Antibacterial-Resistant Pathogens Mechanisms of Transmission and Strategies for Prevention and Control

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ABSTRACT

Antimicrobial-resistant pathogens' transmission threatens the lives of patients. Microbial adaptation to the varied environment, mode of communication, the role of the microbiome in bacteria growth and development, gene expression, resistance selection and transmission between different environments as well as the metabolic reactions upshot spread of resistance. The communal presence of resistant pathogens aids their potential acquisition by wildlife and subsequent transfer to humans either directly or by contaminated foodstuffs. Mechanisms behind the antibiotic-induced conjugative spread of resistance plasmids in pathogens depend on genes and regulatory pathways that are involved in the enlarged frequency of resistance plasmids transfer caused by treatment with antimicrobial drugs. Antibiotic-induced conjugative spread resistance mechanisms aid microbes' survival in an infection, promote their life cycle through replication and spread in host cells. Alteration of microbial physiology and cellular activities through metabolic modifications enhances fitness under varying conditions. This permits persistence and circulation between environments and also the nature of their pathogenesis.

INTRODUCTION

Moist, warm environments (waste or wastewater from pharmaceutical, hospital and water treatment facilities, aquaculture ponds, manures and irrigation water) with abundant nutrients are effectual in the transmission and exchange of genetic materials between resistant microbes and host microbes. Such environments are rich in nutrients; representing extreme environments to life[1,2]. However, environmental and genetic factors cause inter and intra-species differences that can give some ability to survive and thrive in a hostile environment. The acquisition of a resistant gene makes a microbe serve as a reservoir, vector and bio-indicator of resistant microbial pathogens and genetic determinants of antimicrobial resistance[3]. Genetic factors determine susceptibility to disease and environmental factors determine which genetically susceptible individuals are affected.

Because resistant organisms can evolve quickly and rapidly replicate in living cells, they are transferred directly between wildlife and humans or by contaminated foodstuffs. Microorganism replication requires a bacterium direct contact with a host, gain entry into the appropriate cell type, produce more copies of itself, overcome any immediate host response and exit from the cell and transmit to another. Getting contact with a host requires that the adaptive changes necessary to replicate in a foreign host are independent of but necessary for, those required for successful transmission between individuals. The rapid spread of resistant genes can be enhanced by antimicrobial usage, the ability of resistant strains to colonize the host, pathogen relative fitness, pathogen gene mutation rates and efficiencies of horizontal transfer of resistance genes. Imbalances in the intestinal flora, reduce microbiome translocation, hindered intestinal barrier function, the reservoir for transmission that may precede infection and prolonged hospital exposure create prospects for horizontal gene transfer of plasmids encoding antibiotic resistance genes.

Pathogenic microbial genes are naturally amplified and transmitted by horizontal transfer between the same species and/or different species[4]. Sub-lethal stresses (i.e., high/low temperature and osmotic and pH stress) induce transcription and/or translation of stress-response proteins, which convey increased resistance to a multitude of stresses. These generate a reservoir of resistant pathogenic genes with extensive impacts on human health[5]. The changeability and intracellular adaptableness of plasmids tells the distinctiveness of microorganisms' adaptation and survival of genes as well as the complexity for dissemination of antimicrobial resistant-encoding genes[6]. The presence of strains co-harboring resistance determinants limits antimicrobial treatment for the majority of producing strains.

Resistance can persist after the cessation of an antimicrobial use[7]. It can also persist if the resistance determinant is linked to genes or transposons conferring resistance to other agents in continued use. This usually depends on the mode and level of gene expression[8,9].

The purpose of this article was to examine the various antibacterial-resistant pathogens' mechanisms of transmission. The focus will be on patients and the general community, health care centers and food-producing animals.

ANTIBACTERIAL RESISTANT PATHOGENS

Extended-spectrum β-lactamase (ESBL), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), vancomycin-resistant *Staphylococcus aureus* (VRSA), glycopeptide-resistant enterococci (GRE), fluoroquinolone-resistant and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*, penicillin and cephalosporin-resistant *Streptococcus pneumoniae* (PRSP) are drug-resistant pathogens. They can be acquired in healthcare surroundings (e.g., staphylococcal infections in intensive care units), in the community (e.g., pneumococci acquired from a neighbor) and through the food supply (e.g., *Salmonella* acquired from meat or eggs), both domestically and internationally.

Healthcare surroundings are one of the reservoirs and sources of dissemination of multidrug-resistant microorganisms. Microbial infections in such environments might be caused by more than one multidrug-resistant organism[10]. These microorganisms can transmit through aerosol, physical contact and bodily fluids or instruments. Health workers and discharged patients can also infect several community members through physical contact. Health professionals interacting with patients colonized by multi-resistant microorganisms are susceptible to becoming reservoirs and broadcasters.

Patients with drug-resistant infections (pneumonia, bloodstream infections, tuberculosis, malaria, HIV, influenza) may randomly transmit to other patients, leading to an outbreak or endemic colonization or infection with the resistant organism. Such patients consume more healthcare resources (more antimicrobial therapy, lengthier hospital stays because of their illness or complications of therapy)

and are at increased risk of worse clinical outcomes and death due to underlying disease and immunosuppression. Older patients suffer severely from microbial infections which may be associated with a higher frequency of comorbidities. Patients display diverse pathologic and clinical features, some of which have prognostic significance. In women, epidemiological evidence indicates that antibiotic use increases the risk of breast cancer[11], colitis caused by *Clostridium difficile*[12,13] and vaginal candidiasis[14].

