ISSN: 3065-5145
Research Article
World Journal of Medicine and Health Care

Healthcare-Associated Infections: Evolution by Natural Selection

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Submitted: 19 February 2024 **Accepted:** 25 February 2025 **Published:** 28 February 2025

https://doi.org/10.63620/MKWJMHC.2025.1027

Citation: *Salazar-Holguín, H. D. (2025). Healthcare-Associated Infections: Evolution by Natural Selection. Wor Jour of Medic and Heal Care, 3(1), 01-16.*

Abstract

Introduction: *Since "nothing in biology makes sense except in the light of evolution," the biological basis of infections associated with health care cannot be clearly and effectively explained, understood, or combated if we ignore the evolutionary process of Natural Selection, which is also influenced by actions for its prevention, treatment, and control and by modifying the Hospital and organic environment of the hosts.*

Methods: *Using a descriptive, longitudinal, and retrospective analytic method, the main components of the complex evolutive process of 12 513 infections and 2 473 deaths associated with health care were studied for 11 years: their incidence and fatality due to medical services and surgical procedures, their causal agents with their sensitivity and resistance to antimicrobials (with 7 758 cultures and antibiograms) and, concomitantly, hospital actions for their prevention, treatment, and control.*

Results: *The evolutionary process of healthcare-associated infections (HAI) was confirmed by observing their variations over 11 years, with differential upward trends due to morbidity, mortality, typology, hospital service, hosts, and, above all, its causal agents and their sensitivity and resistance to antimicrobials. Variations in HAI occurred through particular ups and downs and contradictions but generally tended to increase, exceeding the expected reference rates. This behavior indicates an evolutionary process that is neither rectilinear nor unidirectional but dialectical in its development.*

Conclusion: *Healthcare-associated infections are subject to a dialectical process of Evolution, basically due to competition, Natural Selection, and adaptation of their causal agents, both to the hospital environment and the tissular and organic microenvironments of the hosts. Their Evolution depends, in principle, on their genomic potential to contaminate and colonize inert surfaces, adapt to the crossed transmission of contagion, colonization, and infection of a host, and concomitantly, their interaction with the conformation and variations of the hospital environment and the organic microenvironment of the host.*

Keywords: Evolution, Natural Selection, Healthcare-Associated Infections, Antibiotic Resistance

Introduction

Healthcare-associated infections (HAI) develop through a complex sociobiological dialectical process, as it constitutes a concrete totality with a biological basis of the causal agent and the host, in the first instance, whose development occurs due to social determinations, in the last instance, when carried out in an environment built, structured and organized for the operation and functioning of the social institution that constitutes a hospital.

The biological basis of HAI has two aspects: the hosts and their causal agents, both concur through an evolutionary process; as such, as Theodosius Dobzhansky stated, “nothing makes sense

in biology if it is not in the light of evolution [1]. Without its knowledge, nosocomial infections cannot be fully explained or understood, nor can the increasing morbidity and mortality due to the development of antimicrobial resistance due to its causal agents experienced in hospitals around the world be effectively combated [2].

The evolutionary process of HAI is evident when observing their variations. Although they are not rectilinear or unidirectional but rather dialectical in their development, beyond their ups and downs and even contradictions, they show differential ascending trends in their morbidity, mortality, typology, hospital service, host patients, and, above all, the causal agents and in particular, their sensitivity and resistance to antibiotics [3].

The Evolution of HAI depends, in the first instance, on the evolutionary capacity of their causal agents (bacteria, fungi, yeasts, and viruses), which through Natural Selection confers their aptitudes for competition between multiple microbial species and, ultimately, on their correlation with the environment they manage to inhabit. In principle, competition is not only between members of different species. All organisms are also more threatened by the competitiveness of their species since they compete for the same resources in the same environment [4].

Like all living beings, the Evolution of HAI causal agents occur as Charles Darwin described and demonstrated in the mid-19th century, establishing the process of the origin of species through Natural Selection:

"Since many more individuals are born from each species than can survive, and as, consequently, there is a struggle for life, which repeats frequently, it follows that every being, if it varies, however weakly, in some way profitable for him under the complex and sometimes variable conditions of life, it will have a greater probability of surviving and thus being naturally selected. According to the powerful principle of inheritance, every selected variety will tend to propagate its new and modified form." He concluded: "I call Natural Selection this conservation of favorable variations and the rejection of harmful variations." Evolution is a cumulative process, the selective addition of small favorable variations leads to divergence and, eventually, the origin of a "new species [5].

As Richard Dawkins has specified: "Darwinism is the only theory capable of explaining life as the adaptation of complexity... and Natural Selection is the driving force of Evolution. If there were no Natural Selection, there would be no evolution. To fulfill its purpose, "the selective criterion is always short-term, simple survival or, in more general terms, success in reproduction". And survival is not random; success in reproduction 'writes' throughout generations improved instructions for survival in the collective genetic memory of the species. Thus, the choice of which germs develop as causal agents of HAI is not random but based on the criteria of Natural Selection. "Evolving is something that species do, not individuals; one cannot speak of an organism in Evolution without taking its courses at a constant rate, since the evolutionary rate constantly fluctuates, from very fast to very slow, and stop or ultra-slow Evolution. And with evolutionary leaps that are not in a single generation, they extend over many generations".

In the specific case of bacteria, according to Dawkins, there are two ways in which the construction of evolutionary complexity can occur: (1) 'coadapted genotypes' and (2) an 'arms race'; 'coevolution' and 'genes that act as another's environment.'4 And for his part, Richard E. Lenski has described its current evolution process, observed experimentally; which is constituted by three outstanding aspects through their dialectical interrelation: their genetic variation, the divergence of species and populations between themselves and their ancestors, and the manifest adaptation or adequacy to the environment where they live [6].

In the first instance, "the process of adaptation by Natural Selection requires genetic variation of those characters that influence the survival and reproduction of organisms." Genetic variability occurs by spontaneous mutation or by mixing (mixis). Mutations refer to a single gene locus change in status from one allele to another (abcd → Abcd), and they can be punctual (mild, with little or no effect), rearrangements, or transposition of mobile genetic elements from one locus of the genome to another. Mutations are spontaneous in that they are "blind" or indistinct whether their effects are beneficial or harmful and, therefore, whether they are favorable to their Evolution or extinction. Some cause important changes in the phenotype of the bacteria, such as making them resistant to attacks by a bacteriophage or an antimicrobial. Several factors affect their mutation rates, from the genetic constitution itself (presence or absence of transposons, for example) to various environmental agents (detergents, disinfectants, antimicrobials, ultraviolet radiation, and so on.).

Mixture involves the production of some new multilocus genotype by recombining two different genotypes (abcd + ABCD → aBcD). This recombination between genomes, typical of eukaryotic sexual cells, is carried out in bacteria by conjugation (mediated by plasmids), transduction (through viruses), or transformation. Unlike mutations, they do not necessarily produce organisms with new genes but rather with a new combination of genes. Without admixtures, mutations can be incorporated into an evolving population only if they occur sequentially in a single lineage. With mixing, however, mutations occurring in separate lineages can be incorporated simultaneously. Thus, the rate of adaptive Evolution can be accelerated by combining favorable combinations of alleles.

Secondly, individual genetic variation, so abundant in microorganisms, causes divergence within a local population or when differentiating one population from another. Internally, it occurs in three main ways: transient polymorphism (when two or more genotypes are present), selective neutrality (when the polymorphism is for an almost indefinite period, with little or no effect on adaptation to the environment), or frequency-dependent selection (when in the course of growth and competition in an environment, microorganisms modify it, by decreasing the resources of the environment, with the secretion of metabolites). On the other hand, genetic variation between different populations of microorganisms occurs through the coevolution of genomes interacting in two opposite ways: exploitative (parasitic) or mutualistic. For example, a single mutation can defend against a bacteriophage, and a plasmid can confer antibiotic resistance. However, such an effect can be beneficial in an environment

with antimicrobials and harmful in their absence due to its metabolic cost and overload.

Thanks to genetic variation, microorganisms can acquire and develop new metabolic functions in three basic ways: genetic exchange, changes in one's genes, and reactivating encrypted genes. The simplest way is the transfer of genes from one individual with a function to another without it. For example, some antimicrobial resistance functions are encoded by plasmids, which are transmitted from donors to recipients by conjugation.

Both mutation and gene mixing depend on the properties of the "genetic system"; that is, the conjunction of aspects and factors of an organism's physiological, biochemical, and reproductive biology determines its genes' mutation and mixing rates. However, the gene mix in many bacteria may influence adaptation less than parasitic entities, such as viruses (transduction) and plasmids (conjugation).

Ultimately, the Evolution of an organism involves its insertion or adaptation to the environment (fitness). Genes only work when there is some structure on which they can act. "They are not selected for their intrinsic qualities, but by their interactions with the environment… and the most important environmental part may be the other genes they encounter… The genes themselves do not evolve; they only survive or are not in the pool of genes (genetic pool). The 'team' evolves in cooperation towards solutions to different problems", such as antimicrobials.

Evolution continually 'tracks' environmental changes. Because of Natural Selection, the environment prevails over the species, and the genetic variants best adapted to the environment will survive. In the process of Natural Selection, genes are always selected for their ability to thrive in the environment in which they are found. Each gene is selected for its ability to cooperate with populations of other genes successfully. A thriving gene will be one that works well in the environments provided by the other genes. 'Functioning well' consists of 'collaborating' with other genes in the environment. Thus, the hospital environment and the organic microenvironment of the host patient prevail, and the species evolve to adapt to them in the HAI process.

The "arms race," for its part, is "the most satisfactory explanation for the existence of the advanced and complex machinery that living beings possess for their survival and reproduction." Between members of the same or different species, there is a struggle for existence to obtain limited vital resources to survive and reproduce in the face of a competitive and hostile environment. In this way, those with the best "armament" to compete and defend themselves from environmental aggressions are more likely to survive and prosper. Such is the case of resistance mechanisms to detergents, antiseptics, and antibiotics activated, acquired, developed, and transmitted by bacteria. However, up to a certain limit, when they become too metabolically expensive for their production and operation [7]. The arms race constitutes the other great force that drives 'progressive' Evolution and complex 'designs' in bacteria.

