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COMMUNITY FOCUSED AND CURRENT CONCEPTS FOR INSITU IDENTIFICATION OF MICROORGANISMS CAUSING SYSTEMIC CLINICAL MANIFESTATIONS: A CONCISE REVIEW

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ABSTRACT

The impact of microorganisms on infectious diseases has been extensively studied and reviewed using different approaches to elicit their possible role in treatment. These have ranged from highlighting the occurrence of particular species or groups of organisms, to assessing the impact of microbial populations on clinical outcomes. In many cases, studies are difficult to compare due to the use of different methods of specimen collection and microbial analysis as well as differences in patient demographics, etiology and infection status. In addition, clinical analyses tend to be limited in scope and based on assumptions regarding relative pathogenicity. A range of clinical criteria have been used to define infectious diseases. The Consensus Development Conference on Diabetic Foot Wound Care agreed that infections are characterized and manifested as purulent secretions or the presence of two or more signs of inflammation (erythema, warmth, tenderness, heat, induration). Guidelines for the management of chronic infections by British Association of Dermatologists and Royal College of Physicians, recommend that infection should be considered if one of the following is present: pyrexia, increased pain, increasing erythema of surrounding skin or lymphangitis. Microbiologically, a critical bacterial load, synergic relationships between bacterial species and the presence of specific pathogens have been proposed as indicators of infection. The presence of microbes *per se* is not indicative of infection. However, the possibility that a critical microbial load might directly affect the treatment outcome in both acute and chronic diseases has been considered for several decades.

KEYWORDS: Taxonomical classification, Inflammatory signs, Gram staining, Pathogenicity, Clinical specimens, Spectinomycins.

MICROBIOLOGICAL PROFILES

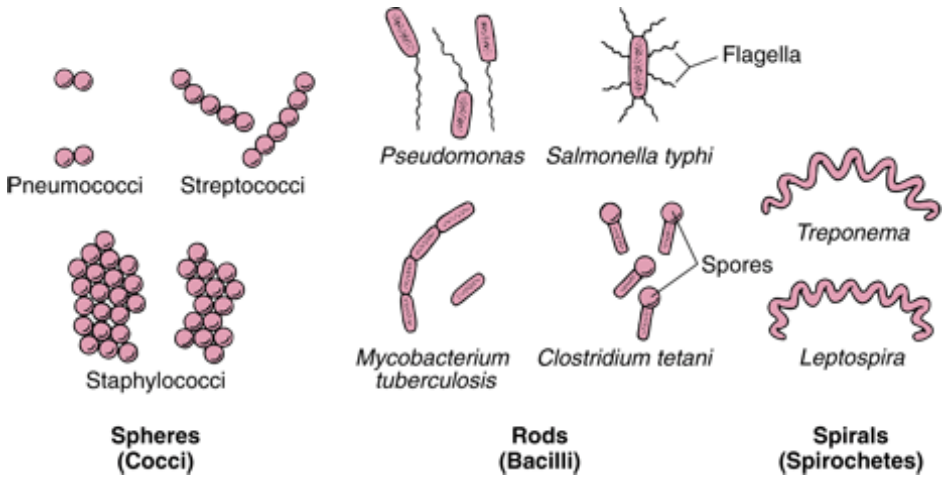
MICRO-ORGANISMS

Micro-organisms and their activities are vitally important to all processes on Earth. Micro-organisms matter because they affect every aspect of our lives – they are in us, on us and around us. Microbiology is the study of all living organisms that are too small to be visible with the naked eye. This includes bacteria, archaea, viruses, fungi, prions, protozoa and algae, collectively known as 'microbes'. These microbes play key roles in nutrient cycling, biodegradation/biodeterioration, climate change, food spoilage, the cause and control of disease, and biotechnology. Microbes helps humans in many ways: making life-saving drugs, manufacture of biofuels, cleaning up pollution, and producing/processing food and drink. Microbiologists study microbes, and some of the most important discoveries that have underpinned modern society have resulted from the research of famous microbiologists, such as Jenner and his vaccine against smallpox, Fleming and the discovery of penicillin, Marshall and the identification of the link between *Helicobacter pylori* infection and stomach ulcers, and zur Hausen, who identified the link between papilloma virus and cervical cancer.[1] Microbiology research has been continued to meet many of the current global aspirations and challenges, such as maintaining food, water and energy security for a healthy population on a habitable earth. Microorganism is a microscopic organism, which may exist in its single celled form or in a colony cells. The possible existence of unseen microbial life was suspected from ancient times, such as in Jain scriptures from 6 century BC India and 1st century BC book on agriculture by Macrus terentius varro. Microbiology, the scientific study of microorganisms, began with their observation under the microscope in 1670 by Antonie van Leewenhoek. In 1850, Louis Pasteur found that microorganisms caused

food spoilage, debunking theory of spontaneous generation.[2] In 1880, Robert Koch discovered that microorganisms caused the disease tuberculosis, cholera and anthrax. Microorganisms include all unicellular organisms and are extremely diverse. Of 3 domains of life identified by carl woese, archaea and bacteria are microorganisms. These were previously grouped together in 2 domains like Eukaryotes and prokaryotes, 3rd domain Eukaryota includes all multicellular organisms and many unicellular protists and protozoans. Major groups of microorganisms are bacteria, archaea, fungi (Yeast and molds), algae, protozoa and viruses.

