Bacteria Emerging As an Opportunistic Pathogen

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ABSTRACT: Due to the re-emergence of infectious diseases, the causative pathogenic microorganisms are becoming the major microbiologic public health threat. It seems to be difficult to control the emergence of new and severe bacterial diseases. However, efforts are continuously being made to identify the main cause to prevent the uncontrolled spread of emerging diseases. This review focuses on emerging bacterial diseases and their causative bacteria and the pathway of pathogenesis.

KEYWORDS: Infectious Diseases, Public Health Threat, Pathogens, Pathogenesis

INTRODUCTION
Microorganisms, in a general realm of biology, are known to cause several diseases and infections in otherwise healthy individuals. A pathogen is a microorganism such as a bacterium, or fungus (may be yeast) or virus that causes disease in its plant or animal host. The ability of the pathogen to infect is called its pathogenicity which can be expressed by means of their virulence, that is, the relative and quantitative degree of pathogenicity [1]. However, in an attempt to control the infection, a host's immune system can also cause damage to the host itself. Therefore, infectious microorganisms can be classified according to the status of host defense—either as primary pathogens or as opportunistic pathogens [2].

Our body can be considered as an extreme environment with a variety of human microbiota, referring to microorganisms colonizing the surfaces of human body; the body itself is a sterile environment unless an infection occurs. The entrance of a pathogen in this ecosystem requires either the acquisition of virulence determinants to cope with the human defences, or a decay in these defences. However, in order to colonize the human host a microorganism requires to survive under the physicochemical conditions of human body: a narrow range of temperature oxygen tension and pH; some specific nutrients and low iron availability [3].

OPPORTUNISTIC PATHOGENS
The pathogens that cause disease as a result of their presence or activity within the normal and healthy host are considered as primary pathogens. An opportunistic pathogen is the one that generally does not harm its host but when the host’s resistance is low, it can cause disease. The severity of the disease that they cause known as their intrinsic virulence is a necessary consequence of their need to reproduce and spread. These are capable of infecting only within a narrow host range, but can infect healthy, immune competent individuals of susceptible host species when conditions become favourable for them called as opportunistic conditions. Usually, these pathogens are having low pathogenicity, but they cause serious infections mainly when the host's defense mechanisms against infection are impaired [4].

Some of these conditions are mentioned in this section. When the normal flora moves into areas of the body where they do not normally occur, if the immune system isn’t working properly. When a person takes broad-spectrum antibiotics, the balance of normal microbes present in the body is disrupted. When normal flora is traumatically introduced to an area of the body that they do not normally occur in (that is axenic). When there are genetic defects (such as Chronic granulomatous disease), exposure to antimicrobial drugs or immunosuppressive chemicals following poisoning or cancer chemotherapy, exposure to ionizing radiation or as a result of an infectious disease with immunosuppressive activity such as with measles, malaria or HIV disease resulting in the impairment of host defences [5].

Primary pathogens may also cause more severe disease in a host with depressed resistance than would normally occur in an immune sufficient host. All of the above conditions result in infectious disease in a host with depressed resistance (immunodeficiency). It may be caused by microbes normally present inside the host, such as pathogenic bacteria or fungi in the gastrointestinal or the upper respiratory tract, and they may also come from the environment or other hosts or due to traumatic fractures and infections. There is an adequate ‘key-and-lock’ interaction between hosts and pathogens. In order to render a host susceptible to colonization or...
infection, the genetic make-up of both parties needs to support the molecular interactions between them. So, the fundamental processes for tweaking the interactions are genetic variation, selection of the best-fitting mutants and retention or progression into a disease [6].

SUBGROUPS OF OPPORTUNISTIC PATHOGENS

**Colonizing Opportunistic Pathogens (COP)**
- Present on the human body as part of the “normal” human microbiome
- For example, *Staphylococcus aureus* can colonize the human nose asymptomatically and transmit from person-to-person without causing disease thereby taking up long-term residence

**Simple Opportunistic Pathogens (SOP)**
- These are non-colonizing organisms and are only present in environmental reservoirs.
- Examples are *Vibrio vulnificus, Mycobacterium marinum* and *Legionella pneumophila* [7]

**Opportunistic premise plumbing pathogens (OPPP)**
- These are normal residents of premise plumbing, drinking water and water distribution systems
- Examples are *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Escherichia coli, Salmonella spp., Mycobacterium avium* and *Acinetobacter baumannii* [8].

