the general population. In Ontario, Canada, among a cohort of 69,998 individuals with a positive CPE surveillance test, 20.3% developed an infection within a median of 10 days [86]. In another study of 6,828 CPE carriers, the cumulative incidence of CPE bacteremia was 2.4%. Certain species, like Klebsiella pneumoniae, carry a higher risk of infection than others like Escherichia coli. Among resistance mechanisms, MBLs seemed to carry a lower risk than KPCs, although the difference was not statistically significant [87]. The highest risk of infection occurs within 10 to 14 days after initial CPE colonization detection [88].

In colonized patients, the study by Gianella et al. found that ICU admission, history of invasive abdominal procedures, chemotherapy/radiotherapy, and the number of additional colonization sites were independent risk factors for developing CPE bacteremia [89].

In patients with sepsis or septic shock, the decision to include an anti-MRSA agent in the empirical treatment regimen depends on a risk assessment based on patient characteristics and the infection site [1]. Risk factors for MRSA in community-associated infections include recent hospitalization, long-term care facility residence, recent surgery, chronic hemodialysis, prior infection or colonization, and prior quinolone use [90,91]. In skin and soft tissue infections, due to high local prevalence, empirical coverage is always recommended in purulent infections [92].

In a cohort study of 17,430 adults with community-onset sepsis and positive cultures admitted to 104 U.S. hospitals, 67.0% received broad-spectrum empirical antibiotics.

However, Gram-positive cocci (GPC) were isolated in only 13.6% and Gram-negative bacilli (GNB) in 13.2%. Both undertreatment (uncovered pathogen) and overtreatment (resistant organisms identified but not isolated) were associated with increased mortality after detailed risk adjustment [52].

In patients diagnosed with infection and suspected sepsis, initiating appropriate empirical antibiotics within one hour of recognition is one of the key measures to reduce mortality. For every hour of delay within the first 24 hours, the risk of death increases by 4% [93]. The Surviving Sepsis Campaign guidelines emphasize the immediate administration of broad-spectrum empirical antibiotics upon suspicion of sepsis [1].

To date, there is no universally validated methodology to predict AMR in patients with sepsis, which remains one of the greatest challenges. Empirical treatment is generally prescribed within the first 48 to 72 hours after sample collection. In terms of patient care, validated prediction of AMR could improve the adequacy of empirical treatment by reducing the risk of using an antibiotic to which the causative microorganism is resistant [94]. These predictions could also have local and global benefits by reducing broad-spectrum antibiotic prescribing and decreasing the risk of MDRO transmission [95].

The challenges of antibiotic treatment in sepsis include proper stewardship programs based on infection-related knowledge in critically ill patients and the context of multidrug-resistant organisms [96]—especially Gram-negative bacteria—focused on carbapenem-sparing strategies and the rational empirical use of new antibiotics [5]. Predicting the occurrence of MDRO infections requires consideration of individual patient characteristics, the infectious focus, the community to which the patient belongs, and the likely bacteria along with their natural and acquired resistance mechanisms.

1.5. Relevance and Purpose

Sepsis remains a daily clinical challenge, especially in emergency departments, due to the urgent need for early detection, timely antibiotic treatment, and high mortality, especially if treatment fails. In countries with high prevalence of antimicrobial resistance (AMR), choosing the right antibiotic treatment can be especially difficult due to the possibility of AMR on one hand, and the duty to rationally use antimicrobials to avoid the emergence of multidrug-resistant organisms (MDRO) on the other. In this context, a predictive model for AMR that anticipates this probability and makes better use of antibiotics could be a highly useful tool for improving patient care and combating AMR.

Challenges in antibiotic treatment in sepsis include proper management programs based on knowledge related to infections in critically ill patients and in the context of multidrug-resistant pathogens [96], particularly Gram-negative bacteria, focusing on carbapenem-sparing and the empirical and rational use of new antibiotics [5]. The challenge is to predict the occurrence of MDRO infections based on the patient's individual characteristics, the infectious focus, the community they belong to, and the likely bacteria and their natural and acquired resistance mechanisms.

This project directly aligns with two of the Sustainable Development Goals (SDGs) proposed by the United Nations [97]: SDG 3 ("Good Health and Well-being"), SDG 9 ("Industry, Innovation, and Infrastructure"), and SDG 10 ("Reduced Inequality").