Adaptation to the environment by Natural Selection is not a linear or unidirectional process but variable periodically, with ups and downs and contradictions, but with an upward trend. This variation is because the frequency of favorable mutations does not grow jointly or continuously. While some genes duplicate and increase their complexity, others are delayed. In any case, Evolution causes the population density of the clone to grow more and more easily than the ancestral population. The insertion and adaptation to a particular environment (fitness) is determined by three basic effects: the possession of disused functions, the variation in essential metabolic activities, and the genetic background. For example, the effects of conserving and expressing superfluous gene functions, such as bacteria with plasmid-encoded antibiotic resistance mechanisms in an antimicrobial-free environment, are at a disadvantage compared to bacteria without such resistance.

Richard C. Lewontin has pointed out that "a genotype does not give rise to a single type of development, but to a norm of reaction, a scheme of different types of development in different environments." The exact pathogenic germs do not evolve in the same way in the community as in a hospital environment. Therefore, the infections they cause are different in outpatients and hospitalized patients. Hence, the error of even the most refined deterministic theses in genetics is that "genes determine the ability of an organism" to evolve or that "a genotype has the tendency to produce a certain phenotype ."On the contrary, an "organism is not specifically determined by its genes, but is the unique product of an ontogenetic process linked to the sequence of environments in which the process takes place ."Four fundamental aspects must be considered regarding this relationship: (1) "organisms determine which elements of the external world will constitute their environment" and which of them are relevant to relate to; (2) thus, "they continually alter their environment"; (3) they even "actively construct the world around them"; and with all this, (4) "the external conditions become part of the organism's environment".

Lewontin et al. have noted the dialectic of the evolutionary process: "It is neither the genes nor the environment that determines an organism, but a particular combination of both… the organism depends on both the genes and the environment… All organisms are not only the product but also the creators of their own environments [an example of this is bacterial biofilms] … It is not simply an interaction of internal and external factors but also a dialectical development of the organism in response to their mutual influence. Therefore, “identical genotypes will evolve differently in different environments, just as different genotypes will evolve differently in the same environment [8, 9].

The similarities and differences in adaptation processes result in the divergence of bacterial populations, even between identical genotypes and environments. They occur due to different genetic variations (genes with beneficial mutations), due to changes in the physiological bases that improve performance (such as increased transport of limited nutrients into the cell), or due to the extension of the improvement of ecological performance (for example, the relative better insertion and adaptation to an environment -fitness-, compared to a common ancestor).

Selected causal agents of HAI should adapt to two environments: hospitals and the tissular and organic microenvironments of the host. Generally, "built environments comprise chemical and physical habitats unprecedented in the natural world, which can

have unpredictable consequences on the selection and development of microorganisms. Despite the exquisite control imposed on its biological matrix, the hospital environment remains home to an astonishing diversity of microorganisms. Understanding the ecology of these complex communities will pay considerable dividends in the control of healthcare-associated infections and the spread of antibiotic resistance [10]. This is indispensable and urgent since "the extensive use and accumulation of antibiotics in the environment during the past decades have become a global crisis of bacterial resistance to antibiotics [11]. And in light of this, "with the understanding and manipulation of the hospital environment, the ecological future and the structure and pathogenicity of its internal microbial world can be controlled." The hospital environment is constituted and continually modified through programmatic activities, such as air conditioning, order, cleaning and disinfection, management of hazardous biological-infectious waste and hospital linen isolation precautions, and sterilization of equipment, instruments, and materials, among other activities. Therefore, the first Natural Selection of successful germs in the arms race against such conditions occurs in this environment.

A second Natural Selection occurs during the contagion, generally through cross-contamination, of a patient who becomes the host of an HAI causal agent. Only germs able to adapt to the microenvironments of the tissues and organs to which they have access will survive and reproduce, evading or nullifying the immune system with their virulence to cause an infectious process with the development of its pathogenicity. This adaptation is not defined in advance for each agent. However, it must be developed in response to the tissue and organ accessed, which leads to an infectious specialization of the germ, turning it into a new strain. Also, this microenvironment is continually created and modified through medical and nursing interventions for diagnosis and treatment, mainly through invasive procedures and devices, such as Surgery and surgical implants, mechanical ventilation, venous and bladder catheters, antiseptics, and, above all, antibiotics. Furthermore, in all of this, the hand hygiene of health personnel is decisive, particularly in preventing pollution and cross-transmission of HAI.

The development of antimicrobial resistance due to its causal agents is paramount in the evolutionary process of HAI. Antimicrobials, particularly antibiotics, attack vital bacterial processes, especially those that use different enzymes or structures, absent or not common in eukaryotic cells. There are four main targets of attack: the synthesis of the cell wall (Beta lactams and non-lactams), of proteins (aminoglycosides and tetracyclines), of nucleic acids or DNA topoisomerases (fluoroquinolones) and of folic acid (sulphonamides) [12, 13]. And bacteria have developed defense weapons against them extracellularly (biofilms and quorum sensing signals), in the cell membrane (porins, enzymatic hydrolysis and efflux pumps), intracellular (redox modifications, transferases, ribosomes and alterations in their protein synthesis), and genetic (gene expression, mutations, plasmids, transposons, integrons and genetic cassettes) [14]. Such inhibitory mechanisms and their targets characterize and differentiate antimicrobials and antibiotics and, at the same time, evolutionarily define resistance to them by the causative agents of HAI [15].

Methods

At the Regional General Hospital No. 1 (HGR 1), a clinic with 300 registered beds, the main components of 12 513 infections and 2 473 deaths associated with health care were studied. We analyzed the clinical and epidemiological data using a descriptive, longitudinal, and retrospective method including several variables: incidence and mortality classified by medical and surgical services; its causal agents and their sensitivity and resistance to antimicrobials (7 758 cultures and antibiograms); and hospital actions for its prevention, treatment, and control.

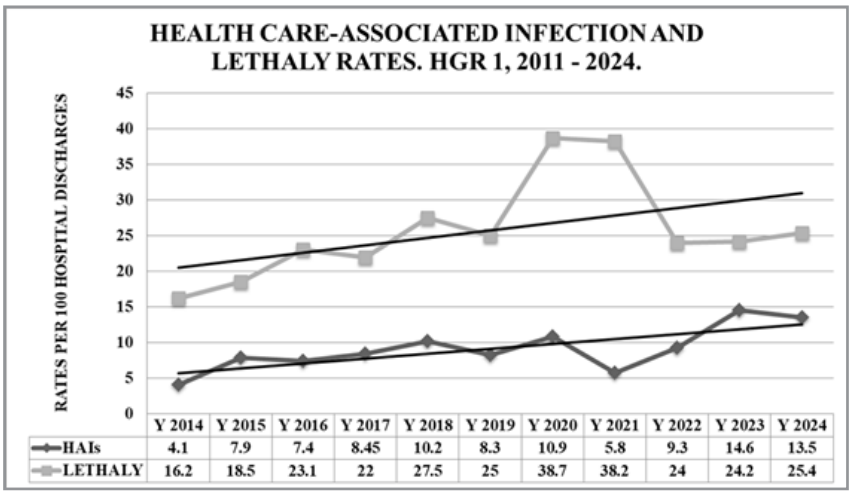
Detection, risk identification, and confirmation of HAI were carried out through active daily epidemiological surveillance by an epidemiologist and four nurses specialized in public health. Cultures and antibiograms were carried out by the Microbiology Laboratory of HGR 1, using a VITEK® 2 Compact device, an advanced, fully automated system for microbial identification and sensitivity to antibiotics detection. With the gathered information, a data collector created an Excel database for descriptive and inferential statistical analysis, using calculations with 95% reliability of chi-square, odds ratio, and p with OpenEpi Version 3.01.

Results

At the Regional General Hospital 1 (HGR 1), during eleven years (from 2014 to 2024), a total of 12 513 confirmed cases and 2 473 deaths of patients with health-associated infections (HAI) were studied; analyzing their incidence and mortality, and differentiating them by medical and surgical services, their causal agents with their sensitivity and resistance to antimicrobials through 7 758 cultures and antibiograms, 62 % of the total cases and, concomitantly, hospital actions for their prevention, treatment and control.

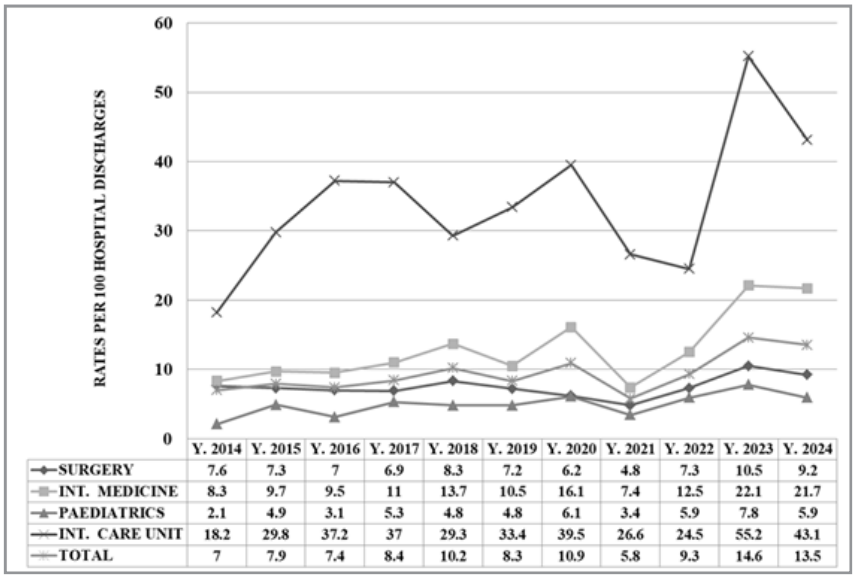
The association of HAI incidence and hospitalization time was contradictory and caused bias, confusion, and errors. The axiom of the directly proportional relationship between hospitalization days and the frequency of nosocomial infections is contradictory and irregular. For example, in 2023, Surgery had the highest annual average with 9.6 days of hospitalization and a rate of 10.9 HAI per 100 discharges; while the lowest, 5.5 Days/Patient, corresponded to the Intensive Care Unit with a rate of 99.5 HAI; this is 1.7 Days/Patient less and a 10.4 times higher rate. Also, although Internal Medicine with 8.9 days/patient was lower than in Surgery, with a rate of 24.9 HAI, it exceeded that by 2.3 times. In pediatrics, a shorter stay of 6.5 days per patient compared to the total HGR 1 of 8.8 corresponded to a rate of 12.1 HAI, lower than that of the total HGR 1 of 16.5. On the other hand, the HAI indicator about hospital discharges was more coherent in analyzing its incidence and fatality.