Animals aid the transmission of pathogenic microbes. They harbor and enable pathogens to survive and as well active cause of pathogen spread in the environment and to other animals, including man. Transmission of zoonotic (and non-zoonotic diseases) requires three components: A disease agent or pathogen, a host and a mode of transmission for the pathogen. Transmission of zoonoses occurs through three main mechanisms, contact (via ingestion, open, mucous membranes exposure, or an open wound), aerosol (droplets from an infected animal or person inhaled through mucous membranes and vector-borne (mosquito, flea, tick or another arthropod). The emergence of zoonotic agents is increasing due to close contact between human and livestock animal populations, exposure to new pathogens through ecologic and environmental changes brought about by human activity, bioterrorist activities and transportation advancements that enable global circumnavigation in less than the incubation period of most infectious agents.

PATHOGEN ADAPTIVE MECHANISMS AND PERSISTENCE OF RESISTANCE

Resistant microorganisms have diverse complex strategies used to adjust to various environmental stresses that may result from host defenses (chemical bactericidal components, phagocytosis) and other immune (adaptive) responses. These strategies aid the pathogen's survival, promote the life cycle through replication and spread in host cells. Resistant microorganisms colonize new habitats through:

Genes translation: The sustainability of microbial life depends on safeguarding the existing microbial genes. The RND protein ensures proper timing and coordination of DNA replication, chromosome segregation, cell division and proliferation and morphological changes. Gene duplication occurs in evolutionary expansion. This duplication makes extra gene copies available for sub-functionalization or neofunctionalization[15], with the resultant phenotype, potentially contributing to an organism's survival, adaptation and overall fitness. Differences in the expression patterns of duplicate genes may contribute to the evolutionary divergence of species. Divergence of lineages results from the strong selection on certain loci[16,17]. The RNA molecules transmit coded messages interpreted by enzymes through inactivation, induction as well as other factors. The interpretation generates signals which initiate chemical differentiation and morphological differentiation. Ribosomes may or may not produce the required protein even if mRNA delivers the copied genetic code.

Plasmid-mediated transmission is a common mechanism of horizontal gene transfer (HGT)[18]. Plasmids normally carry genes that impart some discriminating advantage to the host bacterium. They are diverse in size, copy number (the number contained within a bacterial cell) and the number of accessory genes that they contribute to the host cell. The potential arrangement of accessory resistance genes on a plasmid is nearly unlimited and may arrive as constituents of other mobile elements such as transposons and integrons.

Motility and attachment: Resistant pathogens use a diverse range of enzymes capable of catalyzing various biochemical reactions (metabolism, toxin production, modification of the drug through the addition of protective groups) to aid survival in a wide range of environmental conditions. This characteristic aid very structured, sophisticated microbial groups to attach to surfaces for more efficient nutrient cycling and enhanced protection from external threats. This characteristic stress response ability protects against a broad range of otherwise lethal environmental stresses such as solid surfaces in the body such as prosthetics, catheters, or implants, as well as surfaces in food and chemical factories or water treatment plants.

Adherence is the initial stage of virulence. The adhesive fimbriae facilitate the pathogens to adhere to a specific receptor(s). The microbial adherence is followed by intracellular growth. They secrete toxins (e.g., hemolysin) which disrupt the epithelial barrier to gain access to the underlying tissues. These organisms then form complex networks that are regulated through nutrient cycling, competition, antagonism and chemical communication mediated by a diverse array of signaling molecules. Polymicrobial aggregates following successful colonization result in biofilms. The biofilms are thus communities of microbial populations of surface-attached cells surrounded by an extracellular matrix that is self-produced. These aggregate microbes communicate via quorum sensing. These inter and intracellular signaling triggers the expression of genes contributing to pathogenicity, virulence and survival of pathogens[19].

Biofilm formation allows microbes to survive under hostile conditions (nutrient availability, environmental stresses and the presence of toxic compounds). Few colonies of the microorganisms reversibly adhere to the surface via van der Waals' forces to create an initiation site. This is followed by an irreversible attachment of the cells through the production of the exopolysaccharide matrix and cell growth[20]. The cell growth is not uniform and results in the formation of channels[21]. A combination of cell division and recruitment occurs during the maturation stage and only biofilm shape and size are changed[22]. Finally, the detachment of individual cells and dispersion enables the biofilm to spread and colonize new surfaces or to join another biofilm[23,24].

Cell envelope modifications: The microbial cell wall represents the first and major line of its internal defense. It is composed of inhibitors that include broad-spectrum classical antibiotics, metabolic by-products (organic acids) and lytic agents (lysozyme). Protein exotoxins and bacteriocins, which are biologically active peptide moieties with the bactericidal mode of action[25,26] as well as peptides which are heat-stable bacteriocins that lack post-translational modifications as found in lantibiotics[27]. Chitinase is an essential component in the maintenance of cell wall plasticity during growth and proliferation. The cell envelope, cell wall or cell membrane, is an effector of cell morphology and robustness, the major point of contact with the host, an active modulator of host immune defenses and a prime target for antimicrobial drugs. It adapts the cell under different conditions, transient or long-term to environmental challenges and maintains homeostasis. The composition varies significantly in reaction to changes in carbon source, temperature, pH and aeration[28].

