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Comprehensive review of pharm D professionals' impact on viral fever management: From prevention strategies to therapeutic innovations

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Abstract

Viral fevers pose a significant global health challenge, requiring a multidisciplinary approach for effective management. In this context, Pharm.D professionals play a crucial and empowering role in addressing the complexities associated with viral fever management. This abstract explores the diverse responsibilities and contributions of Pharm.D professionals in optimizing patient care during viral fever outbreaks. Pharm.D professionals possess a comprehensive understanding of pharmacology, therapeutics, and clinical pharmacy, enabling them to actively engage in the management of viral fevers. Their involvement starts by educating communities about viral fever prevention and promoting vaccination campaigns, Pharm.D professionals contribute to the overall reduction of disease transmission. In the clinical setting, Pharm.D professionals collaborate with healthcare teams to ensure accurate and timely diagnosis of viral fevers. Furthermore, Pharm.D professionals actively engage in research and community outreach programs related to viral fevers. Their involvement in clinical research facilitates the development of new treatment modalities and enhances our understanding of the epidemiology and pathophysiology of viral infections. In summary, Pharm.D. professionals have a powerful role in managing viral fever that goes beyond preventive strategies to include patient care, education, pharmacovigilance, and research. Their diverse skill set positions them as essential contributors to the holistic approach needed for effective viral fever control and mitigation. As an integral member of the healthcare team, Pharm.D professionals play a vital role in safeguarding public health during viral outbreaks.

Keywords: Viral Fever; Pharm.D professionals; therapeutic guidelines; patient counselling; Pharmacology

1. Introduction

Fevers were useful indicators of infection according to Hippocrates. Latin fever is derived from the word "heat," while Greek word "pyr" denotes fire or fever is the source of the Greek word pyrexia. Certain sources define "fever" as an elevated body temperature resulting from thermoregulatory pyrogens acting on the hypothalamus, whereas other sources use the terms interchangeably (6). In their common usage, the terms "hyperthermia," "fever," and "pyrexia" are still not properly defined. The International Statistical Classification of Diseases, the Infectious Diseases Society of America, and the American College of Critical Care Medicine define fever as a core temperature of 38.3°C or higher, slightly above the upper range of normal human temperature, regardless of the reason (5), Fever is a common clinical characteristic of several viral illnesses, such as hemorrhagic fever renal syndrome (HFRS), hantavirus pulmonary syndrome (HPS), and chikungunya fever (CHIKV). Simple malaria caused by numerous infections with the Hantavirus (HTV); simple malaria brought on by Plasmodium falciparum infections; enteric fever brought on by Salmonella serovars; or a common symptom of pulmonary tuberculosis brought on by Mycobacterium tuberculosis infections in infants or young adults (1). The management of critically sick patients with fever frequently involves the administration of antipyretic medicine, despite the paucity of evidence supporting the positive function of fever in the host response. Increasing patient comfort, lowering cardiovascular stress, and preventing higher oxygen use are common justifications

