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Isolation of Multidrug-Resistant Bacteria as an Independent Mortality Factor in Patients with Suspected Sepsis at National Medical Center of the West

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ABSTRACT

Introduction: In the changing epidemiological landscape sepsis corresponds to one of the main causes of in-hospital mortality, in third level care units the presence of multidrug resistant bacteria to antimicrobials correspond to a severe health problem, there are studies in intensive care units on mortality related to the appearance of multidrug resistant bacteria in cultures, however infection by multidrug resistant bacteria can appear at any instant of hospital stay which can become an independent risk factor for the appearance of mortality.

Aims: To associate the isolation of multidrug-resistant bacteria as an independent mortality factor in patients with suspected sepsis at the Centro Médico Nacional De Occidente.

Materials and methods: Place of study: Centro Médico Nacional De Occidente Guadalajara, Jalisco, Mexico. Type of study: Clinical, retrospective cohort type. The clinical records of patients admitted during the study period were searched. Patients with suspected sepsis according to the definition of the Third International Consensus were identified from continuous medical admission and followed up throughout their stay in the hospital. Patients with culture results were evaluated. Two follow-up cohorts were identified: those who presented isolation of multidrug-resistant bacteria at any time during hospitalization and the second cohort those who did not present isolation of multidrug-resistant bacteria; an initial determination of the variables was made and then the clinical records of the patients during their stay in the services were reviewed to search for in-hospital mortality. The association between the occurrence of multidrug-resistant bacteria and mortality was estimated by Hazard Ratio (with 95% confidence intervals).

Results: A total of 94 patients were included with a minimum age of 16 years and a maximum age of 91 years with a mean of 48 years with a standard deviation of 20 years. A total of 93 cultures were included of which 21 (22.3%) were isolated with bacterial resistance. Of the positive cultures 42 % (9) were blood culture, 10 % (2) were surgical wound cultures, urine culture 23 % (5), bronchial aspirate 23 % (5). Regarding mortality, 57 % of the patients who presented bacterial resistance presented mortality, presenting a Hazard Ratio of 3.371 with 95% CI (1.125-10.100) p=0.02 Table 2 and 3. Regarding mortality with the different types of bacteria, it was 40 % in Gram negative bacteria with a Hazard Ratio of 1.875 (0.291-12.089), while it was 20 % in Gram positive bacteria, which was not statistically significant p=0.3.

ARTICLE DETAILS

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Conclusion: Isolation of multidrug-resistant bacteria is an independent mortality factor in patients with suspected sepsis at Centro Médico Nacional De Occidente. There is no relationship with the isolation of Gram-positive and Gram-negative bacteria type with respect to patient mortality.

KEYWORDS: Bacterial multidrug resistance, sepsis, hospital mortality.

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection, a definition established by the Third International Consensus that emphasizes the importance of its early recognition and potential lethality. (1). There are clinical signs and biochemical tests that increase the likelihood of organ dysfunction as a result of infection. (2).

Assessing which best represented an increased risk of organ dysfunction, the 2016 expert consensus established that an increase in the SOFA (Sequential Organ Failure Assessment) scale score (3) score greater than or equal to two points identifies precisely that subgroup of patients, from which the operational definition of sepsis is based and which renders the SIRS (Systemic Inflammatory Response Syndrome) criteria obsolete.(4).

Sequential [Sepsis-Related] Organ Failure Assessment Score[9]					
System	0	1	2	3	4
Breathing (PaO /FIO22, mmHg)	>400	<400	<300	<200 with respiratory support	<100 with respiratorysupport
Coagulation (Platelets, x10^3 /uL)	>150	<150	<100	<50	<20
Liver Bilirubin, mg/dl	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	PAM ≥70 mmHg	PAM <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.0-1.5 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Central Nervous System Glasgow ComaScale	15	13-14	10-12	6-9	<9
Renal Creatinine,mg/dl	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	<5.0
Urine output. ml/d				<500	<200

Abbreviations: PaO2, Partial pressure of oxygen; FIO2 Fraction of inspired oxygen; MAP, Mean Arterial Pressure. a Doses of vasoactive amines expressed in ug/kg/min.

The Quick SOFA (qSOFA) scale is also proposed as a measure that can be performed at the patient's bedside without the need for biochemical tests and without the delay that their determination could represent for the timely identification of this entity, taking into account respiratory rate, alertness and blood pressure figures as the variables associated with a higher risk of sepsis and therefore organ dysfunction. It also proposes the disappearance of the term severe sepsis as redundant and evidently superfluous, and defines septic shock as a state of acute circulatory failure not responding to hydric therapy which implies the need for the use of vasopressors, a concept which coincides with previous definitions. (5).

qSOFA criteria (Quick SOFA)[9]
Respiratory rate >22
Altered alertness
Systolic blood pressure ≤100 mmHg

Few data exist on the incidence of sepsis in Latin America, the BASES study was the first epidemiological study carried out in Brazil, which evaluated 1,383 patients admitted consecutively to five ICUs in two large regions of Brazil. (6). Information on SIRS, sepsis, severe sepsis, septic shock and organ failure was collected according to a daily report, for the complete cohort the mean age was 62.2 years, the overall 28-day mortality rate was 21.8%, considering 1 383 patients; incidence density rates for sepsis, severe sepsis, septic shock were 61.4, 35.6, and 30% per 1 000 patient days, respectively; the mortality rate for patients with SIRS, sepsis, severe sepsis, and septic shock increased progressively from 24.3, 34.7,

47.3, and 52.2%, respectively; the main source of infection was the lung or respiratory tract(7).

