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Review Article

# Microbial Resistance: Mechanisms, Impacts, and Challenges for the Treatment of Bacterial and Fungal Infections

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## Abstract

This review addresses the growing threat of antimicrobial resistance, focusing on pathogenic bacteria such as *Staphylococcus aureus* and *Escherichia coli*, and fungi like *Candida* spp. Initially, various mechanisms of bacterial resistance are discussed, including antibiotic target modification and horizontal gene transfer. Both intrinsic and acquired resistance are explored, highlighting how these microorganisms adapt and survive antimicrobial treatment. Additionally, the challenges faced in the treatment of fungal infections, such as resistance to azoles and echinocandins among *Candida* species, are addressed. The review also discusses the importance of discovering new antifungal agents and strategies to overcome emerging resistance. It concludes that antimicrobial resistance remains a significant threat to global health, requiring innovative and coordinated approaches to tackle this growing problem.

***Keywords:** Resistance mechanisms, Antibiotics, Nosocomial infections, Candida spp., Staphylococcus aureus, Escherichia coli.*

## 1. Introduction

Microbial resistance is one of the major public health threats of the 21st century. This phenomenon occurs when certain types of microorganisms, such as bacteria and fungi, develop the ability to resist the action of drugs that were previously effective, thereby facilitating the survival and proliferation of pathogenic strains [1]. This resistance capability is often acquired through genetic mutations or the horizontal transfer of resistance genes between different species of microorganisms.

The inappropriate and excessive use of antibiotics and antifungals is one of the main factors contributing to the emergence and spread of microbial resistance. The indiscriminate use of antibiotics promotes a favorable environment for the selection of potentially resistant microorganisms. Additionally, various factors contribute to the development of resistance, such as lack of adherence to medical guidelines, premature discontinuation of treatment, incorrect dosage, and self-medication. All these conditions favor the increase of microbial resistance, causing a public health problem as they hinder the treatment of infectious diseases [2].

The impacts of microbial resistance are broad and concerning. From a clinical perspective, resistance makes the treatment of infections more difficult, as it prolongs patient hospitalization, increases healthcare costs, and raises mortality rates due to infections by resistant strains [3]. Moreover, it also threatens the advances of modern medicine, as common clinical procedures depend on the effectiveness of antimicrobials to prevent nosocomial infections.

Among the microorganisms causing nosocomial infections with a high propensity to develop resistance are pathogenic bacteria such as *Staphylococcus aureus* and *Escherichia coli* [4]. Regarding clinically relevant fungi, infections caused by yeast of the genus *Candida* are the most frequent in hospital settings and also show resistance to conventional antifungals [5].

In light of these assumptions, the objective of this review was to synthesize and analyze the current scientific literature on the mechanisms of microbial resistance, the economic and clinical impacts, and the main challenges faced in the treatment of bacterial and fungal infections, in order to provide a solid foundation for future research and alternative strategies.

## 2. Microbial Resistance

The discovery and introduction of antimicrobials in clinical practice represented one of the most important medical interventions in the history of global health, reducing human morbidity and mortality caused by infections. Today, antibiotics are essential for various hospital procedures, including the control of severe infections, recovery after invasive surgeries, organ transplants, treatment of cancer patients, and immunocompromised patients, among others [7, 8].

There are various chemical classes of antibiotics, and these can be grouped according to their biological target in the bacterial cell: cell wall synthesis inhibitors (Penicillins, Cephalosporins, and Polypeptides); protein synthesis inhibitors (Aminoglycosides, Pleuromutilins, Tetracyclines, Macrolides, Streptogramins, Oxazolidinones, and Glycylcyclines); plasma membrane disruptors (Lipopeptides); nucleic acid synthesis inhibitors (Rifamycins, Quinolones, and Fluoroquinolones); and competitive inhibitors of essential metabolite synthesis (Sulfonamides) [9].

Despite the vast arsenal of antibiotics available, cases of infections caused by multi-resistant microorganisms are increasing worldwide, and the spectrum of untreatable infections is becoming a reality. Many antimicrobials previously employed in controlling pathogenic microorganisms are declining in use and efficacy, increasing the risks of returning to the pre-antibiotic era [9, 10].