BACTERIA (EUBACTERIA AND ARCHAEA)

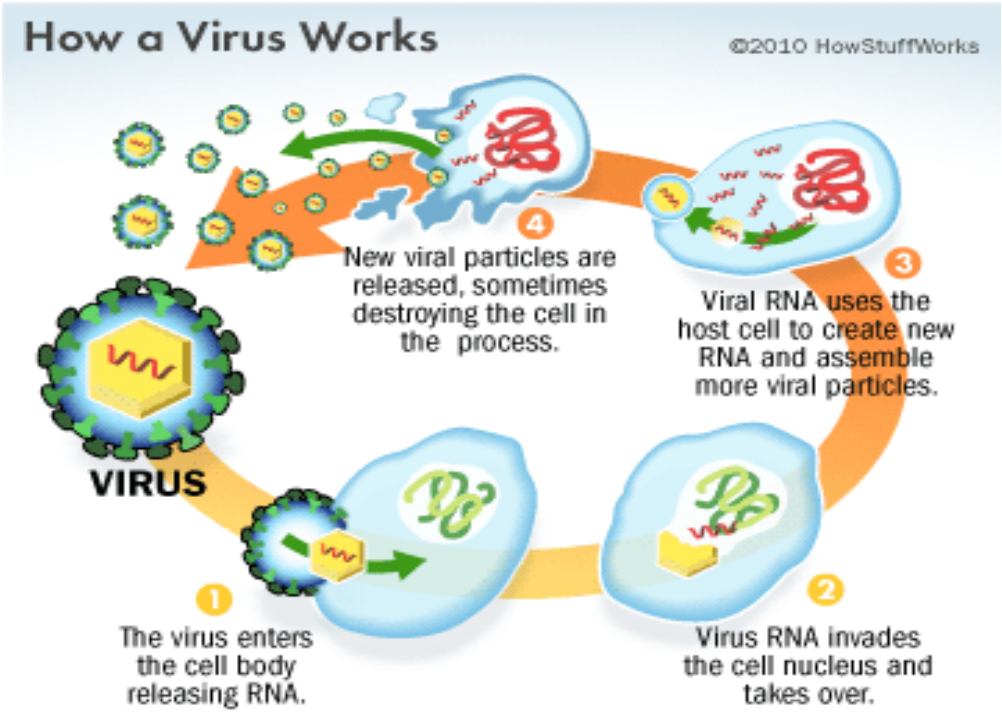
Bacteria are often maligned as the causes of human and animal disease (*Leptospira*, which causes serious disease in livestock). However, certain bacteria, the actinomycetes, produce antibiotics such as streptomycin and nocardicin; other bacteria live symbiotically in the guts of animals (including humans) or other bodies, or on the roots of certain plants, converting nitrogen into a usable form. Bacteria put tang in yogurt and the sour in sourdough bread; bacteria help to break down dead organic matter; bacteria make up the base of the food web in many environments. Bacteria are of such immense importance because of their extreme flexibility, capacity for rapid growth and reproduction, and great age - the oldest fossils known, nearly 3.5 billion years old. Microbiology came largely through studies of bacteria.[3] The experiments of Louis Pasteur in France, Robert Koch in Germany, and others in late 1800 established the importance of microbes in humans. As stated in historical background section, research of the scientists provided proof for germ theory of disease and germ theory of fermentation. It was in their laboratories that techniques were devised for microscopic, isolating pure culture from mixed culture population and other laboratory manipulations. These techniques originally used for studying bacteria have been modified and hence the transition from bacteriology to microbiology occurred. Bacteria are prokaryotes with single- celled organism without a membrane bound nucleus. The DNA (genetic material of cell), exists as a long, folded thread with no specific location within the cell without Nucleus. Until, late 1970 it was generally accepted that all bacteria are closely related in evolutionary development. This concept was challenged in 1977 by Carl R. Woese and co-investigators at University of Lllonis, conducted a study on ribosomal RNA from a broad spectrum of living organisms and established that 2 groups of bacteria evolved by separate pathways from a common and ancient ancestral from. This discovery resulted in establishment of a new terminology to identify the major distinct groups of microbes namely, eubacteria (traditional or true bacteria), archaea (bacteria that diverged from other bacteria at an early stage of evolution and distinct from the eubacteria). Bacteria have a variety of shapes such as spheres, rods and spirals. Individual cells generally range in width from 0.5 to 5 micro-meter. Although unicellular bacteria appear in pairs, chains tetrads (group of four) or clusters. Some bacteria have flagella, external whip-like structures that propel organisms through liquid media, some bacteria have capsule an external coating of cell, some bacteria produce spores i.e., reproductive bodies. One of the major characteristic feature of bacteria is their reaction to Gram stain. Depending on chemical and structural composition of the cell-wall classified into 2 types namely Gram-positive bacteria and Gram negative bacteria.[4]



