A Handbook for Physicians

FEVER

From Evidence to Action

Compilation of articles from

FeFCon-2018

Fever Foundation Conference 2018, Bengaluru

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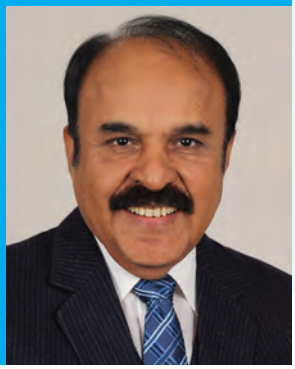
FOREWORD



It is not once nor twice
but times without number
that the same ideas
make their appearance in the world.
Aristotle

Happy to know Fever Foundation is coming up with a book covering various facets of fever!

Topics like Pyrexia without localising signs, Fever investigation, evaluation & interpretation, Zone Specific Infectious Disease, Scrub Typhus, Approach to Fever, Management of Fever and Fever in special circumstances augurs Well.

With the rapid expansion of the frontiers of knowledge, the medical profession requires updated, vibrant & alert practitioners. A book like this enables the practitioner to have comprehensive understanding of diseases and their management.

I assume that this book will benefit & augment physicians & paediatrics in day to day practise, providing better health care for the patients!

"A room without books is like a body without a soul." Hope this book finds a place in every doctor's chamber & remains a Ready Reference Guide!

"A little reading is, all the therapy a person needs sometimes"

Happy Learning & Happy Learning!

Dr. A. Muruganathan
Chairman – Fever Foundation CME Committee
Governor – American College of Physicians India Chapter
Past Dean – India College of Physicians of India
Past President – Association of Physicians of India
Past President – Hypertension Society of India

PROLOGUE

Fever Foundation is an Independent, non commercial foundation supporting the educational/ academic activities to address the unmet needs in fever management. The foundation is committed to conceive, build, and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals.

The First Annual National conference of Fever Foundation, FeFCon 2018 was held on 17th and 18th November, 2018 at Le Meridien, Bengaluru. Interesting presentations by highly esteemed and renowned speakers from across India was delivered in the two days academic feast.

This book is the salient capture of the sessions on fever management which can be of substantial help in day to day practice.

Happy Reading!

Dr Manjula S
Organizing Secretary,
FeFCon 2018

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Infectious diseases: Current Issues

Dr. M. Maiya
Chief Patron, Fever Foundation of India, Bengaluru,
Former Professor of Medicine, Karnataka Medical Service,
Senior Physician, Rangadore Memorial Hospital, Bengaluru, India.

Introduction

Infectious diseases are disorders caused by pathogenic organisms such as viruses, bacteria and fungus.[1] Infectious diseases still remain a major cause of death and debility in the 3rd world countries. Recent years have seen the emergence of new diseases like HIV, SARS, swine and bird flus and resurgence of older ones like malaria, typhoid and tuberculosis. Despite the advanced knowledge and novel therapeutic modalities, clinicians are witnessing newer challenges in the diagnosis and management of infectious diseases.[2]

Fever is the most common manifestation of the disease, with many diagnostic possibilities. In most cases of febrile illness, initial clinical examination and basic investigations provide clues for diagnosis and management. Documentation of fever is essential to know the pattern and exclude cases with 'feverishness'.

Current challenges in managing infection

The major challenges confronted by clinician in the management of infectious diseases are listed below:

- Changing pattern of diseases: typhoid, tuberculosis, leptospirosis etc.
- Newer Infections: HIV, SARS, swine and avian flu (H1N1)
- Multiple infections: typhoid, malaria, leptospirosis, and brucellosis in various combinations
- Patients: Partially treated and immunocompromised

- Nosocomial and opportunistic infections due to frequent hospitalizations
- Septic shock syndrome
- Intravascular and artificial valve infection
- Bacterial resistance
- Investigations: too many investigations causing confusion in diagnosis
- Pharmacoeconomics: balancing efficacy and safety of drug with utility and cost of the drug

1. Changing pattern of the diseases

Case scenario 1: A case of nephro-neuro typhoid

A 40-year-old male patient presented as fever presented as acute nephrotic syndrome requiring dialysis. Nephrologist and neurologist referred the case, as the fever was not subsiding after 10 days. *S.Typhi* was identified in blood culture and confirmed the condition as typhoid presenting as acute nephrotic syndrome, which was responding only to an older drug chloramphenicol. The patient improved with chloramphenicol treatment and developed cerebellar ataxia on 13th day, which is common during recovery. His condition slowly progressed and completely recovered from typhoid within four weeks.

Case scenario 2: Typhoid hepatitis

A 16-year-old girl, treated as typhoid a week ago with pefloxacin, returned with jaundice, fever and splenomegaly. The current symptoms confused the diagnosis as enteric fever, malaria, viral hepatitis or leptospirosis. Ultimately, the blood culture showed the growth of *S. Typhi* sensitive to chloramphenicol, and resistant to ciprofloxacin and pefloxacin. The patient was treated for typhoid hepatitis with chloramphenicol 500 mg and furoxone 100 mg.

2. Multiple infections

Case scenario 1: Coinfection of typhoid and malaria

The coinfection of malaria and typhoid fever is comparatively very common. Their mimicking symptomatology often leads to misdiagnosis and mistreatment.[3]

A 30-year-old male presented with the history of fever for 7 days and jaundice for 5 days. On examination he was febrile, mildly jaundiced and had hepatosplenomegaly. He was treated with chloroquine for malaria, as the infection was due to *Plasmodium falciparum*. Since the fever was persisting after 5 days of treatment, Widal test was done and was positive. The patient was subsequently started with ciprofloxacin treatment. The patient could achieve improvement in fever and other associated symptoms.

Case scenario 2: Combination of malaria, typhoid and leptospirosis infections

A 35-year-old agriculturalist, during his first admission, was found to be positive for *P. Vivax* and started with chloroquine treatment for malaria. Due to the persistence of fever, Widal test was carried out and was found to be positive for typhoid. Though the patient was started with ofloxacin for 5 days, the fever did not subside. When he was referred to Dr. Maiya, he had conjunctival suffusion, post-auricular and post-cervical lymphadenopathy, and hepatomegaly. He also demonstrated the signs of meningeal irritation. The patient was prescribed to undergo microscopic agglutination test (MAT) and

CSF culture. These tests helped in diagnosing leptospirosis. Fine needle aspiration cytology (FNAC) and silver staining also confirmed the presence of leptospira (Fig. 1). His fever subsided on treatment with crystalline penicillin injection (Fig. 2). This is a clear case of multiple infection: malaria, typhoid and leptospirosis.

Fig. 1: Leptospira in silver stain

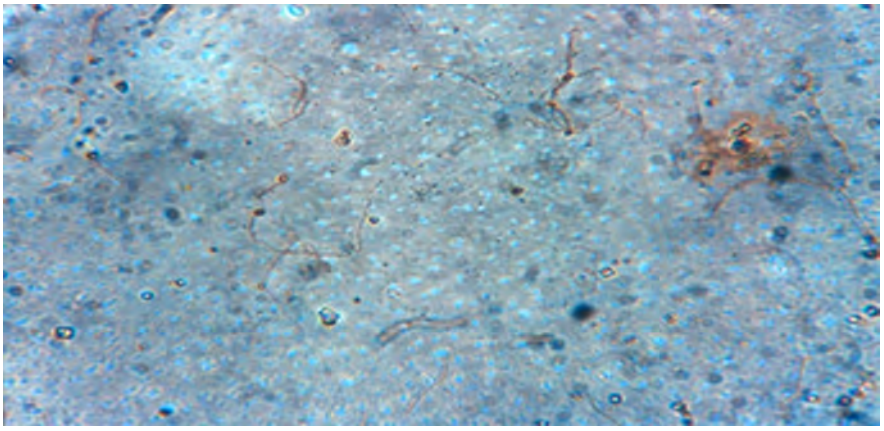
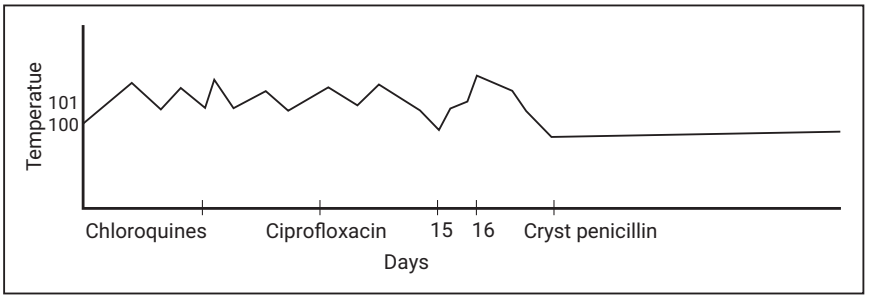


Fig.2 Response of fever in multiple infection treatment



Case scenario 3: Combination of glomerulonephritis, tuberculosis and lymphadenopathy

A 42-years-male, a diagnosed case of chronic glomerulonephritis on conservative management, presented with fever, weight loss, loss of appetite and vomiting. Routine examination could not raise any suspicion. But reexamination and biopsy of supraclavicular lymph node led to the diagnosis of tuberculosis. Chest X-Ray confirmed the presence of hilar lymphadenopathy.

Case scenario 4: Combination of rare diseases

A 22-year-old female presented with complaints of high-grade fever, oral ulcers, swellings in the neck and loss of weight. She was treated for multiple lymphadenopathy with antibiotics ciprofloxacin, amoxicillin and cephalosporins and anti-malarials. Since the patient was not responding to any of these treatments, a reexamination and investigation were carried out and brucellosis was identified. She was subsequently treated with rifampicin and doxycycline. Fever subsided in 8 days but the lymphadenopathy persisted, and the patient was prescribed to undergo lymph gland biopsy. Biopsy showed histiocytes, necrosis and karyorrhexis, which are the classical histopathologic features of

Kikuchi's disease. This case is a definite example for combined occurrence of rare diseases i.e. brucellosis and Kikuchi's. Since Kikuchi's disease does not need any treatment, the patient recovered within 6 months.

Kikuchi-Fujimoto disease is a benign and self-limited disorder that affects lymph nodes. It is marked by regional cervical lymphadenopathy with tenderness, mild fever and night sweats. [4] Spontaneous recovery occurs in 1 to 4 months. However, such patients should be followed-up closely for several years to rule out the development of systemic lupus erythematosus.[4]

3. Immunocompromisation

Immunodeficiency (or immune deficiency) is a state in which the immune response is compromised to fight against infectious diseases. Most cases of immunodeficiency are acquired.[5] The conditions and diseases that are associated with secondary immunodeficiency (acquired) include AIDS, extremes of age, pregnancy, malnutrition, trauma/surgery, dialysis, Cushing's disease, IV drug abuse, splenectomy, alcohol abuse, chronic kidney disease, diabetes, liver disease, malignancy, and therapeutic immunodeficiency with immunochemotherapy and steroids. If an immune compromised person gets an infection; onset pattern, course and response are different.

Case scenario 1: Atypical tuberculosis infection in lymphatic leukemia

A 65-year-old female presented with complaints of fever, cough and mucopurulent sputum for 8 days. She was a known case of chronic lymphatic leukemia and was on Leukeran and prednisolone. Chest X-ray showed right lower lobe pneumonia. But the patient did not respond to Augmentin, and ceftriaxone. Sputum AFB was positive for tuberculosis and was treated with antituberculous medication. This is a very good example for the atypical pattern of infection in immunocompromised patients.

4. Nosocomial infection

Infection acquired during or as a result of hospitalization. Infection incubating at the time of hospital admission (infection occurring less than 48 hours of hospital admission) is not nosocomial. If the patient is infected during hospitalization, but the disease manifests after discharge is nosocomial[6]. The most common types of hospital-acquired infections are:[6]

- Urinary tract infections (UTIs)
- Surgical site infections
- Lower respiratory tract infections
- Blood stream infections

5. Bacterial resistance

Primary resistance is comparatively rare than acquired bacterial resistance. Various mechanisms of bacterial resistance are listed below:[7]

1. Inactivation of drugs by enzymes like β-lactamases, chloramphenicol acetyl transferase and amino-glycoside modifying enzyme
2. Decreased permeability of drugs
3. Active elimination of compound from peri-plasma or interior of the cell

4. Acquisition of new genes encoding drug-insensitive target or over production of antibacterial target. Eg: quinolones, rifampicin and vancomycin

The major mechanisms of resistance to the anti-bacterial agents are listed in table 1.[7]

Table 1: Major mechanisms of resistance to the anti-bacterial agents

Antibacterial agents	Major mechanisms of resistance
β lactams (Penicillins and Cephalosporins)	Drug inactivation (β- lactamase) Insensibility of target Decreased permeability Active efflux
Chloramphenicol	Drug inactivation (Chloramphenicol acetyl transferase) Active efflux
Aminoglycosides	Drug inactivation (Aminoglycoside modifying enzyme) Decreased permeability Active efflux
Quinolones	Insensitivity of target (mutation of gyrate genes) Active efflux
Rifampicin	Insensitivity of target (mutation of polymerase genes)
Vancomycin	Alteration of target (alteration of target)

Bacterial resistance can be prevented by avoiding unnecessary and ineffective use of antibiotics, and improper dosage, duration of therapy and drug combinations. Preventing the transfer of resistant organism by barrier nursing, aseptic precautions and hand washing is another effective strategy.

6. Investigations

Investigations should be able to detect:

Organisms by microscopy

- Culture techniques
- Molecular technology
- Indirectly by serology

There are many limitations for investigations like malaria: slides vs. dipstick/ card tests, typhoid: Widal test, Montoux test and PCR (Sensitive and specific, but does not indicate activity). All these tests are not 100% accurate. It is important to interpret the test finding based on the background of the patient. Ultrasound examination is the single most useful investigation for diagnosing pyrexia of unknow origin. It is a simple, bedside, and inexpensive investigation. It is useful in diagnosing abdominal / pelvic conditions, like organomegaly, lymph node enlargement, vascular obstruction, and various masses inaccessible to palpation. CT and MRI scans are comparatively costlier and shuld be reserved for necessary conditions.

7. Economics of managing infections

In the recent years, cost of management of infectious diseases has increased due to the availability of vast number of investigations and drugs. If feasible, it is appropriate to use older antibacterial

drugs, which are less costly. Recently detected costlier antibiotics can be used for empirical therapy. It is recommended to weigh benefit vs. cost, in each case, while prescribing the drug.

Conclusion

Points to be remembered, while managing infectious diseases, are the following: Document the fever, proceed with relevant investigations, understand the immune status of the patient, identify the uncommon manifestations, check whether the patient is in partially treated state (with or without drug resistance), reexamine for multiple infections, and identify whether the fever is drug induced.

Points to ponder

Uncommon manifestations of common diseases are more relevant than common manifestation of uncommon disease.

Re-examination of the patient is more useful than re-investigation.