The World Health Organization [11] warns that antimicrobial resistance is rising to alarming levels in several countries around the world. The emergence of complex mechanisms and the rapid spread of pathogenic microorganisms pose a barrier to treating common microbial diseases, causing great concern for global health.

Many microorganisms can easily adapt to their environment, so exposure to antimicrobials results in a natural resistance process. Antibiotics, for example, effectively eliminate sensitive bacteria but simultaneously promote the survival of multi-resistant strains through a process of selective pressure, mainly caused by self-medication and indiscriminate use of these drugs [12].

Bacteria can be intrinsically resistant to antibiotics or acquire resistance mechanisms. In intrinsic resistance, the microorganism has morphological and enzymatic characteristics that naturally make it resistant to a particular antibiotic. In contrast, acquired resistance can be characterized by mutations in genes that reduce drug susceptibility or by horizontal gene transfer [13, 14].

Mutations occur randomly during DNA replication and arise when the antibiotic selects strains with growth advantages, resulting in the proliferation of a genetically resistant population. Although this resistance does not spread among bacteria, the dissemination of resistance can occur through the expansion of a bacterial clone or lineage [7].

However, horizontal gene transfer poses the risk of rapid dissemination of a single strain to a set of strains of the same or different species. The transfer of genetic material from a resistant donor to a susceptible recipient occurs through transformation (incorporation of DNA from the environment), transduction (phage-mediated genetic exchange), or conjugation (cell-to-cell contact) involving mobile genetic elements such as plasmids and transposons [7, 15].

Thus, bacteria can acquire or develop antibiotic resistance through various mechanisms falling into three main groups: first, those that minimize the intracellular concentrations of the antibiotic due to weak penetration into the bacterium or active efflux of the substance; second, those that modify the antibiotic target by genetic mutation or post-translational modification of the target; and third, those that inactivate the antibiotic by hydrolysis or enzymatic modification of active functional groups of the molecule [16, 17].

By employing these mechanisms, either isolated or combined, pathogenic strains have been able to overcome promising antibiotics from various chemical classes [18]. *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp. are just a few examples of bacteria that are resistant to multiple drugs [19, 20]. The Centers for Disease Control and Prevention have declared the rapid growth of antibiotic resistance as one of the main global concerns, estimating that more than 700,000 people die worldwide from diseases caused by resistant strains [7, 21].

The number of infections and deaths associated with pathogenic fungi is also alarming. It is estimated that up to 150 million people are infected annually by invasive fungi, with 1.5 million deaths resulting from these infections [22]. Among the most virulent fungal pathogens are *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp. [23]. *Candida* species are the most prevalent invasive fungal pathogens in humans, causing severe systemic infections in immunocompromised patients with mortality rates approaching 40% [24, 25].

Currently, the arsenal of antifungals available for clinical use in such infections consists of three main classes: polyenes, azoles, and echinocandins, which act by different mechanisms of action [22]. Polyenes act by forming complexes that extract ergosterol from the phospholipids of cell membranes; additionally, at high concentrations, they can inhibit chitin synthesis in the fungal cell wall [26]. Azoles inhibit enzymes involved in ergosterol biosynthesis, forming a modified cell membrane that does not perform essential functions for fungal development [27]. Echinocandins inhibit the enzyme β-1,3-glucan synthase, which catalyzes the polymerization of glucose-uridine diphosphate (UDP-glucose) into β-1,3-glucan. This mechanism causes the leakage of important components from the fungal cell due to the high osmotic pressure exerted on the weakened membrane [28].

Resistance to azoles among *Candida* and *Aspergillus* species is one of the major challenges for clinical treatment, followed by the multi-resistance of *Candida glabrata* and other *Candida* species to echinocandins. The resistance mechanisms against these drugs include modifications in drug-target interactions, reduced cellular concentrations of the drugs through efflux pump channels, and permeability barriers associated with biofilms [29, 30].

Despite the currently available treatment options, since fungi are eukaryotes like their human hosts, there is a limitation of targets that can be selectively inhibited with minimal toxicity to the host. Most antifungals used target the sterol ergosterol in the cell membrane, as well as its biosynthesis, or the cell wall-binding molecule 1,3-β-d-glucan. Resistance to the available classes of antifungals has emerged as a serious problem, with fungal infections becoming increasingly difficult to treat [31].