VIRUSES

Virus, an infectious agent of small size with simple composition that can multiply only in living cells of animals, plants, or bacteria. The name is from a Latin word meaning “slimy liquid” or “poison.” The earliest indications of the biological nature of viruses came from studies in 1892 by the Russian scientist Dmitry I. Ivanovsky and in 1898 by Dutch scientist Martinus W. Beijerinck. first surmised that the virus under study was a new kind of infectious agent, designated as contagium vivum fluidum, meant as a live, reproducing organism that differed from other organisms[5]. Both of these investigators found that a disease of tobacco plants could be transmitted by an agent, later called tobacco mosaic

virus, passing through a minute filter that would not allow the passage of bacteria. This virus and those subsequently isolated would not grow on an artificial medium and were not visible under the light microscope. In independent studies in 1915 by the British investigator Frederick W. Twort, lesions in cultures of bacteria were discovered and attributed to an agent called bacteriophage ("eater of bacteria"), known to be viruses that specifically infect bacteria. Viruses are considered as borderline of living organisms, also included in science of microbiology seen in several shapes and widely distributed in nature, infecting animal cells, plant cells and microorganisms. Study of viruses is termed as virology. All viruses are obligate parasites, lacking metabolic machinery to generate energy and to synthesize proteins, depending on host cells to carry out vital functions. Inside a cell, viruses have genes for usurping the cells energy generating and protein synthesizing system. In addition to intracellular form, viruses have an extracellular form that carries viral nucleic acid from one host cell to another host.[6] In viral infection, viruses are central core of nucleic acid surrounded by a protein coat called a capsid. This capsid protect genes outside the host cell also serves as a vehicle for entry into another host cells as it binds to receptors on cell surfaces. Structurally mature, infectious viral particle is called as virion. With the electron microscope, it is possible to determine morphological characteristics of viruses. Virions generally range in size from 20 to 300 nano-metres. Since most viruses measure less than 150nm and so, viruses are visible only by electron microscopy.



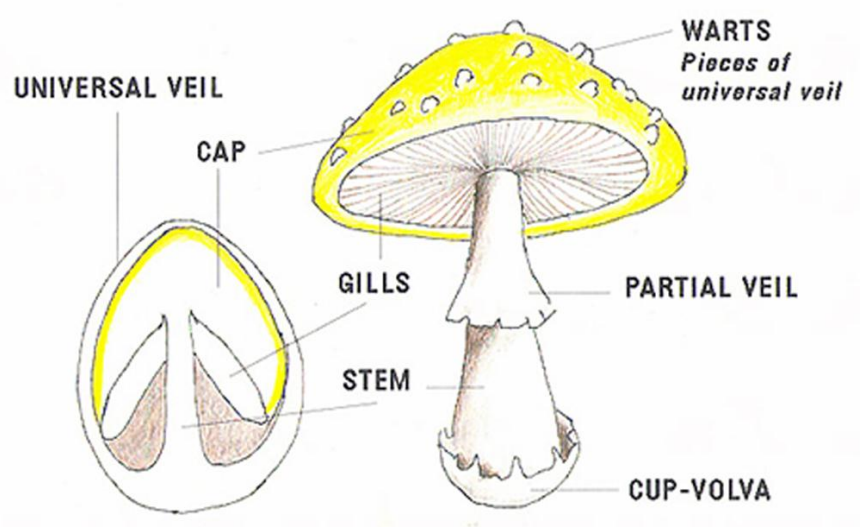
PRIONS

Even smaller than viruses, prions are the simplest infectious agents. Like viruses they are also obligate parasites, but they do not possess genetic material. Although prions merely self-perpetuating proteins, they have been implicated as cause of various diseases, including bovine spongiform encephalopathy (Mad cow disease) and other disorders.[7]