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for this kind of care (3). There are various types of thermometers available for taking your temperature: rectal, mouth, forehead (occipital artery), ear (tympanic membrane), and ear. The most accurate way to determine the interior body temperature is typically with an oral or rectal thermometer. by comparing the homeostatic temperature of 37°C with hyperthermic incubation conditions (5). One of the most significant indicators of infection is fever, and Even after William Osler's speech at the 47th Annual Meeting of the American Medical Association about 120 years ago, infectious diseases remain the leading cause of morbidity and mortality. Nevertheless, it is not evident if the fever itself is the primary adversary or if the body uses the febrile response as a useful weapon to combat infection. Humans have a hypothalamus, a primary processing center that regulates body temperature. The afferent limb contains both cold- and heat-sensitive thermoreceptors. The activation of cold-sensing receptors triggers efferent reactions regulated by the hypothalamus, which decrease heat loss and enhance heat production. Shivering is one of these reactions, which also involves a decrease in blood flow to peripheral regions and an increase in heat generation. Conversely, activation of thermosensitive receptors ultimately results in increased heat loss by peripheral vasodilation and sweating, which is an evaporative cooling mechanism (4). Pharmacists can continue to treat patients with chronic illnesses, work in hospital pharmacies, and use medications to treat patients with viral infections as members of the medical community throughout the pandemic. They may also have reliable information about controlling, identifying, treating, and preventing viral infections. Consequently, certain challenges have emerged, and pharmacists are utilizing innovative strategies to address them. During the viral outbreak, pharmacists could be very important. Three categories were used to classify the results: " "Adequate storage and drug supply," "disease prevention and infection control," and "patient care and support for healthcare professionals". These categories generally reflect the duties that pharmacists should play in hospital and primary care settings, including community pharmacies and healthcare facilities, according to the International Pharmaceutical Federation (FIP). Pharmacist intervention can be guided by additional guidelines from scientific societies. This investigation identified medication The two primary services that pharmacists offer are patient counseling and information for medical professionals. Enhancing the patient's problem-solving skills to improve or maintain their quality of life is the aim of these interventions. In addition, some research has suggested other actions (such as managing the drug supply and implementing safety precautions to prevent infections) (1) Pharmacists have a responsibility to ensure that patients with a variety of underlying medical disorders, including diabetes, cancer, heart disease, infections, and chronic obstructive pulmonary disease (COPD), receive further care and counseling. Serious viral fever symptoms and severe impairment are more likely to occur when certain underlying medical conditions are combined. When all these underlying medical conditions are present, There is a higher chance of developing serious impairment and even severe viral fever symptoms. Patients with compromised immune systems, long-term liver and renal illness, or both may find themselves in a similar scenario. Patients with coexisting conditions may experience a more severe decline in their health. Pharmacists should educate these patients on proper medication administration. The importance of medication adherence in maintaining the control of their conditions should also be highlighted. Pharmacists have vital responsibilities in minimizing the risk of illness transmission through pharmacy items, providing consultations, ensuring staff safety, and raising public awareness. Additionally, implementing preventive steps like regularly cleaning surfaces and promoting good hand hygiene among employees and customers. They are ensuring public safety and reducing the likelihood of the virus spreading by implementing these measures. The public should be given instructions by community pharmacists on how to use disinfectants and hand rub alcohol correctly. When it comes to handling crises, like the present COVID-19 outbreak, pharmacists encounter a number of challenges. Many people mistakenly believe that a pharmacist's only responsibility is to sell and distribute pharmaceuticals, and many more lack the information and training required to deal with these emergencies. These people don't realize how many different kinds of jobs there exist in the pharmacy industry, which makes it difficult for pharmacists to take on new responsibilities or enroll in courses that teach crisis management. (2) We can learn about the role of pharm d in viral infection in detail from this thorough review article, along with information about viral infection treatment options and how to overcome obstacles.

2. Epidemiology and common viral fever causes

2.1. Influenza

The family Orthomyxoviridae includes influenza viruses. This family includes enveloped viruses whose genomes are made up of single-stranded RNA segments segmented in a negative sense. Humans can contract influenza viruses of three different types: A, B, and C. Hemagglutinin (subgroups H1 to H18) and withdrawal (antigens on the surface of the viral envelope) are the two antigens used to classify influenza A, the most prevalent and dangerous human infection. Comprising N1 to N11 subtypes of neuraminidase (7). Based on variations in the hemagglutinin glycoprotein, Type B is classified into two separate genetic lineages: Yamagata and Victoria. The natural reservoir of Type A is aquatic birds, and in addition to humans, it can infect a wide range of species. Type C can infect both humans and pigs, however infections are often moderate. Type B is limited to human circulation. Influenza A H3N2 and influenza A H1N1 are the two primary subtypes that have been circulating globally recently (8). The most notable characteristic of influenza

viruses is their high diversity resulting from their fast evolution (9). when tiny aerosols are released by an infected individual when they cough, sneeze, or talk, they spread from person to person through the respiratory system. severe Rapid onset of systemic symptoms such as fever, malaise, headache, myalgia, and respiratory symptoms like cough and sore throat (8). The influenza A virus can infect pigs and horses even though influenza A infection exclusively affects humans. Influenza A (7) viral reservoirs include wild birds, particularly aquatic species of all HA and NA forms. In addition to other birds, chickens can also contract the more virulent variants H5 and H7. Viral shedding is the primary source of the clinical manifestation of classical avian plague, also referred to as avian influenza in immunocompromised hosts or highly pathogenic avian influenza (HPAI). extended breathing contact, which could raise the chance of transmission. The influenza virus can linger up to seven days in healthy individuals and spreads most on the second day (8). Rarely, acute myositis with rhabdomyolysis can happen. It usually happens in kids who have severe pain in their lower extremities and lab results that clearly demonstrate elevated levels of urine myoglobin and creatinine phosphokinase (9). The following conditions can occur: influenza pneumonia, secondary bacterial pneumonia, influenza ARDS, sepsis, secondary bacterial sepsis, myositis and rhabdomyolysis, acute myocarditis, acute cardiomyopathy, transverse myelitis, aseptic meningitis, acute disseminated encephalomyelitis, acute encephalitis(9). Seasonal influenza can strike year-round in tropical and subtropical regions. In the winter months, it is a common cause of respiratory ailments in both the northern and southern hemispheres. The illness is a major cause of death for susceptible people, including young children, expecting mothers, the elderly, and those with compromised immune systems, even though it is typically not severe. Annual seasonal influenza epidemics, depending on the circulating virus strain, can infect up to 20% of the population and result in between 290,000 and 650,000 deaths worldwide. Because they lower labor productivity and put more strain on health services, they have a major negative economic impact (7). According to late 20th-century data, the average hospitalization rate for influenza in the general population for individuals aged 50 to 64 was 37.9 per 100,000 person-years (8). Pneumonia acute is identified in between 30 and 40 percent of hospitalized patients with influenza confirmed by laboratory testing. The patients who had pneumonia had higher odds of being Caucasian, staying in a nursing home, and younger than five (9).