More recently, the Brazilian Society of Critical Care has coordinated a multicenter study involving 75 ICUs in different regions of Brazil. A total of 3 128 patients were selected and 521 of them were diagnosed as septic patients (16.7%), the mean APACHE was 20% and the mean SOFA was 7 points, while the overall mortality rate at 28 days was 46.6%. The percentages of mortality attributed to sepsis, severe sepsis, and septic shock were 16.7, 34.4, and 65.3%, respectively (8).

The study by Carrillo et al (9) is the only one that reports on the behavior of sepsis in our country. They carried out a multicenter, cross-sectional study in which they included 135 public and private ICUs in 24 states of the Mexican Republic; of the 49 957 annual hospitalizations, there were 11 183 cases of sepsis (27.3 %), mortality due to this cause was 30.4 % . Almost 87% (2 953 patients) corresponded to public units and 13% (449 patients) to private units.

The most frequent causes were: abdominal 47%, pulmonary 33%, soft tissues 8%, urinary tract 7% and miscellaneous 5%. Of the isolated bacteria, 52% were gram-negative, 38% gram-positive, and 10% fungi. In 60% of the private ICUs there was knowledge of SSC, compared to only 40% of the public ICUs. The conclusions of this study are that sepsis has a high incidence and mortality rate and entails important costs to the health system, and that the lack of knowledge of the campaign to increase survival in sepsis among health professionals is a regrettable fact.(9).

Trends in incidence and mortality

There are at least three large, retrospective studies on sepsis based on US National Health databases, such as the National Hospital Discharge Survey(10) and the National Inpatient Sample(11). These groups have concluded that there has been an increase in the incidence of sepsis of about 13.7% each year, from 82.7/100 000 inhabitants in 1979 to 240/100 000 in 2003.

Several factors may have contributed to this scenario, among them:

a. The large population of elderly, often living with chronic comorbidities.

b. Increased survival in the ICU of patients who suffer severe trauma or acute myocardial infarction, who are then predisposed to infections during their convalescence.

c. Increasing reliance on invasive procedures for diagnosis and treatment for a wide range of diseases

d. The increasing number of diseases treated with immunosuppressive drugs.

e. Increased bacterial resistance to antibiotics.

f. among the factors known to influence the incidence of sepsis, chronic diseases and invasive procedures have been most strongly associated with a predisposition to infection(1). Esteban et al (12).found that severe sepsis was more common in patients with chronic kidney disease (46% vs. 27%, p0.004), chronic liver disease (43% vs. 27%, p0.03) and surgical patients (17% vs. 7%, p<0.001), when compared to patients with other diseases.

Geriatric patients have a greater number of chronic diseases, are more susceptible to exposure to invasive procedures, such as urethral catheterization, and to infections. In fact, 3/5 of patients with sepsis are older than 65 years of age, and the incidence of sepsis in the population over 85 years of age is 2 500/100 000, which means a relative risk of 13.1 (95% CI, 112.6-14.6) when compared to the general population(13).

Interestingly, some studies have assessed the relationship between ethnicity and sepsis. Dombrovskiy et al (14) found that blacks had a higher risk of sepsis compared to whites, especially among the adult population (RR 4.35; 95% CI, 3.9-4.8).

Blacks with sepsis were also younger (mean age 61.6 ± 0.25 for blacks and 72.8 ± 0.11 for whites), had a higher likelihood of ICU admission (odds ratio [OR, odds ratio], 1.14; 95% CI, 1.07- 1.21)and a longer ICU stay (17.9 ± 0.26 days vs. 15.2 ± 0.12 days, p0.0001)(14).

Older adults have linked this discrepancy to a higher incidence of hypertension and diabetes among people of color and lower coverage under their insurance policy in this group. However, Barnato et al found that the relative risk for blacks remained 1.44 (95% CI, 1.42-1.46) even after standardization for zip codes, suggesting that social inequalities alone do not explain this difference (15).

Some groups have found an increased risk of mortality from sepsis in men, such as Cheng (16)(64.8% of patients were male, p<0.01).

Of course, total mortality depends on the incidence of severe sepsis and septic shock, which is about 35 to 45% of patients with sepsis.(17). The total mortality per hospital for sepsis is about 40%, which means about 215,000 deaths per year in the USA and places this syndrome in tenth place among the causes of death in that country.

Gebremedhin et al.(18) found a decrease in case mortality from 27.8 to 17.9% between 1979 and 2003, but as the number of septic patients increased, mortality doubled: from 21.9/100 000 to 43.9/100 000. Dombrovskiy (14)obtained similar results, with a significant increase in age- adjusted mortality rates of severe sepsis from 66.8/100 000 in 1993 to 132/100 000 in 2003 (annual increase of 5.6%).