As shown in Graph 1, the incidence of HAI had annual variations, with relative increases in 6 years (2015, 2017, 2018, 2020, 2022, and 2023) and relative decreases in another 4 years (2016, 2019, 2021, and 2024). The majority and largest increases defined an upward trend during the period studied, exceeding the maximum expected rate (8.8 HAI per one hundred hospital discharges) in 5 years, particularly between 2022 and 2023, the average for the period of 9.4 HAI per one hundred discharges.



Graph 1: Healthcare-Associated Infections and Lethality Rates, 2011 - 2024

Oscillating variations in HAI incidence differ between clinical services (Graph 2). The rates for the 2014 - 2024 period was from 4.9 HAI per discharge in Pediatrics and 7.5 in Surgery (the first below and the second within the expected limits: from 7.4 to 8.8 HAI per one hundred discharges) up to 34 HAI per discharge in the Intensive Care Unit (ICU), whose 10-year rates (2015 to 2024) exceeded the rate expected for this Service (20 HAI per one hundred discharges). Internal Medicine's rate of 12.9 HAI per one hundred discharges in the period also exceeded the maximum expected (8.8 HAI per one hundred discharges). In fact, patients hospitalized in Internal Medicine have an almost three times higher risk of acquiring HAI compared to those in other hospital services (Odds ratio = 2.879 and p = 0.000). The worst year was 2023, with the highest rate of the period, 14.6, and with the highest rates in all hospital services, in which only Pediatrics did not exceed the expected 8.8. On the other hand, in the ICU, it was 2.8 times higher, and in Internal Medicine, 2.5 times higher than expected.



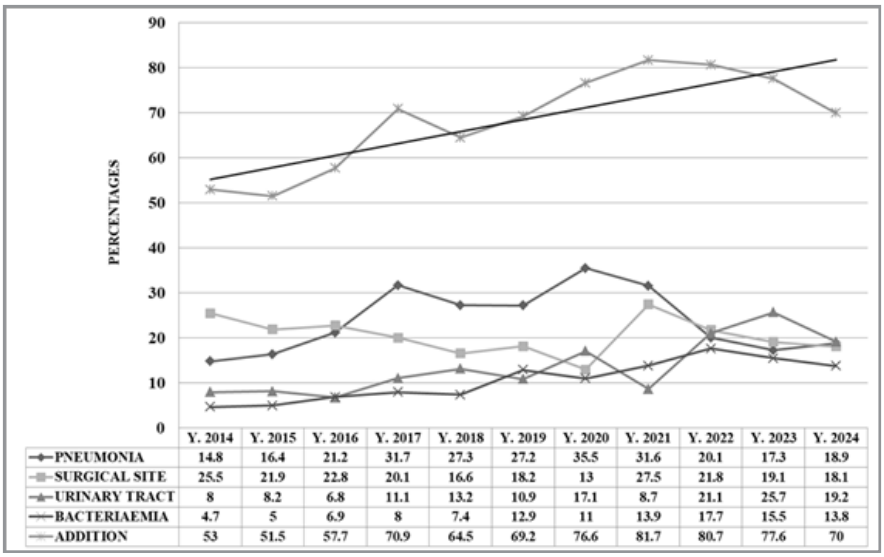
Graph 2: Trends of Healthcare-associated Infections for Hospital Services, 2014 – 2024

The mortality rate due to HAI also had an upward trend. The death percentage of patients with HAI with respect to total hospital mortality ranged around the average of 19.5; from a minimum of 13.2% in 2014, up to 23.3% in 2018. Corresponding rates varied from the average in the period of 26.8 deaths per one hundred patients with HAI: from 16.2 (2014) to 38.7 deaths per one hundred patients with HAI. Thus, fatalities due to HAI exceeded that expected every year (10 deaths per one hundred patients with HAI), with a maximum of 3.9 times this reference in 2020. The Pearson correlation coefficient (r) calculated for the possible incidence/fatality correlation was 0.22, and the paired Student t distribution value was positive (7.0268 versus 1.7341 tabulated at 18 degrees of freedom and 95% reliability). Moreover, the odds ratio obtained (Odds ratio = 2.879) shows that

significantly (p = 0.000) hospitalized patients who acquire a HAI have an almost three times greater risk of dying compared to those who do not become infected.

Healthcare-associated infections' lethality significantly impacted total hospital mortality in 2022, although it decreased during the next two years, except in ICU: 29.4 deaths for every one hundred discharges. Internal Medicine reported a 24.9 rate; its patients had a 3.5 higher death risk in comparison with other services (Odds ratio = 3.496 y p = 0.000). Thirdly, the mortality rate in Surgery, of 7.7, also exceeded the expected reference (≤ 4.8 hospital deaths per 100 discharges). Only Pediatrics was below its expectation: 3.4. A particular risk factor in the Internal Medicine service is its considerable number of elderly patients (for example, those over 59 years of age were a relative majority of 43.9% in 2022). Both HAI incidence and mortality were significantly higher in this age group (Odds ratio = 1.23 and p = 0.001; and Odds ratio = 2.18 and p = 0.000, respectively) and its association with the risks was trivalent: no relationship (days of stay and Surgery service), with a relationship but not statistically significant (communicable diseases and trauma upon admission, surgical site infections, urinary tract and bacteremia and causal agents), and with association and statistical significance: admission for non-communicable disease, mechanical ventilation, central venous catheter, urinary catheter, pneumonia and discharge for septic shock. Regarding death risk factors in general, in 2022, the main ones were significantly (p = 0.000) and in decreasing order: septic shock (Odds ratio = 9.23), mechanical ventilation (OR = 7.28), venous catheter central (OR = 4.939), urinary catheter (OR = 4.33), nosocomial pneumonia (OR = 2.99) and admission due to non-communicable disease (OR = 1.98).

During the entire study period, four types of HAI stood out, with an average of 68.5%, and all the other thirteen were detected with 31.5%, among which only nosocomial infections of the skin and soft tissues, peritonitis, and vascular lines (venoclysis) stood out. The four predominant ones in our eleven-year study were in descending order: pneumonia (23.8%), surgical site infections (20.4%), urinary tract infections (13.6%), and bacteremia (10.6%). Graph 3 shows its eleven-year Evolution, which had a clear upward trend with ups and downs: increases in 5 years (2016, 2017, 2019, 2020 and 2021) and relative decreases in 4 years (2015, 2018, 2023 and 2024). These are due to the relative decrease in pneumonia and surgical site infections and due to the relative increase in 2023 and 2024 in skin and soft tissue infections (13.6%) and peritonitis (4.5%). The four main ones had different evolutions, ranging from 30.2%, going from a minimum of 51.5% (2015) to a maximum of 81.7% (2021). They varied in ascending order: pneumonia (range 20.7%, minimum 14.8%, and maximum 35.5%), urinary tract infection (range 17.7%, minimum of 8% and maximum 25.7%), surgical site infections (range 14.5%, minimum 13% and maximum 27.5%) and bacteremia (range 13%, minimum 4.7% and maximum 17.7%).



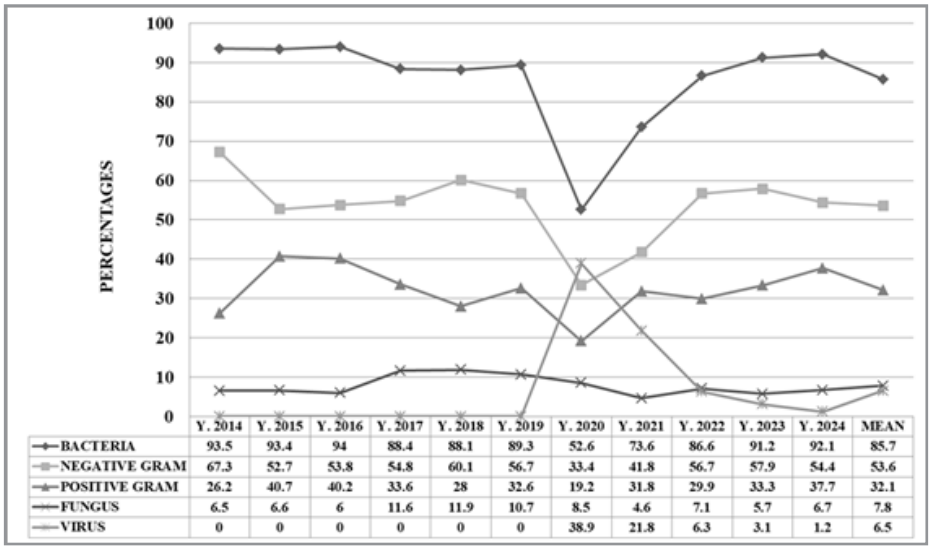
	Y. 2014	Y. 2015	Y. 2016	Y. 2017	Y. 2018	Y. 2019	Y. 2020	Y. 2021	Y. 2022	Y. 2023	Y. 2024
PNEUMONIA	14.8	16.4	21.2	31.7	27.3	27.2	35.5	31.6	20.1	17.3	18.9
SURGICAL SITE	25.5	21.9	22.8	20.1	16.6	18.2	13	27.5	21.8	19.1	18.1
URINARY TRACT	8	8.2	6.8	11.1	13.2	10.9	17.1	8.7	21.1	25.7	19.2
BACTERIAEMIA	4.7	5	6.9	8	7.4	12.9	11	13.9	17.7	15.5	13.8
ADDITION	53	51.5	57.7	70.9	64.5	69.2	76.6	81.7	80.7	77.6	70

Graph 3: Evolution of the Main Categories of Healthcare-Associated Infections, 2014 - 2024

Most cases of these major HAI were related to invasive procedures and implantation of medical devices. From 2017 to 2024, 91.6% of detected bacteremia was associated with a central venous catheter, from a minimum of 42% to 100% in three years (2028, 2020, and 2024). 81.6% of the urinary tract infection cases were associated with a catheter, with a minimum of 69% (2021) and up to a maximum of 96.1% (2024). More than half (52.7%) of nosocomial pneumonia were associated with mechanical ventilation, from 42.9% (in 2020) to 61.9% (in 2017). And 51.4% of clean surgeries, especially with surgical implants, became infected: at least 34.2% (in 2024) and more, up to 59.9% (in 2019).