SDG 3: Ensure healthy lives and promote well-being for all at all ages [98]. This project contributes directly to SDG 3 by addressing one of the most urgent challenges in global health: AMR, especially in patients with sepsis, a critical condition with high mortality. By developing a predictive model to identify individuals at high risk of infections from multidrug-resistant pathogens, the goal is to optimize antibiotic use in emergency services, improve clinical outcomes, reduce mortality, and promote more rational use of healthcare resources. In this sense, the development of a predictive tool that enables more rational and targeted prescribing is in line with SDG 3 goals, contributing to access to safe, effective, and quality treatments and reducing avoidable mortality.

SDG 9: Build resilient infrastructure, promote inclusive and sustainable industrialization, and foster innovation [99]. The project promotes innovation in the field of medicine and public health by applying predictive models and data analysis tools in real clinical contexts. This integration of data science, epidemiology, and artificial intelligence in clinical decision-making represents a commitment to smarter, more efficient healthcare systems capable of adapting to emerging challenges.

SDG 10: Reduce inequality [100]. The burden of disease associated with AMR disproportionately affects low- and middle-income countries [40], where limitations in diagnostic infrastructure, access to new therapies, and infection control resources exacerbate existing health inequalities. Furthermore, the mortality associated with sepsis disproportionately affects lower-income regions within the same country [101] and across countries [13]. In this context, a tool that can be applied in high-demand settings such as emergency departments, and that favors the rational use of antimicrobials even in resource-limited scenarios, could help reduce these inequities. Therefore, this project also aligns with SDG 10 by proposing a potentially replicable strategy that promotes equity in addressing sepsis and AMR locally and globally.

2. Question and Objectives

2.1. Questions

In adult patients who present to an emergency department in a tertiary care center with sepsis or septic shock:

- What is the prevalence of AMR/resistance patterns with clinical significance?
- What are the predictive factors associated with AMR in this population?
- Is it possible to generate and validate clinically useful predictive models to predict the probability of AMR?

2.2. Objectives

In adult patients who present to an emergency department in a tertiary care center with sepsis or septic shock:

2.2.1. Prevalence and Associated Factors

- Estimate the prevalence of AMR/resistance patterns with clinical significance.
- Describe the predictive factors associated with AMR in this population.
- Generally, and in clinically relevant subgroups: by probable focus, clinically relevant pathogens, severity.

2.2.2. Generation and Validation of Predictive Models

- Generate and validate clinically useful predictive models to predict the probability of AMR.
- Generate and validate clinically useful predictive models to predict the probability of common/relevant pathogens.
- Evaluate the performance of stepwise predictive models in three stages: 1. Prediction of positive culture, 2. Intermediate prediction of pathogen, and 3. Prediction of AMR.
- Describe and evaluate point statistics on deterministic and unpredictable individuals based on the best predictive models.

3. Methods

3.1. Design

A cross-sectional study will be conducted on patients presenting with sepsis or septic shock at the emergency department of the Hospital Italiano de Buenos Aires (HIBA) in both its central and San Justo "Agustín Rocca" campuses who are subsequently admitted. All individuals with sepsis will be included at the time of their entry to the adult emergency department.

Since the goal is to develop stepped predictive models capable of validly predicting culture positivity, pathogen identification, and antimicrobial resistance (AMR), all potentially predictive variables will be measured at the time of study inclusion (time zero).

The events of interest in the study will also be measured at time zero. Although culture results might seem like an event that occurs over time, the measurement occurs at time zero upon inclusion in the study. The delay in results is simply due to technical reasons and does not constitute patient follow-up.

The study period will span 70 months, from 01/01/2017 to 20/03/2020 and from 01/05/2022 to 10/08/2025. During the COVID-19 pandemic, emergency services were restructured, with an increase in telemedicine as a protective strategy for both staff and patients, avoiding crowding in waiting rooms. The total number of consultations decreased, and the proportion of low-complexity consultations declined, while high-complexity consultations increased [102]. The Hospital's infection control committee action plan and recommendations restricted usual practices for the initial management of sepsis patients, such as the decision to perform invasive procedures for respiratory sample collection, like bronchoalveolar lavage [103]. Some specialties, such as pulmonology and otorhinolaryngology, also restricted their practices for safety reasons [104].