In contrast to inpatient and population-based mortality rates, the crude case fatality rate for severe sepsis declined from 45% in 1993 to 37.7% in 2003 (p 0.001). Several independent variables have been associated with sepsis mortality(19). Barnato(15) found that certain patient factors are associated with worse outcomes: age older than 34 years (RR 1.43; 1.38-1.49), older than 85 years (RR 59; 57-61); male sex, urban poverty, black race (deaths per case 26.1 vs. 24% for white males, p < 0.0001). Cheng et al(20) described disease severity as influencing outcome, with the following predictors of worse outcomes: malignancy (OR 4.6; 95% CI, 1.8-11.5),

fungal infections (OR 2.2; 95% CI, 1.2-4.2); acute physiologic score [APS] (OR 1.8; 95% CI, 1.5-2.3) and cardiovascular SOFA score (OR 1.6; 95% CI, 1.3-2), and Martin et al found that the number of organ dysfunctions was strongly associated with mortality (15%, in the case of no organ failure, to 70% for three or more organ failures)(14).

Finally, Vincent et al have pointed out that mortality rates may vary according to different types of ICU or different countries. This could be due to different factors associated with different types of ICU or different countries.(21).

Considering that septic patients are progressively older and have several associated comorbidities, including immunosuppressive comorbidities.

Undoubtedly, comorbid conditions and the most prevalent infectious agents are the main factor in the evolution and behavior of sepsis in each individual, and at this time the isolation of multidrug- resistant strains is of vital importance (22).(22).

Determination of the causative agent of the infection leading to sepsis is a task that requires great effort, since, given the severity of the disease, targeted antibiotic treatment usually begins before the appropriate diagnosis is made. Various authors have reported isolation rates of the infectious agent among populations with sepsis ranging from 40 to 71.7%(23). The prevalence of causative infectious agents varies among countries and regions, institutions and over time, making comparison between studies difficult.(24).

However, certain points of interest should be considered, including the following:

a. Sepsis is mainly a community-acquired disease, although it has a high incidence in hospitals. Rates of community-acquired infections range from 25% to 72.3%. Vincent et al(1) observed that 28.8% of septic patients admitted to the ICU came from the emergency department. In the United Kingdom, Majuran et al (25) have estimated that 30-50% of septic patients are diagnosed in the emergency department.

b. The sites of infection vary depending on whether the infection is hospital-acquired or community-acquired. Esteban et al 35 have reported that the most common sites of infection among patients with community-acquired sepsis are respiratory tract (56%), urinary tract (20%) and gastrointestinal tract (13.5%).

This profile changes for hospital-acquired infections (26% respiratory tract, 27% gastrointestinal, 24% urinary-gynecological) and for ICU-acquired infections (55% respiratory tract, 18% urinary tract and 18% catheter-associated).(4).

Overall, the main site of infection is pulmonary, which has an incidence of 15.6 to 69% (26).(26).

An exception is made for geriatric patients, in whom the risk of infection is of urinary tract infections by gram-negative bacteria is higher (OR 2.5; $p < 0.001$).(27)

In the past, gram-negative bacteria were the most prevalent agent isolated in patients with sepsis. Due to the development of new antibiotics with action against them and the growing population of highly resistant gram-positive strains, the number of infections caused by the latter has increased year by year since the 1970s, and today the incidence of both types of bacteria is similar.(28).

There are about 200 000 cases of gram-positive sepsis per year, compared with about 150 000 cases of gram-negative sepsis. (29).

Wang et al(19). describe that there are differences between patients who are admitted to the ICU and those who are not, the former have less infection by both gram-negative (18.8 vs. 31.8%, $p< 0.001$) and gram-positive (20.5 vs. 23.8%, p 0.12).

Multidrug-resistant bacteria and sepsis mortality.

Epidemiologically, multidrug-resistant (MDR) germs are defined as microorganisms that are resistant to one or more classes of antibiotics. There is no universally accepted definition of multidrug-resistant bacteria that is applicable to all these microorganisms; the concept may have different nuances depending on whether the approach is clinical, microbiological or epidemiological. From a general point of view, the definition should include at least two conditions: that there is resistance to more than one family or group of commonly used antimicrobials, and that this resistance has clinical relevance (i.e., it is or may be a difficulty for treatment) and epidemiological relevance (possibility of epidemic outbreaks, transmission of the resistance mechanism, etc.). Accepting these conditions, the term "multidrug-resistant microorganism" has been used mostly for classically hospital-acquired bacteria that have developed resistance to multiple(30). Antimicrobials, and which are capable of causing outbreaks, such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus spp. (VRE), extended-spectrum beta-lactamase-producing enterobacteria (ESBL) and non-fermenting gram-negative bacilli (GNB) such as Acinetobacter baumannii or Pseudomonas aeruginosa resistant to different groups of antimicrobials. In addition, bacteria that are intrinsically or naturally resistant to multiple antimicrobials, such as Stenotrophomonas maltophilia or Clostridium difficile, are often described as multidrug-resistant. More specifically, we speak of multidrug-resistant GNB when they are resistant to three or more families of antibiotics, to which they are usually sensitive, including beta-lactams (penicillins and cephalosporins), carbapenems, aminoglycosides, and quinolones(31). For practical epidemiological purposes, antimicrobials that act as markers of multidrug resistance have been defined and are different for each microorganism.

