A STUDY OF CLINICAL PROFILE OF PATIENTS WITH FEBRILE THROMBOCYTOPENIA

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Under the guidance of

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ABSTRACT

Febrile thrombocytopenia is one of the unrecognized complication which may be missed if platelet count is not done routinely. Increased awareness and early recognition of thrombocytopenia can avoid catastrophes like fatal bleed. The aim of study is to find clinical presentation of patients with febrile thrombocytopenia and find causes and complications associated with febrile thrombocytopenia.

Materials and methods:

In the present study 107 patients who presented to Shri B. M. Patil Hospital with fever with thrombocytopenia who fulfil inclusion criteria are included in study, a detailed history general physical examination, investigations were performed and patients were treated symptomatically and specifically after diangnosis.

Results:

In the present study subjects were in the age group of 18-80 years. Youngest was 18 years old and oldest 80 years. In the present study out of 107 cases of fever with thrombocytopenia, 79 were males and 28 were females. Out of 107 patients of fever with thrombocytopenia, 102 had definitive diagnosis with Dengue 54 cases as the commonest cause, followed by Malaria which constituted 40 cases, Mixed infections 3 cases(Dengue fever with enteric fever, Vivax malaria, falciparum malaria), Acute Gastroenteritis 2 cases, Urinary tract infections 1 case, Leptospirosis 2 cases and Enteric fever 2 cases and Unknown causes accounted for 5 cases. In our study 61 patients had platelet count less than 60,000 cells/cumm, whereas 46 had above 60,000 cells/cumm. Common range of platelet count was from 41,000 – 60,000 cells/cumm in 27 cases.Of 107 patients 104 of them recovered and 3 expired with mortality of 2.8% with All 3 patients had MODS.

Conclusion: In all cases of Febrile thrombocytopenia, thrombocytopenia led to various bleeding manifestations and influenced the clinical profile of these illnesses. Petechiae were the most common bleeding manifestation . The spectrum varied from mild self limiting disease to severe fatal disease. This highlights the need for rapid diagnosis and appropriate management of patients to prevent complications.

ABBREVIATIONS

AGE	- ACUTE GASTROENTERITIS
BBB	- BLOOD BRAIN BARRIER
CMV	- CYTOMEGALOVIRUS
CNS	- CENTRAL NERVOUS SYSTEM
CR	- COMPLEMENT RECEPTORS
CRP – C	- REACTIVE PROTEIN
DEN	- DENGUE FEVER
ENT	- ENTERIC FEVER
EBV	- EPSTEIN BARR VIRUS
EP	- ENDOGENOUS PYROGENS
FM	- FALCIPARUM MALARIA
HAV	- HEPATITIS A VIRUS
HCV	- HEPATITIS C VIRUS
HBV	– HEPATITIS B VIRUS
HHV	– HUMAN HERPES VIRUS
HIV	- HUMAN IMMUNODEFICIENCY VIRUS
IE	– INFECTIVE ENDOCARDITIS
IFN	– INTERFERONS
IL	– INTERLEUKINS
ITP	– IMMUNE THROMBOCYTOPENIC PURPURA
LBP	– LIPOPOLYSACCHARIDE BINDING PROTEIN
LPS	– LIPOPOLYSACCHARIDES
LEPTO	– LEPTOSPIROSIS

MM	– MIXED MALARIA
MODS	– MULTIORGAN DYSFUNCTION SYNDROME
OVLT	- ORGANUM VASCULOSUM OF LAMINA TERMINALIS
PAF	– PLATELET AGGREGATING FACTORS
PF	– PLASMODIUM FACTORS
PMP	- PLATELET MICROBICIDAL PROTEIN
PG	– PROSTAGLANDINS
ROS	– REACTIVE OXYGEN SPECIES
SLE	– SYSTEMIC LUPUS ERYTHEMATOSUS
TLR	– TOLL LIKE RECEPTORS
TF	– THROMBIN FACTORS
TNF	– TUMOUR NECROSIS FACTOR
UTI	– URINARY TRACT INFECTION
VM	– VIVAX MALARIA
VWF	– VON WILLEBRAND FACTOR

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INTRODUCTION

Medicine presents nothing which more forcibly arrests our attention, than the great fever epidemics, notices of which are to be found in the records of all ages, and in the annals of every race and people.

Fever is such a common manifestation of infectious illness that it is not surprising to find accurate descriptions of the febrile patients in early-recorded history.

Normal body temperature is 37.0 °C or 98.6 °F. The normal range is quite wide, being affected by site of measurement, diurnal variation, heavy exercise, hormonal and menstrual status, individual variation, and environmental factors. A patient's body temperature is often estimated by measurements taken in the mouth for reasons of convenience, but oral temperatures can be affected by mouth-breathing, by the respiratory rate, and by recent drinking of hot or cold liquids.[1]

"Febrile thrombocytopenia is one of the common complications which may be missed if platelet count is not done routinely. Increased awareness and early recognition of thrombocytopenia can avoid catastrophes like fatal bleed. The common causes of febrile thrombocytopenia are Dengue, Malaria, Leptospirosis, Enteric fever, HIV infection"

There are 3 mechanisms by which platelet count mainly decreased which includes production, increased destruction and sequestrations. Thrombocytopenia in fever episodes occurs mainly due to immune destruction, bone marrow suppression, clumping of platelet, DIC and sometimes hypersplenism.[2]

“Clinical manifestations of thrombocytopenia commonly include purpura, epistaxis, gingival bleed .Gastrointestinal bleed, intracranial bleed and hematuria are rare complications. Counts less than 20,000 are associated with serious bleeding manifestations like intracranial bleed. Serial monitoring is said to have prognostic value in febrile thrombocytopenia”.

Thrombocytopenia has an inverse relation to mortality and morbidity is various febrile illness, serial monitoring of platelet counts has prognostic value. This highlights the importance of thrombocytopenia in various febrile disorders. As the fever course is prolonged and fever with thrombocytopenia narrows the differential diagnosis of the clinical entity.[2]

Septicemia, Infections like malaria, dengue, leptospirosis, typhoid, HIV and military TB are some of the common causes of fever with thrombocytopenia.

Therefore a well organized systemic approach that is carried out with an awareness of causes of fever with thrombocytopenia can shorten the duration of investigations and bring out diagnosis and thus treatment.

Hence, a need for study to know the causes and complications and varied manifestations thrombocytopenia of infective etiology.

AIMS AND OBJECTIVES OF THE STUDY

- To study the clinical presentation of febrile thrombocytopenia.
- To identify the cause of febrile thrombocytopenia.
- To study the complications in relation to febrile thrombocytopenia.

REVIEW OF LITERATURE

Fever was recognized as a cardinal feature of disease as depicted in the Sumerian pictographs.[1]

“The idea that fever is a method of therapy may be traced back to the early days of written history. Give me the power to produce fever, and I will cure all disease is a quotation attributed to Hippocrates more than twenty-three hundred years ago”. Ruphos of Ephesus, four hundred and fifty years afterwards, said: "If indeed any were so good a physician as to be able to produce fever, it would not be necessary to look for any other remedy in sickness."[1]

The production of fever as a therapeutic procedure had to wait centuries, however, for advances in chemistry, physics, mathematics, and medical sciences. The development of fever therapy can be divided into empirical and scientific eras[2]. The borderline between these two eras was thermometry which was introduced in the early part of the seventeenth century by Galileo and Sanctorius, and developed in the second half of the nineteenth century by Wunderlich and Allbutt.[2]

EMPIRICAL ERA

“The origin of therapeutic fever lies buried in medical antiquity. While the rays of the sun have therapeutic value, other than their heating effects, nevertheless, early physicians used them solely for these effects”. Heat was also applied to locally affected parts of the body and to its entirety by means of hot water, steam, sand, and mud baths. It is probably true that the ancient therapist might not have been aware of

the fact that by these physical means he produced a rise in body temperature. However, our present knowledge of thermotherapy leads us to the reasonable conclusion, based upon the descriptions of the techniques used, that sufficient heating energy was frequently employed to accomplish such an elevation of systemic temperature.[3]

Egyptian physicians during the fifth Century B. C. applied rules for sun and heat therapy. In the encyclopedic compilations of Oribasius (325-403 A. D.) of Constantinople, are found quotations from Herodotus, the historian of the fifth century B. C., referring to this phase of Egyptian medicine"[4]

Natural hot air caverns connected with volcanic sources were utilized (Oribasius, X, 40). The epic poet Homer (Fifth Century B. C.) clearly established that hot baths for medical purposes were common among the Greeks before the Age of Pericles.[3]

"Hippocrates had ideas as to the significance of fever, and modern concepts as to its possibilities. He prescribed hot water and steam baths for thickened and tense skin, for spasticity and for pains of the extremities as well as of the torso". Illustrative is the case history of a man of Athens who was affected with a severe pruritus of his entire body. The skin in all regions was so thickened that he had the appearance of a leper and it was impossible to pinch up the skin anywhere. No one had been able to relieve him. Hippocrates ordered him to go to the Island of Melos where there were hot baths. There he became entirely cured of his itching and the thickening of the skin, but he developed a dropsy and died. This man may have had one of the chronic dernatoses for the treatment of which dermatologists are now finding fever therapy to be of value.[2]

During the reign of Tiberius Caesar, 42 B. C.-37 A. D., Aurelius Cornelius Celsus described the prevailing medical procedures and ideas regarding fever and heat. He wrote of a certain Pretonius who treated persons attacked by fever somewhat as follows: "He had the patient well covered up to excite at the same time a violent heat and thirst. When the fever began to abate somewhat, he made him drink cold water. If he broke out in a violent sweat, the patient was considered cured." "Heat," Celsus wrote, "acts well in eye diseases which are without pain and lacrimation.[5]

The techniques of heat application included wet fomentations, dry packs, steam baths, hot air baths, and sun baths. Celsus claimed that ordinarily heat would "relax the skin and draw forth corrupt humors, and change the condition of the body."[5]

Galen wrote: "It is probable that Erasistratus (an Alexandrian anatomist of the Fourth Century B. C.) was not unaware of the method of treating cases of dropsy by heating in the barrel, a treatment which is highly estimated by other ancient physicians. Indeed, the patients experienced for the entire body an evacuation (sweating) much greater, and sooner than in the bath. However, they did not suffer from the heat because they breathed cold air, their heads being outside. If they are deprived of this air, they die quickly."[4]

Coelius Aurelianus treated wasting, hemoptysis, and dropsy with dry hot air and hot sand baths. A description of the early hot sand bath is found in the works of Oribasius (Orib. Col. X, 8). "The summer time is the best because one can then choose the hottest day. Towards morning, these are prepared on the river bank in the deep sand, two or three trenches. These are allowed to become thoroughly heated by the sun. The patient should have digested his last meal and also taken a previous walk or at least had some passive movement. When the air is sufficiently warm and the sand

sufficiently heated the patient is laid in the trench and covered with the hot sand as much as he can comfortably bear. The head must be protected from the sun. His face is wiped with a sponge dipped in cold water and if he suffers much he is given something with which to rinse his mouth. If the patient perceives that his body does not heat up at all or that he even becomes chilly because of the sweating he should say so. The attendant will then remove the sand, take him out of the trench, and will place him in the trench alongside in the same way as described above. If necessary, this may be done a third time being guided by the different conditions and according to their strengths."[4]

"The American Indians treated fevers with heat. William Penn in a letter to Edward Baynard, a fellow of the Royal College of Physicians, described how an Indian Chief obtained almost immediate relief from an illness associated with fever by the use of hot vapor baths". Among the early Americans, the sweat bath was a favorite therapeutic measure, especially for acute fevers. Arthritis, neuritis, and rheumatism, common among these Indians, were not distinguished from each other, but were all treated alike with the sweat bath. Carolina Indians used hot mud holes for treating various diseases of the extremities. Remittent and other forms of fever prevalent among the inhabitants of Northern Africa, were treated by sweating induced by hot sand and hot water baths.[5]

"The Chinese and the Japanese were among the earliest peoples to use their intensely hot springs for therapeutic purposes. In Japan the volcanic formations gave rise to many hot springs. These thermal springs were used for the treatment of all forms of syphilis, arthritis, rheumatism, acute genito-urinary infections, and respiratory, digestive, nervous and ocular diseases". They have been very popular throughout the Japanese empire since the Sixteenth Century and enjoyed local renown for several

centuries before that time. Indeed, the use of the thousands of hot springs in Japan was common among all classes of the populace as one of the most important cures long before the introduction of European medicine. At Kusatsu, water gushes out of the bases of ancient volcanoes at a temperature between 100' F. and 160' F. As the water flows into reservoirs, it is unbearably hot, and the bathers stir it with large wooden paddles, thereby cooling it. They then immerse themselves to the neck and pour hot water over their heads with wooden dippers. After three to six minutes of this refined torture, they bob out almost parboiled with a body temperature of between 103' and 105' F.[5]

SCIENTIFIC ERA

The research techniques developed during the Seventeenth, Eighteenth, and Nineteenth Centuries, permitted medical practice to pass from the stage of philosophic argument to scientific reasoning. Galileo

"In 1595 invented the thermometer, which may be said to have brought science to fever and heat therapy. Galileo's thermometer was the open air alcohol thermoscope. Shortly afterward, in 1611, Sanctorius, introduced this device to clinical medicine. Sanctorius investigated the cause and nature of body temperature. To carry out his studies, he devised the Pulsilogium, an instrument for studying the pulse, and applied Galileo's thermoscope. He recognized that the human body has a normal temperature and determined variations from the normal as an aid to diagnosis".[6]

In 1868, "Carl Wunderlich published his classic on animal heat. Wunderlich demonstrated the diagnostic and prognostic importance of continued temperature observations during the course of a disease". He recorded the temperature of patients

every four hours and constructed charts showing its variations. When he stated that fever was a symptom and not a disease, Wunderlich prepared the way for studies on heat production and fever.

Wunderlich's method of attaining rectal temperature curves characteristic of various diseases spread quickly through England and Germany.[7]

The period of the Nineteenth Century that witnessed the introduction of thermometry into clinical medicine was characterized also by advances in knowledge concerning infectious diseases. The record of the temperature of the body became one of the principal means of characterizing various febrile affections and of recognizing complications of these diseases. The close association of infection with fever was soon established and stressed so energetically that at present physicians find it difficult to avoid using one as an indication of the other. Thermometers had begun to make their appearance in numerous English hospitals during 1866-1867, and became generally accepted within the next two years.

Temperature regulation and its physiology.

In the body, heat is produced by muscular exercise, assimilation of food, and all the vital processes that contribute to the basal metabolic rate. It is lost from the body by radiation, conduction, and vaporization of water in the respiratory passages and on the skin. Small amounts of heat are also removed in the urine and feces. The balance between heat production and heat loss determines the body temperature. Because the speed of chemical reactions varies with the temperature and because the enzyme systems of the body have narrow temperature ranges in which their function is optimal, normal body function depends on a relatively constant body temperature.[8]

Normal Body Temperature

In homeothermic animals, the actual temperature at which the body is maintained varies from species to species and, to a lesser degree, from individual to individual. In humans, "the traditional normal value for the oral temperature is 37 °C (98.6 °F), but in one large series of normal young adults, the morning oral temperature averaged 36.7 °C, with a standard deviation of 0.2 °C. Therefore, 95% of all young adults would be expected to have a morning oral temperature of 36.3–37.1 °C (97.3–98.8 °F; mean ± 1.96 standard deviations). Various parts of the body are at different temperatures, and the magnitude of the temperature difference between the parts varies with the environmental temperature".

The extremities are generally cooler than the rest of the body. The temperature of the scrotum is carefully regulated at 32 °C. The rectal temperature is representative of the temperature at the core of the body and varies least with changes in environmental temperature. The oral temperature is normally 0.5 °C lower than the rectal temperature, but it is affected by many factors, including ingestion of hot or cold fluids, gum chewing, smoking, and mouth breathing.

The normal human core temperature undergoes a regular circadian fluctuation of 0.5–0.7 °C. In individuals who sleep at night and are awake during the day (even when hospitalized at bed rest), it is lowest at about 6:00 AM and highest in the evenings. It is lowest during sleep, is slightly higher in the awake but relaxed state, and rises with activity. In women, an additional monthly cycle of temperature variation is characterized by a rise in basal temperature at the time of ovulation. Temperature regulation is less precise in young children and they may normally have a temperature that is 0.5 ° or so above the established norm for adults.[8]

HEAT PRODUCTION

A variety of basic chemical reactions contribute to body heat production at all times. Ingestion of food increases heat production because of the specific dynamic action of the food, but the major source of heat is the contraction of skeletal muscle . Heat production can be varied by endocrine mechanisms in the absence of food intake or muscular exertion. Epinephrine and norepinephrine produce a rapid but short-lived increase in heat production; thyroid hormones produce a slowly developing but prolonged increase. Furthermore, sympathetic discharge decreases during fasting and is increased by feeding.[8]

Box 1.

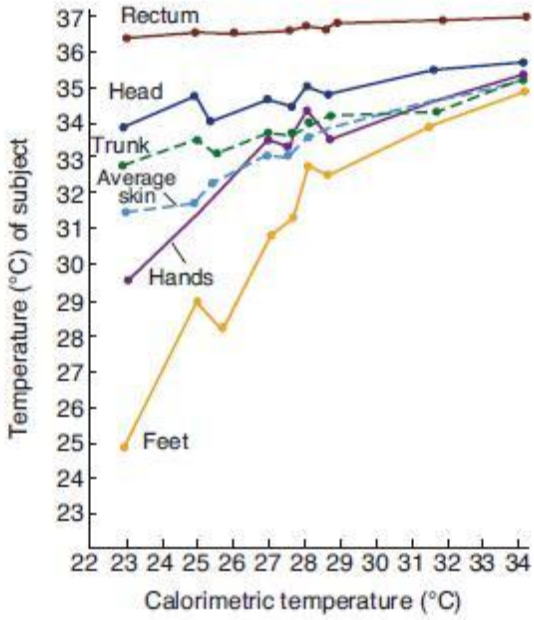
Body heat is produced by:
Basic metabolic processes
Food intake (specific dynamic action)
Muscular activity

Body heat is produced by:

Food intake (specific dynamic action)

Body heat is lost by:	Percentage of heat lost at 21 °C
Radiation and conduction	70
Vaporization of sweat	27
Respiration	2
Urination and defecation	1

Figure 1



Temperature of various parts of body[8]

Temperature-Regulating Mechanisms

The temperature regulating mechanisms include autonomic, somatic, endocrine, and behavioral changes. One group of responses increases heat loss and decreases heat production; the other decreases heat loss and increases heat production. In general, exposure to heat stimulates the former group of responses and inhibits the latter, whereas exposure to cold does the opposite.

Box 2
Mechanisms activated by cold
Shivering
Hunger
Increased voluntary activity
Increased secretion of norepinephrine and epinephrine
Decreased heat loss
Cutaneous vasoconstriction
Curling up
Horripilation
Mechanisms activated by heat
Increased heat loss
Cutaneous vasodilation
Sweating
Increased respiration
Decreased heat production
Anorexia
Apathy and inertia

Thermoregulatory adjustments involve local responses as well as more general reflex responses. When cutaneous blood vessels are cooled they become more sensitive to catecholamines and the arterioles and venules constrict. This local effect of cold directs blood away from the skin. Another heat-conserving mechanism that is important in animals living in cold water is heat transfer from arterial to venous blood in the limbs. The deep veins (venae comitantes) run alongside the arteries supplying

the limbs and heat is transferred from the warm arterial blood going to the limbs to the cold venous blood coming from the extremities (countercurrent exchange). This keeps the tips of the extremities cold but conserves body heat.

