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Drug-Resistant Bacterial Infections in HIV Patients

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Additional information is available at the end of the chapter

Abstract

The human immunodeficiency virus (HIV) was first detected in 1982 among homosexual men, and subsequently, it was further detected in various regions of world. In 2016, WHO estimated that 36.7 million people were living with HIV, 1.9 million were newly infected HIV patients and approximately 1 million people died worldwide. HIV attacks CD4 T cells and causes immunodeficiency. Weakened immune system of HIV patients increases the opportunity to acquire various infections caused by fungi, bacteria, parasites and other viruses. Bacterial infections that cause huge threats to HIV patients are tuberculosis, syphilis, bacterial enteric diseases and bacterial pneumonia. Important bacterial etiologies are *Streptococcus pneumoniae*, *Salmonella* spp. *Haemophilus influenzae*, *Staphylococcus aureus*, *Citrobacter freundii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*. Frequent bacterial infections in HIV patients increase the usage and also highly expose bacteria to antibiotics. Most problematic multidrug-resistant bacteria are extended-spectrum β-lactamases producing *P. aeruginosa*, *Acinetobacter baumannii*, *E. coli* and *K. pneumoniae*; vancomycin-resistant enterococci; methicillin-resistant *S. aureus* and multidrug-resistant and extensively drug-resistant *M. tuberculosis*. These antibiotic-resistant bacteria complicate the treatment of infections in HIV patients with available antibiotics and sometimes cause death. It also causes higher medical costs, prolonged hospital stays, increased mortality and economic burden on families and societies.

Keywords: HIV patients, multidrug resistant, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, antibiotic resistance

1. Introduction

Human immunodeficiency virus (HIV) is a lentivirus belongs to the family of Retroviridae and it causes Acquired Immunodeficiency Syndrome (AIDS) in an advanced stage of HIV

infection. HIV was first detected in 1981 among homosexual men in the New York City who had unusual clusters of *Pneumocystis jirovecii* pneumonia and Kaposi sarcoma [1, 2]. After that, HIV positivity was detected in the various regions globally and actively spread in the community with increased rate of HIV infection. In 2016, the World Health Organization (WHO) has reported that HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. One million people died from HIV-related causes; furthermore, approximately 36.7 million people are living with HIV and 1.8 million people becoming newly infected worldwide. African region is the most affected area with 25.6 million people living with HIV in 2016. It accounts for almost two-thirds of the global total number of new HIV infections [3, 4].

HIV spreads from one person to another by sexual contact such as vaginal sex, anal sex and oral sex and also spreads by sharing injection equipment, getting tattoos or body piercings with unsterilized needles, accidental needle sticks, contaminated blood transfusions and splashing blood in eyes. HIV can pass from HIV-positive pregnant women to their babies in the womb and during birth. It can also be transferred to other persons through certain body fluids such as blood, semen, vaginal fluid and breast milk [5]. After entry into the human body system, HIV infects vital immune cells such as helper T cells (specifically CD4+ T cells), macrophages and dendritic cells [6]. Hence, HIV infection leads to low level of CD4+ T cells through three important mechanisms. First mechanism is direct viral killing of the infected cells; second is increased rate of apoptosis in infected cells; and third is killing of infected CD4+ cells by CD8 cytotoxic lymphocytes. Virus multiplication declines the number of CD4+ cells below a critical level; therefore, the cell mediated immunity is lost and the weaken immune system signal to various opportunistic infections (OIs) and cancers [6–9]. Compromised immune system of HIV patients increases the chances of acquiring various OIs caused by fungi, bacteria, parasites and other viruses based on the CD4 cell counts. Tuberculosis (TB) generally develops at CD4 count of 200–500 cells/mm^3, as does *Candida albicans* infection *Pneumocystis jirovecii* pneumonia (PCP, earlier known as *Pneumocystis carinii*) occurs at CD4 count <200 cells/mm^3 and cytomegalovirus (CMV) infection occurs when the CD4 count falls below 100 cells/mm^3 [10]. As compared to other microbes, bacteria cause high rate of infections such as tuberculosis, syphilis, bacterial enteric diseases, pneumonia and bartonellosis. Bacteria causing various infections associated with HIV patients include *Streptococcus pneumoniae*, *Salmonella* spp., *Haemophilus influenzae*, *Staphylococcus aureus*, *Citrobacter freundii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* and *Mycobacterium avium* complex, and they have emerged as an important cause of morbidity and mortality in HIV individuals [11, 12].