2.2. Dengue virus

Arthropods are the means by which the four different serotypes of the dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4) are spread. Flavivirus is a genus within the family Flaviviridae. The world's fastest-moving virus, dengue fever (DF), is predominantly carried by Aedes aegypti and Aedes albopictus mosquitoes. The dengue virus can infect a host in a number of ways, including direct viral skin infection, chemical mediation caused by the virus's contact with the host, and viral reproduction, especially in macrophages. When bitten by an infected mosquito, the dengue virus enters the host's body through the skin. A biphasic, high fever lasting three days to one week is the hallmark of the start of symptoms. Severe headache (mostly retrobulbar), exhaustion, aches and pains in the muscles and joints, metallic taste, anorexia, diarrhea, vomiting, and upset stomach are among other symptoms that have been described. First identified in 2007, a patient in Sarawak State, Malaysia, had blood tested positive for the recently identified fifth serotype (DENV-5). There is a significant risk of bleeding or shock-related death from severe dengue fever. There isn't a specific antiviral therapy available, though, and the licensed vaccinations are under scrutiny because of the higher risk of hospitalization brought on by antibody-dependent effects (ADE)(11). Extensive research and control measures have not stopped the rapid spread, which has a significant financial cost. Its epidemiology, which includes illness incidence and distribution, risk factors, and control and preventative strategies, has been greatly enhanced by extensive study conducted in recent decades The dengue virus (DENV), which causes dengue fever, has grown to be a significant public health concern in recent decades. What matters more is that it is categorized as a "neglected tropical disease." Every year, some 400 million cases of dengue are reported worldwide, with 22,000 deaths. Around the world, human dengue infection can occur in both endemic and nonendemic cycles and is typically asymptomatic. Pathogenic dengue virus (DENV) can cause a variety of diseases, ranging from mild and classic dengue to severe dengue (DHF) and dengue shock syndrome (DSS), increasing the risk of infection and death. Additionally, these infections may be inapparent or subclinical. WHO estimates that of the 2.5 billion people living in endemic areas, 50 million develop DENV annually, leading to 25,000 deaths. Over 100 nations have annual dengue virus infections, putting an estimated 3.6 billion people at risk. Dengue fever cases have grown thirty-fold in the last fifty years (CDC 2014). Every year, there are DENV outbreaks that impact travelers from endemic locations as well as those in the Americas, Asia, Africa, and Australia. Beyond their effects on public health, these diseases have a major economic impact on the affected countries, especially India. In 1779, there were reports of the first dengue outbreaks in Cairo, Egypt, and Jakarta, Indonesia. In the early 1800s, there were reports of dengue epidemics in East, West, and Southern Africa. Dengue virus serotypes generated by blood 1, 2, and 3 were responsible for multiple dengue epidemics in East and West African nations between 1980 and 2000 (12).

2.3. Zika virus

The Zika virus (ZIKV) belongs to the family Flaviviridae and genus Flavivirus, which are viruses spread by arthropods. Most cases of the Zika virus are caused by mosquito bites. The term "arbovirus" refers to an ecological term for viruses

that are spread physiologically between susceptible vertebrate hosts and hematophagous arthropods like mosquitoes. Previously, serological criteria were used to classify arboviruses. There are clades, species, and clusters in the genus Flavivirus. Three categories are used to classify the 53 different viral species that make up the genus Flavivirus: viruses that are spread by ticks, viruses that are spread by mosquitoes, and viruses that lack a known vector (15). Flaviviruses can cause eye pain, muscle aches, maculopapular rash, and acute fever. The virus is more similar to YFV and DENV in terms of vector transmission (15). The first Zika virus isolation was performed via intracerebral mouse injection, a standard procedure for isolating arboviruses (16). Aedes africanus mosquitoes from the same woodland in Uganda carried the Zika virus when it was initially discovered in 1947. The virus was recovered from a febrile rhesus macaque monkey in the Zika woodland. Nigeria reported the first three cases of human illness in 1954 (14). Panic ensued when the Zika virus, also known as ZIKV, spread over the world, particularly in countries in Latin America and the Caribbean. There were between 440 000 and 1300 000 cases in brazil during the 2016 pandemic. Northeastern Brazil saw the largest-ever Zika virus outbreak in May 2015, which eventually spread to pandemic levels. The Pacific, Americas, and West African coast regions saw the highest number of ZIKV cases; an estimated 1.62 million persons worldwide, spread over more than 70 countries, were affected (15). Most people believed that the Zika virus only spread to a limited geographic area until 2007. Still, many scientists were intrigued by the virus's potential to induce anomalies in a newborn's neurological system and by subsequent outbreaks of infection in South America and the Pacific Islands. While Zika virus transmission is a global health concern, the epidemiology section has primarily focused on data from nations in the Eastern Mediterranean Region (EMRO). The WHO declared a Public Health Emergency of International Concern (PHEIC) at the start of 2016 due of the infections' strong correlation with an increase in cases of microcephaly and Guillain-Barré syndrome in the affected areas. (16)

