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An In-Depth Review Of: Recently Fda-Approved Antibiotics For Combating Bacterial Infections

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Abstract:

Bacterial infections cause a universal health problem i.e Bacterial infections occur in numerous shapes and forms and affect a vast population. In this abstract, more focus has been on major bacterial infections those with specific pathogens Streptococcal infections, TB, UTIs.

The most common causative agent of Streptococcal infections is the streptococcus species in fact Streptococcus pyrogens is the most often implicated as it causes strep throat and other fever to skin lesions. Management is mostly dependent upon the use of antibiotics and the drug of choice is penicillin, since it achieves good response without high resistance rates.

TB is one of the oldest and most important public health problems in developing countries. The two major forms are pulmonary and extrapulmonary disease which might cause a serious morbidity if not treated properly In general the treatment is a course of antibiotics over a longer period and is generally called DOTS (Directly Observed Treatment Short course). FDA approves Pteromalid was recently approved in 2019 as a part of combination regimen for the treatment of multidrug resistant.

Urinary Tract Infections (UTIs) are most commonly caused by Escherichia coli. However, many other pathogens may also be involved. UTIs are very common among women and a source of potential complications if they are not dealt with promptly. Standard initial treatments usually include antibiotics like nitrofurantoin or trimethoprim-sulfamethoxazole; the specific choice will depend on local resistance patterns. Good diagnosis and management will help prevent recurrence and renal complication. The agency approved pivmecillinam (Pivya) in April 2024, an encouraging development, since germs that cause UTIs have become more resistant to existing medications, making the drugs less effective.

Summarily, bacterial infections such as streptococcal infections, tuberculosis, and UTIs present unique challenges that require a reasonable understanding of their pathophysiology, effective antibiotic therapies, and the implications of drug resistance.

Keywords: Bacterial Infection, Streptococcal Infection, Urinary tract Infection, Tuberculosis, Antibiotic Therapy, FDA, Pretomanid, Pivmecillinam, Prevention, Treatment.

1.Introduction:

Bacterial infections are diseases that can affect your skin, lungs, brain, blood and other parts of your body. You get them from single-celled organisms multiplying or releasing toxins in your body. Common bacterial diseases include UTIs, food poisoning, STIs and some skin, sinus and ear infections. They're often treated with antibiotics.

1.1 Bacteria

Bacteria are living things with only a single cell that can reproduce quickly. There are millions of bacteria that live all around us — in soil or water and on surfaces in our homes and workplaces. There are even millions of bacteria that live on your skin and inside of your body.

Most bacteria aren't harmful, and many are even helpful. They can help you digest food and kill off other harmful forms of bacteria that try to invade your body. But even the helpful ones can hurt you if they grow where they're not supposed to.

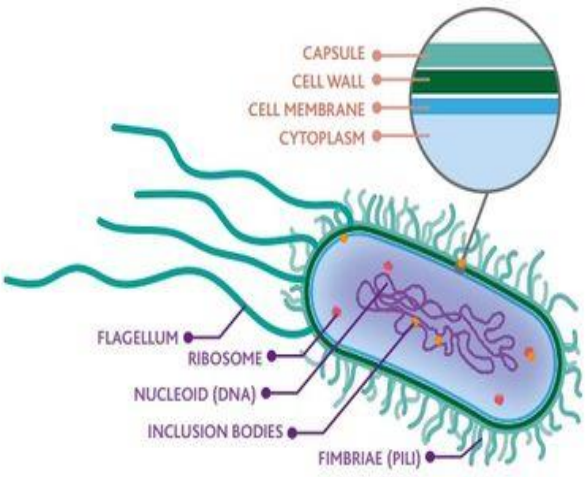


Figure 1: Image of bacteria

Bacteria are prokaryotic organisms that carry their genetic information in a double-stranded circular molecule of DNA. Some species also contain small circular plasmids of additional DNA. The cell cytoplasm contains ribosomes and there is both a cell membrane and, in all species except *Mycoplasma*, a complex cell wall. External to the cell wall, some bacteria have capsules, flagella, or pili. Bacteria normally reproduce by binary fission. Under the proper conditions, some bacteria can divide and multiply rapidly. Consequently, some infections require only a small number of organisms to cause potentially overwhelming infection.

Bacteria are classified as Gram-positive or Gram-negative based on the characteristics of their cell wall, as seen under a microscope after stains have been administered, a procedure called Gram staining, that was

developed in 1882 by Hans Christian Gram. Most, but not all, bacteria fall into one of these two categories. Clinically, one of the main differences between gram-positive and gram-negative organisms is that gram-negative bacteria tend to produce an endotoxin that can cause tissue destruction, shock, and death. The two classes of bacteria differ in their antibiotic susceptibilities as well.

1.2 Bacterial infection:

Bacterial infections are any illness or condition caused by bacterial growth or poisons (toxins). You can get sick from getting harmful bacteria in your skin, gut (GI tract), lungs, heart, brain, blood or anywhere else in your body.

Harmful bacteria from the environment, an infected person or animal, a bug bite or something contaminated (like food, water or surfaces) can cause infections. Bacteria that's not normally harmful but that gets into a place in your body where it shouldn't be can also cause infections.

Gram-positive and gram-negative bacteria are classified by their cell wall structure and how they stain in a Gram stain:

- **Gram-positive bacteria**

Have a thick cell wall (20–80 nm) and stain blue in a Gram stain.

Examples include TB and streptococci.

- **Gram-negative bacteria**

Have a thin cell wall (<10 nm) and an outer membrane, and stain red in a Gram stain.

Example UTIs

Gram-positive bacteria show blue or purple after gram-staining in a laboratory test. They have thick cell walls. Gram-negative bacteria show pink or red on staining and have thin walls

What causes bacterial infections?

Bacterial infections occur when bacteria enter your body. Once in your body they increase in number. This causes an immune reaction in your body.

Bacteria can enter your body through:

- a cut on your skin
- eating or drinking contaminated food or water
- breathing in droplets from an infected person
- touching dirty surfaces and then touching your eyes, nose, or mouth

Bacteria can also be transmitted by contact with blood and other bodily fluids.

