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Research Article

Study The Bacterial Resistance of Antibiotic From Opportunistic Bacteria

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ABSTRACT

Globally, antibiotic resistance results in considerable morbidity and mortality. The introduction of antibiotics in the 1900s led to the belief that humans had triumphed over microorganisms. Bacteria's ability to develop antibiotic resistance was swiftly recognized. Antimicrobial resistance seems to be prevalent in the majority of harmful microorganisms. The main mechanisms of resistance include restricting drug absorption, altering a drug target, inactivating a drug, and active efflux. These mechanisms may be intrinsic or obtained from other microorganisms. Comprehending these systems will improve the treatment of infectious diseases and facilitate the development of antimicrobial agents capable of withstanding microbial resistance.

1. INTRODUCTION

'Opportunistic infections' what' are they? Opportunistic infections are highly contagious and often worsen over time. Microorganisms, normally incapable of causing disease, become capable of doing so due to the predisposing effects of other diseases or their treatments. When an organism causes an opportunistic infection, even in the absence of predisposing variables, the infection becomes more severe than it would be in the absence of these factors. Predisposing variables not only weaken the patient's resistance to the infection, but also facilitate its growth and progression to an unprecedented level, resulting in a swift, hematogenous spread of the illness. The term "opportunistic infection" can only be useful if used to describe illnesses that meet the criteria laid forth in the above description. An opportunistic infection is caused by a weakly pathogenic organism that can only spread to a lot of people when the patient's defenses are weak or when other diseases or their treatment expose them to tissues that can't fight off the threat properly.

1.1. Opportunistic Bacteria

This term effectively describes a variety of infectious complications, including carbuncles in diabetic patients, bronchopneumonia caused by pneumococcal or streptococcal bacteria in children or adults with influenza, tuberculosis recurrence in starving people, cryptococcosis in sarcoidosis or Hodgkin's disease, thrush in marasmic babies, and uremia in elderly men with prostate enlargement.

The first reference to diseases or microorganisms as opportunistic occurred about a decade earlier. In 1954, Seeliger addressed pulmonary mycoses.,[1] He noted that most of the fungi responsible for these infections are opportunists that only reveal their destructive effects after disrupting the host's biological homeostasis.

Utz (1962) [2] teleology suggests that microorganisms are capable of opportunistic, as has been pointed out. However, the phrase "opportunistic infection" is both descriptive and fitting, and the fact that it is unique may help bring more attention to these infections that cause complications.

'Opportunistic infections' are significant for two reasons: (1) Rather of making things worse, therapeutic interventions usually make them better. (2) Death is caused or hastened by them often. Opportunistic infections often strike terminally sick people. However, it must be noted that not all patients who succumb to opportunistic infections would have passed away from the underlying condition that made them susceptible to the infection or necessitated the treatment that ultimately proved fatal

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- The identification of opportunistic infections often transpires after mortem in a significant number of instances. At this point, a comprehensive diagnosis is unattainable, since it requires the isolation of the causal organism. The inadequate clinical knowledge of the incidence and symptoms of these illnesses significantly contributes to this poor condition. Early identification is essential for a viable opportunity to effectively treat these illnesses, since very few infections in these situations have a distinctly established therapy. [2]
- Under What Conditions Do 'Opportunistic Infections' Arise?
  1. Opportunistic infections occur as consequences of other illnesses or medical treatments. Pharmacological interventions or other modalities that predispose individuals to these infections increase the risk. Let us quickly examine these etiological aspects. [2]
  2. Diseases are factors that predispose to opportunistic infections: Individuals with severe diseases are at an increased risk of acquiring infections from prevalent pathogens such as pneumococcus, Staphylococcus aureus, and Candida albicans. Suppurative bronchopneumonia and oral candidiasis are two prominent instances. These disorders are not classified as 'opportunistic infections' since the organisms involved are naturally existing pathogens that generally induce such illnesses. In contrast, organisms with little or absent innate pathogenic ability induce 'opportunistic infections,' which mostly occur as consequences from disorders that particularly impair the body's defenses against microbial invasion. Severe hematological disorders, including agranulocytosis and leukemia, as well as systemic illnesses of the lymphoreticular system, such as Hodgkin's lymphoma, exemplify opportunistic infections. Diseases that disrupt the body's metabolic balance facilitate the proliferation, invasion, and establishment of infections by organisms, hence predisposing individuals to opportunistic infections. Examples include severe and inadequately managed diabetic mellitus, renal failure, and hyperemesis. [2]
  3. Therapeutic measures are factors that predispose to 'opportunistic infections'**:** Both pharmacological agents and radiation may have this effect. "Opportunistic infections" explicitly denote the use of any therapeutic modality that may disrupt the immune defenses against infection or promote the entry of bacteria into tissues. Therapeutic interventions, especially pharmaceuticals, are more often the primary causes of these consequences than the disorders that serve as alternative etiological variables.

Medications that increase susceptibility to infections by diminishing resistance include corticotrophin, corticosteroids, cytotoxic agents, and antibiotics, especially broad-spectrum antibiotics. The impact of medications on the body's capacity to fight infections remains ambiguous. A obvious example is that cytotoxic medications may reduce the production of granulocytes. Corticosteroid action may hinder antibody synthesis or function, possibly leading to inadequate resistance in individuals undergoing treatment with these hormones. Historically, some have overstated the influence of antibacterial drugs in facilitating infections by resistant organisms; however, their contribution to the proliferation of Candida albicans in the large intestine and other sites is indisputable. The eradication of bacteria that typically inhibit fungal proliferation significantly enhances the fungus's likelihood of invading skin lesions and then disseminating to surrounding tissues.

1.2. The combined or cumulative effect of illness and its treatment on the emergence of 'opportunistic infections' is a crucial subject:

It seems that the likelihood of developing these consequences is greatly increased when medical treatments for diseases that are prone to 'opportunistic infections' are also prone to them. The danger of tissue invasion is already high before procedures like surgery, lumbar puncture, or intravenous infusion. Clinical monitoring is required in all patients due to the substantial danger posed by the cumulative impact of these several predisposing variables.

1.3. aim of this study:

Stopping people from utilizing awareness-raising to induce others is the goal. Our fast-acting medications and treatments cure the severe diseases. Failure to diagnose such an ailment early is inexcusable. If a patient can avoid or treat their ailment, they may heal faster, with fewer side effects, and more efficiently.

2. CHAPTER ONE

2.1 Literature review:

If you have a serious infection that usually gets worse over time, it's probably an opportunistic infection. This is because it's caused by a microbe that normally doesn't cause illness but can do so because of another disease or its treatment. Infections caused by bacteria in food or drinkable water may show up for no clear reason. Many different types of pathogens, such as viruses, bacteria, fungi, and parasites, can cause opportunistic illnesses (OIs). The pathogens that cause OI can spread through the air, body fluids, and tainted food and drink sources, among other ways. People who have HIV can get infections like thrush, Salmonella illnesses, toxoplasmosis, and tuberculosis when the conditions are right.HIV virus weakens the immune system, which makes people more likely to get other illnesses. This makes people with HIV more likely to get sick and die around the world. Whole world.

Opportunistic infections, which are dangerous illnesses caused by germs that are usually harmless or only slightly harmful, are very important in modern medicine. These infections can happen because of health problems that make the body less able to fight off potential germs or because of bad effects from medicines and other treatments. Because they often happen as side effects of medical treatments, they are a common and serious threat that needs to be closely watched for in people who are getting corticosteroids, chemotherapy drugs, broad-spectrum antibiotics, or radiation. When someone has a long-term illness that makes them weak, like cancer, opportunistic diseases are often the direct cause of death. When figuring out how important they are in these situations, it's important to remember that they have partly replaced final bronchopneumonia as the last stage of the disease. Numerous cancer patients today live much longer than they did before modern advances in the treatment of neoplastic disorders. Additionally, the chance of uncomplicated pneumonia in these individuals has greatly decreased, as antibiotics can both prevent and treat the condition. Many of the bacteria that cause "opportunistic infections" are resistant to certain drugs or need to be treated with certain drugs, like the antifungal medicine amphotericin B. This can have serious side effects on people who are already very sick. There are times when it's hard to fight a "opportunistic infection."