2.4. Chikungunya

Aedes mosquitoes (family Togaviridae) carry the alphavirus known as Chikungunya virus (CHIKV), which poses a hazard to international health. Acute feverish disease called chikungunya is the primary symptom of CHIKV infection. On the Makonde Plateau in East Africa, CHIKV was initially identified in 1952. Kimakonde kungunyala, the root verb of the word Chikungunya, means "one who bends down," "to stoop," or "to walk stooped" (17). The most prevalent alphavirus that infects people is CHIKV, which is spread by an Aedes mosquito bite. Although Aedes aegypti concentrations in urban areas are linked to CHIKV infection, Aedes albopictus, a zoophilic (mostly non-human, animal-blooded) mosquito species native to Asia, has emerged as a major CHIKV vector in recent years. After an infected mosquito bites, the virus builds up on its skin and becomes more noticeable. the virus and prolonging its cycle of replication by contaminating an uninfected person with mosquito saliva (18). Phylogenetic analysis has revealed that their geographic origins are threefold: West African, Central South African (ECSA), and Asian. The Makonde Plateau Southern Province of Tanzania (previously Tanganyika) was isolated in 1952. The anticipated incubation period for this period is two to ten days. The early stages of acute disease and the latter stages of chronic arthritis are now the two phases of the condition that are explained. The icosahedron capsid of the virion has a diameter of 60–70 nm and is encased in a lipid sheath. It can withstand temperatures of up to 58 °C and desiccation. The genome is a single-stranded positive RNA molecule with a length of about 12 kb (19). However, in 2004, a pandemic that started close to the coast of Kenya spread to Réunion, Comoros, and several other Indian Ocean islands during the course of the following two years. Between the spring of 2004 and the summer of 2006, there were around 500,000 cases. The disease spread from the islands in the Indian Ocean to India, where there were notable outbreaks in 2006. After being first discovered, CIKV expanded to 17 of India's 28 states, infecting about 1.39 million people by the end of the year. Furthermore, diseases from India have been introduced to Singapore, Malaysia, Indonesia, the Maldives, the Andamans and Nicobar Islands, and Sri Lanka by male tourists. The year 2007 marked the height of concerns over the spread of CIKV. Due to the phenomenon of tourism being global, CIKV has reported from more than 60 nations in Africa, Asia, Europe, and the Americas.(19)

2.5. Nipah virus

The Nipah virus, sometimes referred to as NiV, is one of the Paramyxoviridae family's Henipa virus genus members. The reason behind the zoonotic infection known as Nipah (Nee-pa) viral sickness is this, with Pteropus spp. fruit bats being the primary carrier of the infection(20). Additionally, the Hendra virus (HeV) and the Cedar virus (CedPV) are found in this genus. The primary host of the Nipah virus The Malayan flying fox, known as P. vampyrus, and the island flying fox, P. hypomelanus, both reside in Malaysia and share this virus. Immunohistochemistry was utilized to confirm infections in dogs, cats, horses, and goats. It is thought that respiratory droplets, contact with the secretions of the pigs' throats or nasal passages, or contact with their tissue are the routes of transmission. In the Malaysian epidemic area, sick dogs, cats, goats, and horses were noted. Experiments have shown that guinea pigs, cats, ferrets, pigs, mice, golden hamsters (Mesocricetus auratus), and nonhuman primates can all contract the Nipah virus (22). The illness was first discovered in 1998 close to the Malaysian state of Perak, close to the village of Kampung Sungai Nipah. Since then, the Nipah virus—a single-stranded, non-segmented, enveloped RNA virus with helical symmetry—has been found to be the causal agent.

