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GRAM-NEGATIVE BACTERIA EXHIBIT UNIQUE BIOCHEMICAL CHARACTERISTICS IMPORTANT FOR THEIR SURVIVAL, ADAPTABILITY, AND PATHOGENICITY

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ABSTRACT

Gram-negative bacteria are a group of microbes characterized by their particular cell wall structure, biochemical processes, and metabolic pathways. In infections, Gram-negative bacteria play a critical role in pathology, antibiotic resistance, and host interactions. Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, can cause infections that are difficult to treat and sometimes fatal. Gram-negative bacteria take advantage of diverse molecular mechanisms to infect the host and evade the immune system. These bacteria have both intrinsic and acquired resistance mechanisms, thus making therapy difficult. The molecular pathways underlying their pathogenicity are quite complex and therefore, in-depth studies on these topics can generate new therapeutic strategies and combat resistance.

KEYWORDS: *Gram-negative, bacteria, infection, immune evasion, resistance*

INTRODUCTION

Gram-negative bacteria are a diverse group of microorganisms characterized by their unique cell wall structure, biochemical processes, and metabolic pathways. These bacteria play significant roles in various ecosystems and human health, both as commensals and pathogens.

Gram-negative bacteria exhibit unique biochemical characteristics that are integral to their survival, adaptability, and pathogenicity. Their complex cell wall structure, diverse metabolic capabilities, and mechanisms of resistance and virulence underscore the need for continued research to develop effective therapeutic strategies. Understanding these biochemical aspects is essential for addressing the challenges posed by Gram-negative bacterial infections and for advancing clinical and microbiological interventions.

DISCUSSION

One of the defining features of Gram-negative bacteria is their distinctive cell wall, which includes an outer membrane, a periplasmic space, a peptidoglycan layer, and a cytoplasmic membrane (1). The outer membrane is an asymmetric bilayer that contains lipopolysaccharides (LPS) in the outer leaflet and phospholipids in the inner leaflet (2). LPS, or

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endotoxin, is composed of the core polysaccharide lipid A and O antigen (3). Lipid A is responsible for the toxic effects associated with Gram-negative bacterial infections, including fever, inflammation, and septic shock (4).

The periplasmic space is located between the outer membrane and the inner cytoplasmic membrane. This space contains a thin layer of peptidoglycan and various enzymes involved in nutrient acquisition and transport, as well as antibiotic resistance (5). Unlike Gram-positive bacteria, Gram-negative bacteria have a relatively thin peptidoglycan layer. This layer provides structural support and is crucial for maintaining cell shape and integrity (6). The cytoplasmic membrane is the innermost membrane that controls the influx and efflux of substances, playing a key role in energy production and nutrient transport.

Gram-negative bacteria exhibit a variety of biochemical pathways that enable their survival and pathogenicity. Metabolism includes catabolism and anabolism, which are important processes for the integrity of these bacteria (7). Gram-negative bacteria can utilize diverse carbon sources through aerobic and anaerobic respiration, fermentation, and other metabolic pathways (8). For example, *Escherichia coli* can grow in both aerobic and anaerobic conditions, metabolizing sugars like glucose through glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (9). Gram-negative bacteria synthesize essential biomolecules, including amino acids, nucleotides, and lipids, using intermediates from central metabolic pathways.

Gram-negative bacteria produce enzymes such as beta-lactamases, proteases, and lipases, which have important effects for the biological activity of the bacteria (10,11). Beta-lactamases are enzymes that confer resistance to beta-lactam antibiotics by hydrolyzing the antibiotic's beta-lactam ring (12). Various beta-lactamases, such as extended-spectrum beta-lactamases (ESBLs) and carbapenemases, contribute to the resilience of pathogens like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Proteases and lipases are enzymes that degrade host tissues and promote nutrient acquisition. For instance, *P. aeruginosa* produces elastase, which degrades elastin in host tissues (13).

Gram-negative bacteria possess complex efflux systems, such as the AcrAB-TolC pump in *E. coli*, which expel toxic substances, including antibiotics, out of the cell (14). These pumps contribute significantly to multidrug resistance by reducing the intracellular concentration of antimicrobial agents.

Several biochemical factors contribute to the pathogenicity of Gram-negative bacteria, including toxins, adhesion molecules, and biofilm formation (15). LPS induces strong immune responses, leading to inflammation and septic shock, and exotoxins secreted by bacteria disrupt host cellular processes (16). Examples include Shiga toxin from Shigella species and *E. coli*, and cholera toxin from *Vibrio cholerae*. The adhesion molecules Pili and Fimbriae are hair-like structures that facilitate attachment to host cells. For example, type 1 fimbriae in *E. coli* enable binding to urinary tract epithelial cells, contributing to urinary tract infections (17). Gram-negative bacteria can form biofilms, complex communities of bacteria adhering to surfaces and encased in a self-produced extracellular matrix (18). Biofilms protect bacteria from antibiotics and the host immune system. *P. aeruginosa* is notorious for biofilm formation in chronic infections such as those in cystic fibrosis patients (19).

Molecular Mechanisms of Gram-Negative Bacterial Infections

Gram-negative bacterial infections pose significant challenges due to their intricate molecular mechanisms that facilitate infection, survival, and resistance within the host. Understanding these mechanisms is crucial for developing effective treatments and preventing the spread of infections.

Gram-negative bacteria successfully infect the organism by means of adherence and colonization, invasion and intracellular survival, evasion of the host immune response, the production of toxins, and by utilizing mechanisms of resistance to antibiotics (Table I).

Table I. *Infectious stages of Gram-negative bacteria.*

Adherence:	Bacteria use pili and fimbriae to adhere to host cells, creating a tissue infection.
Invasion:	Bacteria can invade host cells or tissues, using secretion systems to manipulate host cell functions.
Immune Evasion:	Bacteria modify their surface antigens or produce enzymes that degrade host immune components to escape the immune system.
Pathological effect:	The release of lipopolysaccharides (LPS) and the destruction of host tissues allows bacteria to spread into the tissue, causing severe pathogenic effects such as septic shock.

In the initial phase of adherence and colonization, Gram-negative bacteria use adhesins, including pili (fimbriae) and non-pilus adhesins, to attach to host cells (20). This attachment is the first step in colonization and infection. For instance,

uropathogenic *E. coli* (UPEC) use type 1 pili to bind to mannose residues on the bladder epithelium (21), while *Neisseria gonorrhoeae* uses type IV pili for attachment to mucosal surfaces (22).

Many Gram-negative bacteria can form biofilms, which are communities of bacteria embedded in a self-produced extracellular polymeric matrix (23). Biofilms enhance bacterial survival and resistance to antibiotics and host immune responses. *P. aeruginosa* forms biofilms in the lungs of cystic fibrosis patients, contributing to chronic infection and treatment difficulties.

To assist invasion and intracellular survival, some Gram-negative bacteria, such as *Salmonella* spp. and *Shigella* spp., use type III secretion system (T3SS) to inject effector proteins into host cells (24). These effectors manipulate host cell processes to facilitate bacterial invasion and evasion of the immune response. For example, *Salmonella* Typhimurium uses T3SS to induce membrane ruffling in host cells, promoting bacterial uptake and creating a niche for intracellular survival (25). Similar to T3SS, the type IV secretion system (T4SS) is used by bacteria like *Legionella pneumophila* to transfer effector proteins into host cells, promoting intracellular replication and survival within macrophages (26).

To evade the host immune response, Gram-negative bacteria can modify LPS (27). LPS is a major component of the outer membrane of Gram-negative bacteria and is recognized by the host immune system, however, to evade detection, bacteria can modify their LPS structure. For example, *Helicobacter pylori* alter LPS to avoid recognition by toll-like receptors (TLRs), helping it persist in the gastric mucosa (28). Some Gram-negative bacteria, such as *K. pneumoniae*, produce a polysaccharide capsule that protects them from phagocytosis and complement-mediated killing (29). The capsule inhibits opsonization, thereby allowing the bacteria to evade the host immune system.