Pathogens can internalize their plasma membrane by rapidly remodeling their protein content[29], which is essential for polar growth, cytokinesis, hormone perception and transport, response to pathogens and pollutant detoxification[30,31]. Structural modification enhances the metabolic stability, receptor-binding affinity as well as the formation of chemically stable metabolites with pharmacological activity[32,33]. Ribosome proteins protect microorganisms from the action of chemical substances. Cytoplasmic proteins bind to the ribosome and cause an alteration in ribosomal conformation, which prevents drugs from binding to the ribosome, without altering or stopping protein synthesis.

Temperature-induced modifications: Adaptation to temperature changes is particularly fundamental for microbes as they inhabit and circulate between many natural and manmade environments, several host species, varying anatomical sites, fomites and food matrices, where they are susceptible to temperature fluctuations that can adversely impair the cell envelope and interfere with its intricate functions[34]. Commonly observed stress responses in cell adaptation are cell wall thickening. Thickened cell wall structures are associated with significant alterations in amino acid profiles[35]. Modifications in amino acid content concerning temperature adaptation are a result of the increase in cell wall-associated proteins, particularly cold-shock proteins which are essential in maintaining the integrity of this structure and functionality in cold temperatures[36]. Susceptibility to heat stress impairs bacterial growth and permeability and may render cells vulnerable to other stress conditions[37]. To maintain cellular homeostasis in extreme

heat stress, heat-shock proteins (Hsps) protect against protein damage-misfolding and aggregation and promote their refolding and proper assembly and movement across membranes[38]. The Hsps also aid in successful host colonization and infection[38].

Cells exposed to cold temperatures showed a significant upregulation of ten ribosomal proteins and a reduction in cytoplasmic AA concentrations. Ribosomal proteins act as temperature sensors and the upregulation in their synthesis reflects their role in microbial acclimatization to prolonged instances in cold temperature[39]. The cell membrane is also rich in fatty acids and lipid content, essential to its adaptive functions in the presence of host defenses, antimicrobial challenges and acclimatization to environmental fluctuations[40]. Branched saturated fatty acids which determine membrane fluidity prevent temperate-induced impairments (home viscous adaptation)[41]. At low temperatures, the cell membrane consists of monounsaturated FA. These lower melting point FA significantly improve membrane fluidity in colder environments to maintain cellular function[42]. Carotenoid pigments are involved in membrane stabilization under both cold and heat stress[43].

Osmotic pressure induced modifications: Resistant microbes can synthesize ectoine as an osmoprotectant and large amounts of proline when exposed to high osmolarity to balance the environmental and cytoplasmic differences in osmolarity and maintain turgor and cellular crowding within physiological boundaries. This makes these microorganisms capable of colonizers of environments with low water content and high salinity[44]. Halo tolerance aid microbes in human health and disease[45].

Halo-tolerant microbes adapt their cytoplasmic content to maintain osmotic pressure in the presence of a broad range of salt concentrations. High salt concentrations in the external environment can severely dehydrate the cell and interfere with turgor pressure but can affect DNA replication and the structure of many cytoplasmic proteins and their associated functions. To circumvent these adversities, bacteria can employ halophilic proteins that maintain soluble and active conformations in these conditions via protein halo-adaptation[46].

Proline and glycine betaine are examples of effective osmoprotectants that accumulate within cells in environments of high osmotic stress[47].

Antimicrobial-induced modifications: Antimicrobial administration represents a strong destabilizing factor in the microbial ecosystem[48,49]. The broad use of antimicrobial compounds in human and veterinary medicine, agriculture and agro-food industries, negatively affects microbial community diversity and hence resilience, potentially allowing microbiome communities to become more susceptible to invasions by pathogens[50]. These environmental stressors which may concentrate in organisms along trophic chains interfere with specific systems (e.g., enzymes, receptors and effectors) or stimulate a physiological response even at low concentrations[51]. Different antimicrobial agents can influence the normal microbiota in different ways. Short-term effects of antimicrobials use include:

- Decreased colonization by commensal microbes
- Alterations in the composition of normal flora
- Disturbances in metabolism and absorption of nutrients
- Overgrowth of microbes
- Increased susceptibility to infections
- Long-term effects
- Persistence of antimicrobial resistance genes in the compositional microbiome
- Recurrent infections
- Loss of microbial diversity and representation of specific taxa
- Cell wall is a major target of antibiotic therapy. Cell wall active antibiotics act by interfering with one or more of the steps involved in cell wall synthesis and assembly

Cytoplasmic modulations: The cell envelope provides significant protection and adaptability in the presence of external adversities. Cytoplasmic-level modulations are also possible in the event of challenge and envelope compromise.