High frequency of bacterial infections in HIV patients increases the chance of consumption of high level of antibiotics. Over usage and mishandling of antibiotics develop various resistance mechanisms among bacteria. The dramatic increase in the incidence of multidrug-resistant (MDR) bacteria and transfer of resistance from one organism to another make bacterial infections more difficult to treat with current antibiotics, so the treatment options are often extremely limited [13]. This chapter describes about various bacterial diseases and antibiotic-resistant bacteria from HIV patients.

2. Bacterial infections among HIV patients

2.1. Respiratory tract infections

Respiratory tract infection (RTI) is defined as infectious disease of upper or lower respiratory tract of human body system. RTI is classified as an upper respiratory tract infection and a lower respiratory tract infection. Pneumonia is an infection in one or both side of lungs causing inflammation in the air sacs (alveoli). In this condition, alveoli fill with phlegm (mucus) or pus making difficult to breathe. Bacterial pneumonia is a common cause of HIV-related morbidity with the symptoms of body chills, rigors, pleuritic chest pain and purulent sputum, fever, tachypnea, tachycardia, rales or rhonchi and other signs. Incidence of bacterial respiratory infections among HIV-positive population has been reported approximately 90 cases per 1000 per year, which is higher than noninfected population [14]. Bacterial pneumonia among HIV infection was 7.8 times more likely to develop bacterial pneumonia than HIV sero-negative persons. The count of CD4+ T lymphocyte is the most consistent predictor of bacterial infections and other factors are also involved that include qualitative B-cell defects (reduced ability to produce antibody), impaired neutrophil function or both and non-HIV related factors such as cigarette smoking, use of crack cocaine, IDU, alcoholism, or liver diseases [15, 16]. The causative of bacterial pneumonia among persons with HIV has been relative prominence of *Streptococcus pneumoniae* followed by *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Some studies encountered *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are causative organisms for atypical pneumonia. *S. pneumoniae* infection is 15–300 times more common among HIV individuals than among age-matched non-HIV individuals and also rate of recurrent pneumococcal pneumonia is 8–25% within 6 months. The second most common cause of bacterial pneumonia is *H. influenza* and in an advanced immunosuppression, *S. aureus* and *P. aeruginosa* can cause invasive pneumonias, sometimes associated with bacteremia. HIV patients ill over a period of weeks to months are more likely to have *Pneumocystis jirovecii* pneumonia, tuberculosis (caused by *Mycobacterium tuberculosis*) or chronic fungal infection.

2.2. Enteric infections

Rates of Gram-negative bacterial enteric infections are at least 10 fold higher among HIV infected persons than in the general population. Risk of bacterial enteric infections varies according to CD4 T-cell with the count of <200CD4 cells/mm³. The common causes of bacterial diarrhea among persons with HIV are Salmonella (*Salmonella enterica* serotypes Typhimurium and Enteritidis), *Campylobacter* and *Shigella* species. Patients with HIV are at increased risk for developing salmonellosis and they have the incidence rates of salmonellosis as 20–100 folders higher than the non-HIV patients. *Campylobacter jejuni* has been reported among HIV patients particularly men who have sex with men (MSM) with the incidence rate of 39 times higher than general population. Other than these infections, *Shigella* bacteremia is more common among HIV patients and might occur in both mild and severe cases of clinical shigellosis.

The major clinical syndromes of salmonellosis among person with HIV infection include a self-limited gastroenteritis; a more severe and prolonged diarrheal disease, associated with fever, bloody diarrhea and weight loss and *Salmonella* septicemia, which might present with or without gastrointestinal symptoms. Sometimes, bacteremia can occur with each of these syndromes and is more likely to occur among those with advanced immunosuppression. Diarrheagenic *E. coli*, particularly enteroaggregative *E. coli* also contribute to the burden of diarrheal disease. The lower CD4 cell count of <50 cells/mm^3 is an independent risk factor for *Clostridium difficile* associated infection (CDI) among HIV population [15].

2.3. Urinary tract infections

The urinary tract system of human is divided into two major divisions such as upper urinary tract (kidneys, renal pelves and ureters) and lower urinary tract (urinary bladder and urethra). Urinary tract infections (UTIs) are an infection in any part of urinary system, but most UTIs occur in lower urinary tract especially bladder (cystitis). Women are at high risk of developing a UTIs then men. UTIs occur when bacteria enter and infect the urinary tract and sometimes spread to the kidneys (pyelonephritis) [17]. UTIs are one of the significant illnesses that cause clinical burden among HIV individuals. It is the most common nosocomial infection [7] and cause high rate of morbidity [18]. HIV disease is associated with a variety of renal syndromes in patients with low CD4+ cell counts, causing neurologic complications such as bladder areflexia and hyporeflexia, which lead to urinary stasis and ultimately infection [19, 20]. Once a patient's CD4+ T-cell count falls below 200 cell/mm^3, the individual is then at risk of a variety of opportunistic infection. The most predominant causative organisms are encapsulated bacteria which include *Streptococcus pneumoniae* and *Haemophilus influenzae*, but non-typhoidal *Salmonella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* have also been implicated. Among opportunistic infections, UTI accounts for 60% of AIDS defining illness [21]. Signs and symptoms of UTIs are pain or burning while urinating, frequent urination, feeling urinate even having an empty bladder, fever (less than 101°F), cloudy and bloody urine and pressure or cramping in the groin or lower abdomen [22].