Through 7,758 microbiological cultures appropriate to each HAI, we detected forty-nine species of its causal agents. The statistical means of their distribution in the study were 85.7% bacteria (53.6% Gram-negative and 32.1% Gram-positive), 7.8% yeasts, and 6.5% viruses (SARS-CoV-2 during the COVID-19

pandemic in the years 2020 and 2021). As shown in Graph 4, all causal agents' detection frequencies varied over eleven years. As a whole, even when bacteria prevailed, they had a downward trend, going from a maximum of 94% (year 2016) to a minimum of 73.6% (year 2021); mainly due to Gram negatives, which varied from 67.3% (in 2014) to 33.4% (2020), and to a lesser extent Gram positive, despite their increase from 26.2% (in 2014) to 40.7% (2015). This result was due to two causes: on the one hand, yeasts had significant increases in the 2017-2019 period, doubling their frequency as causes of HAI, from 6% (in 2016) to 11.9% (in 2018); However, its trend decreased slightly in the eleventh year of the study. On the other hand, the SARS-CoV-2 virus reached great importance as an etiology of HAI, surpassing Gram-negative and positive bacteria with 38.9% in 2020 of the COVID-19 pandemic, dropping to a minimum of 1.2 % in 2024.



	Y. 2014	Y. 2015	Y. 2016	Y. 2017	Y. 2018	Y. 2019	Y. 2020	Y. 2021	Y. 2022	Y. 2023	Y. 2024	MEAN
BACTERIA	93.5	93.4	94	88.4	88.1	89.3	52.6	73.6	86.6	91.2	92.1	85.7
NEGATIVE GRAM	67.3	52.7	53.8	54.8	60.1	56.7	33.4	41.8	56.7	57.9	54.4	53.6
POSITIVE GRAM	26.2	40.7	40.2	33.6	28	32.6	19.2	31.8	29.9	33.3	37.7	32.1
FUNGUS	6.5	6.6	6	11.6	11.9	10.7	8.5	4.6	7.1	5.7	6.7	7.8
VIRUS	0	0	0	0	0	0	38.9	21.8	6.3	3.1	1.2	6.5

Graph 4: Percentual Annual Distribution of HAI Causal Agents, 2014–2024

In particular, among the variety of 49 causal agents of HAI detected, only six bacteria predominated, with an average in the eleventh of the study of two-thirds of the total, 66.4% (going from the minimum 56.2% in 2013 to 74.8% in 2021); distributed as follows: 16.3% Staphylococcus aureus, 15.6% Escherichia coli, 12.5% Acinetobacter baumannii, 9.6% Pseudomonas aeruginosa, 7.1% Klebsiella pneumoniae and 5.6% Staphylococcus epidermidis. And in turn, each presented significant variations during the studied period. The rest of the 43 causal agents were divided into two subgroups: those that continued to be detected, although with minimal frequencies, such as bacteria of other species of Staphylococcus, Enterococcus faecalis, Enterobacter cloacae, Enterococcus faecium, Proteus mirabilis, and Pseudomonas putida; and yeasts like other non-albicans Candida species. Moreover, a second group of bacterial species that were only occasionally detected without reappearing, such as Burkolderia cepacia, Cryptococcus laurentiis, Rautella planticola, and Rothia kristinae. And the SARS-CoV-2 virus, which, after the pandemic, was detected very minimally (0.8% in 2024) as a HAI cause.

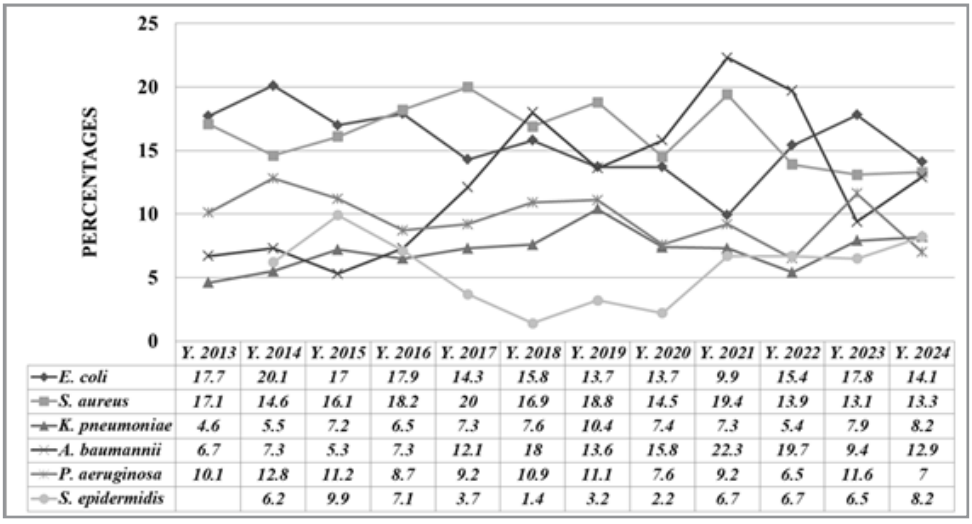
To verify if the HAI processes differ from those in the community, in 2018, we performed a comparative study of urinary tract infections in hospitalized patients and outpatients attending the Family Medicine Unit. In the community, bacteria were the most frequent causal agents (94%), compared to 84% in the Hospital, especially Gram-negative (87.8% vs 61.5%) and with a higher predominance of Escherichia coli (75.7%) compared to 35% in the Hospital, in which the causal microbiota was more diversified thanks to other Gram-negative (in particular, higher percentages of Klebsiella pneumoniae and Pseudomonas aeruginosa). On the contrary, other causal agents were more frequent in the Hospital: Gram-positive bacteria (such as Staphylococcus aureus, S. haemolyticus, and Enterococcus faecium) exceeded 3.7-fold those in the community and yeasts (Candida albicans and C. tropicalis) 2.6-fold.

In 2024, through microbiological analysis of surfaces, our staff detected the following pathogenic microorganisms in the Hospital Services. In the Intensive Care Unit: Acinetobacter baumannii, Escherichia coli, Staphylococcus hominis, Pseudomonas luteola, Klebsiella oxytoca, Enterococcus spp., Enterobacter aerogenes and yeasts. There are Escherichia coli, Enterococcus spp., and yeasts in the operating rooms. In the Equipment and Sterilization Center (EASC): Escherichia coli and Enterococcus spp.

Graph 5 shows the quantitative changes of the main causal agents of HAI from 2013 to 2024. From second place in the 2013 – 2015 period, Staphylococcus aureus went to first place in the next two years, went back to second in 2018 and to first position in 2019, 2020 and 2021, was third in 2022 and second in 2023 and 2024. Nevertheless, during the thirteen-year study, it was the most frequent infectious agent (16.3%). The second place during the period was for Escherichia coli (15.6%). It remained in first place in the first three years, falling back to second place in 2016 – 2017 and third in 2018. Then, it went back to first position in 2023 and 2024. Acinetobacter baumannii stood out in the third position with a total of 12.5%; from fourth to

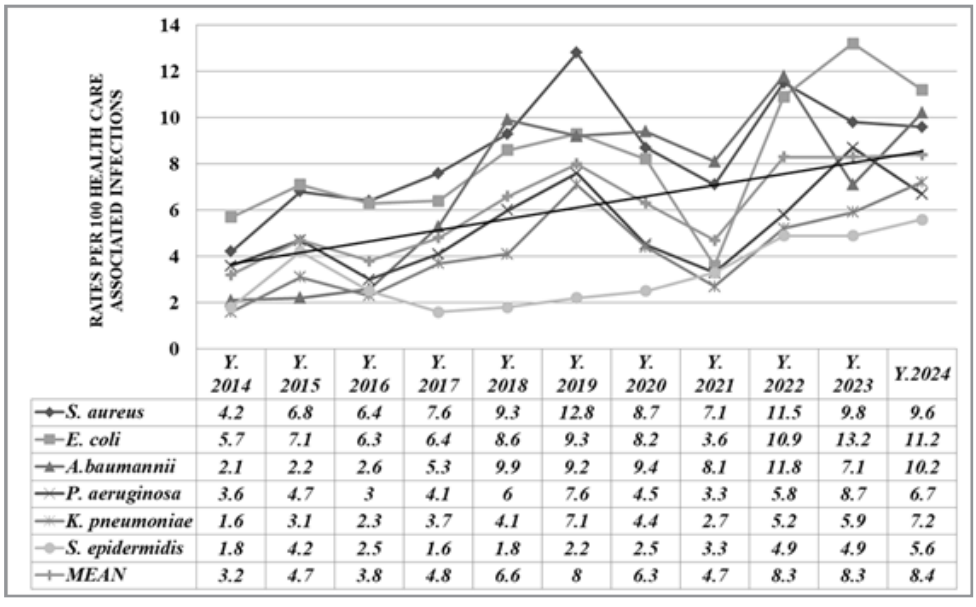
sixth place in the first four years of the study, it moved to third place in 2017 and reached first place in 2028 and, after falling to third place in 2019, it recovered first place in 2020 to maintain it for two more years, declining to fourth place and third places. During the study period, Pseudomonas aeruginosa was ranked fourth with 9.6% of the total; from the third place from 2013 to 2016, it dropped to fourth the following five years and to fifth in 2022, rose to third in 2023, and moved to sixth place in 2024. With 7.1%, Klebsiella pneumoniae placed fifth in the total etiological frequency of HAI. Except for 3 years in sixth place (2014, 2016, and 2022), it maintained fifth place for the other 8 years. In position six of the main causative agents of HAI was Staphylococcus epidermidis with 5.6% of the total for the period, which it did not reach in 2013, in 2014 it joined this group in fifth place and ranked sixth for six years, fifth again in two (2016 and 2024) and fourth place only in 2022.

Although all bacteria had a quantitatively decreasing trend during the eleven years, their virulence and pathogenicity increased compared to yeasts and viruses, the other classes of HAI causal agents (Graph 6). From 2014 to 2020, the incidence medium rate increased 2.6-fold from 3.4 to 8.4 per 100 HAI). The six most frequent bacteria increased their nosocomial infection rates: Acinetobacter baumannii increased its ability to cause HAI 4.5 times in these seven years; Klebsiella pneumoniae 2.7 times, Staphylococcus aureus 2.1, Escherichia coli 1.4, Pseudomonas aeruginosa 1.2 times and Staphylococcus epidermidis increased it 28%.