Microorganisms lack intracellular organelles for energy-producing processes such as respiration or photosynthesis. Instead, the cytoplasmic membrane carries out these functions. Microorganisms concentrate substances (specific sugars, amino acids, anions or cations that are of nutritional value) inside their cytoplasm against the concentration (gradient) of the environment. The concentration of solutes in the cytoplasm requires the operation of an active transport system, of which there are two types: Ion-driven transport systems (IDT) and binding-protein dependent transport systems (BPDT). Active transport processes can occur through the movement of molecules across the membrane at the expense of a previously established ion gradient (K^+, Na^+ or H^+ gradient). Active transport processes may also depend on the energy from ATP hydrolysis to mediate the movement of solutes across the membrane, the high affinity of solute transport comes from the affinity of the binding protein for the specific substrate. Binding protein-dependent transport systems belong to a large group of transporters known as the ABC (ATP-binding cassette) superfamily of transport proteins. When the electron transport system operates, it establishes a pH gradient across the membrane due to an accumulation of protons (H^+) outside and hydroxyl ions (OH^+) inside. Thus, the outside is acidic and the inside is alkaline. Operation of the ETS also establishes a charge on the membrane called proton motive force (PMF). The outer face of the membrane becomes charged positively while the inner face is charged negatively, so the membrane has a positive side and a negative side, like a battery. The pmf can be used to do various types of work including the rotation of the flagellum, or active transport as described above. The pmf can also be used to make ATP by the membrane ATPase enzyme, which consumes protons when it synthesizes ATP from ADP and phosphate. The connection between electron transport, the establishment of pmf and ATP synthesis during respiration is known as oxidative phosphorylation, during photosynthesis, it is called phosphorylation.

Nutritional adaptations: Nutrition is a strong determinant of microbiome composition and diversity. Nutrient-limiting environments circulate between terrestrial habitats, clinical settings and hosts. Aquatic and marine environments are subject to large spatial and temporal nutrient fluxes arising from seasonal and geographic variations in temperature, salinity, nutrient input, etc. Environments abundant with proteins are known to increase the abundance of bile-tolerant microorganisms like Bilophila and Bacteroidetes, whereas plant materials increase the abundance of Firmicutes that metabolize plant polysaccharides.

Hyphal development associated: Cyclic dinucleotides are highly versatile signaling molecules that control and coordinate diverse aspects of bacterial growth and behavior, including motility, cell cycle progression, virulence and biofilm formation as well as osmotic and cell wall homeostasis. A decrease in cellular c-di-AMP levels has been shown to render microorganisms more susceptible to antibiotics. The c-di-GMP determines cell polarity, morphogenesis and cell cycle progression. The switch between the sessile and the planktonic lifestyle is controlled by cyclic di-GMP (bis-(3"-5")-cyclic dimeric guanosine monophosphate).

FACTORS INFLUENCING RESISTANT PATHOGEN TRANSMISSION
Host factors
Natural barriers: Bacteria use the ADI pathway to exhaust arginine in the host cell. Exhaustion of arginine reduces NO production, avoids NO-mediated killing in the phagocytes and increases bacterial survival. The ADI pathway protects bacteria from being killed in the phagolysosome, by arresting the pH decrease, thereby preventing the phagosome and lysosome from fusing. ADI pathway has the property of increasing the cytoplasmic pH. The ammonia produced by the ADI pathway can neutralize the cytoplasmic pH and protect the cell from the potentially lethal effects of acidic extracellular environments[52].

Microorganisms regulate their survival and proliferation with the aid of specialized proteins that protect the vital periplasmic compartment from stress-induced damage. The series of trans-membrane proteins ubiquitously expressed in the periplasmic membranes regulate the transport of metabolites, nutrients, ions and drugs across cellular membranes across the concentration gradient. However, high intracellular concentrations are achieved by hijacking the ability of these membrane proteins to transport metabolites against their concentration gradient with electrochemical gradients mechanisms to drive the uptake of numerous metabolites and xenobiotics against a concentration gradient including amino acids, peptides, vitamins, metals, salts, nucleic acids, drugs and environmental toxins.

Host immunity: The immune system is composed of a complex network of innate and adaptive components endowed with an extraordinary capacity to adapt and respond to highly diverse challenges. Immune cells, Treg, B cells, T and associated subpopulations, gamma delta (γδ) T, NK, dendritic, monocytes and macrophages and neutrophils, play pivotal roles in composing host immune response. Macrophages are essential in maintaining and activating host inflammatory responses. Myeloid cells such as neutrophils, macrophages and dendritic cells recognize and remove bacteria from the innate immune system. Neutrophils, the most abundant leukocyte in systemic circulation are responsible for microbial eradication. Neutrophil deficiency hastens the development of nosocomial and secondary infections, which is probably due to impaired bacterial clearance and altered pulmonary cytokine response.

Widespread lymphocyte apoptosis (a regulated form of cell death) occurring in the lymphoid (spleen, thymus and lymph nodes) and other organs results in impaired immune cell activity (including that of neutrophils, monocyte and macrophages, B cells, natural killer cells (NK cells) and dendritic cells contributes to the development of immunosuppression. Compromised immune systems are susceptible to infections because it favors microbes' growth. Age and developmental stage are important factors influencing stress responses in animals and plants.

Pathogen or infectious agent factors
Infectivity: Processed food with exposed surfaces that exude nutrients utilized by pathogens (*E. coli* and *Listeria monocytogenes*) provides the conditions for the proliferation and survival of human pathogens. Consumption of resistant microbial strains contaminated food products ensures that the resistant genes thrive in the intestines where new resistant strains are created across different microbial species. Once the drug-resistant strain infects a farm worker, it readily transfers to family, friends and other members of the community. Animal-to-human transfer can also occur during the slaughter and processing of food products. In the environment, the use of animal excreta on agricultural fields as manure transfers antibiotic-resistant microbes to humans as well as to plants.