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Fever pathophysiology

Dr. G.Narsimulu Gumdal
Rheumatologist , GVN Medical Centre, Dean, ICP /API
Former Prof & HOD Rheumatology NIMS, Past President,
Indian Rheumatology Association
Hyderabad, India

Introduction

Fever, an adaptive mechanism noted in vertebrates in response to an infection, is caused by substances known as pyrogens.[1] These pyogenes may act directly or indirectly on the hypothalamic thermoregulatory center. The present paper summarizes control mechanisms of body temperature, the circadian rhythm of body temperature, pathogenic and physiologic factors associated with the temperature elevation, normal and abnormal body temperature, etiologic classification of fever and treatment of the fever (in high-risk patients).

Control mechanisms of body temperature

Fever is defined as any elevation of body temperature mediated by an increase in the hypothalamic heat regulatory set-point.[2] The body maintains its core temperature at around 37° C by physiological adjustments mediated by the brain, more specifically hypothalamus. The preoptic area of hypothalamus serves as temperature-regulating centers (the anterior portion). This area receives signals from the peripheral cold and warm neuronal receptors present in the skin and mucous membranes (peripheral thermoreceptors) as well as from central thermoreceptors (from internal structure. The sensory signals from the preoptic area and periphery are combined in the posterior hypothalamus to regulate the heat generating and conserving reactions of the body. Other hypothalamic, autonomic and higher nervous thermoregulatory centers also play a crucial role in keeping the temperature constant.[3]

The hypothalamus sends signals to the skin, glands, muscles, and organs for regulating the

temperature (Fig. 1). For example, when the body senses hot external environment or high levels of exercise activity, the temperature of the body rises, causing the hypothalamus to send signals to the skin cells for producing sweat and for inhibition of the adrenergic activity of the sympathetic nervous system. This in turn causes cutaneous vasodilation and basal metabolic rate (BMR) reduction. In contrast, in response to a cold environment, the body sends signals for shivering reflex and activation of arrector pili muscles in the skin. These processes in turn assist in bringing warmth and heat to the body.[4] The gradual decrease in environmental temperature contributes to the release of thyroid stimulating hormone (TSH), which in turn induces thyroid gland to increase metabolic rate to increase the production of body heat. As the body gets warmer, the hypothalamic sensors reduce the heat production and the stimulus activating heat loss prevention responses.[3] The factors determining the rate of heat production in the body include: BMR, muscle activity, and effects of thyroid hormones, epinephrine and norepinephrine.

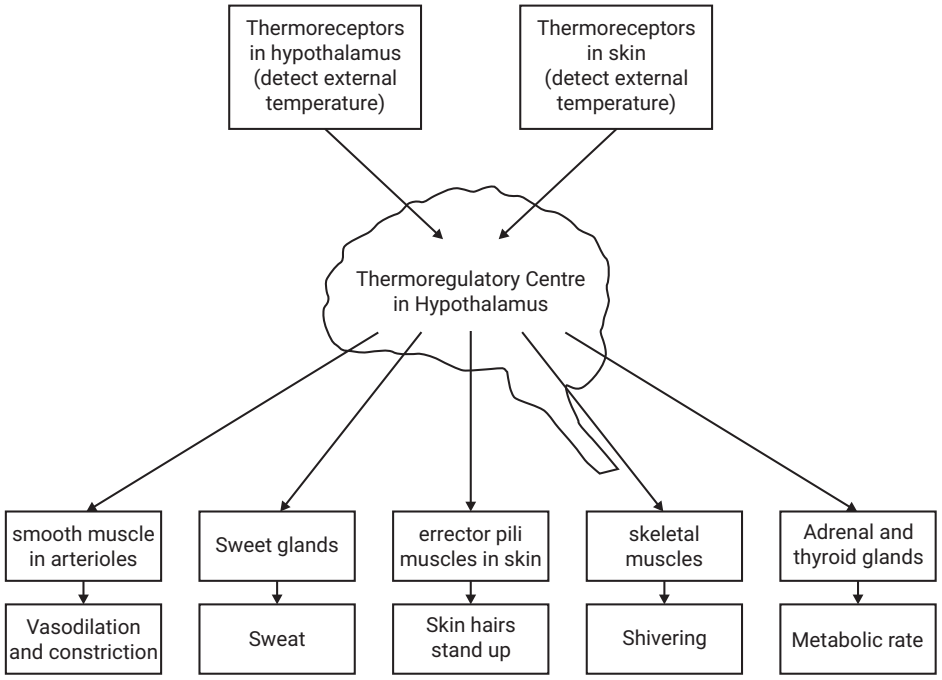

Fig. 1: Action of thermoregulatory center in hypothalamus[5]

The mechanisms through which the body regulates the temperature are listed below:[6]

Heat loss

- Radiation: Loss of heat from body in the form of infrared rays.
- Conduction: Heat is conducted from body to objects in contact, e.g. chair, bed, etc.
- Convection: Heat is lost from body through air currents.
- Evaporation: Evaporation of water from body surface in the form of sweat
- Vasodilation

Heat production

- Increased cell metabolism
- Muscle activity
- Involuntary shivering
- Heat conservation
- Vasoconstriction

Stages of fever

The fever generally develops through 4 stages. However, not all patients pass through all the 4 stages. The stages noted are describe below:[7]

- Prodromal stage

The patient may show non-specific symptoms including fatigue, mild headache, general malaise and body pain

- Second stage

In this stage, the patient's skin may appear pale with generalized shaking, chills and feeling of being cold. Vasoconstriction and piloerection are commonly noted.

- Third stage or flush

The patient feels too hot, as the cutaneous vasodilation makes the skin warmer and flushed.

- Defervescence

The patient's body temperature becomes normal and the stage is marked by sweating.

Pathogenesis of fever

Bacterial products and other external fever-causing substances constitute exogenous pyrogens.[8] For example, lipopolysaccharide (endotoxin) of gram-negative bacteria and enterotoxins of *Staphylococcus aureus*. Whereas endogenous pyrogens are host-derived, fever producing molecule (example: cytokines). Pyrogenic cytokines include IL-1, IL-4, IL-6, TNF, ciliary neurotropic factor (CNTF), IFN-alpha.[8] The endogenous pyrogenic cytokines mediate the resetting of temperature regulatory set point through prostaglandin E2. The fever response to endogenous pyrogens happens within 10-15 minutes, the response to exogenous pyrogens may take 60- 90 min, as it requires the production and release of pyrogenic cytokines.

Physical factors influencing body temperature

Gierse in 1842 studied the circadian rhythm of core body temperature based on his own oral temperature. The researcher demonstrated that minimum temperature occurs early morning and the maximum in the early evening between 4-6 PM.[9] The physical factors that may influence the body temperature include physical activity (maximum 1.1° C), digestion, changes in environmental temperature, after ovulation in women, first 3 months of gestation and excitement.[10]

The comparison table given below provides the approximated range of fever for each type of fever

Table 1: Temperature scales based on the fever grade

Fever grade	Celsius (°C)	Fahrenheit (F)
Hypothermia	<35	<95
Subnormal	35-36.7	95-97
Normal	36.7-37-2	98-99
Mild fever	37.2-37.8	99-100
Moderate fever	37.8-39.4	100-103
High fever	39.4-40.5	103-105
Hyperpyrexia	>40.5	>105

Patterns of fever

Though the clinical usefulness of fever patterns is still unclear, generally 5 patterns are noted. The 5 patterns are intermittent, remittent, continuous or sustained, hectic, and relapsing. The characteristics and examples of each pattern is listed in table 2.[11]

Table 2: Characteristics and examples of each fever pattern

Fever patterns	Characteristics	Examples
Continuous fever	Temperature >37°C throughout the day, does not fluctuate > 1° C in 24 hrs	Lobar pneumonia, urinary tract infection, infective endocarditis, brucellosis
Remittent fever	Temperature may persist above normal throughout the day, fluctuate > 1° C in 24 hrs	Typhoid, viral upper respiratory tract, legionella, mycoplasma infections
Intermittent fever	Elevated temperature persists for some hours in a day and remits to normal	Pyogenic infection, lymphoma, miliary TB
Relapsing fever	Fever spikes are noted with intermittent normal temperature for days or weeks • Daily spike- quotidian • Every alternate day- Tertian • Every third day –Quartan	Malaria, kala-azar, cholangitis, infections with *Borrelia recurrentis,* Hodgkin's disease (Pel-Ebstein fever), and other neoplasms

Diseases with distinct fever patterns

Some diseases are associated with characteristic fever pattern. Aseptic fever is noted in: acute myocardial infarction, sarcoidosis, chronic renal failure, collagen vascular diseases, drug fever, radiation sickness, and post-surgical patients. Some of the diseases with distinct patterns are discussed below:[11]

Drug fever

It is characterized by prolonged fever, relative bradycardia and hypotension. It persists 2-3 days even after drug is withdrawn. Eg. fever related to penicillin, procainamide, propylthiouracil, sulphonamides, and anticonvulsant

Fever with relative bradycardia

This characteristic fever pattern is noted in typhoid fever, meningitis, viral fever (influenza), brucellosis, leptospirosis and drug-induced fever.

Fever with rigors

This pattern is generally found in malaria, kala azar, UTI, septicemia, infective endocarditis, Collection of pus in body, lobar pneumonia, cholangitis and pyelonephritis.

Fever with rash

In chicken pox, the rashes appear on the 1st day of fever. Whereas, in measles and typhoid, the rashes commonly appear on the 4th and 7th day respectively.

Fever with delirium

It is commonly seen in encephalitis, typhoid, meningitis and hepatic encephalopathy.

Hyperpyrexia

The extremely elevated temperature beyond 105°F is termed as hyperpyrexia. The causes include: pontine hemorrhage, rheumatic fever, meningococcal meningitis, cerebral malaria, septicemia and encephalitis.

Pyrexia of unknown origin (PUO)

The key features of PUO are persistence of temperature >102.2°F, fever >3weeks duration and failure to conclude the diagnosis even after 1 week of evaluation. The causes of PUO include: abscesses – subphrenic / liver / retroperitoneal, UTI, endocarditis, hepatobiliary infections, osteomyelitis, HIV, parasitic infections, malignancy, collagen vascular disease, factitious fever, hyperthyroidism and sarcoidosis.[12] The following are the malignancies associated with PUO: Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, hepatoma, renal cell carcinoma and colon cancer.

Neuroleptic malignant syndrome

It is a rare, life-threatening, idiosyncratic reaction to neuroleptic medications. The disease is characterized by lead pipe muscle rigidity, extrapyramidal side effects, autonomic dysregulation and hyperthermia. The disease is generally indistinguishable from malignant hyperthermia. The drugs that can cause the syndrome include succinylcholine, phenothiazine, haloperidol fluoxetine, loxapine etc.[13]

Malignant hyperthermia

It is a rare autosomal dominant disorder that manifests as a hypermetabolic reaction to volatile anesthetic agents (e.g., desflurane, enflurane, halothane, sevoflurane) or the depolarizing muscle relaxant, succinylcholine. Absence of the hypothalamic regulated circadian rhythm is seen in affected subjects. It is also noted in patients with various myopathic disorders.[14]

Limitations of current treatment

The use of antipyretic therapy is controversial in normal children, as it does not alter the course of common infectious diseases.[15] It is recommended in high-risk patients with chronic cardiopulmonary diseases, metabolic disorders, neurologic diseases and febrile seizures. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the commonly used antipyretic agents with proven antifever effect.[16]

The widely used NSAIDs include aspirin, ibuprofen and acetaminophen. Studies report that administration of aspirin may increase the risk of Reye's syndrome.[17] High dose acetaminophen is associated with renal injury and hepatic failure. The continuous use of Ibuprofen may increase the risk of dyspepsia, gastrointestinal bleeding, reduced renal blood flow, aseptic meningitis, hepatic toxicity, and aplastic anemia.

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Immunology of fever and interpretation of immune markers

Dr. Chandrashekara S
Managing Director,
ChanRe Rheumatology and Immunology Centre,
Bengaluru, India

Introduction

Inflammation is body's natural response against any external or internal stimuli that perturb the normal homeostasis.[1] Although inflammation was initially noted as a part of simple clinical symptoms; over the years, it has evolved to define a more complex phenomenon. Despite the recent advances in understanding immunology, the exact definition of inflammation is still uncertain.

Over 600 million years of evolution, fever has evolved as a cardinal response to infection that has been conserved in vertebrates.[2] Integrated physiological and neuronal circuitry is essential for executing fever response during infection and it offers a survival benefit.[2] Generally, elevated body temperature helps the person to resolve an infection and the recent research has identified that fever enhances the functioning of certain immune cells.[3] However, in certain scenarios, the increase in temperature may be too high, which can be serious leading to several complications.[4]

Even the temperature elevation is seen in highly localized inflammation like cellulitis. This response, termed as calor, is one of the cardinal signs of inflammation. In general terms, it is considered as fever. The fever response, which has been identified as a hallmark of infections and inflammatory diseases, assists in limiting the multiplication of infectious agents and enhancing the host immunological response against infections.[5] Febrile temperature is closely associated with inflammatory response, subsequently contributing to survival and resolution of infections.[2]

Elevated temperature enhances the innate immunity

Fever-range temperatures play a paramount role in triggering several important aspects of innate immunity. They induce the production of neutrophils from the bone marrow in a granulocyte–colony-stimulating factor (G-CSF)-driven manner. They are responsible for neutrophil recruitment to the lungs and other local infection sites in a CXC-chemokine ligand 8 (CXCL8)-dependent fashion. The thermal stress at the site of infection further accentuates the respiratory burst, which in turn contributes to the bacteriolytic activity of neutrophils. Thermal treatment enhances the cytolytic activity of natural killer (NK) cell in 2 ways: 1) induction of MHC class I polypeptide-related sequence A (MICA) expression on target cells (for example, tumor cells) 2) promoting the clustering of the MICA counter-receptor NKG2D on the surface of NK cells.

The febrile-range temperatures enhance the potential of antigen-presenting cells in eliciting adaptive immune response. The phagocytic potential of the macrophages and dendritic cells (DCs) is enhanced by the heat and it also improves their responsiveness to invading pathogens by increasing the expression of both Toll-like receptor 2 (TLR2) and TLR4. Elevated temperature also enhances the production of various immunomodulatory molecules such as cytokines (for example, TNF), nitric oxide (NO) and heat shock protein 70 (HSP70). It also enhances the expression of MHC class I and II molecules as well as co-stimulatory molecules (CD80 and CD86) by mature DCs and their CC-chemokine receptor 7 (CCR7)-dependent migration via the afferent lymphatics. The exposure of DCs to febrile temperatures improves their efficiency in cross-presenting antigens and inducing T helper 1 (Th1) cell polarization. [2]

Elevated temperature and adaptive immune response

In lymph nodes, fever-range temperature augments adaptive immunity by targeting two distinct aspects of T cell activation. In peripheral lymph nodes, the effects of heat on each step of the adhesion cascade enhance the rate of lymphocyte trafficking across high endothelial venules (HEVs). The heat exposure of lymphocytes increases the frequency of L-selectin-dependent tethering and rolling interactions. The independent action of febrile-range temperatures on HEVs improves the transition of lymphocytes from transient rolling to stable arrest by enhancing the intravascular density of CC-chemokine ligand 21 (CCL21) and intracellular adhesion molecule 1 (ICAM1). Lymphocyte crawling to inter-endothelial cell junctions and transendothelial migration are also supported by ICAM1. Within the lymphoid organs, elevated temperature has a direct effect on the T cells by pre-clustering components of the immunological synapse (TCRβ and CD8) into lipid rafts. This assists in persisting the contacts with APCs and promoting $CD8^+$ T cell differentiation towards an effector phenotype marked by enhanced cytotoxic function, L-selectin downregulation, and production of interferon-γ (IFNγ) (Fig. 1).[2]

Increased temperature helps in achieving optimal immune response, but at the cost of elevated metabolic and neuro-endocrinal functions.