Infection by an MMR compared to that caused by a sensitive MMR increases costs by between 5,000 and 25,000D(32). In the United States, both the extra annual cost (4,000 and 5,000

million dollars) and the direct mortality (19,000 deaths per year) caused by these microorganisms have been quantified. The most frequent MMR are implicated in an increase in hospital stay and costs(33). There are other additional expenses that have not been adequately quantified and which derive from an increase in the workload of microbiology laboratories, the cost caused by educational programs and the delay in the patient's return to work. Other repercussions not well evaluated have to do with the contribution of MMR to the shortage of active antibiotics against the main etiologic agents, to the dissemination of these microorganisms in the community, and to the influence on the credibility of the health system due to media pressure or the increase in legal complaints due to the acquisition of nosocomial infections, especially by MMR(34).

The intermediate figures in the United States (38.8%) are similar to those in our country. Speaking specifically of the ICU, according to HELICS data, S. aureus accounts for 12.8% of global isolates in intra-ICU infections vs. 20.4% (35).(35). These disparities are repeated in differences, sometimes significant, between different studies and depend on the methodology used (incidence or prevalence), the infections referred to, the setting studied (critical care units exclusively or the entire hospital) or the antibiotic policies used. For one reason or another, it is clear that what is fundamental is the local ecology. The useful data for daily work are those obtained through incidence studies in which the infections related to exposure to risk factors are quantified in our country there are no data or studies of large populations(22).

There are few data on multiresistance in the UMAES in a study published by Benavides-Plascencia in 2005 in UMAE establishes the prevalence in third level centers Based mainly on these data we can deduce that our problems in multiresistances are: Gram positive - High incidence of MRSA although declining in recent years. - The vast majority of S. epidermidis are resistant to oxacillin.

- Occasionally, the appearance of some S. aureus and S. epidermidis strains resistant to linezolid has been reported in ICUs in different countries, including Spain.(36). In both cases they seem to be related to a local increase in linezolid consumption and subsequent clonal dissemination. In the treatment section, the therapeutic problems posed by the increase in the minimum inhibitory concentration (MIC) of vancomycin for S. aureus that has been observed in recent times will be discussed. Gram-negative - A. baumanii with high and increasing rates of resistance to carbapenems in addition to the existing resistance to beta-lactams, quinolones and aminoglycosides.

Some important concepts in MMR transmission What should we know? Once a given MMR appears in a healthcare institution, the transmission and persistence of the resistant strain are related to the existence of vulnerable patients, the selective pressure of antibiotics, the colonization pressure46,47 understood as the percentage of colonized or infected patients and the impact of adherence to prevention measures. Patients vulnerable to MMR are the most severely ill, with compromised defenses due to underlying medical conditions and with greater intrinsic and extrinsic risk factors (intubated, with venous catheters or bladder catheters, etc.).(37). These factors are common, to a greater or lesser extent, to the different MMR and are frequent in the critically ill patient. According to several studies, there is a temporal relationship between a decrease in the pressure of a specific antibiotic and a reduction in the incidence of a given MMR, especially BGN. The appropriate use, in dose and time, of narrower-spectrum antibiotics has also been associated with a decrease in MMR colonization.(38) . The relationship between colonization pressure and MMR acquisition has been studied especially for VRE and MRSA (39). There is ample epidemiological evidence on the transmission of MMR between patients through contamination of the hands of healthcare personnel by contact with the patient or their environment; however, there are no studies in our setting that associate mortality related to isolation with multidrug-resistant bacteria.

Materials and methods Type of design:

Retrospective cohort type

Place of the study: Place of the study: hospitalization area of centro médico nacional de occidente

. Located in Colonia Independencia Oriente, Belisario Domínguez, number 1000. CP 44340.

Level of care - Third level.

Area of influence: Jalisco, Sonora, Sinaloa, Baja California Norte, Baja California Sur, Michoacán, Nayarit and Colima.

Study Period:

Period of study: 01 September to 31 October 2018.

Study population: Patients over 18 years of age who were admitted to continuous medical admission with suspected sepsis (quick sofa of 2).

Sample

Type of sampling: Non-probabilistic, consecutive cases, all patients who met the inclusion criteria during the study period were included.

The Mexican Institute of Social Security in the area of AMC has an updated census in 2018 where 670 patients with a diagnosis of septic shock are registered.

Selection criteria Inclusion criteria

- Subjects older than 16 years of age with a diagnosis of sepsis according to the definition of the Third International Consensus (quick initial couch of 2).
- Admitted to the continuous medical admission service and hospitalized in any service of the unit.
- To have at least one bacteriological culture of any kind taken at any time during their hospital stay in the unit.

Exclusion criteria

- Pregnant and postpartum women.
- Patients who do not wish to participate in the study.

- Patients with localized infection, without general symptoms or alteration of vital signs, in whom laboratory studies are not considered necessary.