3.2. Setting

HIBA is an integrated care network comprising two hospitals: the central hospital and San Justo (HISJ). It is a high-complexity university hospital in Buenos Aires, with 789 beds, 246 of which are for critical care; approximately 2.5 million outpatient consultations annually, 41,000 discharges, and about 45,000 surgical procedures performed in 57 operating rooms [105]. Additionally, HIBA offers a prepaid health plan with about 184,000 members. Care across all areas is centralized in a unified Electronic Health Record (EHR). This data repository contains both administrative information about patients (such as studies, appointment requests, outpatient visits, hospitalizations, and drug consumption) and all clinical information (health problems, clinical diagnoses, medical evolutions, study results, etc.). All health issues or comorbidities are automatically coded through a terminology server with a local thesaurus that maps and encodes the information using the controlled vocabulary SNOMED [106].

At the Adult Emergency Department (CEA) of HIBA's central hospital, approximately 500 consultations are handled daily. It has 23 patient care stations for patients arriving by their own means and 30 observation/inpatient beds covering the full spectrum of complexity and specialties. Around 6% of patients are admitted. Given the closed prepaid system, 80% of ambulances arriving at the CEA are not referred to another emergency department outside the HIBA care network.

Patients with infections presenting to the CEA are initially triaged by trained nurses, who assess severity by dividing patients into four sectors: A for critical patients, B for moderate complexity, C for low complexity, and D for spontaneous demand. Vital signs are recorded in the EHR when potential severe cases are detected. Patients arriving by ambulance bypass this step and are directly assigned to sector B. Once in sector B, patients undergo further evaluation by doctors and nurses to determine the definitive site for initial assessment (A or B depending on sepsis or septic shock), and blood samples for laboratory tests, blood cultures, and urine cultures (if prescribed) are collected. The first dose of antibiotics is administered within the first hour [107,108]. Other cultures may require further evaluation and are often deferred during the first 12 to 24 hours, as are other complementary studies such as imaging. There is a clinical practice guideline for sepsis management for emergency doctors [109] and one from the adult infectious diseases section of the medical clinic service [110], both based on SSC guidelines [1].

3.3. Population

The study population will include all individuals aged 18 years or older who present to the CEA at HIBA.

3.3.1. Inclusion Criteria	● Adults aged 18 years or older. ● Presenting to the emergency department at the Hospital Italiano de Buenos Aires between 01/01/2017 and 20/03/2020, and from 01/05/2022 to 10/08/2025. The period affected by the COVID-19 pandemic, starting on 20/03/2020 with mandatory confinement, will be excluded [111]. Given changes in care practices, such as the exclusion of respiratory sample collection to avoid exposure to infections, the study will also exclude the three waves of COVID-19 in Argentina. ● Presenting with sepsis or septic shock (see section 5.3.3 for definitions) and requiring at least 48 hours of observation or admission. ● Bacterial cultures taken during the initial evaluation.
3.3.2. Exclusion Criteria	● Patients without an indication for antibiotics within the first 48 hours of hospital admission. ● Patients without bacterial cultures performed within the first 48 hours of hospital admission. ● Patients diagnosed with SARS-CoV-2 infection within the first 72 hours of hospital admission.

3.3.3. Definitions

Sepsis

Individuals meeting any of the following two criteria within the first 24 hours of hospital admission:

- Sepsis or septic shock and its subset, as the reason for consultation, discharge from the emergency department, or reason for hospitalization.
- SOFA score (Sepsis-related Organ Failure Assessment) upon admission to the Adult Intensive Care Unit or Adult Intermediate Care Unit with a score of 2 or higher.
- Vital sign recordings within 24 hours of hospital admission with a SOFA score of 2 or more. **SOFA Scale**: A scale that assesses organ dysfunction. In patients with infection, a SOFA score ≥ 2 points (or a 2-point increase from baseline in patients with chronic organ dysfunction) is diagnostic of sepsis.