The reflex responses activated by cold are controlled from the posterior hypothalamus. Those activated by warmth are controlled primarily from the anterior hypothalamus, although some thermoregulation against heat still occurs after decerebration at the level of the rostral midbrain. Stimulation of the anterior hypothalamus causes cutaneous vasodilation and sweating, and lesions in this region cause hyperthermia, with rectal temperatures sometimes reaching 43 °C (109.4 °F). Posterior hypothalamic stimulation causes shivering, and the body temperature of animals with posterior hypothalamic lesions falls toward that of the environment.[8]

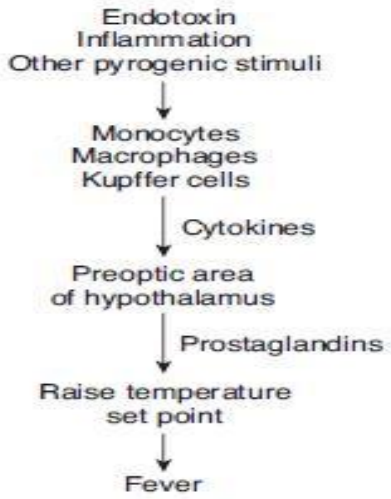
"Afferents - The hypothalamus is said to integrate body temperature information from sensory receptors (primarily cold receptors) in the skin, deep tissues, spinal cord, extrahypothalamic portions of the brain, and the hypothalamus itself. Each of these five inputs contributes about 20% of the information that is integrated". There are threshold core temperatures for each of the main temperature-regulating responses and when the threshold is reached the response begins. The threshold is 37 °C for sweating and vasodilation, 36.8 °C for vasoconstriction, 36 °C for nonshivering thermogenesis, and 35.5 °C for shivering[8].

Fever is perhaps the oldest and most universally known hallmark of disease. It occurs not only in mammals but also in birds, reptiles, amphibia, and fish. When it occurs in homeothermic animals, the thermoregulatory mechanisms behave as if they were adjusted to maintain body temperature at a higher than normal level, that is, "as if the thermostat had been reset to a new point above 37 °C. The temperature receptors then

signal that the actual temperature is below the new set point, and the temperature-raising mechanisms are activated. This usually produces chilly sensations due to cutaneous vasoconstriction and occasionally enough shivering to produce a shaking chill". However, the nature of the response depends on the ambient temperature. The temperature rise in experimental animals injected with a pyrogen is due mostly to increased heat production if they are in a cold environment and mostly to decreased heat loss if they are in a warm environment.[9]

Toxins from bacteria such as endotoxin act on monocytes, macrophages, and Kupffer cells to produce cytokines that act as endogenous pyrogens (EPs). There is good evidence that IL-1, IL-6, interferons and TNF can act independently to produce fever. These cytokines are polypeptides and it is unlikely that circulating cytokines penetrate the brain. Instead, evidence suggests that they act on the OVLT, one of the circumventricular organs. This in turn activates the preoptic area of the hypothalamus. Cytokines are also produced by cells in the central nervous system (CNS) when these are stimulated by infection, and these may act directly on the thermoregulatory centers.[8]

Figure 2



Pathogenesis of fever

The fever produced by cytokines is probably due to local release of prostaglandins in the hypothalamus. Intrahypothalamic injection of prostaglandins produces fever. In addition, the antipyretic effect of aspirin is exerted directly on the hypothalamus, and aspirin inhibits prostaglandin synthesis. “PGE2 is one of the prostaglandins that causes fever. It acts on four subtypes of prostaglandin receptors—EP1, EP2, EP3, and EP4—and knockout of the EP3 receptor impairs the febrile response to PGE2, IL-1, and bacterial lipopolysaccharide” (LPS).[10]

The benefit of fever to the organism is uncertain. It is presumably beneficial because it has evolved and persisted as a response to infections and other diseases. Many microorganisms grow best within a relatively narrow temperature range and a rise in temperature inhibits their growth. In addition, antibody production is increased when body temperature is elevated. Before the advent of antibiotics, fevers were artificially induced for the treatment of neurosyphilis and proved to be beneficial. “Hyperthermia benefits individuals infected with anthrax, pneumococcal pneumonia, leprosy, and various fungal, rickettsial, and viral diseases. Hyperthermia also slows the growth of some tumors. However, very high temperatures are harmful. A rectal temperature over 41 °C (106 °F) for prolonged periods results in some permanent brain damage”. When the temperature is over 43 °C, heat stroke develops and death is common.[8]

In malignant hyperthermia, various mutations of the gene coding for the ryanodine receptor lead to excess Ca^{2+} release during muscle contraction triggered by stress. This in turn leads to contractures of the muscles, increased muscle metabolism, and a great increase in heat production in muscle. The increased heat production causes a marked rise in body temperature that is fatal if not treated.

Periodic fevers also occur in humans with mutations in the gene for pyrin, a protein found in neutrophils; the gene for mevalonate kinase, an enzyme involved in cholesterol synthesis; and the gene for the type 1 TNF receptor, which is involved in inflammatory responses. However, how any of these three mutant gene products cause fever is unknown.[8]

Pyrogens:

"The febrile response is thought to be mediated by endogenous mediators, generically called endogenous pyrogens. In the classical model of pathogenesis, induction of fever is mediated by the release of pyrogenic cytokines such as tumor necrosis factor (TNF), interleukin (IL)- 1, IL-6, and interferons into the bloodstream in response to exogenous pyrogens. These mediators act at the level of the organum vasculosum of the lamina terminalis in the central nervous system (CNS), inducing synthesis of prostaglandins, which are the central mediators of the coordinated responses leading to fever. However, analysis of recent data suggests that multiple pathways may be involved in the induction of fever by cytokines, such as local cytokine production leading to signaling through vagal fibers, release of cytokine-induced circulating mediators at the tissue level, the use of membrane-bound cytokines as mediators, or the local release of cytokines in the hypothalamus by circulating activated monocytes. In addition, certain bacterial products can stimulate cytokine production directly at the level of hypothalamus, probably by activation of Toll-like receptors. A multipathway mechanism for the induction of fever is therefore suggested."[14]

"The current concept of fever physiology is that host cell – derived molecules induce fever. Three different cytokines – interleukin-1, (IL-1), Tumor Necrosis Factor (TNF) and Interleukin-6(IL-6) account for endogenous pyrogen activity, and it is clear that exogenous pyrogens by themselves do not cause fever unless they elicit cytokine release."[11]

Microorganisms, microbial toxins, Ag-Ab complexes, compliment components, drugs are examples of many different substances capable of causing fever. Lipopolysaccharides and peptidoglycans are are 2 common pyrogens in gram negative bacterias.[14]

Circulating Cytokines as EP

The role of proinflammatory cytokines in the pathogenesis of fever has been discovered at the end of the 1970s and the beginning of the 1980s, with the purification of IL-1 and demonstration of its pyrogenic properties. Later it became apparent that other cytokines such as TNF, IFNs, and IL-6 are also able to induce fever and can be considered independent EP.[14]

"IL-1a and IL-1b are considered to be the most important EPs. LPS is the most potent stimulus known for TNF production and release. TNF causes fever by affecting brain prostaglandin production. LPS binds to Lipopolysacharide Binding Protein (LBP) which is present in the normal human sera and its concentration rises 100-fold during acute phase response. LBP catalyses the binding of LPS to LPS receptor known as CD14, which is present on macrophages and granulocytes". This markedly enhances LPS induced inflammatory cytokine production by cells. Gram positive bacteria lack LPS, but contain peptidoglycon, Lipotechoic acid and a group of rhamnose glucose polymers. The basic structure responsible for peptidoglycan's pyrogenicity is

muramy1 peptide (MDP-N-acety1 muramy1- Lalanine- D-isoglutamine). Gram positive bacteria release exotoxins, which can also cause fever.

Exotoxins act by binding to Major Histocompactibility Complex – Class I molecules on antigen-presenting cells, which then is able to bind to T-cell receptor, which then become activated and release TNF and IL-1. The ability of exotoxins to activate large numbers of T-cells has led to its designation as superantigen.[11]

Figure 3

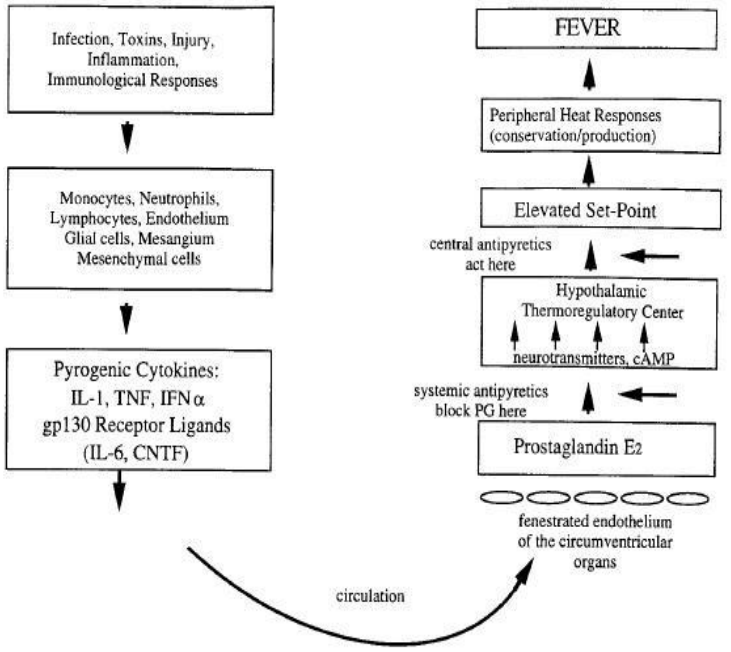


Figure 1. Scheme for pathogenesis of fever. IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; PG, prostaglandin; CNTF, ciliary neurotrophic factor.

Like interferon (IFN), TNF and IL-6, IL-1 is produced by many different (non leucocytic) cells and acts on many non leucocytic targets, hence these polypeptides are regarded as a special class of substances called "Cytokines"10. The following cytokines are known to be intrinsically pyrogenic, in that they produce rapid onset of fever by acting directly, on the hypothalamus (i.e. Without a requirement for the

formation of another cytokine): they are IL-1a, IL- 1b, TNF-y, TNF-B, IFN-a, IL-6. These now include a family of cytokines using the cell-signalling apparatus gp130. Cells using this receptor are pyrogenic and currently include IL-6, IL-11, oncostatin-M, Ciliary Neurotrophic Factor (CTNF), Cardiotrophin-1 and Leukemic Inhibitory Factor (LIF).[12]

Some endogenous molecules can also induce EP not requiring an exogeneous stimuli, for e.g. Antigen-antibody complexes, certain ancrogenic steroid metabolites, inflammatory bile acids, and some lymphocyte products. Endotoxin is an example of a pyrogen that can both act directly on the hypothalamus to cause fever and induce EP synthesis in various host cells, which then induce fever Eps reaching the brain via the systemic circulation do not actually penetrate the Blood Brain Barrier (BBB). It seems more likely that EPS have their effect on the rich vascular network close to the cluster of neurons in the preoptic anterior hypothalamus. These sites called the circumventricular organs or Organum Vasculosum Laminae Terminalus (OVLT), possess little if any BBB. Thus it is likely that endothelial cells lining OVLT either offer no resistance to the movement of EPS into the brain or release arachidonic acid metabolites themselves when they encounter EPS in circulation. Alternatively PGE2a and other prostaglandins might be produced by endothelial cells, which in turn induce a neurotransmitter – like substance that acts to raise the thermal set–point. PGE2 increases the levels of Cyclic AMP, which does have neurotransmitter properties in brain tissue and has been implicated in the pathogenessis of fever., IL–1 and TNF induced effects on vascular tissue would make the endothelial surface in OVLT a prime site of action of EPS, in the initiation of fever.[11]

Interleukins

Interleukin 1 (ILl - formerly called Lymphocyte Activating Factor) is a peptide of macrophage origin that stimulates T-lymphocyte proliferation in the presence of lectin or antigen and so enhances, or may even be essential for, immune responses. The mitogenic action of ILI on T cells is probably mediated by the lymphocyte product interleukin 2 (IL2). There is now substantial evidence, based on functional and biochemical properties, to indicate that EP and ILl are identical.[13]

IL-1 activates cultured vascular endothelial cells in < 1 hour at relatively low concentrations by inducing the expression of Inter Cellular Adhesion Molecule-1 (ICAM-1), on the cell surface. This molecule interacts with the leucocyte-glycopotein complex designated leucocyte function antigen.[13]

TNF

"TNF is a proinflammatory cytokine that shares many biologic properties with IL-1. TNF injection induces a typical fever in rabbits that is indistinguishable from IL-1. Moreover, TNF induces a second fever peak 3–4 h after challenge, which is suggested to be mediated through induction of endogenous IL-1 production. Recombinant human TNF is highly pyrogenic in humans, and the fever induced is rapid and associated with generalized malaise and joint pain. It is of note that when mice challenged with LPS were treated with TNF-soluble receptors or anti-TNF antiserum, they responded with higher temperature peaks. Similarly, TNF double receptor knockout mice responded with exacerbated febrile responses to LPS, showing that TNF has cryogenic properties in this model."[14]

Recombinant IL-1 and recombinant TNF both stimulate synovial cell production of PGE and collagenases, endothelial cell procoagulant activity and release of Platelet Activating Factor (PAF). Both molecules are cytotoxic for certain tumor cells and both induce hepatic Acute Phase Response (APR). In addition, lymphocyte activation, cytotoxicity for insulin producing-beta cells are also shared properties of IL-1 and TNF. The receptors for TNF, however are distinct from those of IL-1. TNF also has the property of inducing the production of IL-1 in vivo. TNF increase PGE2 production within 30 minutes. This property is shared by IL-1. Recent studies indicate the TNF-alpha, a lymphokine also known as lymphotoxin, shares considerable (78%) homology with TNF. The biological activity of TNF most often measured is its cytotoxic effect on various susceptible cells.[14]

Interferons

"IFNs were described as antiviral substances, with potent immunostimulatory activities such as enhanced expression of class I and II major histocompatibility complex antigens and stimulation of natural killer activity". When injected into rabbits, IFN-a induces a monophasic fever that peaks 80–90 min after the injection, which is mediated through induction of PG synthesis in the brain. "IFNs were the first cytokines to be administered to humans, and fever was a constant side effect encountered with treatments with IFN-a, IFN-b, or IFN-g. Species specificity made it difficult to study the pyrogenic properties of IFNs in animals, and it is still unclear whether some of the EP properties of IFNs are due to indirect stimulation of IL-1, TNF, or both".[14]

The concept of cytokines inducing other cytokines is vital to the understanding of how non-infectious disease produce fever. Vasculitis, rheumatoid arthritis, lupus, trauma, hemorrhage, thrombophlebites, drug fever and cancer are examples of non-infectious diseases in which both fever and acute phase response are common. Fever is also a prominent side effect of cancer chemotherapy, and the treatment of transplant rejection with antibodies to CD3 is also associated with fever. It has been implicated that in all these diseases cytokines such as IL-1, TNF and IL-6 are involved in pathogenic process.

In addition to the proinflammatory cytokines acting as direct EP, other endogenous inducers can have indirect pyrogenic properties through their capacity to induce synthesis of EP. Infusion of recombinant IL-2 into humans induces fever that starts 3–4 h after injection. However, the fact that by the time of fever, the IL-2 concentrations in the patients are low, and considering the capacity of IL-2 to induce production of IL-1 and TNF, together suggest that the pyrogenic properties of IL-2 are mediated through induction of IL-1 and TNF. Other potentially important endogenous inducers are granulocyte-macrophage–colony stimulating factor, immune complexes, and uric acid crystals, all molecules with pyrogenic potential through their capacity to induce production of IL-1 and TNF.

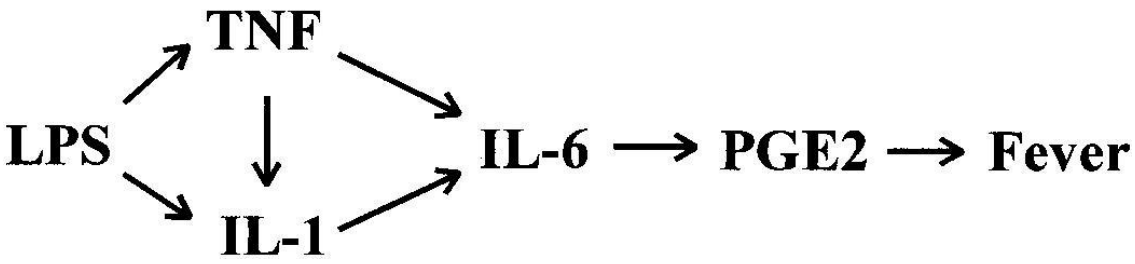
Circulating versus Local EP

A key event in the induction of fever in the "classical model of pathogenesis described above is the release of pyrogenic cytokines into the bloodstream to mediate the signal leading to a febrile response from the site of inflammation to the thermoregulatory center in the hypothalamus". However, there are aspects in the induction of fever that contradict this dogma. Experimental studies have shown that

after LPS injection, fever precedes the appearance of cytokines in the circulation. Clinical studies have failed in finding detectable levels of EP in specific patient groups with febrile conditions such as typhoid fever, fever of unknown origin, and Pneumocystis carinii pneumonia. In severe infections with septic shock, proinflammatory cytokines are detected in the circulation only for a short time compared with the period the duration of fever. In addition, release of high amounts of anti-inflammatory cytokines has a strong inhibitory effect on the action of pyrogenic cytokines. Moreover, continuous infusion of cytokines in animals leads to transient rather than ongoing fever. Although it is conceivable that a combination of cytokines acting at very low concentrations may provide the signal for the induction of fever or that as-yet unidentified pyrogenic cytokines act as circulating EP, there are data in the literature that suggest that alternative pathways besides circulating pyrogenic cytokines may efficiently induce fever in response to peripheric stimulation. [14,15]

"Production of cytokines at the tissue level has been suggested as an alternative pathway for the induction of the signal leading to fever, rather than in circulation. Local production of proinflammatory cytokines in the infected tissues may induce release of secondary mediators with pyrogenic properties". One possible candidate for this role may be soluble type II phospholipase A2. Phospholipase A2 can stimulate PG synthesis at the OVLT level, and it has been suggested to function as EP. However, the arguments for its involvement in the pathogenesis of fever are circumstantial, and infusion of recombinant phospholipase A2 into rabbits have failed to induce fever.[14,15]

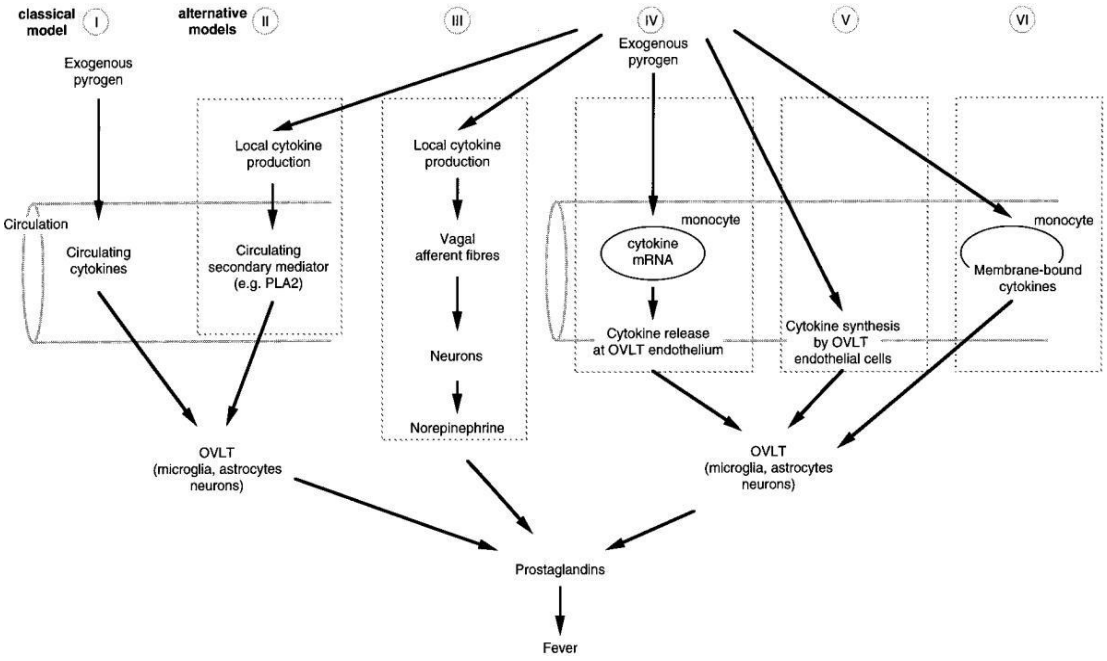
Figure 4



Release of EP at the CNS Level

"In addition to production and release of proinflammatory cytokines in the peripheral tissues and in the circulation, release of these mediators at the level of the OVLT endothelium may also represent an important mechanism in the induction of fever". In this model, activation of monocytes may result in little or no production of cytokines. However, the activated monocytes may subsequently enter the bloodstream and adhere to the endothelium in the circumventricular organs, where release of EP from either the monocytes themselves or from endothelial cells can induce the signal leading to fever. Indeed, activated monocytes are present in the bloodstream with low or absent circulating cytokine concentrations, and production of cytokines by perivascular cells in the circumventricular organs has been demonstrated

Figure 5



The classical model for the induction of fever, in which circulating pyrogenic cytokines represent the key event.[14]

An important pathway through which exogenous pyrogens such as LPS may induce fever is through direct induction of proinflammatory cytokine production by endothelial cells in the circumventricular organs. It has been recently discovered that the signaling chain of the LPS receptor is a member of the Toll-like receptor (TLR) family. In humans there are at least 5 TLRs, and it appears that TLR4 is involved in mediating the intracellular signals to LPS. Although LPS has a relatively low affinity for TLR4, its binding is greatly enhanced by CD14 in either membrane or soluble form. An additional important factor for the ligand-receptor interaction is a plasma factor, LPS-binding protein, which transfers LPS from the circulating micellae to the receptor complex.