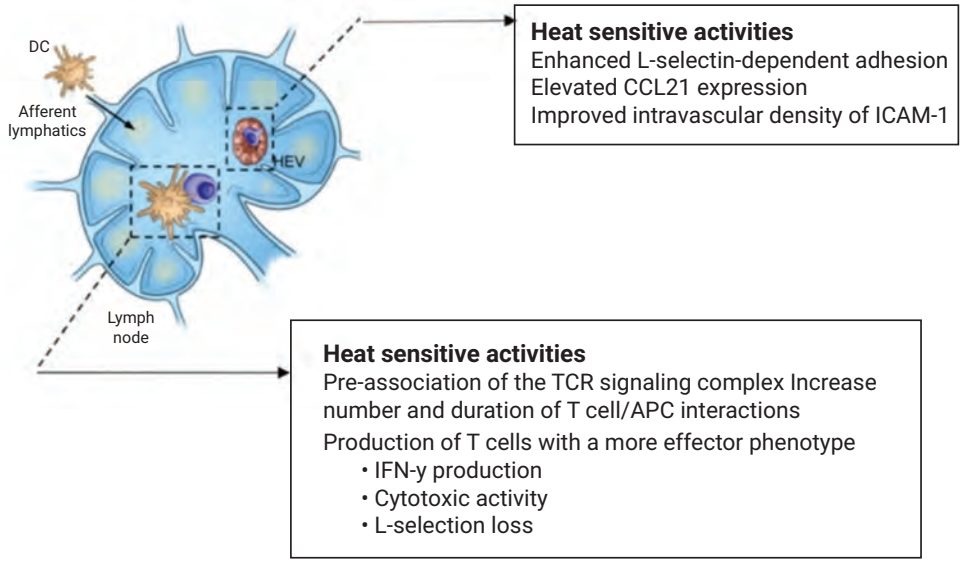


Fig. 1: Role of elevated temperature in eliciting adaptive response[2]

Markers of inflammation

The inflammation may be intense and may sometimes spill over to the surrounding milieu. This may be reflected in multiple organs at various levels. Hence, a measure of inflammation should consider all the associated factors to quantify the effect. The markers of inflammation may depict different perspective of this spill. For example, acute phase response from the liver for the localized inflammation (septic arthritis) suggests a systemic spill. This effect depicts the quantum of spill rather than the intensity of inflammation (Fig. 2).[6]

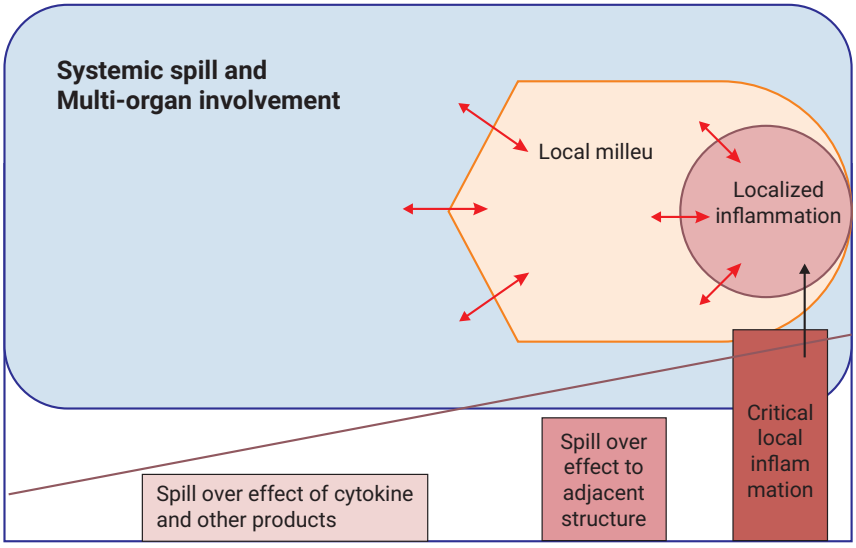
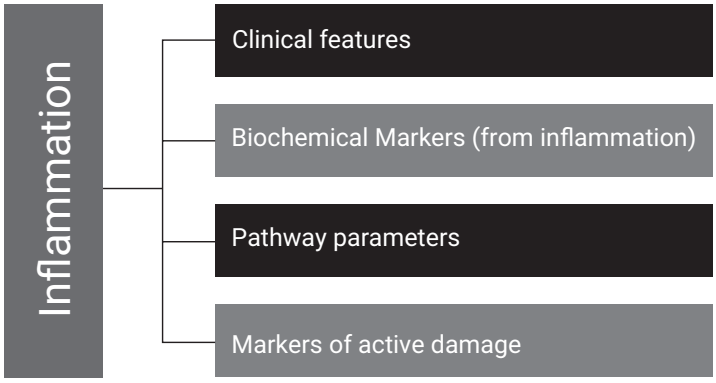


Fig. 2: Effects of inflammation at various levels and sites

The observable variables, indicating inflammation, can be broadly classified as clinical variables and biological markers. The clinical variables assist in qualifying and quantifying the cause of inflammation. Whereas, the biological markers employed represent different stages of inflammation. Several possible ways to measure an inflammation are depicted in figure 3. Acute phase responses occur as a consequence of inflammation. They assist physician in decision making on management strategies.

Fig. 3: potential biomarkers of inflammation



The role of inflammatory parameters, especially in acute phase response, is already well established in clinical conditions like fever and infections, autoimmune diseases including rheumatological disease, and in risk profiling of cardiovascular diseases.[7] The probable role of inflammatory parameters is yet to be established in cancer treatment, diabetes and other metabolic syndrome, ischemic heart disease and stroke, psychiatric disorder and neurological disorders of degenerative nature. Increase in the levels of serum proteins, which are referred as acute phase reactants (APR), occur as a consequence of set of systemic and metabolic changes associated with inflammation. Increase in APR levels is noted in tissue injury, infection, trauma, rheumatoid and systemic inflammatory disease, advanced malignancy, child birth, and sometimes in extraneous exercise.[8] APRs are highly non-specific and need to be investigated along with other clinical features. Assessment of clinical features, along with APR, assists in regionalizing the site of inflammation/infection as well as in identifying the reason for altered lab investigations. CRP, ESR, procalcitonin and ferritin are already established parameters used to measure inflammation. The role of other parameters like NLR, PLR, IL6 and other hematological parameters is yet to be established.

Some of the markers like pro-calcitonin may indicate the cause for the inflammation. Their levels assist in concluding the presence of infection. NLR ratio can suggest the possibility of sepsis and increased mortality. Non-specificity is the major limitation of these inflammatory markers. Their ratios and proportions may vary, based on the etiological factors responsible for the trigger, and they are yet to be elucidated.

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HYPOTHERMIA

DR. B A. Muruganathan., MD
FICP., FACP (USA), FRCP (GLASG, LONDON & IRE), FPCP (Philippines),
Emeritus Professor – The Tamil Nadu Dr.M.G.R Medical University

Introduction

In low-resource settings, hypothermia has been identified as the major contributor of neonatal morbidity and mortality.[1] Hypothermia is defined as falling of the body's core temperature below 35°C (95°F or less). It is broadly categorized into three: mild hypothermia (35-32°C), moderate hypothermia (32-2°C), and severe hypothermia (below 28°C). It can occur even without cold exposure.

Hypothermia in newborns

During foetal development, the core body temperature is closely related to that of mother, and as such, the core temperature of the fetus will normally remain consistent and approximate 1°C above that of the mother. After birth, skin temperature falls by 0.3 C/min and core temperature by 0.1 C/min due to the starting of heat loss mechanisms.[1] In developing countries, the prevalence of hypothermia in newborns is attributed to be around 15%. An 8-year study conducted in Ethiopia has noted that 67% of low birth weight and high-risk infants admitted to a special care unit from outside were hypothermic.[2] In addition, neonatal mortality rate in hypothermic babies is reported to be twice that of normal newborns.[3] Though, it has been identified as a significant problem in neonates at birth and beyond, its contribution to neonatal mortality and morbidity is still elusive.

Vulnerability of newborns to hypothermia

Neonates are at high risk to rapid heat loss and leads to hypothermia because of increased body surface area compared to their weight. Relative to body weight, the body surface area of a newborn

is 3 times higher than that of adult. Hypothermia is relatively high in low birthweight babies and preterm babies due to lesser subcutaneous fat or brown fat, underdeveloped shivering and sweating mechanisms, and limited calorie intake to provide nutrients for thermogenesis.[4]

The conditions that may increase the risk of hypothermia in newborns are briefed below: substrate deficiency, central nervous system conditions, drug overdose with agents that cause vasodilation, generalized infection, endocrine or metabolic diseases that impair energy utilization or basal metabolic rate, increased insensible losses due to disruption of skin, decreased calorie intake and other conditions like hyponatremia, episodic spontaneous hypothermia with hyperhidrosis, child abuse and maltreatment.[5]

Hypothermia in elderly

Older adults lack the ability to shiver due to reduced muscle strength, which in turn impairs the mechanism of thermogenesis. Since, elderly people have thin epidermis, it affects the thermal insulation. Lack of cardiovascular reserve for compensation and lower cardiovascular stability also lead to hypothermia in elderly. Limited activity and reduced metabolic rate affect the thermogenesis mechanism in elderly. The risk of hypothermia in such subjects is very high because their bodies' response to cold can be influenced by the presence of some diseases like diabetes and by the use of some medicines including over-the-counter medications.[6]

Measuring core temperature

Hypothermia in neonates is generally measured using a low-reading rectal probe thermometer. Ideally, the core temperature should be measured using nasopharyngeal, esophageal, bladder or central venous catheter temperature probes. The rectal lags behind esophageal during rewarming.[7]

The clinician should not use standard clinical thermometers in hypothermic patients because they do not read below 34°C (93°F). The oral, axillary, infrared, and indirect tympanic membrane sites are unreliable. Electronic thermometers may not be accurate if left in the cold.

Pathophysiology

Body temperature reflects the balance between heat production and heat loss.

(A)Thermogenesis

As a response to cold stimulus, the hypothalamus attempts to induce heat production through shivering and increasing the production thyroid and catecholamine, and adrenal activity. This process is known as non-shivering thermogenesis. Sympathetically mediated vasoconstriction minimizes heat loss by reducing blood flow to peripheral tissues, where cooling is greatest.

(B) Heat loss

Heat is generated by cellular metabolism (most prominently in the heart and liver) and lost by the skin and lungs via. the following four processes: evaporation, radiation, conduction, convection (Fig. 1).[8]

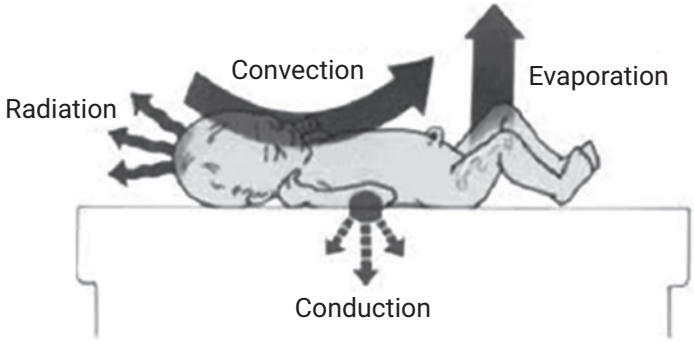


Fig. 1: The four ways in which a newborn achieves thermal balance

Impaired thermoregulation, a known complication associated with diverse diagnoses, is commonly seen among patients attending physical medicine and rehabilitation clinic. The causes of impaired regulation can be broadly classified as central, peripheral, metabolic and medication-related (Table1).[9]

Table 1: Causes of impaired thermoregulation

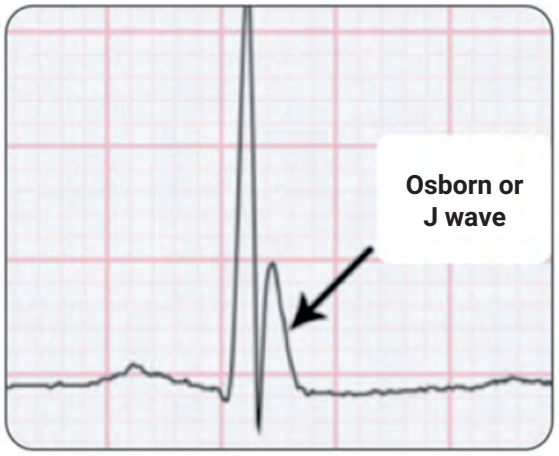
Central	Trauma or Neoplastic lesions, degenerative processes, congenital
Peripheral	Acute spinal cord transection (loss of peripheral vasoconstriction)
Metabolic	DKA, uremia, hypoglycemia, sepsis, pancreatitis
Medications	Narcotics (stops shivering response) barbiturates, benzodiazepines, anti-seizure meds, anti-psychotics and sedative, NSAIDS

Signs of hypothermia

Early clinical signs that should arouse suspicion of cold stress due to hypothermia are: cold lower extremities, weak sucking ability, reduction in activity-lethargy, weak cry, pale extremities, central cyanosis, and sclerema.[10]

Laboratory investigations suggestive of hypothermia

- **Arterial blood gas (ABG) test:** 30% show acidosis and 25% alkalosis
- **CBC:** Rise in hematocrit (hemoconcentration), increase in viscosity, leukopenia, and thrombocytopenia
- **Glucose:** High-acute, low-chronic and subacute
- **Amylase:** Elevated in up to 50%
- **PT/PTT:** Coagulopathies common at <35°C
- **Cultures** if infection is suspected
- **Electrocardiography (EKG)**: Bradycardia/Osborne J waves in lead V3 and V4/atrial or ventricular arrythmias. Though not pathognomonic, the J wave or 'Osborn' wave is commonly noted in many cases of hypothermia (Fig. 2).[11]



- Size of wave correlates with degree of hypothermia
- Typically appears below 32°C
- Usually resolves with warming
- No prognostic value

Fig. 2: 'Osborn' wave commonly noted in hypothermia[12]

General management of hypothermia

Intensive care is preferred for management of hypothermia. The management strategies are briefed below: airway, breathing and circulation (ABC) management; continuous core temperature and cardiac monitoring; rewarming measures; continuous rehydration via central line for elderly; insertion of Foley's catheter and NG tube; and assessment and treatment of associated illnesses/ injuries. Handling the patient and physical examination need to be gentle to avoid cardiac dysrhythmias.[13]

Prevention of hypothermia – warm chain

The World Health Organization (WHO) has proposed a series of interlinked procedures, termed as 'warm chain', to minimize/prevent the risk of hypothermia in newborns. This include: warming the delivery room (>25^0 C), warm resuscitation, immediate drying, postponing bathing, appropriate clothing, placing mother and baby together, skin-to-skin contact, breastfeeding, professional alert warm transportation, application of oil and liquid paraffin to reduce skin evaporation, and educating mother and health workers.[9]

First aid management of hypothermia

Immediately transfer the victim to a dry sheltered area and change the wet clothes. Wrap the person in a blanket including head and neck. Provide warm pads or other warm objects behind the neck and armpits, and provide warm drink and high energy food. The patient should be encouraged to perform light physical activity to generate heat.[10]

Rewarming techniques

The decision to use passive or active rewarming techniques may depend upon the degree of hypothermia and diverse clinical parameters. The passive rewarming is intended to prevent further heat loss and the steps include shifting the patient to a warm, dry environment and providing adequate

insulation.[14] Active external rewarming techniques involve direct application of heat to raise the core body temperature. Th methods used are air rewarming, radiant heat, or direct heat from heating pads or chemical heat packs. Active internal rewarming are the techniques used to heat the patient internally. The non-invasive techniques include providing warmed oral fluids and heated humidified oxygen, and warm intravenous normal saline.[15]

The common core rewarming techniques adopted are: administration of heated, humidified oxygen/ warmed IV Fluids, peritoneal dialysis, bladder, gastric or colonic lavage, thoracic cavity lavage, extracorporeal blood rewarming, and hemodialysis.