Human-to-animal transmission of methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, multidrug-resistant enterococci and multidrug-resistant Gram-negative pathogens creates the potential for further transmission back to humans or to other animals[53,54]. Geographic areas with high antimicrobial consumption are associated with increased antimicrobial resistance[55].

Pathogenicity: Phenotypic variant cells of a genetically homogenous culture can tolerate and endure selective pressures that other members of the population are susceptible to. Persisters are highly tolerant and repopulate environments after the stress has vanished. During a persister life cycle, cells first enter the persistent state and then eventually recover to resume growth. Through environmental modification, an organism's phenotypic effects are extended beyond its genome since the host integrates the extended effects of the microbiome into its phenotype[56]. The persistent state is characterized by a particularly low metabolic turnover and is probably controlled by toxin-antitoxin systems. Their response to imposed stress is accomplished by changes in their patterns of gene expression. In very severe stressful situations, the loss of the ability to recognize and elimination results in cellular dysfunction or exhaustion.

Persister cells display several metabolic characteristics that promote their survival and persistence in adverse environments. Persister cells remain active, but with minimal metabolic capacity (arrested growth and replication) that can maintain viability even for prolonged durations. When stressed, persisters decreased membrane fluidity by increasing their membrane saturated-FA content while concurrently reducing branched-FA content. They, however, maintain reduced oxygen consumption. This downregulation of cellular activities (a reduction of intracellular adenosine triphosphate (ATP) and the expression of stationary-state markers) hinders the action of chemotherapeutic agents that depend on active targets. Altered metabolism also adapts them to the host's intracellular milieu and impedes their clearance. Persister phenotypic tolerance is not genetically determined, characteristics are non-heritable by future progeny[57] but stress tolerance is maintained in several generations due to mechanisms of epigenetic inheritance[58].

Virulence: Microbes cause virulence by reprogramming the metabolism of the host to support pathogen growth and development. Apart from immunological adaptation towards the host, the microbe singularly undergoes the production of receptors and proteins for adhesion to tissues, formation of pilli to avoid desquamation and use of nutrients like iron for growth and colonization. Commensal microbes are known to produce hemolysins, to break host hemoglobin and use the iron from it or to produce human transferring-like receptors for iron-capturing in the gut, that compete with the human transferrin receptors. This could have evolved because of the exchange of genes encoding the transferring receptors from host to microbe or through polymorphisms in the microbial genes[59,60].

Resident microbial species are not always optimally adapted to their environment[61]. Invaders are better adapted to the host environment[62]. However, resident bacterial taxa may have some highly specialized traits. Virulence does not affect pathogen fitness so there may not be direct selective pressure on the traits expressed in this hosting type as long as it remains an evolutionary dead-end but can persist if it confers an advantage in the between-host life cycle of the pathogen[63]. Stressful conditions can modify the stability of the microbiota. A stable host-associated microbial community can resist disturbance that would shift the community and cause harm to the host. Several microbes are mainly commensal, but their persistent carriage of them can lead to pathogenic effects.

Size of inoculum: Microbes reduce the endogenous metabolic rate to endure starvation under sparse nutrient conditions. Limiting carbon, nitrogen or phosphorus leads to spore development. The spore state is very resistant to destructive agents such as temperature, desiccation, pesticides, antibiotics and dyes[64].

Most antimicrobials bind to proteins such as albumin, α-globulin, β-globulin and γ-globulin as well as α1-acid glycoprotein, lipoproteins and erythrocytes[65]. The degree of protein binding can vary highly between different species. Binding and the presence of infection reduce the quantity and concentration of free, unbound drugs in plasma. Infection alters tissue site penetration, while infections of the bloodstream expand the volume of distribution and enhance drug clearance[66]. A decrease in plasma albumin is seen in critical illness, potentially leading to an increase in the free fraction of the drug that is ordinarily highly bound to this protein[67]. An increase in the volume of distribution for drugs may occur, resulting from a combination of fluid resuscitation and renal failure. Only the free (unbound) fraction of the drug is available for pharmacological activity[68]. Obesity increases the volume of adipose tissue and hence the volume of distribution of drugs. While the thermal injury is marked by an increase in capillary permeability and hypovolemia. Expansion in extravascular volume and fluid resuscitation may lead to an expanded volume of distribution for many agents.

Route of exposure: Proteins aid microbes' ability to withstand harsh environmental conditions. The protein conformation is crucial for the binding affinity of substrate molecules. Such proteins (enzymes) are activated to inhibit the molecules from penetrating/attaching to specific target sites. The common consequence of these modifications is increased steric hindrance that leads to reduced exposure of molecule to its target[69].

Mutations at non-structural ribosome genes frequently appear to confer resistance, including the genes encoding the different AdoMet-dependent methylases responsible for post-transcriptional modification of rRNAs. Mutations inactivating the RsmA function allow resistance. The RsmA is a methyltransferase enzyme that catalyzes the synthesis of the m62A ribonucleotide at positions 1618 and 1619 of 16S rRNA in *E. coli*. This family of proteins is widely distributed in Eukaryota, archaea and bacteria.