	Y. 2013	Y. 2014	Y. 2015	Y. 2016	Y. 2017	Y. 2018	Y. 2019	Y. 2020	Y. 2021	Y. 2022	Y. 2023	Y. 2024
E. coli	17.7	20.1	17	17.9	14.3	15.8	13.7	13.7	9.9	15.4	17.8	14.1
S. aureus	17.1	14.6	16.1	18.2	20	16.9	18.8	14.5	19.4	13.9	13.1	13.3
K. pneumoniae	4.6	5.5	7.2	6.5	7.3	7.6	10.4	7.4	7.3	5.4	7.9	8.2
A. baumannii	6.7	7.3	5.3	7.3	12.1	18	13.6	15.8	22.3	19.7	9.4	12.9
P. aeruginosa	10.1	12.8	11.2	8.7	9.2	10.9	11.1	7.6	9.2	6.5	11.6	7
S. epidermidis		6.2	9.9	7.1	3.7	1.4	3.2	2.2	6.7	6.7	6.5	8.2

Graph 5: Main Bacteria Causing Healthcare-Associated Infections, 2013-2024



	Y. 2014	Y. 2015	Y. 2016	Y. 2017	Y. 2018	Y. 2019	Y. 2020	Y. 2021	Y. 2022	Y. 2023	Y.2024
S. aureus	4.2	6.8	6.4	7.6	9.3	12.8	8.7	7.1	11.5	9.8	9.6
E. coli	5.7	7.1	6.3	6.4	8.6	9.3	8.2	3.6	10.9	13.2	11.2
A.baumannii	2.1	2.2	2.6	5.3	9.9	9.2	9.4	8.1	11.8	7.1	10.2
P. aeruginosa	3.6	4.7	3	4.1	6	7.6	4.5	3.3	5.8	8.7	6.7
K. pneumoniae	1.6	3.1	2.3	3.7	4.1	7.1	4.4	2.7	5.2	5.9	7.2
S. epidermidis	1.8	4.2	2.5	1.6	1.8	2.2	2.5	3.3	4.9	4.9	5.6
MEAN	3.2	4.7	3.8	4.8	6.6	8	6.3	4.7	8.3	8.3	8.4

Graph 6: Incidence of the Main Causal Agents of Healthcare-Associated Infections, 2014 – 2024

The pathogenicity of each germ is different. In the etiology of all HAI, bacteria are the majority but not equally. As shown in Table 1, in 2020, Gram-negative infections caused most of the four main HAI (54.7%), predominating in urinary tract infections, causing 63.1% of them (mainly due to Escherichia coli: 31.1%), and the incidence of pneumonia and bacteremia was

reduced (48.8%). Acinetobacter baumannii caused pneumonia frequently (24.4%), less often, surgical site infections and bacteremia (15%), and a minimum of urinary tract infections (5.8%). Pseudomonas aeruginosa was ranked third in the etiology of pneumonia (10.4%), had low percentages in the other HAI, but caused an epidemic outbreak of postsurgical septic arthritis in 2019. Klebsiella pneumoniae only stood out in bacteremia (8.2%), even causing an epidemic outbreak in 2016 and another with pneumonia associated with mechanical ventilation in that same year.

On the other hand, Gram-positive bacteria caused less than a third (31.4%) of the 4 main HAI, mainly bacteremia (40.6%), primarily due to Staphylococcus epidermidis (52.3% of their HAI) and very few urinary tract infections (8.7%). Yeasts (especially Candida albicans) caused 14% of the four main HAI, highlighting these urinary tract infections (28.2%) and probably pneumonia (20.7%), without its causality being confirmed, being minimal in surgical site infections (4.7%) and bacteremia (1.1%).

Table 1: Percentual Distribution of The Main Etiological Agents of Healthcare-Associated Infections IN 2020

ETIOLOGICAL AGENTS	PNEUMONIA	UTI	SURGICAL ZONE	BACTERIEMIA	TOTAL
GRAM-NEGATIVES	48.8	63.1	56.7	48.8	54.7
Acinetobacter baumannii	24.4	5.8	15.7	15.1	15.8
Escherichia coli	4.3	31.1	22	10.6	13.7
Pseudomonas aeruginosa	10.4	7.7	5.5	4.7	7.6
Klebsiella pneumoniae	5.5	7.7	6.4	8.2	7.4
GRAM-POSITIVES	30.5	8.7	34.6	47.7	31.4
Staphilococcus aureus	16.5	3.9	20.5	19.8	14.5
Staphilococcus epidermidis	5.5	0	2.3	8.2	3.7
YEASTS	20.7	28.2	8.7	3.5	13.9
Candida albicans	12.8	11.6	4.7	1.1	10

However, such pathogenicity is variable and evolutionary. Acinetobacter baumannii, for example, increased its percentage among all HAI causative agents from 7.3% (2014) to 18% (in 2018), to decrease to 13% (in 2024). Its percentage in HAI causality also increased from 2.1% (in 2014) to 11.8% (in 2022) and 10.1% (in 2024). So, even with oscillations, both the detection and the etiology of HAI had an increasing trend in the eleven-year study. However, the etiology of the four main HAI decreased from 82.7% in 2012 (without causing any bacteremia) to 61% in 2020, diversifying and increasing, consequently, other HAI from 17.3 to 39% in this period. Particularly, it went from 0 to 15.1% of bacteremia and relatively decreased its causality of pneumonia (from 37.9 to 24.4%), surgical site infections (from 34.5 to 15.7%), and urinary tract infections (from 10.3 to 5.8%). The considerable and rapid development of the pathogenicity of Acinetobacter baumannii also manifested by causing 8 hospital epidemic outbreaks during the eleven years studied: pneumonia associated with mechanical ventilation on 7 occasions (from 2015 to 2019, 2021, and 2022), one of peritonitis-associated with a Tenckhoff catheter in 2018 and another of urinary tract associated with a urinary catheter (also in 2018).

Staphylococcus aureus detections increased from 14.6% in 2014 to 18.8% in 2019, decreasing to 13% in 2024, and those years with lower values defined a downward trend in the eleven-year study. On the contrary, their percentages in the causality of HAI with frequent increases (from 4.2% to 10.5% in the period) show an increasing trend. In particular, it presented considerable increases in the etiology of 3 main HAI from 2014 to 2022: in surgical wound infections from 14.3 to 25%; pneumonia from 17.7 to 28%; and bacteremia from 21 to 22.5%; adding these three 54.5% in 2014 and 74% in 2022 and, therefore, the etiology of S. aureus of all the other HAI in this period did not diversify and did decrease from 45.5 to 26%. In this way, Staphylococcus aureus became the primary causal agent of HAI thanks to its superior virulence and pathogenicity, rather than its resistance to antimicrobials; Therefore, it was the cause of 4 epidemic outbreaks in the Hospital: 3 of pneumonia associated with mechanical ventilation (in 2017, 2019 and 2020) and 1 of urinary tract infection associated with a urinary catheter (in 2019).

A third evolutionary factor is resistance to antibiotics. As shown in Table 2, bacteria have greater potential for development than yeasts (mainly of the genus Candida); those that presented the minimum values in total and in all cases (from 1.6 to 11.1%), without being detected in bacteremia. The top ranking corresponded to Gram-negatives, which in 2020 achieved a total resistance of 64.9%, whereas the Gram positives only 37.1%. Acinetobacter baumannii had the highest overall resistance with 86.7% and the largest also in cases of urinary tract infections (89.1%), pneumonia (82.6%), and surgical site infections (88.1%), except in bacteremia (87.2%). In second place was Pseudomonas aeruginosa with a total resistance of 73.8%, but the largest in bacteremia (95.4%) and second in urinary tract infections (74.4%) and surgical site infections (70.9%) and, although to a lesser extent, also in pneumonia (54.8%). In the third place, Klebsiella pneumoniae was found with total resistance in 49.9% of the HAI cases, with a maximum of surgical site infections (63.3%), urinary tract infections (62.2%), and a minimum of pneumonia (40.3%). After standing out years ago, Escherichia coli ranked fourth with a total resistance of 49.2%, higher in cases of the surgical site (52.8%) and pneumonia (50.4%) and lower in urinary tract infections (47.1%) And bacteremia (46.5%).

TABLE 2: Percentual Broad Resistance to Antibiotics of The Most Common Causal Agents of Hai in 2020

CAUSAL AGENTS	PNEUMONIA	UTI	SURGICAL SITE	BACTERIEMIA	TOTAL
GRAM-NEGATIVES	57	68.2	68.8	65.8	64.9
Acinetobacter baumannii	82.6	89.1	88.1	87.2	86.7
Escherichia coli	50.4	47.1	52.8	46.5	49.2
Pseudomonas aeruginosa	54.8	74.4	70.9	95.4	73.8
Klebsiella pneumoniae	40.3	62.2	63.3	34	49.9
GRAM-POSITIVES	32.1	0	34.9	40.6	37.1
Staphilococcus aureus	18.1	0	28.5	20.1	16.7
Staphilococcus epidermidis	29.7	0	42.9	52.3	41.6
YEASTS					
Candida albicans	1.6	5.8	11.1	0	6.2

For their part, Gram-positive bacteria presented their highest resistance to antibiotics in cases of bacteremia (40.6%), followed by surgical site infections (34.9%) and pneumonia (32.1%), without being detected in the urinary tract, except Enterococcus faecalis. The main one was Staphylococcus epidermidis, with a total resistance of 41.6%; higher in bacteremia (52.3%), lower in pneumonia (29.7%), intermediate in surgical site infections (42.9%) and without being detected in the urinary tract. Moreover, despite the absolute predominance of Staphylococcus aureus in the etiology of HAI, it presented the minimum broad resistance to antibiotics (16.7%): from 18.1% in pneumonia to 28.5% in surgical site infections and without being detected in the urinary tract.

Such antimicrobial resistance is variable, dynamic, and evolutionary. Comparing the total resistance between 2014 and 2022, we observed a decrease in three microbes and an increase in two. Their resistances decreased: Staphylococcus aureus (– 24.5%), Escherichia coli (– 11.9%), and Pseudomonas aeruginosa (– 9.5%) after a slight increase in 2020 (+ 0.4%). On the contrary, their resistance to antimicrobials increased: Klebsiella pneumoniae (+ 33.8%) and Acinetobacter baumannii (+ 12.7%).