Interestingly, an intracytoplasmic domain of the TLRs is homologous to a segment of the IL-1R type I, resulting in striking similarities in the intracellular signals induced by LPS and IL-1, respectively. In terms of fever, injection of a small amount of LPS into rabbits induces a monophasic fever identical to that observed after IL-1 or TNF, probably through intermediary production of IL-6. These findings provide the theoretical basis for the hypothesis that certain bacterial products can circumvent the need of stimulating a circulating EP in order to be able to induce fever.[14]

Historical overview of the role of platelets

"The existence of a constant blood particle, differing from red and white blood cells, has been suspected by several authors for some time"

With this simple opening statement, in 1882 Giulio Bizzozero started his paper on a new blood particle and its role in thrombosis and blood coagulation.

"Platelets were discovered by G. Bizzozero in 1882 and rediscovered in the 1960s after many decades of oblivion. Interestingly enough, their role was initially more clearly associated with thrombosis than with hemostasis. For many years a serious unresolved problem was that the clotting time was normal even in severe thrombocytopenia. The concept of coagulation as an enzymatic cascade had not yet been elaborated".

During the 1960s, the interest of many experts moved from the interaction of platelets with the process of blood coagulation to the interaction of these cells with the vascular wall (adhesion) and each other (aggregation). The discovery of the role of ADP as the principle of platelet aggregation stimuli was rapidly followed by other important discoveries such as the aggregating properties of collagen and thrombin, the

release reaction, the metabolism of arachidonic acid, and the inhibitory effect of aspirin. The use of aspirin as a potential antithrombotic drug has made the history of clinical trials in the last 30 years. The last two decades have been characterized by an explosion of cell and molecular biology approaches. There are presently people who study platelet signal transduction or platelet-leukocyte interactions but who know almost nothing about hemostasis or thrombosis. This is due not only to the intrinsic limitations of the biological approach but also to the progressive recognition of the role of platelets in other physiopathologic and clinical conditions such as inflammation, cancer growth and dissemination, and organ transplant rejection.

Overlooked for more than two centuries after the microscope was made available to hematologists, considered as an artifact or a Cinderella, the platelet has mainly been considered in the past 30 years as a dangerous cell to be inhibited by drugs.[16]

"It was only in 1883 – the year after Bizzozero's publication – that Krauss, in his inaugural dissertation in Heidelberg, mentioned that his chief, Dr. Brohme, had noted a marked decrease of platelets in the blood of children with purpura hemorrhagica. It was, however, Hayem who firmly established the relationship of platelets to purpura a few years later".[16]

Both Bizzozero and Hayem presented evidence that platelets (or hematoblasts) participate in the early phase of blood coagulation, as they observed that fibrin strands appear at loci where platelets adhere and undergo morphologic changes. "Both investigators concluded that platelets supply a factor needed in the clotting reaction. However, the observation that the clotting time was normal even in severe

thrombocytopenia led many other investigators to conclude that platelets are not necessary in the coagulation of blood".

Despite the excellency of these and other contributions, the platelet remained for many years the neglected stepchild in the family of blood cells. Finally, around 1960, the platelet emerged from the Cinderella stage to that of royal prominence. The work by Hugues and Bounameaux in Roskam's group in Liège showed that the collagen component of connective tissue leads to platelet adhesion and aggregation culminating in viscous metamorphosis. Some other important discoveries were made at about the same time: the isolation and description of a contractile protein resembling actomyosin in platelets, and the recognition that adenosine- 5'-diphosphate (ADP) is a potent inducer of platelet aggregation.

This only attained its full significance with the observation that platelets themselves, under the influence of a suitable agent such as thrombin, release enough of this dinucleotide to induce their own aggregation. The recognition of this phenomenon remains a most important step in the understanding of the mechanism of platelet aggregation, which accordingly appeared as a self-perpetuating process.

"In the years 1967-1968, aspirin and the platelet met each other officially for the first time and a never-ending story was begun. In reality, already in the fifties French investigators, had observed that aspirin, in relatively small doses, resulted in a prolongation of bleeding time. They also noted that this effect was exaggerated in patients who had underlying bleeding disorders. These clinical observations were confirmed in the USA by Quick who also made the important observation that, unlike aspirin, sodium salicylate had no effect on bleeding time".[17]

The general conclusion was that aspirin – possibly by a poorly defined platelet membrane stabilizing effect – inhibited the platelet release reaction. The effects of aspirin ingestion occurred very rapidly but were of long duration (4 to 7 days), suggesting an irreversible damage to platelet population, which persisted until the affected platelets had been replaced by a sufficient number of new platelets. The critical role of the acetyl group in the aspirin effect was also rapidly singled out. Altogether, these findings reasonably explained the mild hemostatic defect produced by aspirin and indicated that it should be avoided in patients in whom control of hemostasis could be a problem.[16,17]

Platelets – morphology and role in the body

"Platelets are the smallest of the three major types of blood cells. Platelets are only about 20% of the diameter of red blood cells. The normal platelet count is 150,000-350,000 per microliter of blood, but since platelets are so small, they make up just a tiny fraction of the blood volume". The principal function of platelets is to prevent bleeding. Platelet Production- "Platelets are produced in the bone marrow, the same as the red cells and most of the white blood cells. Platelets are produced from very large bone marrow cells called megakaryocytes. As megakaryocytes develop into giant cells, they undergo a process of fragmentation that results in the release of over 1,000 platelets per megakaryocyte. The dominant hormone controlling megakaryocyte development is thrombopoietin (often abbreviated as TPO)".[18]

Platelet Structure-

"Platelets are actually not true cells but merely circulating fragments of cells. But even though platelets are merely cell fragments, they contain many structures that are critical to stop bleeding. They contain proteins on their surface that allow them to

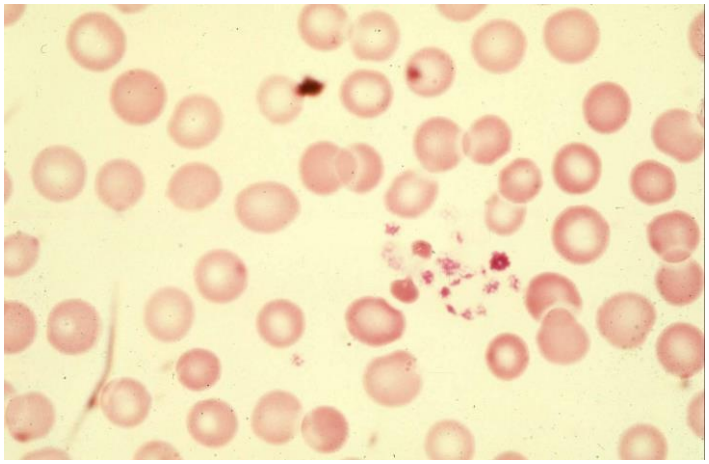
stick to breaks in the blood vessel wall and also to stick to each other. They contain granules that can secrete other proteins required for creating a firm plug to seal blood vessel breaks. Also platelets contain proteins similar to muscle proteins that allow them to change shape when they become sticky".

They are shaped like a plate, therefore their name. When platelets are stimulated by a break in the blood vessel wall they change shape as shown in the other three pictures. They become round and extend long filaments. They may even look like an octopus, with long tentacles reaching out to make contact with the broken blood vessel wall or with other platelets. With these long filaments, platelets then form a plug to seal the broken blood vessel.[18]

Platelet Function-

"In addition to being the smallest blood cell, platelets are also the lightest. Therefore they are pushed out from the center of flowing blood to the wall of the blood vessel. There they roll along the surface of the vessel wall, which is lined by cells called endothelium. The endothelium is a very special surface, like Teflon, that prevents anything from sticking to it. However when there is an injury or cut, and the endothelial layer is broken, the tough fibers that surround a blood vessel are exposed to the liquid flowing blood. It is the platelets that react first to injury". The tough fibers surrounding the vessel wall, like an envelop, attract platelets like a magnet, stimulate the shape change that is shown in the pictures above, and platelets then clump onto these fibers, providing the initial seal to prevent bleeding, the leak of red blood cells and plasma through the vessel injury.

Figure 6



The color photograph is a microscopic picture of a drop of blood spread out onto a glass slide. The magnification is not as high as the pictures above, so the platelets seem very small. It can be seen that as the platelets touch the glass, they begin to stick together forming a long string. This illustrates the basic function of platelets, to stick to any foreign surface and then to stick together. The red blood cells in this picture are normal, with their round shape and their thin center.[18]

Platelets in hemostasis.

"Platelets contribute to the hemostatic process in two different ways. First, through their adhesive and cohesive functions that lead to the formation of a hemostatic plug. Second, they can activate coagulation mechanisms through the exposure of an adequate phospholipidic surface, acting as a catalytic site for the development of coagulation and the consolidation of the hemostatic plug. To promote a correct hemostasis, platelets should ideally retain their adhesive and procoagulant properties".

Platelets possess important secretory functions. During the process of activation, platelets express internal membrane proteins and release adhesive proteins, coagulation and growth factors. Some of the proteins facilitate the cross-talk of platelets with leukocytes and endothelial cells. Thus platelets play and important role in imflamatory and proliferative events and play a critical role for tissue remodeling and wound healing. [19]

Figure 7

Scanning electron micrographs of different stages of platelet adhesion are shown: Resting platelet (left, x10,000); Attached platelet showing shape change and pseudopodia emission (center, x3,000); Spread platelet (right, x3,000).[19]

Platelet morphology

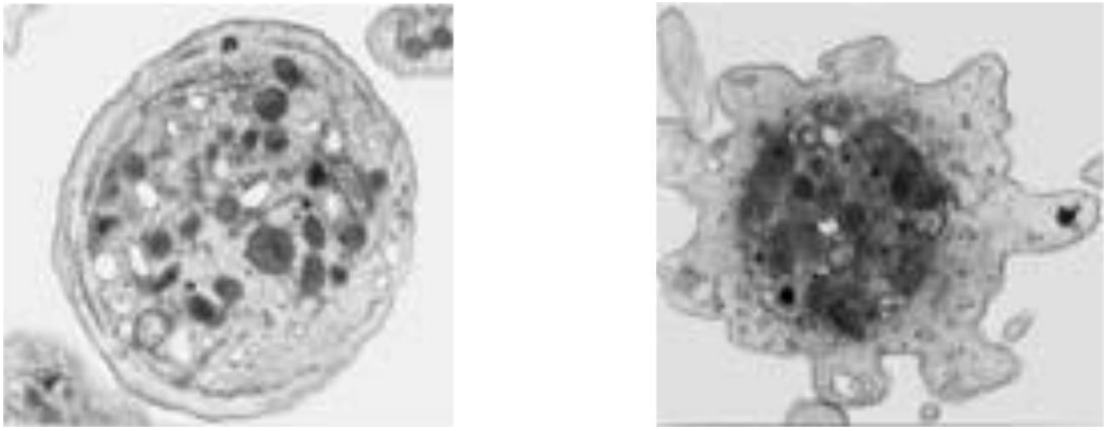
Platelets are 2.5 μm in average normal diameter and have a discod shape. The resting platelet is divided into three zones:

"Peripheral zone: responsible for adhesion and aggregation. Consists of fluffy glycocalyx coat, cytoskeleton and platelet membrane. Contains absorbed coagulation factors I, V, VIII, XI, XII, receptors for ADP, thrombin, vWF, collagen, fibrinogen, fibrin, fibronectin, epinephrine, PAF, thrombospondin, thromboxane A2, prostacyclin, epinephrine, serotonin and glycosyl transferase".

Sol-Gel zone: responsible for contraction and support microtubule system. Contains the connecting system called the open canalicular system and the dense tubular system.

Organelle zone: contains the dense body system, non-metabolic ADP, serotonin, catecholamines, calcium, alpha granules; platelet factor 4, platelet mitogenic factor, fibrinogen, beta thromboglobulin, lysosomal granules, mitochondria and glycogen granules.[19]

Figure 8



Electron micrographs from a resting platelet (left, x10,000), or from an activated platelet showing pseudopodia emission (right, x5,000).[19]

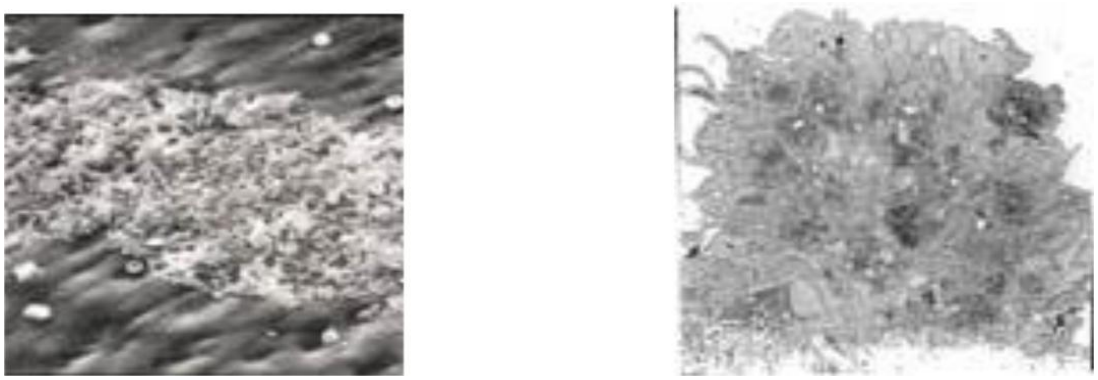
Adhesion and Aggregation.

Initial attachment of platelets onto vascular subendothelium is a critical step for hemostasis. Several factors are known to participate in platelet-subendothelium interactions: subendothelial and plasma adhesive proteins, their receptors on platelet membrane, and rheological factors. Alteration of any of these factors may imply disorders of physiologic hemostasis, leading to thrombosis or bleeding episodes.

"Laminin, von Willebrand factor, fibronectin, and different types of collagen are the main components of subendothelial structures. It is known that the binding of von Willebrand factor to subendothelium and to platelet glycoprotein Ib is of critical importance for platelet attachment to subendothelial components. Subsequent platelet spreading and aggregate formation is mediated by platelet glycoprotein IIb-IIIa".

The contribution of platelets to hemostasis does not depend exclusively on adhesive and cohesive functions mediated by membrane receptors. Activated platelets offer a phospholipid surface of critical importance for the activation of coagulation mechanisms[19].

Figure 9



Electronic micrographs showing some attached and aggregating platelets on a thrombogenic surface (left, x1,000) and a cross-section of a thrombus (right, x5,000).

"Platelet activation takes place after attachment and adhesion events or after other stimuli that triggeres activation mechanisms such as thromboxane A2, ADP, thrombin or PAF (platelet activating factor, released from endothelial cells, PMN or monocytes)".

"In a first step of activation, platelets undergo shape change, cytoskeleton rearrangement and organelle centralization. Release of dense granule contents (ADP and ATP) and serotonin, occurs. In a second step, there is alpha granule release of fibrinogen, fibronectin and vWF, exposure of fibrinogen and fibronectin receptors on platelet surface, and finally, release of arachidonic acid to be converted to thromboxane A2, which is a powerful mediator of platelet aggregating response". Cyclooxygenase is the key enzyme responsible for synthesis of thromboxane A2 in platelets. Aspirin and other anti-inflammatory drugs interfere with an early step of prostaglandin pathway, suppressing the formation of pro-aggregatory cyclic endoperoxides precursors of thromboxane A2.

Mediators involved as receptors, molecular mechanisms, signaling pathways and platelet responses that are triggered after activation, as well as their regulatory and modulatory mechanisms :

- Actin polymerization and lamellipodia formation
- Granule content secretion
- Arachidonic acid mobilization
- Phospholipid scrambling and coagulation
- PAF thrombin receptors (Gi, Gq and G12/13)
- Thromboxane A2 receptors (Gq and G12/13)
- P2Y1 and P2Y12 ADP receptors (Gi and Gq)
- Glycoprotein Ia-IIa
- Glycoprotein Ib-IX-V
- Glycoprotein IIb-IIIa
- Glycoprotein IV
- Glycoprotein VI

Cellular interactions between platelets and vascular endothelium or other blood cellular components regulate the hemostatic process. Platelets can even interact and play a role in the activity of pathologic elements such as tumoral cells or infectious agents. Moreover, it has been described that platelet interactions can interfere with the effectivity of antiplatelet drugs.

Vascular endothelium: The endothelium does not form a passive barrier for bloodcirculation. “Endothelial cells and several of their active metabolites, including eicosanoids such as prostacyclin (PGI2) and endothelial-derived relaxing factor (nitric oxide), are known to directly influence platelet reactivity”.