SOFA (*Sepsis related Organ Failure Assessment*)					
Criteria	**0**	**1**	**2**	**3**	**4**
CNS Glasgow Coma Scale	15	13-14	10-12	6-9	<5
Renal Creatinine (mg/dl) Urine output (ml/day)	<1,2	1,2-1,9	2-3,4	3,5-4,9 o <500 ml	>5 o <200 ml
Hepatic Bilirubin (mg/dl)	<1,2	1,2-1,9	2-5,9	6-11,9	>12
Coagulation Plaquetas $10^3/mm^3$	≥150	<150	<100	<50	<20
Respiratory PaO2/FiO2 (mmHg)	≥400	<400	<300	<200 ventilatory support	<100 ventilatory support
Cardiovascular MAP(mmHg) Vasoactive drugs (µg/kg/min)	≥70	<70	Dopamina <5 o dobutamina at any dose	Dopamina 5-15 Noradrenalina o adrenalina ≤0,1	Dopamina >15, noradrenalina o adrenalina >0,1
Abreviaturas: CNS Central Nervous System, PaO2 Arterial oxygen pressure, FiO2 Fraction of inspired oxygen, MAP Mean arterial pressure.					

Septic shock

Individuals who, within 6 hours of hospital admission, require vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and have a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia [8].

3.4. Data collection

A coded and de-identified database will be requested through a help desk from the Research Department at HIBA.

3.5. Variables

3.5.1. Outcome variables

1. Culture positivity	Variable dicotómica. Se considerará positivo o negativo.
2. Bacterial species	Categorical variable; the following will be considered: Escherichia coli, Salmonella, Shigella, Klebsiella pneumoniae, Proteus mirabilis, other Proteus species (P. penneri or P. vulgaris), Morganella morganii, Providencia stuartii, Providencia rettgeri, Serratia marcescens, Citrobacter koseri, Citrobacter freundii, Enterobacter cloacae, Klebsiella aerogenes, Hafnia alvei, Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, coagulase-negative Staphylococcus, Streptococcus pneumoniae, group A beta-hemolytic Streptococcus, Streptococcus pyogenes, Haemophilus influenzae, Neisseria meningitidis, Listeria monocytogenes, others.
3. Multidrug-resistant microorganism [43]	Categorical variable; the following will be considered: Multidrug-resistant (MDR): resistant to at least one antibiotic in three of the antibiotic groups tested for that family, as described below. Extensively drug-resistant (XDR): non-susceptible to at least one agent in all but two or fewer antimicrobial categories. Pandrug-resistant (PDR): resistant to all antibiotics available for that family.

For enterobacterales

Group of antibiotics	Penicillins				Cephalosporins					Carbapenems			Mono-bactams	Aminogly-cosides		Fluoro-quinolones	Folate pathway inhibitors	Tetracyclines		Glycylcyclines	Phosphonic acids	Polymyxins
Antibiotics	Ampicillin	Ampicillin-sulbactam	Amoxicillin-clavulanic acid	Piperacillin-tazobactam	Cefazolin	Cefuroxime	Ceftriaxone / Cefotaxime	Ceftazidime	Cefepime	Imipenem	Meropenem	Ertapenem	Aztreonam	Gentamicin	Amikacin	Ciprofloxacin	Trimethoprim-sulfamethoxazole	Doxycycline	Minocycline	Tigecycline	Fosfomycin	Colistin
Especies bacterianas																						
Escherichia coli																						
Salmonella																						
Shigella																						
Klebsiella pneumoniae	R																					
Proteus mirabilis																				R		R
Other species of Proteus *P. penneris o P. vulgaris*	R				R	R												R	R	R		R
Morganella morganii	R		R		R	R	!	!					!					R	R	R		R
Providencia stuartii	R		R		R		!	!					!	R				R	R	R		R
Providencia rettgeri	R	R	R		R		!	!					!	R				R	R	R		R
Serratia marcescens	R	R	R		R	R	!	!					!									R
Citrobacter koseri	R	R																				
Citrobacter freundii	R	R	R		R		!	!					!									
Enterobacter cloacae	R	R	R		R		!	!					!									
Klebsiella aerogenes	R	R	R		R		!	!					!									
Hafnia alvei	R	R	R		R		!	!					!									

The yellow exclamation mark corresponds to species carrying the AmpC gene, which can become deregulated and produce inducible chromosomal cephalosporinases (ICC), with yellow indicating low-risk species and orange indicating high-risk species [69].

For non-fermenters (Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia).