Furthermore, such variations occur differentially among antibiotics. In the same period, for those that target the synthesis of the bacterial cell wall (β-lactams, monobactams and nitrofurantoin), Staphylococcus aureus (– 28.8%) and Escherichia coli (– 19.3%) decreased their resistance; Klebsiella pneumoniae (+ 39.2%) and Acinetobacter baumannii (+ 18.4%) increased theirs; and Pseudomonas aeruginosa remained stable. When faced with protein synthesis inhibitors (aminoglycosides, tetracyclines and chloramphenicol), all the etiological agents of HAI decreased their resistance, although in very different proportions: Acinetobacter baumannii (– 50.6%), Pseudomonas aeruginosa (– 37.1%), Escherichia coli (–20.1%), Staphylococcus aureus (–12.3%) and Klebsiella pneumoniae (–6.4%). Resistance to nucleic acid synthesis inhibitors (fluoroquinolones) increased in Klebsiella pneumoniae (+ 36.4%), Acinetobacter baumannii (+ 26.7%), and Escherichia coli (+ 5%) and decreased in Pseudomonas aeruginosa (– 29.4%) and Staphylococcus aureus (– 10.5%). In the case of folate biosynthesis inhibitors (sulfonamides and trimethoprim), all the bacteria increased their resistance: Klebsiella pneumoniae (+ 36.4%), Pseudomonas aeruginosa (+ 25%), Staphylococcus aureus (+ 16.7%), Acinetobacter baumannii (+ 11.1%) and Escherichia coli (+ 1.3 %).

To verify if the development and evolutionary changes in antimicrobial resistance were different in the community's causal agents and the Hospital, Escherichia coli, which causes urinary tract infection, was compared in 2018 at those two levels of attention. With some exceptions (carbapenems, nitrofurantoin, amikacin and trimethoprim-sulfamethoxazole), the significant results ($p = 0.000$) of the odds ratio, with 95% reliability, were in total in favor of the hospital strains of 2.4; being particularly high in the cases of cephalosporin (16.8), monobactams (11.9), penicillin (5.7), β-lactams (5.0), gentamicin (3.4), aminoglycosides (2.6), ciprofloxacin (2.2) and fluoroquinolones (2.2).

Acinetobacter baumannii was the causal agent that developed the most antibiotic resistance in HGR 1. Overall, it increased by 16.9% in five years (from 2012 to 2017), but in various proportions depending on the type of antibiotic: 34.9 % cephalosporins, 23.5% β-lactams, 22.2% carbapenems, 17.6% sulfonamides, 8.7% fluoroquinolones, and 7.7% aminoglycosides. Thus, although it remained sufficiently sensitive to tigecycline, its resistance to tetracyclines increased by 12.1% in that period. Resistant in 2022, this antibiotic was in 33.3% of the surgical site and urinary tract infections; It was 62.1% in pneumonia and up to 100% in bacteremia.

Consequently, Acinetobacter baumannii in 2022 was only sufficiently sensitive to Colistin, from 92.9% (pneumonia) to 100% (surgical wound infection and bacteremia). However, by 2023 it was already resistant to this antibiotic: 33.3% in urinary tract infection, 7.1% in pneumonia, but maintained 0.0% in surgical wound and bacteremia. For its part, Pseudomonas aeruginosa was only 100% sensitive to Colistin in the surgical wound, with low percentages of sensitivity to aminoglycosides (64 to 73%) and fluoroquinolones (60%); and even worse in urinary tract infection: 20% to fosfomycin, 25% to carbapenems and aminoglycosides and 29% to fluoroquinolones. On the other hand, Klebsiella pneumoniae in 2022 was 100% sensitive to amikacin in surgical wound infections, urinary tract infections, and bacteremia, as to fosfomycin (in bacteremia) and carbapenems (surgical wound). Escherichia coli maintained 100% sensitivity to carbapenems and 85.7% to amikacin in surgical wound in-

fection, 100% to fosfomycin, and 89% to nitrofurantoin, Meropenem, and amikacin in cases of urinary tract infection. Moreover, Staphylococcus aureus was relatively the most sensitive, with 100% of cases of pneumonia to vancomycin, tigecycline, linezolid, daptomycin, and 95% to doxycycline.

Starting in 2014, with the reorganization of the current Committee for the Detection and Control of Infections Associated with Health Care (CODECIAAS) and with the beginning of the Institutional Program for the Prevention and Control of Health Care Associated Infections, the operation of seventeen Priority Care Processes began, aiming for actions and monitoring of the main risk factors for these infections. There are eight main processes: Epidemiological surveillance of HAI, Cleaning and disinfection, Hand Hygiene, Rational use of antimicrobials, and Invasive procedures and devices. However, its activities were frequently carried out partially or inadequately, and the CODECIAAS itself obtained an evaluation of "Insufficient" in several years during the study. In general, the Hospital Epidemiological Surveillance Unit completed its functions on time, collecting, documenting, and recording all information regarding HAI for statistical and epidemiological analysis.

In May 2024, in response to an ongoing outbreak of ventilator-associated pneumonia (VAP) due to Acinetobacter baumannii in the Intensive Care Unit, prior to extensive cleaning and disinfection (including rubbing surfaces with 70% ethyl alcohol and with sodium hypochlorite), 114 samples from cubicles and annexes were collected for microbiological analysis of contact surfaces; resulting 17 positive sites (14.9%), mainly detecting this causal agent (64.7%) and three other pathogens. After exhaustive cleaning, 91 contact areas were sampled for microbiological analysis, resulting in 5.5% contamination, in which A. baumanni was “absent”, but Pseudomonas luteola, Klebsiella oxytoca, and Staphylococcus hominis were detected.

The compliance percentages with the priority attention process for Hand Hygiene between 2015 and 2024 ranged from 50.4% to 73%, meeting the goal of > 70% in only three of 10 years. When graphing hand hygiene next to the incidence of HAI, the trends are generally divergent: HAI increases as the hygiene percentage decreases. A Paired Student's t-test was calculated for their possible relationship, resulting in 9.8824 for 9 degrees of freedom and a 95% reliability of 1.8331. However, Pearson's r was -0.4145.

In 2023, Hospital personnel analyzed the adequacy of the antibiotic therapy prescribed against HAI using microbiological cultures and antibiograms. In most cases (43.6%), the prescribed antibiotic did not appear in the antibiogram because it did not correspond to the identified bacteria or by omission. Only in 27.7% of the cases was the prescription appropriate, and the causal agent was sensitive to the prescribed antibiotic. In 26.9% of cases, bacteria were resistant; the resistance was partial in 1.8%. Resistance to the prescribed antibiotic differed for each HAI: 30.4% in urinary tract infections, 24.2% in pneumonia, 23.8% in surgical site infections, and 22.5% in bacteremia.

Resistance was also different for each pathogen. Resistant microbes for urinary tract infections: 55% P. aeruginosa (100% to Linezolid and Piperacillin/Tazobactam, 80% to Carbapenems; and >70% to Aminoglycosides and Cephalosporins); 36.2% E. coli (100% Vancomycin, 77.8% Fluoroquinolones and 66.7% Ceftriaxone); and K. pneumoniae (100% to Clindamycin and Ceftriaxone, and 75% to Ciprofloxacin). In cases of surgical site infections: 41.7% P. aeruginosa (100% to Cephalothin and Ceftriaxone, 72.7% to Carbapenems); 37.5% A. baumannii (100% Cephalothin, 88.9% Cefepime, 83.3% Meropenem); 33.3% K. pneumoniae (87.5% to Ceftriaxone and 71.4% to Moxifloxacin); 31.8% E. coli (85.7% to Ciprofloxacin, 71.4% to Ceftriaxone and Cefepime); and 14.8% S. aureus (69.2% to Clindamycin and 54.1% to Moxifloxacin). In pneumonia: 53.8% A. baumannii (97% to Ciprofloxacin, Ceftriaxone, Meropenem, and Cefepime, and 62.1% to Tigecycline); 37.5% P. aeruginosa (100% to Imipenem, 57.1% to Meropenem, 33.3% to Norfloxacin and Amikacin); S. aureus 59.1% to Clindamycin and 40.9% to Moxifloxacin. And in cases of bacteremia: 63.6% A. baumannii (95% to Ceftriaxone and 90% to Meropenem); 35.7% P. aeruginosa (100% to Piperacillin/Tazobactam, Meropenem, Gentamicin and Ciprofloxacin); 51.4% Staphylococcus spp. (69.2% to Clindamycin and 37.5% to Moxifloxacin); and 14.3% K. pneumoniae (100% Cefotaxime).

Between 2016 and 2024, compliance percentages of the four priority attention processes for invasive procedures and devices resulted as follows. Those related to mechanical ventilation and inhalation therapy varied from 67.1% to 95.7%. Only in 2023 was the 95% goal achieved. The percentage of pneumonia associated with mechanical ventilation was an average of 52.7% in this period, ranging from 42.9% to 61.9%. Therefore, the goal of 95% was not reached. Statistical analysis resulted in Student's t being 0.0002, andPearson's r being -0.55. Compliance with urinary catheter installation protocols ranged from 42.4% to 94.6%, achieving the goal of 95% only in 2024. But this year its management was only fulfilled by 70%. The mean percentage of urinary tract infection associated with the urinary catheter in those 9 years was 81.6%; from the minimum of 53.8% to the maximum of 96.1%, with Student's t of 0.3778 and Pearson's r of -0.044. Central venous catheter compliance rates ranged from 73.5% to 98%, and the goal of 95% was only met in three of nine years. The mean percentage of bacteremia associated with this device was 91.6%; its installation ranged from 42% to 100% in two years, with Student's t of 0.3439 and Pearson's r 0.34. However, it was found in 2024 that its management was only 66%. Compliance with the surgical process had a minimum of 43.1% and a maximum of 78%, consistently below its goal of 95%. Infections from clean surgeries averaged 51.4% in this period, rising from 34.2% to 59.9% with Student's t of 0.0034 and Pearson's r 0.5374.