Extracorporeal rewarming techniques are used only in severe or life-threatening hypothermia or in scenarios where other warming techniques have failed. The techniques include cardiac bypass and extracorporeal membrane oxygenation (ECMO).[15]

Medications and precautions

IV corticosteroids have no clear benefit in most patients, especially in minor cases. Their use (at least 100 mg hydrocortisone or equivalent) is reserved only in the case of adrenal insufficiency or suspected myxedema coma. Antiarrhythmic medications are generally ineffective if the core temperature is <30° C.[16] There are case reports on the successful use of 'chemical defibrillation' by bretylium at core temperature <30°C. Early administration of medications may show sudden exaggerated effects after the elevation of core temperature and restoration of circulation restored (especially insulin).

Conclusion

To avoid the risk of morbidity and mortality in newborns, it is paramount to prevent hypothermia by maintaining warm chain and strict close monitoring, especially in low birthweight and high-risk neonates. Early detection by human touch and prompt remedial measures are key for reducing this preventable morbidity. Hypothermia in the elderly has a very poor prognosis, and without treatment, it can cause significant morbidity and mortality.

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Investigating a fever outbreak -An overview

Dr. M.K. Sudarshan
Project Lead - WHO –APCRI Rabies Survey
Ex-Dean/Principal KIMS, Bangalore
Prof & Head, Dept. of Community Medicine, KIMS, Bengaluru, India.

Introduction

According to World Health Organization, "*a disease outbreak is the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season*". The extent of outbreakmay vary from a limited area to several vast countries.[1] The present review discusses how the investigations need to be carried out for a fever outbreak, which helps in preventing similar outbreaks happening in the future.

Fever investigation: Basics and objectives

Investigating a fever outbreak is necessary to identify the source of illness and to formulate guidelines on public health intervention. An outbreak can be recognized through surveillance activities (e.g. Integrated Disease Surveillance Program[IDSP])and by analyzing the reports of clinicians, laboratories, press and media.[2]

The key objectives of outbreak investigations are:[3]

- To control ongoing outbreaks and prevent future outbreaks
- To provide statutorily mandated services
- To strengthen surveillance at local level
- To advance knowledge about a disease
- To provide training opportunities

Steps involved in outbreak investigations

The following are the steps to be followed for investigating an outbreak (Fig. 1).[4]

1. Verify the diagnosis and confirm the outbreak
2. Define a case and conduct case finding
3. Tabulate and orient data: time, place, person
4. Take immediate control measures
5. Formulate and test hypothesis
6. Plan and execute additional studies
7. Implement and evaluate control measures
8. Communicate findings

In practice, it may be inevitable to do several steps simultaneously or to follow a different order, depending on the circumstance of the outbreak.[5]

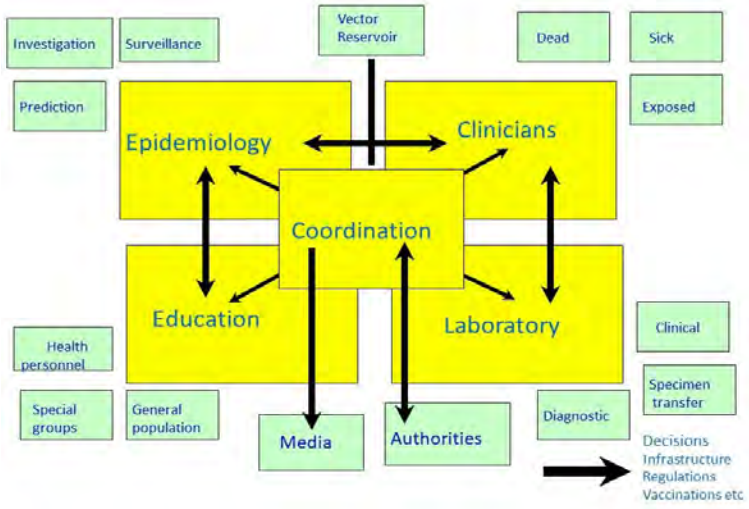

Fig. 1: Flow chart depicting the coordinated team work involved in outbreak investigation

1:Verify the diagnosis and confirm the outbreak

The primary step is to confirm the diagnosis through laboratory tests after ruling out misdiagnoses and laboratory errors. The occurrence of outbreak, i.e. the exact number of cases in excess of normal expectancy, needs to be established. It is important to compare current data with previous incidence happened in the area during the same timeof the year to establish whether the observed number of cases exceeds the expected.[6]

2. Define a case and conduct case finding

This step involves developing a case definition based on symptoms or lab results, time period and location. This is followed by conducting surveillance for identifying and counting cases. The two types of surveillance carried out are passive surveillance (e.g. cases coming to health centres/hospitals) and active surveillance (e.g. community searches, review medical records, etc.);interviewing and examination of patients are performed to establish the cases.[6]

3. Tabulate and orient data

Investigators should organize the data obtained from medical records and patient interviews in a line listing (Fig. 2).[7]

Fig. 2: Example of a line listing

		Signs/Symptoms			Labs	Demographics	
Case #	Date of Symptom Onset	Diarrhea	Vomiting	Fever >37°C	Positive stool culture	Age	Gender
1	22/10/05	Y	Y	Not done	Y	19	M
2	25/10/05	N	Y	N	N	17	M
3	22/10/05	N	Y	N	Y	23	F
4	27/10/05	Y	?	?	Pending	18	?
5	23/10/05	N	Y	N	Y	21	M
6	21/10/05	Y	Y	Y	Not submitted	18	F

Creating a line listing assists in easy tabulation of the data, and organizing and reviewing the information about place, time and person. The person details to be entered include: who was affected and what do the cases have in common.[8] Each row indicates a different case and each column an important variable (e.g. identifier, age, gender, Fig. 3).

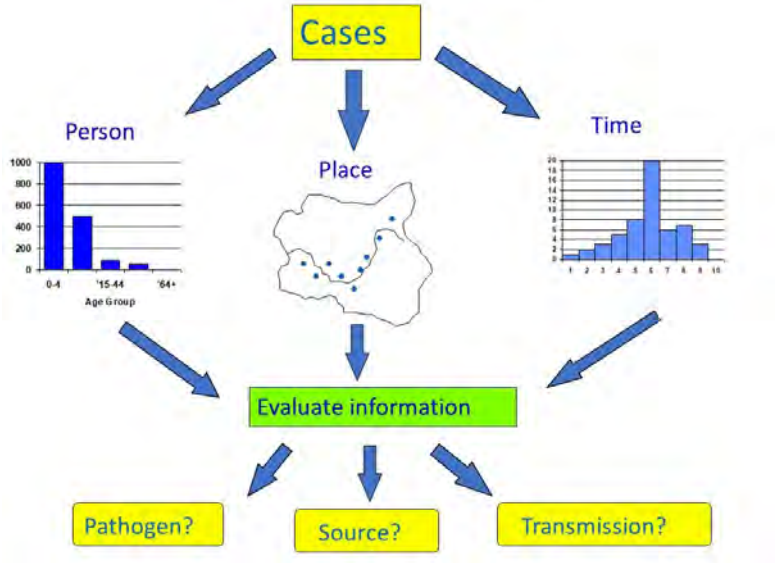

Fig 3: Flow chart depicting the tabulation of data

The location details to be collected include estimating the attack rates of cases at different locations such as at the place of employment, residence and at the site of exposure. Location with increased attack rates signifies the source of infection. Drawing a spot map with locations is helpful to identify the source of infection (Fig. 4). Moreover, it can provide clues to potential exposure patterns.

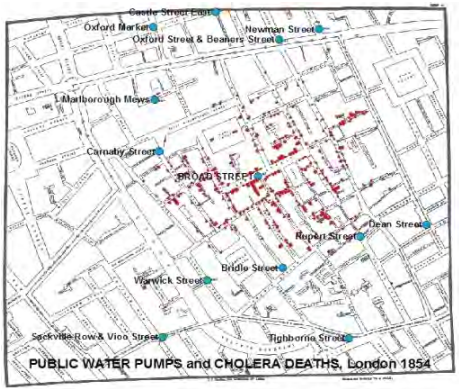

Fig. 4: Spot map of outbreak of cholera in London, 1854

It is recommended to draw an epidemic curve to depict the frequency of new cases over time, based on the date of disease onset. Examples of epidemic curves are point source, continuing common source and multiple waves-person to person or further outbreak. These forms of distribution assist in proposing the nature of the disease and mode of transmission (Fig. 5).[9]

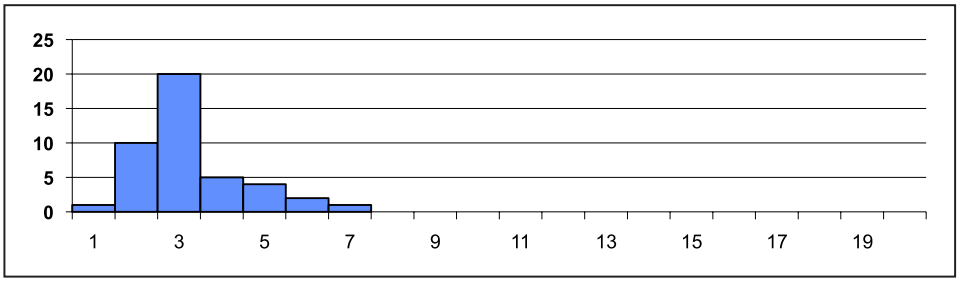

Fig. 5: Point source epidemic curve

4. Take immediate control measures

The outbreak investigation team comprises of epidemiologist, clinician, public health personnel, microbiologist/lab personnel and others. Conducting public heath announcement and implementing plant closure or product recalls are examples for control measures.[7]It is necessary to take immediate control measures, if an obvious source of contamination is identified. The use of barrier and isolation precautions are important infection control measures.[10]

5. Formulate and test hypothesis

Formulating a hypothesis helps in understanding the source of outbreak, the most probable cause and the case distribution. Developing a hypothesis requires reviewing of literature of previous outbreaks, conducting patient interviews, and evaluating the microbiology and epidemiology of the pathogen. In order to test the hypothesis, it is necessary to conduct analytic studies such as case control and retrospective cohort studies.[7]

6.Plan and execute additional studies

It is advocated to parallelly perform environmental sampling. If analytic study results are conclusive, it is necessary to implement preventive measures before obtaining positive samples of infection.

7. Implement and evaluate control measures

In the final stages of outbreak investigation, the team needs to closely work with health educators, directorate, and public health personnel to implement infection control measures. These measures are aimed at preventing further exposure and future outbreaks by eliminating or treating the source. The team should formulate mechanisms to assess the short- and long-term success of infection control.

8. Communicate findings

At the end, the team should summarize investigation, make recommendations, and disseminate report to authorities, all participants and stake holders. Communication within the team and with public is crucial for the success of outbreak investigation. One individual from the team should serve as the point of contact (usually epidemiologist) to interact with media and communicate the progress and findings.[7]

Conclusion

This paper provides a brief summary ofoutbreak investigation to be carried out to plan and implement necessary measures to control outbreak and to prevent further infections. Investigations help in identifying risk factors associated with outbreaks,andproviding newer researchinsights on the emerging pathogen. Only by participating ininvestigations repeatedly, public health professional scan learn the 8-step process of outbreak investigations.

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Serological markers in fever

Dr. Bhavana MV
Manipal hospital,
Bengaluru

Introduction

Fever can be referred to a Pandora's box, as it is surrounded by so many mysteries. The proper investigation of fever is important, as it provides important diagnostic clues. This review discusses the microbiological experiences with fever from the perception of a physician, which could assist in fever investigation.