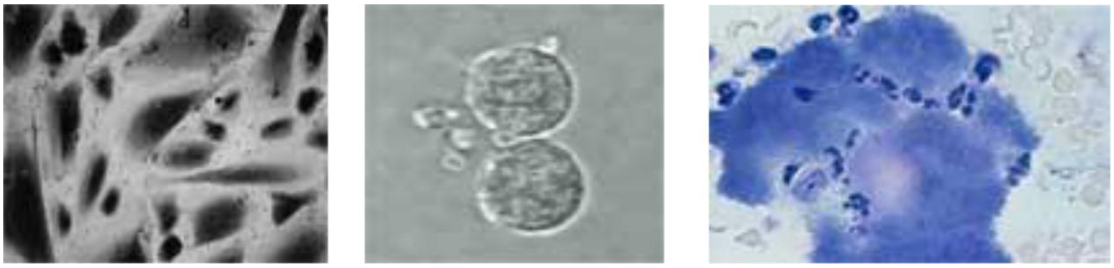
Leukocytes: The activating and inhibitory mechanisms triggered by the interactionsbetween platelets and leukocytes are widely recognized. Lipoxygenase products and several surface glycoproteins play a role in platelet-leukocyte cross-talk, which is favored by pathophysiologic events at sites of inflammation, thrombosis and vascular injury.

Erythrocytes: Red blood cells play an important role in modulating platelet reactivity withsubendothelial structures, mainly through rheological mechanisms (i.e., erythrocyte deformability and erythrocyte aggregation), although the influence of red cell metabolites on platelet functions is also important.

Tumoral cells: Platelet ability to interact with tumor cells is involved in the success of metastatic spread. Moreover, thrombotic events are often associated with cancer due to the capacity of tumor cells to produce and secrete procoagulant/fibrinolytic substances and inflammatory cytokines.

Infectious agents: Platelet binding by bacterial pathogens is thought to facilitate theestablishment of certain infections. Furtehrmore, association of virus with platelets may represent a viral transfer and a passive vehicle for viral dissemination.

Figure 10



Left: endothelial cells in culture (micrograph by M. Diaz-Ricart); middle:platelet-leukocyte heterotypical aggregation (micrograph by M.R. Hernández) ; Right: platelet and leukocyte interaction with a tumor cell (micrograph by A. Ordinas).[19]

PLATELETS AS IMMUNE CELLS IN INFECTIOUS DISEASES

Besides their role in hemostasis, they have immunological functions and thus participate in the interaction between pathogens and host defense. “Platelets have a broad repertoire of receptor molecules that enable them to sense invading pathogens and infection-induced inflammation. Consequently, platelets exert antimicrobial effector mechanisms, but also initiate an intense crosstalk with other arms of the innate and adaptive immunity, including neutrophils, monocytes/macrophages, dendritic cells, B cells and T cells”. There is a fragile balance between beneficial antimicrobial effects and detrimental reactions that contribute to the pathogenesis, and many pathogens have developed mechanisms to influence these two outcomes.[20]

Immunocompetence of Platelets

Despite being acaryote cell fragments, platelets share a number of properties of host defense with their big nucleated relatives and represent important elements in innate immunity. For these purposes, they have developed a number of physiological skills. They sense pathogens by various surface receptors, attach to them and become activated, thereby releasing the content of their granules. Consequently, antimicrobial peptides exert direct effects against pathogens, and a number of cytokines/chemokines attract and activate other immune cells. Endocytosis of pathogens, production of reactive oxygen species (ROS) and various interactions with the complement system and cells of the innate and adaptive immune systems could be shown, as described in the following sections. All these mechanisms support the fight against infections, but can also harbor deleterious sequelae such as thrombosis and exceeding inflammatory reactions. Since platelets can be described as immune cells with a broad range of antimicrobial functions, it is difficult to decide which function or aspect is the most relevant for the clinical outcome.[21]

Box 3. Antimicrobial capacities and effector mechanisms of platelets.

(A) Sensing of pathogens & pathogen-induced inflammation
GP1ba Direct binding of bacterial surface proteins or via vWF as bridging molecules GPIa–IIa (α 2 β 1 integrin) Binding of rotavirus VP4 surface protein GPIIb–IIIa (α 2b β 3 integrin) Direct binding of bacterial surface proteins or via fibronectin and fibrinogen as bridging molecules; binding to adenoviru s and hantavirus GPVI Binding of HCV TLRs Direct binding of bacterial LPS FcγRIIa (CD32) Binding of IgG in immune complexes with all pathogens Complement receptor(s) Binding of complement factors bound on pathogen surface Direct binding of EBV by CR2 Binding of anaphylatoxins by C3aR and C5aR Thrombin receptors Bacteria-induced TF catalyzes thrombin generation that activates platelets Cytokine/chemokine receptors Sensing of inflammatory cytokines and chemokines Binding to HIV N -formyl peptide receptors Binding of bacteria-derived formyl peptides with subsequent gradient-driven chemotaxis C-type lectins Binding of HIV to DC-SIGN and CLEC-2 CAR Binding of adenovirus

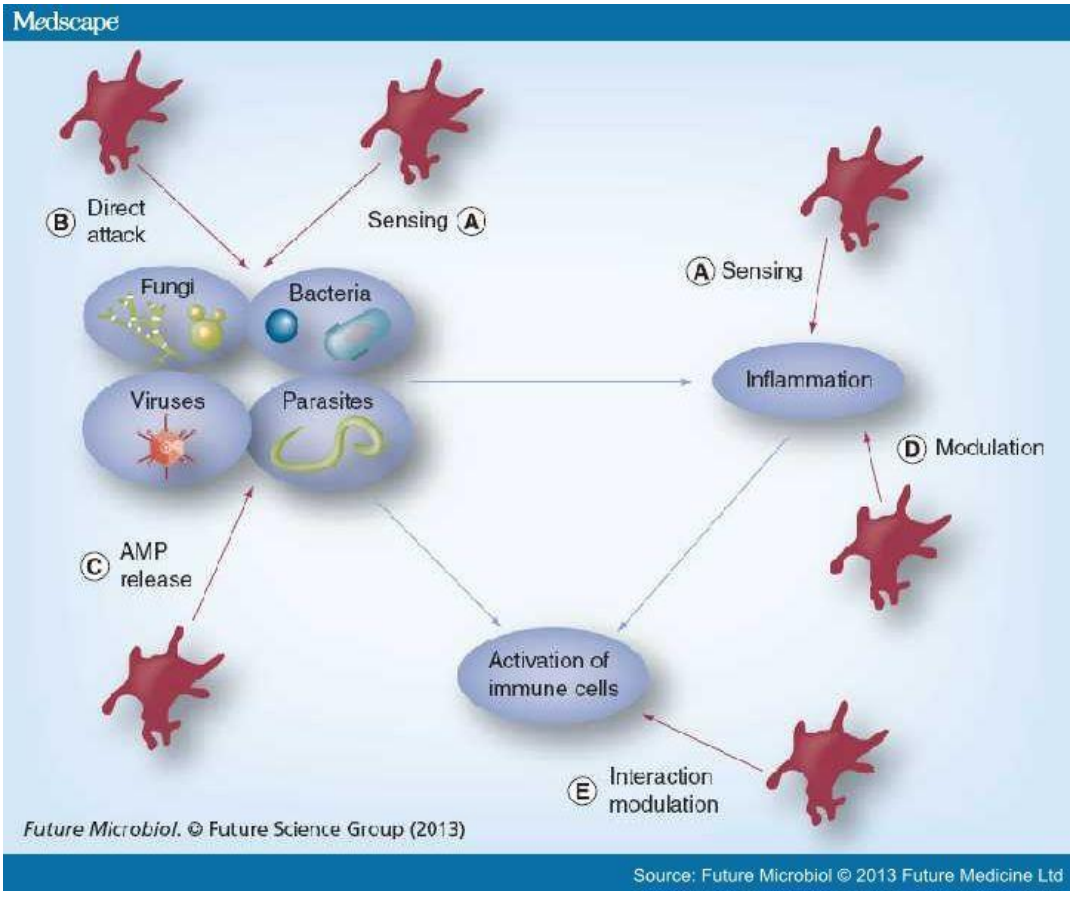
(B) Antimicrobial attack
Endocytosis, internalization Platelets endocytose IgG-containing immune complexes Platelets internalize HIV Activated platelets can uptake Staphylococcus aureus ROS Platelets stimulated via TLR2 or ITAM receptor generate ROS Platelets triggered by bacterial LPS generate ROS
(C) Release of antimicrobial peptides & enhanced efficiency of antimicrobial drugs
Thrombocidins Directly active against some bacteria and yeasts Enhance the fungicidal effect of antimycotic drugs Kinocidins Class of chemokines and chemokine-derived fragments with antimicrobial properties Serotonin Affects hyphal growth and fungal cell membrane integrity Enhances the activity of amphotericin B against Aspergillus
(D) Modulation of inflammation
Microparticles Platelet-derived microparticles deliver CD154 signaling Cytokines/chemokines Platelets secrete a variety of pro- and anti-inflammatory chemokines and cytokines; for example, IL-1, IL-8, CCL5, NAP-2, MIP-1α and PF4, among others, which also activate endothelial cells

(E) Interaction with other immune cells (i) Phagocytes (neutrophils & monocytes/macrophages)
Chemotaxis Platelets secrete cytokines/chemokines that attract neutrophils and monocytes or T cells to the site of infection Respiratory burst Platelets potentiate the bacteria-induced respiratory burst in neutrophils Enhancement of phagocytosis Platelets deliver immune complexes to neutrophils, monocytes for destruction Neutrophils, when aggregated with platelets, show enhanced clearance of bacteria Enhancement of cytokine secretion Activated platelets stimulate macrophages to secrete TNF-α, IL-6 and IL-23 Induction of neutrophil degranulation Platelets enhance the release of defensins, myeloperoxidase and lysozyme by neutrophils Enhancement of NET generation TLR-4 on platelets activates NET formation by neutrophils to ensnare bacteria in sepsis
(ii) Interaction with other immune cells: dendritic cells
Induction of maturation and activation Platelets stimulate maturation and activation of dendritic cells
(ii) Interaction with other immune cells: adaptive immune cells (B cells & T cells)
Support of IgG antibody production by B cells Platelet receptor CD154 interacts with CD40 on B cells and triggers B-cell

proliferation, differentiation, isotype switching and memory B-cell generation T-cell activation Platelets process and present antigen via MHC class I Platetets express T-cell costimulatory molecules Platets induce differentiation, cytokine production and direct activation of naive T cells in a MHC class I-dependent manner Germinal center formation by T cells Platelets cooperate with T cells to enhance germinal center formation [22]

Ref - Future Microbiol. 2013;8(11):1431-1451.

Figure 11



Antimicrobial capacities and effector mechanisms that can be exerted by platelets.

Platelets have various functions that target the different pathogens; however, they also modulate the extent of inflammation and interact with other immune cells of innate and adaptive immunity.

Platelet Receptors to Recognize Pathogens &/or Pathogen-induced Inflammation

A variety of surface receptors enable platelets to sense the presence of invading pathogens or induced inflammation. GPIIb/IIIa (α 2bβ 3 integrin) is platelet-specific and the most abundant receptor on the plasma membrane; its ligands fibrinogen and fibronectin can, when bound to the pathogen surface, act as bridging proteins, mediating adhesion of microbes to GPIIb/IIIa on platelets and subsequent activation. Direct binding of GPIIb/IIIa to bacteria and viruses is also possible.[24,25]

GPIbα is another surface receptor exclusively expressed on platelets and megakaryocytes, and can attach to bacteria either directly or with vWF as a bridging molecule; however, not all of these binding reactions result in platelet activation. The platelet glycoproteins GPIa/IIa (α 2β 1 integrin) and GPVI (a member of the Ig superfamily and primary signaling receptor for platelet activation by collagen) are also capable of binding viruses.[24]

Platelets express the Fc receptor FcγRIIa, which binds to IgG in immune complexes with all pathogens. It plays an important role in pathogen-induced aggregation and/or activation of platelets and can also enhance interactions mediated by GPIIb/IIIa and GPIbα.

Toll-like receptors (TLRs) are a family of receptors that play a key role for sensing conserved pathogen-associated molecular patterns. Platelets were shown to express TLR1– 9 to respond to a broad range of foreign molecules. Platelet activation, release of immunomodulatory agents, activations of other cells and presentation of pathogens for phagocytosis are mediated by TLRs. For example, TLR2 recognizes a variety of bacterial structures such as lipoproteins, lipoteichoic acid and peptidoglycan, but also viral structural proteins and fungal β-glucan and mannan.

TLR4 is another central receptor on platelets that mediates recognition of bacteria, but also interaction with and activation of neutrophils. A newly discovered electron-dense tubular system-related compartment, called T granule, has been shown to harbor TLR9 in particular, which is found in bacterial and viral DNA.[25]

The complement system, triggered by different pathways, implements multiple functions, including direct and indirect antimicrobial host defense (e.g., cell lysis, opsonization and chemotaxis). The reciprocal activation of complement and platelets guarantees an optimal immune network. Stimulated platelets and platelet microparticles could be demonstrated to mediate complement activation by exposure of P-selectin (CD62P), complement receptor gC1qR or chondroitine sulphate. Furthermore, the expression of complement receptors CR2, CR3, CR4, C3aR, C5aR, gC1qR and cC1qR were shown on platelets. However, the precise functions of complement–platelet interactions in host defense and inflammatory processes remain to be clarified. A range of cytokine/chemokine receptors on platelets can sense the pathogen-induced inflammatory reaction and induce activation, aggregation and release of granule contents. [26]

Platelet Microbicidal Peptides

Antimicrobial peptides are small, cationic, amphipathic polypeptides that mainly target microbial cell membranes, but may also affect intracellular molecules or cell walls of microbes. Platelets store a variety of platelet microbicidal peptides (PMPs), also called thrombocidins, in their α-granules. They are released during platelet activation and can kill a range of bacteria, fungi and viruses. Several PMPs are related to the CXC and CC chemokine families; these peptides are termed kinocidins. For example, platelet factor-4 (PF-4; CXCL4), PBP and NAP-2 are members of the CXC chemokines, while RANTES and MIP-3a belong to the CC family. More detailed overviews are given in. Kinocidins indeed show both microbicidal activity and properties of classical chemokines, such as attraction and activation of phagocytes and lymphocytes. Recently, extragranular occurrence of β-defensin 1 was detected in platelets, which exerts potent antimicrobial properties. This multitude of PMPs generated by platelets underlines their role as important antimicrobial players. The storage both in granules and in the cytoplasm guarantees that

PMPs are released both by pathogen-induced platelet activation and by pathogen-induced platelet damage.[27]

Interaction of Platelets With Bacterial Pathogens

Bacteria enter the bloodstream in response to infectious insults, via surgical procedures or indwelling catheters, and sepsis occurs in up to 6–30% of all intensive care unit patients. The balance of pro- and anti-inflammatory reactions critically determines the severity and lethality of sepsis, a fact that turns the spotlight onto understanding the immune reaction in order to develop appropriate therapies.[28]

Bacterial contact with the platelets is a key event for the pathogenesis of sepsis, as deduced from the correlation between sepsis outcome and decreased platelet numbers: the more profound the thrombocytopenia the more severe the sepsis and the greater the mortality of affected patients.

There are two main causes for the bacteria-induced thrombocytopenia:

- Bacteria induce platelet activation. Activated platelets show shortened survival and are targets of phagocytic clearance
- Bacterial compounds induce apoptosis and cytotoxic effects in platelets.

Both main mechanisms can complement and overlay each other.[29]

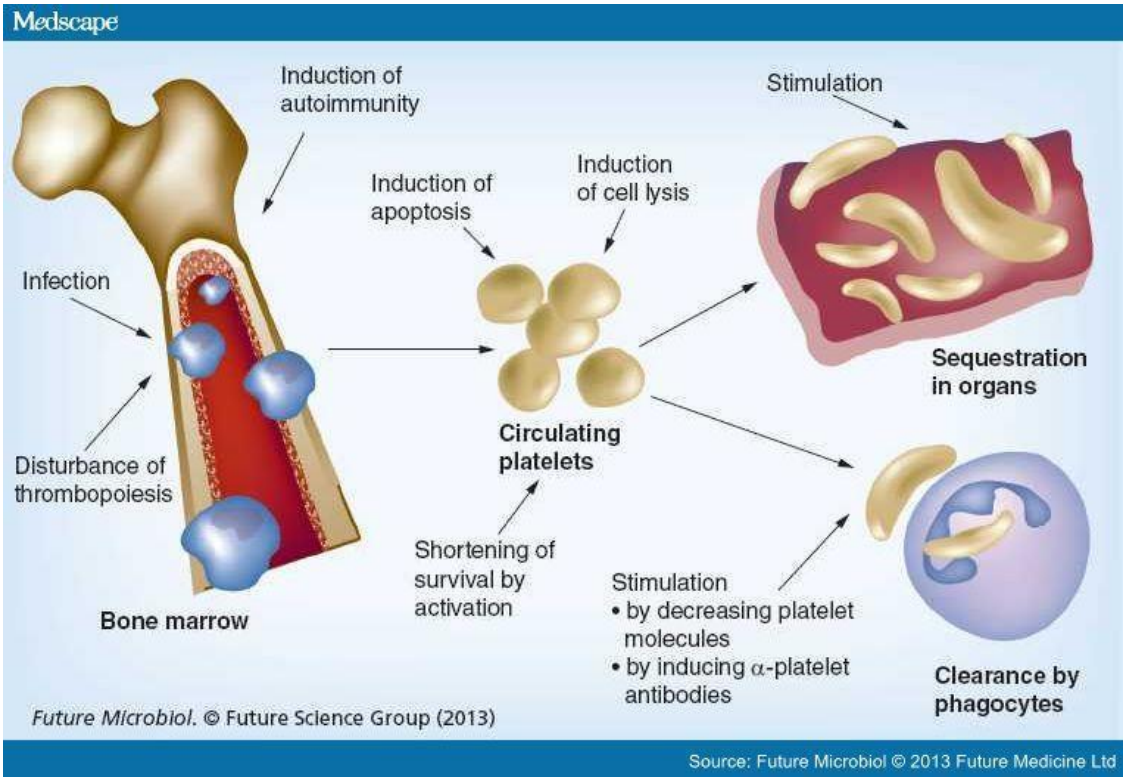
Box 4. Platelet evasion and exploitation mechanisms exerted by microorganisms.