FUNGUS

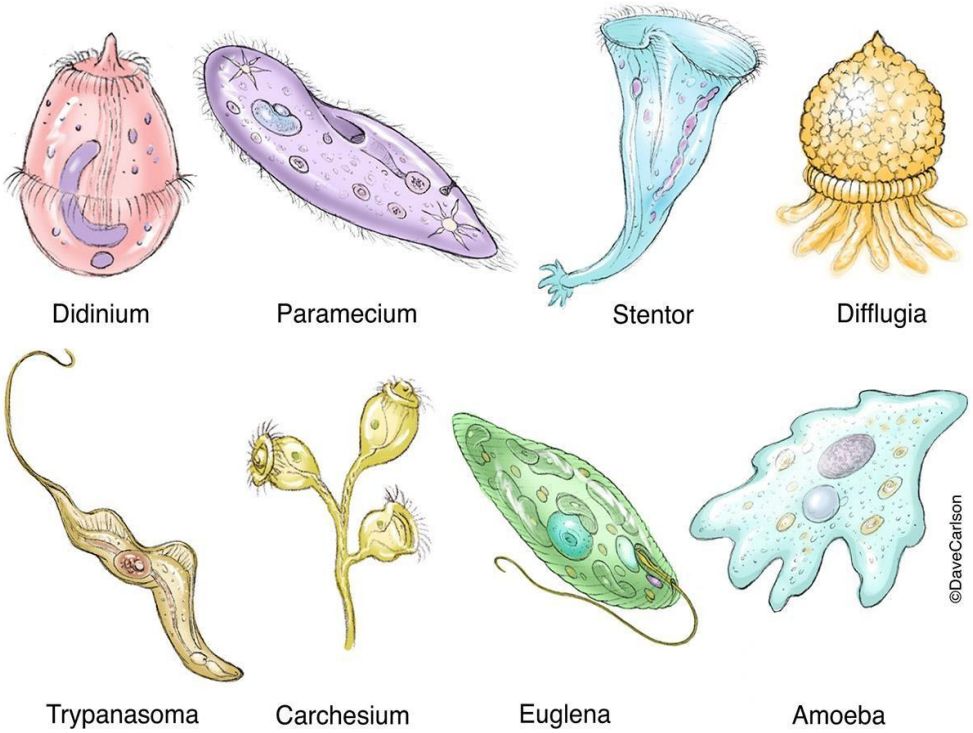
It is a member of eukaryotic organisms group that includes microorganisms such as yeasts molds and mushrooms. These organisms are classified under fungi kingdom, which is separate from other eukaryotic life kingdoms of plants and animals. Similar to animals, fungi are heterotrophs require food by absorbing dissolved molecules by secreting digestive enzymes into their environment. Fungi do not undergo photosynthesis. Growth occurs by means of mobility, except for spores (a few of which are flagellated), which travel through air or water. Fungi are principal decomposers in ecological systems. In the past, mycology was regarded as a branch of botany as fungi are genetically more closely related to animals when compared to plants. Abundant worldwide, most fungi are inconspicuous due to small size structure and their cryptic lifestyles in soil or on dead matter.[8] Fungi become noticeable during fruiting mechanism either as mushrooms or as molds. Fungi perform an essential role in decomposition of organic matter and have fundamental roles in nutrient cycling and exchange in environment. Fungi also used as a direct source of human food, in form of mushrooms and truffles as a leavening agent for bread and in fermentation of various food products such as wine, beer, and soy sauce. Fruiting structures of few species contain psychotropic

compounds and consumed recreationally in traditional spiritual ceremonies. Fungi can break down manufactured materials and buildings, and become significant pathogens for humans and other animals.