Types of bacterial infections:

Bacteria can cause many types of infections, depending on how you're exposed and what part of your body it infects. Some common types of bacterial infections include:

- Food poisoning (gastroenteritis).
- Some skin,ear or sinus infections.
- Some sexually transmitted infections.
- Bacterial pneumonia.
- Most urinary tract infections (UTI`s)

1.3 Mode of transmission:

Bacterial infections can spread through droplets or dust in the air, direct or indirect contact, a vector (like a tick or mosquito) or contaminated food or water (vehicular).

- **Airborne or droplet**

bacterial infections can get through the air from contaminated dust or droplets of water or mucus (like phlegm or snot). Legionaries' disease, tuberculosis, meningococcal disease and strep throat spread this way.

- **Contact**

Bacterial infections can spread from direct contact with infected skin or mucous membranes, or from indirect contact with contaminated surfaces. Bacterial diseases you get by contact include skin infections and some sexually transmitted infections (STIs) like gonorrhoea and chlamydia.

- **Vector**

Infections you get from bugs (like mosquitos, ticks or fleas) are called vector-borne. You can get Rocky Mountain spotted fever, Lyme disease and shigellosis through vectors.

- **Vehicular**

While it sounds like something you get from your car, "vehicular" usually means you get sick from water or food (the "vehicle" of transmission). You can get gut (gastrointestinal) infections from *E. coli*, *Campylobacter* and *Salmonella* bacteria in contaminated food or water.

Who do bacterial diseases affect?

Anyone can get a bacterial disease, and most of us will at some point in our lives. You're at higher risk for getting an infection if you have:

- Diabetes
- A weakened immune system (due to HIV/AIDS, cancer, cancer treatments or immunosuppressive medication).

- An open wound.
- Had surgery recently.

1.4 Symptoms of a bacterial infection

Symptoms of bacterial infections vary depending on where in your body is infected. The main symptom is often fever, except skin infections, which usually cause redness or pain on your skin. Common symptoms of bacterial infections include:

- ✓ Fever.
- ✓ Chills.
- ✓ Fatigue (tiredness).
- ✓ Headache.

Additional symptoms can include:

- ✓ **Skin:** Redness, blisters, ulcers, swollen or painful skin.
- ✓ **GI tract:** Diarrhoea, stomach pain, nausea and vomiting.
- ✓ **Lungs:** Cough, shortness of breath, chest pain and phlegm (sputum).
- ✓ **Lining around your brain (meningitis):** Neck stiffness, nausea or vomiting, sensitivity to light and confusion.
- ✓ **In your bloodstream and spreading :** High fever, weakness, sweating and low blood pressure.

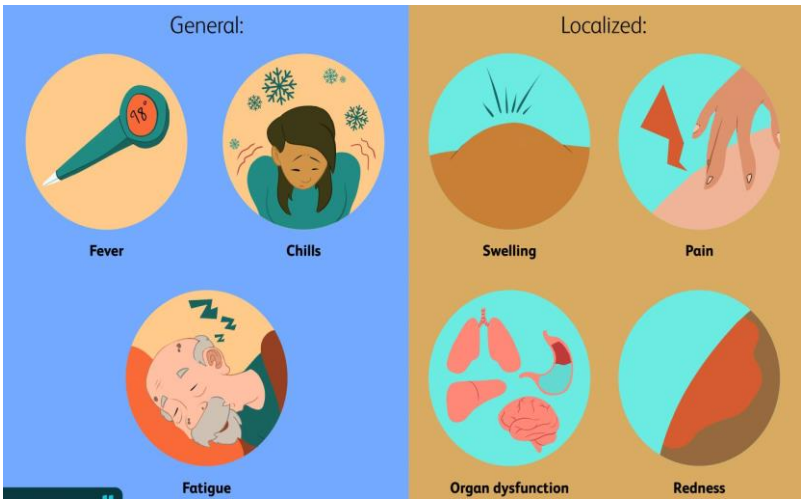


Figure 2: symptoms of bacterial infections

- **Heart (endocarditis):** High fever, chest pain, night sweats, shortness of breath, cough, muscle and joint pain.
- **Urinary tract or genitals:** Burning or pain when you pee, discharge from your penis or vagina, increased need to pee and painful intercourse.

Causes bacterial diseases

Many kinds of bacteria cause infections. You usually get bacterial infections when bacteria get into your body through your mouth, your nose, your eyes or a cut in your skin. Sometimes, bacteria that normally live on your skin or in your body get into places they're not supposed to (like through an injury) and reproduce.

How do you get a bacterial infection?

Common ways you can get bacterial infections include:

- Eating or drinking contaminated food or water.
- Eating or drinking unpasteurized dairy products.
- Antibiotic use, which can kill the good bacteria that usually fight off bad bacteria.
- From contaminated surfaces.
- From other people (through coughing or close contact).
- From getting contaminated water into your lungs (aspirating).
- Through oral, anal or vaginal sex.
- Through contaminated dirt (soil).
- From a bite from an infected tick, mosquito or flea.
- From a surgery or intubation (tube in your throat).

1.5 Prevention of Bacterial Infection

Among the top causes of mortality in the world, lower respiratory infection is the third most common and diarrhea is the sixth. Both are often caused by bacteria. Tuberculosis is the seventh most common cause of death. Clearly, measures to prevent infection have a dramatic impact on morbidity and mortality. Prevention is especially important in this age of increasing antibiotic resistance, because treatment can be so difficult to achieve. There are three major principals of control of bacterial infection: Eliminate or contain the source of infection, interrupt the chain of transmission, and protect the host against infection or disease. In addition,

there is increasing recognition that elimination of important cofactors, such as air pollution from vehicles or from indoor cooking, can markedly reduce the incidence of bacterial

Figure 3: Prevention of bacterial infection

infections. Which measure is most effective often depends on the reservoir for the infection. Prevention of infection, e.g., through a vaccine, is generally called primary prevention, treatment of infected people to prevent symptomatic infection is called secondary prevention, and treatment of infected people to prevent transmission to other humans is called tertiary prevention.