N. gonorrhoeae and *Neisseria meningitidis* can alter the expression of surface proteins, such as pili and outer membrane proteins, through antigenic variation (30,31). This mechanism helps them evade immune detection and persist within the host.

LPS, specifically the lipid A component, acts as an endotoxin and triggers a strong inflammatory response when released into the host bloodstream (32). Even with a low concentration of LPS, this can lead to fever, septic shock, and multiple organ failure, as seen in severe Gram-negative bacterial infections (33). Gram-negative bacteria also produce exotoxins that directly damage host tissues or interfere with normal cellular functions. For example, the cholera toxin produced by *Vibrio cholerae* induces severe watery diarrhea by disrupting ion transport in intestinal epithelial cells (34).

Gram-negative bacteria can also resist antibiotics by utilizing enzymes such as beta-lactamases and mechanisms including efflux pumps and porin alterations (35). Enzymes such as ESBLs and carbapenemases degrade beta-lactam antibiotics, rendering them ineffective. This mechanism is prevalent in Enterobacteriaceae, including *E. coli* and *K. pneumoniae* (36). Many Gram-negative bacteria possess efflux pumps that expel antibiotics from the cell, reducing drug accumulation and effectiveness. The AcrAB-TolC efflux system in *E. coli* is an example that contributes to multidrug resistance (37). Changes or loss of porins in the outer membrane can decrease antibiotic uptake. *P. aeruginosa* often exhibits reduced porin expression, contributing to its high level of intrinsic resistance to many antibiotics.

CONCLUSIONS

Gram-negative bacteria employ a variety of sophisticated molecular mechanisms to establish infections, evade host defenses, and resist antimicrobial treatments. These mechanisms include adherence and colonization, invasion and intracellular survival, immune evasion, toxin production, and antibiotic resistance. Understanding these processes at the molecular level is essential for developing new therapeutic strategies and combating the growing threat of antibiotic-resistant Gram-negative bacterial infections. Continued research in this field is vital to improve clinical outcomes and public health.

Conflict of interest

The author declares that they have no conflict of interest.

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URINARY TRACT BACTERIAL INFECTIONS: *ESCHERICHIA COLI, KLEBSIELLA PNEUMONIAE, PROTEUS MIRABILIS, STAPHYLOCOCCUS SAPROPHYTICUS, ENTEROCOCCUS FAECALIS*

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ABSTRACT

Urinary tract infections (UTIs) are very common bacterial infections that occur more often in women than in men and mainly affect the kidneys, ureters, bladder, and urethra. Bacteria enter the urinary tract through the urethra and travel up to the bladder, the route that is responsible for most UTIs. In rarer cases, bacteria can spread to the urinary system from the bloodstream, especially in immunocompromised patients. Once inside the urinary tract, bacteria adhere to the lining cells of the urinary tract using Pili (as in E. coli), type 1 fimbriae that bind to mannose receptors, and P-fimbriae that bind to specific receptors on kidney cells, contributing to pyelonephritis. The classic symptoms of UTIs include the frequent urge to urinate, a burning sensation during urination, the passage of frequent, small amounts of urine, cloudy or strong-smelling urine, and pelvic pain in women and rectal pain in men. If left untreated, these can progress to more serious symptoms and other complications such as kidney infection or sepsis. UTIs are frequently treated with antibiotics such as Trimethoprim-sulfamethoxazole, Nitrofurantoin, Ciprofloxacin (used less frequently due to potential side effects), and Amoxicillin/clavulanate.

KEYWORDS: *urinary tract, infection, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus saprophyticus, Enterococcus faecalis*

INTRODUCTION

Urinary tract infections (UTIs) are predominantly caused by bacteria, although viruses can also contribute to these infections. Understanding the biological and molecular mechanisms of UTIs involves examining how pathogens invade, adhere to, and propagate within the urinary tract. UTIs are infections that affect any part of the urinary system, including the kidneys, ureters, bladder, and urethra. Most infections involve the lower urinary tract in the bladder and urethra. UTIs are typically caused by bacteria entering the urinary tract through the urethra and multiplying in the bladder (1). These infections can lead to persistent or severe symptoms, including high fever, back pain, or blood in the urine, and can be recurring. Proper diagnosis and treatment are essential to prevent complications, such as kidney infections or sepsis, which can arise from untreated UTIs (2).

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Common bacteria that cause UTIs include *Escherichia coli*, *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis* (3). Uropathogenic *E. Coli* (UPEC) is the most common cause of UTI (4). *S. saprophyticus* is the second- leading cause, especially in younger women (5). In addition to these, other bacteria, viruses, or fungi can also cause UTIs (Table I).

Table I. *Common bacterial and viral pathogens that cause urinary tract infections (UTIs).*

Bacterial pathogens	• Uropathogenic *Escherichia coli* (UPEC): The most common causative agent • *Klebsiella pneumoniae* • *Proteus mirabilis* • *Staphylococcus saprophyticus* • *Enterococcus faecalis*
Viral pathogens	• Adenoviruses • Polyomaviruses: BK virus and JC virus • Cytomegalovirus (CMV)

DISCUSSION

UTIs begin with the colonization of the urethra, and subsequently the bladder, by uropathogens through the action of specific adhesins. UTIs are commonly initiated by UPEC which enter the urinary tract through the urinary meatus and ascend the urethra into the bladder lumen (6). The bacterium can adhere to the urothelium and UPEC strains and uses mannose-sensitive type 1 fimbriae and papG adhesion P pili to adhere to epithelial cells of the bladder and kidney (7,8).

Adhesins are proteins that help bacteria bind to glycoproteins on the surface of uroepithelial cells (9). Pathogenic bacteria begin invasion after attachment to targets and can invade uroepithelial cells, creating intracellular bacterial communities (IBCs) (10). At the intracellular level, these bacteria replicate and evade the host's immune response (11). Bacteria can form biofilms, which protect them from antibiotics and the host immune system, on urinary catheters and inside the bladder, contributing to chronic and recurrent infections (12).

These bacteria can produce hemolysin, toxins such as alpha-hemolysin produced by *E. Coli*, capable of lysing host cells and releasing nutrients for bacterial growth (13). The release of bacterial cytotoxins damages host tissues and causes the immune reaction. Additionally, bacterial pathogens produce siderophores to scavenge iron from the host, which is essential for bacterial growth (14). The bacteria are capable of evading the immune system by forming a protective layer around the capsule, which allows them to protect themselves from the phagocytosis of macrophages and polymorphonuclear cells (15).

Escherichia coli

E. Coli is the most common cause of UTIs, responsible for up to 80-90% of all cases (16,17). *E. Coli* bacteria normally live in the intestines and are harmless there. However, when they enter the urinary tract, they can cause an infection. *E. Coli* can enter the urinary tract from the intestines through several pathways. By ascension through the urethra, *E. Coli* from the intestines can reach the urethra and travel up into the bladder or can transfer *E. Coli* from the anal area to the urethra due to improper hygiene (18). Sexual transmission is another route for infection and can facilitate the movement of *E. Coli* from the vaginal or anal area to the urethra.

Symptoms of UPEC UTIs are similar to those of other UTIs and can include the frequent urge to urinate, a burning sensation during urination, the passage of frequent, small amounts of urine, cloudy or strong-smelling urine, pelvic pain in women and rectal pain in men (19). The diagnosis of the infection is made by collecting urine which is analyzed for the presence of bacteria, white blood cells, and red blood cells. A urine culture is then performed, which helps to identify the specific bacteria causing the infection and determines sensitivity to antibiotics.

E. Coli infections are primarily treated with antibiotics. The choice of antibiotic and duration of treatment depend on the severity of the infection and any patterns of antibiotic resistance. Commonly used antibiotics include Trimethoprim/sulfamethoxazole (Bactrim, Septra), Nitrofurantoin (Macrobid, Macrodantin), Fosfomycin (Monurol), Ciprofloxacin (Cipro), and other fluoroquinolones (usually reserved for more complicated cases) (20).