2.4. Bloodstream infections

Even reduction of AIDS-related deaths and opportunistic infections after introduction of combined antiretroviral therapy (cART), infection with HIV causes the increased risk of bloodstream infection (BSI). It is a frequent complication found in HIV-infected patients and is usually associated with a poor prognosis, responsible for the immediate cause of death up to 32% of HIV-infected patients, especially under particular conditions (e.g., intravenous drug abuse, use of a central venous catheter (CVC), neutropenia, and a low CD4 T-cell count) [23]. BSI is associated with increased mortality rate, length of hospital stay and intensive care unit (ICU) admission rate, and it is more frequent cause of ICU admission than *Pneumocystis jirovecii* pneumonia in HIV-infected patients. In majority of cases, the BSI is due to bacterial pathogens. The infectious agents begin infecting almost any part of any organ (from skin, lung [pneumonia], gastrointestinal tract [bacterial penetration or ruptured intestine from trauma]) or through implanted devices (surgical instruments, intravenous catheter, etc.).

The infecting microorganisms or their toxins spread directly or indirectly into the bloodstream that allows spreading from infection site to any other organ system. Common bacterial causes of BSI are nontyphoidal salmonella, *Streptococcus pneumoniae*, *Escherichia coli* and *Staphylococcus aureus* are the most important pathogens of BSI. Fungal and mycobacterial infections are less frequent but have considerable clinical and economic impact. Among the pathogens responsible for BSI, *Mycobacteria* spp., *Cryptococcus neoformans* and recurrent nontyphoidal salmonella constitute AIDS-defining conditions [24]. Symptoms of BSI are altered mental status (altered consciousness, mental confusion or delirium), fast respiratory rate, low blood pressure, elevated heart rate (tachycardia), fever, body chills, dizziness, fatigue, shivering, facial flushing, skin discoloration, shock and sleepiness.

2.5. Syphilis

Syphilis is a bacterial infection caused by *Treponema pallidum* which is usually spread by sexual contact and associated with an increased risk of sexual acquisition and transmission of HIV. The disease starts as a painless sore-typically on genitalis, rectum and mouth. Direct contact with sores would spread syphilis from person to person, and the bacteria enter through minor cuts and abrasions in the skin or mucous membrane. It is contagious during its primary and secondary and early syphilis can be cured sometimes with a single dose of penicillin. Clinical manifestations of syphilis are similar to persons without HIV infection, difference is genital lesions may be more apparent and accelerated progression of disease seen in HIV population. Syphilis has various stages like primary syphilis, secondary syphilis and latent syphilis. The symptoms are small bumps or tumors called gummas, which develop on skin, bones, liver or any other organ in the late stage of syphilis. It also causes some neurological problems such as stroke, meningitis, hearing loss, visual problems, dementia, loss of pain and temperature sensations and sexual dysfunction in men, bladder incontinence and sudden lightning like pains along with fever, malaise, anorexia, arthralgias and headache. It may also cause inflammation of the aorta and miscarriage, can transfer from mother to fetus [15].

2.6. Tuberculosis

Tuberculosis (TB) is a potentially serious infectious disease mainly affects lungs. TB is mainly caused by *Mycobacterium tuberculosis* (MTB) and also caused by other organisms of *Mycobacterium tuberculosis* complex—*M. bovis*, *M. africanum*, *M. canetti*, and *M. microti* [25]. TB can also attack any part of the body including kidneys, spine and brain. TB is spread from person having lung TB to another person through the air, while cough, sneeze or spit. Transmission of TB occurs when a person inhales droplet nuclei containing *M. tuberculosis*, the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract and bronchi to reach the alveoli of the lungs. In 2010, there were 8.8 (8.5–9.2 million) incident cases of TB, 1.1 million (0.9–1.2 million) deaths from TB among HIV-negative people and other 0.35 million deaths from HIV associated TB. In 2016, there were an estimated 10.4 million new cases of tuberculosis (TB) worldwide. Seven countries accounted for 64% of the total, with India leading the count, followed by Indonesia, China, Philippines, Nigeria, Pakistan and South Africa. A total of 1.7 million people died from TB in 2016 (0.4 million people with HIV) [26].