1.6 Treatment

An ideal antimicrobial agent acts at a target site that is present in the infecting organism but not the host cells. Four major sites in the bacterial cell can be targeted by antibiotics because they are sufficiently different from human cells. These are the cell wall, the cell membrane, the nucleic acid synthetic pathway, and the ribosome. Antibacterial agents, or antibiotics, are typically products of other microorganisms, elaborated by them in order to compete for space and resources. There are three ways to classify an antibacterial agent:

1.Based on whether it is bactericidal (kills bacteria) or bacteriostatic (inhibits growth of bacteria)

2.By its chemical structure

3.By its target site.

Some bacteria are innately resistant to certain classes of antibiotics, either because they lack the target or are impermeable to the drug. Others are innately susceptible but develop resistance by one of a growing variety of mechanisms. Resistant strains of bacteria have a selective advantage, surviving in the presence of antibiotics, and can spread throughout the host and even be transferred to other hosts. This phenomenon is important where antibiotic use is common, such as in hospitals or in congregate housing such as nursing homes. Some resistance genes are carried on plasmids, autonomously replicating circular extrachromosomal DNA molecules, and can thus be transferred to bacteria of other species. There are three main mechanisms of resistance:

1.Alteration in the target site

2.Alteration in access to the target site (by decreasing permeability or pumping antibiotic out of the cell)

3. Production of enzymes that inactivate the antibiotic.

When an individual takes an antibiotic, all of the microbes in his or her body are exposed to the drug, not just the organism causing infection. Since use of antibiotics is associated with the development of resistance, the prudent use of antibiotics is an essential component in the effort to combat the problem of antibiotic resistance. Throughout the world, antibiotics are overused and misused. Examples of improper use include the use of antibacterial agents for viral infections, for infections that resolve spontaneously without treatment and without a high risk for negative sequelae, and for infections caused by organisms not susceptible to the antibiotic used. Another example of misuse is the consumption of broad-spectrum antibiotics, which inhibit or kill a wide variety of organisms simultaneously, when a narrower spectrum agent will suffice.

SOME OF THE EXAMPLES FOR BACTERIAL INFECTIONS ARE

1. **Streptococcal Infections:**

Streptococcal infection is a bacterial infection caused by group A streptococcus (GAS) bacteria, which are commonly found on the skin and in the throat.

Streptococci are gram-positive aerobic organisms that cause many disorders, including pharyngitis, pneumonia, wound and skin infections, sepsis, and endocarditis. Symptoms vary with the organ infected. Sequelae of infections due to group A beta-haemolytic streptococci may include rheumatic fever and glomerulonephritis. Most strains are sensitive to penicillin, but macrolide-resistant strains have recently emerged.

2.1 Classification of Streptococci

Three different types of streptococci are initially differentiated by their appearance when they are grown in culture on sheep blood agar:

- Beta-haemolytic streptococci produce zones of clear haemolysis around each colony.
- Alpha-haemolytic streptococci (commonly called viridians streptococci) are surrounded by green discoloration resulting from incomplete haemolysis.
- Gamma-haemolytic streptococci are nonhemolytic.

Subsequent classification, based on carbohydrates in the cell wall, divides streptococci into 20 Lancefield groups A through H and K through V. In the Lancefield classification, enterococci were initially included among the group D streptococci but are now classified as a separate genus even though they do express Lancefield group D antigens. Lancefield groups K through V are streptococcal species of limited virulence that can cause infections in people who are immunocompromised.

Viridians streptococci form a separate group that is difficult to classify. Some streptococci such as streptococcus pneumonia are alpha-haemolytic, i.e., they are a type of viridians streptococci and do not express Lancefield antigens.

2.2 Diseases Caused by Streptococci

The most significant streptococcal pathogen is *S. pyogenes*, which is beta-haemolytic and in Lancefield group A and is thus denoted as group A beta-haemolytic streptococci (GABHS).

The most common acute diseases due to GABHS are

- Pharyngitis
- Infections
- Throat infection (pharyngitis)
- Tonsil infection (tonsillitis)
- Scarlet fever,
- skin sores

2.3 Delayed complications of streptococcal Infections The mechanism by which certain strains of GABHS cause delayed complications is unclear but may involve cross-reactivity of streptococcal antibodies against host tissue.

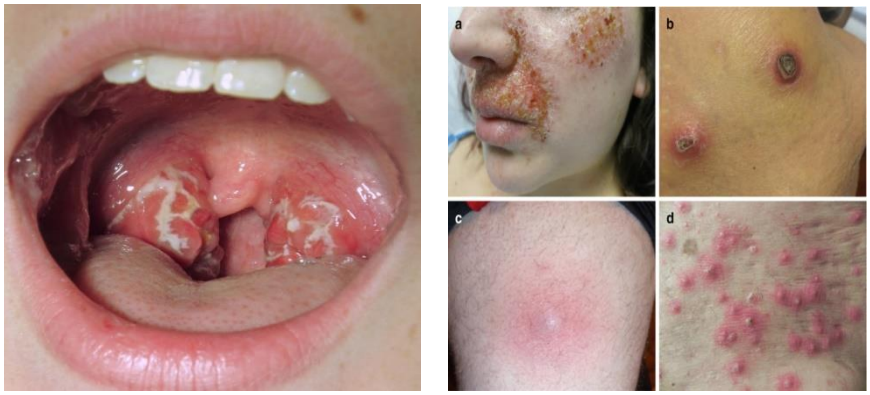


Figure 4: Streptococcal infections

Rheumatic Fever, an inflammatory disorder, occurs in < 3% of patients in the weeks after untreated GABHS pharyngitis. It has become much less common in developed countries, but incidence is still high in resource-limited regions.

Diagnosis of a first episode is based on a combination of arthritis, carditis, chorea, specific cutaneous manifestations, and laboratory test results

One of the most important reasons for treating GABHS pharyngitis (strep throat) is to prevent rheumatic fever.

Post-streptococcal glomerulonephritis is an acute nephritic syndrome following pharyngitis or skin infection due to a certain limited number of nephritogenic strains of GABHS (eg, M protein serotypes 12 and 49). After a throat or skin infection with one of these strains, about 10 to 15% of patients develop acute glomerulonephritis. It is most common among children, occurring 1 to 3 weeks after infection. Nearly all children, but somewhat fewer adults, recover without permanent renal damage. Antibiotic treatment of GABHS infection has little effect on the development of glomerulonephritis.