Epidemiology and causes

Fever is highly variable. In western countries, inflammatory causes are more common and infection plays a major role in causing fever in low- and middle-income countries. The most commonly reported infections are enteric fever, brucellosis, tuberculosis, endocarditis and intra-abdominal abscesses.[1]

The infectious etiologies of fever include enteric fever, tuberculosis, dengue/viral fever, malaria, leptospirosis, brucellosis, typhus fever, focal abscesses, infectious mononucleosis, and infective endocarditis. The non-infectious etiologies include connective tissue disorders, autoimmune disorders and malignancies.[1]

History collection

The methodology to investigate a fever starts from the history. A careful history should be comprised of previous infectious illnesses, family history of infection, exposure to similar infections, residence and country of origin, recent travel, zoonotic exposure and leisure activities. Physical examination

requires special attention to the eyes, heart, spinal tenderness point, liver/spleen, lymphadenopathy, skin lesions and oropharynx.[1]

Approach to undifferentiated fever

Thangarasu et al. (2011) have formulated a protocol to manage acute undifferentiated febrile illness in adult Indian patients. The interesting article, published in the *International journal of emergency medicine*, suggested how to carry out the investigation of an undifferentiated fever in the OPD. According to the protocol, if the patient presented with fever to the outpatient department is a case of sepsis, the sepsis protocol should be followed. The authors recommended to carry out investigation of localizing signs, if present, or to go by the day of fever. Only symptomatic treatment is required on the day 1 or 2 of the fever and antimicrobials should be deferred. On day 3 or 4, it is advocated to perform WBC count, malaria parasite detection by quantitative buffy coat and urine routine examination. On day 5 or 7, blood cultures, liver function test, dengue serology and Weil-Felix test can be carried out based on the requirement. The study has reported non-specific infection (n=107) in majority of the subjects, followed by dengue (n=21), malaria (n=21), UTI (n=16), enteric (n=14) and other specific diagnosis (n=20).[2] D'Acremont et al. (2014) has reported higher incidence of malaria (23%) among Tanzanian children. The common cause of febrile illness noted in children included non-bacterial infection such as the upper respiratory tract infection (15%), non-radiologically (16%) and radiologically (6%) confirmed pneumonia, UTI (4%), nasopharyngeal infection (4%) and meningitis (1.2%).[3]

Basic laboratory and radiology to start with

The basic laboratory investigations include CBC, peripheral blood smear, erythrocyte sedimentation rate, CRP, liver function tests, and blood and urine culture. Radiological investigations such as the chest radiograph, CT and MRI scans of the abdomen and pelvis are performed, if required.[1]

CBC is the most important non-definite investigation performed in cases with fever. The observations from CBC are suggestive of the following diseases:

- Leukopenia: enteric fever, TB, HIV, SLE
- Leukocytosis: pyogenic infection, vasculitis
- Reactive lymphocytosis: EBV, CMV
- Eosinophilia: drug reactions, parasitic infections
- Eosinopenia: enteric fever
- Thrombocytosis: pyogenic infection, inflammation
- Thrombocytopenia: malaria, SLE, HIV
- Pancytopenia: bone marrow infiltration, SLE

Liver function test also play a vital role in the investigation. Elevated ALT/AST indicates viral hepatitis or infectious mononucleosis. Elevated alkaline phosphatase and gamma glutamyl transpeptidase indicate granulomatous hepatitis, sepsis or cholangitis.[4]

Segal et al. (2014) have reported CRP as the most useful marker in children to differentiate bacterial and viral infections. CRP increases during the first 36 h of fever and declines more rapidly with viral infections. Ina patient with fever duration >24 hours, If CRP is >11 mg/dL, the probability of having a

bacterial infection is 75%; whereas if CRP is ≤5 mg/dL, the chance of a bacterial infection is unlikely (>95% accuracy).[5]

Procalcitonin is more specifically elevated in bacterial infections and the levels can correlate with the severity of sepsis. It can be used as a trend to monitor a sepsis patient, rather than a single diagnostic marker.[6]

Enteric fever

Timing of tests is very important in the investigation of enteric fever.

Week 1: Isolation of Salmonella from blood/bone marrow. Automated culture systems do better. The success of a culture lies in the blood volume and proper timing of the collection of the sample. Sample collection before the initiation of antibiotic therapy is preferred.

Week 2: Widal by tube method is preferred. Slide method can also be used, but there are chances of false positive results.

Week 3: Stool culture

Week 4: Urine culture

As per the WHO, there is no definitive role for rapid typhoid antibody tests like tubex, typhidot, typhidot rapid and IgM dipstick, and there are no other molecular tests in the market for routine diagnosis. Culturing remains the gold standard.[7]

Brucellosis

IgM raises first and peaks at around 3 months (Fig. 1). IgM ELISA is usually preferred, followed by Brucella agglutination test. However, blood culture remains the gold standard, but prolonged incubation may be required.[8]

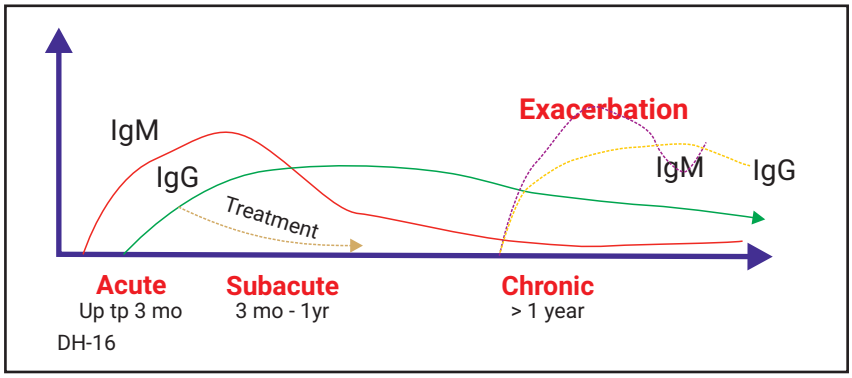

Fig. 1: Immune response during brucellosis

Dengue

NS1 antigen level elevates during the first 5 days of fever, followed by IgM and IgG in a primary infection. Secondary infection witnesses an accelerated IgG response. The serological markers include ELISA for NS1, IgM and IgG.[9] Real time PCR is helpful during an acute viremic phase. Rapid test does not have any role.

Chikungunya

Markers include IgM, IgG and circulating viruses. According to the testing algorithm by CDC, if the disease onset is <6 days, PCR should be performed and if it is >6 days, IgM ELISA should be carried out.[10]

Leptospirosis

Around 90% of the infection is presented as undifferentiated febrile illness. Itis often misdiagnosed at onset as aseptic meningitis, influenza, hepatic disease or fever (pyrexia) of unknown origin. The tests available for the diagnosis of leptospirosis include dark field microscopy, IgM ELISA, microscopic agglutination test and PCR. Dark field microscopy requires 104 leptospires/ml to be visible under the microscope. However, it lacks sensitivity and specificity. IgM ELISA has chances of false positivity. The gold standard is the microscopic agglutination test, followed by PCR.[11]

Infectious mononucleosis

The immune response of infectious mononucleosis involves several antigens and antibodies, and they include early antigens, followed by heterophile antibodies and later viral capsid antigens (VCA IgM, VCA IgG and Epstein Barr nuclear antigen (EBNA)-1 IgG). A positive VCA IgM and negative VCA IgG and EBNA-1 IgG, and a positive VCA IgM and IgG and negative EBNA-1 IgG indicate acute infection. A positive EBNA-1 IgG and VCA IgG indicate past infection. A late primary infection is indicated when all three markers are positive.[12]

Malaria

The target antigens are *P. falciparum*-specific proteins like histidine-rich protein II or lactate dehydrogenase and pan-specific antigens (aldolase or pan-malaria pLDH). PCR, generally used to confirm malaria infection, detects only 1-5 parasites/µl of blood. However, peripheral smear and rapid tests can detect 50-100 parasites/µl of blood.[13] Recently the Ministry of Health and Family Welfare prohibited the use of antibody detecting rapid diagnostic tests for the diagnosis of malaria.[14]

Typhus fever

Scrub typhus and Indian tick typhus predominate in India. Weil-Felix test can be used only after 1 week and has low sensitivity and specificity due to cross-reactivity of *Proteus* antigens used. However, ELISA has good sensitivity and specificity. IgM ELISA and *R. conorii* ELISA IgG/IgM kit are used correspondingly for the detection of scrub typhus and Indian tick typhus.[15] Scrub typhus IgM should be interpreted with caution, as IgM levels persist for a longer duration and there are possibilities for false positive results when single serum samples are interpreted.[16] Therefore, further research should focus on antigen detection assays.[17]

Tuberculosis

The Ministry of Health and Family Welfare, Government of India has banned the use of inaccurate serological blood tests for the diagnosis of TB.[18] Quantiferon TB gold test (QFT) measures the release of interferon gamma produced in whole blood in response to stimulation by purified protein derivative. The Centers for Disease Control and Prevention (CDC) recommends initial and serial testing of persons with an increased risk for latent TB (recent immigrants, injection drug users, residents and employees of prisons and jails) and also for individuals who are, by history, at low risk for latent TB

but whose future activity might place them at increased risk for exposure (health-care workers and military personnel).[19] However, Quantiferon gold is contraindicated in the evaluation of suspected active tuberculosis; assessment of contacts of persons with infectious tuberculosis; screening of children aged <17 years, pregnant women, or for persons with clinical conditions that increase the risk for progression of latent to active TB; detection of latent TB after suspected exposure; confirmation of tuberculin skin test results; and diagnosis of *M. avium* complex disease.[20]

Invasive fungal infections

Biologic markers include galactomannan Aspergillus antigen and the fungal wall component (1–3)-β-D-glucan. However, it is associated with high negative predictive value. The 2016 Infectious Diseases Society of America (IDSA) guidelines for Aspergillosis recommends that galactomannan and 1,3-β-D-glucan assays are useful in high risk patients and is not recommended for routine blood screening in patients receiving antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens from these patients.[21] Invasive fungal infection should be tested in conjunction with other methods for the diagnosis of invasive fungal infections and should precede antifungal therapy. Positive test results should be confirmed with a second new specimen or repeated from the initial specimen.[22]

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Pyrexia of unknown origin

Dr. T. S. Ravindra
Consultant physician & intensivist
Mallige medical center

Introduction

Pyrexia of unknown origin (PUO) is a classification of various unrelated conditions that shows a unique feature of persistent unexplained fever, despite basic clinical investigations.[1] It presents a formidable challenge to clinicians, as the management requires continuous review and knowledge of less commonly used investigation strategies. Petersdorf and Beeson in 1961 developed criteria for prolonged fevers. They have defined PUO as persistence of temperature >38.3°C (101° F) on several occasions for more than 3 weeks, for which no diagnosis has been arrived, despite 1 week of inpatient investigation.[2]

Durack and Street (1991) proposed a newer classification of PUO, based on the emergence of HIV. The details of classification are given in table 1.[3]

Table 1: Updated classification of PUO

Category	Classic PUO	Nosocomial PUO	Neutropenic PUO	HIV PUO
Definition	>3 weeks or >2 OPD visits or >3 days of indoor investigation	> 3 days, not present or incubation on admission	> 3 days, absolute neutropenia (< 500/ml)	3 weeks of outpatients or 3 days indoor
Leading causes	Infections, collagen vascular disorders, neoplasms	Lower and upper RTI, UTI catheter sepsis, Post-operative complications	Infections but can be found in only 50%	Typical or atypical mycobacteria, cytomegalovirus, toxoplasma
Characteristics	Time course may take up to months	Temp. not present during admission	Neutrophil count <500 cells/cmm	Confirmed HIV infection
*AII required temperature of > 38° C				

The present paper mainly deals with diagnosis and management of classic PUO.

Prevalence and causes

Nearly 200 described causes of PUO have been identified and they can be broadly classified as infections, neoplasm, collagen vascular disease, vasculitis and granulomatous disorders.[4] In Indian scenario, infections account for 53% of PUO, among them TB accounts for 45% of the cases. Neoplasms and collagen vascular diseases are responsible for 17% (NHL 47%) and 11% (SLE 45%) of the PUO etiologies respectively.[5] The study conducted at Nizam Institute of Medical Sciences (NIMS) evaluated 100 cases of PUO, and identified 64 males and 36 females within the age range of 18-70 years. The peak incidence was noted within the age range of 30-40 years.[5]

The prospective multicenter study by Bleeker-Rovers et al. has noted that the cause of PUO had not been identified in 51% of the subjects. Infections, neoplasms, and inflammatory diseases were identified as causes in 16%, 7%, and 22% of the subjects respectively.[6]

Clinical approach to PUO

A comprehensive and meticulous history and epidemiology collection is important for arriving at the final diagnosis and deciding the management strategies. It is crucial to collect travel and residence history for the past 6 months, history of animal and drug exposure, and sexual history. Some of the examples highlighting the significance of history/epidemiology collection are discussed below:

1. In certain areas of Karnataka, the chances of brucellosis are higher among individuals exposed to animals and those who consume unpasteurized milk.[7]
2. Risk of contracting leishmaniasis or kala azar is more among residents of Bihar and Jharkhand with pancytopenia and large spleen.[8]
3. Histoplasmosis should be suspected in residents of north east India with oral ulcers, skin lesions, and adrenal enlargement.[8]
4. Rickettsia fever should be suspected among residents of Arsikere, Chikmagalur, and Hassan, presenting with fever with rash and those who had gone trekking to hilly areas.
5. Chances of drug-resistant malaria should be considered in individuals who have travelled to Chennai, Mangalore, Kolar and Madanpalli.
6. Drug-induced fever should be suspected in patients receiving cephalosporins, allopurinol, hydralazine, methyldopa, isoniazid, nifedipine, penicillin, phenytoin, procainamide etc.

Diseases commonly causing PUO are listed in table 2.

Table 2: Common causes of PUO[9]

Categories	Diseases
Bacterial	TB, endocarditis, brucellosis (disease of mistakes), salmonella
Viral	HIV
Parasites	Malaria
Rickettsia	
Neoplasms	Lymphoma, leukemia, renal cell carcinoma, hepatocellular carcinoma
Collagen vascular disease	SLE, adult onset Still's disease
Other diseases	Sarcoidosis, Gaint cell arteritis, subacute thyroiditis, drug fever, Kawasaki disease, Kikuchi -Fujimoto disease, familial Mediterranean fever, habitual hyperthermia and factitious fevers

Physical examination

Proper documentation and conducting physical examination from head to toe are paramount. Physical examination clues to the causes of PUO are as follows:[9]

- Skin rashes: HIV, Infectious mononucleosis, Still's disease
- Lymphadenopathy: Lymphoma, chronic lymphocytic leukemia, TB, HIV
- Joint swelling: RA, Still's disease, gout
- Deep palpation of the abdomen for any mass: Hepatosplenomegaly, leukemia, lymphoma
- Icterus: Hepatocellular carcinoma, chronic active hepatitis, cholangitis
- Heart murmurs: endocarditis

Axioms to conclude the diagnosis

The probability of dengue should be ruled out in fever exceeding 2 weeks, because fever related to viremia and other viral infections persists only for 2 weeks.

The fever due to infection recedes with increase in number of days. Whereas, those with neoplasms or collagen vascular disease increases as the days pass on (exception-HIV, TB, and brucellosis).

Prevalence of various causes of PUO

In pediatric population, infections including viral syndromes have been identified as the causes for 50% of the PUO, while neoplasms and rheumatologic diseases account only <10%. However, nearly 40% of the cases have been left undiagnosed. In geriatric population, the prevalence of infections, inflammations and malignancy as causes of PUO is comparable. In fever lasting for >6 months, though relatively uncommon, no causes have been identified in 20% of the subjects. In addition, nearly 30% of the subjects diagnosed with PUO do not show fever as the prominent symptom.[10] However, prognosis of such patients is generally good, once diagnosed.