Six genes, numbered from 3 to 24, are arranged in the RNA genome: nucleocapsid (N), phosphoprotein (P), matrix (M), fusion glycoprotein (F), attachment glycoprotein (G), and long polymerase (L). Malaysian pigs harbor two main strains that are distinct from the strains identified in human cases in Bangladesh and India (22). Pigs incubate for seven to fourteen days on average, although it can take as little as four. Clinical symptoms were seen in these animals at 6–8 days and 6–10 days, respectively, for experimentally infected ferrets (23). Fever, coughing, headaches, and labored breathing are some of the clinical signs and symptoms of NiV infection. Seizures and encephalitis are among the side effects. Viral isolation, nucleic acid or antigen detection, and serology can all be used to diagnose Nipah virus infections. Furthermore, histology aids in diagnosis (23). Henipa viruses are being studied in therapeutic treatment trials using a variety of animal models, including guinea pigs, hamsters, ferrets, cats, pigs, and African green monkeys. Pteropus bats, specifically Pteropus vampyrus, Pteropus hypomelanus, Pteropus lylei, and Pteropus giganteu, have been linked to outbreaks of the Nipah virus disease in a number of South and Southeast Asian nations, including Bangladesh, Cambodia, East Timor, Indonesia, India, Malaysia, Papua New Guinea, Vietnam, and Thailand (20).

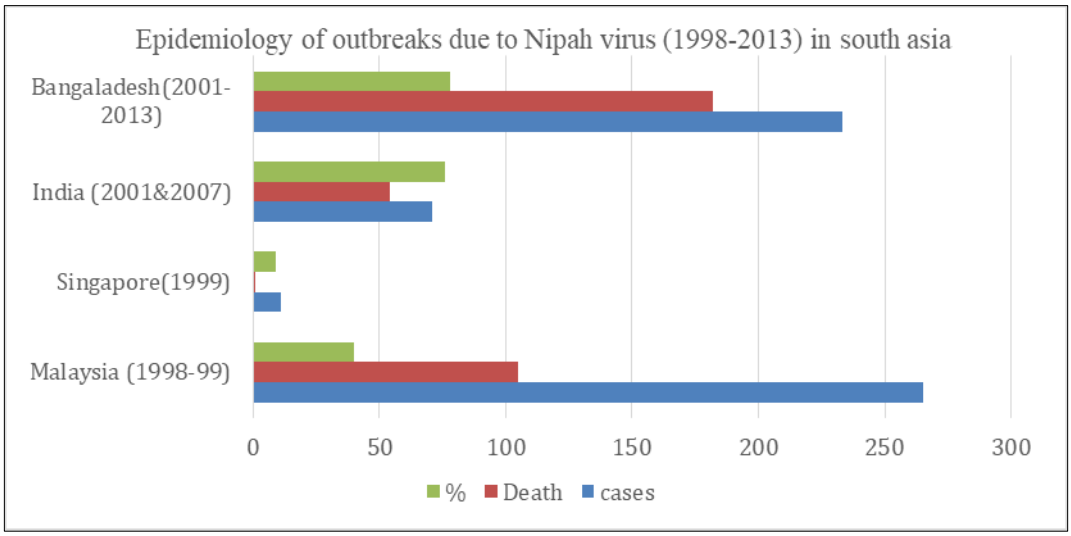

Figure 1 Epidemiology of outbreaks due to nipah virus (1998-2013) in South Asia

A recent outbreak in Kerala in May 2018 brought attention to the reemerging Nipah virus (21). There have been 639 documented cases of NiV infection in humans, and in 2018 the fatality rate was approximately 59% (20). There are cases from Bangladesh (261 cases), Malaysia (265 cases), Singapore (11 cases), India (85 cases), and the Philippines (17 cases) that have been documented.