2.4 Treatment of streptococcal infections

Pharyngitis

Ordinarily, pharyngeal GABHS infections, including scarlet fever, are self-limited. Antibiotics shorten the course in young children, especially those with scarlet fever, but have only modest effect on symptoms in adolescents and adults. However, antibiotics help prevent local suppurative complications (e.g., peritonsillar abscess), otitis media, and rheumatic fever.

Penicillin is the drug of choice for pharyngeal GABHS infections. No isolate of GABHS has shown penicillin resistance clinically. However, some streptococcal strains appear to have in vitro tolerance to penicillin (ie, significantly decreased bactericidal effect of penicillin); the clinical significance of such strains is unclear.

A single injection of benzathine penicillin G 600,000 units IM for small children (< 27 kg) or 1.2 million units IM for children weighing ≥ 27 kg, adolescents, and adults usually suffices.

Oral medications may be used if the patient can be trusted to maintain the regimen for the required 10 days. Choices include

- Penicillin V 500 mg (250 mg for children < 27 kg) orally every 12 hours
- Amoxicillin 50 mg/kg (maximum 1 g) once a day for 10 days (which is an effective substitute for penicillin V)

Oral narrow-spectrum cephalosporins (eg, cephalexin, cefadroxil) are also effective and can be used unless patients have an anaphylactic reaction to penicillin. Azithromycin can be used for a 5-day course of therapy, although macrolides are inactive against *Fusobacterium necrophorum*, a common cause of pharyngitis in adolescents and adults. Delaying treatment 1 to 2 days until laboratory confirmation increases neither the duration of disease nor the incidence of complications.

When penicillin and a beta-lactam are contraindicated, choices include

- Clindamycin 600 mg (7 mg/kg for children) orally every 8 hours for 10 days
- Clarithromycin 250 mg (7.5 mg/kg for children) orally every 12 hours for 10 days
- Azithromycin 500 mg (15 mg/kg for children) orally once a day for 5 days
- Cephalexin 500 mg (20 mg/kg for children; maximum dose is 500 mg/dose) orally every 12 hours for 10 days
- Cefadroxil 1000 mg (30 mg/kg for children; maximum dose is 1000 mg/dose) orally once a day or 500 mg (15 mg/kg for children; maximum dose is 500 mg/dose) every 12 hours for 10 days

Because resistance of GABHS to macrolides has been detected, some authorities recommend in vitro confirmation of susceptibility if a macrolide is to be used and there is macrolide resistance in the community. Clindamycin 7 mg/kg orally every 8 hours is preferred in children who have relapses of chronic tonsillitis, possibly because of the following:

- Clindamycin has good activity against penicillinase-producing staphylococci or anaerobes coinfecting the tonsillar crypts and inactivating penicillin G.
- It appears to halt exotoxin production more rapidly than other medications. Amoxicillin/clavulanate is also effective.

Skin infection

Cellulitis is often treated without doing a culture because isolating organisms can be difficult. Thus, regimens effective against both streptococci and staphylococci are used; for example, one of the following may be used:

- Dicloxacillin or cephalexin if methicillin-resistant *Staphylococcus aureus* (MRSA) is not likely
- TMP/SMX, linezolid, minocycline, or clindamycin if MRSA is suspected.

Necrotizing fasciitis should be treated in an intensive care unit. Extensive (sometimes repeated) surgical debridement is required. A recommended initial antibiotic regimen is a broad-spectrum beta-lactam (eg, piperacillin/tazobactam) or a carbapenem (eg, meropenem, imipenem) (until etiology is confirmed by culture) plus clindamycin. Vancomycin should be added if infection with MRSA is suspected. Although streptococci remain susceptible to beta-lactam antibiotics, animal studies show that penicillin is not always effective against a large bacterial inoculum because the streptococci are not rapidly growing and may lack penicillin-binding proteins, which are the target of penicillin activity.

2.5 Prevention:

To prevent the spread of streptococcus infections,

- **Wash your hands**: Wash your hands frequently with soap and water, especially after using the bathroom, before and after preparing food, and after coughing or sneezing. If soap and water aren't available, use an alcohol-based hand sanitizer.
- **Cover your mouth**: Cover your mouth and nose with a tissue or your elbow when you cough or sneeze.
- **Avoid sharing**: Don't share eating utensils or drinking glasses with someone who is sick.
- **Clean surfaces**: Clean and disinfect high-touch surfaces and objects often.
- **Improve ventilation**: Open a window or door to improve indoor ventilation.
- **Stay home when sick**: If you have a sore throat, stay home from work, school, or daycare for at least 24 hours after starting antibiotics.
- **Keep wounds clean**: Watch wounds for signs of infection, like increasing redness, swelling, or pain. If you notice these signs, especially if you also have a fever, consult a doctor immediately.

3. Tuberculosis (TB)

Tuberculosis (TB) is an infectious disease 6that most often affects the lungs and is caused by Mycobacterium Tuberculosis. It spreads through the air when infected people cough, sneeze or spit. Tuberculosis is preventable and curable. About a quarter of the global population is estimated to have been infected with TB bacteria.

Types

- Pulmonary Tuberculosis
- Avian Tuberculosis
- Bovine Tuberculosis
- Miliary Tuberculosis / Disseminated Tuberculosis

3.1 Symptoms

People with latent TB infection don’t feel sick and aren’t contagious. Only a small proportion of people who get infected with TB will get TB disease and symptoms. Babies and children are at higher risk.

Certain conditions can increase a person’s risk for tuberculosis disease:

- diabetes (high blood sugar)
- weakened immune system (for example, HIV or AIDS)
- being malnourished
- tobacco use.

Unlike TB infection, when a person gets TB disease, they will have symptoms. These may be mild for many months, so it is easy to spread TB to others without knowing it.

Common symptoms of TB:

- prolonged cough (sometimes with blood)
- chest pain
- weakness
- fatigue
- weight loss
- fever
- night sweats.

The symptoms people get depend on where in the body TB becomes active. While TB usually affects the lungs, it also affects the kidneys, brain, spine and skin.