Elimination criteria

- Patients who have requested voluntary discharge.
- Patients with infection ruled out in later notes
- Patients with incomplete records
- Patients who have tests that do not allow for bacterial identification
- Patient in which the record does not state whether mortality or discharge was found.

The study of the patients was carried out by means of a census described on admission. The unit has an adequate control of the follow-up of the patients, in addition to having a note per shift, and laboratorials in an electronic system that allows minimizing the loss of patients.

Patients were admitted during the period from September 01 to October 31, 2018, assessing whether they met the selection criteria which is the presence of a probable site of infection that met the criteria for sepsis as defined by the third definition of sepsis and ruled out the exclusion criteria for the study.

The consensus defined "sepsis" as "life-threatening organ dysfunction caused by a dysregulated host response to infection". This new definition implies a non-homeostatic host response to infection and includes the concept of organ dysfunction, which implies severity, the need for early diagnosis and management, and renders the term "severe sepsis" superfluous. The Task Force proposes the Sequential Organ Failure Assessment (SOFA) score, which includes a series of clinical, laboratory and management criteria, and assumes that the baseline SOFA score is ZERO in patients with no pre-existing organ dysfunction, whereas, to define clinical criteria that identify infected patients with sepsis, the Task Force recommends using a change in the baseline SOFA score of 2 points or more to represent organ dysfunction.

Another concept introduced by this consensus is the qSOFA (quick SOFA) which can be used to consider possible infection in patients who have not previously been diagnosed with infection, does not require laboratory testing, can be performed rapidly, and can be used to screen patients suspected of probable sepsis. It is suggested that the qSOFA criteria can be used immediately by clinicians to assess for organ dysfunction, to initiate or intensify therapy if appropriate, and to consider referral to critical care or increase the frequency of follow-up if such actions have not already been taken.

Conformation of the cohorts

Once the selection criteria had been applied and the eligible population had been defined, two cohorts of subjects were formed, one exposed and the other unexposed. The unit of analysis and the unit of information corresponded to patients and health care records.

Definition of the exhibition.

Exposure was defined as the presence of exposure to a culture of any kind in which multidrug- resistant bacteria are identified.

Exposure was considered in those patients where pathogenic multidrug-resistant bacteria were isolated.

Definition of the outcome variable.

For the exposed and unexposed cohort, the outcome variable under study will correspond to in- hospital mortality.

The outcomes set out in the research will correspond to the development of death Methods.

The unit of analysis and information corresponded to the individuals and the health care records (their respective clinical histories) during hospitalization in the study period. In the individuals of both cohorts, the method used was the review of records, which allowed a direct relationship to be established between the researcher and the researched so that, through a series of sections applied to the unit of information, concrete answers were obtained on the variables of interest

Techniques.

The technique applied corresponded to the review of health care records when the patient was hospitalized in a structured instrument when the research subjects were discharged. The data collected during the research will be recorded in an instrument that will identify the individual, guaranteeing anonymity at all times in order to relate the variables of interest at the beginning and during follow-up.

The review of the records and patient data was carried out by the thesis student, who will receive training in the filling out of the forms used and who also had the function of following up the two cohorts.

Some files were randomly reviewed by the assessors to ensure adequate data collection as a supervisory tool to guarantee the internal validity of the project.

Cohort follow-up.

The monitoring of the cohorts clearly explains the censors' censorships.

A data collection sheet was used to monitor the records prepared by

The outcome was first identified by reviewing the medical history and other health care records of each of the individuals included in the two cohorts.

Censorship.

In the follow-up of the cohorts, the following right censorships were considered:

-Death .

-Loss in follow-up.

Completion of the follow-up period of the study subjects.

Tabulation and analysis plan.

Tabulation of information.

The information was tabulated in a database created for this purpose in the EpiInfo™ 3.5.3 program (Centers for Disease Control and Prevention). This database and its registry was managed exclusively by the principal investigator of the

study, who will enter the information collected during the follow-up of the patients in the database and then export the information in a format compatible for data processing.

Statistical analysis.

For the description of the individual characteristics of the subjects in each of the cohorts and of the variables in general, measures of central tendency (averages) and dispersion (standard deviation) were used for quantitative variables, after verifying the normality of their distribution with a Shapiro-Wilk test; if this assumption was not verified, they were described by median and interquartile ranges. Qualitative variables were measured and analyzed using proportions. For the comparison between the two groups, a one-way analysis of variance test (ANOVA) of mean difference was used when the data were normally distributed or, failing that, nonparametric statistics (Kruskal-Wallis). A Z test of difference of proportions was used for qualitative variables. The association between multidrug-resistant bacteria and mortality was estimated by Hazard Ratio (with 95% confidence intervals).

Statistical tests were considered significant at a p-value <0.05, and 95% confidence intervals were used when appropriate. Statistical analysis was performed with STATA software (Version 10 SE; Stata Corporation, College Station, Texas) and SPSS software (version 22 SE; IBM).

Bias and confounding control Selection bias.

The non-exposed subjects were selected from the same service that originated the exposed one, ensuring that they belonged to the same population base and had the same probability of developing the event and of being identified as the outcome.