2.2 Illustrative Cases With Different Types Of Opportunistic Bacteria.

Four case studies show "opportunistic infection" under unexpected conditions. Researchers found several predatory microorganisms. This section covers "opportunist" germ infections.

1. Case 1 : [3]
   A 1919-born guy was treated for Hodgkin's illness from 1951 to 1963 . Deep X-rays and cytotoxic medicines (mustine, tretamine, chlorambucil, thiotepa, cyclophosphamide) were utilized. I Streptomycin, isoniazid, and sodium amino salicylate effectively treated acute widespread tuberculous lymphadenitis with large nodal mycobacteriosis in July 1960. icin B cured cryptococcal meningitis in December 1960. cin B. He suffered acute 'blast cell' leukemia nine weeks before his death in April 1963, which methotrexate and dexamethasone cured. asone. Necropsy: Hodgkin's. 2'blast cell' leukemia. Pyimia and Staphylococcal pneumonia are infections. Severe oropharyngeal and cesophageal thrush, atheromatous aortic valve candida endocarditis, and septicimic candidosis with numerous visceral lesions are infections. Aspergillus infection of pulmonary infarct; septicimic aspergillosis with numerous visceral lesions(d) Lung phycomycetous infection with pulmonary and meningeal thromboangiitis and necrotizing encephalitis. f) Cryptococcal pneumonia. Pneumocystis. Cytomegalovirus infected lungs and bronchi. Created no cultures. The case details above show how the lesions and parasites in histological preparations differed, allowing us to identify the infections. No postmortem tuberculosis was found. The only plasma protein tests throughout the illness were quantitative assessments of total albumin and total globulin, which were normal (the latest was three months before death). [3]
   Hodgkin's disease predisposed each instance, mostly by happenstance. Researchers are interested in lymphoreticular tumors, thus the lab's "opportunistic infections" include several of them.
2. Case 2 :[4]
   After 21 years in California, a 24-year-old white student in England had Hodgkin's disease. The patient started mustiness after four months of failed X-ray therapy. He died of pneumonia six weeks later. Necropsy: Hodgkin's. Patient showed severe pneumonic and homogenous visceral coccidioidomycosis (Fig. 1). Comment: We only obtained the patient's 'geographical history' after his death. We discovered he had childhood coccidioidomycosis. The deadly pneumonia was initially identified by histological study of lung parts. Researchers traditionally considered yeast-like organisms discovered regularly in films and sputum cultures during terminal sickness saprophytes and did not research them. They may have been Coccidioides. Hodgkin's disease and X-rays and mustiness to treat it may have revived the latent Coccidioides infection. Coccidioidomycosis can cause progressive infection and homogenous dissemination, but this is rare. Most cases in endemic areas have only minor effects from the initial lung lesion. Acute bloodstream infection may occur with corticosteroid treatment [5] . A similar result was seen in histoplasmosis. [6] .

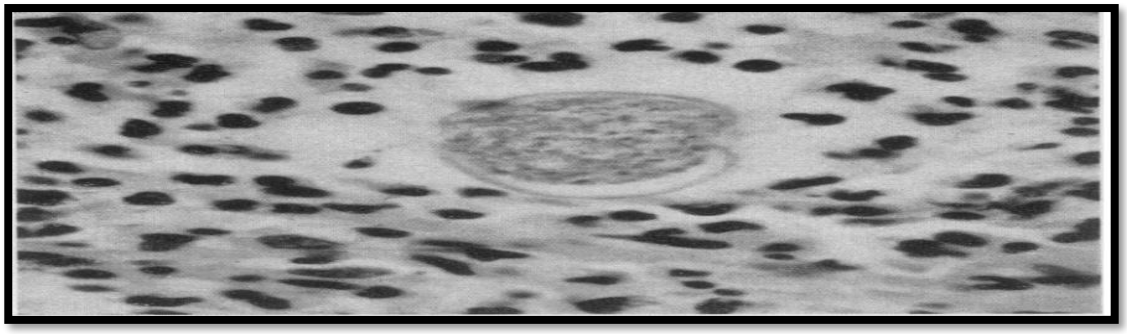

Fig .1. Case 2 Sporangium of Coccidioides immitis in pneumonic focus Hamatoxylin- eosin. x 600

3. Case 3: [7]
   A young woman who had just completed an intensive course of deep X-ray therapy for widespread and advanced Hodgkin's disease refused to stay in hospital but agreed to go to a convalescent home. For man She had been receiving large doses of mustine and chlorambucil in alternating courses for many months prior to the radiotherapy course. day of her admission to the convalescent home, there was an outbreak of food poisoning due to Salmonella Newport. Most of the patients and staff suffered a mild attack of enteritis and recovered quickly. The patient with Hodgkin's disease died eighteen hours after admission. Necropsy: (1) Hodgkin's disease. (2) Hea Salmonella Newport heavily colonized all organs and tissues (Fig. 2). We performed the necropsy within twenty-five minutes of the patient's death. : Presumably the combined effect of Hodgkin's disease and the measures used in its treatment left the patient defenseless against the salmonella. It would have been fascinating to know the white cell count and the plasma protein composition, but no data were available to the pathologist who carried out the post-mortem examination or have been obtainable from the hospital concerned.: [7]

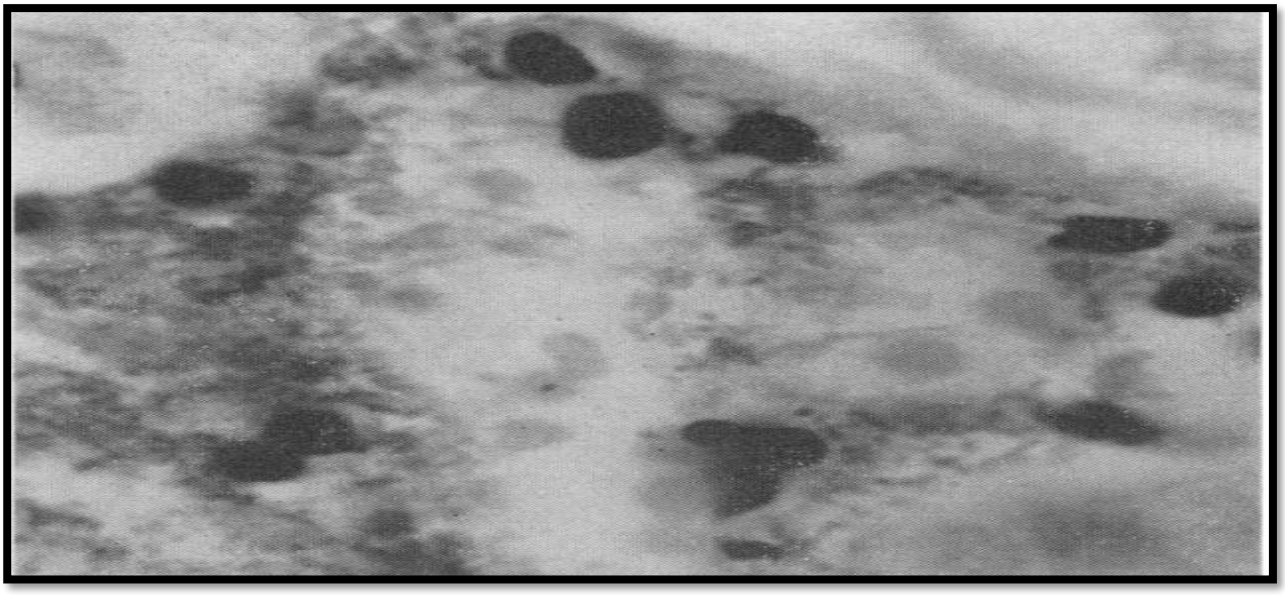

Fig .2. Case 3 The endothelial cells of this capillary in a kidney are packed with large numbers of bacilli (Salmonella newport). The organisms are also present in the cytoplasm of nearby fibroblasts or macrophages. Some lie free in the lumen of the blood vessel. Hwmatoxylin-eosin. x 1,050