Two types of TB conditions exist: latent TB infection and TB disease. (1) Latent TB infection: Among persons with latent TB infection (LTBI), bacteria present in the body in an inactive state and cause no symptoms. It is also called inactive TB or TB infection; it has positive reaction to tuberculin skin rest or TB blood test. Persons with LTBI are not infectious and do not spread TB infection to others. Chest X-ray would be normal and negative sputum test, they do not feel sick. (2) TB disease: The symptoms of TB disease include feel of sickness or weakness, weight loss, fever and night swears, coughing, chest pain, and coughing up of blood. The signs and symptoms of active TB include coughing (lasts three or more weeks), coughing up blood, chest pain or pain with breathing or coughing, unintentional weight loss, fatigue, fever, night sweats, body chills and loss of appetite. Tuberculosis in spine may develop back pain and in kidneys might cause blood in urine.

3. Bacterial resistance to antibiotics

Antibiotics are natural microbial drugs used for the treatment and control of bacterial infections. First time the antibiotic penicillin was discovered by Fleming [27] while examining some colonies of *Staphylococcus aureus*. He observed that *Staphylococcus* colonies became transparent and undergo lysis around a large colony of mold. Finally, he identified that mold as penicillium and concluded that certain types of penicillium produced a powerful antibacterial substance that acts against pyogenic cocci and the diphtheria bacilli. Since the discovery of penicillin, many other antibiotics have been discovered or developed. Antibiotics may either kill or inhibit the growth of the bacteria and they are commonly classified based on their mechanism of action, chemical structure and spectrum of activity. Penicillins, cephalosporins and carbapenems are cell wall synthesis inhibitors, polymyxins are cell membrane synthesis inhibitors, rifamycins, lipiarmycins, quinolones, and sulfonamides interfere with the activity of essential bacterial enzymes and macrolides, lincosamides and tetracyclines are protein synthesis inhibitors [28]. The time line of antibiotic discovery was given in **Table 1**.

Antibiotic resistance is the ability of bacteria to resist the effects of drugs previously used to treat them [13]. Resistant bacteria are more difficult to treat, requiring alternative medications or higher doses, both of which may be more expensive or more toxic. Microbes resistant to multiple antimicrobials are called multidrug resistant (MDR); those extensively drug resistant (XDR) or totally drug resistant (TDR) are sometimes called "superbugs." Bacteria have various drug-resistant mechanisms contributing toward inactivation of antibiotics [30, 31] following as

- novel penicillin-binding proteins (PBPs),

- enzymatic mechanisms of drug modification,

- mutated drug targets,

- enhanced efflux pump expression and

- altered membrane permeability.

Timeline	Antibiotics	Resistance
>1910	Salvarsan	—
1921–1930	Penicillin; Prontosil	—
1940–1050	Gramicidin; Neomycin; Streptomycin; Bacitracin; Nitrofurans; Chloramphenicol; Polymyxin; Chlortetracycline; Cephalosporin	Sulfonamide; Penicillin; Spectinomycin; Bacitracin; Chloramphenicol; Streptomycin
1950–1960	Erythromycin; Isoniazid; Vancomycin; Virginiamycin; Cycloserine; Novobiocin; Kanamycin; Rifamycin; Metronidazole	Macrolide; Tetracycline; Neomycin; Nalidixic acid
1960–1970	Methicillin; Ampicillin; Nalidixic acid; Trimethoprim; Fusidic acid, Fosfomycin; Actinomycin D; Lincomycin	Methicillin; Cephalosporin; Polymyxin; Rifamycin; Vancomycin; Erythromycin; Kanamycin
1970–1990	Gentamicin; Mupirocin; Azithromycin; Carbapenem; Imipenem; Ciprofloxacin; Oxazolidinone	Metronidazole; Ampicillin; Gentamycin; Carbapenem
1990–2010	Linezolid; Telithromycin; Daptomycin; Tigecycline; Retapamulin; Garenoxacin; Telavancin; Besifloxacin; Ce-aroline fosamil	Imipenem; Ciprofloxacin; Mupirocin; Azithromycin; Linezolid; Daptomycin; Tigecycline
2010–2016	Fidaxomicin; Bedaquiline; Teixobactin	—

Table 1. Timeline of antibiotic discovery and emergence of antimicrobial resistance [29].