## 3. Pathogenic Bacteria

Nosocomial bacterial infections are frequent in healthcare services and are responsible for high mortality and morbidity rates among hospitalized patients worldwide [32]. Among the pathogens causing infections in hospital settings, the bacteria *Staphylococcus aureus* and *Escherichia coli* stand out, as they not only have a great capacity for adaptation but also show resistance to antimicrobial agents [33].

*Staphylococcus aureus* is a gram-positive bacterium of great clinical interest, responsible for causing severe superficial or invasive infections in humans, such as carbuncles, folliculitis, bacteremia, endocarditis, pneumonia, osteomyelitis, and biofilm formation on implanted surgical instruments [34-36]. In healthy individuals, *S. aureus* can be found in various anatomical sites, primarily on the skin, oropharynx, nasal passages, and intestinal microbiota [37].

The versatility of *S. aureus* is mainly due to its various virulence factors, many of which are genetically coded and transferred within the species, facilitating adherence, colonization, cellular interactions, evasion of host defense systems, and tissue damage [38, 39]. The virulence factors can be grouped into three types:

a) Factors related to cellular adhesion or extracellular matrix, through the synthesis of fibrinogen, fibronectin, collagen, or the enzyme coagulase.

b) Factors related to immune evasion, through the production of important enterotoxins, which can cause toxic shock, and the production of biomolecules such as protein A, lipases, and encapsulated polysaccharides; and

c) factors related to invasion of the host cell and penetration into tissues or adhesion to implanted surgical instruments, which include α, β, δ, γ, and δ-hemolysin proteins (toxins) [40].

The species can present intrinsic or acquired resistance, with the acquisition of the mecA gene being of great clinical importance as it confers resistance to methicillin and beta-lactams [37]. The emergence and spread of methicillin-resistant *S.* aureus (MRSA) strains have increased nosocomial infection rates, causing great concern in the hospital community. MRSA is the leading cause of skin and soft tissue infections in North America, with the USA 300 clone responsible for 98% of these infections [41].

Among Gram-negative bacteria, *Escherichia coli* is of medical importance due to its virulence and pathogenicity, being the etiological agent of various diseases, such as diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome. It is found as a commensal in the gastrointestinal tract of animals and humans, specifically in the large intestine, and is expelled from the body through feces. Its dissemination and survival depend on ideal conditions of temperature, water and nutrient availability, competition with other microorganisms, and biofilm formation [42].

Pathogenic strains of *E. coli* are classified into different pathotypes, each causing a specific type of disease: enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC) [43, 44]. The intestinal pathotypes of *E. coli* are responsible for intestinal disorders ranging from mild diarrhea to severe colitis, while the extraintestinal pathotypes are asymptomatic in the intestinal tract but can cause infections after migrating to other parts of the body, such as the circulatory system and the urinary tract [45].

*Escherichia coli* is the pathogen responsible for more than 80% of urinary tract infections. Women are generally more affected due to anatomical characteristics (proximity of the urethra and anus) and physiological factors (absence of an antimicrobial mechanism, such as prostatic fluid in men). Additionally, various virulence factors and antigens that facilitate the dissemination and adherence of this bacterium to the urinary epithelium contribute to the effectiveness of the infection [46].

Intrinsically, *E. coli* is susceptible to almost all clinically relevant antimicrobials, but this species has a great capacity to accumulate resistance genes, especially through horizontal gene transfer. The most evident mechanisms in *E. coli* include the acquisition of genes encoding extended-spectrum beta-lactamases (conferring resistance to cephalosporins), carbapenemases (resistance to carbapenems), 16S rRNA methylases (pan-resistance to aminoglycosides), plasmid-mediated PMQR genes (resistance to quinolones and fluoroquinolones), and mcr genes (resistance to polymyxins). In addition to multi-resistance plasmids, other mobile genetic elements, such as transposons and gene cassettes in class 1 and 2 integrons, also play an important role in the dissemination of resistance genes in *E. coli* [47].

## 4. Pathogenic Fungi

Among medically important fungi, representatives of the genus *Candida* are associated with the most common fungal infections in humans [48]. These yeasts are part of the human microbiota from birth, without causing clinical symptoms in healthy hosts. However, the compromise of the host's immune response, among other factors, can lead to the emergence of superficial opportunistic infections such as vulvovaginal candidiasis, candiduria, onychomycosis, and oropharyngeal candidiasis, and in more severe cases, invasive systemic candidiasis, such as candidemia and organ infections, especially in the brain, kidneys, and eyes [49, 50].