Klebsiella pneumoniae

K. pneumoniae is a bacterium that can cause a variety of infections, including UTIs. This pathogen is known for its ability to acquire resistance to multiple antibiotics, making infections challenging to treat (21). Symptoms of a *K. pneumoniae* UTI can include the frequent urge to urinate, pain or a burning sensation during urination, cloudy or strong-smelling urine, blood in the urine, lower abdominal pain or discomfort, and fever and chills, particularly if the infection has spread to the kidneys.

Proteus mirabilis

P. mirabilis is a gram-negative, facultatively anaerobic bacterium that is a well-known cause of UTIs. *P. mirabilis* is a rod-shaped bacterium with numerous peritrichous flagella and is very motile. It is characterized by rapid movements with ease of colonizing tissues. *P. mirabilis* produces the enzyme urease, which hydrolyzes urea into ammonia and carbon dioxide, leading to an increase in urine pH (22). In humans and some animals, it is present in the gastrointestinal tract and can play an important role in the pathogenesis of UTIs (23). It can colonize and infect the bladder and kidneys. *P. mirabilis* alkalizes urine, promoting the formation of struvite (magnesium ammonium phosphate) and apatite (calcium phosphate) kidney stones (24). *P. mirabilis* can cause acute cystitis with inflammation of the bladder and painful urination (dysuria), and pyelonephritis with fever. Therapy uses first-line agents such as trimethoprim-sulfamethoxazole, fluoroquinolones, or ampicillin (25). Understanding the specific features and behaviors of *P. mirabilis* helps in effectively diagnosing and treating UTIs caused by this bacterium, thereby reducing complications and recurrence rates.

Staphylococcus saprophyticus

S. saprophyticus is a notable pathogen in the context of UTIs, particularly among young women. *S. saprophyticus* is a Gram-positive, coagulase-negative bacterium that is a common cause of UTIs. Its ability to adhere to the urinary tract and form biofilms, along with its production of urease, contributes to its pathogenicity (26). Prompt diagnosis and appropriate antibiotic treatment are essential for effective management and to prevent complications. Its incidence in causing UTIs is 5-15% (27) and in addition to women, it can also infect men of all ages. Very often, there is a high rate of infectivity in autumn. *S. saprophyticus* has the ability to adhere to the lining of the urinary tract (urothelium) using proteins and lipoteichoic acids (28). It can hydrolyse urea into ammonia and increase the pH of urine, an action that contributes to its colonization (29). Some strains of *S. saprophyticus* can form biofilms that aid their ability to persist in the urinary tract and resist host immune responses (30).

The typical symptoms of UTI infection by *S. saprophyticus* include painful urination, pain in the lower abdomen, and the presence of hematuria. Untreated or recurring infections can lead to complications such as pyelonephritis. These UTI infections are usually treated with antibiotics such as Nitrofurantoin, Trimethoprim-sulfamethoxazole or Fluoroquinolones of which *S. saprophyticus* are sensitive (31). However, resistant *S. saprophyticus* models can also be formed.

Enterococcus faecalis

UTIs caused by *E. faecalis* require careful diagnosis and targeted treatment. Given its potential for antibiotic resistance, appropriate antibiotic selection is crucial (32). Preventive measures and proper hygiene can significantly reduce the risk of UTIs. *E. faecalis* is a facultative anaerobic Gram-positive bacterium that causes UTI infection, can cause various symptoms such as frequent urination with pain and burning, and can alter the urine making it cloudy and blood-filled. Furthermore, *E. faecalis* can induce fever and chills and promote the development of UPEC. *E. faecalis* is part of the intestinal bacterial flora, can become pathogenic under certain conditions, and can develop considerable resistance (32).

CONCLUSIONS

UTIs are very common bacterial infections caused by several bacterial species. The main bacteria responsible for these infections are *E. Coli, K. pneumoniae, P. mirabilis, S. saprophyticus,* and *E. faecalis*. Each of these bacteria has particular characteristics and mechanisms that allow them to cause infection after colonizing the urinary tract and evade the host immune response.

Conflict of interest

The authors declare that they have no conflict of interest.

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TWO CLASSES OF ANTIBIOTICS, BETA-LACTAMS AND MACROLIDES, WHICH ARE COMMONLY USED FOR THE TREATMENT OF INFECTIONS

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ABSTRACT

Infections, particularly respiratory ones, are often treated with two classes of antibiotics, beta-lactams and macrolides, which inhibit bacterial growth. Beta-lactams exert their effect by inhibiting the synthesis of the bacterial cell wall, while macrolides (bacteriostatic antibiotics) work by inhibiting the bacterial protein synthesis. The beta-lactams imitate the natural substrate of penicillin-binding proteins (PBPs) and bind to specific proteins, while the macrolides achieve this by binding to the 50S ribosomal subunit of the bacterial ribosome. Common types of beta-lactams include penicillins, cephalosporins, carbapenems, and monobactams. For macrolides, common types include erythromycin, clarithromycin, and azithromycin. The choice of antibiotic for treatment is based on the type of infection, the characteristics of the microbe, and the physiopatological aspect of the patient. Beta-lactams and macrolides antibiotics act through complex mechanisms that are not yet completely clear and therefore, further insights on this theme would help to formulate a better and more precise therapy.

KEYWORDS: *antibiotic, beta-lactam, macrolide, quinolone, infection*

INTRODUCTION

The pharmacological criteria underlying the effect of antimicrobials has been better understood in the last 10 years. Beta-lactams and macrolides are two classes of antibiotics commonly used in the treatment of respiratory infections. They work through different mechanisms to inhibit bacterial growth and are often chosen based on the type of infection and the suspected or known causative organism. The clinical efficacy of an antibiotic is related to the mechanism of action and chemosensitivity (pharmacodynamics), to the patient's exposure to the drug (pharmacokinetics), and the pharmacokinetic/pharmacodynamic relationship (1).

Beta-lactams are a broad class of antibiotics that include penicillins, cephalosporins, carbapenems, and monobactams (2). They share a common structural feature: a beta-lactam ring, which is essential for their antibacterial activity. Beta-lactams exert their effect by inhibiting bacterial cell wall synthesis (3). The bacterial cell wall is composed of peptidoglycan, a polymer that provides structural integrity. The synthesis of peptidoglycan involves a series of enzymatic steps, one of which is the cross-linking of the peptidoglycan strands by penicillin-binding proteins (PBPs) (4). Beta-lactams mimic the natural substrate of PBPs and bind to these proteins, thereby inhibiting their activity (2). This inhibition

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prevents the cross-linking of peptidoglycan strands, leading to a weakened cell wall and ultimately causing bacterial cell lysis due to osmotic pressure (5).

Macrolides are another class of antibiotics that include drugs such as erythromycin, azithromycin, and clarithromycin. These antibiotics are characterized by a large macrocyclic lactone ring. They work by inhibiting bacterial protein synthesis by binding to the 50S ribosomal subunit of the bacterial ribosome (6,7). This binding interferes with the translocation steps in protein synthesis, specifically by blocking the exit tunnel from which newly synthesized polypeptides emerge (8). As a result, the elongation of the protein chain is interrupted, leading to the cessation of bacterial growth (9). This mechanism classifies macrolides as bacteriostatic antibiotics, meaning they inhibit the growth and reproduction of bacteria rather than directly killing them.

DISCUSSION

The two classes of antibiotics commonly used in the treatment of respiratory infections are beta-lactams and macrolides. Beta-lactams work by inhibiting the synthesis of the bacterial cell wall. They bind to PBPs located inside the bacterial cell wall, preventing the cross-linking of peptidoglycan chains, which are essential for cell wall strength and rigidity. This leads to cell lysis and death, particularly in actively growing bacteria.

Beta-lactams vary in their spectrum of activity (Table I). Penicillins are generally effective against Gram-positive bacteria, while cephalosporins and carbapenems have broader spectrums that include both Gram-positive and Gram-negative bacteria.