3.1. Factors influencing emergence of drug resistance

Various factors are involved in the emergence of antibiotic drug-resistant bacteria, the factors are inappropriate usage of antibiotics, patient movement within and between medical institutions, infection control measures, travel of people and food stuffs, antibiotic residues in the environment, dose duration and treatment, cross selection, gene transfer and clonal spread and socioeconomic factors [31]. The time line of development of antibiotic resistance was presented in **Table 2**.

3.2. β-Lactamases

The production of β-lactamase enzymes is the most common mechanism of bacterial resistance to β-lactam antibiotics such as the penicillins and cephalosporins. These enzymes catalyze the hydrolysis of the β-lactam ring to create ineffective antimicrobials. β-Lactamases were first identified in *Staphylococcus aureus* strains in the late 1940s, prior to the introduction of penicillin into the clinical setting [46]. Some β-lactamases are having substrate specificities relatively narrow and these are often traditionally referred as penicillinases or cephalosporinases. Over 400 β-lactamases have been reported to date, and new β-lactamases continue to

Infections, Reference/ Country	Isolated bacteria	Drug resistance
RTI (Peru) [32]	*M. tuberculosis*	MDR-TB -43% Isoniazid resistance – 4%; Isoniazid, rifampicin and pyrazinamide – 32%; Isoniazid, rifampicin, ethambutol, streptomycin and pyrazinamide – 14%
UTI (India) [33]	*Escherichia coli, 10.3%* *S. aureus, 5%* *K. pneumoniae, 4%* *E. faecalis, 2%,* *P. aeruginosa 1%* *Proteus* spp .1% *S. epidermidis, 1%*	Amp, ctx, cip, sxt-33.3%; amp, ctx, cip, nit, sxt- 27.8%
BSI (Combodia) [34]	*Escherichia coli, 30.7%* *S. choleraesuis, 11.4%* *Nontyphoidal* *Salmonella* spp. 6.8% *S. typhi, 2.3%* *Klebsiella* spp. 5.7% *Enterobacter* spp 3.4% *B. pseudomallei, 2.3%* *Pseudomonas* sp. 3.4% *Acinetobacter* sp.2. 9% *S. aureus, 19.3%* *Streptococcus suis, 1.1%* *Enterococci, 1.1%*	*E. coli:* amx-96%; cot-80%; cip-61%; amc-57%; ctr-46%; gen-57% S. typhi: cip-100%; amx and cot-50% Nontyphoidal *Salmonella* spp.: amx-80%; cot-60%; cip-40% *S. aureus:* oxa-28%; cot-28%
UTI (India) [35]	*E. coli, 100%*	*FQ resistance: 77.6%; ESBL and AmpC-71.1%* *ESBL-3.9%*
RTI (India) [36]	*M. tuberculosis*	MDR-TB – 38%;XDR-TB- 6%; Mono-resistant TB - 21%; Poly-resistant TB – 12%; Extremely drug-resistant TB – 2%
UTI and WI (Tanzania) [37]	*E. coli, 56%;* *K. pneumoniae, 37%* *S. aureus, 72%* *Proteus* spp. 43% *P. aeruginosa, 38%*	Cot-75%; amc-34%; cip-33.3%; amp-86.4%; cro-66.7%; tet-81.3%; ery-27.3%