3.2 Risk Factors

- Close contact with someone who have active TB
- Immuno compromised status (elderly, cancer)
- Drug abuse and alcoholism
- People lacking adequate health care
- Pre-existing medical conditions
- Immigration from countries with higher incidence of TB
- HIV/AIDS
- Diabetes
- Chronic kidney disease
- Head and neck cancer
- Cancer treatments like chemotherapy
- Medications for rheumatoid arthritis or lupus
- Organ transplant medications

- Low body weight

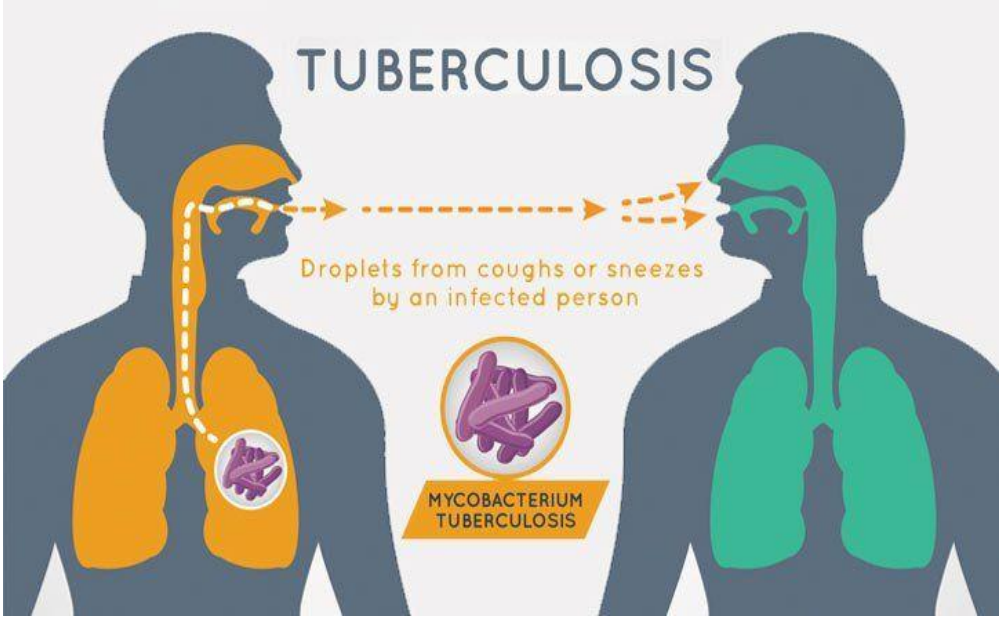


Figure 5: spread of TB

3.3 Pathophysiology:

When a person inhales air that contains droplet nuclei containing M. tuberculosis, most of the larger droplets become lodged in the upper respiratory tract (the nose and throat), where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection may begin. Infection may begin when droplet nuclei reach the alveoli. In the alveoli, some of the tubercle bacilli are killed, but a few multiply in the alveoli and enter the lymph nodes and bloodstream and spread throughout the body. Bacilli may reach any part of the body, including areas where TB disease is more likely to develop. These areas include the upper portions of the lungs, as well as the kidneys, the brain, and bone. Within 2 to 8 weeks, however, the body's immune system usually intervenes, halting multiplication and preventing further spread. The immune system is the system of cells and tissues in the body that protect the body from foreign substances. At this point, the person has latent TB infection (LTBI).

Management and Treatment

3.4Treatment:

Antitubercular drugs:1st line drugs

- Isoniazid.
- Rifampin.
- Ethambutol.
- Pyrazinamide.
- Rifapentine.

2nd line drugs: Fluoroquinolones: Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin.

Other oral drugs: Ethionamide, Protionamide, Cycloserine, Para-Amino salicylic acid, rifabutin.

Injectable drugs: Kanamycin, Amikacin, Capreomycin.

3.5 Mechanism of action of 1st line drugs:

Isoniazid:

Isoniazid is a prodrug and must be activated by bacterial catalase. Specifically, activation is associated with reduction of the mycobacterial ferric KatG catalase-peroxidase by hydrazine and reaction with oxygen to form an oxyferrous enzyme complex. Once activated, isoniazid inhibits the synthesis of mycologic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazid is bactericidal against actively growing intracellular and extracellular *Mycobacterium tuberculosis* organisms. Specifically, isoniazid inhibits InhA, the enoyl reductase from *Mycobacterium tuberculosis*, by forming a covalent adduct with the NAD cofactor. It is the INH-NAD adduct that act as a slow, tight-binding competitive inhibitor of InhA.

Rifampicin: Inhibits bacterial DNA-dependent RNA polymerase, thereby blocking RNA synthesis. This action disrupts protein synthesis and affects bacterial replication.

Pyrazinamide: The exact mechanism is not fully understood, but it is thought to disrupt mycobacterial cell membrane metabolism and transport functions. It is most effective in an acidic environment, such as that found in macrophages.

Ethambutol: Inhibits the synthesis of arabinogalactan, a critical component of the mycobacterial cell wall, by blocking the enzyme arabinosyl transferase.

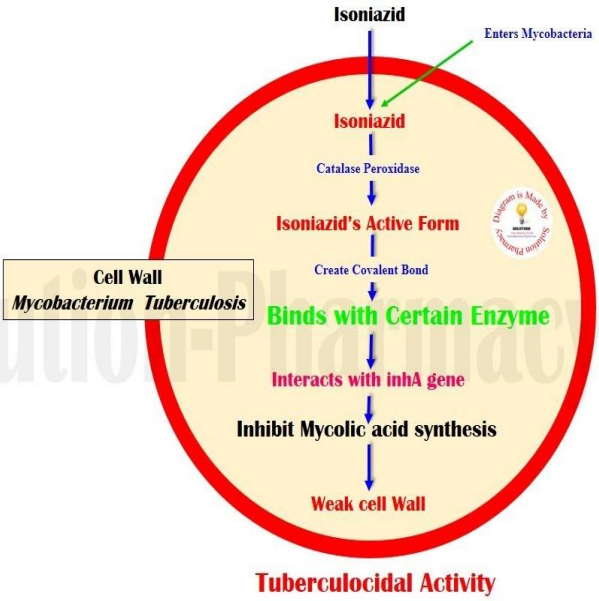


Figure 6: Mechanism of Isoniazid

3.6 Recent approval of FDA drugs for TB:

Pretomanid: Approved in 2019 as part of a combination regimen for the treatment of multidrug-resistant TB. It has a unique mechanism that affects the bacteria's energy metabolism. Pretomanid is an antibiotic used for the treatment of multidrug-resistant tuberculosis (MDR-TB). Its mechanism of action involves several key processes:

