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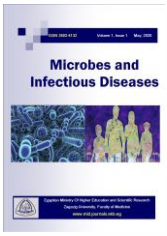

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Review article

Current microbiological trends of microorganisms causing nosocomial infections

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ABSTRACT

Infections related to health care are a major public health problem in Spain, Europe and worldwide. They cause an increase in hospital stays, long-term disability, greater resistance of microorganisms to antimicrobials, additional costs both for the patient and for the health system. The patient is exposed to a wide variety of microorganisms during hospitalization. The potential exposure to infection depends, in part, on the characteristics of the microorganisms, including antimicrobial resistance, intrinsic virulence, and the amount of infectious material (inoculum). The problem of greatest clinical importance is the trend of increasing bacterial resistance, becoming a health threat of great magnitude worldwide with an increase in morbidity and mortality. The incidence of bacterial resistance is also related to the prescription and consumption of antimicrobials. The main objective of this review article is to analyze the current microbiological trends of the microorganisms that cause nosocomial infections.

Introduction

Health care associated infections are acquired in care facilities (acute or chronic hospitals, geriatric hospitals, dialysis centers, medium or long-stay centers, rehabilitation centers or in hospitals) and did not exist before admission. These infections are a major public health problem in Spain, Europe and worldwide. They cause an increase in hospital stays, long-term disability, greater resistance of microorganisms to antimicrobials, additional costs both for the patient and for the health system, and unnecessary deaths [1].

In the middle of the last century, the discovery, commercialization and introduction of antibacterials revolutionized the world of medicine, producing significant changes in the therapeutic paradigm for infectious diseases. Despite this, this progress was once again threatened by the deterioration in the efficacy of antibiotics. Microorganism, mainly Gram-negative bacteria, were able to adapt, with the constant production of resistance mechanisms that allow them to evade the pharmacological effect and survive drug exposure. For this reason, it is important to take into account that in order to combat bacterial resistance, a global, multidisciplinary approach must be taken, based on the support, guidance and training of future professional generations, in order to guarantee its control [2].

Antimicrobial resistance is considered a serious threat to public health in all countries in recent years. Since 2014 with the first global report of the World Health Organization (WHO) on the

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surveillance of antimicrobial resistance, the infections caused the associated mortality and the urgent need to create new antimicrobials to combat this epidemic, considered by some experts as "the post-antibiotic era". Enterobacteriaceae and non-fermenting gram-negative bacilli are emerging pathogens of global importance, responsible for numerous infections and nosocomial outbreaks associated with a high mortality rate. The most important resistance mechanism involved in these pathogens is the production of β-lactamase enzymes, which is why carbapenems are the treatment of choice; however, the emergence of resistance to these antibiotics through the bacterial production of carbapenemases, enzymes capable of hydrolyzing this family of drugs, has limited and made difficult the therapeutic approach to these infections [3].

According to statements by the WHO, bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, followed by *Salmonella spp*, among others, will have such a high degree of resistance with little or no treatment options. At the present time, hospitals around the world have already described more unfavorable clinical outcomes, attributable to this phenomenon: longer hospital stays, higher medical care costs, and a higher rate of death and disability [4].

The problem of greatest clinical importance is the trend of increasing bacterial resistance, becoming a health threat of great magnitude worldwide, since it causes a decrease in the safety of healing processes and causes an increase in morbidity and mortality. The incidence of bacterial resistance is also related to the prescription and consumption of antimicrobials, since it is stated that 40% of the patients admitted to hospitals receive antimicrobial treatment and 50% of them is inappropriate [2]. The main objective of this literature review was to analyze the current microbiological trends of the microorganisms that cause nosocomial infections.

Development

Most relevant microorganisms

The patient is exposed to a wide variety of microorganisms during hospitalization. The potential for exposure leading to infection depends, in part, on the characteristics of the microorganisms, including antimicrobial resistance, intrinsic virulence, and the amount of infectious material (inoculum). Infections can be caused by a microorganism contracted from another person in the hospital (cross infection) or by the patient's own flora (endogenous infection). Infection by some microorganisms can be transmitted by an inanimate object or by newly contaminated substances from another human source of infection (environmental infection) [5].