Infections, Reference/ Country	Isolated bacteria	Drug resistance
UTI (Nigeria) [38]	E. coli, 30% K. pneumoniae, 14.2% P. aeruginosa, 27.6% S. aureus, 28.3%	E. coli: caz-95.2%; oxa-92.8%; amp-88%; chl-73.8%; cro-69%; tet-50%; nit-45.2%; cot & ery-42.9%
UTI & BSI (India) [39]	E. coli, 51% K. pneumoniae, 14.6% K. oxytoca, 12.6% P. aeruginosa, 11.2% Proteus mirabilis, 7.3% P. vulgaris, 2.6%	Ery-99%; amp-94%; cpd-91%; atm-90%; cfp & fox-89.4%; pip-85.4%; caz-84.8%; cro-74.2%; ipm-73.5%; tzp-72.4%; tet-66.9%; cip-66.2%; dox-58.2%
Nasopharynx colonization (Ghana) [40]	M. catarrhalis, 39.8%; Coagulase negative staphylococci, 33.1%; S. pneumoniae, 30.5%; Diphtheroids, 29.7%; Viridian streptococci, 27.1%; S. aureus, 22%; Citrobacter spp. 4.2%;	M. catarrhalis: amp-80%; CoT-60%; mrp-42.6%; chl-23% S. aureus: pcn-100%; tet-80%; cfx-73%; ery-38% S. pneumoniae: cot-58%; tet-33%; ery-33%; oxa-27%
EI(Cameroon) [41]	E. coli, 85.3% Klebsiella spp. 29.4% Enterobacter spp. & Citrobacter spp. 23.5% Salmonella sp. 5.9% Serratia sp. 1.5% Proteus sp. 2.9%	E. coli: amx-60.3%; amc-62%; cro-39.6%; chl-32.7%; dox-91.3% Klebsiella spp: amx, amc – 100%; dox-70%; tet-50%; chl-35 Enterobacter spp: amx, amc-93.7%; dox-87.5%; tet-63.8%; chl and cip-37.5% Citrobacter sp.: amx, amc, cro-43.7%; dox-68.7%; tet-30% Salmonella spp.: dox & chl-75% Serratia spp: amx, amc, chl & dox- 100%
UTI (India) [42]	E. coli, 50.7% K. pneumoniae, 13.2% K. oxytoca, 11.8% P. mirabilis, 6.3% P. vulgaris, 1.4% P. aeruginosa, 5.5%	Azt-94.6%; cpd-93.8%; cefoperazone-91.3%, fox-90.3%; ctx-89%, amp-89%, ipm-72% Enterobacteriaceae- ESBL-52.5%; MBL & AmpC- 62.5% P. aeruginosa- ESBL-50%; MBL and AmpC-62.5%

Infections, Reference/ Country	Isolated bacteria	Drug resistance
UTI (Tanzania)	*E. coli*, 57.7%	*E. coli*: amp-93.3%; sxt-90%; amc-43.3%;
[43]	*K. pneumoniae*, 23.1%	*K. pneumoniae*: amp-100%; sxt-72.7%; nit-33.3%; amc-54.5%
	C. freundii, 3.9%	
	S. aureus, 3.9%	
	P. agglomerans, 1.9%	
	S. agalactiae, 1.9%	
RTI (China)	*P. aeruginosa*, 24.1%	MRSA-3%; VRE-1%; ESBL-62%;
[44]	*E. coli*, 16%	Multidrug resistant TB-22%
	A. baumannii, 15.1%	Extensively drug-resistant TB-3.5%
	K. pneumoniae, 13.4%	
	Stenotrophomonas maltophilia, 11.6%	
	S. aureus, 4.4%	
	S. pneumoniae, 1.8%	
	Tuberculosis-19.3%	
OM (Tanzania)	*P. aeruginosa*, 6.4%	*P. aeruginosa:* amp-73.3%; amc-53.3%; ery-40%
[45]	*E. coli*, 5.3%	*E. coli*: amp & fox- 51.4%; ery-45.9%
	K. oxytoca, 5%	*K. oxytoca*: ery-62.5%; fox-50%; amp-43.8%
	K. pneumoniae, 12.4%	*K. pneumoniae*: amp-51.2%; amc-48.6%
	S. aureus, 45.7%	*S. aureus*: amp-46.5%; fox-42.7%; ery-37.4%
	M. catarrhalis, 3.2%	*M. catarrhalis*: amk & amp-55.6%
	P. mirabilis, 1.1%	*P. mirabilis*: ery-100%; amc & amp- 66.7%
	S. epidermidis, 5.0%	*S. epidermidis*: ery-64.3%; fox-55.5%; amp-50%
	S. pneumoniae, 2.5%	*S. pneumoniae*: ery-71.4%; fox-42.9%
		S. pyogenes: amp-48.7%; ery-42.1%

RTI: respiratory tract infections; BSI: blood stream infection; UTI: urinary tract infection; WI: wound infection; EI: enteric infection; OM: Otitis Media; amk – amikacin; amx – amoxicillin; amc - amoxicillin-clavulanic acid; amp – ampicillin; ctx – cefotaxime; fox – cefoxitin; cpd – cefpodoxime; caz – ceftazidime; cro – ceftriaxone; chl – chloramphenicol; cip – ciprofloxacin; dox – doxycycline; ery – erythromycin; gen – gentamicin; ipm – imipenemmem – meropenem; nit – nitrofurantoin; oxa – oxacillin; pen – penicillin; pip – piperacillin; tzp - piperacillin-tazobactam; tmp – trimethoprim; sxt - trimethoprim-sulfamethoxazole.