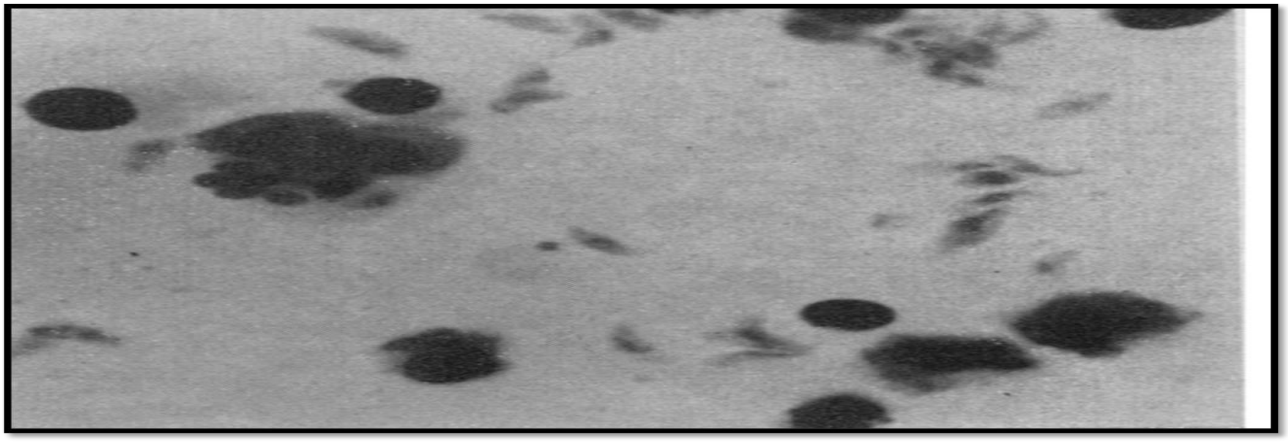

Fig .3. Case 4 Film preparation of uncentrifuged peritoneal fluid obtained by aspiration on the day before the patient died. Numerous crescentic toxoplasnmas and the remnant of a toxoplasmic pseudocyst containing a cluster of spheroidal forms of the parasite are seen. The host cells include neutrophils, lymphocytes and mesothelial cells. Haematoxylin-eosin. x 1,050

4. Case 4 : [8]
   After four years of treatment for Hodgkin's disease with mustines and X-rays, a 50-year-old man developed thrombocytopenic purpura, which required hydrocortisone medication. Toxoplasmosis, manifesting as localized, histologically typical lymphadenitis, struck him five months into his ongoing hydrocortisone therapy. Equally impressive were the improvements in the "dye test" and the complement fixation tests. After five days of treatment with pyrimethamine, we stopped the drug because severe thrombocytopenia developed in. Abdominal distension

owing to fluid accumulation in the peritoneal cavity occurred fast four months later while he was receiving hydrocortisone, mustine, and X-ray treatment. A plethora of toxoplasmas invaded him (Fig 3). Unfortunately, the patient passed away a few days later. Nobody performed a necropsy. It has been observed that Toxoplasmosis is not known to induce peritonitis in humans. In this instance, this event must be regarded as a "opportunistic" effect. It may have been caused by the hydrocortisone, and it occurred as a result of the treatment and the underlying disease.[8]

2.3 types opportunistic bacterial pathogens:

All the reported pathogens and clinical features are intended for patients with congenital immunodeficiencies, HIV disease, or iatrogenic immunosuppression (e.g., transplant, antineoplastic chemotherapy, autoimmune diseases). Some of these infections, such as invasive group B streptococcal disease or invasive infections caused by Enterobacteriaceae, should only be classified as OIs if they occur within a few months (generally 3-6) of birth. This is due to the fact that infections transmitted vertically can result in severe clinical manifestations even in the absence of specific immune system impairment. : [8]

Table I**:** summarizes OIs caused by microorganisms. In general, OIs caused by microorganisms are invasive and recurrent, occasionally with age-specific cut-offs. Disseminated bordetellosis, a condition characterized by multiple and protracted lymphadenitis, may be experienced by children who are undergoing steroidal treatment or receiving transplants. Alternatively, it may manifest as bacillary angiomatosis in children with HIV infection [9]. Normal children can also experience primary Mycobacterium tuberculosis infection and disease, which is generally not considered an OI unless there is no documented dissemination or reactivation of the infection prior to the initiation of immunosuppression. On the other hand, children affected with severe T-cell defects, still undetected at the time of vaccination, can exhibit the dissemination of Bacillus Calmette-Guèrin (BCG) after vaccination. [9]

TABLE I: CLINICAL FEATURES AND PATHOGENS DEFINING THE PRESENCE OF A BACTERIAL OI.

Pathogen	clinical manifestations
Shigella	
Mycobacterium tuberculosis	Latent infection reactivation. Tuberculosis of the meninges. Extrapulmonary or disseminated tuberculosis.
Staphylococcus aureus **Streptococcus pneumoniae** **Pseudomonas aeruginosa**	Multiple and recurrent infections (≥ 2 or more episodes within 12 months) in patients < 6 years: otitis media, pneumonia, sinusitis, skin-soft tissue. Recurrent pneumonia in patients aged ≥ 6 years. Invasive infections (bacteremia, osteomyelitis/arthritis, meningitis).
Salmonella spp	Recurrent bacteremia.
Rhod coccus Equi	The symptoms' presentation is contingent upon the infection's location. The symptoms of immunocompetent patients are identical to those of immunocompromised patients. Symptoms may manifest within 24 hours of the trauma in R equi infections secondary to trauma, including septic arthritis, endophthalmitis, and traumatic meningitis.

1. Shigella:

Shigella species induce acute gastrointestinal infections, sometimes accompanied by extraintestinal symptoms. Shigellosis has significant public health relevance, particularly in poor nations. Dysentery denotes colitis, marked by frequent, painful defecation of stools containing blood or mucus. Shigella organisms are E. coli strains that have evolved to enter human intestinal mucosa and induce illness [10]. These Enterobacteriaceae gram-negative bacilli are nonmotile and nonencapsulated. They lack urease and lactose fermentation.

- pathogenesis and immunity:

Shigellosis is among the most transmissible types of bacterial diarrhea. The primary occurrence in pathogenesis is the infiltration of intestinal mucosa[11] . Macrophages phagocytose by transcytosis via M cells. In the early phase of cellular entrance, Shigella cause actin polymerization in epithelial cells, leading to the development of filopodia. Subsequent to entrance, actin-based movement eradicates bacteria from membrane-bound vacuoles and facilitates their dissemination, a phenomenon referred to as protrusion. Intracellular Shigellae reprogram host cells to produce proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, and IL-8, therefore enhancing local inflammation and recruiting neutrophils. Leukocytes traverse the epithelium into the colonic lumen. Shigella induces necrosis in neutrophils, and the subsequent release of granular proteins exacerbates epithelial disruption. M cells are specialized cells that surround the lymphoid follicles of the intestinal mucosa. Shai Ashkenazim addresses Shigella Species in chapter 3, page 842 of his work, Etiologic Agents of Infectious Diseases [12] . Shigella and invasive E. coli possess distinct plasmid and chromosomal virulence genes. Certain chromosomal genes facilitate replication (e.g., the siderophore aerobactin aids Shigella in tissue growth), enhance bacterial resistance to nonspecific defense mechanisms (e.g., somatic antigens), or inhibit phagocytic cells from destroying bacteria (e.g., superoxide dismutase).

- Pathology

Shigella primarily affects the colon [13]. Microscopic analysis often demonstrates hyperemia, edema, and neutrophilic infiltration of the intestinal mucosa. Neutrophils may diminish the elevation of the surface epithelium during first phases. A thick pseudomembrane is formed at the base of deep necrotic, ulcerated mucosa by neutrophils, erythrocytes, fibrin, and desquamated epithelial cells. Crypt abnormalities include a significant decrease in goblet cells, epithelial cell hyperplasia, crypt abscesses, and distension resulting from exudates. Aphthoid ulcers develop on lymphoid aggregates [15] .