Post-transcriptional modifications of the 23S rRNA by the adenine-N6-methyltransferase alters the binding site of MLSB antibiotics in 23S rRNA. This confers cross-resistance to MLSB antibiotics (MLSB-resistant phenotype) and remains the most frequent mechanism of resistance. The methylation of adenine to obtain N6-dimethylamine rRNA in the 23S subunit prevents the binding of some antibiotics[70-72]. However, methylation-modified ribosomes can be sensitive to the effect of other antibiotics.

Duration of exposure: Microbial cells in the environment vary in size and chemical composition. The variation is induced by fluctuations in environmental conditions[64]. Inequities in chemical substance exposure can increase the risk of developing resistance due to the several physiologic and structural modifications in the cell. Hence nutrient or stressor concentration gradients may induce ecological specializations.

Bacteria gene expression is essential for its response to varying environmental stresses and host defenses[73]. It also facilitates the spread of resistance genes once acquired. The diverse genes can facilitate the biosynthesis of specialized enzymes that inactivate antimicrobials, elimination of the cell target that the antimicrobial is designed to attack, closure of the entry points of antimicrobials into the microbial cell and development of transport mechanisms that export the antimicrobial agent outside the cell so that it never reaches its target point. The transcriptional regulation occurs by binding to the promoter regions in an induction or repression manner[74], which could be mediated by transcription factors, environmental stresses and some other effectors.

Environmental factors
Contamination of environment: Pharmaceutical active compounds are environmentally persistent and resistant to metabolism and physical degradation processes. These compounds (stressors) hit proteins (enzymes) active centers modifying them and preventing the binding of antimicrobials. Development of resistance usually occurs via genetic mutations and these genetic mutations are a result of selection pressure induced by antibiotics. The DNA-damaging chemicals or irradiation increases the proportion of mutants in a population. This gives different adaptive outcomes to microbes in new environments because of the increased mutation supply in a population. Thus, pathogens may be transmitted from the selection and multiplication of resistant mutants over all phases of adaptation. Resistant microbes can transfer sections of their DNA to other microbes (even among different species) via the plasmids, transposons, etc. These sequences might be eventually transmissible by mobile genetic elements such as plasmids, transposable elements, phages, etc. and hence contribute to the emergence and diffusion of antimicrobial resistance in clinical isolates.

Contamination of equipment: Resistant pathogens can be transmitted through cross-contamination from dishcloths, refrigerator handles, oven handles, countertops, drain boards, etc. Transfer can be direct from person-to-person, indirectly in two stages from the person-to-contact surface and from the contact surface to person, indirectly from person to food and from food to person. Transmission depends on the species, the route of inoculum delivery, the contact surface type, the duration of exposure, the temperature and the relative humidity. The concentration of the infectious agent in the inoculum, frequency of shedding, survival of pathogen on hands and in the environment, concentration deposited on the food and degree of temperature abuse (for microbe) aids the transmission of enteric pathogens[75]. Microbial adhesion properties and survival vary with species and even strains[76].

INDUCED ANTIBIOTIC RESISTANCE

Decreased drug uptake primarily via impaired influx transporters: The factors that control competence generally include the nutritional status of the bacterium[77] and environmental stressors, such as antibiotics or DNA damaging agents[78].

Increased drug efflux predominantly due to the overexpression of MDR efflux transporters of the ATP-binding cassette superfamily or due to drug efflux mediated by extracellular vesicles (EVs) or drug-loaded lysosomes undergoing exocytosis. Efflux of antimicrobials occurs through an export protein from the major facilitator superfamily (MFS). These export proteins are membrane-associated proteins, which are coded for by tetefflux genes and export antibiotics from the cell. The export of a metabolite reduces the intracellular drug concentration and thus protects the ribosomes within the cell. Antimicrobial efflux proteins have amino acid and protein structure similarities that are involved in multiple-drug resistance, quaternary ammonium resistance and chloramphenicol and quinolone resistance. Efflux proteins, which pump these antibiotics out of the cell or the cellular membrane, keeping intracellular concentrations low and ribosomes free from antibiotics, are more frequent in gram-positive populations.

The multidrug efflux systems contribute significantly to the increased resistance to multiple antibiotics in bacteria. A major challenge in developing efficacious antibiotics against drug-resistant pathogens is to identify compounds that can counteract the efflux functions. The wealth of bacterial genomics information available suggests the presence of a variety of efflux systems in bacteria. Even a single bacterium may possess multiple efflux transporters of different families, with overlapping substrate spectra. The expression of bacterial multidrug efflux system is usually controlled by transcriptional regulators that either repress or activate the transcription of the multidrug efflux genes.

Deregulation of cell death mechanisms: Regulatory T cells are vital components of a healthy microbial cell but become dysfunctional under prolonged environmental stress. Deleting or mutating the Foxp3 gene leads to the scurfy phenotype characterized by multi-cell inflammation[79,80]. In mature Treg cells, continued expression of FOXP3 maintains their lineage identity; however, a small but significant population of Treg cells may lose FOXP3 expression and acquire effector T-cell activities in normal and particularly inflammatory settings[81]. The FOXP3 is regulated by phosphorylation, acetylation and ubiquitination in response to environmental changes to modulate its protein stability and DNA-binding ability[82].