Table I. *Common types of beta-lactams and their uses in treating respiratory infections.*

Beta-lactams common types	
Penicillins:	*Penicillin, Amoxicillin, Ampicillin*
Cephalosporins:	*Ceftriaxone, Cefuroxime, Cephalexin*
Carbapenems:	*Imipenem, Meropenem*
Monobactams:	*Aztreonam*
Common uses in respiratory infections	
Community-Acquired Pneumonia (CAP):	*Amoxicillin, Ceftriaxone*
Acute Otitis Media:	*Amoxicillin*
Sinusitis:	*Amoxicillin-Clavulanate*
Streptococcal Pharyngitis:	*Penicillin*

Resistance to beta-lactams can occur through the production of beta-lactamases, enzymes that break down the beta-lactam ring, rendering the antibiotic ineffective (10). This has led to the development of beta-lactamase inhibitors (e.g., clavulanate) that are combined with beta-lactams to overcome resistance (11).

Beta-lactams, which include penicillins and cephalosporins, have a similar mechanism of bactericidal action, characterized by the inhibition of the synthesis of peptidoglycan in the bacterial wall. All beta-lactams are made up of an azetidine tetratomic ring (6-aminopenicillanic acid in penicillin, and 7-aminocephalosporadic acid in cephalosporins) which represents a structural analogue of the dextro-alanine dimer, the substrate of bacterial transpeptidases (protein binding proteins penicillins) (12). The binding of the beta-lactam to the transpeptidase enzyme leads to the denaturation of the enzyme and an arrest of the synthesis of the peptidoglycan, and consequently of bacterial growth (13). This mechanism represents the bacteriostatic effect of the antibiotic.

The bactericidal effect is secondary to the genomic depression of murein hydrolases which demolish the murein of the cell wall of the prokaryotic cell and cause its lysis (14). Sensitive beta-lactamase antibiotics, such as amoxicillin, are generally administered in combination with beta-lactamase inhibitors, such as clavulanic acid which, despite having the beta-lactam ring, lacks intrinsic antibacterial activity (2). Beta-lactamase inhibitors bind to beta-lactamases, enzymes responsible for beta-lactam hydrolysis, and inactivate them with a suicidal mechanism. Thanks to this mechanism, clavulanic acid preserves the activity of amoxicillin against *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* species, *Haemophilus influenza*, and *Moraxella catarralis* (15-17). Among beta-lactams, third-

generation cephalosporins (e.g. ceftriaxone, cefixime, cefpodoxime) commonly used in respiratory infections have a broader antibacterial spectrum than penicillins, including enterobacteria such as *Klebsiella*, *Serratia*, *Enterobacter*, and *Clostridia*, due to a greater sensitivity towards plasmid beta-lactamases and good intrinsic activity (18). This class of cephalosporins also includes some antibiotics, such as ceftazidime and cefoperazone, which are also active on *Pseudomonas aeruginosa* (18).

Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. This action blocks the translocation step in protein synthesis, preventing the growth of the bacterial cell (6). Macrolides are primarily effective against Gram-positive bacteria and some Gram-negative bacteria, as well as atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* (19) (Table II).

Table II. *Common types of macrolides and uses in treating respiratory infections.*

Common types of macrolides	
Erythromycin	
Clarithromycin	
Azithromycin	
Common uses in respiratory infections	
Community-Acquired Pneumonia (CAP):	*Azithromycin, Clarithromycin*
Acute Bronchitis:	*Azithromycin*
Pertussis (Whooping Cough):	*Erythromycin, Azithromycin*
Pharyngitis and Tonsillitis (in penicillin-allergic patients):	*Azithromycin, Clarithromycin*

Resistance to macrolides is often due to modification of the target site in the ribosome, efflux pumps that expel the drug from the bacterial cell, or enzymatic degradation (20). This can limit their effectiveness, particularly in certain regions or settings with high levels of resistance.

The macrolides Azithromycin, Clarithromycin, Erythromycin, and Fidaxomicin are antibiotics with bacteriostatic activity that can sometimes carry out a bactericidal action. This occurs in cases of infection with germs that are very sensitive to macrolides, such as *streptococci* and *pneumococci*. Their mechanism of action consists in the inhibition of bacterial protein synthesis through attachment to the 50s ribosomal subunit containing peptidyl transferase, an enzyme that catalyzes the formation of the bond between amino acids and the polypeptide chain in formation (21). Macrolides therefore act only on inactive cell proliferation.

Their spectrum of action is medium and includes, in addition to intracellular pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, also Gram-positive cocci such as *staphylococci*, *streptococci*, *pneumococci* and Gram-positive bacilli such as *Nocardia* and *Listeria*, and some Gram-negative bacteria such as *Bordetella pertussis* and *Bordetella catarralis*. New-generation antibiotics include fluoroquinolones, ketolins, and oxazolidinones. While beta-lactams and macrolides are used in all respiratory infections, quinolones are used only in CAPs resistant to other antibiotics (22).

Among the quinolones, we distinguish the derivatives of nalidixic acid or first-generation quinolones, and the fluoroquinolones which include second and third-generation quinolones. First-generation quinolones such as oxalinic acid, pipemic acid, and others, have a narrow antibacterial spectrum mainly oriented towards enterobacteria, and a pharmacokinetics which, due to rapid elimination and specific tissue rates, allows their use only as urinary antiseptics.

Second-generation fluoroquinolones are characterized by the addition of a fluorine atom to carbon 6, which gives the molecule a highly reinforced and extended activity on Gram-negatives and a reduced urinary elimination (23). Third-generation fluoroquinolones were obtained by adding a heterocyclic substituent at position 7, which broadens their spectrum of action to Gram-positives (24). Third-generation fluoroquinolones such as levofluoxacin and maxifluoxacin are a valid alternative in CAP therapy caused by resistant strains, as they are active against typical agents such as pneumococcus, and atypical agents such as chlamydia and mycoplasmas, as well as on anaerobes and mycobacteria.

These are bacterial antibiotics that bind irreversibly to the A subunit of DNA gyrase (mouse second isomerase), the enzyme responsible for the supercoiling of bacterial DNA, hindering the replication and survival of the bacterium (25). Third-generation fluoroquinolones differ from first- and second-generation quinolones in that they also exert an inhibitory

action on topoisomerase IV, an enzyme homologous to DNA-gyrase with high decatenating power (23). This action would broaden the spectrum of action of quinolones to Gram-positive bacteria. In the 1990s, linezolid was synthesized, a morpholino derivative belonging to the oxazolidinone class, indicated in systemic infections caused by strains resistant to other antibiotics (26). The drug exerts a bacteriostatic action by binding to the 50s ribosomal subunit and is available both in preparation for oral use and for systemic use (27). In pediatrics, it has been used without side effects, as well as for a long time in patients with cystic fibrosis.

Finally, telithromycin belongs to a new class of antibiotics, the ketolides. It is chemically derived from macrolides and therefore equipped with the same mechanism of action but is more effective against Gram-positive cocci (28). The new chemical structure gives the molecule a greater binding affinity to the ribosomes of MLSb pneumococcal strains resistant to lycosamide macrolides and *Streptogramin B* (29). Both linezolid and telithromycin are reserved for the treatment of complicated CAPs.

In some cases, combination therapy is utilized with beta-lactams and macrolides to provide broad coverage, especially for severe or hospitalized cases of pneumonia, where atypical pathogens might be involved (30,31). Beta-lactams can cause allergic reactions in some individuals, ranging from mild rashes to severe anaphylaxis. Macrolides are generally well-tolerated but can cause gastrointestinal disturbances and, less commonly, QT prolongation.