Derived from the global findings, the WHO published the first list of antimicrobial resistant "priority pathogens", which includes the 12 families of bacteria most dangerous to human health, and divided it into three groups. Group 1, critical priority: includes multi-resistant bacteria that are especially dangerous in hospitals, nursing homes and among patients who need to be cared for with medical devices such as ventilators and intravenous catheters. These bacteria include: carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* resistant to carbapenems with the capacity to generate resistance to all antibiotics, Enterobacterales and producers of β-lactamases of extended spectrum ESBLs. Group 2, high priority: Vancomycin-resistant *Enterococcus faecium*, *Staphylococcus aureus* resistant to methicillin and with decreased susceptibility to vancomycin, *Helicobacter pylori* resistant to clarithromycin, *Campylobacter spp*. resistant to fluoroquinolones, *Salmonella spp.* resistant to fluoroquinolones and *Neisseria gonorrhoeae* resistant to cephalosporins and fluoroquinolones. Group 3, of medium priority, includes other bacteria that exhibit increasing resistance to antimicrobials and cause common diseases, *Streptococcus pneumoniae* with decreased susceptibility to penicillin, resistant *Haemophilus influenzae* to ampicillin, *Shigella spp*. resistant to fluoroquinolones [6].

Gram-negative bacilli

E.coli

It is a Gram-negative bacillus that belongs to the Enterobacteriaceae family, mobile, facultative anaerobic, does not have spores, reduces nitrates into nitrites, ferments glucose and lactose with gas production. Like all gram-negative bacteria, consists of a cytoplasmic membrane, an external membrane, the peptidoglycan and periplasmic space. It is a common inhabitant of the intestines of all animals, including humans, and is also found in sewage [2].

Within the Enterobacteriaceae, *E. coli* is currently the main organism responsible for causing both nosocomial and community infections, in addition

to its wide capacity to acquire resistance to antimicrobials. Infections caused by this pathogen can be limited to mucosal surfaces or spread throughout the body. They are commonly found in areas such as: urinary tract, vascular system, lung, prostate gland, bones or meninges; It can also present with septicemia, due to inadequate host defenses, newborns being the most susceptible [7].

The clinical manifestations depend on the strains of *E. coli*, thus traveler's diarrhea is caused by *enterotoxigenic E. coli* (ETEC), hemorrhagic colitis and hemolytic-uremic syndrome caused by *enterohaemorrhagic E coli* (EHEC), persistent diarrhea caused by *enteroaggregative E. coli* (EAEC) and watery infant diarrhea caused by *enteropathogenic E. coli* (EPEC) [8].

Serratia marcescens

Formerly called *Bacillus prodigiosus*, it naturally inhabits soil and water. *S. marcescens* belongs to the group of the Enterobacteriaceae family, it is a gram-negative bacillus, facultative anaerobic. It ferments glucose with gas production, oxidase negative; it develops easily in humid and edible media, especially in starches and carbohydrates, forming red pigmented colonies [8].

This microorganism is transferred from person to person and considered an opportunistic pathogen, associated with a variety of pathologies that can even lead to death. They can be found at an environmental level such as in water, pipes, faucets and intra-hospital supplies such as soaps, antiseptics, etc. So it is important to take into account adequate hygiene both for hands and for hospital instruments. Its acquisition is mostly nosocomial, especially in intensive care units, being respiratory secretions, wounds and urine, frequent sites of colonization. In a greater proportion it affects patients in ICU areas, especially patients with diseases such as diabetes, neoplasia and chronic renal failure. In adults, outbreaks are related to respiratory or urinary infections [2, 7, 8].

Klebsiella pneumoniae

A representative carbapenemase enzyme-producing enterobacterium is *Klebsiella pneumoniae*. It is characterized by being a rod-shaped, facultative anaerobic, immobile gram-negative bacterium. This bacteria have a polysaccharide capsule that fulfills the function of protecting the pathogen from neutrophil-mediated phagocytosis and from bacterial death caused by the complement system. It presents plasmids related to the expression of proteins that mediate its attachment to plastic surfaces, such as those of vascular catheters and bladder catheters [2, 3].

This pathogen is widely disseminated in the environment. In the host, it colonizes the skin, nasopharynx, and gastrointestinal tract, with contaminated hands being one of the vehicles responsible for epidemic outbreaks in the hospital setting. It is currently considered the main causative agent of bacteriemia, septicemia and pneumonia. Clinically it is associated with the production of thick and bloody sputum [2, 3, 7, 8].

Acinetobacter baumannii

The American Society for Infectious Diseases considers *Acinetobacter spp.* as one of the six most important species of multi-resistant microorganisms in the world. It is an aerobic Gram-negative bacillus, which is normally present in soil and water. Has a coccobacillary appearance, is oxidase negative and catalase positive and non-fermenting. It is capable of colonizing skin, mucous membranes, blood, sputum, pleural fluid, urine, and secretions from use of invasive devices in the hospital setting. It survives on animate and inanimate objects. In the hospital environment it has been isolated in humidifiers, fans, the skin of health personnel, mattresses, cushions and other equipment. Survival on dry surfaces greater than 25 days has been reported, which is why it is related to intrahospital outbreaks. In hospitals, *A. baumannii* causes bacteremia, meningitis, pneumonia, urinary tract infections, infections caused by the use of intravascular catheters, abdominal abscesses, and surgical wounds. [2, 7-10]

Pseudomonas aeruginosa

Gram-negative, oxidase-positive, aerobic bacterium with fibrins on the cell surface which facilitate adherence to the epithelial cells of the host. The natural habitat is water, soil, animals and minimal amounts as normal intestinal microflora and human skin. This pathogen is widely distributed causing diseases in human and in some animals, plants and insects. *Pseudomonas aeruginosa* is a microorganism responsible for causing a wide variety of infectious diseases both in the community and hospital settings, especially in patients with a weakened immune system [11].