Group of antibiotics	Penicillins				Cephalosporins					Carbapenems			Mono-bactams	Aminogly-cosides		Fluoro-quinolones		Folate pathway inhibitors	Tetracyclines		Glycylcyclines	Phosphonic acids	Polymyxins
Antibiotics	Ampicilina	Ampicilina-sulbactam	Amoxicilina-ácido clavulánico	Piperacilina-tazobactam	Cefazolina	Cefuroxima	Ceftriaxona / Cefotaxima	Ceftazidima	Cefepime	Imipenem	Meropenem	Ertapenem	Aztreonam	Gentamicin	Amikacin	Ciprofloxacin	Levofloxacin	Trimethoprim-sulfamethoxazole	Doxycycline	Minocycline	Tigecycline	Fosfomycin	Colistin
Especies bacterianas																							
Pseudomonas aeruginosa	R	R	R		R	R	R					R						R	R	R	R		
Acinetobacter baumannii	R		R									R											
Stenotrophomonas maltophila	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R			R			R	R

For Staphylococcus aureus, the antibiotic groups are: Aminoglycosides (gentamicin), Ansamycins (rifampin), Anti-staphylococcal beta-lactams (methicillin / cefazolin), Anti-MRSA cephalosporins (ceftaroline), Fluoroquinolones, Folate pathway inhibitors (trimethoprim-sulfamethoxazole, TMP-SMX), Lincosamides (clindamycin), Macrolides (erythromycin), Glycopeptides (vancomycin / teicoplanin), Tetracyclines, Glycylcyclines (tigecycline), Lipopeptides (daptomycin), Oxazolidinones (linezolid).

For Enterococcus, the antibiotic groups are: Aminoglycosides (gentamicin), Streptomycin, Carbapenems (imipenem or meropenem) or Penicillins (ampicillin), to which Enterococcus faecium is resistant in over 90% of cases, Fluoroquinolones, Glycopeptides (vancomycin / teicoplanin), Tetracyclines (minocycline / doxycycline), Glycylcyclines (tigecycline), Lipopeptides (daptomycin), Oxazolidinones (linezolid).

3.1. Enzymatic resistance mechanisms	Categorical variable, the following will be considered: No enzymatic mechanism; MRSA; VRE; KPC; MBL; OXA.

Group of antibiotics	Traditional Antibiotics					Old Antibiotics				New Antibiotics				
Antibiotics	Piperacillin-tazobactam	Ceftazidime	Cefepime	Aztreonam	Imipenem / Meropenem	Amikacin	Tigecycline	Fosfomycin	Colistin	Ceftolozano-tazobactam	Ceftazdima-avibactam	Imipenem-relebactam	Aztreonam-avibactam	Cefiderocol
BLEA	S	R	R	R	S	S	S	S	S	S	S	S	S	S
BLEE	R	R	R	R	S	S	S	S	S	!	S	S	S	S
AMP-C (CCI)	R	R	S	R	S	S	!	S	!	R	S	S	!	!
OXA	R	R	R	R	R	S	S	S	S	R	S	S	S	S
KPC	R	R	R	R	R	S	S	S	S	R	S	S	!	S
MBL	R	R	R	S	R	S	S	S	S	R	R	R	S	S

3.2. Carbapenemase genotypes	Categorical variable; the following will be considered: Types of carbapenemases if studied (for example, KPC, NDM, VIM, IMP, OXA-48 like).

3.5.2. Explanatory variables - Potential predictors of resistance

Domain	Variables
1. Patient characteristics	Age, Sex, and Place of origin according to the 24 provinces [112,113]. Place of origin (Community / Tertiary level center / Acute hospitalization (<30 days) / Prolonged hospitalization (31 or more days) / Chronic hospitalization (>90 days).
2. Invasive devices	Dichotomous variables for the presence or absence of each of the following: bladder catheter, central venous catheter, tracheostomy, nasogastric tube. This will be recorded according to the first nursing assessment upon admission to the CEA.
3. Immunosuppression	Any of the following will be considered severe [114]: ● Active leukemia or lymphoma. ● Disseminated malignancy. ● Aplastic anemia. ● Graft-versus-host disease (GVHD). ● Congenital immunodeficiencies (e.g., common variable immunodeficiency). ● Recent treatment with checkpoint inhibitors or radiation therapy. ● Solid organ transplant with immunosuppressive treatment. ● Immunosuppressive drugs related to transplant: cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, mycophenolate mofetil. ● Hematopoietic stem cell transplant (HSCT) within two years or ongoing immunosuppressive therapy. ● High-dose systemic corticosteroids (20 mg or less of prednisone per day or its equivalent) for at least two weeks. ● Alkylating agents (cyclophosphamide) or antimetabolites (methotrexate >0.4 mg/kg/week, azathioprine ≥3 mg/kg/day, or 6-mercaptopurine ≥1.5 mg/kg/day). ● Chemotherapy for cancer. ● Tumor necrosis factor alpha blockers (etanercept, adalimumab, certolizumab, golimumab, infliximab). ● Biologics, lymphocyte-depleting agents such as thymoglobulin or alemtuzumab. ● B-cell depleting agents such as rituximab. ● HIV patients with a CD4 count <200 cells/mm³, AIDS diagnosis, or symptomatic HIV. Mild Immunosuppression [115].