Induction of thrombocytopenia
Induction of activation and phagocytosis Survival of platelets is shortened after activation by contact with pathogens; for example, in adenovirus infection, by HIV Tat protein, fungal pathogens (Aspergillus, Candida and Mucormycetes) and secreted compounds of Aspergillus Enhanced platelet phagocytosis by macrophages by inducing downmodulation of platelet CD47 Induction of apoptosis and cell lysis Staphylococcus aureus and Escherichia coli, as well as their secreted toxins, trigger degradation of the antiapoptotic protein Bcl-x L in platelets Bacterial cell wall peptidoglycan stimulates platelet apoptosis The toxins streptolysin O of Streptococcus pyogenes and pneumolysin of Streptococcus pneumoniae form pores in the platelet membrane Dengue virus

infection induces platelet apoptosis Induction of antiplatelet autoimmune antibodies via molecular mimicry Antibodies against microbial antigens of HIV, HCV, Dengue virus and Helicobacter pylori cross-react with platelet glycoproteins Affecting thrombopoiesis in the bone marrow HIV proteins interact with the cell surface of platelet progenitor cells, thus inducing functional defects Mimicry of viral proteins induces autoimmune antibodies that inhibit megakaryocyte differentiation Megakaryocytes are infected by HIV, HCV, CMV and HHV-6 HIV modifies the cytokine pattern in the bone marrow that is necessary for thrombopoiesis Production of thrombopoietin, a growth factor for megakaryocyte differentiation, is impaired in HCV-induced liver disease Sequestration of platelets in the enlarged spleen HCV-induced portal hypertension results in platelet sequestration in the spleen
Impairment of platelet activation/aggregation
Direct interaction Candidal and cryptococcal cells impair platelet aggregation Secreted metabolites Fungal gliotoxin impairs platelet activation and aggregation
Resistance to antimicrobial peptides
Modification of net surface rate S. aureus isolates reduce surface-positive charge thus altering tPMP susceptibility, less charge is associated with enhanced resistance Efflux pumps Staphylococci export tPMP-1 via the multidrug efflux pump QacA

Exploitation of platelets
Endocytosis by platelets shelter pathogens from immune attack Enclosure of HIV within platelet vesicles protects the virus from antimicrobial peptides and attack by other immune weapons Transport of pathogens throughout the body Platelets disseminate endocytosed HIV in the whole body Platelets transport HCV to the liver Replication Viruses can infect and replicate in platelets and megakaryocytes Platelet-derived chemokines can attract susceptible host cells to the site of viral infection[22]

Figure 12



Mechanism for pathogen induced thrombocytopenia

Pathogens can interfere with platelet production in the bone marrow by either infecting the precursor megakaryocytes, by induction of autoimmune antibodies that trigger elimination of the megakaryocytes or by disturbance of thrombopoiesis via dysregulated cytokines or thrombopoietin. Pathogens can also target circulating platelets and induce apoptosis or cell lysis. In addition, platelet activation after contact with the microorganisms shortens their lifespan. Furthermore, pathogens can induce removal of platelets from the circulation by stimulating their sequestration in organs or by triggering their clearance by phagocytes.

Platelets' Benefit in Bacterial Infection: Direct Attack & Guidance of Other Immune Cells

Bacteria-induced platelet activation, apoptosis or disintegration are all processes that result in the release of microbicidal peptides and thus contribute to pathogenelimination. Granule-stored PMPs are secreted by platelet activation, whereas apoptosis or disintegration lead to release of PMP stored in both granules and cytoplasm.

This PMP secretion is a key contribution of platelets to the immune defense against bacterial pathogens. Its relevance was unambiguously proven in vivo using animal models for bacteria-induced infective endocarditis (IE), where thrombocytopenic animals were more susceptible to IE than controls. Detailed in vivo studies directly underlined the efficiency of PMP for antibacterial defense, since rabbits where PMP had been neutralized by antibodies were more susceptible to streptococcal IE than controls. Further experiments revealed an inverse correlation between bacterial virulence and the stimulation of PMP release: those S. aureus variants that activated platelets to a high extent showed reduced virulence. In particular, the microbicidal proteins thrombin-induced platelet microbicidal protein (tPMP)-1, -2 and -3 were supposed to participate in this effect. Strains of S. aureus that were insusceptible to the thrombocidin tPMP caused more severe IE and more effective hematogenous dissemination than did tPMP-susceptible strains.[30,31,22.]

The 'Dark Side' of Platelets in Bacterial Infections

Platelet activation after contact with bacterial pathogens or their secreted compounds can result in detrimental events such as thrombosis and thus might critically contribute to pathogenesis. Thrombotic manifestations can be localized or

occur widespread in the blood vessels of different organs with organ dysfunction as putative consequence. The most severe form is a disseminated intravascular coagulation, characterized by intense microvascular thrombosis, consumption of platelets and coagulation factors, and bleeding. Bacteria-induced platelet activation directly leads to aggregation, and thrombosis is further aggravated by the fact that platelets augment net formation with deposition of platelets and neutrophils.[32]

Another negative effect of platelets in bacterial infections is the enhancement of biofilm formation. Platelets were demonstrated *in vitro* and *in vivo* to be essential for biofilm generation by streptococci. The biofilms on injured heart valves were composed of bacteria embedded in platelet aggregates; the bacteria in the biofilm were able to induce further platelet aggregation, which facilitates the formation of multilayer biofilms. Thus, platelets are hijacked by the streptococci to support biofilm formation and to subsequently

favor survival of the bacteria in the host. In addition, bacteria in this platelet-containing biofilm were refractory to antibiotic treatment.[33,22]

Platelets in Viral Infections

The relevance of virus–platelet interactions for the pathogenesis of viral infections can be deduced from the fact that thrombocytopenia is a common complication of a variety of viral infections; for example, by HIV, dengue virus or HCV. Thrombocytopenia is observed as one of the first clinical signs in approximately 10–50% of HIV patients.[34,35]

Mechanisms of Platelet Loss in Viral Infections

A well-described mechanism that triggers platelet loss in viral infections is immune thrombocytopenia (ITP), frequently found in patients with HIV or HCV infection. In the case of pathogen-induced ITP, antiviral antibodies are produced by the host cross-reacting with glycoproteins on the platelet membrane. As a consequence, the antibody-coated platelets are cleared by the reticuloendothelial system. The direct correlation between high titers of autoantibodies against platelet glycoproteins and accelerated platelet destruction in affected patients was shown for HCV. Detailed studies identified the molecular mimicry of the HCV core envelope protein 1 with the platelet protein GPIIIa as the main reason for HCV-induced thrombocytopenia.[34]

A mechanism is described for dengue fever, wherein thrombocytopenia is one major clinical manifestation. Molecular mimicry between the viral proteins NS1, prM and E and some platelet surface proteins explains the cross-reactivity of the corresponding antibodies. The level of antiplatelet autoantibodies is higher in severe dengue cases than in patients with mild fever. Binding of these autoantibodies to platelets results in dysfunction, impaired aggregation and complement-mediated cell lysis.[36]

The origin of HCV- or HIV-induced thrombocytopenia is not only based on ITP, but is generally considered to have a multifactorial origin. Other mechanisms include platelet activation with shortening of survival, splenic platelet sequestration and impaired platelet production in the bone marrow. Virus-induced platelet activation and thus

shortened survival might be triggered by direct contact to the viral surface; however, secreted viral proteins such as HIV Tat protein can also induce activation and release of microparticles, thus further contributing to thrombocytopenia.

Viral impairment of thrombopoiesis can further augment virus-induced thrombocytopenia. HCV-associated liver dysfunction reduced production of thrombopoietin, the main cytokine governing megakaryocyte proliferation and maturation.[37]

Platelets Affect Fungal Pathogens

In the interplay between fungal and host cells, fungi not only act on platelet function, but are also influenced by platelets. Three mechanisms were reported regarding how platelets can contribute to antifungal defense:

A direct antimycotic activity, mainly described for platelet-derived antimicrobial peptides; An enhancement of effectiveness of antimycotic drugs by platelet-derived antimicrobial peptides;

Stimulation of the antifungal response of other immune cells.[22]

Platelets in Parasite Infections

Although data are limited, there is no doubt that platelets also interact with parasites and play a substantial role in the antiparasitic immune defense. Activation of platelets is triggered by direct adhesion of the parasites to platelet receptors, in addition to other stimuli, such as increased levels of CRP.

After contact with parasites, platelets express defined immune receptors on their surface and secrete prestored cytokines and chemokines from their granules and thus also attract other immune cells such as macrophages, granulocytes and T cells. [22]

In Malaria

Plasmodium can interact with different receptors on human platelets. CD36 (GPIV) mediates attachment of P. falciparum on erythrocytes and is also expressed on platelets. Furthermore, it is thought to be the key platelet receptor in the interaction with infected erythrocytes. Other molecules such as CD31 and the complement receptor gC1qR might contribute to interaction with Plasmodium or Plasmodium-infected erythrocytes.

Plasmodium infection has also been correlated with platelet activation in various studies. Increased CD62P levels and enhanced levels of PF-3 were measured in patients with malaria. Animal models support the hypothesis of Plasmodium-driven platelet activation and reveal an increase in CD62P levels, microparticle formation and thromboxane release.[38]

This process of platelet stimulation can explain the thrombocytopenia commonly found in malaria. Discussions of the consequences of platelet loss are very controversial. On one hand, it might be beneficial for the parasite, at least in early stages of infection, since platelets efficiently bind to infected erythrocytes and kill the intraerythrocytic plasmodia; platelet-deficient mice were more susceptible to death by Plasmodium infection. This beneficial aspect is underlined by the fact that the extent of thrombocytopenia is a predictor for the outcome and severity of disease, and low platelet concentrations, correlate with increased parasite density. Similar to HIV, the platelet-derived chemokine PF-4 plays a central role for antimicrobial killing. PF4

rapidly accumulates within infected erythrocytes and kills intracellular malaria parasites by selectively lysing the parasite digestive vacuole. Conversely, some hints indicate that platelets are involved in the pathogenesis of cerebral malaria in the late stages of infection. In an experimental mouse model, platelets accumulate in brain microvasculature, and antiplatelet therapy can improve the outcome of infection. Platelet accumulation also occurs in the microvasculature of patients with cerebral malaria and thus may contribute to pathogenesis. Platelets also potentiate brain endothelial alterations induced by P. falciparum. In this case of cere*b*ral malaria, thrombocytopenia may provide a protective reaction of the host through reduction of platelet-mediated clumping of infected erythrocytes.[38,39]

MATERIALS AND METHODS

SOURCE OF DATA:

The study was conducted on patients admitted to SHRI B M PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTER.

METHOD OF COLLECTION OF DATA:

INCLUSION CRITERIA:

1. Patients with platelet count less than 1,50,000 cells / cumm.
2. Patients more than 18 years of age.
3. History of fever for less than 2 weeks. Fever defined as oral A.M. temperature of >37.2°C (>98.9°F) or a P.M. temperature >37.7°C (>99.9°F).

EXCLUSION CRITERIA:

1. Patients less than 18 years of age.
2. Patients with chronic diseases like malignancy ,haematopoic disorder.
3. Patients with drug induced thrombocytopenia. Idiopathic thrombocytopenic purpura.

DURATION OF STUDY:

Study was conducted over a period of two years from DECEMBER 2016 TO JUNE 2018.

STATISTICAL METHOD :

Data will be analysed using

1 Mean SD

2. T test

3. Chi-square test

RESULTS

A total number of 107 patients admitted over a period of two years from December 2016 to June 2018 in BLDE (Deemed to be University) SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER were studied.

In the present study subjects were in the age group of 18-80 years. Youngest was 18 years old and oldest 80 years.

In the present study out of 107 cases of fever with thrombocytopenia, 79 were males and 28 were females.

Out of 107 patients of fever with thrombocytopenia, 102 had definitive diagnosis with Dengue 54 cases as the commonest cause, followed by Malaria which constituted 40 cases, Mixed infections 3 cases(Dengue fever withenteric fever,Vivax malaria falciparum malaria), Acute Gastroenteritis 2 cases, Urinary tract infections 1 case, Leptospirosis 2 cases and Enteric fever 2 cases and Unknown causes accounted for 5 cases.

Out of 40 Malaria cases, Vivax Malaria constituted 31 cases, with 5 cases of Falciparum malaria and 4 cases of Mixed Malaria (Vivax and falciparum both).

The 3 Mixed infections included Dengue fever with Enteric fever, Vivax malaria and Falciparum malaria.

In our study 61 patients had platelet count less than 60,000 cells / cumm, whereas 46 had above 60,000 cells/cumm. Common range of platelet count was from 41,000 – 60,000 cells/cumm in 27 cases.

Bleeding manifestations were present in 52 patients and there were no clinical manifestations of thrombocytopenia in 55 patients.

Out of 52 patients with bleeding manifestation 43 patients (82.7%) had petechiae, bleeding gums in 25 patients (48%). Malena was present in 12 patients(23%), epistaxis in 4(7.7%).

Of 107 patients 104 of them recovered and 3 expired with mortality of 2.8% with All 3 patients had MODS.

TABLE 1: STUDY DATA

Total no of patients	107
Age in years	18-80YRS
Male : Female	79:28
Definitive Diagnosis	107
Dengue as commonest cause	54
Bleeding manifestation as	52
RASH	43
ITCHING	36
GUMS	25
MALENA	12
HEMATEMESIS	1
Good recovery	104
Mortality	3
Complications in terms of organ involvement	33
Number of people with mixed infections	3

Study design- A clinical study of 107 patients presenting with fever and thrombocytopeniawas undertaken to study etiology and correlate with clinical features and investigations.

TABLE 2 : AGE DISTRIBUTION

AGE (yrs)	N	%
≤20	15	14
21-30	33	30.8
31-40	29	27.1
41-50	18	16.8
51-60	7	6.5
>60	5	4.7
Total	107	100

Highest number of cases seen in the age group of 21 - 40 years is 62 cases (57.9%) followed by 41 – 60 years in 25 cases (23.3%).youngest was 18 yrs old whereas eldest was 80 years old. Mean age was 33.69 years.

PARAMETER	RANGE	Mean	SD
AGE	18-80	34.7	13.6

Out of 106 patients 84 were male whereas 22 were females.

FIGURE 13: AGE DISTRIBUTION

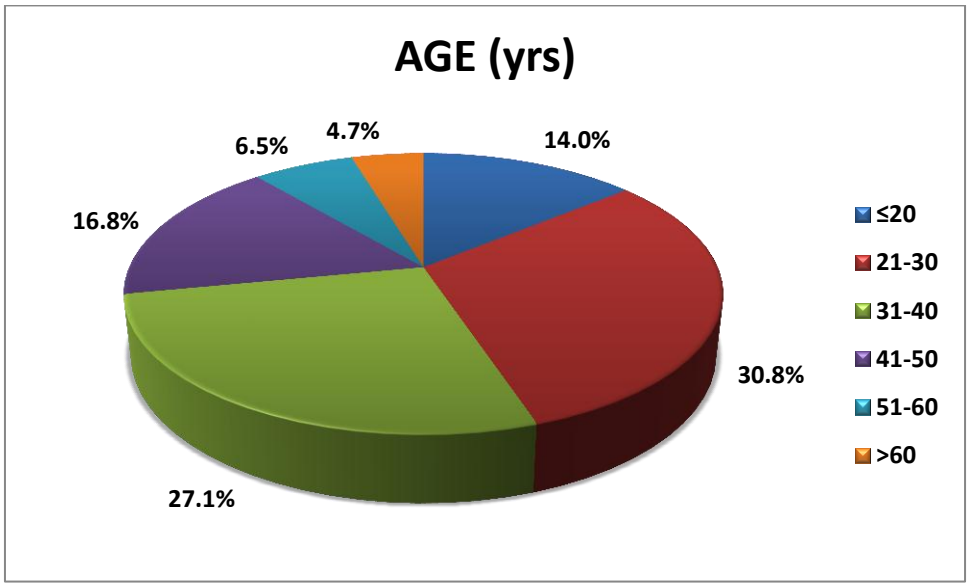


TABLE 3: SEX DISTRIBUTION

SEX	N	%
Male	79	73.8
Female	28	26.2
Total	107	100

MALE FEMALE RATIO= 2.8:1

Out of 107 patients 79 were male whereas 28 were females.

FIGURE 14: SEX DISTRIBUTION

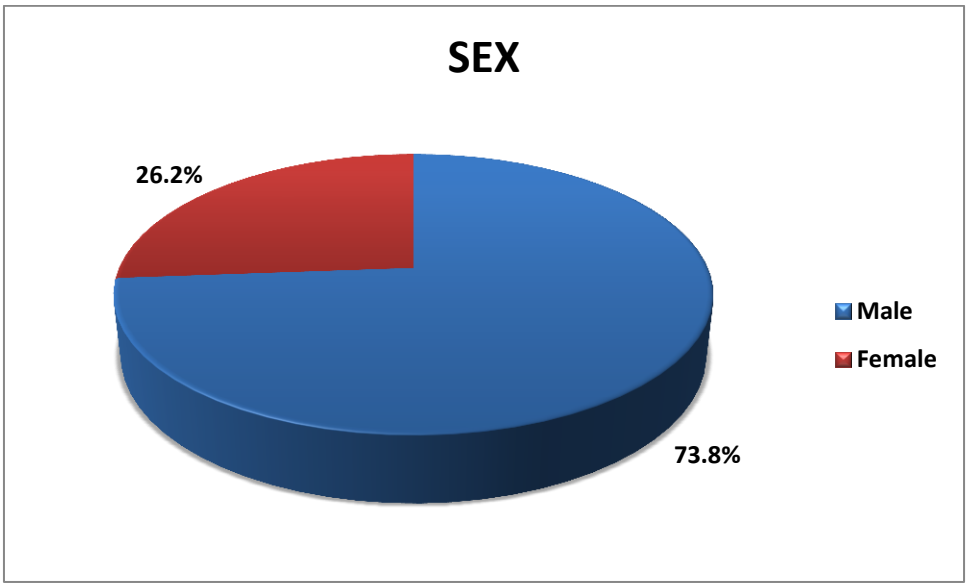


TABLE 4: DISTRIBUTION OF DURATION OF HOSPITAL STAY

PARAMETER	RANGE	Mean	SD
DOH	1-50	6.2	6.2

TABLE 5: SEASONAL VARIATION OF INCIDENCE OF VARIOUS DISEASES

Month	Dengue	Malaria	Unknown	VIR	Lepto	AGE	UTI
January	0	2	0	0	0	1	0
February	4	1	1	0	0	0	0
March	3	2	0	0	0	0	0
April	2	0	0	1	1	1	0
May	5	6	1	0	0	0	1
June	6	12	0	1	0	0	0
July	2	10	0	0	0	0	0
August	3	3	0	1	0	1	0
September	9	2	0	0	0	0	0
October	8	1	0	1	0	0	0
November	7	0	0	0	1	0	0
December	5	1	0	1	0	0	0
Total	54	40	2	5	2	3	1

In the analysis involving seasonal variation of incidence of various diseases 29 out of 54 Dengue fever cases occurred during months from September to December whereas 25 out of 40 Malaria cases occurred during months from June to August

FIGURE15: SEASONAL VARIATION OF INCIDENCE OF VARIOUS DISEASES

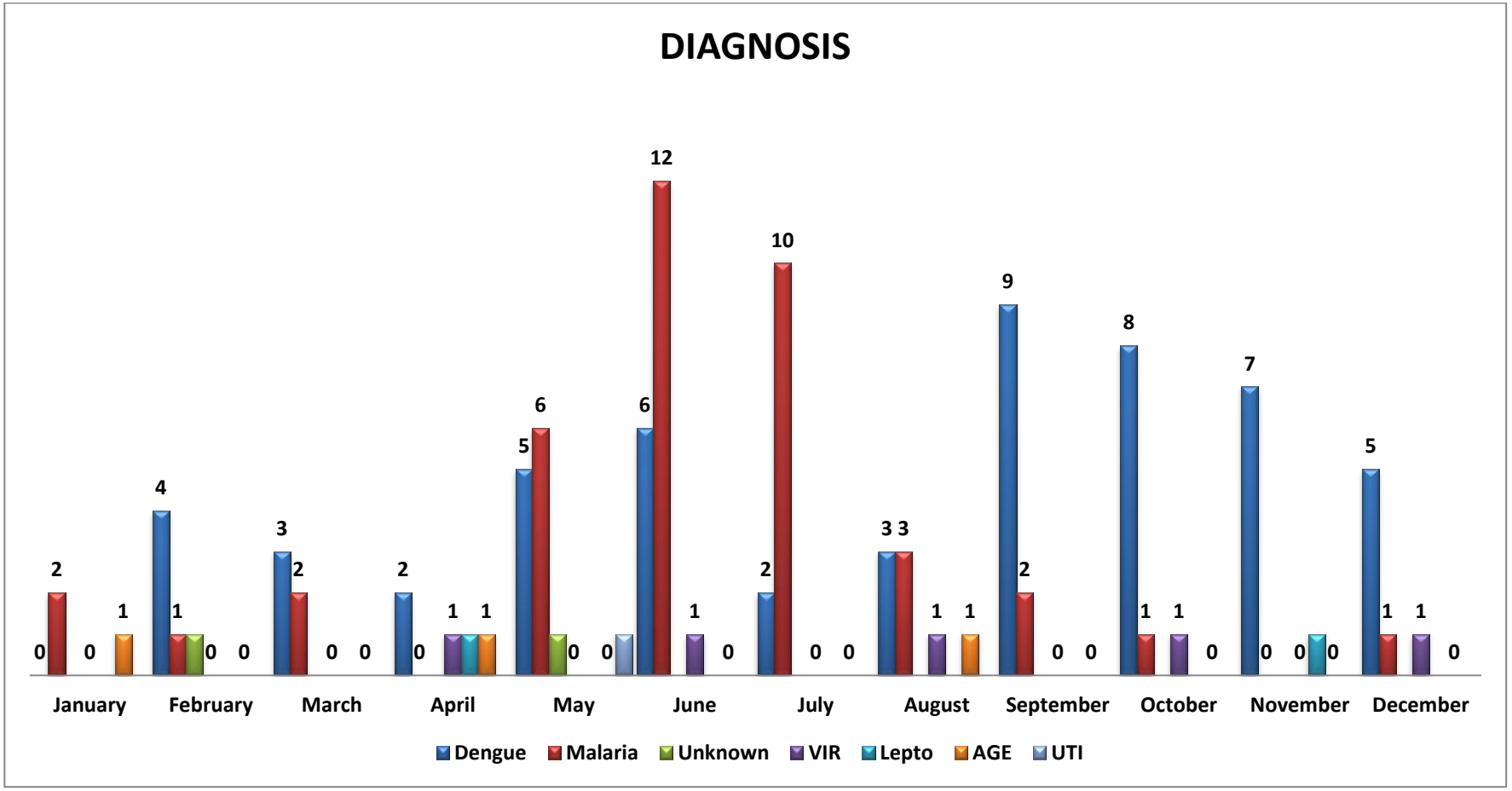


TABLE 6 : CLINICAL PRESENTATION OF PATIENTS STUDIED (N=107)

SYMPTOMS	N	%
CHILLS	98	91.6
RIGORS	62	57.9
COUGH	15	14
HEADACHE	25	23.4
JAUNDICE	7	6.5

98 patients presented with chills, of which 62 had rigors. 25 patients had headache followed by 15 patients with complains of cough and 7 with jaundice.