2.6. Covid-19 virus

Coronaviruses are members of the Coronavirinae subfamily within the Coronaviridae family (26). SARS-CoV-2, or severe acute respiratory syndrome coronavirus, is the virus that causes COVID-19. The virus was originally isolated and detected in patients who had been exposed to shellfish. The introduction took place at Wuhan City, Hubei Province, China in December 2019 (25). There are four primary categories of coronavirus subgroups: α, β, γ, and δ. CoV-HKU1 (2) and Cov-229E are two of the six viruses that make up the αcoronavirus family. The β-coronavirus category includes the human diseases CoV-OC43, SARS-CoV, and MERS-CoV (25). The SARS-CoV-2 positive single-stranded RNA genome has a size of 29,891 base pairs and a diameter that varies from 60 to 140 nm. Typically, the coronavirus particle is spherical or has several forms. Its 120–160 nm-diameter petal-shaped protrusion is composed of three spikes (s) proteins. Person to person contact is primarily how HIV spreads. This patient died from acute respiratory distress syndrome (ARDS), which is marked by increased lymphocyte infiltration, hyaline membrane formation, interstitial inflammation, and pneumocytic desquamation (25). Significantly higher blood levels of cytokines and chemokines (IL1-β, IL1RA, IL7, IL8, IL9, IL10, basal FGF2, GCSF, GMCSF, IP10, MCP1, MIP1a, MIP1p, PDGFB, TNFα, and VEGFA) were seen in COVID-19-infected patients. Certain severe cases that were admitted to the critical care unit had significant quantities of proinflammatory cytokines, such as IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, which are known to influence the severity of the disease (28). 94% of SARS-CoV-2 nucleic acid-positive samples (31/33 cases) were found to have originated from the western section of Huana Seafood Market. A number of other countries from which instances have also been reported include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, the Republic of Korea, the United Arab Emirates, the United States, the Philippines, India, Australia, Canada, Finland, France, and Germany (27). On January 22, 2020, the Chinese National Health Commission announced the first 17 deaths. As of January 25, 2020, 1,975 COVID-19 instances had been confirmed in mainland China. A total of 56 fatalities. A different

report, published on January 24, 2020, projects that China's cumulative incidence will reach 5,502. The Chinese Center for Disease Control and Prevention stated that the CFR was 2.3% based on 44,672 verified cases and 1,023 deaths. The CFR in Italy was 7.2% greater than that in China. The World Health Organization (WHO) reported three (3) 51,174 confirmed cases, with 15,384 severe cases and 1,666 deaths occurred in China. As of now (February 16, 2020), there have been 51,857 confirmed cases worldwide spanning 25 countries (26).

3. Pathophysiology and clinical presentation

A fever (pyrexia) is a controlled body temperature that is higher than normal due to the hypothalamic set point being elevated by IL-1. Just as it is in healthy persons, body temperature is controlled by a net balance between heat production and loss once a fever has started. Uncontrollably raising the body temperature over normal due to an imbalance in heat production and loss is known as hyperthermia. The hypothalamic set point does not change because interleukins are not involved. Any agent that raises fever is called a pyrogen; examples of this include pathogenic organisms and the toxins or cytokines they generate.

It is divided into 2

- Exogenous pyrogens
- Endogenous pyrogens

3.1. Exogenous pyrogens

Exogenous pyrogens are chemicals that originate externally to the body and possess the capacity to activate interleukins.

3.2. Mechanism

Fever often begins two hours after exposure when exogenous pyrogens, which include bacteria, viruses, and toxins, combine with macrophages or monocytes to produce cytokines. Fever can also be caused by other means, like:

- Some endotoxins produced by bacteria directly affect the set point in the hypothalamus. IL-1 performs no role. DDT (dichlorodiphenyltrichloroethane), radiation to the hypothalamus, poisoning, and scorpion venom can also create fever.
- ExP may cause lymphokines to be secreted by lymphocytes, especially INF-y, which in turn prompts the production of IL-1 by monocytes and macrophages.
- Exotoxins are produced by certain bacteria, and these toxins cause monocytes and macrophages to release IL-1. Toxic shock syndrome and scarlet fever both use this mechanism. The poison is what causes the shock in toxic shock syndrome. illnesses caused by exotoxins created
- Fever can be caused by viruses through a variety of mechanisms, such as direct infiltration of macrophages, antibody production in response to viral components, IFN stimulation, and viral necrosis of cells.
- Endogenous pyrogens
- Endogenous pyrogens are compounds that are produced internally in the body and have the ability to raise body temperature by influencing the hypothalamus thermoregulatory center. Albumin and transferrin lowers endogenously produced IL-1, TNF, and IFN (interferon).

3.3. Mechanism

3.3.1. IL-1, or interleukin-1

- IL-1 is composed of three structurally similar polypeptides: IL-1α and IL-1β, two agonists that restrict the function of the other two potent agonists, and IL-1 receptor antagonist, or IL-1ra, an antagonist. Anakinra is natural IL-1ra.
- cells found in all mucosal membrane epithelial cells in healthy individuals.
- Tissue macrophages and blood monocytes.
- Pancreatic Langerhans cells, keratinocytes, and hepatic Kupffer cells.
- Astrocytes in brain tissue may have a function in the CNS's immunological reactions as well as the fever brought on by CNS hemorrhage. cells from specific cancerous tumours, such as renal carcinoma, acute leukemia, and Hodgkin's disease. This explains why fever is frequently associated with these illnesses even when there is no infection