CONCLUSIONS

Beta-lactams and macrolides are cornerstone antibiotics in the treatment of respiratory infections. Their selection is based on the type of infection, the suspected pathogens, and patient-specific factors such as allergies and resistance patterns. Both beta-lactams and macrolides are crucial in the fight against bacterial infections, but they target different aspects of bacterial physiology. Beta-lactams disrupt cell wall synthesis, causing bacterial cell death, while macrolides inhibit protein synthesis, preventing bacterial growth and proliferation. Knowledge of these mechanisms is essential for the effective use of these antibiotics in clinical practice and for developing new strategies to combat antibiotic resistance.

Conflict of interest

The authors declare that they have no conflict of interest.

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ABSTRACT

Acquired immunodeficiency syndrome (AIDS) was first described in the 1980s and the human immunodeficiency virus (HIV) that causes it was identified in 1983-1984. The virus is transmitted sexually and through transfusions of infected blood, or from an infected mother to her child during childbirth. Today, greater knowledge of AIDS, both at the epidemiological and transmission levels, has allowed us to better understand the pathogenetic biochemical mechanisms and to create new therapeutic treatments that have saved millions of lives. Despite the new therapies adopted today, HIV still remains a serious threat to the world's population and the lack of a vaccine represents a defeat for the scientific community. The drugs available today for HIV and immunomodulators are able to slow the progression of the disease, but not to cure it definitively. The most important immunological damage caused by HIV is the reduction of CD4+ cells resulting in infection by *Candida albicans* and *Herpes zoster*. Low CD4+ counts cause opportunistic infections, comorbidities, and, in severe cases, death. Antiretroviral therapy (ART) targets different stages of the HIV life cycle, including reverse transcriptase, integrase, and protease enzymes. ART involves oral combinations of drugs that, with different mechanisms of action, inhibit HIV replication, reducing viral load. Still today, HIV and AIDS remain a significant health challenge despite new therapies. New treatments are better at treating the disease and certainly improving the quality of life, but AIDS is still completely incurable.

KEYWORDS: *HIV, AIDS, CD4+, ART, infection, immunity, therapy*

INTRODUCTION

The first known cases of acquired immunodeficiency syndrome (AIDS) were reported in the early 1980s. Initially, it was a mysterious illness affecting primarily gay men, leading to its early designation as gay-related immune deficiency (GRID). In the years 1983-1984, scientists identified the human immunodeficiency virus (HIV) responsible for AIDS. Key researchers such as Luc Montagnier (France) and Robert Gallo (USA) played crucial roles in this discovery (1). By the mid-1980s, HIV had spread globally, affecting diverse populations across all continents (2). The virus spread through unprotected sexual contact, blood transfusions, the sharing of needles, and from mother to child during birth or breastfeeding. The peak of the AIDS epidemic was in the late 1990s and early 2000s, and sub-Saharan Africa was, and remains, the most severely affected region (3,4). Initial responses to the epidemic were hindered by stigma, misinformation, and lack of public awareness. Activism groups such as ACT UP helped to raise awareness and pressured

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governments to take action. Much more substantial progress has been achieved in our understanding of HIV, the virus that causes AIDS. Today, the epidemiology, route of transmission, and complex pathologies caused by HIV have helped to better understand the biochemical mechanisms involved in AIDS and to create new therapeutic treatments, which have saved innumerable lives to this day.

DISCUSSION

Since the AIDS outbreak, the HIV virus has infected more than 75 million individuals globally (5) and continues to cause approximately 1.2 million deaths annually (6). Despite treatment, HIV still remains a serious threat to the world population and the absence of a vaccine represents a defeat for the scientific community. In 2019, the World Health Organization (WHO) reported that approximately 38 million people were living with AIDS (6). The drugs available today for HIV, and immune modulators, are able to slow down progression of the disease, but there is still no definitive curative therapy, nor an effective vaccine that can stop the epidemic. Therefore, HIV infection continues to threaten the world's population and cause deaths around the world.

Most people infected with HIV, even those who are asymptomatic, develop AIDS. This disease generates a lot of fear amongst the population and public awareness should be improved to educate people about the transmission of the virus, which is essential for preventing infection.

HIV infection is linked to a wide spectrum of diseases, ranging from asymptomatic to acute and chronic, with symptoms such as fever, weight loss, malaise, night sweats, chills, and diarrhea (7). Sick and asymptomatic people can develop opportunistic infections and cancers (e.g., Kaposi sarcoma) (8). Infected patients with compromised immune systems are at increased risk of developing AIDS earlier, within the first years of infection. In these cases, a diagnostic error can occur, especially when it does not appear that there is an HIV infection. HIV is difficult to classify, and the prognosis can be different from classic AIDS, which puts infected patients at risk. Therefore, the diagnosis of the disease must be made very carefully.

HIV transmission occurs directly through genital contact or rectal mucosal contact with seminal fluid or vaginal secretion. Furthermore, the virus can be transmitted through contact with contaminated blood, typically by transfusion or by the sharing of needles. Infected pregnant women can transmit the virus through childbirth. Contact with healthy skin is not a means of transmission. It has been noted that among hemophiliacs who receive blood products, the incidence of HIV infection is higher than in healthy subjects (9).

After individuals become infected with HIV, most remain asymptomatic for about 7 years, however, a small minority may develop AIDS within one or more year after infection. Early in the infection, the illness may present as flu-like and is characterized by fever, malaise, lethargy, and lymphadenopathy (10). The most important characteristic of AIDS is the reduction in the number of CD4+ lymphocytes due to the cytopathic effect of the virus (11). When the damage to the immune system worsens with a decrease in CD4+ lymphocytes, infections from *Candida albicans* and *Herpes zoster* begin to occur, which can result in oral hairy leukoplasia (12). Additionally, infections can occur from opportunistic bacteria, protozoa, herpes simplex, zoster, cytomegalovirus, and various types of fungi (13).

Patients infected with HIV may present neurological conditions such as encephalitis, dementia, and headaches (14). Brain cells, such as microglia, become infected when macrophages cross the blood-brain barrier (BBB) and colonize the central nervous system (CNS) (15). Microglia and macrophages are innate immune cells that phagocytose HIV and are a true viral reservoir which risks introducing a high number of viruses into circulation (15). HIV activates macrophages and microglia in the brain to release pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6 (16). These cytokines are toxic and damage brain tissue, which leads to neurological disorders or worsens pre-existing ones.

Patients diagnosed with HIV face serious mental health implications, including symptoms of depression (17). In some countries, individuals living with HIV infection have a 2 to 3-fold risk of depression, with a higher rate of anti-depressant use, and an increased risk of committing suicide, compared with the healthy population (18-20). However, the cause for this phenomenon has not yet been ascertained. One possible reason could be attributed to the stress faced by infected patients and also to the chronic nature of the disease, which in the long term, becomes increasingly challenging for the patient.

HIV is a retrovirus with an RNA genome, with an outer envelope with glycoproteins gp120 and gp41 that are essential for viral entry into host cells (21). Concerning the mechanism of entry, HIV primarily infects CD4+ T cells. The gp120 glycoprotein binds to the CD4 receptor and a co-receptor (CCR5 or CXCR4) on the host cell, facilitating viral entry (22). Host genetic factors, such as CCR5-Δ32 mutation, can influence susceptibility to HIV infection and disease progression (23), and the virus employs various strategies to evade the immune system, including latency and direct killing of immune cells.

Therapy and health strategies

Efforts to develop a vaccine against HIV have been ongoing but challenging due to the virus's high mutation rate. Some promising candidates are in advanced trial stages. Research is ongoing into potential cures; a functional cure would control the virus without ongoing treatment, while a sterilizing cure would eradicate the virus from the body.

Strategies to end the AIDS epidemic include widespread testing, treatment, and prevention measures like pre-exposure prophylaxis (PrEP). Furthermore, efforts are being made to address inequalities, to reduce disparities in access to treatment and prevention services, especially in resource-limited settings.

Antiretroviral therapy (ART) is used to treat patients infected with HIV using anti-HIV drugs. Current ART targets different stages of the HIV lifecycle, including reverse transcriptase, integrase, and protease enzymes. Research is exploring new therapeutic targets, such as viral entry inhibitors, latency-reversing agents, and gene-editing technologies such as CRISPR-Cas9 to disrupt the HIV genome.