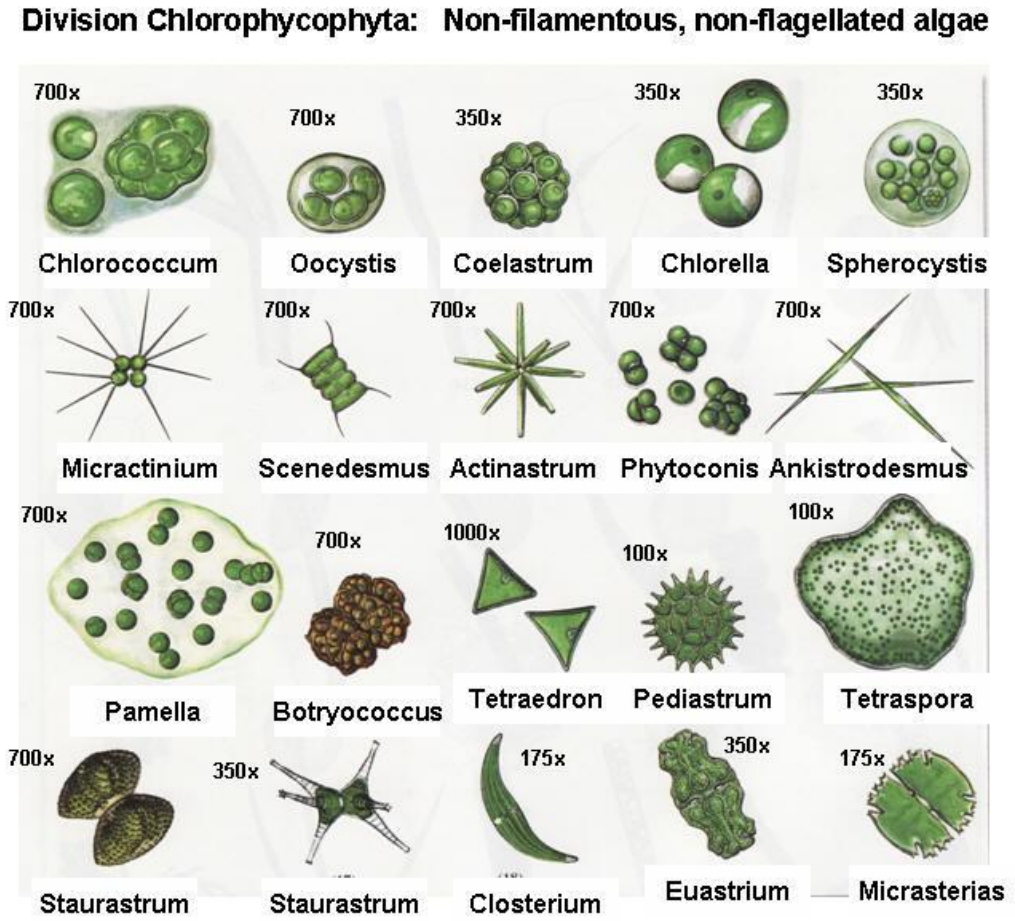
PROTOZOA

It is an informal term for single-celled parasitic eukaryote, which feed on organic matter, microorganisms, organic tissues and debris. Historically, protozoa were regarded as "one-celled animals", because they possess animal-like behaviors such as motility, predation, absence of cell wall. Although, traditional practice of grouping protozoa with animals is no longer considered valid, protozoan term continues to be used in loose way to identify single-celled organisms that move independently and feed by heterotrophy. In system of biological classification, Protozoa is categorized under high-level taxonomic group. During 1818, Protozoa was erected as a taxonomic class, but in later classification schemes, it was classified to a variety of higher ranks like phylum, subkingdom and kingdom.[9] In a series of classifications proposed by Thomas Cavalier-Smith and his collaborators, Protozoa has been ranked as a kingdom since 1981. Seven-kingdom scheme presented by Ruggiero in 2015, eight phyla such as Euglenozoa, Amoebozoa, Metamonada, Choanozoa sensu Cavalier-Smith, Loukozoa, Percolozoa, Microsporidia and Sulcozoa under Kingdom Protozoa are included. Several major groups of organisms like ciliates, dinoflagellates, foraminifera, and parasitic apicomplexans are classified under Kingdom Chromista.



ALGAE

It is an informal term for a large and diverse group of photosynthetic eukaryotic organisms that are polyphyletic in nature. From unicellular microalgae genera (chlorella and diatoms) to multicellular forms (giant kelp a large brown alga) algae grows up to 50 meter in length. Most of algae are aquatic, autotrophic and lack many distinct cell and tissue types such as stomata, xylem and phloem that are commonly seen in terrestrial plants. Largest and most complex marine algae are called seaweeds, while most complex freshwater form is charophyta include spirogyra and stone-worts. Algae have chlorophyll as their primary photosynthetic pigment and lack sterile covering of cells. Cyanobacteria is referred as blue-green algae. Green algae have primary chloroplasts derived from endo-symbiotic cyanobacteria. Diatoms and brown algae have secondary chloroplasts derived from an endo-symbiotic red alga. Algae lack various structures that characterize land plants, such as phyllids of bryophytes, rhizoids in nonvascular plants, roots, leaves and other organs found in tracheophytes.[10] Many algae are phototrophic, some algae are mixotrophic deriving energy from photosynthesis and uptake of organic carbon. Algae have photosynthetic machinery and is derived from cyanobacteria produces oxygen as a by-product of photosynthesis.