Table 2. Bacterial infections and drug resistance in HIV patients.

emerge rapidly worldwide [47, 48]. β-Lactamase producing organisms pose a major problem for clinical therapeutics. The incidence of β- lactamase producing strains among clinical has been steadily increasing over the past few years resulting in limitation of therapeutic options. β-Lactamases are classified based on the molecules (Ambler Classification) and functions (Bush-Jacoby-Medeiros classification) of the enzymes [49]. Most important β-lactamase enzymes are extended spectrum β-lactamases (ESBLs), AmpC β- lactamase (AmpC) and Metallo β-lactamase (MBL).

4. Drug-resistant bacteria from HIV patients

Human immunodeficiency virus (HIV)-infected individuals are highly vulnerable to a various opportunistic infections (OIs) due to their compromised immune system. For the prophylaxis of OIs, HIV patients are frequently exposed to high level of antimicrobial agents which leads to the emergence of multidrug-resistant bacteria. MDR bacteria become a major problem in the clinical management of HIV disease. Treatment of common bacterial infections like acute respiratory tract infections, urinary tract infections, wound infections, meningitis, and blood stream infections are very difficult when they are associated with MDR bacteria leading to increased morbidity and mortality. Multidrug resistant (MDR) pathogens are relentlessly multiplying in HIV patients and thus become an important circulating source of infection in the community. Globally, very few scientific data are available on the drug-resistant bacteria from HIV population.

Co-trimoxazole (also called as trimethoprim-sulfamethoxazole (TMP-SMX)) is a broad-spectrum antibiotic, used as a prophylactic agent against opportunistic infections among HIV/AIDS patients. Especially, TMP-SMX is an active drug against Pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii* among HIV-infected patients [50, 51]. World Health Organization and Joined Nations Programme on HIV/AIDS have recommended TMP-SMX prophylaxis for immunosuppressed adults and children born to HIV-infected women [52–54]. Long-term receiving of TMP-SMX prophylaxis has lead to increase in the development of TMP-SMX-resistant bacteria, which spreading in the bacterial community and cause therapeutic problems for bacterial infections in HIV population. In Enterobacteriaceae, sulfonamide drug resistance genes such as *sul1*, *sul2*, and *sul3* are responsible for dihydropteroate synthases, and more than 20 dihydrofolate reductase (*dfr*) genes conferring resistance to trimethoprim [55] (**Table 2**).

UTI accounts for consumption of large proportion of anti-bacterial drugs [18]. Resistance to commonly prescribed antibiotics for UTI is an expanding global problem both in developed as well as developing countries [56]. UTI became quite alarming as isolated uropathogens exhibit high percentage resistance to almost all antibiotics [57]. The pattern of antibacterial susceptibility of UTI causing pathogen has been changing over the years, and the drug resistant of the bacteria is influenced by the extensive and misuse of antibiotics and changing patient population, especially among immunocompromised patients. β-Lactam antibiotics such as penicillins, cephalosporins and carbapenems are the most commonly used antibacterial drugs. The predominant drug resistance mechanisms against β-lactam antibiotics among Gram-negative bacteria are the production of Extended Spectrum β-lactamases (ESBLs) and AmpC β-lactamases [58] and they are associated with increased morbidity and mortality with immunocompromised individuals. The frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* as community-acquired pathogens is higher in HIV-infected individuals than in those not HIV infected. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection should be considered as a potential etiology for pneumonia, given that community outbreaks of MRSA have been seen in men who have sex with men and nasal carriage of MRSA is more common in HIV-infected individuals, particularly at lower CD4 cell counts. Multidrug resistance (MDR) bacteria like ESBL producers and MRSA are a major public health concern worldwide [21, 39] (**Table 2**).

WHO has documented that MDR-TB is emerging as a major challenge for tuberculosis control programs and is becoming extensively widespread today throughout the world, even in high-income countries with low TB incidence. Resistance to anti-TB drugs occurs due to misuse of drugs such as patients do not compete full course of treatment, wrong treatment provide by physicians, wrong dose or length of time for taking the drugs and supply of poor quality drugs. Multidrug-resistant TB is caused by *Mycobacterium tuberculosis* that is resistant to at least to two most potent TB drugs such as isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is MTB resistant to isoniazid and rifampicin along with any fluoroquinolone and at least one of three injectable second-line drugs includes amikacin, kanamycin or capreomycin. Treatment options for XDR-TB have more side effects, and they are more expensive. XDR-TB can weaken the immune system, and persons are more likely to develop TB disease and they are at high risk of death.

In 2010, about 650,000 cases have MDR-TB, which account for 5% of all newly diagnosed TB patients, and more than 150,000 MDR-TB deaths are estimated to occur worldwide each year with case fatality rate of 30 per 100 individuals [59]. The proportion of MDR-TB reported globally ranges from 0 to 28.3% and 0 to 61.6% among new TB cases and among previously treated TB cases respectively [60]. People living with HIV are at a higher risk of developing MDR and XDR tuberculosis associated with increased mortality, and greatly reduced survival time of patients [61] (**Table 2**).