Measurement bias.

The research variable collection instruments will be tested on a sample of patients who meet the selection criteria of the study, identifying difficulties and ambiguities in them, and will be corrected for a definitive version.

RESULTS

A total of 94 patients were included with a minimum age of 16 years and a maximum age of 91 years with a mean of 48 years with a standard deviation of 20 years. Table 1

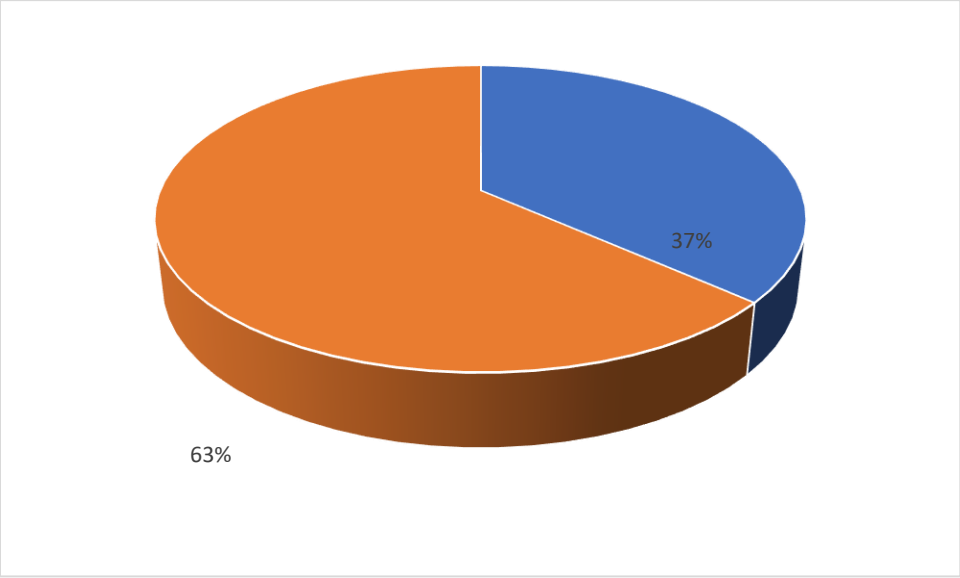
Table 1

	N	Minimum	Maximum	Media	Standard deviation.
Age	93	16.0	91.0	48.000	20.0743

Descriptive statistics age

According to gender, 35 were women (37%) and 59 were men (63%).Graph 1

Graph 1 Gender of Participants



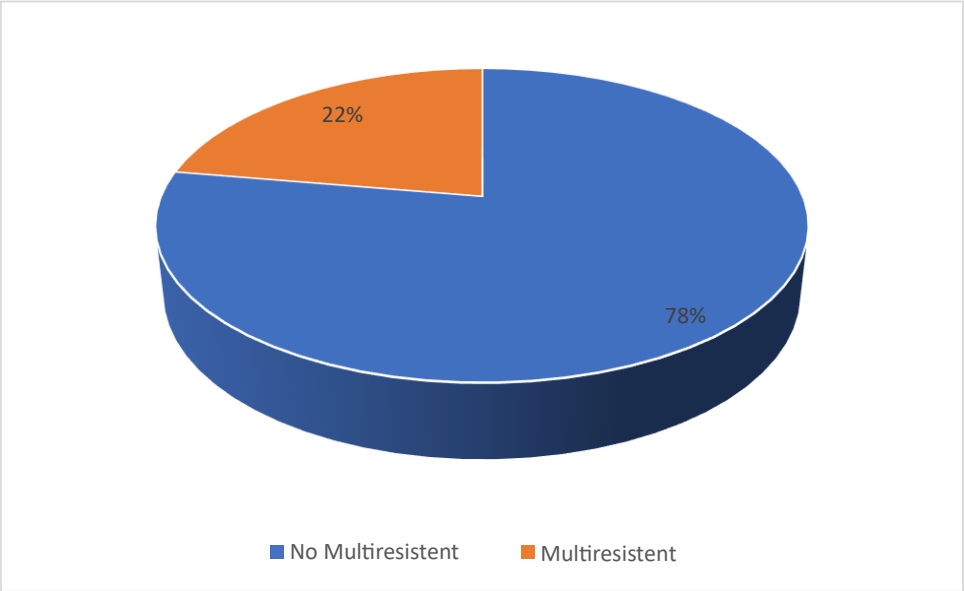
Regarding the origin of the focus of sepsis, 14 cases (15.1), abdomen20 cases (21.5%), Cardiovascular3 cases (3.2%) were considered to be determined.