FIGURE16: CLINICAL PRESENTATION OF PATIENTS STUDIED (N=107)

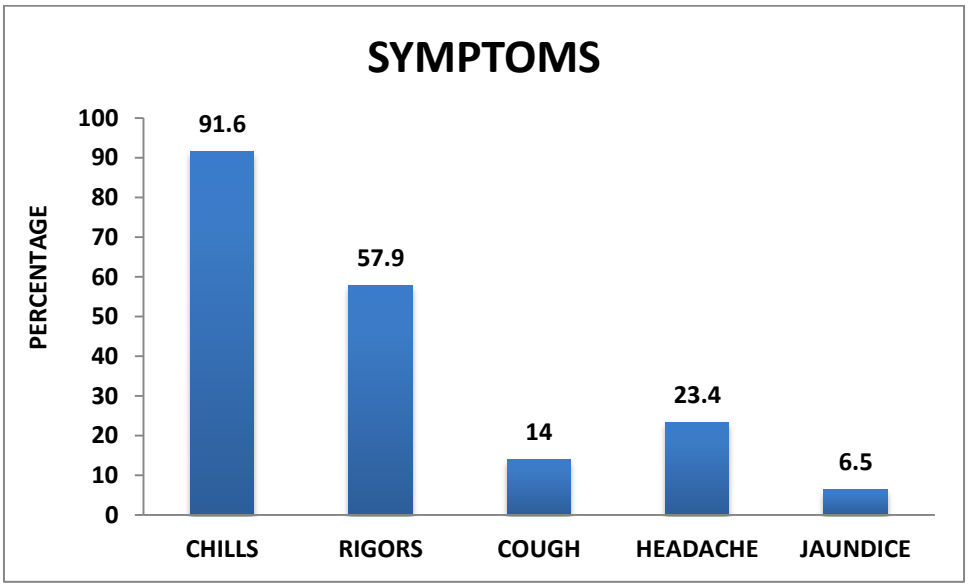


TABLE7 : BLEEDING SYMPTOMS OF PATIENTS STUDIED (N=107)

BLEEDING SYMPTOMS	N	%
RASH	43	40.2
ITCHING	36	33.6
GUMS	25	23.4
MALENA	12	11.2
HEMATEMESIS	1	0.9
OTHERS	11	10.2

Among Bleeding manifestations, 43 presented with petechial rash, 25 with bleeding gums, 12 with malena, 1 with hematemesis.

FIGURE 17: BLEEDING SYMPTOMS OF PATIENTS STUDIED (N=107)

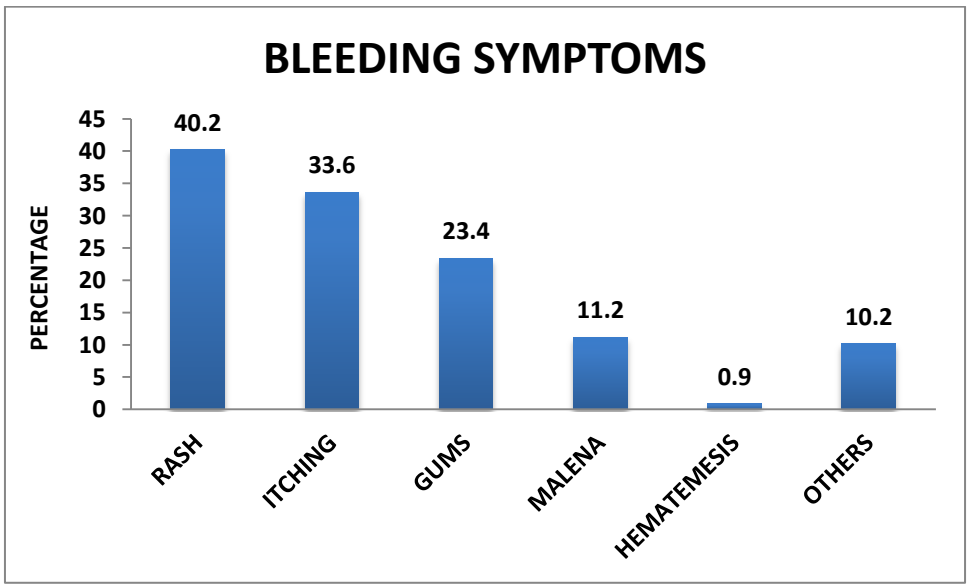


TABLE 8 : CLINICAL PRESENTATION OF DENGUE FEVER PATIENTS (N=54)

CLINICAL SYMPTOMS	N	%
CHILLS	49	90.7
RIGORS	22	40.7
COUGH	2	3.7
HEADACHE	8	14.8
JAUNDICE	1	1.9
RASH	32	59.3
ITCHING	17	31.5
GUMS	17	31.5
MALENA	8	14.8
HEMATEMESIS	0	0.0
OTHERS	3	5.6
TOTAL	54	100.0

Majority of patients with Dengue fever at admission presented with chief complaints of fever with chills (90.7%), while rash and itching was second and third most commonest complaints respectively.

FIGURE18: CLINICAL PRESENTATION OF DENGUE FEVER PATIENTS (N=54)

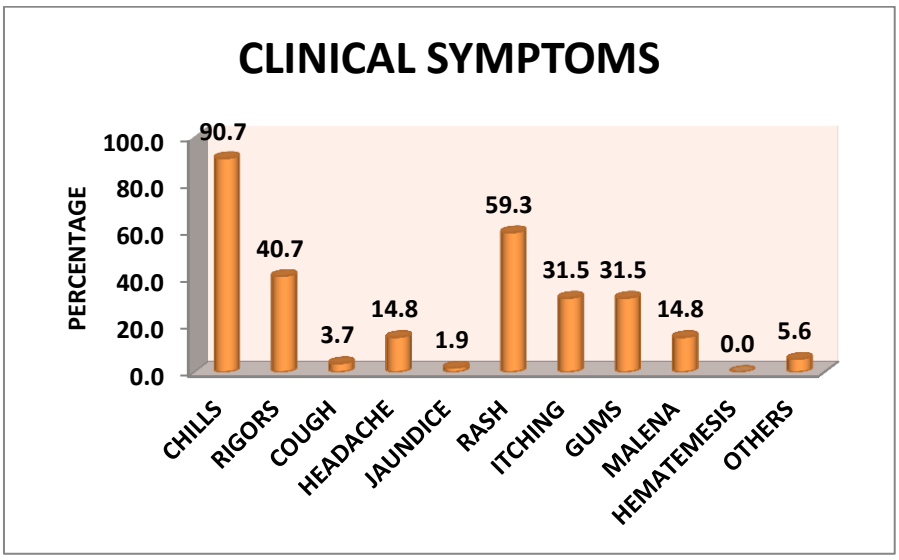


TABLE 9 : CLINICAL PRESENTATION OF MALARIA FEVER PATIENTS (N=40)

CLINICAL SYMPTOMS	N	%
CHILLS	38	95.0
RIGORS	31	77.5
COUGH	10	25.0
HEADACHE	13	32.5
JAUNDICE	5	12.5
RASH	5	12.5
ITCHING	14	35.0
GUMS	4	10.0
MALENA	2	5.0
HEMATEMESIS	0	0.0
OTHERS	5	12.5
TOTAL	40	100.0

Majority of patients admitted with malaria had fever with chills and rigors as chief complaints wherein significant number complained of dry cough and headache.

FIGURE 19: CLINICAL PRESENTATION OF MALARIA FEVER PATIENTS (N=40)

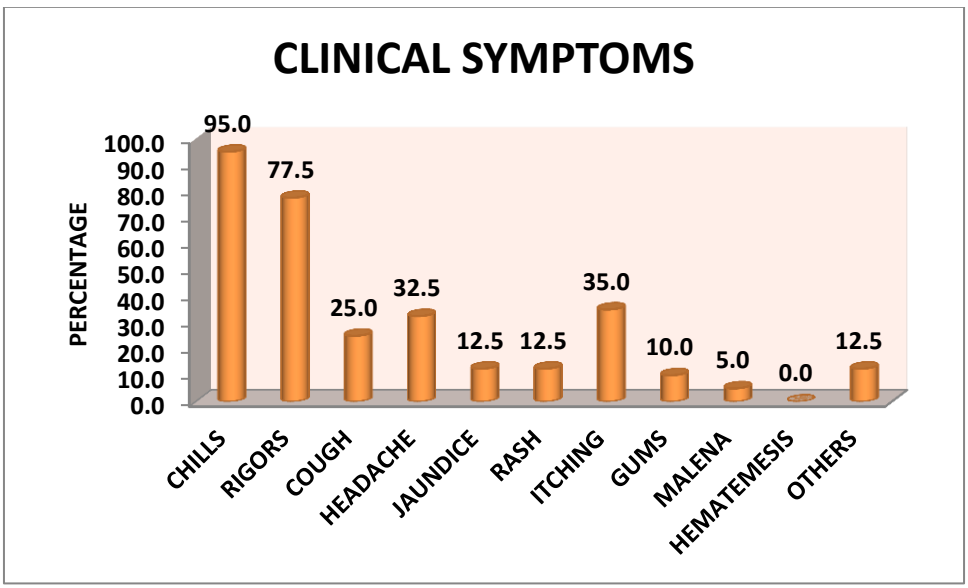


TABLE 10: DISTRIBUTION OF CLINICAL SIGNS

CLINICAL SIGNS	N	%
PALLOR	13	12.1
ICTERUS	18	16.8
PETECHAE	42	39.2
LN	11	10.3
RS	3	2.8
CVS	17	15.9
PA LIVER	17	15.9
SPLEEN	3	2.8
CNS	3	2.8

FIGURE 20: DISTRIBUTION OF CLINICAL SIGNS

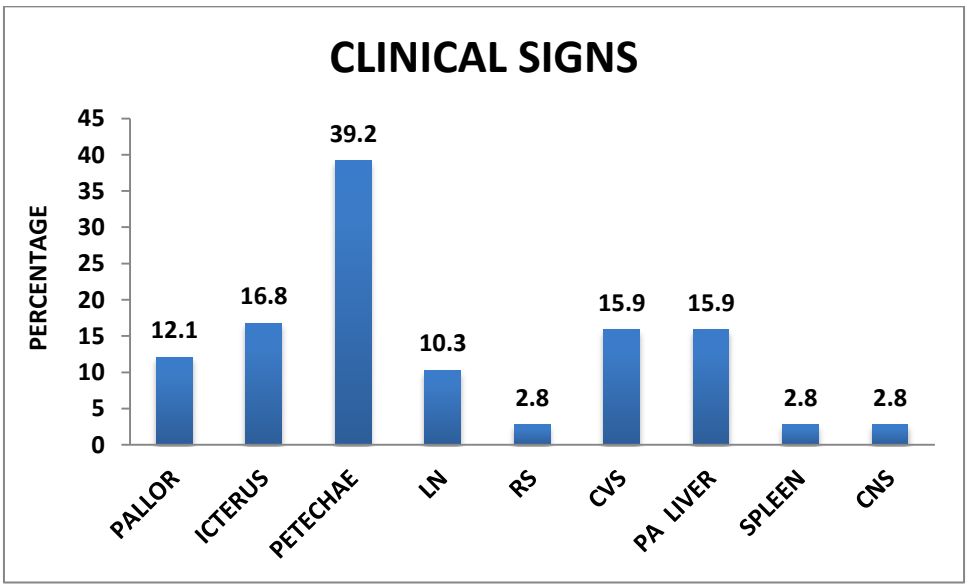


TABLE 11 : LABORATORY INVESTIGATION

PARAMETER	**N**	**%**
Hb		
<13 Male; <12 Female	50	46.7
>13 Male; >12 Female	57	53.3
PLATELET COUNT		
≤20000	12	11.2
21000-40000	19	17.8
41000-60000	30	28
61000-80000	16	15
81000-100000	17	15.9
>100000	13	12.1
Total	107	100
Blood urea (>40)	29	27.1
Serum creatinine (>1.2)	18	16.8
SGOT (>38)	82	76.6
SGPT (>41)	64	59.8

PARAMETER	**RANGE**	**Mean**	**SD**
Blood urea	10-462	42.5	58.8
Serum creatinine	0.1-11.5	1.3	1.5
SGOT	0-305	107.1	83.7
SGPT	0-425	74.6	72.8

TABLE 12 : HEMOGLOBIN LEVEL

Hb	N	%
<13 Male; <12 Female	50	46.7
>13 Male; >12 Female	57	53.3
Total	107	100

PARAMETER	RANGE	Mean	SD
HB	5.5-17.5	12.7	2.8

50 patients of 107 had anemia of which 13 were females and 36 were males with mean Hb of 12.7.

FIGURE 21: HEMOGLOBIN LEVEL

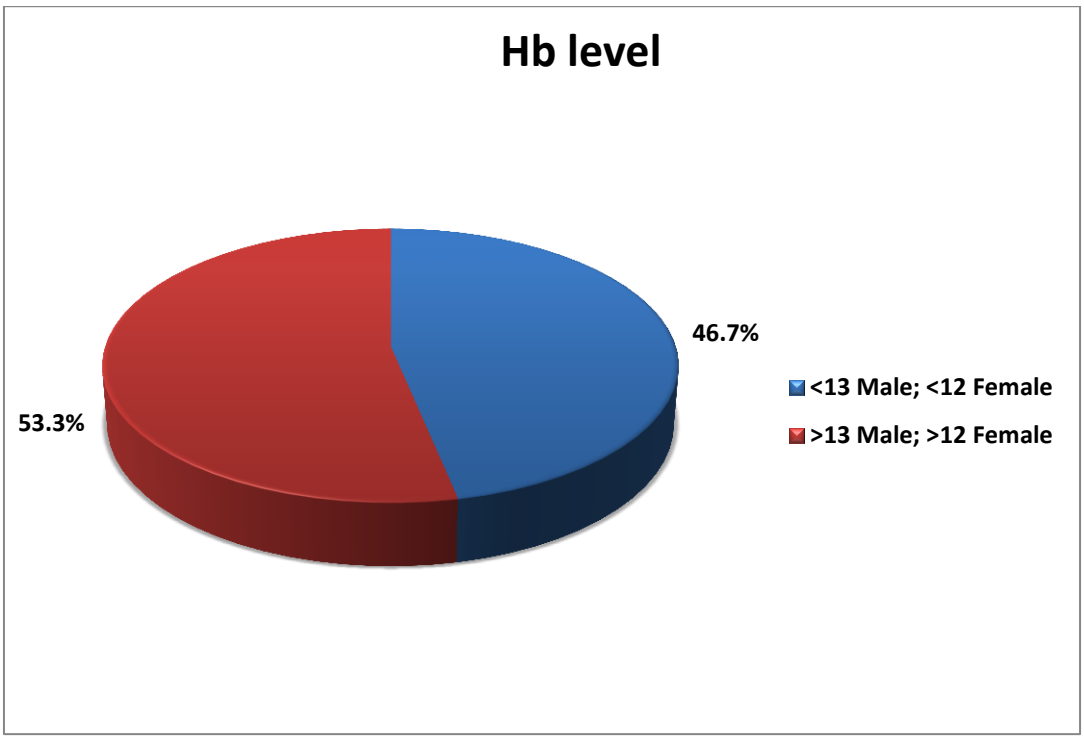


TABLE 13: DISTRIBUTION OF PLATELET COUNT

PLATELET COUNT	N	%
≤20000	12	11.2
21000-40000	19	17.8
41000-60000	30	28
61000-80000	16	15
81000-100000	17	15.9
>100000	13	12.1
Total	107	100

PARAMETER	RANGE	Mean	SD
PLATELET COUNT	12000-144000	64129.9	33841.4

Most common range of platelet count was between 41,000 and 60,000 with 28% patients, followed by 21000 – 40,000 and 81,000 – 1,00,000 with 15.9% patients

FIGURE 22: DISTRIBUTION OF PLATELET COUNT

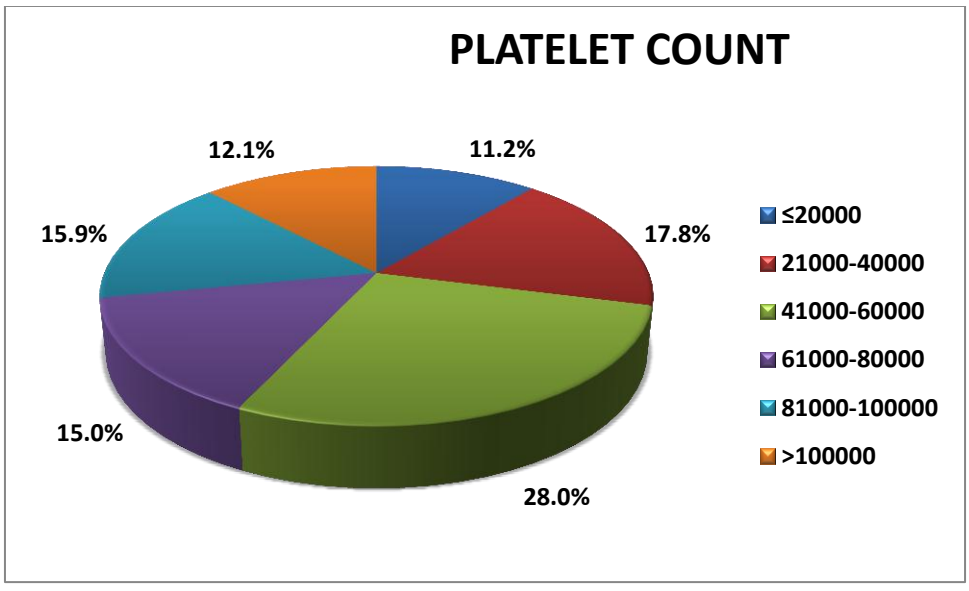


TABLE 14: CORRELATION OF BLEEDING MANIFESTATIONS WITH PLATELET COUNTS

PLATELET COUNT	RASH	ITCHING	GUMS	MALENA	HEMATEMESIS	OTHERS	Total
≤20000	3	2	1	0	0	1	12
21000-40000	12	7	9	4	0	2	19
41000-60000	13	13	8	4	0	5	30
61000-80000	6	4	4	2	1	1	16
81000-100000	4	4	2	1	0	1	17
>100000	5	6	1	1	0	1	13
Total	43	36	25	12	1	11	107