MECHANISM OF TRANSMISSION

**Portals of Entry [9]**

1. Mucosal surfaces within the body (respiratory, digestive, reproductive, or urinary tracts linings)
2. Epithelial surfaces on the outside of the body (skin areas that are damaged)

**Transmission of Microorganisms**
- Horizontal (occurs from one individual to another in the same and can occur by either direct contact causing Contagious Diseases, or indirect contact)
- Vertical Transmission from parent to offspring.

**Colonization and Growth**
- Virulent bacteria produce special proteins at the initial site of entry that allow them to cause systemic infection in different organs and colonize parts of the host body.
BACTERIAL OPPORTUNISTIC PATHOGENS

A bacterial pathogen has a high degree of capability to cause disease (Table 1). The major reasons for the re-emergence of bacterial infections include development of molecular techniques, mass spectrometry and culture methods in microbiology; climatic changes leading to more exposure to these infections; and development of more virulent bacterial strains causing opportunistic infections. It needs an interactive group of virulence determinants to cause infection, which is suitable for the interaction of a particular bacterium with a particular host. In order to survive and persist, these have evolved numerous strategies to exploit their host's cellular processes [10].

Table 1. Some major groups of opportunistic bacteria with the body parts they affect

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Body parts Affected</th>
<th>Bacteria</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intestine</td>
<td>Escherichia coli</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Urinary tract</td>
<td>Escherichia hermannii</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Gastrointestinal Tract</td>
<td>Clostridium difficile</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Respiratory Tract</td>
<td>Staphylococcus aureus, Streptococcus pyogenes</td>
<td>14, 15, 16, 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haemophilus influenzae, Neisseria meningitidis</td>
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<td></td>
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<td>Corynebacterium diphtheriae, Chlamydia pneumoniae</td>
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<td></td>
<td></td>
<td>Legionella pneumophila, Rhodococcus equi</td>
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<tr>
<td></td>
<td></td>
<td>Simkania negevensis, Parachlamydia acanthamoebae</td>
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<tr>
<td>5</td>
<td>Skin</td>
<td>Staphylococcus spp.</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Colon and Liver</td>
<td>Streptococcus bovis group, Capnocytophaga canimorsus</td>
<td></td>
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<tr>
<td>7</td>
<td>Stomach</td>
<td>Helicobacter pylori</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Vascular</td>
<td>Neoehrlichia mikurensis</td>
<td>17</td>
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Escherichia coli normally lives as a microflora of a human body, but only in specific situation, when it moves from the intestine to other organs and tissues, it can cause a very serious infection. The most frequent are the urinary tract and sexual organs infections. It includes three broad variety of different types, including highly specialized pathogenic strains causing worldwide outbreaks of severe diseases, opportunist pathogens which have the potential to cause disease if the human host defenses are compromised and avirulent isolates which are part of the normal intestinal microbiota, or which are well characterized and safe laboratory strains [18]. Virulent strains of E. coli can cause inflammation of the stomach and small intestine (Gastroenteritis), urinary tract infections and colonisation of new born’s intestine (Neonatal meningitis). In rarer conditions, they are also responsible for Hemolytic-uremic syndrome, inflammation of the peritoneum (Peritonitis), inflammation of breast tissues (Mastitis), inflammation of whole body (Septicemia) and Gram-negative pneumonia. When E. coli causes diarrhoea in humans, rabbits, dogs, cats and horses, it has been named as Enteropathogenic E.coli (EPEC), when it causes diarrhoea without fever in humans, pigs, sheep, goats, cattle, dogs, and horses, it has been named as Enterotoxigenic E. coli (ETEC),when found only in humans, as Enteroinvasive E. coli (EIEC), when found only in humans, as Enterohemorrhagic E.coli (EHEC), and when found only in humans, as Enteroaggregative E.coli (EAEC). Serotypes of Pathogenic E. coli strains can be categorised as O antigen (part of lipopolysaccharide layer), K antigen (part of capsule), H antigen (part of flagellin), and F antigen (part of MR fimbriae). Symptoms of E. coli infection includes bad stomach cramps, belly pain, vomiting, diarrhoea, sometimes with blood in it, and painful urination. The main causes of infection may include E. coli in food when the meat is not cooked properly to 160°F (71 °C) or when the food come in contact with raw meat. It can also be transmitted from person-to-person contact when an infected person does not wash his hands properly after a bowel movement. Water bodies such as lakes, pools, and water supplies can also be contaminated with infected persons. Hence, precautions have to
be taken while cooking all types of beef to at least 160°F (71 °C). proper washing of utensils and hands must be done, and only treated, or chlorinated, drinking water must be used [19].