Discussion

The evolutionary process of HAI variations due to Natural Selection was confirmed in HGR 1 when its development was observed for 11 years. Differential ascending trends are due to morbidity, mortality, typology, hospital service, hosts, and causal agents. Related to all this, as well as its sensitivity and antibiotic resistance. The variations in the HAI occurred through oscillations and contradictions but with a general tendency to upsurge, increasingly exceeding the expected reference rates. This analysis indicates an evolutionary process that is neither rectilinear nor unidirectional but dialectical in its development. As has been pointed out, "one cannot speak of an organism in

Evolution without taking its courses at a constant rate, since the evolutionary rate constantly fluctuates, from very fast to very slow, and stoppage or ultra-slow Evolution. And with evolutionary leaps not in a single generation, they extend over numerous generations"4 of the causal agents of HAI in this case.

The evolutive processes of HAI causative agents in HGR 1 occurred through three main factors: 1) the Natural Selection of 49 pathogenic microorganisms that managed to adapt to the hospital environment; 2) the development of its virulence, pathogenicity, and antimicrobial resistance; and 3) in correlation with this, the implementation of actions for its prevention, treatment and control that dynamically shape and modify the hospital environment (hygiene, cleaning and disinfection, sterilization and antisepsis) and, likewise, the modifications of the organic microenvironments of the Hospital and through invasive procedures and devices (such as surgeries, surgical implants, venous and bladder catheters, and mechanical ventilation) and, above all, with the prescription of antibiotics.

This Evolution of HAI depended, in the first instance, on the evolutionary capacity of its causal agents that conferred on them Natural Selection through their competition among multiple microbial species and, ultimately, on the correlation of their genomes with the environment that they achieved. Thus, by comparing urinary tract infections acquired in the community and the Hospital, it was found that they differ with respect to the causal microbes and their respective sensitivities and resistances to antimicrobials, evidencing that such differences are due to their correlations with different environments, which determines Natural Selection and differential evolutionary processes even of the same species, such as Escherichia coli [16].

In a hospital, only germs that have developed the ability to resist, survive, reproduce, and adapt in such a hostile and aggressive environment of detergents, antiseptics, and antimicrobials and have the aptitude for colonization in a tissue or organ of the host to cause an infectious process can become and remain causal agents of HAI.

With the microbial culture analysis of surface in various hospital services, contamination with pathogens such as Staphylococcus spp., A. baumannii, Pseudomonas spp., E. coli, Klebsiella spp., fungi and yeasts (mostly Candida) were detected. Germs have developed the capacity to produce biofilms that favor their covalent adhesion on inert and living surfaces in groups of one or several species. In addition, biofilms help them develop a high tolerance to antimicrobials. The biofilm matrix is a cellulose complex formed mainly by water and exopolysaccharides and, to a lesser extent, other macromolecules such as proteins, DNA, and other products derived from the lysis of microorganisms. Biofilm production is essential for the protection, defense, and survival of the causative agents of HAI in environments as hostile and aggressive as those in hospitals, given that within the biofilm they are protected from the action of detergents and antiseptics and, during infection, from antibodies, phagocytic cells and antibiotics. In particular, coexistence in this environment enables variation and the genetic transfer between its populations, through coevolution of genomes interacting in two opposite ways: exploitative (parasitic) or mutualistic. For example, a single mutation can defend against a bacteriophage, and the transfer of a plasmid can confer resistance to antibiotics.

The over thirty-nine probable HAI do not occur equally; there is also a Natural Selection of them [17]. In the case of HGR 1, in the year 2023 with the highest incidence, only seven-teen HAI were detected (43.6%); of which only four predominated (68.5% of the total detections) during that entire period, in decreasing order: pneumonia, surgical site and urinary tract infections, and bacteremia. All of these were primarily associated with invasive procedures and devices that facilitated contagion through cross-transmission: Surgery, surgical implants, mechanical ventilation, venous, peritoneal, and bladder catheters, among others, to such a degree that all epidemic outbreaks that occurred during the study period were associated with them: surgical site, pneumonia, bacteremia, peritonitis, and urinary tract infection. Such invasive procedures and devices create microenvironments in host tissues and organs in which the causal agent must adapt for its colonization and production of HAI; by combining optimal conditions for survival and reproduction, such as humidity, temperature, and, above all, certain nutrients (such as siderophores for iron uptake "clearly required for a successful infection, in addition to zinc and manganese") and metabolites (amino acids and peptides are primary carbon resources and are critical for environmental adaptation –fitness– during infection) and also the biosynthetic capacity of amino acids is decisive for its growth and development [18]. Regarding this, although the installation of invasive devices technically ranged from fair to good, its handling was deficient with some frequency.

In particular, the higher incidence and fatality due to HAI in the Intensive Care Unit and Internal Medicine were associated with such risk factors. The ICU attends to the most seriously ill patients due to disease and trauma, almost all of which require one or more invasive procedures and devices at the same time. Furthermore, in Internal Medicine, because most of its patients are elderly (and both the incidence and fatality due to HAI were significantly higher in the age group over 59 years), with complicated chronic diseases that require hospitalization, and are frequently immunosuppressed and need some of the invasive procedures and devices. Consequently, patients hospitalized in Internal Medicine had an almost three times greater risk of acquiring HAI compared to those in other hospital services (Odds ratio = 2.879 and p = 0.000) and, likewise, a 3.5 times greater risk of dying (Odds ratio = 3.496 and p = 0.000). This data is indicative of the relationship between HAI morbidity and its fatality, even in general. In this regard, the odds ratio obtained (Odds ratio = 2.879) shows that significantly (p = 0.000) hospitalized patients who acquired HAI had an almost three times greater risk of dying compared to those who were not infected. In turn, in 2022, the main risk factors for deaths in general were related to HAI: septic shock, mechanical ventilation, central venous catheter, urinary catheter, and nosocomial pneumonia.

For “an astonishing diversity of microorganisms” in the very varied hospital microbiota, only 49 pathogenic agents were detected in eleven years due to Natural Selection. Many of them became prevalent, although with minimal frequency. Another portion was only detected eventually and was never detected again. Of the total, only six microbes predominated during the

eleven-year study, in descending order: Staphylococcus aureus, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Staphylococcus epidermidis. Natural Selection indicates their superior capacity for competitiveness, adaptation, virulence, pathogenicity, and resistance to antimicrobials. Their resources could not be matched by the other 43 causal species of HAI "due to the metabolic cost and overload".

In general, bacteria showed superior abilities to cause HAI. Although with variations. Because of the COVID-19 pandemic, the SARS-CoV-2 virus relatively surpassed its Gram-negative and positive causality in 2020. Fungi and yeasts (mainly Candida genus) doubled their HAI percentages from 2017 to 2019, and consequently, bacteria percentages, including Gram-negative ones, decreased relatively. These facts show the close competition between all hospital pathogens as HAI etiological agents. This pattern is because the frequency of favorable mutations in the genome does not grow jointly or continuously. While some genes reproduce and develop, others are delayed and do so later.

"Bacteria, throughout evolution, have acquired virulence factors or determinants that favor their growth or survival during infection,"; which activate in two phases: an early one to promote colonization and invasion of the host (adhesion, mobility, and chemotaxis, invasion); and another late one, properly pathogenic, to develop self-defense mechanisms (survival and intracellular mobility, evasion of the immune response and antigenic variation, submission or confrontation). In this regard, we observed that bacteria such as Escherichia coli and Acinetobacter baumannii were spreading their etiology to different HAI and, as they showed differences between them in their sensitivity and resistance to antimicrobials, it is indicative that they evolve through the development of new strains.19 And even when one has the genomic potential for all of this, it must be activated by environmental stimuli. Furthermore, such capacities are not static but dynamic and have evolutionary meanings.

Evolutionary processes were evidenced thanks to various causal agents' detection and monitoring of HAI. Most were Gram-negative bacteria (55%), mainly A. baumannii; less than a third were Gram-positive (31%), mostly S. aureus; and some fungi and yeasts (14%), such as Candida spp. Furthermore, in the four main HAI, most of the etiology was Gram-negative, from 49% (pneumonia and bacteremia) to 63% (urinary tract infection), especially for A. baumannii, except in the latter by E. coli. In all Gram-positive cases, S. aureus stood out, from a minimum of 4% in urinary tract infections to 20% in surgical site infections and bacteremia. These results show the different evolutionary developments of capacities for colonization, reproduction, and the causality of infections in various tissues and organs of the host.

On the other hand, their resistance against antiseptics and antibiotics, in which the pharmacokinetics and pharmacodynamics of the medications also intervene. Given that the etiology of various HAI is due to the same causal agent not occurring simultaneously but sequentially, their sensitivity and resistance to antimicrobials are different in each. This association indicates that an evolutionary process leads to its differentiation into new strains of each species with distinctive capabilities [19].

In the case of Gram-negative bacteria, having evolved an external membrane (which Gram-positive bacteria lack) enables them to have greater control of external stimuli and better defense against environmental aggressions and, concomitantly, for greater virulence and pathogenicity and antimicrobial resistance. In particular, because this membrane is synthesized and contains a unique component of lipopolysaccharide (LPS) that acts as endotoxin and "plays a critical role in the pathogenesis of infections" and, in bacteria such as Escherichia coli, "particularly in septic shock"; because it provokes a strong immune response through "powerful activation of macrophages and the production of a large number of cytokines with multiple effects." When Gram-negative bacteria manage to "possess the complete LPS structure, it gives these bacteria evolutionary advantages by being more resistant to environmental conditions," despite becoming "hypersensitive to hydrophobic antibiotics" (macrolides) [20, 21].

Thus, Gram-negative bacteria's outer membrane and LPS contribute to their greater pathogenicity and, likewise, to their superior resistance to antibiotic therapy. They caused most of the epidemic outbreaks and the four main HAI (54.7%) in HGR 1; especially urinary tract infections and a relatively lower incidence of pneumonia and bacteremia. Gram positives caused few epidemic outbreaks, less than a third (31.4%) of the four main HAI, mainly bacteremia (40.6%), and very few urinary tract infections. Likewise, all the first places in antimicrobial resistance corresponded to Gram-negatives, which achieved a total resistance of 64.9% and Gram positives of only 37.1%.