	● Asymptomatic HIV infection with a CD4 count between 200 and 499 cells/mm³. ● Low-dose systemic corticosteroids (19 mg or less of prednisone per day or its equivalent) for at least two weeks. ● Methotrexate ≤0.4 mg/kg/week. ● Azathioprine ≤3 mg/kg/day or 6-mercaptopurine ≤1.5 mg/kg/day. Neutropenia. Cytopenias [116]: Leukopenia: white blood cell count below 5000/mL. Absolute neutrophil count (ANC): ● Neutropenia: ANC <1500/mL ● Mild: 1000-1500/mL ● Moderate: 500-1000/mL ● Severe: <500/mL ● Agranulocytosis: <200/mL
4. Comorbidities	Nominal dichotomous categorical variable for the presence or absence of the following: Chronic renal failure, Hemodialysis, Arrhythmia, Cardiac disease, Inflammatory Bowel Disease, Diabetes, Cerebrovascular disease, Psychiatric conditions, Mild hepatic disease, Obesity, Previous infection, Moderate lung disease, Rheumatologic disease, Peptic ulcer, Previous tumor, Valvular heart disease, Severe pulmonary disease, Severe hepatic disease.
5. Therapeutic adequacy	Dichotomous variable for the presence or absence of nursing NEWS assessment or medical indication of: "Do not resuscitate order" or "Do not follow NEWS protocol." Follow-up by palliative care: evolution prior to the event by palliative care.
6. Medical history	Previous hospitalization, Duration of previous hospitalization. Time since discharge. Use of antibiotics during previous hospitalization. Stay in Intensive Care Unit (ICU) during previous hospitalization. Previous colonization by multiresistant germs. Previous infection by resistant germs and time since that event. Invasive procedure in the previous 90 days: VEDA, CVC, ERCP, Cystoscopy, Bronchoscopy, Other invasive procedures. Surgery in the previous 90 days. Hospitalization <48 hours and >48 hours.

	Extended antibiotic prophylaxis. Site of hospitalization. Center of hospitalization. Place of hospitalization. ICU admission in the previous year and time since ICU discharge. Use of medications: chemotherapy, intravenous infusions. Transfusions.
7. Antibiotic use	Use of antibiotics: Outpatient antibiotics (prescription or dispensing), antibiotics in emergency consultation, home hospitalization antibiotics.
8. Clinical status	Numerical value and each category of SOFA. Lactate level. Infectious focus. Sepsis-induced hypoperfusion: defined by any of the following criteria in the context of sepsis: ● Systolic blood pressure (SBP) < 90 mmHg or Mean Arterial Pressure (MAP) < 65 mmHg. ● Lactate > 4 mmol/L. ● Urine output < 0.5 ml/kg/h. PaO2/FiO2 ratio: an indirect marker of lung injury. It measures the ratio of arterial oxygen pressure to the concentration of oxygen in inspired air. It is used to categorize Acute Respiratory Distress Syndrome (ARDS) into: ● Mild: PaO2/FiO2 ≤ 300 and > 200 mmHg. ● Moderate: PaO2/FiO2 ≤ 200 and > 100 mmHg. ● Severe: PaO2/FiO2 ≤ 100 mmHg.
9. Diagnostic studies	Cultures (Blood cultures, Urine culture, Stool culture, Cerebrospinal fluid culture, Sputum, Bronchoalveolar lavage, Tracheal aspirate, Abscess culture). Complementary: Surveillance swab, Nasal swab SAMR, Viral panel, FilmArray. Imaging: Chest X-ray, Abdominal X-ray, CT scan, Ultrasound, MRI.