FIGURE 23: CORRELATION OF BLEEDING MANIFESTATIONS WITH PLATELET COUNTS

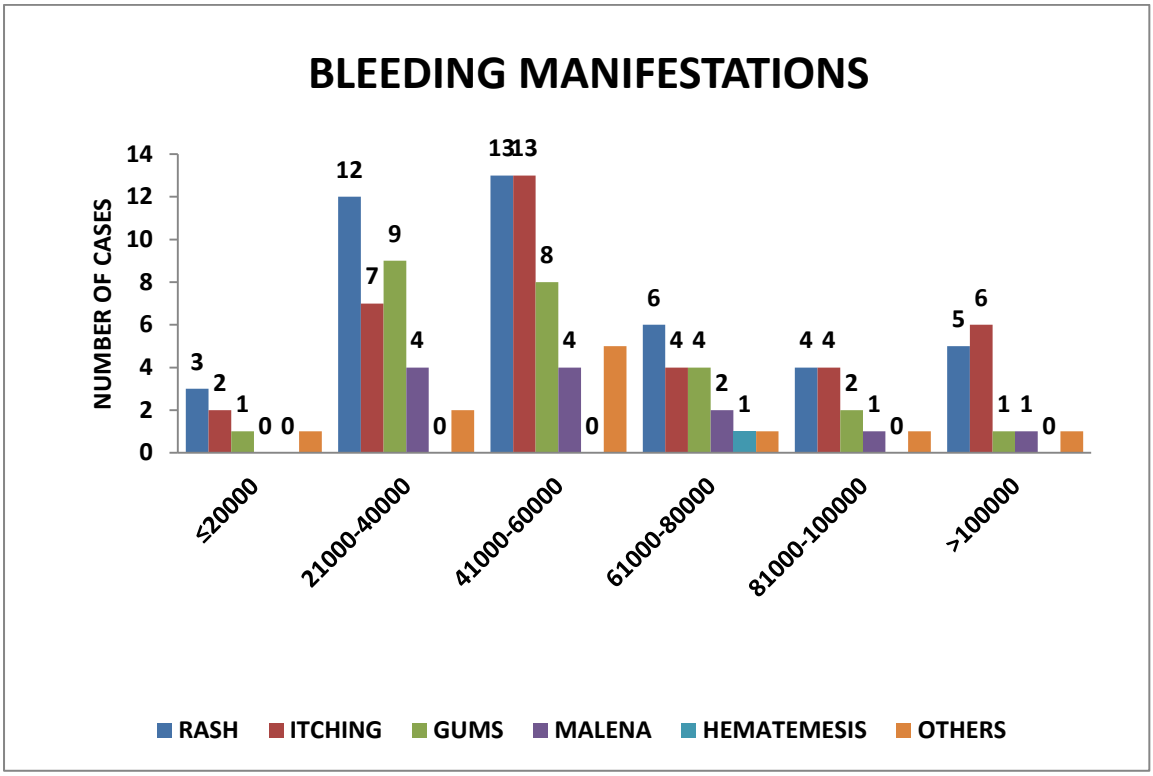
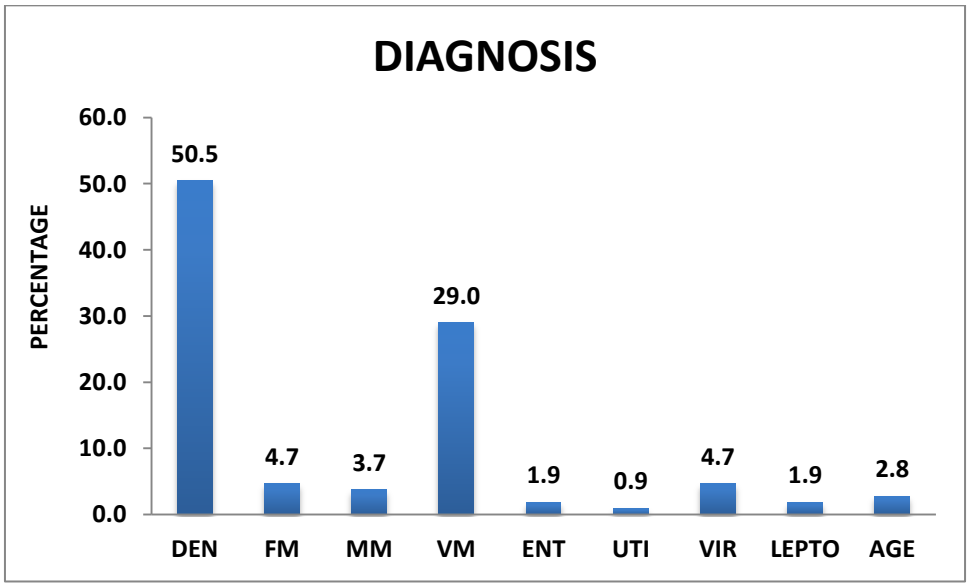


TABLE 15: ETIOLOGY OF INFECTION IN THE STUDY POPULATION

DIAGNOSIS	N	%
DEN	54	50.5
FM	5	4.7
MM	4	3.7
VM	31	29.0
ENT	2	1.9
UTI	1	0.9
VIR	5	4.7
LEPTO	2	1.9
AGE	3	2.8
Total	107	100.0

FIGURE 24: ETIOLOGY OF INFECTION IN THE STUDY POPULATION



Dengue fever consisted of majority of cases with 54 patients followed by malaria accounting for 40 cases of which 31 were vivax malaria rest were falciparum and mixed malaria with 5 and 4 cases respectively

TABLE 16: DIATRIBUTION OF MALARIA CASES

MALARIA	N	%
FM	5	12.5
MM	4	10.0
VM	31	77.5
TOTAL	40	100.0

Malaria consisted of 40 cases of which 31 were vivax malaria, 5 were falciparum malaria and 4 were mixed malaria.

FIGURE 25: DISTRIBUTION OF MALARIA CASES

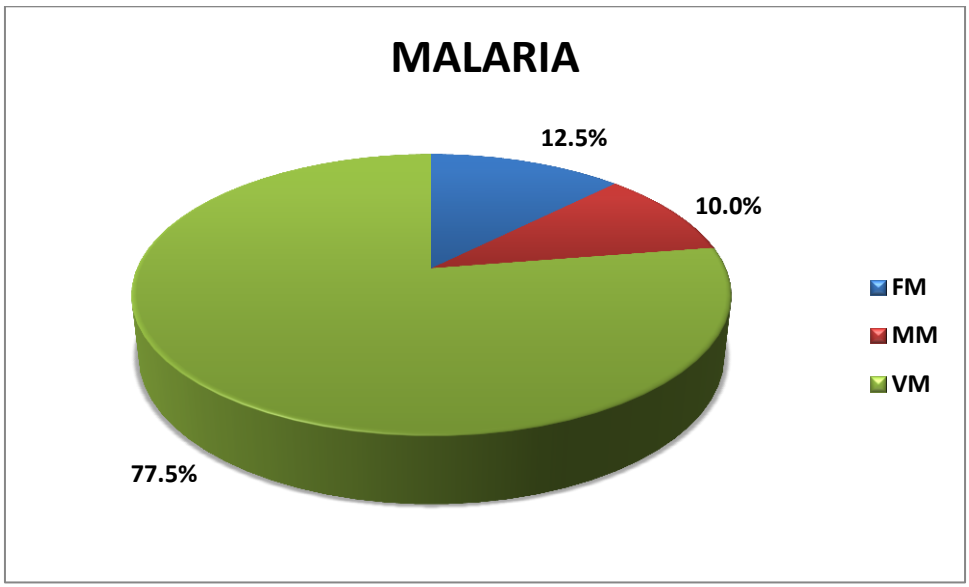


TABLE 17: TREATMENT OUTCOME

OUTCOME	N	%
SURVIVED	104	97.2
DEATH	3	2.8
Total	107	100

FIGURE 26: TREATMENT OUTCOME

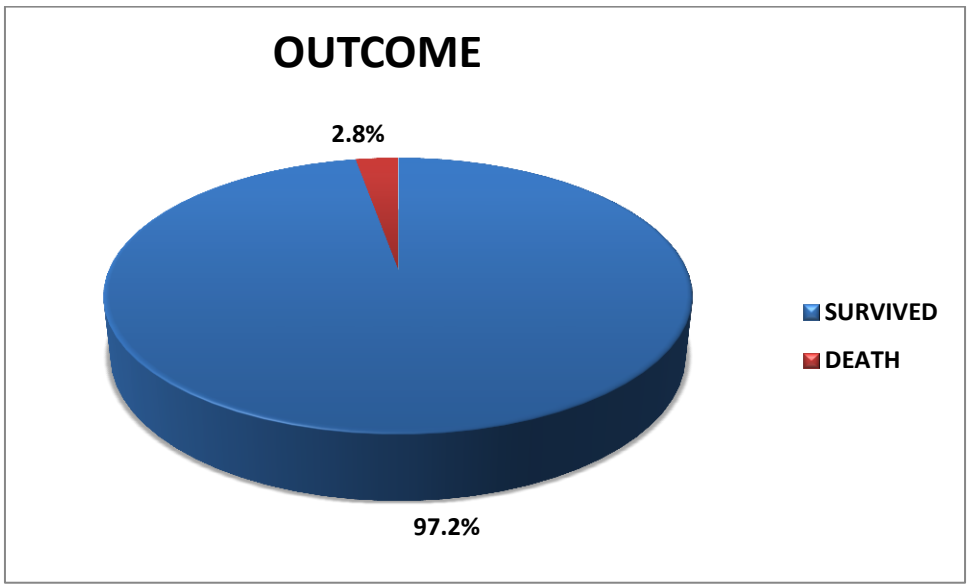


TABLE18: CORRELATION WITH SERIOUS COMPLICATIONS

DIAGNOSIS	COMPLICATIONS	MODS
AGE	1	0
DEN	4	1
ENT	1	1
FM	4	1
LEPTO	1	1
MM	1	0
UTI	1	0
VIR	5	3
VM	15	2
Total	33	9

FIGURE 27: CORRELATION WITH SERIOUS COMPLICATIONS

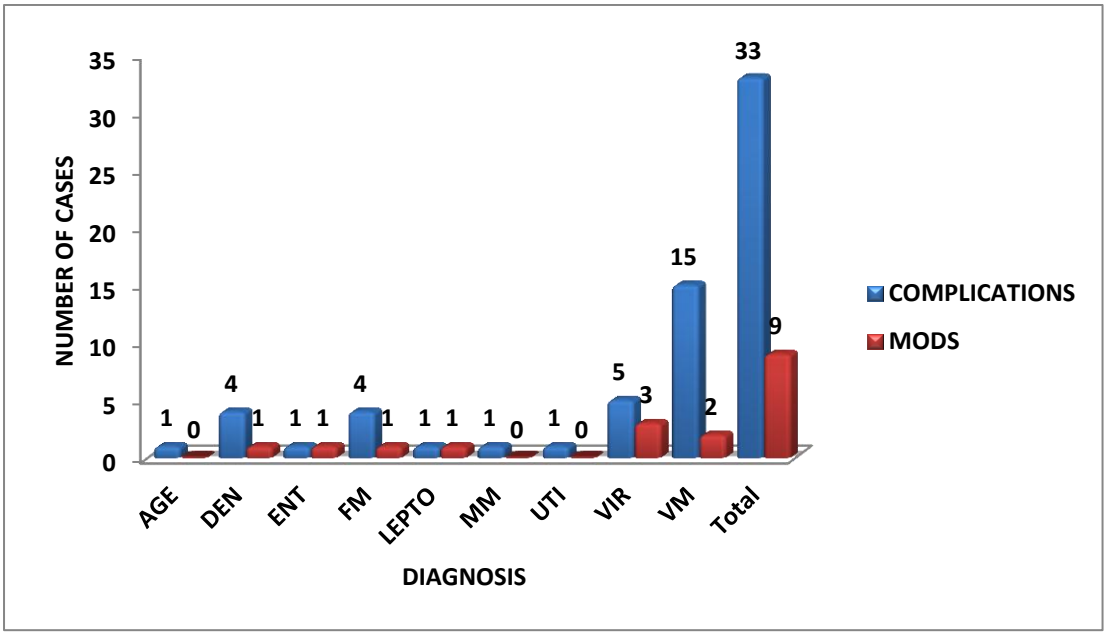


TABLE 19: DISTRIBUTION OF COMPLICATIONS

COMPLICATIONS	N	%
AKI	7	6.6
ARDS	6	5.6
HEMOPERITONEUM	1	0.9
HEMOPTYSIS	1	0.9
HEP	6	5.6
MODS	9	8.4
PNEUMONIA	1	0.9
SDH	1	0.9
Total	32	29.9

FIGURE 28: DISTRIBUTION OF COMPLICATIONS

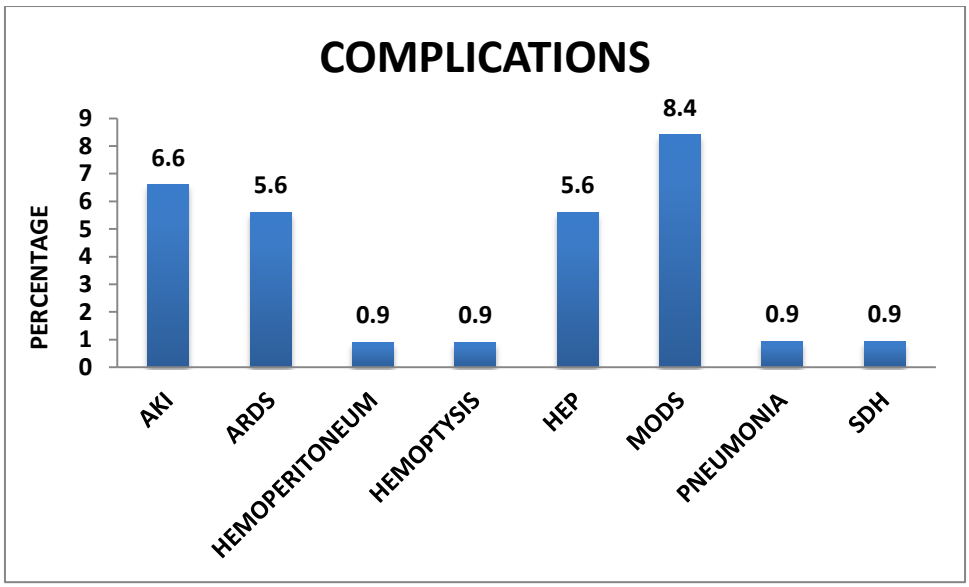
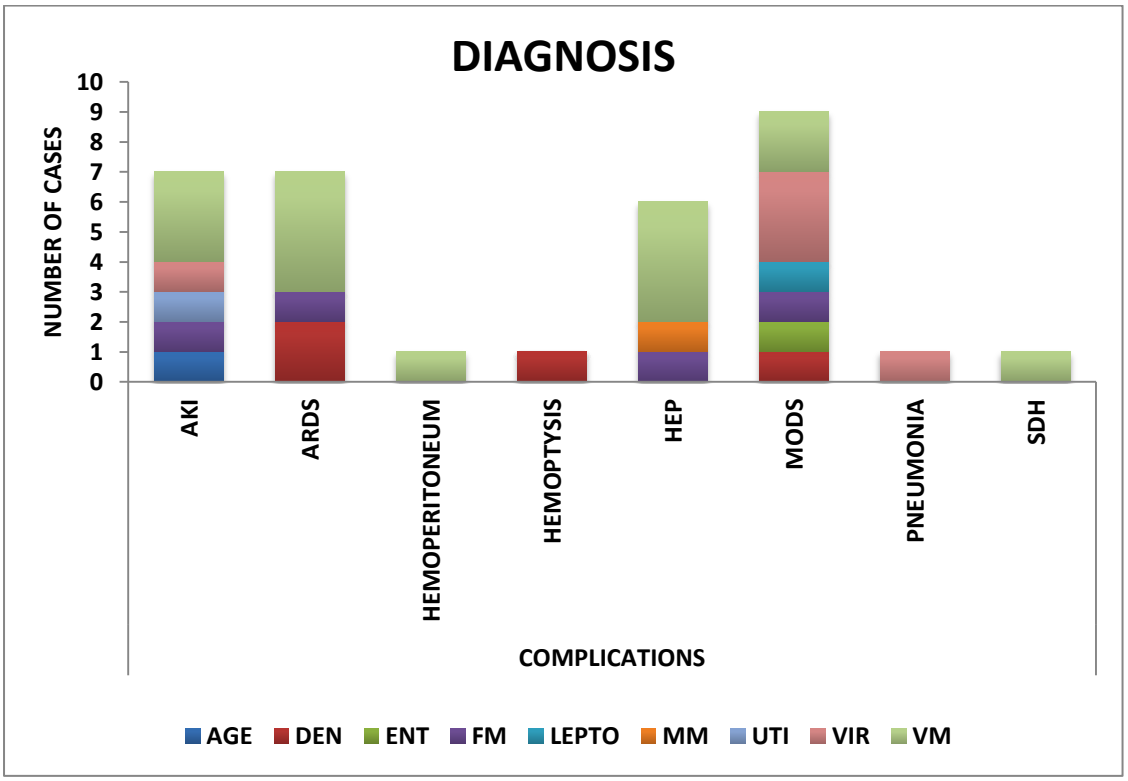


TABLE 20: EVALUATION OF SPECTRUM OF COMPLICATIONS WITH RESPECT TO DIAGNOSIS

DIAGNOSIS	COMPLICATIONS								
	AKI	ARDS	HEMOPERITONEUM	HEMOPTYSIS	HEP	MODS	PNEUMONIA	SDH	Total
AGE	1	0	0	0	0	0	0	0	3
DEN	0	2	0	1	0	1	0	0	54
ENT	0	0	0	0	0	1	0	0	2
FM	1	1	0	0	1	1	0	0	5
LEPTO	0	0	0	0	0	1	0	0	2
MM	0	0	0	0	1	0	0	0	4
UTI	1	0	0	0	0	0	0	0	1
VIR	1	0	0	0	0	3	1	0	5
VM	3	4	1	0	4	2	0	1	31
Total	7	7	1	1	6	9	1	1	107

FIGURE 29: EVALUATION OF SPECTRUM OF COMPLICATIONS WITH RESPECT TO DIAGNOSIS



DISCUSSION

A total number of 107 patients admitted over a period of two years from December 2016 to June 2018 in Shri. B. M. Patil Medical College, Hospital and Research Center were studied.