The programmed death receptor-1 (PD-1) belongs to the family of negative costimulatory molecules that inhibits T-cell activation as well as a wide range of immune responses against pathogens[83]. This family of the negative regulator is mainly expressed on the surface of activated T cells, B cells, monocytes, NK cells, dendritic cells (DCs) and Treg cells. The T cells do not uniformly exhaust during stressful conditions, but specific subsets with different memory-like or proliferative potentials emerge upon exposure to persisting antigens[84].

For the prevention of virulence, T cells are usually activated by their recognition of offending molecules (environmental stress) and the subsequent transmission of a costimulatory signal by the interaction of B7-CD28 in T cells. The T-cell activation is a crucial step in immunity development. However, the presence of inhibitory molecules on the surface of the offending molecules might hinder the T cells from recognizing and eliminating the stress. Exhausted T cells have altered proliferative abilities, upregulation of a wide array of co-inhibitory receptors, unique transcriptional and epigenetic signatures, altered metabolic fitness, failure for transition to quiescence and acquisition of antigen-independent memory T cell responsiveness. Exhausted T cells arise from cells, which initially gained effector function, but become gradually silenced due to continuous T cell receptor (TCR) stimulation from persistent environmental stress[85]. These exhausted T cells have lost functional mitochondria. This metabolic insufficiency underlies both their differentiation and dysfunction.

Enhanced DNA damage repair: Nucleophilic groups on DNA are among those targeted by electrophiles, the interaction of chemical metabolites with DNA can cause point mutations and other genetic lesions, which can result in inactivation or loss of activity suppressor genes. The processing of chemicals into metabolites capable of modifying DNA typically involves initial two-electron oxidation. Some enzymes, particularly the cytochrome P450 superfamily, can catalyze this phase I reaction. A second metabolic step involves the transfer or conjugation of an endogenous, water-soluble substrate to the functional group introduced during phase 1 biotransformation, thereby facilitating the elimination of the toxin. These phase II reactions include sulphation, acetylation, glucuronidation and conjugation with glutathione. Chemopreventive agents can alter the constitutive metabolic balance between the activation and inactivation of carcinogens through their actions on both phase I and II enzymes.

Epigenetic alterations and/or deregulation of microRNA: Epigenetic changes in DNA are heritable and do not involve the DNA sequence, but are rather modifications of DNA that affect the function of a cell. Epigenetic changes (e.g., DNA methylation, histone modifications) can be influenced by the environment and lifestyle and may lead to cancer, autoimmune disease, mental disorder and diabetes. Early diagnosis of epigenetic modifications is therefore of vital importance and is seen as a promising future pathway of personal health care.

**RESISTANT PATHOGEN INFECTION PREVENTION AND CONTROL
FOR PATIENTS INFECTED WITH ORGANISMS OTHER THAN BLOODBORNE PATHOGENS**
Early identification: Nucleic acid technologies (PCR, microarrays, sequence-based diagnostics) or advances in protein science (e.g., Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry; MALDITOF) are current diagnostics capable of detecting specific causative microbes with clinical implications. The early detection and identification of resistant microbes allow healthcare experts to quickly identify strategies to prevent or mitigate the development and/or spread of disease-causing pathogens. Early detection and identification of resistant microbes also strengthen and expands existing national and international surveillance systems for antimicrobial-resistant microorganisms.

Thus, the capacity improvement of health institutions for data collection and analysis of multidrug-resistant organisms and antimicrobial drug use may aid in combating antimicrobial resistance. Such data may be helpful also in maintaining surveillance of pathogens affecting the general population, invasive pathogens, tracking resistance among enteric pathogens and monitoring resistance among non-bacterial pathogens such as influenza, malaria and human immunodeficiency virus, both domestically and internationally.

Prompt isolation: Prompt isolation of infected individuals and animals could be a viable alternative solution when public health is compromised through food-producing animals, companion animals or the environmental spread of resistant pathogens. The prevention and control of antimicrobial-resistant infections require measures to promote the appropriate use of antimicrobial agents and prevent the transmission of infections (whether drug-resistant or not).

Appropriate treatment: All microbial infections require some class of antimicrobial agents for effective treatment. The choice of drug is often based on the results from AMR testing on a case-by-case basis, but usually on treatment procedures. Increasing resistance rates may bring about an adjustment in treatment recommendations to newer and costlier antimicrobials. Microbial infections treatment data, apart from being useful for deciding local policies and targeted interventions, help to evolve a strategy for controlling the spread of infections.

Many antibiotic prescribing errors occur around the selection and duration of treatment. This includes a low threshold for the indication of antibiotics, delayed initiation of treatment when indicated, limited knowledge of local antimicrobial resistance patterns, errors in the final choice of dose, route, or drug and a lack of de-escalation. A proper understanding of the prescribing process can guide interventions to improve treatment. Some of the potential interventions included in a stewardship program are education in antimicrobial prescribing, information on the local resistance patterns and accessibility to a qualified infectious diseases consultant.