- Clinical Manifestations:

These mainly include dehydration due to fluid loss through diarrhea and vomiting, electrolyte imbalance (including hyponatremia and hypokalemia, commonly observed with S. dysenteriae), and less frequently, hypoglycemia due to failure of glycogenolysis and gluconeogenesis, especially in young infants [14] . Bacteremia Mucosal barrier disruption and bacteremia may develop from severe colitis and ulceration [15] . Shigellosis is more prevalent, more severe, and more often linked to bacteremia in individuals with AIDS. Subsequent to Shigella infections, additional enteric gram-negative bacilli may penetrate the compromised mucosa and induce bacteremia [16] .

2. Rhodcoccus (corynebacterium) equi:

Rhodococcus equi (formerly known as Corynebacterium equi) is a gram-positive, encapsulated, intracellular bacillus exhibiting morphological variation from coccoid to elongated and club-shaped forms. R. equi initially forms tiny, white, mucoid colonies that develop into big, salmon-colored colonies on normal medium after roughly four days. The bacteria exhibit a weak acid-fast response, frequently resulting in their misidentification as mycobacteria, due to the presence of mycolic acids in their cell walls[17]. R. equi does not ferment carbohydrates or liquefy gelatin; it is catalase positive and oxidase negative. We have categorized R. equi strains as virulent, intermediately virulent, and avirulent based on virulence-associated antigens and plasmids. [18]

Clinical Manifestations:

Most cases of R. equi infection are reported in HIV-infected individuals, with the lungs being the predominant site of infection in both immunocompetent and immunocompromised patients. The clinical signs include bloodstream infection (BSI), diarrhea, meningitis, brain abscesses, and infections of the thyroid, lung, adrenal glands, liver, spleen, as well as skin and soft tissue infections.Infections include pneumonia (complicated by brain abscesses and cavitary lesions) in AIDS patients, bloodstream infections (either alone or linked with pneumonia), and lymphadenitis [19] .

3. Mycobacterium

The genus Mycobacterium comprises a varied collection of acid-fast bacilli (AFB) characterized by a lipid-dense cell wall. The bacteria are aerobic, non-spore-forming, nonmotile, and have a slightly curved or straight morphology. Tuberculosis (TB) is caused by infection with any species of the Mycobacterium tuberculosis complex, including M. tuberculosis (the predominant cause of human TB), M. bovis, M. canetti, and others.

immunology and pathogenesis:

Exposure to M. tuberculosis can result in elimination of the bacteria and TB infection (an asymptomatic state evidenced only by a positive test of infection).

tuberculosis typically enters the body through the respiratory tract, where mucociliary transport and cough serve as the first line of defense. After M. tuberculosis reaches the alveolus, the Ghon focus develops. Bacilli drain from this granulomatous focus along local lymphatics to regional lymph nodes. Together, the Ghon focus, lymphangitis, and regional lymphadenopathy form the Ghon complex. Most immunocompetent persons contain the infection within the Ghon complex and never develop TB disease. CD4+ T lymphocytes and macrophages primarily mediate immunologic defenses against M. tuberculosis.[20] IFN and TNF- are these cytokines. People with anti-TNF monoclonal antibodies and IFNγ pathway issues are more likely to develop TB, indicating that these cytokines may protect against M. tuberculosis.[21]

- clinical manifestations:
  1. The severity of immunodeficiency affects TB symptoms [22]. In HIV-positive individuals with CD4 counts >200 cells/mm3, TB is similar to TB without HIV. Most patients have lung-limited illness, and chest radiographs show upper lobe infiltrates with or without cavitation. in patients with CD4 counts <200 cells/mm^3, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon [23].
  2. As immunodeficiency intensifies, extrapulmonary manifestations of tuberculosis, including lymphadenitis, pleuritis, pericarditis, and meningitis, or disseminated tuberculosis become more prevalent. In individuals with significant immune suppression, tuberculosis may manifest as a severe systemic illness characterized by elevated fevers, fast progression, and signs of sepsis. HIV-positive patients have similar extrapulmonary TB symptoms to those without HIV.

4. Salmonella:

Salmonella typhi and paratyphi [24] induce enteric fever, which requires antibiotics immediately. Gram-negative, flagellated salmonellae may survive without oxygen. H is the flagellar antigen, O is the somatic antigen, and Vi is the Vi antigen. Like other Gram-negative bacilli, Salmonellae's cell membrane has a complex lipopolysaccharide (LPS) structure

that releases following cell destruction and some throughout culture. Lipopolysaccharide may be an endotoxin and affect virulence.
endotoxin complex consists of three components: [25]

- The outer O-polysaccharide coat, composed of the repeating sugar units in the outer O-polysaccharide chains, is important for O antigen specificity and may also influence the organism's pathogenicity. Salmonellae that do not carry the whole sequence of O-sugar repeat units are termed rough due to the rough look of their colonies; they are often avirulent or exhibit reduced virulence compared to the smooth strains, which include the full complement of O-sugar repeat units.
- The central segment (the R core) of the Lipopolysaccharide structure is significant for several reasons. Antibodies targeting the R core may provide protection against infections caused by several Gram-negative bacteria.
  an internal lipid the coat, an endotoxin component of the cell wall, may significantly contribute to the development of several clinical symptoms of Gram-negative infections. Endotoxins induce fever, stimulate the serum complement, kinin, and coagulation systems, impair myocardial function, and modify lymphocyte activity. Circulating endotoxin may partially contribute to various signs of septic shock that may arise in systemic illnesses.
  - immunology and pathogenesis:
    Salmonellosis includes several syndromes [26] (gastroenteritis, enteric fevers, septicemia, focal infections, and an asymptomatic carrier state. infection can be getting by person to person.
  - To be fully pathogenic, salmonellae must possess a variety of attributes called virulence factors These include:
    1. the ability to invade cells
    2. a complete lipopolysaccharide coats
    3. the ability to replicate intracellularly .
    4. possibly the elaboration of toxin(s).
    5. Following ingestion, the organisms colonize the ileum and colon, penetrate the intestinal epithelium, and multiply inside the epithelium and lymphoid follicles. Upon penetrating the colon, most salmonellae elicit an initial inflammatory reaction, potentially resulting in ulceration. They may generate cytotoxins that impede protein synthesis. The role of these cytotoxins in the inflammatory response or ulceration remains unclear. [27]
    6. Salmonella infiltrates the intestinal epithelial cells; nevertheless, in contrast to Shigella and invasive E. coli, it does not evade the phagosome. The degree of intercellular dissemination and epithelial ulceration is modest. Salmonella breaches the basal surface of epithelial cells and infiltrates the lamina propria. The germs may disseminate systemically, resulting in intestinal fever. Mucosal adenylate cyclase is activated during the invasion of the intestinal mucosa, leading to an increase in cyclic AMP that stimulates secretion.

- clinical manifestations:

In terms of symptoms, salmonellosis [28] can range from the more common Salmonella gastroenteritis (diarrhea, stomach pain, and fever) to enteric fevers (such as typhoid fever), which are life-threatening fever-based systemic illnesses that need to be treated right away with antibiotics.

5. Staphylococcus aureus

Staphylococci are Gram-positive cocci that proliferate in clusters, pairs, and sometimes in short chains. The clusters form due to staphylococci dividing in two planes. The arrangement of cocci differentiates micrococci and staphylococci from streptococci, which often proliferate in chains. must be conducted on cultures cultivated in broth, since streptococci cultured on solid media may manifest as aggregates.

- Classification
  Sauers are coagulase positive. All other staphylococci are coagulase negative. They are salt tolerant and often hemolytic.
- pathogenesis:
  S aureus have many potential virulence factors [29]: *(*1) Surface proteins are known to promote the colonization of host tissues. (2) Factors that likely inhibit phagocytosis include capsules and immunoglobulin-binding protein A. (3) Toxins that damage host tissues and cause disease symptoms. Coagulase-negative staphylococci are normally less virulent and express fewer virulence factors.
- clinical manifestations:
  may induce several types of infections, including superficial skin lesions (boils, styes) and localized abscesses in other areas, as well as deep-seated infections such as osteomyelitis and endocarditis, along with more severe skin infections (furunculosis).