In the present study, subjects were in the age group of 18-80 years, youngest being 18 years old and the eldest 80 years. The mean Age was 34.7 years which was similar in comparison to studies by Majumdar R et al, Riaz MM et al and Sahu S et al[40,41,42]

The most common age group involved was from 18 to 40 years of age including of 72% of patients. This was similar to a study conducted in Kolkata in 2012 by Majumdar R et al[40]. Splitting the age group further, 57 cases from our study had an age group range from 21 to 40 years (53.77%). This was in contrast to a study conducted by Dash et al in 2010 in Andhra Pradesh which had majority as 26% cases ranging in age group 61 to 80 years. The difference in age group probably was due to different admission and treatment policies in different medical institutions[43].

In the present study out of 107 cases of fever with thrombocytopenia, 79 were males and 28 were females depicting a male preponderance. This correlated with various studies conducted by Dash H S et al [43], Debarati Gupta et al [44], Emmanuel Bhaskar et al [45] and many others[46].

Majority of cases in our study were admitted in rainy and early winter season among which 20 cases were admitted in the month of June. Malaria cases had a surge in rainy season similar to a study conducted in Bhavnagar in 2013 by Raikar S R et al[50], whereas Dengue fever had onset in rainy season with post monsoon surge similar in pattern to a study in Lucknow done by Karoli R et al [47].

Fever associated with chills (91.6%) and rigors (57.9%) were the most common symptoms of patients whereas bleeding manifestations were present in 52 patients (49%). This presentation was comparable to studies carried out by Emmanuel Bhaskaret al[45], Gregory C J et al [46], Karoli R et al [47] and Umm-e-Asma, FarhaTaufiq, Wajihullah Khan study in Aligarh [51].

Malaria patients presented with chief complaints of fever with chills and rigors, and also had complaints of cough (26%) and headache (28%). This observation was similar to studies by Umm-e-Asma, Farha Taufiq, Wajihullah Khan[51], Hasan Abu Zaid et al [52].

In contrast patients with Dengue fever were admitted with chief complaints of chills and rigors, but a significant number of patients had complaints of rash (59.3%) and itching (31.5%) similar to a study carried out in Chennai by Emmanuel Bhaskar et al (46%) [45]

The most common sign on examination was petechiae (39.9%) followed by Icterus was present in 18 patients (16.8%). Splenomegaly was present in 3 patients of 107 cases (2.8%) all of which had Malaria. Most common sign was petechiae comparable to many other studies like Emmanuel Bhaskar[45], Christopher C G et al[46],Lee M S et al [53], Karoli R et al[47], Khan et al [48], Nair P S etal[49] , Dash H S et al [43]. Of all the total malaria cases splenomegaly was present in 9 out of 42 cases (21.4%) This similarity was also depicted in various studies conducted in Doha (Qatar) conducted by Hassan Abu Zaid et al [52], Aligarh by Umm-e Asma, FarhaTaufiq, Wajihullah Khan [51] and New Delhi by Sharma S et al [54] which indicates splenomegaly is the most common presentation in cases of malaria. These variations can be attributed to variation in the immune status of patients in different endemic areas of malaria.

Among the bleeding manifestations which were present in 52 patients (49%), Petechiae was the most common bleeding manifestation (95%) which was consistent with other studies such as Dash H S et al (66%) [43], Gregory C J et al (21%) [46], Karoli R et al (26%) [47], Khan et al [48], Nair P S et al [49], Lee M S et al [53]. Bleeding gums was the second most common manifestation present in 25 patients (23.58%). In contrast, gingival bleeding was the commonest bleeding manifestation in the study conducted in Chennai by Emmanuel Bhaskar et al [45] accounting for 68% of bleeding manifestations

Dengue fever with 54 cases was the leading cause of febrile thrombocytopenia in our study, similar to a study conducted in Bhavnagar, Gujarat by Raikar S R et al in 2013 [50]. However the study by Nair P S et al [49] , revealed that Septicemia was leading cause of febrile thrombocytopenia. On the contrary, in a study by Dash H S et al, Malaria was the leading cause of fever associated with thrombocytopenia [43].

Table 21 – Diffrences with respect to etiologies[43, 49,]

Mostcommon causes (%)	**Our study**	**Raikar S R et al**	**Nair P S et al**	**Dash H S et al**
First	Dengue fever (50.5%)	Denguefever (52%)	Septicemia (26.6%)	Malaria (45%)
Second	Malaria (37.4%)	Malaria(45%)	Typhoid fever (14.7%)	Septicemia (21%)

The difference in incidence of etiologies is probably due to epidemic of Dengue fever in the year 2015. Another important factor to be considered is that diagnostic modalities for Dengue fever were limited in year 2003 when Nair P S et al conducted his study in New Delhi [49].

Out of 107 patients, 19 patients (17.8%) had platelet count in range of 41,000 – 60,000 cells/cumm as compared to study by Dash H S et al which had 26 patients (26%) in the range of 61,000 – 80,000 cells/cumm[43]. This difference can be attributed to difference in prevalence of disease, associated drug resistance and varying serotypes of the causative organisms.

Table 22 - Difference of our study with Dash H S et al

Platelet count	Our study(107 patients)	Dash H S et al(100 patients)
0 – 20,000	12	17
21,000– 40,000	19	25
41,000– 60,000	30	13
61,000– 80,000	16	26
81,000– 1,00,000	17	19

Table 23 - Diffrences of our study with Nair P S et al.

Platelet count	Our study (107patients)	Nair P S et al (109 patients)
0 – 20,000	12	19
20000– 40,000	30	28
40,000– 1,00,000	33	62

The current study depicted that Bleeding manifestations were present in 52 patients (49.05%), similar to the study by Nair P S et al and Dash H S et al[43,49].

Table 24 - Comparison of bleeding manifestations between present study and other studies[43,49].

Bleeding manifestations	Present study		Nair et al		Dash et al	
	No.of cases	Percentage	No. of cases	Percentage	No.of cases	Percentage
Present	52	49.05%	45	41.28%	53	53%
Absent	55	50.95%	64	58.72%	47	47%

Petechiae / pupurawas commonest bleeding manifestations in all three studies.

Table 25 – Diffrences of incidence of bleeding manifestations

Bleeding manifestations	Our study	Nair P S et al
Most common	Petechiae (40.2%)	Petechiae (9.2%)
Second most common	Bleeding gums (23.4%)	G I Bleed (9.2%)
Third most common	G I bleed (11%)	Epistaxis (6.4%)
Fourth most common	Epistaxis (3.77%)	Bleeding gums (5.5%)

The present study indicated that 55.50% of patients had platelet count less than 50,000 cells/cumm whereas 39.62% had between 50,000 to 1,00,000 cells/cumm and 3 patients had more than 1,00,000 cells /cumm correlating with results of study by Ruhi Khan et al, who conducted a study in Aligarh on patients with Dengue fever, had 69.7% patients in the range of 0 – 50,000 cells/cumm, 4.7% patients between 50,000 – 1,00,000 cells /cumm, and 25.6% patients above 1,00,000 cells /cumm[55].

Table 26 – Distribution of platelet count among Dengue Fever cases.

Platelet count (cells/cumm)	Our study	Ruhi Khan et al
0 – 50,000	30 (55.50%)	209 (69.67%)
50,000 – 1,00,000	21 (39.62%)	14 (04.67%)
>1,00,000	03 (5.55%)	77 (25.66%)
Total	54	300

In our study out of 54 patients with Dengue fever, 30 patients had platelet count of less than 50,000 cells/cumm out of which 24 patients (80%) had bleeding manifestations. 21 patients had platelet count ranging between 50,000 and 1, 00,000 cells/cumm among whom 14 (66.7%) had bleeding manifestations. Only 3 patients had platelet count above 1, 00,000 cells/cumm out of which 1 had bleeding manifestations.

The study by Ruhi Khan et al analyzed that only 15.6% of patients with platelet count less than 50,000 cells/cumm had bleeding manifestations. 14 patients had platelet count ranging between 50,000 and 1,00,000 cells/cumm among whom 6 (42.6%) had bleeding manifestations. Among remaining 77 patients who had platelet count above 1, 00, 000 cells/cumm only 2 had bleeding manifestations[55].

Table 27 – Occurrence of bleeding manifestations in patients with thrombocytopenia in Dengue fever[55].

Rangeofplatelet count(cells/cumm)	Present study		Ruhi Khan et al	
	Total numberof cases ofdengue fever	Patientswithbleedingmanifestations	Total number ofcases of denguefever	Patientswithbleedingmanifestations
<50,000	30	24 (80%)	204	32 (15.6%)
50,000–1,00,000	21	14 (66.7%)	14	6 (42.6%)
>1,00,000	3	1 (50%)	77	2 (2.6%)

Similarly, a study conducted in Singapore in 2008 by Diaz Quijano F A et al 11 patients out of 32 had bleeding manifestations out of which 5 patients had petechiae (15%) and 3 had GI bleed (9.4%)[56].

Complications of cases with febrile thrombocytopenia were analyzed in our study which indicated that 32 patients out of 107 had one or more organ involvement.

Among complications, hepatopathy consisted of 6 cases, AKI 7 cases, ARDS 6 cases and MODS consisted of 9 cases.

Majority of cases of MODS consisted of triad of AKI, ARDS and Hepatopathy.

All the 3 deaths in our study revealed MODS (Multiorgan Dysfunction Syndrome).

MODS contributed to 67% of mortality consistent with a study in Rajasthan by Kochar D K et al wherein MODS contributed to 71% of mortality causes [57].

20 out of 40 cases of Malaria developed complications. Of these 15 were Vivax Malaria cases, 4 Falciparum Malaria and 1 Mixed Malaria.

Hepatopathy contributed to 12 cases out of 40 (30%) similar to studies in Mangalore by Saya R P et al (38%) [58], New Delhi by Sharma S et al (25.6%) [54], Kolkata by Bhattacharje P et al (16%) [59] and Bikaner by Kochar D K et al (58%)[57]

Table 28 - Complications in cases of malaria in comparison with other studies

Complications in malaria	Our study	Saya R P et al	Sharma S et al	Bhattacharje e P et al	Kochar DK et al
Hepatopathy	30 %	38%	25.6%	16%	58%
AKI	29.16%	-	-	12%	6%
ARDS	18.75%	-	5.6%	13%	2%

This study noticed complications in Vivax malaria at alarming rate which was usually considered as benign infections in the past. This warrants immediate attention and change in treat-ment strategy.

CONCLUSION & SUMMARY

The present study was conducted among admitted patients of Shri. B. M. Patil Medical College, Hospital from December 2016 to June 2018 over a period of two years. 107 patients participated in the study.

1. Maximum prevalence was observed in younger age group.
2. Male preponderance was observed, with male to female ratio of 2.8:1.
3. In our study, maximum number of cases of febrile thrombocytopenia were seen mainly during rainy and early winter season.
4. Fever with chills was the main presenting complaint which was also associated with rigors. Patients with Malaria presented with chief complaints of fever with chills whereas patients with Dengue fever presented with rash over the limbs associated with itching.
5. On clinical examination, Petechiaewas the most common sign followed by Hepatomegaly and then Splenomegaly.
6. In all cases of Febrile thrombocytopenia, thrombocytopenia led to various bleeding manifestations and influenced the clinical profile of these illnesses.
7. Petechiae were the most common bleeding manifestation followed by bleeding gums and then malena.
8. Among the 107 cases, Dengue was the most common cause in 54 patients. Malaria comprised of 40 cases out of which 31 were Vivax Malaria, 5 were Falciparum Malaria, and 4 were mixed malaria.
9. The spectrum varied from mild self limiting disease to severe fatal disease.
10. In the present study there were no bleeding manifestations in many cases, hence signifying that there may not be bleeding manifestations in all cases of febrile thrombocytopenia. In majority of the patients platelet count improved

to almost normal level with treatment, hence thrombocytopenia can be transient and asymptomatic.

11. Among the propensity to cause serious complications, Vivax Malaria had maximum tendency to cause complications.
12. However, of 5 undiagnosed cases, 4 patients had serious complications and 3 patients had MODS (Multiorgan Dysfunction Syndrome). This sadly points towards the conclusion that with the available diagnostic modalities there still exists a darker environment with respect to undiagnosed conditions. So much more awareness, vigilance and research is needed.
13. This highlights the need for rapid diagnosis and appropriate management of patients to prevent complications.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee
BLDE (Deemed to be University)
Shri B.M. Patil Medical College
Bijapur 586 103.
No. 61/2016
Dt. 06/10/16

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 06/10/2016 *at* 3-00pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title A study of clinical profile of Patients with febrile thrombocytopenia

Name of P.G. student Dr. Nikhil Maddur
P.G in General Medicine

Name of Guide/Co-investigator Dr Vijaykumar G. Warad
Professor of Medicine

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

INFORMED CONSENT FORM

TITLE OF RESEARCH : "STUDY OF CINICAL PROFILE OF PATIENTS WITH FEBRILE THROMBOCYTOPENIA"

GUIDE : DR VIJAYKUMAR G. WARAD

M.D GENERAL MEDICINE

P.G.STUDENT : DR NIKHIL MAGDUM

All aspects of this consent form are explained to the patient in the language understood by him or her.

PURPOSE OF STUDY:

I have been informed that the purpose of this study is to study clinical profile patients with febrile thrombocytopenia.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination and investigations

BENEFITS:

I understand that my participation in this study will have no direct benefit to me other than the potential benefit of treatment which is planned to prevent further morbidity and mortality in me.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulation of hospital. If the data is used for publication the identity will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw From study at any time.

(Signature of Guardian) (Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that Dr. Nikhil Magdum has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all above in detail in my own language and I understand the same. I agree to give my consent to participate as a subject in this research project.

DATE SIGNATURE OF PARTICIPANT

DATE SIGNATURE OF WITNESS

SCHEME OF CASE TAKING

Name: CASE NO:

Age: OP/IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Address:

Presenting complaints with duration:

1. FEVER

- Duration (Days)

DIURNAL

GRADE: DURATION:

MI LD / MODERATE / SEVERE

CHILLS:

RIGORS VARIATION:

- Site

- Aggravating/relieving factors

2. Myalgia: Yes/No

3. Loss of weight: Yes/No

- Duration (Days) :

4. Cough

- Onset: Abrupt/Insidious

- Duration (Days)

- Dry cough: Yes/No

5. Expectoration

- Duration (Days):
- Type: Mucoid/Purulent/Blood tinged
- Foul smelling: Yes/No

6. Dyspnea: Yes/No

- Onset: Abrupt/Insidious
- Duration (Days):
- Grade

7. Haemoptysis: Yes/No

- Duration (Days):

8. Chest Pain: Yes/NO

9. Loss of appetite: Yes/No

- Duration (Days)

10. Nausea: Yes/No

11. Vomiting: Yes/No

- Duration (Days):
- Amount: Scanty/Copious
- Type: Projectile/Non-projectile
- Character: Watery/containing food particles/Bilious/Bloodtinged

12. Diarrhea: Yes/No

- Duration (Days):
- Amount: Scanty/copious
- Character: Watery/Mucoid/Blood tinged

13. Constipation: Yes/No

14. Pain abdomen: Yes/No

- Onset: Abrupt/Insidious
- Duration
- Site

15. Distension of abdomen: Yes/No

-Duration:

16. Hematemesis: Yes/No

17. Malena: Yes/No

18.Dysuria: Yes/No

- Difficulty in voiding: Yes/No
- Hesitancy: Yes/No
- Oliguria: Yes/No
- Retention: Yes/No
- Incontinence: Yes/No

19. Haematuria: Yes/No

20. Puffiness of face: Yes/No

- Onset: Abrupt/Insidious
- Duration (Days):

21. Headache: Yes/No

- Onset: Abrupt/Insidious
- Duration (Days)
- Localized/Diffuse
- Character: Throbbing/Pricking/Dullaching/etc.

22. Giddiness: Yes/No

23. Convulsions; Yes/No

- Duration(Days)

-Generalized – Tonic/Clonic

24. Joint pains

- Onset: Yes/No

- Duration(Days)

-Abrupt/ Insidious

- Site: Major/Minor – Joint

- Early morning stiffness: Yes/No

- Recurrent attacks: Yes/No

- Symmetrical involvement: Yes/No

- Restriction of Movement: Yes/No

25. Swelling of the joint: Yes/No

26.Bleeding gums: Yes/No

27. Sore throat: Yes/No

28. Rash: Yes/No

- Onset: Abrupt/Insidious

- Duration

Site

29. Itching: Yes/No

30. Bleeding tendencies: Yes/No

- Site

History of presenting complaints:

Past History:

Family History:

Personal History:

Treatment History:

General Physical Examination

Pallor: present/absent

Icterus:present/absent

Cyanosis:present/absent

Clubbing: present/absent

Generalized lymphadenopathy: present/absent

Odema:present/absent

VITALS:

PR:

BP: in mm of mercury (mm hg)

RR:

Temp:

SYSTEMIC EXAMINATION:

- Cardiovascular system
- Respiratory system
- Per abdomen
- Central nervous system

INVESTIGATIONS

PATHOLOGY:

1.)Complete blood count:	
Hb	gm/dl
Total count	Cells/cumm
Differential count Neutrophils	%
Lymphocytes	%
Eosinophils	%
Basophils	%
Monocytes	%
2.)Platelet Indices	
Platelet Count	
3) PS for malarial parasite	
4)Peripheral smear study	
5)Urine Routine	

BIOCHEMISTRY:

1)Serum sodium	
2)Serum potassium	
3)Serum creatinine	

LFT-

MICROBIOLOGY:

1)Dengue	
IgG	
IgM	
NS1	
2) Widal test	
3)Weil felix test	
4)HIVRapid	

Other relevant investigations will be done when required.

KEY TO MASTER CHART

F - Female

M - Male

N – No

Y – Yes

COLUMN ABBREVIATION

RS – Respiratory system

P - Positive findings

NAD – No abnormality detected

CVS – Cardiovascular system

P - Positive findings

NAD – No abnormality detected

PA – Per Abdomen

Liver – P: palpable

N: - Not Palpable

Spleen – P: palpable

NP - Not palpable

CNS – Central Nervous System

P - positive findings

NAD – No abnormality detected

Urine ALB – Urine albumin

BU – blood urea

SC – serum creatinine

BIL – bilirubin

ALB – albumin

SMP – smear for malarial parasite

PV – plasmodium vivax

PF – plasmodium falciparum

PV+PF – mixed.

N - negative

PV – plasmodium vivax

PF – plasmodium falciparum

PV+PF – mixed.

N – negative

NS1Ag – Dengue NS1 antigen

P - positive

N – negative

ND - not done

IgM DEN – IgM Dengue

N - negative

ND – not done

P - positive

IgG DEN – IgG Dengue

P - positive

IgM LEPTO – IgM Antibody for Leptospira

P - positive

N – negative

HIV – NR: not reactive

HAV – Hepatitis A Virus

DIAGNOSIS

DEN – DENGUE FEVER

MM – MIXED MALARIA

FM – FALCIPARUM MALARIA

VM -VIVAX MALARIA

LEPTO – LEPTOSPIROSIS

AGE – ACUTE GASTROENTERITIS

UTI – URINARY TRACT INFECTION

VIR – VIRAL SYNDROME – UNKNOWN CAUSE

MODS – MULTIORGAN DYSFUNCTION SYNDROME

ARDS – ACUTE RESPIRATORY DISTRESS SYNDROME

HEP – HEPATOPATHY

AKI - ACUTE KIDNEY INJURY