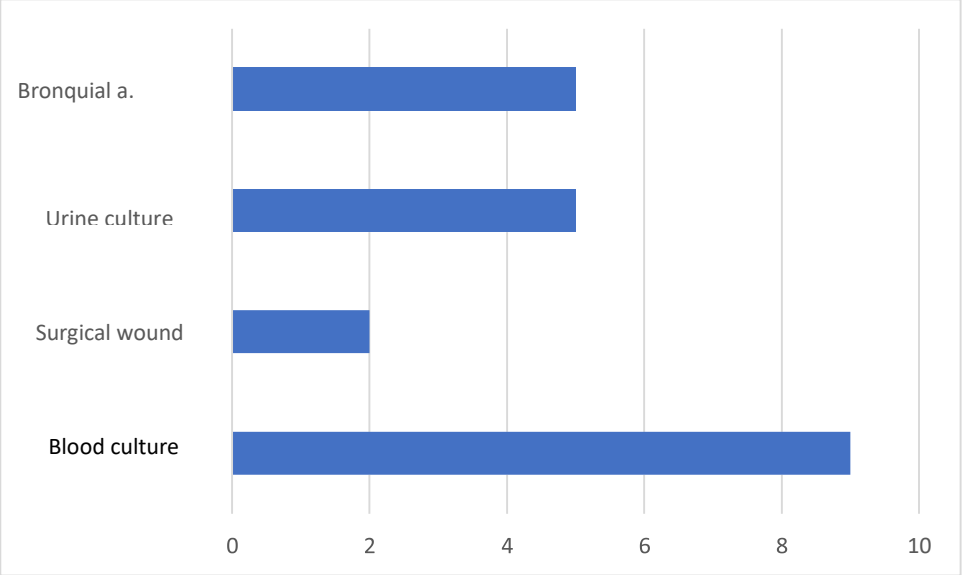
Lung 18 cases (19.4%) nervous system 1 case (1.1%) soft tissues18 cases (19.4%) urinary tract 19 cases (20.4%).

A total of 93 cultures were included of which 21 (22.3%) were isolated with bacterial resistance. Graph 2

Graph 2 Bacterial multiresistance Of the positive cultures 42 % (9) were blood culture, 10 % (2) were surgical wound cultures, urine culture 23 % (5), bronchial aspirate 23 % (5). Graph 3

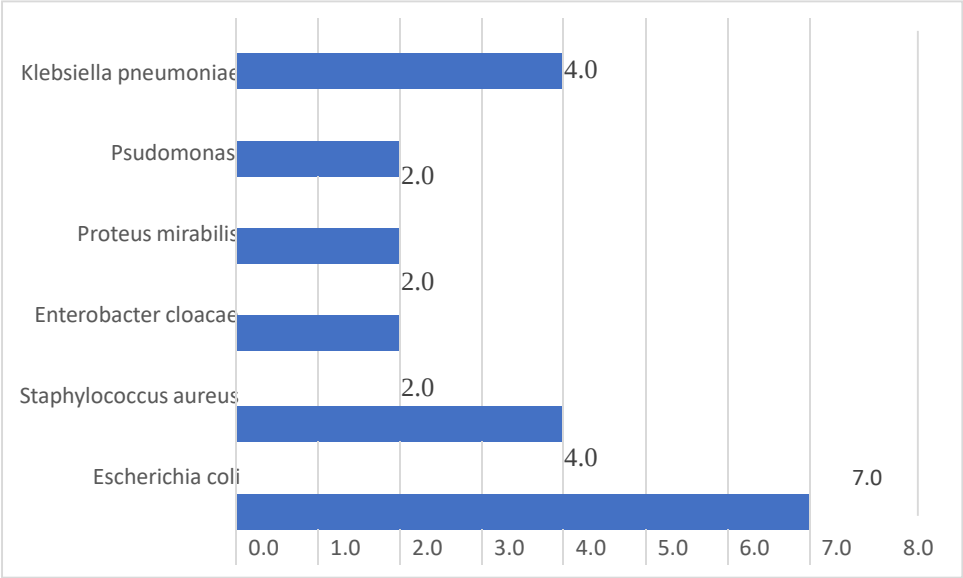
Figure 3 Positive cultures





Regarding the isolated bacteria, Escherichia coli was isolated in 7 (30%) Staphylococcus aureus in 4 (20%) Enterobacter cloacaeen 2.0 (10%) Proteus mirabilis2 (10%) Psudomonas 2 (10%) Klebsiella pneumoniae 4.0 (20%).

Graph 4. Type of bacteria isolated



With respect to mortality, 57% of the patients who presented bacterial resistance presented mortality, with a Hazard ratio of 3.371 with 95% CI (1.125-10.100)

Regarding mortality with the different types of bacteria, it was 40 % in Gram-negative bacteria with a Hazard Ratio of 1.875 (0.291-12.089), while it was 20 % in Gram-positive bacteria.

DISCUSSION

Bacterial multidrug resistance is a problem of global dimensions that requires constant surveillance and control to limit and mitigate it. For this reason, it is already part of public health programs in most nations worldwide. The study of mortality associated with this phenomenon is fundamental to direct actions. The results of this study contribute to the construction and strengthening of knowledge of this problem. The primary exposure for the development of this condition has been determined to be prior antibiotic therapy, a variable that is consistently reported as a risk factor for acquiring infection by any type of multidrug-resistant bacteria as described in multiple studies (4 , 8, 9, 10, 11, 12, 13, 14, 15, 16). In Derde's study (34) an OR of 2.86 (95% CI = 1.05-3.28) of mortality was obtained for exposure in the 48 h prior to infection, in our study a Hazard ratio of 3.37 was found. These results are in agreement with the studies cited; however, this association was not maintained in the multivariate analysis, probably due to sample size.