6. Streptococcus pneumoniae:

Streptococcus pneumoniae [30], or Pneumococcus is a gram-positive, alpha-hemolytic, aerotolerant, and anaerobic species of the Streptococcus genus. Numerous investigations on humoral immunity have identified S. pneumoniae, a prominent human pathogenic bacterium, as a major etiological agent of pneumonia in the late 19th century. Streptococcus pneumoniae exists asymptomatically in the nasopharynx of healthy carriers. Streptococcus pneumoniae

is a prevalent etiological agent of bacterial meningitis in adults and young adults, alongside Neisseria meningitidis, and is the primary cause of bacterial meningitis in adults in the United States.

- pathogenesis:
  The bacteria Streptococcus pneumoniae, often referred to as pneumococcus, is responsible for pneumococcal illness. Infection may lead to pneumonia, bacteremia/sepsis, otitis media, or bacterial meningitis.
- There are two main types of pneumococcal diseases: [31]
  - Non-invasive pneumococcal diseases These infections, occurring outside the primary organs or bloodstream, may be less severe than invasive pneumococcal illness. Streptococcus pneumoniae may disseminate from the nasopharynx, including the nasal cavity and pharynx, to both the upper and lower respiratory tracts.
  - Otitis media infection of the middle ear. The middle ear experiences inflammation, often associated with fluid accumulation, tympanic membrane enlargement, and otalgia. In the event of a ruptured eardrum, pus may leak into the ear canal.
  - Non-bacteremia pneumonia refers to an infection of the lower respiratory tract in which there is no identifiable dissemination of pathogens into the bloodstream.

A. Invasive pneumococcal diseases (IPD) These tend to be more serious and occur inside a major organ, or in the blood. Examples of IPDs include:
   - Bacteremia (sepsis) - bacterial infection of the blood. Bacteremia refers to the presence of live bacteria in the blood, while sepsis means a blood infection which is associated with capillary leak, shock and an increased risk of mortality.
   - Meningitis - inflammation of the meninges. The meninges are the three membranes that cover the brain and the spinal cord.
   - Bacteremic pneumonia - inflammation of one or both lungs, with pneumococcus in the bloodstream. Synergistically with macrolides to improve outcome

- Virulence factors is the majer risk factor in S. pneumoniae:
  Virulence factors S. pneumoniae has cell surface and internal pathogenicity components. These virulence factors contribute to S. pneumoniae infection symptoms.
  - Polysaccharide capsule prevents phagocytosis by host immune cells by inhibiting C3b opsonization of the bacterial cells.
  - Pneumolysin (Ply) a 53-kDa pore-forming protein that can cause lysis of host cells and activate complement.
  - Autolysin (LytA) activation of this protein lyses the bacteria releasing its internal contents (i.e., pneumolysin).
  - Hydrogen peroxide damages host cells and triggers neuronal death during meningitis. Hemophilus influenzae, Neisseria meningitidis, and Staphylococcus aureus are also killed by it.
  - Pili hair-like structures that extend from the surface of many strains of S. pneumoniae. They contribute to colonization of upper respiratory tract and increase the formation of large amounts of TNF by the immune system during sepsis, raising the possibility of septic shock.
- Choline-binding protein A/Pneumococcal surface protein A (CbpA/PspA) is an adhesin that can bind to carbohydrates on the surface of pulmonary epithelial cells and prevent pneumococci from being opsonized by complement.
- clinical manifestation:
  1. Pneumococcal bacteremia - signs and symptoms:
     An elevated body temperature (fever), Muscular soreness and pains, headaches, Rapid respiration and elevated heart rate
  2. Pneumococcal meningitis - signs and symptoms:
     An elevated body temperature (fever), headache, nausea, vomiting, sleepiness, irritability, stiff neck, seizures, and sometimes coma.
  3. Pneumococcal pneumonia - signs and symptoms:
     A fever, cough, The patient may have fast breathing, chest discomfort, diarrhea, and temporary hearing loss.

3. CHAPTER TWO: ANTIMICROBIAL RESISTANCE

Alexander Fleming [32] developed penicillin, the first antibiotic. He predicted bacterium resistance in 1945. Due to overuse of antibiotics in health care and agriculture, many common bacteria developed resistance to older drugs in the 1980s and 1990s. The World Health Organization and the European Centre for Disease Prevention and Control reported alarming increases in resistant pathogens in Europe and globally. One of the biggest worldwide health and food security risks is antibiotic resistance.

Overuse and abuse of life-saving medications have enabled germs to acquire resistance against them rapidly. If unchecked, antibiotic resistance might make treating common human diseases and mild injuries difficult. This article will examine antibiotic resistance, including its causes, effects, and prevention methods.

3.1 What is antimicrobial resistance (AMR), and how is it different from antibiotic resistance?

The phrase "antimicrobial" refers to any medicine (e.g., antibiotics, antivirals, antifungals, and antiparasitic) that kills or inhibits microorganisms to treat and prevent illnesses.

Antimicrobial resistance (AMR) [33], happens when a microorganism becomes resistant to an antimicrobial drug that used to be effective in treating the infections it causes. Antibiotic resistance, on the other hand, is a subcategory of antimicrobial resistance. It refers specifically to the resistance of bacteria to antibiotic drugs the drugs used specifically to treat infections caused by bacteria, such as urinary tract infections or pneumonia.

Antimicrobial resistance (AMR) refers to a microorganism's capacity to withstand the effects of one or more antimicrobial agents. The repercussions can be grave, and timely administration of potent antimicrobials is the paramount intervention to mitigate the likelihood of adverse outcomes in severe infections.

3-1-1 Is antibiotic resistance permanent or reversible?

Antibiotic resistance is often regarded to be permanent due to the fact that bacteria do not normally shed the genes that they have gained when they acquire resistance. If, on the other hand, bacteria are no longer exposed to antibiotics, it is possible that they may lose their genes that confer resistance. As bacteria adapt to their environment without antibiotics, this may occur over the course of several generations. In this scenario, bacteria that are not resistant to antibiotics are able to outcompete those that are resistant.

It is essential to keep in mind that even if a population of bacteria loses their resistance to a particular antibiotic, the genes that confer that resistance are still present in the environment and may be passed on to new bacteria by a variety of methods, such as horizontal gene transfer. As a result, the reintroduction of antibiotics into the environment might result in the reemergence of resistance [34].

Consequently, antibiotic resistance is a chronic issue that requires continual monitoring and intervention, despite the fact that it may not necessarily be permanent at the level of the individual bacterium. Preventing the development of antibiotic resistance and using antibiotics in a responsible manner are two of the most important measures for reducing the devastating effects of this global health crisis.

3.2 Classification of Some Antimicrobial Agents by Their Sites of Action:

- Inhibitors of metabolism: Sulfonamides, Trimethoprim.
- Inhibitors of cell wall synthesis: ß-Lactams, Vancomycin, Daptomycin, Telavancin, Fosfomycin.
- Inhibitors of protein synthesis: Tetracyclines, Aminoglycosides, Macrolides, Clindamycin, Chloramphenicol, Linezolid.
- Inhibitors of nucleic acid function or synthesis: Fluoroquinolones, Rifampin.
- Inhibitors of cell membrane function: Isoniazid, Amphotericin B, Polymyxins.

TABLE II:. ANTIMICROBIAL GROUPS BASED ON MECHANISM OF ACTION.

Mechanism of Action	Antimicrobial Groups
Inhibit Cell Wall Synthesis	β-Lactams
	Carbapenems
	Cephalosporins
	Monobactams
	Penicillins
	Glycopeptides
Depolarize Cell Membrane	Lipopeptides
Inhibit Protein Synthesis	Bind to 30S Ribosomal Subunit
	Aminoglycosides
	Tetracyclines
	Bind to 50S Ribosomal Subunit
	Chloramphenicol
	Lincosamides
	Macrolides
	Oxazolidinones
	Streptogramins
Inhibit Nucleic Acid Synthesis	Quinolones
	Fluoroquinolones
Inhibit Metabolic Pathways	Sulfonamides
	Trimethoprim

3.3 Persistence versus resistance:

In the event that a bacteria is resistant to a particular antimicrobial agent, then all of the daughter cells of that bacterium would likewise be resistant to that agent (unless an additional mutation happened in the meanwhile). However, persistence refers to bacterial cells that are resistant to the medicine but do not carry resistance genes. These cells are no longer vulnerable to the drug. There is little doubt that the persistence is due to the fact that certain cells within a bacterial population may be in a stationary growth phase (dormant), and the majority of antimicrobial drugs do not have any impact on cells that are not actively growing and dividing. Within a culture that is in the stationary phase, the presence of these per sister cells is estimated to be somewhere about one percent [35].