*Candida* spp. exhibit several virulence traits that facilitate adherence, infiltration, and dissemination in host tissues, with the main factors being morphogenic transition, biofilm formation on implanted medical devices, production and secretion of hydrolytic enzymes, expression of adhesin protein complexes, and invasion of epidermal and mucosal cells [50].

Among these virulence factors, the morphogenesis presented by some species of *Candida* is defined as a change from a unicellular yeast form to the projection of filamentous structures (hyphae and pseudohyphae). These morphological transitions are reversible and occur during growth in response to conditions of temperature, pH, serum, nutrient absence, and oxygen. The filamentous forms are well adapted for tissue penetration and damage, being an important factor for pathogenicity and infection efficiency [51, 52]. In cases of candidemia, the formation of hyphae and pseudohyphae allows the fungus to invade the bloodstream to disseminate and reach the host's internal organs [53].

Among the infections caused by representatives of the genus *Candida*, the species *C. albicans* is the most common fungal pathogen in clinical isolates. However, the emergence of non-albicans *Candida* species, such as *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. glabrata*, varies according to the affected anatomical site and geographic location [54]. Within the limited antifungal arsenal, azole compounds such as fluconazole are frequently used to treat Candida infections because they are low-cost, have moderate toxicity, and can be administered orally [55]. However, due to its only fungistatic effect, there are reports of acquired resistance development in yeasts against this antifungal due to selective pressure, and in the case of *C. krusei*, intrinsic resistance [56].

In this sense, identifying molecules with bioactive potential is of extreme necessity, as it can contribute to the formulation of new antifungal agents or assist in the use of combinations between the drug and bioactive molecules to restore the efficacy of these medications against resistant strains [57, 58].

## Conclusion

Analysis of resistance mechanisms revealed the diversity and adaptability of microorganisms, highlighting the urgent need for new approaches to combat this threat. The clinical and economic impacts are profound, resulting in less effective treatments, increased mortality, and overload on healthcare systems. Furthermore, challenges in treating bacterial and fungal infections are exacerbated by the global spread of resistant strains and a shortage of new antimicrobials.

To address these challenges, it is essential to adopt a multifaceted approach. This includes continued research and development of new medicines and alternative therapies, promoting the rational and controlled use of antimicrobials, and implementing rigorous infection control policy strategies. Public education and awareness about the importance of appropriate use of antimicrobials are also crucial. Furthermore, continued research and global surveillance are needed to monitor resistance and develop effective strategies to mitigate this problem.

## Conflict of Interest

The authors declare no conflict of interest.

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## References

1. Abdelaziz SM, Aboshanab KM, Yahia IS, Yassien MA, Hassouna NA. Correlation between the Antibiotic Resistance Genes and Susceptibility to Antibiotics among the Carbapenem-Resistant Gram-Negative Pathogens. *Antibiotics (Basel)* 2021, 10, 255. doi: 10.3390/antibiotics10030255.
2. Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial antibiotic resistance: The most critical pathogens. *Pathogens* 2021, 10, 1310. doi:10.3390/pathogens10101310
3. Garcia JVAS, Comarella L. O uso indiscriminado de antibióticos e as resistências bacterianas. *Saúde e Desenvolvimento* 2021, 10, 78-87.
4. Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, Vila J. The global threat of antimicrobial resistance: science for intervention. *New microbes and new infections* 2015, 6, 22-9. doi: 10.1016/j.nmni.2015.02.007.
5. Mitik-Dineva N, Wang J, Truong VK, Stoddart P, Malherbe F, Crawford RJ, Ivanova EP. *Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus* attachment patterns on glass surfaces with nanoscale roughness. *Current microbiology* 2009, 58, 268-273. doi: 10.1007/s00284-008-9320-8.
6. Durão P, Balbontín R, Gordo I. Evolutionary Mechanisms Shaping the Maintenance of Antibiotic Resistance. *Trends Microbiol* 2018, 26, 677-691. doi: 10.1016/j.tim.2018.01.005.