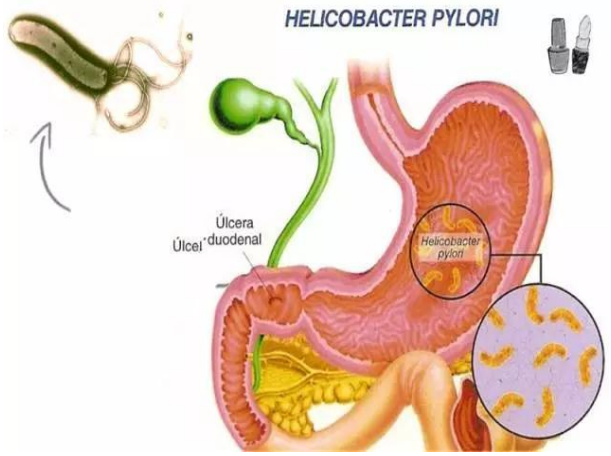


BACTERIAL INFECTIONS

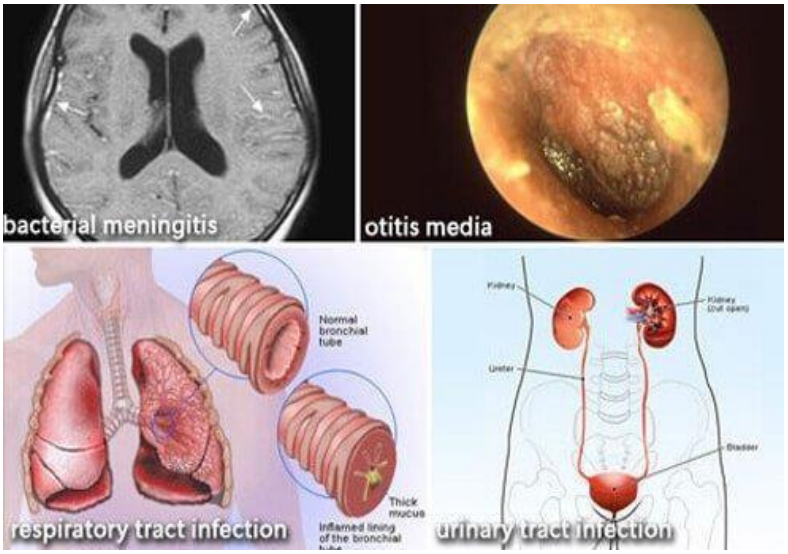
A bacterial infection is a proliferation of harmful strain of bacteria inside the body. Bacteria can infect any organ of the body. Pneumonia, meningitis and food poisoning are just a few illnesses that may be caused by harmful bacteria. Gram staining, bacterial culture with antibiotic sensitivity determination, and other tests are used to identify bacterial strains and help determine the appropriate course of treatment. Bacterial skin infections are usually caused by gram-positive strains of Staphylococcus and Streptococcus or other organisms. Common bacterial skin infections include Cellulitis causes a painful, red infection that is usually warm to touch. Cellulitis occurs most often on the legs. Folliculitis is an infection of the hair follicles that causes red, swollen bumps that look like pimples. Impetigo causes oozing sores, usually in preschool-aged children. The bullous form of impetigo causes large blisters while the non-bullous form has a yellow, crusted appearance. Boils are deep skin infections that start in hair follicles. Boils are firm, red, tender bumps that progress until pus accumulates underneath the skin.

Fig. No. 6: Different types of Dermatological Bacterial infections.

Bacterial infections are one cause of foodborne illness. Nausea, vomiting, diarrhea, fever, chills, and abdominal pain are common symptoms of food poisoning. Raw meat, fish, eggs, poultry, and unpasteurized dairy may harbor harmful bacteria that can cause illness. Unsanitary food preparation and handling can also encourage bacterial growth. Bacteria that cause food poisoning include: Campylobacter jejuni is a diarrheal illness often accompanied by cramps and fever.[11] Clostridium botulinum is a potentially life-threatening bacterium that produces powerful neurotoxins. Escherichia coli is a diarrheal (often bloody) illness that may be accompanied by nausea, vomiting, fever, and abdominal cramps. Listeria monocytogenes causes fever, muscle aches, and diarrhea. Pregnant women, elderly individuals, infants, and those with weakened immune systems are most at risk for acquiring this infection. Salmonella causes fever, diarrhea, and abdominal cramps. Symptoms typically last between 4 and 7 days. Vibrio cholera causes diarrhea when ingested, but it can also cause severe skin infections when it comes in contact with an open wound.