1. **Inhibition of Mycolic Acid Synthesis**: Pretomanid disrupts the synthesis of mycolic acids, which are essential components of the mycobacterial cell wall. This leads to destabilization of the cell wall structure.
2. **Nitroimidazoles Action**: As a nitroimidazole, pretomanid is activated under anaerobic conditions within the bacteria, generating reactive nitrogen species that can damage bacterial components.
3. **Energy Metabolism Disruption**: It interferes with the mycobacterial energy metabolism, which is crucial for the survival and replication of the bacteria.

Clofazimine: Approved for use in 2020 for multidrug-resistant TB, primarily known for its use in leprosy.

3.5 Prevention

Prevent spreading tuberculosis: You usually have to be in contact with someone with active TB for a long time before becoming infected. It helps to follow infection prevention guidelines like:

- Washing your hands thoroughly and often.`
- Coughing into your elbow or covering your mouth when you cough.
- Avoiding close contact with other people.
- Making sure you take all of your medication correctly.
- Not returning to work or school until you've been cleared by your healthcare provider. In the hospital, the most important measures to stop the spread of TB are having proper ventilation and using the correct types of personal protective equipment.

4. Urinary Tract Infection (UTIS):

A urinary tract infection is a very common type of infection in your urinary system. It can involve any part of your urinary system. Bacteria — especially E. coli — are the most common cause of UTIs. Symptoms include needing to pee often, pain while peeing and pain in your side or lower back. Antibiotics can treat most UTIs. A urinary tract infection (UTI) is an infection in any part of the urinary system. The urinary system includes the kidneys, ureters, bladder and urethra. Most infections involve the lower urinary tract — the bladder and the urethra. Women are at greater risk of developing a UTI than are men. If an infection is limited to the bladder, it can be painful and annoying. But serious health problems can result if a UTI spreads to the kidneys.

4.1 The urinary tract

The urinary tract is divided into two parts. The upper urinary tract includes the kidneys and ureters. The lower urinary tract includes the bladder and urethra. The kidneys remove waste and extra fluid from the blood to make urine. The urinary tract is made up of the kidneys, ureters, bladder, and urethra:

Upper urinary tract: The kidneys and ureters remove waste and extra fluid from the blood to make. Urine. **Lower urinary tract**: The bladder stores urine until it leaves the body through the urethra. The urinary tract removes waste and extra fluid from the body, regulates blood pressure and volume, and controls electrolyte and metabolite levels.

The urinary tract makes and stores pee. It includes your:

- Kidneys are small, bean-shaped organs on the back of your body, above your hips. Most people have two kidneys. They filter water and waste products from your blood, which becomes pee. Common wastes include urea and creatinine.

- Ureters Your ureters are thin tubes that carry pee from your kidneys to your bladder.

- Bladder Your bladder is a balloon-like organ that stores pee before it leaves your body.

- Urethra The urethra is a tube that carries pee from your bladder to the outside of your body.

4.2 Symptoms in adults

Lower UTIs affect the bladder or urethra and can cause:

- a frequent need to urinate
- pain, discomfort, or burning sensation when urinating
- a sudden urge to urinate
- cloudy, strong-smelling urine that may contain blood
- the sensation that the bladder is not fully empty
- feeling unwell, tired, and achy

Figure 7: Symptoms of TB

Upper UTIs affect the kidneys and ureters. As well as the symptoms above, they can cause:

- a fever of 100.4 ºF (38 ºC) or higher
- confusion
- agitation
- restlessness
- pain in the back and sides
- chills and shivering
- nausea and vomiting

In children

Additional symptoms in children include:

- a high temperature
- appearing generally unwell — for example, babies may appear irritable and not feed well
- vomiting
- wetting the bed or themselves

In older adults or those with a catheter

- wetting themselves
- new shivering
- new shaking
- agitation
- confusion

4.3 Types of Urinary Tract Infections

An infection can happen in different parts of your urinary tract. Each type has a different name, based on where it is.

1.Cystitis (bladder): You might feel like you need to pee a lot, or it might hurt when you pee. You might also have lower belly pain and cloudy or bloody urine.

2.Pyelonephritis (kidneys): This can cause fever, chills, nausea, vomiting, and pain in your upper back or side.

3.Urethritis (urethra): This can cause a discharge and burning when you pee.

4.4 Causes

Different bacteria live on the skin or around the rectum and vagina. When the bacteria enter the urethra, they can travel to the bladder. The body usually flushes out the bacteria before they reach a person's bladder. However, in some cases, the body is unable to do so, resulting in a UTI.

UTIs occur due to the following bacteria:

- *Escherichia coli*
- *Protus mirabilis*
- *Enterococcus faecalis*
- ***Staphylococcus saprophyticus***
- *Klebsiella pneumoniae*

People of any age and sex can develop a UTI. However, some people are more at risk than others.

Risk factors:

UTIs are more common in females because their urethras are shorter and closer to the rectum. This makes it easier for bacteria to enter the urinary tract.

Other risk factors:

A previous UTI.

Recent sexual activity.

Changes in the bacteria that live inside the vagina or vaginal flora. For example, menopause or the use of spermicides can cause these bacterial changes.

Pregnancy.

Age (older adults and young children are more likely to get UTIs).

Structural problems in the urinary tract, such as enlarged prostate.

Poor hygiene, for example, in children who are potty-training.

4.5 Chronic UTIs:

In some people UTI symptoms do not go away. Short-term antibiotics do not work and urine tests do not show an infection.

This might mean you have a chronic (long-term) UTI. This can be caused by bacteria entering the lining of the bladder.

Because urine tests do not always pick up the infection and the symptoms can be similar to other conditions, chronic UTIs can be hard to diagnose.