4. Statistical Considerations

4.1. Sampling and Sample Size Calculation

A consecutive random sampling will be carried out of all individuals assisted in the adult emergency department at HIBA during the period from 01/01/2017 to 20/03/2020 and from 01/05/2022 to 10/08/2025. That is, the entire 70-month period of the study will be included.
The sample size is fixed, including all individuals with sepsis who consult the emergency department during the study period. Given that temporal trends could potentially change both the incidence of sepsis and the occurrence and frequency of multidrug resistance, it was decided to divide the generation and validation samples into 2/3 and 1/3, respectively. No additional sample size calculation was performed for internal validation.

4.2. Statistical Analysis

4.2.1. Missing Data

Missing data will be considered as missing at random (MAR), and therefore, the general strategy will be to use complete case analysis unless specified otherwise.
Since secondary databases will be used, there will be no missing data for categories where only positive results are recorded. For example, "diabetes" is a variable that only records positive results in databases derived from healthcare systems, as "non-diabetics" are not recorded. In this way, and as is customary, "non-diabetics" will be considered as those not registered with the "diabetes" attribute. In this case, no missing data will exist.
A special case that requires separate mention is negative cultures. By definition, a negative culture represents a missing data point, as the germ or potential antimicrobial resistance is unknown. Although predictive models will include individuals with negative cultures, validation will be repeated in the subset of positive cultures. Multiple imputation strategies for negative cultures could be explored.

4.2.2. Generalities

Although individuals may have more than one episode of sepsis during the study period, considering the intention to generate predictive models for each new episode, each episode will be included as an independent unit of analysis for descriptive analysis, exploration of associated factors, and the generation and validation of predictive models as described below.
Statistical significance will be considered for p-values less than 0.05 unless otherwise specified. In line with current understanding of hypothesis testing, emphasis will be placed on presenting association measures with their confidence intervals rather than p-values. Statistical analysis will be performed using STATA version 16 MP - Parallel Edition (Copyright 1985-2017 StataCorp LLC - StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

4.2.3. Descriptive Analysis

Continuous variables will be presented as mean and standard deviation or median and interquartile range (IQR), depending on the observed distribution. Categorical variables will be presented as absolute and relative frequencies.

4.2.4. Frequency Calculation

For the calculation of frequencies, the positive culture will be used as the numerator, along with each selected relevant bacteria, MOR, MDR, XDR, PDR, resistance mechanisms (non-enzymatic mechanisms, SAMR, EVR, KPC, MBL, OXA) for each case, with the total number of individuals with sepsis (including negative cultures) as the denominator. This will be repeated using positive cultures as the denominator. Assuming sufficiently large proportions, 95% confidence intervals (CI95%) will be presented, estimated with the normal approximation.

4.2.5. Associated Factors

This analysis will include only individuals in the generation sample. Logistic regression models will be used to explore associated factors for each potential predictor. The crude odds ratios (OR) with their CI95% will be presented.

4.2.6. Predictive Models

The sample will be randomly divided into a generation sample (2/3 of the sample) and a validation sample (1/3 of the sample).
For the generation and validation of predictive models, the positive culture, each selected relevant bacteria, MOR, MDR, XDR, PDR will be used as outcome variables.

4.2.7. Generation of Predictive Models

A multivariate logistic regression model will be used with a stepwise backwards algorithm, including potential predictors and interaction terms considered relevant. The different models will be compared using the Akaike Information Criterion (AIC), selecting the model with the lowest AIC. Since STATA does not consider AIC in its stepwise algorithms, a p-value of 0.157 will be used as a proxy [117].
The assumptions of the model, such as logit linearity and the absence of multicollinearity, will be evaluated. The presence of influential or high-leverage data will also be assessed.
All predictors will be presented with OR, CI95%, coefficients, and standard errors. Both the complete predictor model and an adjusted model considering shrinkage will be presented. Discrimination measures (area under the ROC curve of the model) and calibration measures (calibration in the large, slope of calibration, calibration plots) for the generation sample will also be presented.

4.2.8. Validation of Predictive Models

Using the validation sample, measures of discrimination (area under the ROC curve of the model) and calibration (calibration in the large, slope of calibration, calibration plots) will be presented.
The clinical utility of the model will be evaluated in the validation sample, estimating sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for selected events.