The therapies available today offer a better quality of life and an extended lifespan for HIV patients who have developed AIDS (24,25). HIV therapy aims to reduce plasma HIV RNA levels to less than 20-50 copies/ml and bring CD4+ cells back to a physiological number. ART is one of the therapies available today and consists of taking oral combinations of drugs which, with different mechanisms of action, inhibit HIV replication, reducing the viral load (Table I). It has been estimated that antiviral therapies have saved approximately 16.5 million AIDS patients since 2001 (26). Drugs that suppress HIV are associated with a higher count of CD4+ cell recovery. A low CD4+ count causes opportunistic infections, comorbidities, and in severe cases, death.

Table I. *Virus replication cycle of HIV.*

a) Reverse transcription:	Once inside the cell, HIV's RNA genome is reverse-transcribed into DNA by reverse transcriptase.
b) Integration:	The viral DNA is integrated into the host genome by the integrase enzyme, allowing the virus to hijack the host cell's machinery.
c) Transcription and translation:	The integrated viral DNA is transcribed and translated into viral proteins.
d) Assembly and budding:	New viral particles are assembled and bud from the host cell, ready to infect other cells.

The effective ART adopted against HIV has also improved neurocognitive disorders. People using ART have milder signs of the disease, although cognitive impairment and neurological damage remain for a long time and the neurological damage may have occurred due to the virus before ART (27). ART reduces the pathogenesis and cellular storage of the HIV virus as well as the destruction of CD4+ T cells, improving the immune response (28). Experiments on primates have shown that with simian immunodeficiency virus (SIV), viral invasion into the brain occurs within 2 weeks after infection (29). The virus also invades the cerebrospinal fluid (CSF), causing inflammation with the production of cytokines and activation of microglia (30).

HIV attacks immune cells such as dendritic cells, CD4+ lymphocytes, and macrophages. Dendritic cells, sentinels of the immune system, phagocytose the virus and present it to T cells, which collaborate with B cells and plasma cells to produce antibodies (Ab) (31). HIV evades the immune system by changing its viral genetic makeup via antigenic escape variants (32,33). The continuous mutation of the HIV virus makes it difficult to generate a vaccine.

ART uses three drugs in combination that significantly slows the disease process and prolongs life but does not cure the disease. This therapy allows immune recovery in patients with low numbers of lymphocytes. A severe and advanced state of the disease is established based on the number of CD4+ cells. Typically, a patient with a CD4+ cell count of less than 200 cells/mcl begins ART, but many individuals do not know they have HIV until too late when it has ravaged their immune system.

ART has been utilized in HIV treatment for years, but it has side effects that undermine its effectiveness. Recently, gene therapy has emerged as a potential option to combat HIV (34). It involves the administration of intracellular nucleic acids to the patient and has so far given promising results. Therefore, satisfactory ART must not only reduce mortality, but also disease progression. Today, many advances have been made in therapeutic technologies which, together with a better understanding of the immune system and viral infection, can lead to more effective treatments and new strategies.

CONCLUSIONS

HIV/AIDS remains a significant global health challenge to this day despite advancements in treatment. Modern ART, introduced in the mid-1990s, has transformed HIV from a fatal disease to a manageable chronic condition. Patients on ART can achieve undetectable viral loads and have a near-normal life expectancy. Additionally, new treatments, including long-acting injectable ART, are improving adherence and quality of life for patients.

While tremendous progress has been made in treatment and understanding the virus, ongoing research and innovative strategies are essential to achieving the ultimate goals of a functional cure, an effective vaccine, and, eventually, an end to the epidemic.

Conflict of interest

The authors declare that they have no conflict of interest.

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ESCHERICHIA COLI RECEPTORS AND PATHOGENETIC MECHANISMS

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ABSTRACT

Escherichia coli (*E. coli*) is a group of bacteria found in humans and animals. Some strains can be highly pathogenic and cause severe immune and inflammatory reactions. *E. coli* is a member of the Enterobacteriaceae family and is a Gram-negative rod-shaped bacteria that has peritrichous flagella, which allow the bacteria to move. Pathogenic *E. coli* produces various toxins such as Shiga toxin (Stx) that disrupt normal cellular functions, inhibit protein synthesis, and cause cellular. Heat-labile (LT) and heat-stable (ST) enterotoxins are produced by enterotoxigenic *E. coli* (ETEC), and can cause intestinal ion alteration and diarrhea. Pathogenic *E. coli* is capable of injecting virulence factors directly into host cells and uses some antigens to carry out its pathogenic action. *E. coli* also uses immune mechanisms, such as alteration of surface antigens, to escape the immune response. Inhibition of *E. coli* and prevention with the use of vaccines or specific antibodies improves the infectious state and human health.

KEYWORDS: *Escherichia coli, Gram-negative bacterium, pathogenetic mechanism, E. Coli receptor, virulence*

INTRODUCTION

Escherichia coli (*E. coli*) is a diverse group of bacteria commonly found in the intestines of humans and animals. While most strains are harmless, some can cause serious food poisoning, infections, and diseases. *E. coli* is a Gram-negative bacterium that frequently exists in the lower intestine of warm-blooded organisms. This rod-shaped bacterium is a member of the Enterobacteriaceae family and is one of the most extensively studied prokaryotic model organisms in microbiology.

E. coli has specific morphological characteristics. It is a rod-shaped cylindrical bacillus and typically appears as short rods. It has a dimension of about 2 to 4 micrometers (µm) in length and 0.4 to 0.7 µm in diameter (1,2). In the laboratory, this Gram-negative bacillus does not retain the crystal violet stain used in the Gram stain procedure and appears red or pink under the microscope due to counterstaining, usually with safranin or fuchsin.

E. coli is usually found as single bacterium or in pairs. *E. coli* bacteria do not form clusters or chains, which distinguishes them from other types of bacteria. Many strains of *E. coli* possess peritrichous flagella, which are flagella distributed over the entire surface of the cell that allow the bacteria to move. Some strains of *E. coli* have a polysaccharide capsule surrounding the cell, which can help evade the host immune system and increase virulence (3). As a Gram-

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negative bacterium, *E. coli* has a characteristic cell wall structure consisting of a thin layer of peptidoglycan surrounded by an outer membrane containing lipopolysaccharides (LPS) (4). The outer membrane also contains proteins, lipoproteins, and porins (5). *E. coli* does not form endospores, which are a type of dormant, hardy, non-reproductive structure that some bacteria produce to withstand unfavorable conditions (6). These morphological traits aid in the identification and study of *E. coli* in various microbiological and medical research contexts.

DISCUSSION

E. coli presents various molecular mechanisms and biochemical processes essential for its survival, growth, and pathogenicity. Of the molecular mechanisms of *E. coli*, DNA replication is important, which originates from the replication of the circular chromosome, a single origin of replication called oriC (7). *E. coli* primarily uses DNA polymerase III for chromosome replication, with DNA polymerase I involved in the removal of RNA primers and DNA repair (8). Transcription occurs through RNA polymerase which transcribes DNA into mRNA. Sigma factors are proteins that bind to RNA polymerase and direct it to specific promoters.

Translation occurs through ribosomes which translate mRNA into proteins. *E. coli* has 70S ribosomes, composed of 50S and 30S subunits (9). Gene regulation in *E. coli* occurs through the lac Operon which controls lactose metabolism and includes the lacZ, lacY, and lacA genes, regulated by the lac repressor and catabolite activator protein (CAP) (10).