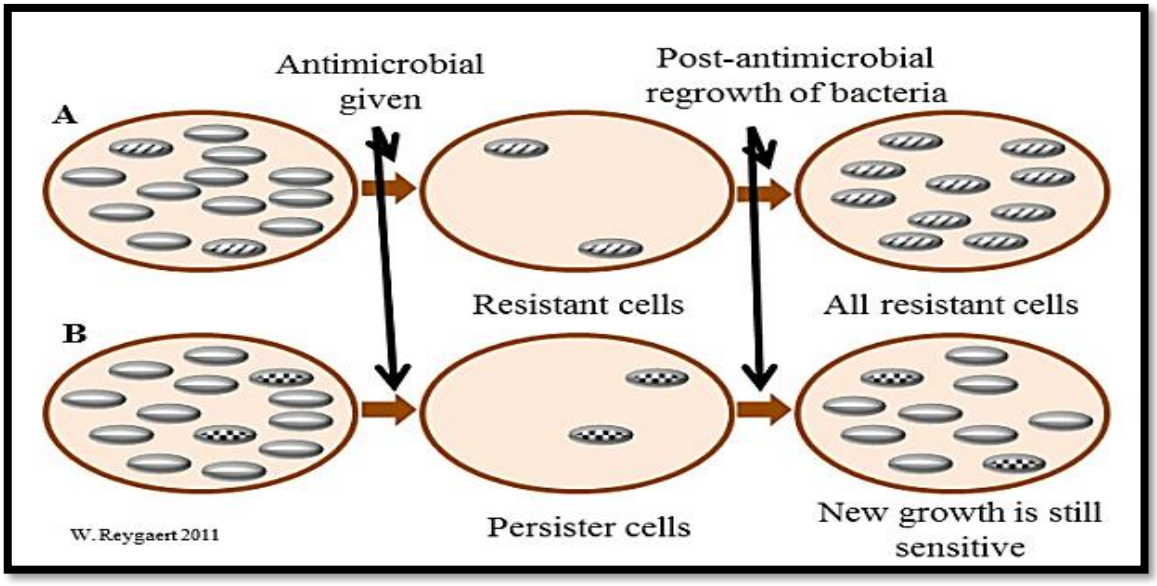

Fig .4. shows the difference between persistent and resistant bacterial cells

Putting up a fight against persistence. In the event that bacterial cells are subjected to an antibiotic substance, there are two distinct opportunities that may arise. It is possible that there are cells which are resistant to the antimicrobial agent (A) that is present. The antimicrobial agent (A) eliminates the cells that are not resistant, leaving only the ones that are now resistant. It is possible to make all of the cells in the culture resistant by regrowing the cells that are resistant.
One such option is the existence of per sister cells, which are cells that are not resistant to the infection and remain inactive, as figure B illustrates. Only the cells that are able to survive are left after the antimicrobial agent has eliminated the cells that do not persist. The per sister cells that are not in a latent condition will continue to be vulnerable to the antimicrobial agent even after they have regrown their original size.

3.3.1 Natural resistance:

There are two types of natural resistance: intrinsic, which is always expressed in the species, and induced, which is when the genes necessary for resistance are normally present in the bacteria but are only expressed to resistant levels after the bacteria have been exposed to an antibiotic. A feature that is shared universally within a bacterial species, is independent of past antibiotic exposure, and is not connected to horizontal gene transfer is referred to as intrinsic resistance. Intrinsic resistance may be described as a property that is shared worldwide [36].
The two bacterial mechanisms most frequently involved in the process of intrinsic resistance are reduced permeability of the outer membrane (particularly the lipopolysaccharide, LPS, in gram-negative bacteria) and the natural functioning of efflux pumps. Multidrug efflux pumps, another prevalent mechanism, can also induce resistance.

3.3.2 Acquired resistance

Resistance that has been acquired It is possible for bacteria to acquire genetic material that imparts resistance via all of the primary ways by which they acquire any genetic material. These processes include transformation, transposition, and conjugation (all termed horizontal gene transfer HGT); plus, the bacteria may experience mutations to its own chromosomal DNA. The acquisition may be temporary or permanent. Plasmid-mediated transmission of resistance genes is the most prevalent method for acquiring genetic material from outside sources, while transfer by bacteriophage is rather uncommon. Certain bacteria, such as those belonging to the genus Acinetobacter, possess the ability to acquire genetic material directly from the surrounding environment because they are inherently competent. Internally, insertion sequences and integrins

have the ability to assist the flow of genetic material. On the other hand, stresses like as hunger, ultraviolet radiation, and toxins may lead to genetic alterations such as deletions and substitutions. It is estimated that bacteria experience a mutation rate of one for every 106 to 109 cell divisions on average. The majority of these mutations will be detrimental to the cell at large [37]. Mutations that aid antimicrobial resistance usually only occur in a few types of genes: those encoding drug targets, those encoding drug transporters, those encoding regulators that control drug transporters, and those encoding antibiotic-modifying enzymes. In addition, many mutations that confer antimicrobial resistance do so at a cost to the organism. For instance, Staphylococcus aureus significantly reduces its growth rate when it acquires methicillin resistance.

3.4 Mechanisms of resistance

In the realm of antimicrobial resistance mechanisms, there are four primary types that may be distinguished: (1) the limitation of drug absorption; (2) the modification of drug targets; (3) the inactivation of drugs; and (4) active drug efflux. While acquired resistance mechanisms may entail alterations to the drug target, drug inactivation, and drug efflux, intrinsic resistance may make use of methods such as restricting uptake, drug inactivation, and drug efflux. Intrinsic resistance can also be referred to as endogenous resistance. Gram-negative bacteria, which are structurally distinct from gram-positive bacteria, use methods that are distinct from those of the former. Gram-negative bacteria make use of all four primary mechanisms, but gram-positive bacteria are less likely to restrict drug absorption owing to the absence of an LPS outer membrane and the inability to employ certain drug efflux mechanisms, which will be covered in a later section of this book. A visual representation of the general processes of antibiotic resistance may be seen in Fig 5.

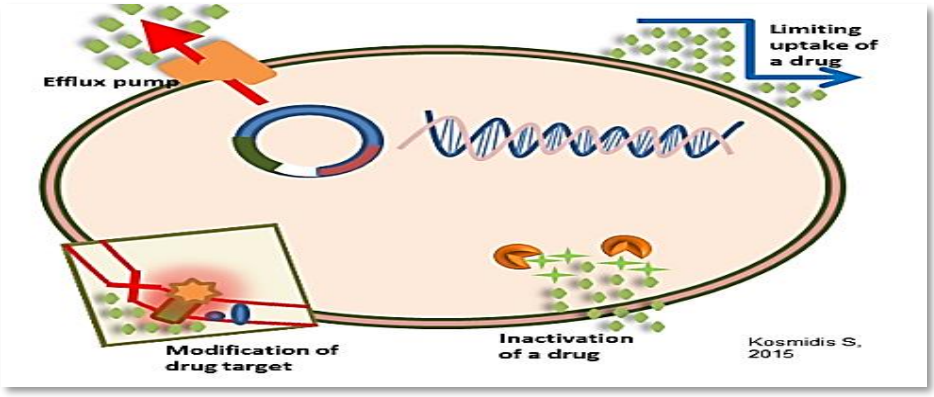

Fig .5. General antimicrobial resistance mechanisms.