Investigation of PUO

For investigating PUO, a battery of tests, termed basket of tests approach, need to be performed. The tests include CBC, blood culture, serology, X-rays, CT abdomen, thorax, echo, collagen work-up, LFT, liver, bone marrow biopsy etc. It is necessary to consider the clinical symptoms and signs while

interpreting the test results. CT guided biopsies, mediastinoscopy, abdominal laparoscopic biopsy, and biopsy of bone marrow are the recommended tests to confirm the diagnosis. The tests such as FDG-PET scan, gallium nitrate scan, technetium 99, indium 111 labeled leukocytes are helpful in localizing tumors, infections and certain inflammatory diseases. But they are not recommended to conclude the actual diagnoses.[11]

The use of fluorodeoxy glucose (FDG) PET scanning is reported to be superior to other forms of nuclear imaging. It has been identified as the imaging and diagnostic modality of choice for PUO, since the measurement of accusation of FDG in tumors, and at the sites of inflammation and vasculitis assist in accurate diagnosis.[9]

Managing PUO

After collecting a through history of drug exposure, the patients should be asked to discontinue the use of antibiotics, pain killers and other unnecessary drugs. After 48-72 hours of discontinuing the medications, the aforementioned clinical tests should be carried out. It may not be possible to carry out theses tests, if the patient is having multiple organ dysfunction syndrome (MODS) and the use of shotgun empirical therapy is unavoidable (broad spectrum antibiotics, antimalarials, doxycycline, and steroids).[12]

Steroids should not be used as empirical therapy for PUO. In addition, Empirical treatment should not be initiated in the following clinical scenarios:[13]

- Cases meeting criteria for culture negative infective endocarditis
- Clinical picture suggestive of disseminated TB
- MODS
- Temporal arteritis with impending visual loss
- Suspected immunocompromised or neutropenic patients

Role of doxycycline in PUO

In PUO management, doxycycline has been identified as the drug of choice for treatment of rickettsial fever, psittacosis, chlamydia pneumonia, mycoplasma pneumonia, Lyme's disease and relapsing fever. It is also found to be effective in the management of brucellosis, tularemia (along with gentamycin), pasteurella bacteremia and infection due to *actinomyces israelii*.

Conclusion

Collecting history and meticulous physical examination remain the mainstay of PUO management. After the initiation of empirical therapy, it is paramount to perform continuous reexamination and evaluation. The essential attributes necessary for a clinician to successfully manage PUO are intellectual flexibility, patience, compassion, equanimity, and vigilance.

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Febrile Neutropenia

Dr. Prasad Narayanan
Senior Consultant
Medical Oncology
Cytecare Cancer Hospitals
Bangalore

Introduction

Febrile neutropenia (FN) is defined as the presence of a single oral temperature spike of >38.3°C (101°F) or >38°C (100 °F) over at least one hour and with a neutrophil count <500/cmm or <1000/cmm with predicted decline to <500/cmm. It is one of the common toxicities assoicated with chemotherapy and has been noted in >80% of the hematological malignancies and 10-50% of the patients with solid tumors. FN is a medical emergency, as it indicates an immunocompromised state.[1]

The presence of FN compromises the clinical outcome; as it increases mortality,hospital stay and diagnostic and treatment costs, delays chemotherapy courses, and reduces the effect of chemotheraphy doses.[2]

Bacterial infections

Schimpff et al. have evaluated the effectiveness of empirical antibiotic therapy in granulocytopenic cancer patients for managing *Pseudomonas aeruginosa* bacteremia. The trial between 1968-69- evaluated the effectiveness of antibiotics started after blood culture results and the mortality recorded was 50%. Whereas, the administration of the same antibiotics soon after the development of fever between 1970-71 reduced the mortality to 26%.[3]

The common pathogens responsible for causing bacterial infections are listed in table 1.

Table 1: The common pathogens responsible for causing bacterial infections

Gram-positive	Gram-negative
Coagulase-negative staphylococci	Escherichia coli
Staphylococcus aureus	Klebsiella species
Enterococcus species	Enterobacter species
Viridans group streptococci	Pseudomonas aeruginosa
Streptococcus pneumoniae	Citrobacter species
Streptococcus pyogenes	Acinetobacter species
	Stenotrophomonas maltophilia

The trends in the global prevalence of bacterial infections in patients with FN shows that gram -ve infections were more common that gram +ve during 1960-80s and the upcoming years witnessed the gradual increase in the prevalence of gram+ve than gram negative. This gradual shift in trend could be attributed to th use of central venous catheters.[4,5] The risk is higher in chemotherapy patients, as most of them require such catheters due to the occurrence of thrombophlebitis, extravasations etc.

The uncommon infections noted in FN patients are CMV infection in allogenic SCT recipients, *Pneumocystis carinii*, legionella, chlamydia and mycoplasma / mycobacteria.

Evaluation of FN

Infectious Diseases Society of America Guidelines, published in 1997 and Updated in 2002 and 2011, and European guidelines for empirical antibacterial therapy are the well accepted guidelines for managing FN.[4,6] The Indian guidelines include those published by ICMR and Assoication of Medical Oncology.

The predminent pathogens assoicated with FN include fungi such as *Candida Sp.* and *Aspergillus,* and viruses namely herpes simplex, herpes zoster and cytomegalo virus. The history collection in neutropenic patient should consider day of onset of fever, day of last cycle of cytotoxic drug, estimated duration of neutropenia , and whether blood product had been adminstered within 6 hours of fever. The subtle signs in the following sites need to be observed closely in such patients: periodontium, pharynx and lung, lower esophagus, perineum and anus, skin lesions, eyes, vascular access site, bone marrow site and tissues around nails.[7] The routine evaluation such as complete blood count, blood cultures (peripheral and catheter), quantitative blood cultures (>500cfu/ml), chest radiograph and blood chemistry should also be carried out.

An ideal diagnostic test for FN should have the following characterisitcs: high sensitivity, high specificity, early detection, simple methodology, quantitative results, fast results and appropriate cost. Since no such diagnostic tests are currently available, which are sufficiently rapid, sensitive and specific for identifying or excluding the microbial cause of a febrile episode, the empirical therapy is highly integral for managing patients with FN.

Risk assessment

The risk evaluation should consider host-, enviormental- and prophylaxis-related factors. The removal of catheter is necessary only in scenarios with recurrent, tunnel and periport infections; patients with shock; and the infections due to any species that is diffcult to eradicate. The risk assement is broadly

done by judging the depth of the neutropenia. If the patient has an absolute neutrophil count >100, normal chest X-ray , LFT and RFT, duration of neutropenia <7 days and no IV catheter *in situ;* the risk is comparetively lesser. An internationally validated scoring system called the MASCC risk index is used to identify patients at low risk, whom can be potentially treated as an outpatient with early antibiotics (Table 2).[8]

Table 2: MASCC risk index factors and weights

Characteristics	Weight
Extent of illness	
No symptoms	5
Mild symptoms	5
Moderate	3
No hypotension	5
No COPD	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age< 60 yrs	2

High risk is usually assoicated with hematologic malignancy, allogenic bone marrow transplantation, neutropenia >14 days, substantial comorbidity, clinically unresponsiveness and slow response to initial therapy.[9]

Management

The use of vancomycin as an intial antiobiotic for managing FN was a matter of debate among oncologists around 5 years ago due to the emergence of vancomycin-resistant organisms. As per the current consensus, vanocomycin is not prescribed, unless there are specific indications such as severe mucositis, quinolone prophylaxis, colonized with MRSA, penicillin- and cephalosporin-resistant *pneumococci*, blood culture showing Gram + ve infection, catheter-related infection, hypotension and sudden increase in temp > 40°C.[10]

The management strategies to be adopted in patients with fever ≧38.3°C and neutropenia are brified in figure 1.[11] All these treatments are accepted as first line therapies and it is necessrary to develop center-based policies based on the drug sensitivty problems experienced by the patients in that partcular locality.

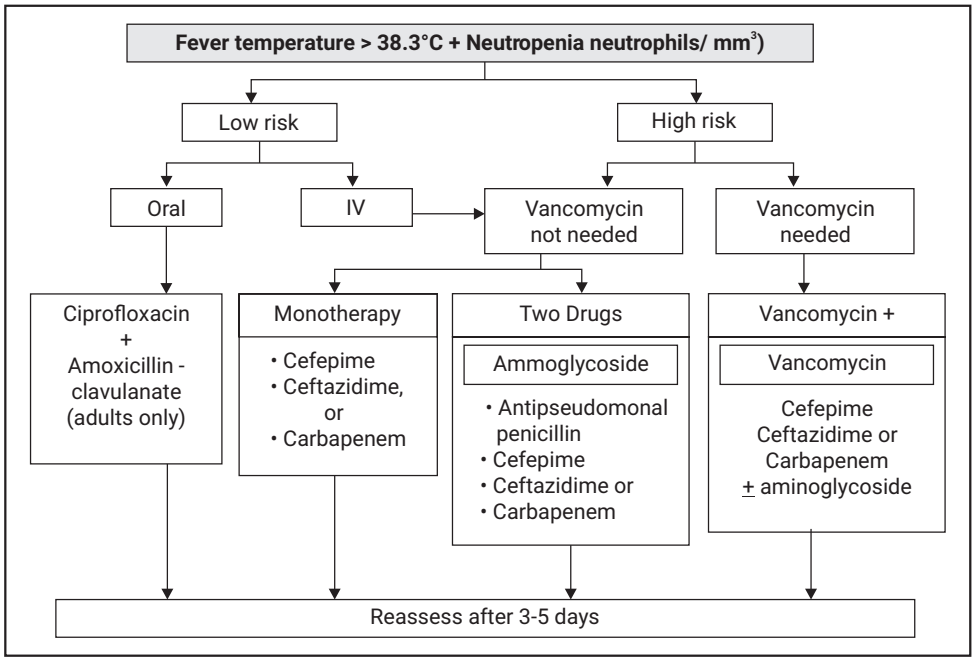
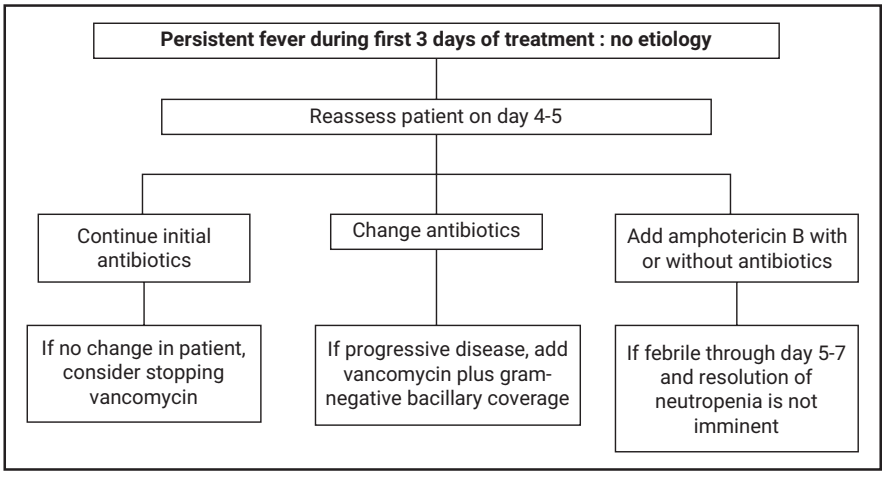


Fig. 1: Flow chart depicting the management strategies to be adopted in patients with fever ≥38.3°C and neutropenia

If the patient has become afebrile within the first 3 days of treatment and the etiology has been identified, the treatment should be customized based on the etiology. If no etiology has been identfied in low-risk patients, the treatment can be changed to oral antibiotic (cefixime or quinolone) and the patient can be discharged. Whereas, in high-risk patients, the same antibiotic should be continued in IP.

If there is persistent fever during first 3 days of treatment and no etiology has been identified, there are 3 approaches to manage the patient as depicted in figure 2.



Upon imprvement in patient's condition, it is necessary to closely monitor the blood count. If, the blood count recovers in a week time, regardless of the present condition, the antbiotics can be stopped. If the blood count is not recovering, the patient should be re-evaluated for the risk.

Role of hematopoietic growth factors (G-CSF or GM-CSF)

Prophylactic use of myeloid CSFs should be considered in patients with the anticipated risk of fever and neutropenia of >20% (A-II). They are not generally preferred for the treatment of established fever and neutropenia. Myeloid CSFs are not recommended as adjuncts to antibiotics for treating established fever and neutropenia. These is no evidence to establish a survival benefit associated with therapeutic CSFs.[4]

Role of antifungals

Empirical antifungal therapy (A-I) can be used in high-risk patients with persistent or recurrent fever after 4-7 days of antibiotics and expected duration of neutropenia >7 days. Preemptive antifungal management is advoated in patients who remain febrile after 4-7 days of broad-spectrum antibiotics and having clinical/chest /sinus CT signs along with positive serologic assays. Routine use of empirical antifungal therapy is not recommended (A-III) in low-risk patients due to the reduced risk for invasive fungal infection. Amphotericin B desoxycholate is the standard empirical treatment and other formualtions used are voriconazole, caspofungin, and posaconazole.

Prophylaxis measures

The following prophylactic measures are recommedned for high-risk patients:[4]

- Hand hygiene is the most effective measure for preventing nosocomial infection.
- Povidone iodine sitz bath is provided to prevent perinneal infections. In some situations, anti-bacterial, anti-fungal or anti-viral prohylaxis may be required.
- Fluoroquinolone prophylaxis is indicated for high-risk patients having prolonged and profound neutropenia (ANC <100 cells/mm^3 for >7 days).
- Prophylaxis against candida infections is indicated for allogeneic HSCT recipients or those undergoing intensive remission-induction or salvage induction chemotherapy for acute leukemia (A-I). The fungal prohylactic agents used are fluconazole, voriconazole, posaconazole, micafungin, and caspofungin.
- Acyclovir antiviral prophylaxis (A-I) is recommended for HSV-seropositive patients undergoing allogeneic HSCT or leukemia induction therapy.
- Yearly influenza vaccination with inactivated vaccine is recommended for all patients undergoing cancer treatment(A-II). Live vaccines are not advocated in patients receving chemotherapy.
- Only disnfected toys, games, and videos should be allowed in patient's room.
- There is no neutropenic diet to be followed in FN patients. The patients should be encouraged to consume natural foods.

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Fever with rash

Prof. K. Shankar MD (NIMS), FIACM, FICP
Professor of Medicine & Superintendent
SRRIT&CD (Govt. Fever Hospital), Nallakunta, Hyderabad. & Director IPM,
Narayanaguda, Hyderabad.