In metabolic processes, *E. coli* breaks down glucose through glycolysis to produce pyruvate, ATP, and NADH (11). The TCA cycle (Krebs Cycle) processes acetyl-CoA to produce ATP, NADH, and FADH2. Furthermore, *E. coli* can perform oxidative phosphorylation under aerobic conditions, using the electron transport chain to generate ATP (12). Under anaerobic conditions, *E. coli* can perform oxidative phosphorylation using the electron transport chain to generate ATP (13). Again, in anaerobic conditions, *E. coli* can ferment sugars, producing organic acids, alcohol, and gases as end products (14). *E. coli* synthesizes all 20 standard amino acids and nucleotides *de novo* (15). Furthermore, in cell wall synthesis, *E. coli* synthesizes peptidoglycan, an important component of its cell wall, which involves the assembly of N-acetylglucosamine and N-acetylmuramic acid (16).

E. coli acts through Tar and Tsr receptors, which sense chemical gradients in the environment and mediate chemotaxis, allowing bacteria to move toward attractants or away from repellents (17). The outer membrane receptors are porins such as OmpF and OmpC that form channels through which small molecules can diffuse (18). TonB-dependent receptors are FepA and FhuA receptors which are involved in the uptake of scarce resources such as iron by use of energy derived from the TonB complex (19). Regarding fimbrial adhesions, type 1 pili mediate adhesion to tissue and are important in the early stages of infection (20). The P Pili are involved in the attachment to the urinary tract epithelium, which is crucial for uropathogenic *E. coli* (UPEC) (21). Understanding these molecular mechanisms, biochemical processes, and receptor functions provides insights into how *E. coli* survives, adapts, and sometimes causes disease in host organisms.

E. Coli is broadly classified into six groups of pathogenic strains (Table I). Each pathogenic group has specific virulence factors that enable it to cause disease. These include adhesins, toxins, invasins, and secretion systems.

Table I. *The broadly classified pathogenic strains of Escherichia coli.*

• Enterotoxigenic *E. coli* (ETEC)	• Enterohemorrhagic *E. coli* (EHEC)
• Enteropathogenic *E. coli* (EPEC)	• Enteroaggregative *E. coli* (EAEC)
• Enteroinvasive *E. coli* (EIEC)	• Uropathogenic *E. coli* (UPEC)

Pathogenic *E. coli* produces various toxins, such as Shiga toxins (Stx), that disrupt normal cellular functions (22). These toxins produced by enterohemorrhagic *E. coli* (EHEC) inhibit protein synthesis, leading to cell death (23). Heat-labile (LT) and Heat-stable (ST) enterotoxins are produced by enterotoxigenic *E. coli* (ETEC), causing diarrhea by altering ion transport in the intestines (24).

Invasins are proteins that facilitate bacterial invasion of host cells. Invasion plasmid antigens (Ipa) are used by enteroinvasive *E. coli* (EIEC) to invade and multiply within intestinal cells (25). Pathogenic *E. coli* employs sophisticated secretion systems to inject virulence factors directly into host cells. The type III secretion system (T3SS) is used by enteropathogenic *E. coli* (EPEC) and EHEC to inject effector proteins into host cells, disrupting cellular processes and facilitating colonization (26).

ETEC adheres to the small intestine using colonization factor antigens (CFA) and produces enterotoxins (LT and ST) that stimulate fluid secretion, leading to diarrhea (27). The virulence factors are CFAs, LT, and ST. EPEC attaches to intestinal epithelial cells using bundle-forming pili (BFP) and forms characteristic attaching and effacing (A/E) lesions

through the T3SS (28). Virulence factors are BFP, T3SS, Esp proteins. EHEC, in particular O157, adheres to the colon using intiman and T3SS, producing Stx that cause severe damage to intestinal and renal cells (29). UPEC colonizes the urinary tract using P type 1 pili and fimbriae, producing hemolysin and cytotoxic necrotizing factor 1 (CNF1) to damage host cells (30). The genes encoding these virulence factors are often located on plasmids, which are extrachromosomal DNA elements that can be transferred between bacteria and contribute to the spread of virulence traits.

The *E. coli* pathogen interacts with host cells in several ways such as adhesion, invasion, toxin production, and immune evasion. In adhesion, initial attachment to the host cell surface is achieved by adhesins. Invasion intends the entry into host cells (e.g. EIEC). Toxin production refers to the disruption of host cellular functions. And immune evasion refers to the mechanisms used by the microorganism to avoid host immune responses, such as alteration of surface antigens (31).

CONCLUSIONS

The molecular aspects of *E. coli* pathogenesis have crucial clinical implications. Diagnosis occurs through molecular techniques, such as PCR and sequencing, that can identify specific virulence genes. Targeting specific virulence factors (e.g., anti-adhesive therapies, neutralizing toxins) can improve treatment outcomes, while prevention is achieved through the use of vaccines targeting the main virulence factors for some *E. coli* pathotypes.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

CHRONIC FATIGUE SYNDROME IN INFLAMMATORY DISEASES

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INTRODUCTION

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a complex and debilitating disorder with an unknown cause that can present with mental disorders, depression, mood swings, and "brain fog". CFS results from complex interactions between molecular and biochemical dysfunctions, immune abnormalities, and chronic inflammation (1). The main symptom of CFS is permanent fatigue, which is combined with skepticism regarding whether it is a real disease (Table I). This doubt often causes significant delays in diagnosing CFS and patients suffering from this disease often complain of low quality of life (2). To diagnosis CFS, the symptoms must have been present for at least six months and the patient must present continuous chronic fatigue that is not relieved by rest.

Table I. *In addition to chronic fatigue, the following symptoms may also be present in chronic fatigue syndrome (CFS).*

Mental fatigue	Depression	Sore throat
Muscle fatigue	Brain fog	Tender lymph nodes in the neck or armpits
Headache	Mood swings	Irritable bowel syndrome
Light sensitivity	Polyarthralgia	Irregular heartbeat
Muscle and joint pain	Sleep disturbances	Chills and night sweats
Difficulty concentrating		

CFS usually causes a significant reduction in work, social, and personal activities. CFS must not originate from a known disease, nor should the state of drowsiness be confused with a lack of motivation or disinterest. Therefore, all secondary medical conditions such as tumors, chronic infections, obesity, chronic flu, dementia, hypothyroidism, pituitary gland malfunction, depression, schizophrenia, fibromyalgia, etc., must be excluded in order to diagnose CFS. Biochemical and molecular studies have provided insight into the various immunological and inflammatory mechanisms at play in CFS and understanding these is crucial for developing effective treatments and improving the quality of life for patients.

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DISCUSSION

Patients with CFS often have abnormalities in mitochondrial function, leading to reduced ATP production and energy deficits (3). Increased levels of reactive oxygen species (ROS) and reduced antioxidant defenses have been observed during oxidative stress, contributing to cellular damage and fatigue (4). Metabolic changes, including disruptions in amino acids, lipids, and energy metabolism, have also been highlighted in CFS (5). The dysfunction of the tricarboxylic acid cycle in glycolysis and fatty acid oxidation suggests that there is a dysmetabolism linked to energy production. It has been reported that in CFS, there is a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis with alteration of cortisol, which may be linked to the stress response and immune reaction (6). In fact, in CFS, there is chronic activation of the immune system with elevated generation of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, which can mediate low-grade inflammation (1).

T lymphocytes are also involved in CFS, where they appear to be altered in their activation and proliferation. It is possible that this syndrome is mediated by the altered relationship between TH1 cells and TH2 cells (7). Natural killer (NK) cells may also have a reduced capacity for cytotoxicity. At the level of cell-mediated immunity, there may be a dysfunction in the activation of T lymphocytes and their proliferation. These alterations may change the balance between different T lymphocyte subsets (8). NK cells have reduced activity, with impaired immune surveillance and immune imbalance leads to elevated levels of inflammatory cytokines and chemokines in the blood and cerebrospinal fluid, markers that indicate ongoing inflammation.

At the cerebral level, immune cells can activate microglia that induce neurological symptoms (9). Even in the intestine, there can be significant alterations in the composition of the microbiota, with increased intestinal permeability ("leaky gut") and local systemic inflammation (10).