3.3.2. Tumour necrosis factor

- TNF-α is an endogenous pyrogen that produces fever by acting on the hypothalamus. Unlike IL-1, TNF does not directly regulate the activation of lymphocytes and stem cells. TNF-α demonstrates several favorable biological effects, including:
- Many biological features, including early strengthening of host defense against infection, normal remodeling of tissue, including wound healing, and improved chemotaxis of neutrophils and macrophages as well as phagocytic and cytotoxic activities, are similar to those of IL-1.Acute-phase response stimulator, in addition to IL-6.
- Physiological processes of the nervous system that are essential for memory, learning, sleep, and food and drink intake. (29)
- In actuality, a 1 C increase in body temperature demands a 10–12.5 percent increase in metabolic rate given to the high metabolic cost of human induction. (30) The effects of fever on metabolism: An increased requirement for oxygen
- elevated cardiac rate
- elevated breathing rate
- Greater utilisation of body proteins as a source of energy. Instead of using glucose, which is a great medium for bacterial growth, metabolism instead uses the byproducts of protein and fat breakdown.
- An improved immune system
- An increase in white blood cell motility and activity
- increases the synthesis of interferon and T cell activation
- Growth inhibition caused by some microorganisms
- At normal body temperatures, many microbiological organisms that cause infections have a tendency to flourish.(31)
- The paths of fever,
- The humoral and cerebral routes are the two main avenues by which the thermoregulatory circuitry is finally reset in response to fever signals supplied by exogenous and endogenous pyrogens.

3.3.3. The route of humour

In this system, pyrogenic cytokines or pieces of microbial products known as pathogen associated molecular patterns (PAMPS) are responsible for the transmission of fever signals. It is known that circulating PAMPS of bacteria, which are identified by gram-negative LPS, bind to TLR-4 on a variety of cells. They induce the blood brain barrier's fenestrated capillaries of the circumventricular organ to bind to and activate TLR-4, which in turn causes the cytoplasmic membranes' arachidonic acid pathway to create prostaglandin E2 (PGE2). Adhering to a specific PGE2 receptor (EP3 receptor) in the preoptic area, prostaglandin E2 is a tiny molecule that easily penetrates the blood-brain barrier. This activation of thermal neurons in the anterior hypothalamus raises the thermal balance point of the region. Uncertainty surrounds whether microbial agents that access the brain directly through BBS disruption also raise the thermal balance point.(34) The fever reaction is separated into two phases: an early, quick phase and a delayed, late phase. Research in animal models with polyphasic LPS-induced fever suggests that PGE2 formed centrally is responsible for the latter phases of this febrile reaction, while PGE2 generated in the liver and lungs prior to migration to the brain is likely to be responsible for the initial phase. It is plausible that peripherally made PGE2 may serve to elicit the febrile reaction, but centrally produced PGE2 may be largely responsible for maintaining it.

3.4. Cerebral pathway

Peripheral fever signals can enter the central nervous system by peripheral nerves such as the vagus nerve and cutaneous sensory nerves. The activation of the neural pathway is another theory for how fever starts quickly.According to some theories, inflammatory regions that produce PGE2 locally set off cold-sensitive cutaneous nerves, which in turn convey fever signals to the brain regions that are in charge of producing fever. There is a more intricate process involved in the vagus nerve's ability to transmit fever signals. When pyrogens, like LPS, are present in the bloodstream, the liver's Kupffer cells respond by releasing endogenous mediators, which include pyrogenic cytokines. Pyrogens also trigger the production of complement and complement products. These cytokines activate the hepatic branch of the vagus nerve, which in turn causes fever signals to be transmitted to the central projection of the vagus nerve within the tractus solitarius nucleus (NST). The ventral noradrenergic bundle carries the signal from the NST to the preoptic and hypothalamic regions, where it causes the intra preoptic release of norepinephrine.

Norepinephrine causes significant increases in core temperature, which mediates the vagal route. Alpha (1)-adrenoceptor (AR)-mediated, PGE2-independent, and having a quick onset is the first; alpha (2)-AR-mediated, PGE2-dependent, and having a delayed start is the second.(33) Childhood fever is frequently caused by viral exanthems. It is

known that over 50 viral agents can result in a rash. Exanthems were traditionally numbered according to how they set themselves out from one another. Measles was the first, followed by scarlet fever, rubella,erythema infectiosum, xanthema subitum, filatov-Dukes disease (which is no longer recognized as a distinct illness), and so on. As additional exanthems were described, it became impossible to assign numbers

3.4.1. viral infections of the upper respiratory tract (URTIs)

URTI, sometimes known as the common cold, are extremely prevalent infections that are characterized by fever, low appetite, sore throats, coughing, nasal obstruction, and restless sleep. Mucopurulent nasal discharge, which may or may not be indicative of bacterial infection, follows the initial watery nasal discharge. It has been projected that early children who attend nursery school can have up to 12 respiratory illnesses each year, whereas children who do not attend school can have 9 infections or 6 or 7 infections. Respiratory tract infections are known to be caused by more than 100 viruses, comprising rhinoviruses, influenza A and B, coronaviruses, parainfluenza 1, 2, and 3, adenoviruses, and respiratory syncytial viruses (RSV), in addition to the most prevalent virus. Inhalation, self-inoculation of the nasal mucosa, or airborne inoculation of the conjunctival mucosa can all cause an illness. Compared to adults, children typically have higher virus concentrations in their nasal secretions and longer viral shed times. Less frequently, viralemia only affects the mucosa, which includes the sinuses and the Eustachian tube. Examples of secondary bacterial infections that exacerbate viral upper respiratory tract illnesses are acute otitis media and sinusitis.[32].