Introduction

Fever, an increase in body temperature due to an elevation in the hypothalamic set point (97.7- 99.5 °F), is caused by the pyrogens/ pyrogenic cytokines produced during infection and inflammatory process. Rash is any abnormal change in skin color, appearance or texture. It may occur due to multiplication of infective organism, autoimmune destruction of skin due to inflammatory response, action of microbial toxins on skin structures, and involvement of the vasculature including necrosis, vaso-occlusion, and vasodilatation.[1]

History collection

The history collection in febrile patients with rash include recent travel, drug ingestion or contact with ill persons, and wood, land or animal exposure. The time of year may be a diagnostic clue in certain cases. A complete medical history may assist in determining whether the patient has any elevated risk for specific conditions associated with sexually transmitted diseases, valvular heart disease, or immunosuppression due to chemotherapy. The patient's immune status is a major diagnostic factor, as many of the diseases that result in fever and rash have varying presentations in immunocompromised patients.[2]

The details of rash to be collected include site of onset, presence or absence of pruritus, rate and direction of spread, and temporal association between rash and fever. It is also paramount to understand whether the patient has received any topical or oral therapies.[2]

Physical examination

In addition to the assessment of vital signs and patient's general appearance, the physical examination should also consider: adenopathy; signs of toxicity; hepatosplenomegaly; genital, oral, or conjunctival lesions; signs of nuchal rigidity or neurologic dysfunction; and evidence of excoriations or tenderness. A basic understanding of the various rashes is integral in making an accurate diagnosis and understanding the severity and acuteness of the underlying illness.[2] The various diagnostic pattern of rashes are maculopapular eruptions, nodular eruptions, purpuric eruptions, vesiculobullous or pustular eruptions, confluent desquamative erythema, eruptions with ulcers or eschars, and urticaria-like eruptions.[2]

1. Maculopapular rashes

Maculopapular eruptions are more commonly noted in viral infections and immune-mediated syndromes. It can be broadly classified as centrally and peripherally distributed eruptions, and each type has separate differential diagnosis.

a. **Centrally distributed eruptions:** Centrally distributed maculopapular eruptions include rashes that arise centrally (first affecting the head and neck) and then progressing to the periphery. They are more common than peripheral eruptions.[2]

1. Viral measles, rubella, erythema infectiosum, exanthem subitum, primary HIV infection infectious mononucleosis, Other viral xanthems- echovirus 2,4,9,11,16,25; coxsackie viruses A9, B1, B5 and dengue fever
2. Exanthematous drug-induced eruptions due to antibiotics, anticonvulsants, and diuretics
3. Bacterial epidemic typhus, endemic typhus, scrub typhus, rheumatic fever, leptospirosis, Lyme disease, relapsing fever, typhoid fever, rickettsial spotted fevers, rat-bite fever, human monocytotropic ehrlichiosis and African trypanosomiasis
4. Autoimmune: SLE and Still's Disease

b. **Peripheral eruptions:** Starts in peripheral areas before spreading centrally. It is commonly noted in rocky mountain spotted fever, secondary syphilis, bacterial endocarditis, rat-bite fever (Haverhill fever), viral chikungunya fever, and hand-foot and mouth disease.

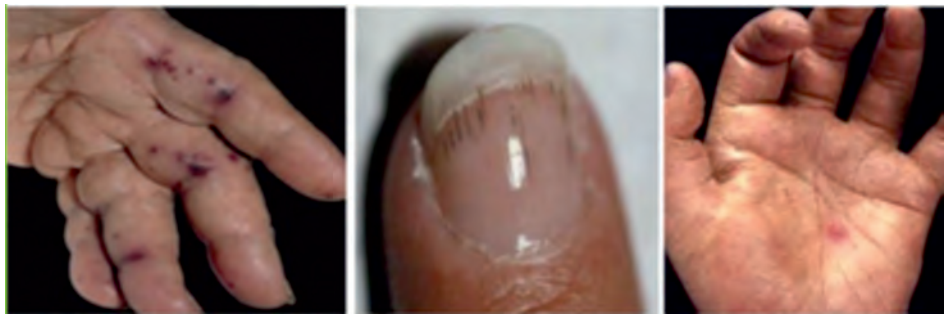
Erythema multiforme

- **Measles (rubeolla, first disease):** The causative agent is measles virus (paramyxovirus) and it commonly affects children and non-immune subjects. Mode of spread is droplet infection and the incubation period is 10 days. Macular-popular rash begins on face (at the hairline), neck and shoulders and spreads centrally and inferiorly. It fades in 4 to 6 days. Clinical features are high-grade fever with cough, irritability, conjunctivitis, coryza, malaise, and Koplik spots (buccal mucosa), which appears 2 days prior to rash. Treatment is only supportive with adequate hydration.[3]
- **Rubella:** The disease is similar to rubeola. However, it causes less severe symptoms, and its exanthem has a characteristically lesser duration (2 to 3 days).
- **Erythema infectiosum** (fifth disease): It is caused by human parvovirus B19 and primarily affects children between 3 and 12 years of age. it may present as a rheumatic syndrome in adults. The prodrome may include fever, sore throat, anorexia, and abdominal pain. The resolution of fever is followed by the appearance of classic bright-red facial rash ('slapped cheek'). The exanthem progresses to a diffuse, lacy, reticular rash within several days, which may wax and wane for 6 to 8 weeks. The infection in pregnant women has been associated with fetal hydrops and subsequent fetal death.[4]

- **Roseola** (exanthema subitem): The disease is caused by human herpesvirus 6 and it occurs in children <3 years of age. The diffuse maculopapular eruption appears after the resolution of 7 days of high fever. It often spares the face and typically fades within 3 days.[5]
- **Infectious mononucleosis:** The causative agent is Epstein-Barr virus and commonly affects young adults (transmitted by intimate contact with bodily secretions). Clinical features are mostly asymptomatic fatigue and malaise fever, pharyngitis, cervical lymphadenopathy, hepatosplenomegaly and atypical lymphocytosis.[6]
- **Primary HIV infection:** It affects subjects recently infected with HIV. Rash appears in 1-2 days of acute illness. Non-specific diffuse macules and papules, commonly urticarial or vesicular, are noted. Oral or genital ulcers may occur.
- **Epidemic typhus:** The causative agent is *Ricketssia prowazekii*. The disease is primarily seen in regions affected by war and disaster. Clinical features are sustained high fever, prominent cough and maculopapular rash. Maculopapular rash appears in axillae, spreading to trunk and subsequently to extremities (spares face, palms, and soles). Treatment is doxycycline 100 mg bd, which should be continued 2-3 days after defervescence. The mortality rate is 10-40%, if untreated.
- **Endemic typhus (murine):** The causative agent is *Rickettsia typhi* and the host is cat or rat fleas. Clinical features include headache, myalgia, arthralgia, nausea, vomiting, and maculopapular rashes (13%) sparing palms and soles. Pulmonary manifestations are interstitial pneumonia, pulmonary edema, and pleural effusion. Treatment is doxycycline 100mg bd and ciprofloxacin.[7]
- **Scrub typhus:** It is caused by *Orientia tsutsugamushi*. Diffuse macular rash on the trunk and eschar at the site of mite bite are seen. Complications are pneumonitis, encephalitis and myocarditis. Mortality rate is up to 30%, if untreated. Treatment options are doxycycline (100 mg bd oral 7-15 days), azithromycin (500 mg od oral 3 days0, and chloramphenicol (500 mg qid oral 7-15 days).
- **Rocky mountain spotted fever:** The causative agent is *Ricketssia rickettsii* and the vector organism is tick. Rash evolves from pink macules to red papules and finally to petechiae (spotted). It begins on wrists and ankles, and spreads centripetally. Involvement of palms and soles is noted late in disease. Treatment is doxycycline 100 mg bd and should be continued for 2-3 days after defervescence.[8]
- **Dengue fever:** It is a mosquito-borne tropical disease caused by the dengue virus.[9] Symptoms typically begin 3-4 after infection, and may include a high fever and a characteristic skin rash.[10] In a small percentage of subjects, the disease may develop into the life-threatening dengue hemorrhagic fever (resulting in bleeding, low levels of blood platelets and blood plasma leakage) or dengue shock syndrome. Management measures include supportive treatment, adequate hydration, blood transfusion and management of complications.
- **Typhoid fever**: It is a bacterial infection caused by *Salmonella typhi*. Symptoms may vary from mild to severe and usually begin 6 to 30 days after exposure. There is a gradual onset of a high fever over several days and the skin rash may appear as rose-colored spots. Treatment options are supportive care and antibiotics (ceftriaxone, azithromycin, and cefixime).
- **Leptospirosis**: It is an infection caused by *Leptospira*. Treatment for mild leptospirosis is doxycycline (100 mg PO bid), amoxicillin (500 mg PO tid) or ampicillin (500 mg PO tid). For moderate/severe leptospirosis, doxycycline (200 mg PO once a week) or azithromycin (250 mg PO once or twice a week) is used.[11]
- **Bacterial endocarditis:** The disease is caused by *Staphylococcus* and *Streptococcus*. Patients having prosthetic heart valve/abnormal heart valve and intravenous drug users are more likely

to contract the disease. Clinical features include vague, high-grade or low-grade fever, Janeway lesions, Osler nodes, Petechial rash on skin and mucosa, and splinter hemorrhages on nails (Fig. 1).[12]

Fig. 1: Clinical features of bacterial endocarditis[13]



Osler Nodes | Splinter Haemorrhages | Janeway Lesions

- **Chikungunya fever:** It is caused by chikungunya virus and the vectors are *Aedes aegypti* and *Aedes albopictus*. Pruriginous maculopapular rash is mostly seen on face, trunk, and extremities The treatment is only supportive.[2]
- **Erythema marginatum (Rheumatic fever):** Caused by Group A *Streptococcus* and the hosts are patients with rheumatic fever. Rash can be erythematous, and annular papules and plaques over trunk and proximal extremities (evolving and resolving within hours) are seen. Clinical Features are fever, polyarthralgia, elevated ESR, carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules.
- **Still's disease** (Systemic-onset juvenile idiopathic arthritis): It is systemic autoinflammatory disease and the clinical features are fever, migrating rash, hepatosplenomegaly, lymphadenopathy and arthritis. The characteristics of adult-onset Still's disease are arthritis, fever, salmon-colored evanescent rash, and elevated serum ferritin. The diagnosis is clinical and not based upon serology. The Yamaguchi criteria have the highest sensitivity in diagnosing the disease. It requires at least five features, with at least two of them being major diagnostic criteria (Table 1). Treatment is mainly oral prednisolone.[14]

Table 1: Yamaguchi criteria for diagnosing Still's disease

Major criteria	Minor criteria
• Fever of at least 39°C for at least one week • Arthralgias or arthritis for at least two weeks • Nonpruritic salmon-colored rash (usually over trunk or extremities while febrile) • Leukocytosis (10,000/microL or greater) with granulocyte predominance	• Sore throat • Lymphadenopathy • Hepatomegaly or splenomegaly • Abnormal liver function tests • Negative tests for antinuclear antibody and rheumatoid factor

2. Nodular eruptions

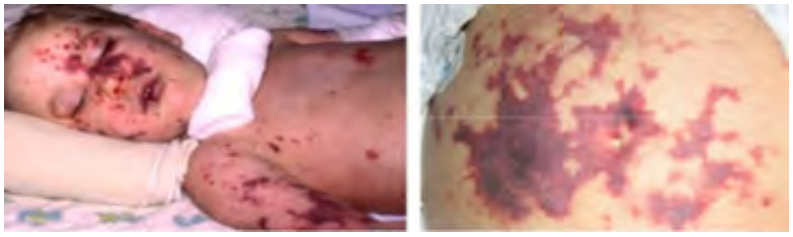
Such eruptions are characteristic for disseminated fungal Infection, erythema nodosum, Sweet's syndrome

- **Erythema nodosum:** It is an inflammatory condition marked by inflammation of the fat cells under the skin, resulting in tender red nodules or lumps seen on both shins. Rashes are large, violaceous, non-ulcerative and tender in nature. The treatment is mainly using NSAIDs.
- **Sweet syndrome (acute febrile neutrophilic dermatosis):** It is a reactive phenomenon and considered as a cutaneous marker of systemic disease. Causes are idiopathic (classic), malignancy (hematological), yersinial infection, drug induced, pregnancy and inflammatory bowel disease. Acute, tender, erythematous plaques; nodes and pseudovesicles, and occasionally blisters with an annular or arciform pattern occur on the head, neck, legs, and arms. Lesions show dense infiltrates by neutrophil granulocytes on histologic examination. Treatment is manly systemic corticosteroids (prednisone).[15]

3.purpuric eruptions

- **Meningococcal infections:** These infections, caused by *Neisseria meningitidis*, occur sporadically or in epidemics. Acute meningococcemia patients have characteristic petechial rash and a high spiking fever (Fig. 2). Treatments include fluid resuscitation and empirical antibiotic therapy (Inj. ceftriaxone 2g IV bd). Quadrivalent vaccines (serogroups A, C, W- 135 and Y) and bivalent vaccines (serogroups C and Y) are used for preventing the disease.[16]

Fig. 2: Acute meningococcemia rash[17]



- **Disseminated gonococcal infection:** Causative agent is *Neisseria gonorrhoeae* (resistant DGI strains) and the clinical features are low- to high-grade fever, skin lesions, tenosynovitis and suppurative arthritis. Peripheral papules or petechiae evolving rapidly to hemorrhagic pustules with grey necrotic center are noted. Papules, bullae, pustules, and hemorrhagic lesions may appear simultaneously. Treatment is with Inj. ceftriaxone (1 g IV q24h).
- **Purpura fulminans:** It may present as a complication of disseminated intravascular coagulation and acute severe sepsis due *N. meningitidis*, *S. pneumonia*, *H. influenza* and protein C deficiency. Clinical features are large ecchymoses with sharply irregular shapes evolving into hemorrhagic bullae and subsequently to black necrotic lesions. Diagnosis will be confirmed by purpuric lesions that are rapidly progressing to necrosis, increased FDP, deranged coagulation profile and thrombocytopenia. Treatments include antibiotics, volume expansion and FFP.
- **Viral hemorrhagic fever (VHF):** Caused by 5 distant families of RNA viruses: *Arenaviridae*, *Filoviridae*, *Bunyaviridae*, *Flaviviridae*, and *Rhabdoviridae*. Signs and symptoms of VHFs include fever and bleeding. Manifestations of VHF are flushing of the face and chest, small red or purple spots (petechiae), bleeding, edema, hypotension, and shock. Treatments are fluid resuscitation and whole blood transfusion.

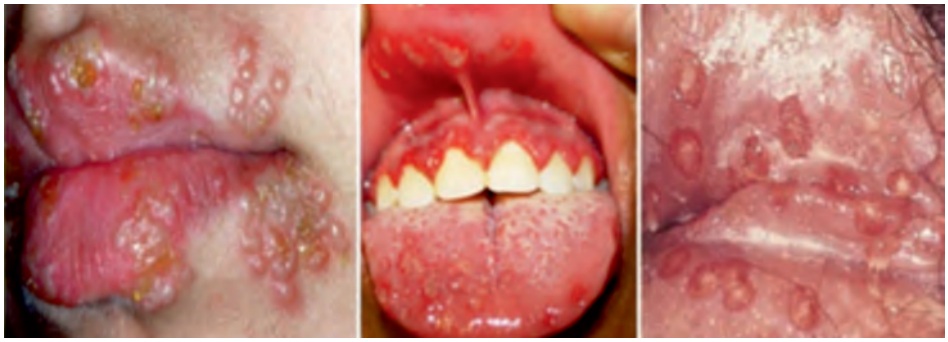
4. Vesiculobullous or pustular eruptions

- **Varicella:** Caused by varicella zoster virus, it is commonly seen in children. The mode of transmission is droplet infection or discharge by ruptured lesions. Rash appears on trunk on 2nd day of illness,

subsequently spreading to face and limbs. Rash appears as macules (2-3mm) evolving to papules, and then to vesicles on an erythematous base. Pustules and crusting lesions appear in crops. Intensely pruritic hemorrhagic lesions are noted in immunocompromised subjects. Treatments include supportive therapy and acyclovir.