7. Khan A, Miller WR, Arias CA. Mechanisms of antimicrobial resistance among hospital-associated pathogens. *Expert review of anti-infective therapy,* 2018, 16, 269-287. doi: 10.1080/14787210.2018.

8. Tortora GJ, Funke BR, Case CL. Microbiologia. Porto Alegre: Artemed 12 ed., 2017.

9. Dias M, Monteiro MS, Menezes MF. Antibióticos e resistência bacteriana, velhas questões, novos desafios. *Cadernos Otorrinolaringologia, clínica, investigação e inovação* 2010.

10. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology* 2015, 13, 42-51. doi: 10.1038/nrmicro3380.

11. WHO – World Health Organization. Antibiotic resistance. WHO Library Cataloguing-in-Publication, 2017.

12. Queiroz NSDA. resistência bacteriana no contexto da infecção hospitalar. *Texto e Contexto Enfermagem* 2004, 13. doi: 10.1590/S0104-07072004000500007

13. Džidić S, Šušković J, Kos B. Antibiotic resistance mechanisms in bacteria: biochemical and genetic aspects. *Food Technology & Biotechnology* 2008, 46.

14. Munita JM, Arias CA. Mechanisms of antibiotic resistance. *Microbiology spectrum* 2016, 4. doi: 10.1128/microbiolspec.VMBF-0016-2015.

15. Thomas CM, Nielsen KM. Mechanisms of, and barriers to, horizontal gene transfer between bacteria. *Nature reviews microbiology* 2005, 3, 711-721. doi: 10.1038/nrmicro1234

16. Poole K. Mechanisms of bacterial biocide and antibiotic resistance. *Journal of Applied Microbiology* 2002, 92. doi: 10.1046/j.1365-2672.92.5s1.8.x

17. Kumar S, Mukherjee MM, Varela MF. Modulation of bacterial multidrug resistance efflux pumps of the major facilitator superfamily. *International journal of bacteriology* 2013, 2013. doi: 10.1155/2013/204141

18. Silveira GP, Nome F, Gesser JC, Sá MM, Terenzi H. Estratégias utilizadas no combate a resistência bacteriana. *Química Nova* 2006, 29, 844.

19. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection* 2012, 18, 268-81. doi: 10.1111/j.1469-0691.2011.03570.x.

20. Saha M, Sarkar A. Review on Multiple Facets of Drug Resistance: A Rising Challenge in the 21st Century. *Journal of Xenobiotics* 2021, 11, 197-214. doi: 10.3390/jox11040013

21. Kadri SS. Key takeaways from the US CDC's 2019 antibiotic resistance threats report for frontline providers. *Critical care medicine* 2020.

22. Ben-Ami R, Kontoyiannis DP. Resistance to Antifungal Drugs. *Infectious Disease Clinics* 2021, 35, 279-311. doi: 10.1016/j.idc.2021.03.003.

23. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. *Journal of fungi (Basel)* 2017, 3, 57. doi: 10.3390/jof3040057.

24. Pfaller MA, Diekema DJ. Epidemiology of invasive mycoses in North America. *Critical reviews in microbiology* 2010, 36, 1-53. doi: 10.3109/10408410903241444. PMID: 20088682.

25. Shapiro RS, Robbins N, Cowen LE. Regulatory circuitry governing fungal development, drug resistance, and disease. *Microbiology and molecular biology reviews* 2011, 75, 213-67. doi: 10.1128/MMBR.00045-10.

26. Anderson TM, Clay MC, Cioffi AG, Diaz KA, Hisao GS, Tuttle MD, Nieuwkoop AJ, Comellas G, Maryum N, Wang S, Uno BE, Wildeman EL, Gonen T, Rienstra CM, Burke MD. Amphotericin forms an extramembranous and fungicidal sterol sponge. *Nature chemical biology* 2014, 10, 400-6. doi: 10.1038/nchembio.1496.

27. Berto C, Wirth F, Barth N, Hermes DM. Bases da resistência antifúngica: uma revisão comentada. *Revista Uningá* 2018, 55, 52-71. doi: 10.46311/2318-0579.55.eUJ773

28. Zaas AK. Echinocandins: a wealth of choice--how clinically different are they? *Current Opinion in Infectious Diseases* 2008, 21, 426-32. doi: 10.1097/QCO.0b013e328307c79c.

29. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *The Lancet infectious diseases* 2017, 17, e383-e392. doi: 10.1016/S1473-3099(17) 30316-X.

30. Revie NM, Iyer KR, Robbins N, Cowen LE. Antifungal drug resistance: evolution, mechanisms and impact. *Current opinion in microbiology* 2018, 45, 70-76. doi: 10.1016/j.mib.2018.02.005.

31. Xie JL, Polvi EJ, Shekhar-Guturja T, Cowen LE. Elucidating drug resistance in human fungal pathogens. *Future microbiology* 2014, 9, 523-42. doi: 10.2217/fmb.14.18.

32. Upreti N, Rayamajhee B, Sherchan SP, Choudhari MK, Banjara MR. Prevalence of methicillin resistant Staphylococcus aureus, multidrug resistant and extended spectrum β-lactamase producing gram negative bacilli causing wound infections at a tertiary care hospital of Nepal. *Antimicrobial Resistance & Infection Control* 2018, 8, 7:121. doi: 10.1186/ s13756-018-0408-z.

33. Poolman JT, Anderson AS. Escherichia coli and Staphylococcus aureus: leading bacterial pathogens of healthcare associated infections and bacteremia in older-age populations. *Expert Review of Vaccines* 2018, 17, 607-618. doi: 10.1080/14760584.2018.1488590.

34. Cavalcanti SM, França ER, Cabral C, Vilela MA, Montenegro F, Menezes D, Medeiros AC. Prevalence of Staphylococcus aureus introduced into intensive care units of a University Hospital. *Brazilian Journal of Infectious Diseases* 2005, 9, 56-63. doi: 10.1590/s1413-86702005000100010.

35. Foster TJ, Geoghegan JA, Ganesh VK, Höök M. Adhesion, invasion and evasion: the many functions of the surface proteins of Staphylococcus aureus. *Nature Reviews Microbiology* 2014, 12, 49-62. doi: 10.1038/nrmicro3161.

36. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clinical microbiology reviews* 2015, 28, 603-61. doi: 10.1128/ CMR.00134-14.

37. Benito D, Lozano C, Gómez-Sanz E, Zarazaga M, Torres C. Detection of methicillin-susceptible Staphylococcus aureus ST398 and ST133 strains in gut microbiota of healthy humans in Spain. *Microbiology ecology* 2013, 66, 105-11. doi: 10.1007/s00248-013-0240-1.

38. Holden MT, Feil EJ, Lindsay JA, Peacock SJ, Day NP, Enright MC, Foster TJ, Moore CE, Hurst L, Atkin R, Barron A, Bason N, Bentley SD, Chillingworth C, Chillingworth T, Churcher C, Clark L, Corton C, Cronin A, Doggett J, Dowd L, Feltwell T, Hance Z, Harris B, Hauser H, Holroyd S, Jagels K, James KD, Lennard N, Line A, Mayes R, Moule S, Mungall K, Ormond D, Quail MA, Rabbinowitsch E, Rutherford K, Sanders M, Sharp S, Simmonds M, Stevens K, Whitehead S, Barrell BG, Spratt BG, Parkhill J. Complete genomes of two clinical Staphylococcus aureus strains: evidence for the rapid evolution of virulence and drug resistance. *Proceedings of the National Academy of Sciences of the United States of America* 2004, 101, 9786-91. doi: 10.1073/pnas.0402521101.

39. Otto M. Staphylococcus aureus toxins. *Current opinion in microbiology* 2014, 17, 32-7. doi: 10.1016/ j.mib.2013.11.004.

40. Jarraud S, Peyrat MA, Lim A, Tristan A, Bes M, Mougel C, Etienne J, Vandenesch F, Bonneville M, Lina G. egc, a highly prevalent operon of enterotoxin gene, forms a putative nursery of superantigens in Staphylococcus aureus. *The Journal of Immunology* 2001, 166, 669-77. doi: 10.4049/jimmunol.166.1.669.

41. Thurlow LR, Joshi GS, Richardson AR. Virulence strategies of the dominant USA300 lineage of community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). *Immunol Med Microbiol* 2012, 65, 5-22. doi: 10.1111/j.1574 -695X.2012.00937.x.