There are no specific therapies for CFS, and it is therefore necessary to use antioxidant agents and anti-inflammatory drugs. Antioxidants such as coenzyme Q10, N-acetylcysteine, and vitamins C and E are being studied to counteract oxidative stress. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors are used to help reduce inflammation.

Research is presently focusing on new therapies aimed at restoring the balance of the immune system, such as low-dose naltrexone or immunoglobulin therapy. In addition, supplements that regulate mitochondrial function and metabolic pathways have also been targeted to restore an efficient immune state.

CONCLUSIONS

CFS is characterized by complex interactions between molecular and biochemical dysfunctions, immune abnormalities, and acute and chronic inflammation. However, the mechanisms regulating this complicated disease are not yet clear, and more in-depth studies are needed to improve therapy and the quality of life of patients.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

IMMUNOLOGICAL AND BIOCHEMICAL MECHANISMS OF BACTERIAL TRACHEITIS

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KEYWORDS: *bacterial tracheitis, immunology, pathogenesis, infection, bacteria*

INTRODUCTION

Bacterial tracheitis, also known as bacterial croup or bacterial laryngotracheobronchitis, is an acute infection of the trachea caused by various bacterial pathogens. This condition primarily affects young children and can lead to severe airway obstruction and respiratory distress. Understanding the molecular mechanisms underlying bacterial tracheitis is crucial for developing effective treatments and preventive measures. This paper explores the pathogenesis, bacterial virulence factors, host immune responses, and potential therapeutic targets associated with bacterial tracheitis.

DISCUSSION

Bacterial tracheitis typically begins with a viral upper respiratory infection that disrupts the normal mucosal barriers and ciliary function of the respiratory tract. This disruption allows bacteria to adhere to and colonize the tracheal epithelium. Common bacterial pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (1). These bacteria possess various adhesins that facilitate attachment to epithelial cells. For instance, *S. aureus* expresses fibronectin-binding proteins (FnBPs) and clumping factors (ClfA and ClfB), which bind to host extracellular matrix components such as fibronectin and fibrinogen, respectively (2). Bacterial tracheitis infection includes different pathogenetic steps which are outlined below (Table I).

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Table I. *Progression of the pathogenesis of bacterial tracheitis*.

Step 1:	Initial Viral Infection
	• Upper respiratory viral infection
	• Disruption of mucosal barriers
	• Impairment of ciliary function
Step 2:	Bacterial Colonization and Adherence
	• Bacteria such as *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*
	• Adhesins and surface proteins facilitate attachment
	- **S. aureus*: FnBPs, ClfA, ClfB
	- **H. influenzae*: Hap, Hib
	- **M. catarrhalis*: UspA1, UspA2
Step 3:	Bacterial Invasion and Biofilm Formation
	• Bacterial invasion of epithelial cells
	• Production of toxins and enzymes
	- **S. aureus*: Alpha-toxin, leukocidins, proteases
	• Biofilm formation by *H. influenzae* and *M. catarrhalis*
Step 4:	Host Immune Response
	• Innate Immune Response
	- Mucociliary escalator
	- Neutrophils, macrophages, dendritic cells
	- Recognition of PAMPs by PRRs (e.g., TLRs)
	- Activation of NF-κB, production of cytokines (IL-6, TNF-α)
	• Adaptive Immune Response
	- B cells produce specific antibodies
	- CD4+ helper T cells enhance phagocyte function and B cell activation
	- CD8+ cytotoxic T cells kill infected cells

Once attached, bacteria can invade the epithelial cells and evade the host immune system. *S. aureus* secretes several toxins and enzymes, including alpha-toxin, leukocidins, and proteases, which damage epithelial cells and disrupt the integrity of the mucosal barrier (3). This facilitates bacterial invasion and dissemination. Additionally, *H. influenzae* and *M. catarrhalis* produce biofilms, complex communities of bacteria embedded in a self-produced extracellular matrix (4). Biofilms protect bacteria from phagocytosis and antibiotic treatment, contributing to chronic and recurrent infections.

Virulence factors play a critical role in the pathogenesis of bacterial tracheitis. Exotoxins, such as *S. aureus* alpha-toxin, are cytolytic toxins that form pores in the host cell membranes, leading to cell lysis and death (5). Leukocidins, another group of toxins produced by *S. aureus*, specifically target and kill leukocytes, impairing the host's immune response (6). Additionally, bacterial proteases degrade host proteins, including immunoglobulins and complement proteins, further undermining immune defenses.

Adhesins and surface proteins are essential for bacterial attachment and colonization. In *H. influenzae*, the *Haemophilus* adhesion and penetration protein (Hap) and the *H. influenzae* type b antigen (Hib) are key adhesins that mediate attachment to respiratory epithelial cells (7). Similarly, *M. catarrhalis* expresses the ubiquitous surface proteins A1 and A2 (UspA1 and UspA2), which bind to host epithelial cells and immune molecules like immunoglobulin D (IgD) (8).

The host immune response to bacterial tracheitis involves both innate and adaptive mechanisms. The innate immune response is the first line of defense and includes physical barriers, cellular responses, and soluble factors. The mucociliary escalator, consisting of ciliated epithelial cells and mucus, traps and removes inhaled pathogens. However, when this system is compromised, innate immune cells such as neutrophils, macrophages, and dendritic cells play a crucial role. These cells recognize pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs) like toll-like receptors (TLRs). For instance, TLR4 recognizes lipopolysaccharide (LPS) from gram-negative bacteria, leading to the activation of nuclear factor-kappa B (NF-κB) and the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) (9).

The adaptive immune response is also critical in controlling bacterial tracheitis. B cells produce specific antibodies that neutralize bacterial toxins and promote opsonization and phagocytosis. T cells, particularly CD4+ helper T cells,

secrete cytokines that enhance the antimicrobial functions of phagocytes and stimulate B cell antibody production. CD8+ cytotoxic T cells can directly kill infected cells, limiting the spread of intracellular pathogens. The interplay between the innate and adaptive immune responses is essential for effective clearance of the infection and prevention of recurrence.

The cornerstone of bacterial tracheitis treatment is antibiotic therapy. The choice of antibiotics depends on the causative pathogen and its susceptibility profile. Empirical treatment often includes broad-spectrum antibiotics such as ceftriaxone, cefotaxime, or clindamycin until the specific pathogen is identified. For *S. aureus* infections, particularly methicillin-resistant *S. aureus* (MRSA), vancomycin or linezolid may be necessary. However, the increasing prevalence of antibiotic resistance highlights the need for alternative therapeutic strategies.

Targeting bacterial virulence factors represents a promising approach to treating bacterial tracheitis. Inhibitors of bacterial adhesins, exotoxins, and biofilm formation can potentially reduce bacterial pathogenicity without exerting selective pressure for resistance. For instance, monoclonal antibodies against *S. aureus* alpha-toxin have shown efficacy in neutralizing the toxin's activity and protecting against infection in preclinical models (10). Similarly, small molecules that disrupt biofilm formation or enhance biofilm dispersion could improve the efficacy of antibiotic treatment.

Modulating the host immune response is another potential therapeutic strategy. Enhancing the innate immune response through the administration of cytokines or immune stimulants could boost the body's ability to fight off bacterial infections. For example, granulocyte-macrophage colony-stimulating factor (GM-CSF) has been investigated for its potential to enhance neutrophil function in bacterial infections (11). Additionally, targeting specific inflammatory pathways with anti-inflammatory agents could reduce tissue damage and improve clinical outcomes.

CONCLUSIONS

Bacterial tracheitis is a severe infection of the trachea caused by various bacterial pathogens. Understanding the molecular mechanisms underlying its pathogenesis, including bacterial entry, colonization, virulence factors, and host immune responses, is crucial for developing effective treatments. While antibiotic therapy remains the primary treatment, emerging strategies targeting bacterial virulence factors and modulating the host immune response hold promise for improving outcomes and combating antibiotic resistance. Continued research into these mechanisms will be essential for advancing the management and prevention of bacterial tracheitis.

Conflict of interest

The author declares that they have no conflict of interest.

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