However, three main capacities are essential to establish and maintain itself as a causal agent of HAI. Eventually, one of them predominates. For example, Staphylococcus aureus (a Gram-positive bacterium) became the main causal agent of HAI thanks to its superior virulence and pathogenicity rather than due to its resistance to antimicrobials; Therefore, it was the cause of 4 epidemic outbreaks in the Hospital: 3 of pneumonia associated with mechanical ventilation and 1 of urinary tract infection associated with a urinary catheter. On the other hand, Pseudomonas aeruginosa was ranked fourth in the etiology of HAI, having developed pan-resistance to antimicrobials. Acinetobacter baumannii was particularly outstanding in third place in detections during the eleven years studied by developing combined virulence, pathogenicity, and resistance. The rate of HAI that it caused in 2014 increased by 471% in just 4 years. In 5 years, the etiology of HAI diversified with bacteremia, peritonitis, upper respiratory tract infection, and skin and soft tissue infection. It caused nine hospital epidemic outbreaks: 7 of pneumonia associated with mechanical ventilation, one of peritonitis associated with a Tenckhoff catheter, and another of urinary tract infection associated with a urinary catheter; and has become extremely resistant as it is now only sensitive to Colist. Thus, although virulence and pathogenicity are potentially superior to antimicrobial resistance in the causation of HAI, a comprehensive and combined development of these three capacities provides the greatest potential for morbidity and mortality due to IAAS and, concomitantly, the greatest difficulties with its prevention, treatment, and control.

Except for S. epidermidis, the other 5 main causative agents of HAI generally coincide with ESKAPE, the acronym that the

World Health Organization has included in its “priority list of bacterial pathogens of importance for global public health”: both in the group of “critical” importance (A. Baumannii, E. coli, and K. pneumoniae) and in the group of "high priority" (P. Aeruginosa and S. aureus). In HGR 1, Enterococcus faecium has not had such relevance. Instead, Staphylococcus epidermidis has it. The central concern regarding these germs is that with "antibacterial resistance being the most important challenge for global public health," the "development of strategies to prevent and control antimicrobial resistance" of these pathogens is required. So, the predominance of such causal agents of HAI in HGR 1 is part of a global evolutionary process, but in a particular way with some differences, which must be specified.

Regarding all this, since 2014, with the reorganization of what would become HGR 1 Committee for the Detection and Control of Infections Associated with Health Care (CODECIAAS), the Institutional Prevention Program was adopted and adapted and Control of HAI, which included 17 Priority Care Processes, in order to address their risk factors comprehensively, However, concentrating on Epidemiological surveillance, Cleaning and disinfection, Hand hygiene, on the four invasive procedures and devices related to the main HAI, and Rational use of antimicrobials [22]. The first was performed, in general, efficiently during our study, allowing adequate description and analysis of the evolutionary development of incidence and fatality and the main attributes of HAI.

Although "surfaces of contaminated hospital environments can be a risk factor for infections" and, in general, "cleaning and disinfection of the environment can reduce the incidence of colonization or infection [23]. Even when they are exhaustive, they do not sterilize since they eliminate some germs, but not all. Only those microbes resistant to detergents, antiseptics, and antibiotics survive. In fact, "there is no evidence demonstrating that surface cleaning and disinfection protocols can safely eliminate multiresistant strains [24]. These microorganisms survive because “the microbial density, mainly staphylococci, to quickly recover in between 2.5 and 6.5 hours [25]. In particular, “it was found that 27% of the hospital rooms remained contaminated with Acinetobacter baumannii [and Staphylococcus aureus] even after four cycles of disinfection with sodium hypochlorite”. Thus, cleaning and disinfection is paradoxical in its results, temporarily eliminating susceptible strains, but selecting resistant ones that can evolve towards multi, broad and extreme resistance to detergents, antiseptics and antimicrobials, thereby adapting to the very hostile and aggressive hospital environment and lasting in it.

Upon supervision and evaluation of hand hygiene, subjects who interact with hospitalized patients frequently showed deficits in compliance, more so do doctors and surgeons than nursing personnel; in fact, its goal of >70% was only met in three of the 10 years studied. Although compliance with the surgical processes and installation of mechanical ventilation, the central venous catheter, and the urinary catheter were frequently adequate, we have found that, on the contrary, their handling and manipulation were deficient. As has been noted: “The hands of health professionals represent the main mode of transmission of cross infections, when rigorous asepsis measures are not adopted... 20 to 40% of hospital infections have etiology associated with cross-infection, through the hands of health workers" that become contaminated, in addition to contact with patients, with the utensils they handle: invasive devices, medication drawers, cabinet interiors, dressing rooms, glucometers, oximeters, monitors, parenteral feeding pumps, door handles, bathrooms.26 In the case of HGR 1, when the percentages of compliance with the Hand Hygiene process were compared with the incidence of HAI in 9 years of our study, the trends were generally divergent. As this percentage decreases, HAI increases, although with oscillations.

During this period, the average percentage of central venous catheter bacteremia was 91.6%. The mean percentage of urinary tract infections associated with catheters was 81.6%. The rate of pneumonia associated with mechanical ventilation was 52.7%. Infections from clean surgeries, especially with surgical implants, averaged 51.4%. Such invasive procedures and devices were clearly decisively related to the causality of the main HAI detected. As confirmed, deficits occurred mainly in managing and manipulating such invasive devices rather than in their installation, which is indicative of cross-transmission of the corresponding HAI through the hands of health personnel.

The use of antimicrobials is a determining factor for the Evolution of both HAI and their causal agents. "The bacterial mechanisms involved in pathogenicity and virulence have experienced a long evolutionary process dependent on the host-pathogen relationship. These changes have been due to [natural] selection pressure caused by introducing antimicrobials in Medicine. This pressure has forced microorganisms to adapt to changing conditions, acquiring or developing new mechanisms of pathogenicity and resistance. When they are ignored, then the mechanisms by which we can combat bacteria are unknown." In the present study, the fact that only in 28% of the cases, the prescribed antibiotic coincides with the sensitivity of the causal agent is indicative of inappropriate use of antimicrobials in HGR 1, which favors the development of resistance and is a factor in Natural Selection of the causal agents of HAI. This disparity was evident because the six bacteria species associated with HAI are multi-, pan- and extremely resistant to antibiotic therapy. In cases of pneumonia, bacteremia, and surgical site infection, inappropriate antimicrobial prescriptions were higher against Acinetobacter baumannii and Pseudomonas aeruginosa, and in urinary tract infections, Pseudomonas aeruginosa and Escherichia coli. Therefore, the bacteria that have become the most common causative agents of HAI are extremely resistant to antibiotic therapy.

Antimicrobial resistance is neither equitable nor constant for all its targets and modes of action. From 2014 to 2022, the main causative agents of HAI showed greater capacity to relatively increase their resistance to folate biosynthesis inhibitors (sulfonamides). E. coli, A. baumannii, and K. pneumoniae also increased their use for inhibitors of nucleic acid synthesis or DNA topoisomerases (fluoroquinolones). Only A. baumannii and K. pneumoniae did so against cell wall synthesis inhibitors (beta-lactams and non-lactams). On the contrary, they all have a relatively decreased ability to resist protein synthesis inhibitors (aminoglycosides and tetracyclines). These evolutionary changes occur through a defensive arms race to protect themselves against extracellular aggressions (biofilms and quorum sensing signals), in the cell membrane (porins, enzymatic hydrolysis, and

efflux pumps), intracellular aggressions (redox modifications, transferases, ribosomes and alterations in protein synthesis) and genetic (gene expression, mutations, plasmids, transposons, integrons, and genetic cassettes). As such, these responses and changes in sensitivity and resistance to different antimicrobials are obviously due to the varied and changing exposure to them by the antimicrobials prescribed for treating patients with HAI [26].

In this regard, "the rapid increase in antibiotic resistance is largely driven by the lateral transfer of antimicrobial resistance genes between bacterial taxa, which represents one of the most dramatic and harmful consequences of anthropogenic impacts on the evolution of other species". “The saturation of the environment with antibacterial compounds has placed a strong selective pressure on antimicrobial resistance genes, which are frequently contained in complex DNA vectors, also carrying resistance against disinfectants and heavy metals [27, 28]. Therefore, “the genomic analysis of individual organisms, the characterization of their population dynamics and the microbial ecological community facilitate the identification of emerging pathogens, the monitoring of epidemic disease outbreaks and the study of the evolution of antibiotic resistance”.

Conclusion

Healthcare-associated infections (HAI) in hospitals are subject to a dialectical process of Evolution due to competence, Natural Selection, and adaptation of their causal agents to the hospital environment in general and host tissues and organs. Their Evolution depends, in principle, on their genomic potential to contaminate and colonize inert surfaces, adapting to cross-transmission mechanisms for contagion, colonization, and, finally, host infection. Its Evolution depends on its interaction with the conformation and variations of the hospital environment and the organic microenvironment of the host.

In the hospital environment, cleaning, disinfection, hand hygiene, and other activities cause paradoxical results. They eliminate germs susceptible to detergents and antiseptics. Meanwhile, they cause a Natural Selection of resistant microbes, empowering them for their survival, adaptation, and reproduction, eventually spreading the contamination of surfaces of areas, furniture, equipment, devices, and medical materials. The main HAI (surgical sites, pneumonia, bacteremia, and urinary tract) are mostly related to invasive (surgical) procedures and devices (e.g., implants, mechanical ventilation, venous and bladder catheters). In the infected host, a second Natural Selection of pathogens occurs capable of colonizing and infecting the tissues and organs to which they have access, thanks to their defenses of the host's immune system and, also, of resisting the prescribed antimicrobials, with which paradoxical results also occur, killing germs sensitive to them and empowering those that manage to develop resistance to antibiotics. Whether due to contamination and colonization of the hospital environment or contagion from other infected patients or health personnel, HAI are cross transmitted until epidemic outbreaks arise.

Ultimately, the frequency and severity of HAI morbidity and mortality in a hospital depend on the degrees of inadequacy, insufficiency, and ineffectiveness of the specific actions for its prevention, treatment, and control; to the extent that, instead of containing them, they allow and even favor the Evolution of their causal agents by Natural Selection for contamination, contagion, colonization and infection of hospitalized patients and, furthermore, with the development of resistance to the antibiotic therapies.

Acknowledgement

To Héctor D. Salazar-González, PhD in Cell Biology, for his kind and excellent contribution to the study supervision, interpretation of the results, corrections and translation of the manuscript.

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