3.4.1 Limiting drug uptake:

There is a natural variation among bacteria in their capacity to limit the absorption of antimicrobial drugs to varying degrees. Certain kinds of chemicals are unable to pass through the LPS layer of gram-negative bacteria because of its structure and activities. Inherent resistance to certain classes of major antibacterial drugs is conferred onto those bacteria as a result of this [38] . Mycobacteria have an outer membrane that is composed of a large amount of lipids; thus, medications that are hydro phobic, such as rifampicin and fluoroquinolones, have an easier time entering the cell, while drugs that are hydrophilic have a more difficult time entering the cell. Bacteria that lack a cell wall, such as Mycoplasma and related species, are therefore intrinsically resistant to all drugs that target the cell wall including β-lactams and glycopeptides [39] As a result of the absence of an outer membrane, Gram-positive bacteria are less likely to impede medication access than other types of bacteria. Intrinsic resistance to aminoglycosides is shown by enterococci due to the fact that polar molecules have a difficult time entering the cell wall. Recent research has shown that Staphylococcus aureus, a gram-positive bacterium, has evolved resistance to the antibiotic vancomycin. It is typically the case that gram-negative bacteria have porin channels that enable them to access hydrophilic substances. A reduction in the number of porins that are present and mutations that modify the selectivity of the porin channel are the two primary ways in which changes within porins might restrict the amount of medicine that is taken up by the body. There is evidence that members of the Enterobacteriaceae family may develop resistance to antibiotics by decreasing the quantity of porins they produce (and in some cases, even completely ceasing synthesis of specific porins). As a collective defensive strategy against carbapenems, these bacteria reduce the quantity of porins in their cells.

3.4.2 Modification of drug targets:

Modification of the objectives of the medicine antimicrobial medicines have the potential to target various components inside the bacterial cell. Bacteria have the ability to change these targets in order to develop resistance to these medications. Alterations in the structure and/or number of penicillin-binding proteins (abbreviated as PBPs) are the mechanism by which gram-positive bacteria develop resistance to β-lactam medicines, which are virtually exclusively used by these bacteria.

PBPs are transpeptidases that play a role in the formation of peptidoglycan inside the boundaries of the cell structure. The quantity of medication that is capable of binding to a target shift in proportion to the number of PBPs that are present. There is a possibility that this will occur if the number of PBPs that have normal drug binding decreases or increases. The capacity of the medicine to bind may be reduced or completely inhibited if there is a change in structure, such as the acquisition of the mecA gene in S. aureus, which causes PBP2a to be altered. While glycopeptides, such as vancomycin, act by blocking the formation of cell walls, lipopeptides work by depolarizing the cell membrane. Both of these mechanisms are effective. Gram-negative bacteria that have a thick covering of lipopolysaccharide (LPS) have an inherent resistance to these medications. There are two forms of bacteria that are very difficult to eradicate with vancomycin. These include Staphylococcus aureus (MRSA) and enterococci (VRE, which stands for vancomycin-resistant enterococci). Through the acquisition of van genes, resistance is mediated, which results in a change in the structure of peptidoglycan precursors and a reduction in the capacity of vancomycin to bind. It is comycin،

Daptomycin requires the presence of calcium for binding. A change in genes, like mprF, makes the cell membrane surface positively charged. This stops calcium and, by extension, daptomycin from binding. Resistance to drugs that target the ribosomal subunits may occur via ribosomal mutation (aminoglycosides, oxazolidinones), ribosomal subunit methylation (aminoglycosides, macrolides, gram-positive bacteria, oxazolidinones, streptogramins), most commonly involving erm genes, or ribosomal protection (tetracyclines). These mechanisms interfere with the ability of the drug to bind to the ribosome. The level of drug interference varies greatly among these mechanisms.

Changes in enzymes (DHPS, dihydropteroate synthase, and DHFR, dihydrofolate reductase) cause resistance to drugs that block metabolic pathways.

Sulfonamides and trimethoprim bind to their respective enzymes because they are structural analogs of their natural substrates, namely p-aminobenzoic acid for sulfonamides and dihydrofolate for trimethoprim. These drugs work by binding in the active site of the enzymes, thereby causing competitive inhibition [40] .

3.4.3 Drug inactivation:

Bacteria may inactivate pharmaceuticals in two primary ways: either by physically degrading the medication or by transferring a chemical group to the drug. Both of these methods are effective. One of the most extensive groups of enzymes that hydrolyze drugs is known as the β-lactamases. Tetracycline is yet another medication that comes with the capability of being hydrolyzed by the tetX gene [31]. When it comes to inactivating drugs by chemical group transfer, the most typical approach includes the transfer of acetyl, phosphoryl, and adenyl groups to the medication. There are a significant number of transferases that we have discovered. Acetylation, which is the most diversified process, is known to target aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones when it comes to drug resistance. For the purpose of combating the aminoglycosides, phosphorylation and adenylation are used. lycosides. Research conducted by Blair JM, Webber MA, Bayley AJ, and others in 2015 looked at the molecular processes that underlie antibiotic resistance. 42–51 in the National Review of Microbiology. [40]

3.4.4 β-Lactam resistance:

Inactivation of β-lactamases is the cause of resistance to β-lactam antibiotics. Antibiotics that belong to the family of molecular A-serine-lactamases are known as penicillinases. These penicillinases include families such as PSE, TEM, and CARB, with PSE being the most frequent of the three. The presence of extended-spectrum β-lactamases does not provide resistance to carbapenem; nevertheless, the presence of other enzymes that are capable of breaking down carbapenem does confer resistance. P. aeruginosa is in possession of blaAmpC, which is responsible for the production of a wide variety of class C-lactamases.The enzyme known as β-lactamase confers resistance to a wide range of compounds, including aminopenicillins, first- and second-generation cephalosporins, and others.

However, if a mutation triggers overproduction, AmpC can significantly contribute to resistance. On the other hand, dacB plays a role in ampC expression by encoding the production of penicillin-binding protein 4 (PBP4) [41].

Therefore, the deactivation of PBP4 results in high levels of AmpC and β-lactam resistance. Also, the gene essential in regulation of AmpC is ampD, and the deactivation of ampD will potentially repress the ampC exBecause of changes in genes such as dacB, ampD, and penicillin-binding protein, PAHM4 became resistant to penicillin, cephalosporin, and meropenemDue to a mutation in the mucA gene that generates a stop codon, PAHM4 is known for its ability to produce alginate. This mutation results in the production of a mutant allele known as mucA22, which is mucoid by nature and contributes significantly to alginate production.

3.5 Antimicrobial resistance of opportunistic bacteria

1. Shigella

TABLE II: REGIMENS FOR TREATMENT OF SHIGELLOSIS INFECTION [42]

Drug[b]	Dosage
Cefixime	8 mg/kg/day PO once daily
Ceftriaxone	50 mg/kg/day IV or IM in one dose daily (maximum 1.5 g/day)
Trimethoprim-sulfamethoxazole[c]	10 mg/kg/day (TMP) PO in two divided doses (maximum 320 mg TMP/day)
Ampicillin[c]	100 mg/kg/day IV or PO in four divided doses
Azithromycin	12 mg/kg (maximum 500 mg) on the first day, then 6 mg/kg (maximum 250 mg) for 4 days

[a]Therapy is given for a total of 5 days. Susceptibility test results are used to tailor therapy.
[b]Ciprofloxacin or other fluoroquinolones may be appropriate.
[c]Resistance is common.
IM, intramuscular; IV, intravenous; PO, by mouth; TMP, trimethoprim.

The World Health Organization (WHO) recommends that all suspected cases of shigellosis based on clinical features be treated with effective antimicrobials (antibiotics). The following antibiotics were used to treat Shigella dysentery: [42]

- class: beta-lactams: ampicillin, amoxicillin, first and second generation cephalosporins (cefixime, ceftriaxone) and pivmecillinam;
- class: quinolones: nalidixic acid, ciprofloxacin, norfloxacin, ofloxacin;
- class: macrolides: azithromycin sulphonamides, tetracycline, cotrimoxazole, and furazolidone.
- as first line treatment, WHO now recommends that clinically diagnosed cases of Shigella dysentery be treated with ciprofloxacin and pivmecillinam, ceftriaxone, or azithromycin as second line treatment and lists the others as ineffective.
- Azithromycin is effective in the treatment of moderate to severe shigellosis caused by multidrug-resistant Shigella strains.
- Ampicillin and cotrimoxazole fulfil these criteria, and for the last 15 years have been the drugs of choice for treatment of shigellosis.
- metronidazole, believing that the drug will cure both shigellosis and amoebic dysentery. Metronidazole should be used only if E. histolytica has been positively identified, or if treatment for shigellosis has failed[42]