Chronic UTIs might be treated with antibiotics that you take for a long time.

Chronic UTIs can have a big impact on your quality of life. If you have been treated for a UTI but you still have symptoms, speak to your GP about chronic UTIs and ask to be referred to a specialist.

4.6 Management of UTIS

The first step is to increase the intake of fluid, to help flush infection out. There is a temptation to drink less fluid if it is painful to pass urine, but it makes things worse to get dehydrated. At least 2 litres of fluid a day (5 large glasses) should be taken; the more, the better. Some urine infections can be treated with these measures, and antibiotics may not be necessary.

If antibiotics are needed, the best choice is one to which the bug has been proven to be sensitive in the laboratory. However, it takes 2 days to get this result so in most cases it is best to start treatment right away, using the antibiotic which is most likely to work. The choice of antibiotic depends on which have worked or caused side effects in the past, and on the local guidelines for antibiotic use. If you have an allergy to an

antibiotic, or have had side effects from antibiotics in the past, tell the person prescribing, do not wait to be asked or assume this information will be on your records.

Antibiotics are usually given for a course of 3-7 days, depending on the severity of the infection and whether there is underlying kidney disease or diabetes. In severe infections it may be necessary to give antibiotics and fluids through a drip into a vein, but this is not often needed.

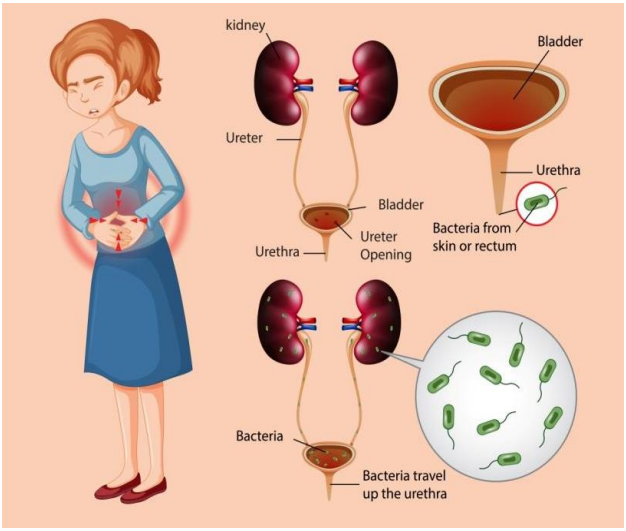
Mostly antibiotics are these may also include drugs like

Quinolones: Nalidixic Acid, Norfloxacin, Enoxacin, Ciprofloxacin, Ofloxacin, Moxifloxacin, Gatifloxacin,

Nitrofurantoin: Nitrofurantoin is an antibiotic used to treat urinary tract infections.

Nitrofurantoin is a nitrofuran antibiotic used to treat uncomplicated urinary tract infections. Nitrofurantoin is converted by bacterial nitroreductases to electrophilic intermediates which inhibit the citric acid cycle as well as synthesis of DNA, RNA, and protein. This drug is more resistant to the development of bacterial resistance because it acts on many targets at once. Nitrofurantoin is a second line treatment to trimethoprim. Nitrofurantoin was granted FDA approval on 6 February 1953. Nitrofurantoin interferes with vital processes in bacteria, which leads to their death. Nitrofurantoin rapidly reaches therapeutic concentrations in the urine and is also cleared rapidly.

Figure 8: Effect of bacteria on kidney



Management of Uncomplicated UTIs

Antibiotic treatment has varied historically from 3 days to 6 weeks. There are excellent cure rates with "mini-dose therapy," which involves just 3 days of treatment.

E. coli resistance to common antimicrobials varies in different areas of the country. Another drug should be chosen if the resistance rate is >50% to any particular antibiotic.

First-line agents for uncomplicated UTIs include nitrofurantoin, sulfamethoxazole/trimethoprim, Fosfomycin, and first-generation cephalosporins. Outside the US, pivmecillinam is also considered first-line therapy.

- **Nitrofurantoin** is perhaps the preferred choice for uncomplicated UTIs, but it is bacteriostatic, not bactericidal, and must be used for 5 to 7 days. It has several mechanisms of action that affect bacteria, so resistance is relatively uncommon. It is only effective in the lower urinary tract due to poor tissue concentrations and cannot be used for presumed or possible pyelonephritis. It is the preferred drug for low-dose long-term prophylaxis in patients with recurrent UTIs.

- **Sulfamethoxazole/trimethoprim** for 3 days is good mini-dose therapy, but resistance rates are high in many areas. It should not be used if local bacterial resistance is >20% or in patients with a sulfa allergy. Sulfamethoxazole/trimethoprim is generally the alternate drug of choice for long-term prophylaxis in patients with recurrent UTIs.

- **Fosfomycin** is FDA-approved as a single-dose therapy for uncomplicated UTIs. It may be effective when there is significant resistance to other antimicrobials. A single dose will provide therapeutic urinary concentrations for 2 to 4 days and is comparable to 7- to 10-day therapy with other agents. Adjunctive therapy with phenazopyridine for several days may provide additional symptomatic relief.

- **First-generation cephalosporins** are good choices for mini-dose (3-day) therapy but should not be overused to avoid resistance.

- **Fluoroquinolones** have high resistance but are preferred for pyelonephritis and prostatitis due to their high tissue penetration levels, especially in the prostate. For this reason, fluoroquinolones are not preferred for uncomplicated UTIs but may be used when other agents are not acceptable. Fluoroquinolones and nitrofurantoin are mutually antagonistic and should not be used together. Recent precautions from the FDA about fluoroquinolone side effects should be considered carefully. For simple, uncomplicated cystitis, norfloxacin is suggested. It is a quinolone specifically designed for lower urinary tract infections as it cannot be used for pyelonephritis.

- **Pivmecillinam** is considered first-line therapy for uncomplicated UTIs elsewhere in the world. It is not recommended in pyelonephritis or suspected systemic infections due to inadequate tissue penetration.

Even without treatment, UTIs will spontaneously resolve in about 20% of women, especially with increased hydration. The likelihood that a healthy nonpregnant female will develop acute pyelonephritis is very small.