During the year 1982, *Escherichia hermannii*, of the *Escherichia* genus, was determined as a distinct non-pathogenic species. It is a member of the Gamma Proteobacteria, and is gram-negative, aerobic rod that belongs to family Enterobacteriaceae. It is responsible for causing infections in the urinary tract, respiratory system, dermatitis, bacteremia, bone and joint and in gastrointestinal. Being an opportunistic and nosocomial pathogen, it caused infections particularly in patients with severe burns, cystic fibrosis, cancer, AIDS. It is currently among the most prevalent causes of chronic infections in cystic fibrosis patients that are frequently infected by a single clone that remains and evolves in the lung of the patient for decades. It is ubiquitous in soil and water, and on surfaces in contact with soil or water. It shows active swimming by means of its flagellum. Its metabolism is respiratory and never fermentative, and it can grow in the absence of O2 if NO3 is available as a respiratory electron acceptor. It has minimal nutritional requirements with the simplest growth medium consists of acetate as a source of carbon and ammonium sulfate as a source of nitrogen [20]. It is able to grow at temperature as high as 42 degrees, and shows tolerance to physical conditions, as well as resistance to high conc. of salt, dyes, weak antiseptics, antibiotics and phagocytes. The resistance is because of the permeability barrier afforded by its Gram-negative outer membrane. The stages of pathogenesis include bacterial attachment and colonization by using its flagella, Pilii and exopolysaccharide (alginate or slime); local invasion by producing extracellular enzymes and toxins that break down physical barriers, damage host cells and immune defence involving two exocellular proteases (Elastase and Alkaline protease, hemolysins and cytotoxins proteins); and finally disseminated systemic disease involving spread of infection to other parts mediated by same extracellular products that produce localized infection [21].

*Pseudomonas aeruginosa* is an environmental bacterium, it can grow at temperatures ranging from 11 up to 44 °C. It can also use over 80 organic compounds for growth, and it is able to survive under oligotrophic aquatic habitats and high-redox stress conditions such as wounded tissue. Several of the strains of *P. aeruginosa* have the capability of infecting patients presenting underlying diseases reflecting its broad range of hosts like humans, including plants, protozoans, worms or insects [22]. The enteric bacterium *Morganella morganii* is a gram negative facultative anaerobic rod. It was first isolated from a paediatric faecal culture in 1906 by Morgan et al. its genomic size is about 4,000,000 bp, and it has 4,000 protein coding sequences (CDSs). It was formerly classified as Proteus morganii and later based on DNA–DNA hybridization it was assigned to the genus Morganella, which belongs to the tribe Proteeae of the Enterobacteriaceae family. Although, members of the tribe Proteeae, including Proteus, Providencia and Morganella, the overall G+C contents in the genomes of *M. morganii* (51%) is higher than other Proteaceae members (39% to 43%), distinguishing *M. morganii* from other species. There are two subspecies in the single species *M. morganii* of genus Morganella, which are, namely, *morganii* and Sibonii. Biologically, it is a motile, non-lactose fermenting bacterium, having capacity for urease production and has phenylalanine deaminase [23]. It is commonly found in the environment and intestinal tracts of humans, mammals, and reptiles as part of the normal flora. Because of the extra genetic and mobile elements, it is resistant to various drugs making it multidrug resistant or even extensively drug-resistant, such that it often results in clinical treatment failure. Generally, it can produce virulence factors, such as urease, haemolysis, and lipopolysaccharide (LPS) which pose it an opportunistic pathogen that mainly causes wound and urinary tract infections. The disease spectrum of infection varies and is changeable according to its virulence evolution [24].