42. Jang J, Hur HG, Sadowsky MJ, Byappanahalli MN, Yan T, Ishii S. Environmental Escherichia coli: ecology and public health implications-a review. Journal of Applied Microbiology 2017, 123, 570-581. doi: 10.1111/jam.13468.

43. Kaper JB, Nataro JP, Mobley HL. Pathogenic Escherichia coli. *Nature reviews microbiology* 2004, 2, 123-40. doi: 10.1038/nrmicro818.

44. Silveira L, Marques A. Machado J. Patotipos de Escherichia coli associados a infecções entéricas entre 2002 e 2012. *Boletim Epidemiológico do Instituto Nacional de Saúde* 2013, 1, 1–4.

45. Köhler CD, Dobrindt U. What defines extraintestinal pathogenic Escherichia coli? *International Journal of Medical Microbiology* 2011, 301, 642-7. doi: 10.1016/j.ijmm.2011.09.006.

46. Lopes PM, Queiroz TFF, Rodrigues FC, Castro ASB. Análise da freqüência e do perfil de sensibilidade da Escherichia coli como agente causador de infecções do trato urinário na microrregião de viçosa, mg. *Anais Simpac* 2015, 2.

47. Poirel L, Madec JY, Lupo A, Schink AK, Kieffer N, Nordmann P, Schwarz S. Antimicrobial Resistance in Escherichia coli. *Microbiology Spectrum* 2018, 6. doi: 10.1128/microbiolspec.ARBA-0026-2017.

48. Kołaczkowska A, Kołaczkowski M. Drug resistance mechanisms and their regulation in non-albicans Candida species. *Journal of Antimicrobial Chemotherapy* 2016, 71, 1438-50. doi: 10.1093/jac/dkv445.

49. Tong Y, Tang J. Candida albicans infection and intestinal immunity. *Microbiological research* 2017, 198, 27-35. doi: 10.1016/j.micres.2017.02.002.

50. Ahmad Khan MS, Alshehrei F, Al-Ghamdi SB, Bamaga MA, Al-Thubiani AS, Alam MZ. Virulence and biofilms as promising targets in developing antipathogenic drugs against candidiasis. *Future science* 2020, 6, FSO440. doi: 10.2144/fsoa-2019-0027.

51. Braun BR, Kadosh D, Johnson AD. NRG1, a repressor of filamentous growth in C.albicans, is down-regulated during filament induction. *The EMBO journal* 2001, 20, 4753-61. doi: 10.1093/emboj/20.17.4753.

52. Vila T, Romo JA, Pierce CG, McHardy SF, Saville SP, Lopez-Ribot JL. Targeting Candida albicans filamentation for antifungal drug development. *Virulence* 2017, 8, 150-158. doi: 10.1080/21505594.2016.1197444.

53. Kornitzer D. Regulation of Candida albicans Hyphal Morphogenesis by Endogenous Signals. *Journal of Fungi (Basel)* 2019, 5, 21. doi: 10.3390/jof5010021.

54. Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiological trends. *Clinical Infectious Diseases* 2006, 43, S3-S14. doi: 10.1086/504490

55. Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Azole Antifungal Resistance in Candida albicans and Emerging Non-albicans Candida Species. *Frontiers in microbiology* 2017, 7, 2173. doi: 10.3389/fmicb.2016.02173.

56. Berkow EL, Lockhart SR. Fluconazole resistance in Candida species: a current perspective. Infection and drug resistance 2017, 10, 237-245. doi: 10.2147/IDR.S118892.

57. Braga AL, Cruz RP, Carneiro JNP, Santos ATL, Sales DL, Bezerra CF, Morais-Braga MFB. Piper regnellii (Miq.) C. DC.: Chemical composition, antimicrobial effects, and modulation of antimicrobial resistance. *South African Journal of Botany* 2021, 142, 495-501. doi: 10.1016/j.sajb.2021.07.017

58. Rodrigues FC, Santos ATL, Cruz RP, Almeida-Bezerra JW, Coutinho HDM, Ribeiro PRV, Oliveira AFM. Antimicrobial activity, modulatory effect and phytochemical analysis of Sida galheirensis Ulbr.(Malvaceae). *South African Journal of Botany* 2022, 147, 286-293. doi: 10.1016/j.sajb.2022.01.021


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