5. Future impact of antimicrobial resistance

The two multidisciplinary research teams such as RAND Europe and KPMG, have provided their own high-level assessments of the future impact of antimicrobial resistance, based on scenarios for rising drug resistance and economic growth to 2050. The studies estimate 300 million people are expected to die prematurely due to drug resistance over the next 35 years and the world's Gross Domestic Product (GDP) will be 2% to 3.5% lower than it otherwise would be in 2050. This means that between now and 2050, the world can expect to lose between 60 and 100 trillion USD worth of economic output if antimicrobial drug resistance is not tackled. This is equivalent to the loss of around 1 year's total global output over the period, and will create significant and widespread human suffering. Furthermore, in the nearer term, they expect the world's GDP to be 0.5% smaller by 2020 and 1.4% smaller by 2030 with more than 100 million people having died prematurely [62].

6. Tackle of antimicrobial resistance

WHO developed a global priority of pathogens list (global PPL) of antibiotic-resistant bacteria to help in prioritizing the research and development (R&D) of new and effective antibiotic treatments. Drug-resistant bacteria were categorized into critical priority, high priority and medium priority pathogens (**Table 3**) [63].

Type of priority	List of drug-resistant pathogens
Critical priority	Carbapenem-resistant *Acinetobacter baumannii*; Carbapenem-resistant *Pseudomonas aeruginosa*; Carbapenem-resistant, 3rd generation cephalosporin-resistant *Enterobacteriaceae*
Medium priority	Penicillin-non-susceptible *Streptococcus pneumonia*; Ampicillin-resistant *Haemophilus influenza*; Fluoroquinolone-resistant *Shigella* spp.
High priority	Vancomycin-resistant *Enterococcus faecium*; Methicillin-resistant, Vancomycin-intermediate and resistant *Staphylococcus aureus*
	Clarithromycin-resistant *Helicobacter pylori*; Fluoroquinolone-resistant *Campylobacter*; Fluoroquinolone-resistant *Salmonella* spp.
	3rd generation cephalosporin-resistant, fluoroquinolone-resistant *Neisseria gonorrhoeae*

Table 3. Global priority of pathogens list by World Health Organization.

7. Global action plan, WHO

WHO developed the global action plan with five strategic objectives to achieve the goal of ensuring continuity of successful treatment and prevention of infectious diseases with effective and safe medicines [64]. They (1) improve the awareness and understanding of antimicrobial resistance through effective communication, education and training, (2) strengthen the knowledge and evidence base through surveillance and research, (3) reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures, (4) optimize the use of antimicrobial medicines in human and animal health and (5) develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

7.1. Examples for global impact of antimicrobial resistance research and interventions

Examples of global research into antimicrobial resistance and its impact are given below [29]:

- Chinese Ministry of Health in 2011, reduced unnecessary prescription of antimicrobials by 10–12%.

- The Swedish Strategic Programme against Antibiotic Resistance (STRAMA): decrease in antibiotic use for outpatients from 15.7 to 12.6 daily doses per 1000 inhabitants and from 536 to 410 prescriptions per 1000 inhabitants per year from 1995 to 2004. The decrease was most evident for macrolides (65%).

- WHO essential medicines policies: reductions in antibiotic use of ≥20% in upper respiratory tract infections and 30% of reduction in the use of antibiotics in acute diarrheal illness.

- Antimicrobial stewardship programme (2009–2014) in 47 South African hospitals: reduction of antibiotic doses daily per 100 patient days from 101.4 to 83.04.

- Antimicrobial Resistance Monitoring and Research Programme (United States): Infections with carbapenem-resistant Enterobacteriaceae declined and there were no further reports of outbreaks of colistin-resistant *Acinetobacter* spp.

- In the Netherlands, a decrease of CTX-M^{-1}-1-like ESBL genes (from 44 to 25%) in livestock was seen during 2010–2014 due to >60% reduction in antibiotic use in livestock.

8. Conclusion(s)

Spread of antibiotic-resistant bacteria is leading to untreatable infections causing a major public health threat. Handling of new approaches such as combination therapeutics, organism specific drugs and repurposing of antibiotics might helpful in the treatment of drug-resistant bacterial infections on stipulated time and reduce the burden in clinical settings. Effective global investments are needed to improve the way prevent, control and monitor the emergence and global spread of drug resistance.

Conflict of interest

There is no conflict of interest to declare.

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