Here are some recently approved drugs for urinary tract infections (UTIs) in India:

- **Plazomicin**: An intravenous aminoglycoside antibiotic approved by the Central Drugs Standard Control Organization (CDSCO) to treat complicated UTIs, including kidney infections
- **Enmetazobactam**: Approved by DCGI
- **Cefepime/enmetazobactam (Exblifep)**: An intravenous fourth generation cephalosporin plus beta-lactamase inhibitor.

For the first time in 20 years, doctors will have a new antibiotic to treat urinary tract infections (UTIs) in women. The FDA approved **pivmecillinam (Pivya)** in April 2024 — an encouraging development, since germs that cause UTIs have become more resistant to existing medications, making the drugs less effective. Here's how pivmecillinam might affect treatment Pivmecillinam is a type of penicillin taken orally. It's been prescribed in European countries more than 30 million times over the past 40 years as a first-line treatment for "uncomplicated" urinary tract infections.

4.7 Prevention:

To prevent a urinary tract infection (UTI), you can

Drink fluids: Drink at least 50 ounces of fluids daily to keep your bladder tissue healthy and hydrated.
Empty your bladder: Regularly empty your bladder to remove urine that has been sitting in your bladder for a long time.

Urinate after sex: Urinate before and after sexual activity to help prevent bacteria from getting into the urethra. You can also drink an extra two glasses of water after sex.

Practice good hygiene: Wipe from front to back after using the bathroom and after a bowel movement. Avoid douching, spray s, or powders in the genital area. Take showers instead of baths.

Wear cotton underwear: Wear cotton-cloth underwear and pantyhose, and change both at least once a day. Avoid tight-fitting pants.

Eat high-fibre foods: Eat foods like bananas to encourage regular bowel movements and relieve pressure on urine flow.

Consider cranberry supplements: Cranberry supplements or juice may help prevent UTIs, but you should talk to your doctor first, especially if you take blood-thinning medications or aspirin.

Avoid spermicidal jelly: Spermicidal jelly can kill normal vaginal florae, which are important in suppressing colonization with pathogenic bacteria.

Future Scope:

In the United States, novel antibiotics approved by the FDA in recent years are a critical component of efforts to address global challenges in antimicrobial resistance, but the war against drug-resistant bacteria is far from over. With the new onslaught of multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens, therefore, research and development in antibiotics will have a great responsibility in defining the future skyline in terms of infection control and treatment. We outline here some of the potential future directions and opportunities for research into recently FDA-approved antibiotics.

Answer to the Challenge of Multidrug-Resistant Gram-Negative Pathogens Current Landscape: Recently approved antibiotics include cefiderocol, plazomicin, and relebactam. Current Landscape: These target Gram-negative bacteria: considered one of the most challenging due to their ability to easily acquire resistance mechanisms, such as the production of beta-lactamases, efflux pumps, or alterations in porin channels.

Synergistic Combinations: New antibiotic combinations with older existing antibiotics or beta-lactamase inhibitors may overcome resistance more effectively. Relebactam, cefazidime-avibactam, and combinations that include betalactamase inhibitors can be formulated to fight resistance. **Antimicrobial compounds targeting bacterial resistance mechanisms:** potential sources for the next generation of antibiotics: Part of the challenge in identifying molecules that can block or overcome bacterial resistance mechanisms involves research on those that block or modify beta-lactamases, inhibit efflux pumps, or alter porin genes.

Optimizing drug delivery and formulation

Current Landscape: Most of the FDA-approved antibiotics, such as omadacycline and delafloxacin, have advantages with regard to oral bioavailability, while these drugs for patients who suffer from more severe infections are still in intravenous formulations.

Future Research: Oral Antibiotics in Severe Infections. More research will be devoted to developing a library of orally deliverable antibiotics that may become as potent in combating severe infections due to MDR. The development and improvement of oral antibiotics are crucial for the management of serious pneumonia, sepsis, intra-abdominal infections among others, and to prevent potential hospitalizations.

Long-acting formulations: The development of extended release or injectable long-acting formulations may be possible. These would likely decrease the frequency at which the drug would need to be administered, optimize patient compliance, and manage steady-state drug concentration for an extended period.

Targeted delivery: In the near future, advanced drug delivery systems like nanoparticles or liposomal formulations could ensure direct delivery of antibiotics to the site of infection with minimal systemic side effects and greater efficacy, particularly when the drug cannot easily reach the site of action - the brain, for instance, or the bones, or any abscess.

Examining Anti-Biotics for Non-Traditional Infections

Current Landscape Most of the newly approved antibiotics in recent years, however, have targeted more common hospital-acquired infections, such as cUTIs, cIAIs, and pneumonia. For skin and soft tissue infections, omadacycline and delafloxacin are only the latest additions to this class.

Emerging Pathogens: The area here is for investigation into antibiotics targeted against less common but emerging bacterial pathogens, for example, Nocardia, Mycobacterium tuberculosis or Burkholderia cepacia increasingly showing resistance to existing therapies.

Biofilm-Forming Infections: Most chronic infections are biofilm associated and protect pathogens from antibiotics and the immune system. An important avenue for improvement in treating chronic infections such as cystic fibrosis or infections of prosthetic joints may be opened by a search for antibiotics or adjunctive therapies that can disrupt or penetrate biofilms.

Conclusion:

In summary, bacterial infections represent a significant health challenge, affecting various systems within the human body. While many bacteria play beneficial roles in our daily lives, the pathogenic strains can lead to serious illnesses that require timely and appropriate treatment. Understanding the nature of bacteria—specifically their classification as Gram-positive or Gram-negative—is crucial for effective diagnosis and management, especially considering the differences in antibiotic susceptibility between these groups.

Preventive measures, such as practicing good hygiene, proper food handling, and being mindful of environmental exposure, can significantly reduce the risk of bacterial infections. Awareness of how bacteria enter the body and the common types of infections they cause empowers individuals to take proactive steps to protect their health. FDA Approved Pretomanid in 2019 as a part of combination regimen for treatment of multidrug resistant TB. FDA also approved Pivmecillinamin April 2024 since UTIs have become more resistant to existing medication making the drug less effective. Ultimately, a comprehensive understanding of bacteria and their impact on health is vital for both individual well-being and public health initiatives.