Nosocomial infections include pneumonia, urinary tract infections, bacteremia, surgical wound and skin infections in burn patients. It is pathogenic when it is introduced into regions devoid of defenses such as

injured by direct tissue damage; use of intravenous or urinary catheters; or when there is neutropenia. Bacteria attach to and colonize mucous membranes or skin, invade locally, and cause systemic disease [2, 7, 8, 11].

Stenotrophomonas maltophilia

It is a non-fermenting, aerobic, Gram-negative bacillus with oxidative metabolism, with a characteristic ammonia odor and generally lives in water. It is currently considered an opportunistic nosocomial pathogen of clinical emergency. *Stenotrophomonas. maltophilia* was isolated at the hospital level from different objects such as blood pressure measuring equipment, blood sample collection tubes, dialysis machines, inhalation therapy equipment, and nebulizers. It is isolated from many anatomical sites, including respiratory tract secretions, urine, skin wounds, and blood [12]

It is manifested by pneumonia, bacteremia, endocarditis and meningitis. The colonization and infection caused by this pathogen, mainly in immunosuppressed patients, is related to both intrinsic factors (hematological diseases, chronic pathologies, cystic fibrosis, cancer or neutropenia) and extrinsic factors (venous catheters, ICU stay and prolonged hospitalization). In the last 10 years, the presence of *S. maltophilia* has been found more frequently in the lungs of patients with cystic fibrosis [2, 7, 8, 12].

Gram positive cocci

Coagulase-negative Staphylococcus such as *Staphylococcus epidermidis* and the other species are normal commensals of the skin, anterior nasal passages, and external auditory canal of humans. These isolated microorganisms are the most frequent in the clinical laboratory. Microorganisms can contaminate prosthetic devices during implantation, seed them during a subsequent bout of bacteremia, or gain access to shunt lumens and catheters when devices are temporarily disconnected or handled [12, 13].

Staphylococcus aureus is a Gram-positive cocci of regular size, and they clump together in clusters. The typical human habitat of *S. aureus* is the anterior portion of the nostrils. About 30% of people carry the organism at that site at any given time. Community outbreaks are often the result of poor hygiene and fomite transmission between individuals [13].

Hospital outbreaks caused by a single strain of *S. aureus* often affect patients who have undergone surgical or invasive procedures of other kinds. The source of the outbreak may be a patient experiencing an overt or inapparent staphylococcal infection (ulcers) that spreads directly to other patients via the hands of hospital staff. Another source of infection may be a nasal or perineal carrier from medical or nursing staff. [12-14]

Streptococcus viridians are normal inhabitants of the oral, respiratory, gastrointestinal, and urogenital mucosa. Clinical infections by *Streptococcus viridians* occur, mostly, after a lesion in the areas of its normal habitat. [13]

Enterococcus faecalis

They are part of the normal flora of the human gastrointestinal tract and urogenital tract. They can also be found in soil, food, water, plants, animals, birds, and insects. *E. faecalis* with *E. faecium* are the dominant species in the human gastrointestinal tract [12, 13].

The study of the opportunistic and habitual bacterial components is of great importance because hospitalized patients, are colonized or carry germs resistant to several antibiotics, present a greater risk of developing infection from their own flora. These patients also carry these resistant bacteria into the hospital, which can be tranmitted to other patients by the hands of health personnel, instruments or other fomites [12, 13].

Fungus

Candida

It is a unicellular, globose, oval or elongated microorganism, measuring 3 to 7(micrometer in diameter) and reproduces by multipolar budding, giving rise to daughter cells called blastoconidia or blastospores. Under suitable conditions it produces pseudomycelium, does not have capsules, does not produce carotenoid pigment and does not assimilate inositol. [15]

They are yeasts of the genus *Candida* that are part of the normal microbiota of the skin and mucous membranes (mouth, vagina, upper respiratory tract, gastrointestinal tract) of mammals. This genus includes approximately 150 identified species. The main agent is *C. albicans*, other species may be involved such as: *C. tropicalis, C. famata, C. krusei, C. lusitaniae, C. parapsilosis, C. dubliniensis, C. pseudotropicalis, C. zeylanoides and C. guilliermondii* [16, 17].