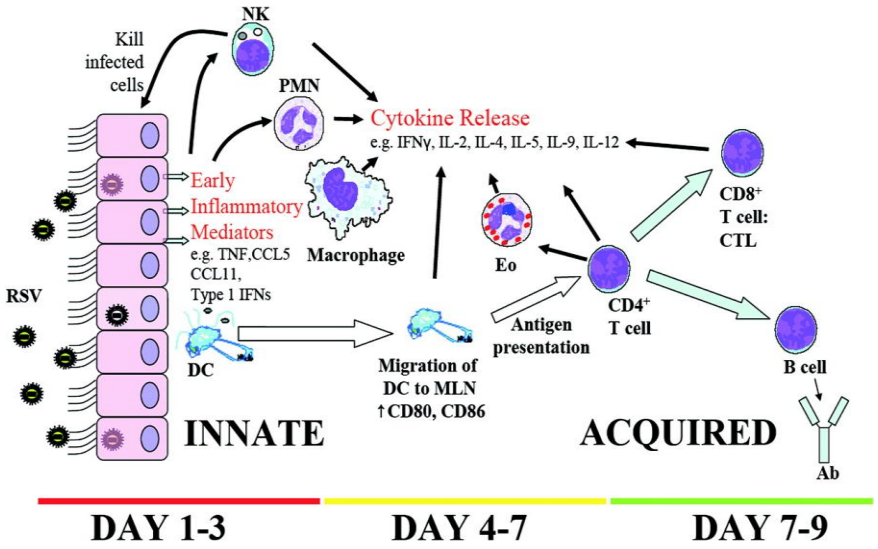


Many sexually transmitted diseases (STDs) are caused by harmful bacteria. Sometimes, these infections aren't associated with symptoms but can still cause serious damage to the reproductive system. Common STDs caused by bacterial infections include: Chlamydia is an infection in men and women caused by Chlamydia trachomatis. Chlamydia increases the risk of pelvic inflammatory disease (PID) in women. Gonorrhea, also known as "clap" and "the drip," is caused by Neisseria gonorrhoeae. Men and women can be infected. Gonorrhea also increases the risk of pelvic inflammatory disease (PID) in women. Syphilis can affect men and women and is caused by the bacteria Treponema pallidum. Untreated, syphilis is potentially very dangerous and can even be fatal. Bacterial vaginosis, which causes an overgrowth of pathogenic bacteria in the vagina.[12] Harmful bacteria can affect almost any area of the body. Other types of bacterial infections include Bacterial meningitis is a severe infection of meninges, lining of brain. Otitis media is the official name for an infection or inflammation of middle ear. Both bacteria and viruses can cause ear infections, which commonly occur in babies and small children. Urinary tract infection is a bacterial infection of bladder, urethra, kidneys, or ureters. Respiratory tract infections include sore throat, bronchitis, sinusitis, and pneumonia. Bacteria or viruses may be responsible for respiratory tract infections. Tuberculosis is a type of bacterial lower respiratory tract infection. Antibiotics are medications that fight bacterial infections. They work by disrupting the processes necessary for bacterial cell growth and proliferation. It is important to take antibiotics exactly as prescribed. Failure to do so could make a bacterial infection worse. Antibiotics don't treat viruses, but they're sometimes prescribed in viral illnesses to help prevent a "secondary bacterial infection." Secondary infections occur when someone is in a weakened or compromised state due to an existing illness.[13]



VIRAL INFECTIONS

When most people hear the word "virus," they think of disease-causing (pathogenic) viruses such as influenza, chickenpox, human immunodeficiency virus. Viruses can affect many areas in the body, including the reproductive, respiratory, and gastrointestinal systems. They can also affect the liver, brain and skin. A viral infection is a proliferation of a harmful virus inside the body. Symptoms of the viral illness occur as a result of cell damage, tissue destruction, and the associated immune response. Certain viruses that cause chicken pox and cold sores may be in-active. For example, cold sore erupts and heals. Cold sore virus remains in cells in a dormant state. Later, triggers such as stress or sunlight may reactivate virus and leads to occurrence new symptoms. The virus makes more copies of itself, releases new virus particles, and kills more host cells.[14] Contagiousness refers to ability of a virus to be transmitted from one person (or host) to another. Viral infections are contagious for varying periods. An incubation period refers to the time between exposure to a virus (or other pathogen) and the emergence of symptoms. The contagious period of a virus is not necessarily the same as the incubation period.