2. Anti-microbial resistance of Mycobacterium tuberculosis: Current Treatments
   A. types of Drug-resistant TB
      - Multidrug-Resistant TB (MDR TB): Multidrug-resistant TB (MDR TB) is caused by TB bacteria that are resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. TB experts should be consulted in the treatment of MDR TB.
      - Pre-Extensively Drug-resistant TB (pre-XDR TB): TB bacteria that are resistant to isoniazid, rifampin, and a fluroquinolone or TB bacteria that are resistant to isoniazid, rifampin, and a second-line injectable (amikacin, capreomycin, and kanamycin) are the culprits behind pre-extensively drug-resistant tuberculosis (pre-XDR TB), which is a kind of multidrug-resistant tuberculosis (MDR) that is caused by TB bacteria.
      - Extensively Drug-resistant TB (XDR TB): Extensively drug-resistant tuberculosis (XDR TB) is an uncommon variant of multidrug-resistant tuberculosis (MDR TB) resulting from Mycobacterium tuberculosis strains that exhibit resistance to isoniazid, rifampin, a fluoroquinolone, and a second-line injectable (amikacin, capreomycin, or kanamycin), or to isoniazid, rifampin, a fluoroquinolone, and bedaquiline or linezolid. XDR-TB poses a significant risk to those with HIV infections or other immunocompromising disorders. Upon infection, these people have an increased likelihood of developing tuberculosis and encounter a heightened risk of death.

   B. Levofloxacin and moxifloxacin are the two most often endorsed agents, and the WHO has advocated for the use of these medications in the treatment of multidrug-resistant tuberculosis (MDR-TB). The recommended dosage of levofloxacin is 750 mg administered once day, whereas moxifloxacin is prescribed at 400 mg once daily. Individuals with MDR/RR-TB are prescribed a regimen consisting of bedaquiline (B), pretomanid (Pa), linezolid (L), and moxifloxacin (M), known as BPaLM; for those with pre-XDR-TB, the regimen may be administered without moxifloxacin, referred to as BPaL.

TABLE IIII: CLASSIFICATION OF MEDICATION FOR MULTIDRUG-RESISTANT TUBERCULOSIS INFECTION. IN 2019 [43]

Group	Medicine	Step
A	Levofloxacin or moxifloxacin, Bedaquiline Linezolid ,	Include all three medicines (unless they cannot be used)
B	Clofazimine, Cycloserine or terizidone,	Add one or both medicines (unless they cannot be used)
C	Ethambutol, Delamanid, Pyrazinamide Imipenem-cilastatin or meropenem, Amikacin or streptomycin, Ethionamide or prothionamide, Para-aminosalicylic acid	Add to complete a four- to five drug regimen when medicines from groups A and B cannot be used

1. Anti-microbial resistance of Salmonella spp.
   Enteric fever is a bacterial illness induced by Salmonella typhi and Salmonella paratyphi. Salmonella infections are often treated with fluoroquinolones or third-generation cephalosporins, including ciprofloxacin and ceftriaxone. The medicine Ciprofloxacin is beneficial in treating salmonella. Ceftriaxone, Trimethoprim-sulfamethoxazole (TMP/SMX), and Azithromycin.
   Salmonella typhi exhibit sensitivity to Ampicillin, Azithromycin, and Cefotaxime, with a lesser degree of sensitivity to Chloramphenicol.

TABLE V: CLASSIFICATION OF MEDICATION FOR MULTIDRUG-RESISTANT IN EFFLUX PUMP INHIBITORS IN SALMONELLA. FOR TREATMENT OF TYPHOID FEVER.

compound	Target efflux pump	Substrate	Reference
• Compound (OU33858)	• MacAB	• Macrolids	• Yamagishi et al., 2020 [44]
Trimethoprim	AcrAB-ToIC	Ciprofloxacin	Piddock et al., 2010 [45]
Cathinone			
Carbonyl cyanide m chlorophenylhydrazone, norepinephrine and trimethoprim			
Tetraphenylphosphonium and ethidium cations		Polymyxin B and Gramicidin D	
olyaminoisoprenyl derivatives		Erythromycin Doxycycline Nalidixic acid Chloramphenicol	
Hexadecanoic acid		Ciprofloxacin	
Pyranopyridine		Fluoroquinolones, B-lactams Chloramphenicol Minocycline Erythromycin Linezolid	Aron and Opperman, 2016 . [46]

TABLE IV: ANTI-MICROBIAL RESISTANCE OF REGIMENS FOR DAILY DOSE TREATMENT OF TYPHOID FEVER. INFECTION CAUSED BY THE BACTERIUM SALMONELLA TYPHI.

Antibiotic	Daily dose	route	Dose	Duration (days)
Ampicillin	100 mg/kg	oral	Tid/qid	6 – 12weeks
amoxycillin	30 mg/kg			6 – 12weeks
Co-trimoxazole	4-20 mg/kg	Oral	bid	6 – 12weeks
Ciprofloxacin	1500 mg	Oral	bid	4 weeks
Norfloxacin	800 mg	oral	bid	4 weeks

2. Anti-microbial resistance of Rhodococcus equi

TABLE IIV: REGIMENS FOR TREATMENT OF INFECTION CAUSED BY THE BACTERIUM RHODOCOCCUS EQUI. [49]

Antibiotics	MIC (mg/L)	Antibiotics	MIC (mg/L)
Rifampin	1	Imipenem	1
Levofloxacin	1	Penicillin	8
Vancomycin	0.25	Clindamycin	4
Erythromycin	0.5	Sulfamethoxazole	2
Linezolid	1	Daptomycin	4

Antibiotic	Dose
Nitrofurzntoin monohydrate	100 mg
TMP-SMX	160/800 mg
Fosfomycin	3 g once
Pivmecillinam	400 mg
Fluoroquinolones	Ciprofloxacin 250 mg
	Ofloxacin 200 mg
Amoxicillin-clavulanate	500/125 mg
Cephalosporins	Cefdinir 100 mg
	Cefaclor 250 mg
Cefpodoxime	
Ciprofloxacin	500 mg

1. Anti-microbial resistance of Staphylococcus saprophyticus: TableVIII : Regimens for Treatment of Infection caused by the bacterium Staphylococcus saprophyticu .
2. Anti-microbial resistance of Streptococcus pneumoniae: Regimens for Treatment of Infection caused by the bacterium Streptococcus pneumoniae [48]
   - The bacterium known as Streptococcus pneumoniae is capable of causing a variety of life-threatening infections in humans, including pneumonia, meningitis, and other conditions. Amoxicillin, an antibiotic, is now used to treat a significant number of S. pneumoniae infections. It does this by weakening the structure known as the cell wall, which surrounds each bacterium.
   - Penicillin (or amoxicillin because of more reliable absorption after oral administration and a much longer half-life) remains the drug of choice for treating susceptible pneumococcal infection.
   - MDR stands for multidrug-resistant. In the case of Streptococcus pneumoniae, the term "multidrug resistance" refers to the bacteria's ability to withstand three or more kinds of antibiotics. The typical Thera Typically, -lactam antibiotics such as benzylpenicillin, amoxicillin, or ampicillin are used to treat pneumococci disease, including invasive cases. Pneumococcal clones that were resistant to many antibiotics evolved around the globe as a result of widespread antibiotic use.

- Carbapenems also are effective against S pneumoniae but should be reserved for specific cases given their broad coverage and the potential for development of resistance by multiple organisms.
- Cefotaxime (Claforan) , Penicillin G (Pfizerpen), Amoxicillin (Moxatag) Ampicillin, Cefazolin., Ceftriaxone (Rocephin)

4. CONCLUSIONS

Bacteria are creatures that are not only flexible but also adaptive. In order for them to survive, they need to be able to control potentially hazardous substances. Bacteria that are able to live independently must be able to withstand harmful attacks and waste products that are produced by cells of other species. That germs that infect humans have the capacity to withstand antimicrobial agents is not something that should come as a surprise. In light of the alarming increase in antibiotic resistance, it is of the utmost importance to research and develop methods for combating these infections. Unfortunately, there is no obvious solution to this issue that is also likely to be within a reasonable price range. It is possible that we will need to rethink our strategy for the development of new antimicrobial medications or investigate natural chemicals in order to improve our understanding of potential solutions to this conflict.

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