4.2.9. Staged Models

Considering the structure between positive culture, germ, and multidrug resistance, a predictive model of multidrug resistance will be built, considering this information and structure. Initially, a predictive model of positive culture will be constructed. The second step will involve constructing models of specific relevant germs, considering the predicted value for positive culture as an explanatory variable. The third step will be to generate predictive

models for MOR, considering as explanatory variables the predicted probabilities for relevant germs. All potential predictors could participate in the construction of predictive models at each stage.

4.2.10. Visualization of Predicted Probabilities

All objectives of this study aim to generate useful tools for clinical decision-making. Therefore, we will develop a visual interface to represent the probabilities of relevant germs and potential multidrug resistance. Structures similar to microarrays could be used with heatmaps, where colors represent probabilities that are easily identifiable by simple visual inspection.

4.2.11. Exploration of Predictable and Unpredictable

A predictive model can be considered a diagnostic test for classifying observations or individuals [118]. Each predictive model generated with different algorithms can be considered a distinct diagnostic test and compared to the known observed results, similar to the standard approach for exploring the validity of predictive models. In this comparison, observations can be correctly classified in two ways: the model predicts that the individual will achieve the outcome, and it does so (True Positive - TP), or the model predicts that the individual will not achieve the outcome, and it does not (True Negative - TN). Conversely, the predictive model can incorrectly classify individuals in two ways: the model predicts that the individual will achieve the outcome, but does not (False Positive - FP), or the model predicts that the individual will not achieve the outcome, but does (False Negative - FN). These four classification cells depend on the cutoff values in the continuous output of the predictive model, which can take a range of values. Thus, those that the model correctly predicts, true positives and negatives, can be called deterministic; while false positives and negatives might be called unpredictable.

Using cutoff points that leave 10% of individuals above and 10% below, it is possible to define at one extreme TP and FP, and at the other extreme TP and FN. By comparing the characteristics between TP and FP on one hand, and TN and FN on the other, we aim to expose the differences between these subgroups of individuals in order to better understand the errors of the model in correctly identifying individuals; to describe and evaluate point statistics about deterministic and unpredictable individuals according to the best predictive models.

Predictors, multidimensional distances, heterogeneity, information, point estimates (such as influence and leverage) in the outcome (subtypes of events or severity), and many other statistics and metrics will be compared.

5. Ethical Considerations

This is a retrospective observational study, which does not involve any procedures or activities beyond standard care during patient evaluation and treatment. Therefore, it poses no risk to patient health and entails no additional costs for patients or their healthcare coverage. Patients will only be evaluated retrospectively through their electronic health records (EHR).

Given that this study involves only minimal risk due to the handling of participant data, we request a waiver of informed consent, based on CIOMS 2019 Guideline 10: Modifications and Waivers of Informed Consent, on the grounds that:

A. it would not be feasible or practical to conduct the research without such a waiver;
B. the research has significant social value; and
C. the research entails only minimal risk to participants.

Regarding point A, this is a retrospective observational study involving hospitalized individuals who have already signed an informed consent upon admission, which includes authorization for the use of clinical data for academic and scientific purposes, while ensuring confidentiality. Due to the retrospective nature of this study, it would not be feasible to obtain prospective informed consent from participants.

Regarding point B, this research has social value as it will provide insight into the epidemiology of resistant microorganisms (ROs) in sepsis and contribute to the development of a tool to optimize antimicrobial use—particularly relevant in a country with a high incidence of carbapenemase-producing Enterobacterales (CPE), and in the broader context of low- and middle-income countries.

Finally, regarding point C, the study involves only minimal risk to patients, as it is retrospective and observational. The primary risk relates to patient privacy; therefore, all data will be processed with maximum confidentiality and codified, with access restricted solely to authorized study personnel. Data management will comply with national regulations, including Argentina's Personal Data Protection Law No. 25.326/00 (Habeas Data Law) and Law No. 26.529/09 on patient rights.

We remain fully available for any audits, monitoring, or reviews of processes, documentation, or datasets (intermediate or final versions) that the Ethics Committee may deem necessary for the study.

6. Funding

The project will be fully funded by the Internal Medicine Service and its Adult Infectious Diseases section of the Italian Hospital of Buenos Aires.

7. Schedule

Meses **Actividades**	02-03/2025	03/2025	04-08/2025	09-12/2025	01-04/2026	05-07/2026
Literature review						
Definition of question and hypothesis						
Writing of the protocol						
Presentation Ethics Committee						
Database setup						
Data collection						
Database validation						
Statistical analysis						
Final report of results						

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