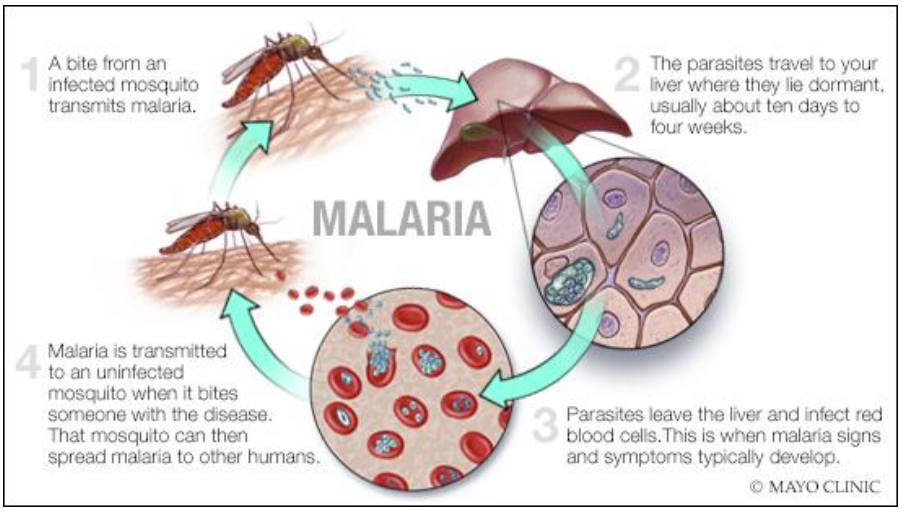
FUNGAL INFECTIONS

Fungal infections are also called as mycoses characterized by invasion of tissues by one or more species. They range from superficial, localized skin conditions to deeper tissue infections (serious lung, blood or systemic diseases). Some fungi are opportunistic while other fungi are pathogenic there by causing various diseases. Most fungal infections occur when a person is exposed to a source of fungi such as spores on surfaces, air, soil or bird droppings. Usually, infections develop due to deficiency in the body's immune system defenses or person may provide "right environment" for the fungi to grow. Only small proportion of population are at increased risk of fungal infections and recurrence of infections. These include organ transplant recipients, people with HIV/AIDS, chemotherapy or immune suppressants medications and underlying conditions like diabetes or lung disease. Fungal infections develop on

surface of the skin, especiallywithin skin folds and other warm and moist areas. These infections typically remain confined to small areas such as between the toes, but may spread over the skin and penetrate into deeper tissues. Fungal nail infections are quite common involving mucous membranes such as mouth and genitals. The sinuses are prone to fungal infections in population residing in specific regions. Infections that start in lungs may spread to blood and is carried throughout the body. Some superficial fungal infections may resolve, but serious infections require medical attention and need to be treated for extended periods of time, if left untreated, may cause permanent damage and in some cases may eventually cause death. A few fungal infections may be easily transmitted to other people, while other infections are not contagious. Some of the fungal diseases include Aspergillosis is caused by fungus Aspergillus and usually occurs in people with lung diseases or weakened immune systems. Candidiasis is caused by yeast Candida. Candidiasis can occur in mouth throat, vagina or bloodstream.[15] Fungal Nail Infections is a common infection of fingernails or toenails. Mucormycosis is a rare infection that mainly affects people in patients with weakened immune systems. Pneumocystis pneumonia (PCP) Caused by fungus Pneumocystis jirovecii and mainly affects people with weakened immune systems. Sporotrichosis caused by fungus Sporothrix, lives throughout the world in soil and on plants. Cryptococcus neoformans Infection is caused by Cryptococcus neoformans, infect brain, causing meningitis in people with weakened immune systems, particularly in patients having co-morbidities like HIV/AIDS. Fungal Eye Infections is a rare infection that develop after an eye injury or eye surgery. Mycetoma is Caused by certain types of bacteria and fungi found in soil and water. Ringworm is a common fungal skin infection that often looks like a circular rash.

PROTOZOAL INFECTIONS

These are parasitic diseases caused by organisms formerly classified in Kingdom Protozoa. They include organisms classified in amoebozoa, Excavata and chromaveoata. The species traditionally collectively termed "protozoa" are not closely related to each other, but have only superficial similarities. The terms "protozoa"and protists are usually discouraged in modern biosciences. However, this terminology is still encountered in medicine. This is partially due to conservative character of medical classification and also due to necessity of making identifications of organisms based upon appearances.[16] Protozoan infections in animals may be caused by organisms in the sub-class Coccidia (Coccidiosis disease) and species in the genus Besnoitia (Besnoitiosis disease). Several pathogenic protozoans have capable of sexual processes involving meiosis. Examples are plasmodium falciparum (malaria), Toxoplasma gondii (toxoplasmosis), Leishmania species (leishmaniases), trypanosoma brucei (African sleeping sickness), Trypanosoma cruzi (chagas disease) and Giardia intestinals (giardiasis).



DISCUSSION

The human body is colonized by a diverse community of microorganisms collectively referred to as the microbiota. Here, microbiota influences susceptibility to infectious diseases such as respiratory, gastrointestinal and female reproductive tract. Interactions between the host, the indigenous microbiota and non-native microorganisms, including bacteria, viruses and fungi, alter the outcome of infections. This Review Article will highlight the complex mechanisms involved by which microbiota mediates colonization resistance, both directly and indirectly, against infectious agents. Strategies for the therapeutic modulation of the microbiota to prevent or treat infectious diseases can also be done as a part of medical oriented trials and potential therapies that directly target the microbiota, including prebiotics, probiotics, synbiotics and faecal microbiota transplantation also be performed under many clinical trials[17]. Clinical Microbiology have a primary interest to clinical microbiologists, medical microbiologists and immunologists, public health workers, infectious disease clinicians, and others interested in the pathogenesis, laboratory diagnosis, epidemiology, and control of human and veterinary pathogens. This article also present comprehensive, critical summaries of current knowledge in the field and is not limited to a discussion. Appropriate parameters such as addressing pathogenic mechanisms, specific or groups of microbial pathogens, clinical and laboratory aspects of newly recognized or reemerging infectious diseases, recently developed antimicrobial agents and their application, and new diagnostic laboratory technology can also be made in routine practice.[18]

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