3.4.2. Associated symptoms

Simple viral illness

When symptoms of the upper respiratory tract and constitution, such as rhinitis, fever, chills, myalgia, headache, malaise, sore throat, and nonproductive cough, develop suddenly, it's usually a sign of a simple influenza illness. Fever is not always present in influenza virus-infected patients, nevertheless, especially in the elderly and immunocompromised. Even in old, institutionalized, and vulnerable residents of long-term care facilities, influenza virus infections can exhibit peculiar signs and symptoms. Children who have influenza may also experience respiratory symptoms including nausea, vomiting, or diarrhoea. Simple influenza symptoms usually go away in three to seven days, although cough and malaise might last longer, especially in older people and people with underlying respiratory conditions.(34)

Serious sickness is just one of the many outcomes that might result from an influenza virus infection of the respiratory system. Some people are more prone than others to influenza-related complications. Otitis media and respiratory diseases such bronchiolitis, tracheitis, and croup can strike young children. In addition, children may experience musculoskeletal (severe myositis), cardiac (myocarditis and pericarditis), and neurological (encephalopathy, encephalitis, transverse myelitis, and acute disseminated encephalomyelitis) disorders.(33) Reye syndrome is linked to influenza (infections with the influenza B virus are more common than those with the influenza A virus) and exposure to salicylates; however, influenza-related Reye syndrome is extremely uncommon because aspirin usage was banned in 1982 when children had influenza or varicella. Influenza can cause people of all ages who already have long-term health problems to become more dehydrated. Fever with any of the following is the most typical sign of dengue:

- Vomiting and nausea
- Rash
- Pains and aches (bone, joint, or muscular pain; usually behind the eyes)

Any cautionary indication

Dengue usually effects people for two to seven days. The majority of people heal in around a week.(35)

3.4.3. Complications and severity

A persistent, dangerously high temperature can have fatal consequences for several organ systems:

3.5. Brain

After a bout of hyperthermia, there may be an acute neurologic and cognitive function deficit; in about half of heatstroke survivors, there is permanent neurologic impairment. Particularly, heat exposure can cause long-lasting cerebellar dysfunction because it damages the Purkinje cells in the cerebellar cortex.(36)

3.6. Heart related

When a patient is overheated, they may have hypotension and a high cardiac output as a result of blood redistribution and vasoconstriction brought on by nitric oxide. An ECG may reveal conduction faults, QT and ST abnormalities, and T-wave abnormalities in cases of acute temperature, such as heatstroke. Serum troponin I levels may also be noticeably elevated.(37)

3.7. The digestive system

Over 40 C (104 F), there is a reduction in blood flow to the GI tract. Additionally, there has been evidence of oxidative stress, denatured proteins, and damaged cell membranes, all of which raise the risk of GI inflammation, edema, and the generation of pro-inflammatory cytokines (38).

3.8. Liver

It is well known that individuals with body temperatures over 40 C have raised liver enzymes (AST/ALT), and severe cases may cause irreparable hepatic damage that calls for the purpose of liver transplantation. It's crucial to remember that liver function may continue to deteriorate even after heat treatment. To make sure there is no ongoing liver damage, a doctor should keep an eye on the patient's liver enzyme levels.(39) Fever increases the risk of acute kidney damage (AKI) in renal patients significantly. As the body temperature rises, the glomerular filtration rate (GFR) starts to drop as soon as it climbs by 2 degrees Celsius. Laboratory research will demonstrate a rise in urea and plasma creatinine. Kidney blood flow is also decreased by the hyperthermic condition's renin-angiotensin-aldosterone system activation (RAAS) (40). hematomasis, Historically, it has been observed that hyperthermic individuals display thrombocytopenia, increased synthesis of plasma fibrin olysis, spontaneous bleeding, suppression of platelet aggregation, and longer clotting times.(41)

4. Conclusion

Pharmacists are able to gather data, evaluate and advise patients on how to prevent transmission. Pharmacist can be ready for further outbreaks by participating in the ongoing immunization campaigns and activities.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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