Candida species are the most frequently isolated fungal pathogens in opportunistic infections and can cause a variety of localized or generalized clinical manifestations. Currently, *Candida* infections are an important cause of healthcare-associated infection, due to advances in medical techniques and the increase in pediatric patients at risk of acquiring invasive fungal infections [18, 19].

Predisposing factors

The risk factors that have been reported in cases of infection/colonization by enterobacteria resistant to carbapenems are mainly: contact with cases infected/colonized by these germs, comorbidities (immunosuppression, advanced age, end-stage renal disease), stay in the intensive care unit, or undergone invasive and/or surgical procedures. Another factor described is the previous use of antimicrobials; have been reported with the use of broad-spectrum antibiotics such as carbapenems, quinolones, and antipseudomonal penicillins, as well as a prolonged duration of these treatments. [3]

In fungi, the triggering factors for the disease are generally modifications in the host's defense mechanisms, which, secondarily, induce changes in the behavior of the fungus. The clinical manifestations and severity of the infection are related to the nature and degree of compromise of the host's normal defenses [20, 21].

The predisposing causes can be grouped into: Local: maceration, contact with water, poor hygiene. Physiological: pregnancy, extreme ages. Endocrine: diabetes mellitus, hypothyroidism and other endocrinopathies. Alteration of the normal flora: due to the use of antibiotics. Hematological diseases: lymphomas, leukemias, aplastic anemia, neutropenia, hypo and aganmaglobulinemia, agranulocytosis. Iatrogenic factors: prolonged use of corticosteroids, chemotherapy, immunosuppressants, cytotoxic agents, parenteral nutrition, transplants, abdominal surgery, use of probes and catheters, radiotherapy, prostheses, hemodialysis. Debilitating diseases: neoplasms, AIDS, starvation, severe and extensive burns, drug addiction, tuberculosis and other infectious diseases [20, 21].

Antimicrobial resistance

Antimicrobial resistance, is a transformation of the bacteria, which became no longer being destroyed by antibiotics, which at first presented sensitivity. Because the bacteria mutate or acquire resistance genes. Microorganisms (bacteria, viruses, parasites, fungi) have the ability to counteract or resist the functionalities of antimicrobials (antibiotics, antiparasitics, antivirals and antifungals). Resistance can be natural or acquired. The natural or intrinsic is a specific property of each of the microorganisms, which appears before the use of antimicrobial, and acquired resistance appears after being exposed to antimicrobials [2].

The resistance of Gram-negative bacteria occurs through genetic changes basically expressed by mechanisms of beta-lactamase enzymes and modifying enzymes, which facilitate the degradation of antibacterials. The biggest problem attributed to microbial resistance is due to the misuse and excessive use of antibiotics in humans and animals [2].

Resistance types

Multidrug resistance: It is called multidrug resistance (MDR), when a bacteria presents resistance to more than one antibiotic, a microorganism can have several resistance genes, each of which provides resistance only to a specific antibacterial from at least three families of antimicrobials. Non-sensitivity genes are found on small pieces of DNA called plasmids that can spread between bacteria [22]. Gram-negative bacteria with MDR include *A. baumannii*, *P. aeruginosa*, and enterobacteria such as *K. pneumoniae* and ESBL-producing *E. coli* [23, 24].

Extensively drug-resistance (XDR) is a term applied especially to clinically relevant bacterial species. That resistance that presents to at least one drug of all the antimicrobial families used in the treatment of bacterial infections, with the exception of one or two. Here are found *P. aeruginosa* and *Acinetobacter spp.* [22, 24].

Pandrug-resistance: The term "pan" is a Greek prefix called as "everything", therefore it is defined as resistance to all approved antimicrobials, in other words it means that up to now there is no antibiotic capable of treating infections caused by by these microbial agents. Grouping resistance genes into integrons, transposons and plasmids facilitates multiresistance for bacteria, since the accumulation of two or three multiresistant plasmids and a couple of chromosomal alterations is enough to generate pandrug resistance (PDR). Outstanding microorganisms are *Acinetobacter spp, P. aeruginosa*, and *K. pneumoniae* [22, 24-26].

Another aspect to take into account is the role of intestinal colonization in the subsequent development of infections. These colonized patients show a high risk of developing infections caused by resistant strains and increased morbidity and mortality when infected, especially in the context of inappropriate empirical antibiotic regimens [1, 4, 27, 28].

Conclusion

Our society is gradually approaching a time of great epidemics with no available treatment. The indiscriminate use of antibiotics exhausts the therapeutic options. It is our premise not only to research and create new medicines but to wisely use the ones we already have. Microorganisms were there before humanity and even today new species continue to emerge with more force. Preparing future generations of healthcare workers to deal with these diseases must be a priority.

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