Another severe manifestation of antibiotic-associated diarrhoea is caused by *Clostridium difficile*. These bacteria release toxins that damage the bowel and cause severe diarrhoea. In turn this leads to the release of *C. difficile* spores into the environment where they can remain for weeks waiting to infect the next person with a disturbed gut microbiome [25]. In addition, the use of antibiotics can result in the accumulation of antibiotic resistant microbes within the gut environment.

*Mycobacterium leprae*, the causative organism of leprosy, was described as human bacterial pathogen by Armauer Hansen, in 1873. Among the different mycobacterial species, *M. leprae* has not received as much attention as widely known killers such as *M. tuberculosis* and it is not widely recognized as a stealthy pathogen like *M. avium*-intracellulare, but now it has clearly been recognised as an opportunistic pathogen [26]. Today only a few million registered cases were there as estimated by the World Health Organization (WHO). Its prevalence is decreased by the implementation of multidrug therapy (MDT) in WHO'S intensive effort to eliminate leprosy as a public health problem by the end of the millennium. The route of transmission is through nasal cavity as evident by the expulsion of enormous numbers of organisms in the nasal discharge of lepromatous patients and depositions of bacilli in the nasal mucosa. The incubation period for leprosy is unclear; but usually longer periods of incubation have been observed.
Methylobacterium spp. are the normal inhabitants of drinking water distribution systems and premise plumbing. It has natural habitats as soil, dust, air, fresh water, and aquatic sediments. Specifically, high numbers of Methylobacterium spp. have been identified in shower curtains and showerhead biofilms. Infection shows mild clinical symptoms such as fever, but are also responsible for bacteremia, peritonitis, and pneumonia [27]. Nocardia is a gram positive actinomycete. Persons with low or impaired cell mediated immune power or the immunocompromised patients or patients having other infections like tuberculosis are more prone to infections [28]. Rhodococcus is very active in persons with low cellular immunity and patients who were immunocompromised due to malignancies. Pneumonia is very common infection of Rhodococcus [29]. Salmonella infection, Salmonellosis and bacteremia has an increased rate in HIV infected populations. It is during an appropriate antibiotic therapy that Salmonellosis relapses in AIDS. In the United States, S. typhimurium and S. enteridis are commonly isolated form the blood of patients with AIDS [30]. The immunocompromised persons infected with AIDS are more prone to getting plague through Yersinia pestis which is a gram-negative, and facultative aerobic rod. Being a rodent pathogen, its vector is a rat flea, Xenopsylla cheopis [31]. From the evolutionary history and the phylogenetic reconstruction, it has been revealed that the ancestor of these pathogenic Yersiniae acquires a virulence plasmid named pCD1 and emerged from a non-pathogenic environmental Yersinia. This plasmid is having genes that code for a Type III secretion system that is required for the virulence of this pathogen. It is considered to be a recent process for the speciation of Y. pestis from Y. pseudotuberculosis. It involves the acquisition as well as loss of some genes [32]. In immunocompromised patients, as stated earlier also, tuberculosis is the most potent opportunistic infection that makes HIV infection more complicated. It is caused by Mycobacterium tuberculosis which is responsible for more than 2 million deaths and 8 million new cases annually in India. Shigella belongs to family Enterobacteriaceae, having four species: Shigella dysenteriae, Shigella flexneri, Shigella sonnei, and Shigella boydii. It is rod-shaped, facultatively anaerobic, non-lactose fermenting, non-motile and is gram-negative. The infection spread from human to human via the fecal oral route. Morphologically, it is spherical, 1 µm in size with a thick gram-positive cell wall. It is a facultative anaerobe, immobile, coagulate positive and resistant to 122 °F temperatures and high salt concentrations [33].

CONCLUSION
When an infection caused by any microbial pathogen (fungi, bacteria or virus) that take advantage of a weak immune system within a host is termed as an opportunistic infection. These pathogens can easily cause diseases in immunocompromised patients, with HIV, leukopenia, malnutrition, ageing and genetic predisposition as some of the examples. This review is an overview of such bacterial pathogens developing the capacity of causing opportunistic infection. For completing the process of infection, the pathogenic microorganisms followed some steps starting from exposure, adhesion, invasion, colonization, toxicity, and finally leading to the tissue damage. For a better understanding of the pathogenesis of severe human diseases caused by opportunistic bacteria, a detailed epidemiological, microbiological and clinical study is needed urgently.

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