Regarding Gram-positive cultures, there is a high incidence of MRSA, although it has been decreasing in recent years. In our study, MRSA was found in 20% of the cases of multiresistance, but oxacillin-resistant S. epidermidis was not isolated (22,23).

The treatment section will not discuss the therapeutic problems posed by the increase in the minimum inhibitory concentration (MIC) of vancomycin for S. aureus that has been observed in recent times.

Gram negative

A. baumanii was not isolated with high and increasing rates of resistance to carbapenems added to the already existing resistance to beta-lactams, quinolones and aminoglycosides. Resistance to colistin is anecdotal in ENVIN. Local differences may be important. P. aeruginosa was isolated with variable but increasing resistance to carbapenems and ciprofloxacin (16).

BLEE-producing GNBs: Prospectively until recently, but there are abundant data on the situation in our country. Before the year 2000, to speak of BLEE was fundamentally at the expense of in- hospital outbreaks of K. pneumoniae, which was found in 20 %, currently there is an important increase in bacteremias, urinary tract or abdominal infections, whether out-of-hospital or associated with health care (24). E. coli is more related to urinary tract infections in non- hospitalized patients, while Klebsiella spp. is preferably of hospital origin and related to respiratory infections.

According to several studies, there is a temporal relationship between a decrease in the pressure of a specific antibiotic and a reduction in the incidence of a given MMR, especially BGN1,49-53. The appropriate use, in dose and time, of narrower-spectrum antibiotics has also been associated with a decrease in MMR colonization54.

The relationship between colonization pressure and MMR acquisition has been studied mainly for VRE and MRSA (26,27).

There is ample epidemiological evidence on the transmission of MMR between patients through contamination of the hands of healthcare personnel by contact with patients or their environment (32,33).

Strategies to reduce the incidence of infection or colonization by MMR include the following: Develop educational programs aimed at optimizing antibiotic utilization (the focus of another article in this series).

Decrease the time of exposure to the main risk factors (mechanical ventilation, endovenous and urinary catheterization). Improve epidemiological and microbiological surveillance programs. This improvement includes the introduction of active surveillance systems for early detection of patients colonized or infected by germs of special relevance. Active surveillance is based on a systematic microbiological assessment at the time of admission and periodically thereafter. The frequency will depend on the real problem in each unit and the capacity of the microbiology services. Perhaps the most widespread form is the performance of screening samples on admission and on a weekly basis.

Implement control measures that decrease cross-transmission within the unit. These measures include both the optimization of hand hygiene and isolation, in general contact isolation, when these microorganisms appear.

Perspectives

The importance of active surveillance lies in the objective of early identification of colonization/infection of our patients in order to:

1. Quickly implement the necessary control measures to minimize the dispersion of the same to other patients. This policy allows the so-called blind period, i.e. the interval between the colonization/infection of the patient and its identification, to be drastically reduced.

Improve the rate of adequate antibiotic therapy in empirical treatment of in-hospital infections. There is evidence that the rate of adequate empirical antibiotic therapy in MMR bacteremia and MV-associated pneumonia is higher when the previous colonization status is known(22-29).

The introduction of molecular techniques with real-time PCR or the more economical use of chromogenic culture media allows rapid identification that can range from 2 to 24 hours. Using this strategy allows early implementation of prevention and decolonization measures, reducing the spread and rates of infection63. This strategy has proven to be effective and cost-effective from the economic point of view in different endemic situations(34). For practical purposes and in our country, it would be justified to perform active surveillance in all patients regardless of the identification method used. This recommendation is endorsed by most national and international scientific societies (12,16).

In summary, it is advisable to perform active surveillance in hospitalized patients, assessing with the services involved (microbiology, preventive, etc.) the problem microorganisms in the unit and the available resources in order to protocolize the periodicity and the samples to be extracted to initiate isolation and other measures (decolonization in case of MRSA, etc.) as soon as possible.

When an infection is suspected in a hospitalized patient, we will consider: possible focus, MMR carrier status of the patient and the surrounding patients in order to optimize empirical treatment and contribute as little as possible to the development of resistance.

As limitations of this study, it is important to report that, since it is a retrospective study with a secondary source, it is possible that there is underreporting or incomplete information on some of the variables studied. In addition, the level of depth is limited because all multidrug-resistant microorganisms detected during the study period were included in the analysis and no distinction was made between hospital-acquired and community-acquired infections. Having found a lower OR than expected with which the sample size was calculated reduces the statistical power of the study, so that some of the factors that were not significant could have a real association with the event of interest. The reference population of this study is the population attending the hospital where it was performed, therefore, the inference of the results is limited to the institutional setting.

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CONCLUSIONS

Isolation of multidrug-resistant bacteria was shown to be an independent mortality factor in patients with suspected sepsis at the Centro Médico Nacional de Occidente. Describing hospital mortality in patients with suspected sepsis was 20 per 100 patients. In-hospital mortality of patients in whom large-positive bacteria were isolated compared to patients in whom multidrug-resistant large-negative bacteria were isolated did not differ from each other.

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