CONTROL OF ROUTES OF TRANSMISSION
Hand hygiene:

- Appropriate selection and use of agents (e.g., soap and water, alcohol-based hand sanitizers)
- Factors influencing hand hygiene efficacy
- Sources of potential contamination or cross-contamination of hand hygiene materials
- Use of appropriate barriers
- Appropriate selection, donning, doffing and disposal of personal protective equipment (PPE)
- Appropriate isolation/cohorts of patients infected with communicable diseases
- Standard precautions for all patients
- Isolation of infected animal or man. Immuno-depressed persons and seronegative pregnant women are especially at risk from zoonoses[86]
- Education of farmers, personnel in slaughterhouses and biological laboratories
- Proper food hygiene (especially regarding food of animal origin) and safe dietary habits
- Pasteurization or boiling of milk and sterilization of dairy products
- Cooking of meat and meat products before consumption, high standards of hygiene in kitchens and catering facilities)
- Destruction of pathogenic material (safe disposal of aborted fetuses, destruction of dog feces and infected viscera from secondary hosts, destruction of infected offal, carcasses and skins to control infections
- Transmission-based precautions for other pathogens
- Contact (direct, indirect)
- Droplet
- Airborne
- Host support and protection
- Vaccination of animals and at-risk categories of veterinary personnel against rabies (in infected areas), tetanus and any other vaccine-preventable infection, which may be a hazard in their region
- Pre-and post-exposure prophylaxis. Post-exposure treatment is sometimes imperative as in the case of rabies infection
- Protecting skin and immune system integrity
- Environmental control measures
- Cleaning, disinfection and sterilization of patient care equipment
- Environmental cleaning (housekeeping)
- Appropriate ventilation
- Waste management
- Linen and laundry management
- Food services

Engineering and work practice controls: Sharps injuries are which can occur when manipulating contaminated needles and other sharp objects by hand, removing scalpel blades from holders and removing needles from syringes, spreading disease-casing pathogens like Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), etc. Such injuries are obtained through percutaneous contacts, during handling, disassembly, disposal and reprocessing of contaminated needles and other sharp objects, or via human bites, cuts and abrasions. It can also occur through mucous membrane/non-intact skin exposure. The direct blood or body fluids contact with the eyes, nose, mouth, or other mucous membranes via contact with contaminated hands, contact with open skin lesions/dermatitis and from splashes or sprays of blood or body fluids (e.g., during irrigation or suctioning). A parenteral exposure occurs as a result of injection with infectious material during the administration of parenteral medication, sharing of blood monitoring devices such as glucometers, hemoglobinometers, lancets and lancet platforms/pens and infusion of contaminated blood products or fluids.

Engineering and work practice controls are used to reduce the opportunity for patients and healthcare workers to be exposed to potentially infectious pathogens through sharps injuries. Sharp disposal containers, self-sheathing needles and safer medical devices (sharps with engineered sharps injury protections and needleless systems) are required to manage high-risk practices and procedures capable of causing healthcare-acquired infections (HAIs) from bloodborne pathogens. Work practice controls decrease the prospect of exposure by altering how a task is performed (e.g., prohibiting the recapping of needles by a two-handed technique). Engineering and work practice controls are intended to reduce the risk of percutaneous, mucous membrane/non-intact skin or parenteral exposures of workers.

Training and education of healthcare workers: Huge quantities of antimicrobials, in particular antibiotics, are usually prescribed to patients and animals who do not need them at a particular period. Although antibiotics may be required in agriculture and aquaculture to maintain animal welfare and food security, their use to prevent infections or simply to promote growth in animals drives microbes to resist older antimicrobials while new ones are insufficient to keep up with the increase in drug resistance. Thus, education regarding antimicrobial stewardship is needed in training programs for health professionals to reduce the improper use of antimicrobials, duration of hospitalization, resistant infection rate and cost.

Enlightening on the judicious use of drugs identifies with modern infection prevention. In addition, the use of some specific drugs should base on studies linking such drugs to decreased rates of transmission and infection with high-priority multidrug-resistant organisms[87]. Frequent and prolonged exposure to any drug tends to increase the risk of drug hypersensitivity. Prior drug exposure is a strong risk factor for colonization and infection from drug-resistant pathogens[88,89]. The extent and period of the exposure might initiate genomic alterations resulting in changes in survival and reproduction activities, or the genotoxic disease syndrome.

CONCLUSION

Antibacterial-resistant pathogens are transmitted through genes and regulatory pathways that are involved in the increased frequency of resistance plasmids transfer caused by treatment with antimicrobial drugs. Microbes rapidly alter their physiology and cellular activities through metabolic modifications to enhance their fitness under varying conditions, allowing their persistence and circulation between environments and also the nature of their pathogenesis. Thus, strategies for prevention and control include diagnosis, prompt isolation of infected individuals and appropriate treatment of patients.

SIGNIFICANCE STATEMENT

This study discovers that resistant microbes spend their half-life cycle in extremely external moist, warm environments with abundant nutrients. Such environments (healthcare settings, animals, patients with drug-resistant infections) are ideal places for rapid adaptation, survival, exchange and transmission of genetic materials. Chemical bactericidal components, phagocytosis and other immune (adaptive) responses aid replication. This study will help the researcher uncover the critical areas of antibacterial resistant pathogens transmission that many researchers could not explore. Thus, new techniques for the control of resistant pathogens may be arrived at.

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