- **Primary herpes infection:** Causative agent is herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Clinical conditions are herpetic gingivostomatitis, herpes labialis, herpes genitalis, herpes encephalitis and herpes oesophagitis. painful sores in the genital area, anus, buttocks, or thighs are noted along with itching, painful urination, vaginal discharge, and tender lumps in the groin. Treatment includes antivirals.[18]

Fig. 3: Herpes infection in different areas[19]

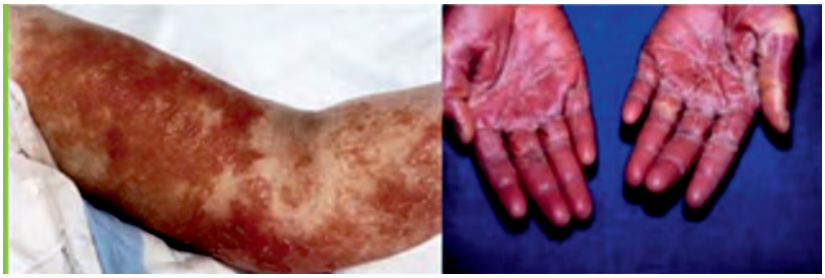


Herpes Labialis | Herpetic Gingivostomatitis | Genetal Herpes

5.Confluent desquamative erythemas

- **Scarlet fever:** Causative agent is *Streptococcus pyogenes* and the clinical features include sore throat, fever, characteristic rash, bright red tongue ('strawberry' tongue) Forchheimer spots, paranoia and hallucinations. Rash is diffuse blanchable erythema beginning on face and spreading to trunk and extremities. Circumscribed oral pallor accentuation of linear erythema in skin folds (Pastia's lines) is also noted. Treatment is mainly antibiotics.
- **Streptococcal toxic shock syndrome:** Caused by *Streptococcus pyogenes* (streptococcal pyrogenic exotoxins A and/or B or certain M types) and the clinical features include hypotension, multi-organ failure, bacteremia and rash. Rashes are generalized erythroderma with desquamation and localized cellulitis, along with vesiculation or bulla formation. Treatments include supportive management and antibiotics.
- **Kawasaki disease:** Clinical features include acute febrile illness, rashes after 3 day of fever, cervical lymphadenopathy, coronary artery vasculitis, erythema of the lips or oral cavity, and bilateral non-suppurative conjunctivitis. Diffuse maculopapular erythematous rashes on the trunk followed by desquamation are seen. Treatments include intravenous immunoglobulin and corticosteroids.
- **Staphylococcal toxic shock syndrome:** The disease is caused by *Staphylococcus aureus* (TSST 1, enterotoxin B or C). Clinical features are high fever (104° F), hypotension, malaise, confusion (which can rapidly progress to stupor), coma and multiple organ dysfunction. Rash appears as diffuse erythema involving palms and mucosal surfaces. Desquamation occurs 7-10 days after illness. Treatment involves ICU care with antibiotics.

Fig. 4: Rashes in staptococal toxic shock syndrome[20]



6.eruptions with ulcers and/ or eschars

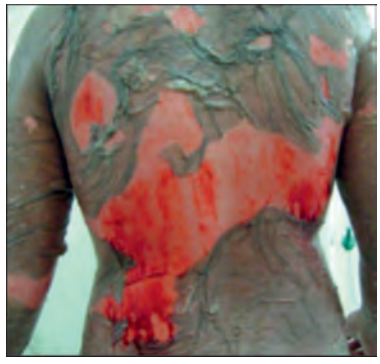
- **Tularemia:** Also known as rabbit fever, it is an infectious disease caused *by Francisella tularensis*. The disease spreads by ticks, deer flies or contact with infected animals. Symptoms include fever, skin ulcer, and enlarged lymph nodes. Preventive measures include using insect repellent, wearing long pants, rapidly removing ticks, and not disturbing dead animals. Treatment is typically with the antibiotics; streptomycin, gentamicin, doxycycline or ciprofloxacin.[21]
- **Anthrax:** It is an infection caused by *Bacillus anthracis*. Anthrax spreads by contact with the bacterial spores, which often appear in infectious animal products. Small blister with surrounding swelling is a characteristic feature of the disease.[22]

7.Drugs induced rash/eruptions

- Most drug-induced cutaneous reactions are mild and disappear following the withdrawal of the offending drug. Such diseases are diagnosed mainly on the basis of medical history and clinical examination. Maculopapular/ morbilliform eruptions are most common eruptions, followed by urticaria. Less commonly causes are anaphylaxis, Steven-Johnson syndrome and toxic epidermal necrolysis.
- **Morbilliform/maculopapular eruptions:** It primarily **a**ppears on the trunk and spreads to extremities. The eruptions may be associated with moderate to severe pruritus and fever. They are typically delayed in onset and are mediated by T cells. The first symptoms occur between 2 and 14 days of exposure to drugs. Beta-lactam antibiotics (mainly penicillin) and sulphonamides are the common offending drugs. Treatments include discontinuation of the drug, oral antihistamines, emollients, and topical glucocorticoids.
- **Drug-induced urticaria:** Urticaria or hives is characterized by pale red, raised, well-demarcated pruritic lesions of varying size. It may cause a burning or stinging sensation. Drug induced is mainly due to IgE-dependent mechanism and it typically appears within minutes to 36 hours of drug exposure. Circulating immune complexes (serum sickness) occur 6-12 days after first exposure. Drugs causing urticaria are NSAIDS, penicillin, ACE inhibitors, angiotensin receptor II and antagonists.
- **Serum sickness**: It is a type III hypersensitivity reaction (immune complex-mediated) resulting from the injection of heterologous or foreign protein or serum. Serum sickness can develop within 1-2 weeks following the initial exposure to a foreign antigen, in the absence of a pre-existing antibody. Characteristic symptoms include fever, chills, urticaria, myalgias, arthralgias and renal or neurologic dysfunction. Drugs causing serum sickness include allopurinol, barbiturates, captopril, penicillin, phenytoin procainamide, cephalosporins, griseofulvin, quinidine, streptokinase, sulfonamides, rituximab, ibuprofen, antitoxins, antivenoms, hormones from other species, streptokinase vaccines, and monoclonal antibodies.

- **Drug reaction with eosinophilia and systemic symptoms (DRESS):** It is a drug-induced hypersensitivity reaction characterized by rash, fever, inflammation of internal organs, lymphadenopathy, and characteristic hematologic abnormalities such as eosinophilia, thrombocytopenia, and atypical lymphocytosis. The syndrome is associated with a mortality rate of 10%. Drugs associated with DRESS are phenytoin, phenobarbital, carbamazepine, lamotrigine, sulfasalazine, cefixime, celecoxib, vancomycin, minocycline, sulfamethoxazole, allopurinol, abacavir, amitriptyline, mexiletine, captopril, nevirapine, oxcarbazepine, hydroxychloroquine, dapsone and ibuprofen. Maculopapular eruptions often progress into exfoliative erythroderma and profound edema. Treatments include immediate discontinuation of suspected drug, supportive care and corticosteroids.
- **Erythema multiforme:** It is an acute, self-limiting, recurring hypersensitivity reaction linked to drugs and infections. The exact cause is unknown. It may begin with damage to the blood vessels of the skin, followed by damage to skin tissues. Medications involved are sulphonamides, macrolides, penicillin, barbiturates, carbamazepine, phenytoin, allopurinol, and aspirin. The infections associated with the diseases are herpes simplex and mycoplasma pneumoniae. Clinical features are fever, itching and burning at the site of eruption, maculopapular lesions evolving to plaques, central erythema surrounded by area of clearing and another rim of erythema symmetric on extremities (knees, elbows, palms, soles) and it spreads centripetally on mucous membranes.
- **Steven-Johnson syndrome and toxic epidermal necrolysis:** These are two forms of a life-threatening skin condition. It usually occurs as a reaction to drugs, characterized by blisters and epidermal detachment, causing epidermal necrosis in the absence of substantial dermal inflammation (Fig. 5). Drugs involved are sulphonamides, lamotrigine, phenytoin, phenobarbitone, carbamazepine, allopurinol, oxicam, NSAIDs and nevirapine. Clinical features are high fever, painful skin lesions, sore throat, conjunctivitis, erythematous and purpuric macules, and diffuse erythema progressing to bullae, with epidermal necrosis and sloughing. Management includes immediate discontinuation of suspected drug, supportive therapy, transferring of the patient to burn units or ICU and adequate hydration.[23]

Fig.5: Rashes in Steven-johnson syndrome



Conclusion

- The differential diagnoses for febrile patients with rashes are very diverse. A thorough history and a careful physical examination are paramount to arrive at the correct diagnosis. Laboratory investigations are useful in concluding the diagnosis, however they are not immediately available. Since the severity of these illnesses can vary from self-limiting to life-threatening, prompt management decisions regarding empiric therapy play a major role in prognosis.

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Recurrent UTI in the elderly

Dr. M M Satish Kumar
M.D. (Internal Medicine)., D.N.B. (Nephrology)
Former Associate Professor of Nephrology
Sr Consultant Nephrologist & Transplant Physician
Vikram Hospital, Bengaluru & Mallige Hospital

Introduction

Differentiating symptomatic UTI from asymptomatic is paramount while managing UTI in elderly. The present review is aimed at providing a key message of not to prescribe unnecessary treatment by relying only upon urine routine and culture.

Defining UTI

UTI is broadly defined as an infection of the urinary system (or) both the lower and upper urinary tracts.[1] Bacteriuria is defined as the presence of bacteria in urine on microscopy or quantitative culture.[2] Symptomatic UTI generally requires the presence of urinary tract-specific symptoms in the setting of significant bacteriuria with a quantitative count of $\geq 10^5$ CFU/mL in one urine specimen. However, it should be remembered that the presence of bacteriuria does not always represent disease. The presence of lower urinary tract symptoms such as dysuria, scalding, double voiding and urgency in urinating along with culture positivity help in identifying symptomatic UTI.

The term pyuria indicates the presence of white blood cells in urine. White blood cells may present without bacteriuria and are often noted in patients with urinary catheter, stone, tumor, and infection.[3] Asymptomatic bacteriuria (ASB) is defined as the presence of bacteria in the urine without clinical signs or symptoms suggestive of a UTI. Whereas, asymptomatic pyuria is defined as the presence of white blood cells in the urine, in the absence of urinary tract-specific symptoms.

UTI is subclassified into complicated and uncomplicated UTI. Complicated UTI implies that the urinary

tract has a functional or structural abnormality. The term also covers all upper UTI and UTI in men.

Incidence and prevalence of UTI and ASB

Incidence of UTI is higher in women compared to men across all age groups.[4] The incidence is more frequent in young sexually active women (0.5 to 0.7 per person year) and in younger age group of 18-24 years (0.01 per person year). The incidence of infection is comparatively lesser in middle age group, but it increases with advancement in age.[1]

The most common cause for UTI is ascending infection with gram -ve organisms via the urethra in the perineal region from bowel flora. However, UTI is frequently over diagnosed and overtreated on the basis of non-specific clinical signs and symptoms, and this is one of the key reasons for developing antibiotic resistance. Overwhelming evidence suggests that it is not necessary to treat asymptomatic bacteriuria.[6]

Urinary system infections

It is one of the serious infections associated with significant morbidity. In a minor proportion of the cases, it may travel up the ureters causing renal damage and kidney failure. Based on the location of infection, such UTIs are named as urethritis, cystitis, nephritis and prostatitis. Most of the system infections are bacterial in origin and some are fungal.

UTI and risk factors

The common risk factors for UTI and their causes are listed in table 1.

Table 1: common risk factors for UTI and their causes

Risk factors	Causes
Incomplete bladder emptying	• Bladder outflow obstruction • Neurological problems (e.g.: multiple sclerosis, diabetic neuropathy) • Gynecological abnormalities (e.g.: uterine prolapse)
Foreign bodies	• Urethral catheters • Ureteric stent
Loss of host defenses	• Atrophic urethritis and vaginitis in post-menopausal women • Diabetes mellitus

The risk for developing UTI is higher in the following population: women; patients with voiding abnormalities related to diabetes, neurogenic bladder, spinal cord injury, pregnancy and benign prostatic hyperplasia; and those with urinary tract instrumentation (catheter).[6]

The lifestyle factors and comorbid conditions that may increase the risk of UTI are listed below:[7]

- Diabetes
- Foreign bodies in urinary system
- Diseases associated with neurogenic bladder
- Premenopausal women: sexual intercourse, spermicides, pregnancy, previous UTI, maternal history of UTI, and age of 1st UTI (genetic component)
- Perimenopausal women: changes in vaginal microbial flora

- Post-menopausal women: mechanical and physiologic factors affecting bladder emptying and estrogen deficiency

Symptoms of UTI

The characteristic features of cystitis, urethritis, and prostatitis are the following:[8]

Cystitis and urethritis

- Abrupt onset of frequency of micturition
- Scalding pain in the urethra during micturition
- Lower back pain, abdominal pain, and tenderness over bladder
- Suprapubic pain during and after voiding
- Intense desire to pass more urine after micturition due to spasm of inflamed bladder (urgency)

Prostatitis

- Pain in the lower back, perirectal area and testicles
- High fever, chills and symptoms similar to bacterial cystitis
- Inflammatory swelling of prostate, which can lead to urethral obstruction
- Urinary retention, which can cause abscess formation or seminal vesiculitis

UTI in geriatric patients

UTI is the most frequent infection among infectious diseases in elderly. The risk for developing UTI in such patients include dementia, incontinence, and decreased mobility. Asymptomatic bacteriuria is common in elderly and the incidences in men and women are around 15-30% and 25-50% respectively.[9] Evaluation of ambulatory visits by ≥65 years of age demonstrated that the urology visits constituted 47.9%. The incidence of important geriatric infectious diseases and their relative mortality rates in comparison to young adults indicated that UTI was around 5-10%.

The signs and symptoms of UTI are less pronounced in geriatric patients and the atypical symptoms noted in such subjects include altered mental status, confusion, behavior changes and changes in eating habits.

Asymptomatic bacteriuria

The presence of ASB can be concluded in patients with a quantitative count of > 10^5 CFU/mL on 2 consecutive occasions and there should be no UTI symptoms. The prevalence of ASB is higher in women (5%) than in men (0.1%) of 40- 60 years age and the corresponding prevalences are even higher over 80 years of age (25-50% vs. 21%).[10]

ASB is more common in patients with cognitive impairment and urinary and fecal incontinence. Cerebrovascular accidents, Alzheimer's disease and Parkinson's disease are associated with impaired bladder emptying. Patients with diabetes have increased prevalence of ASB and the contributing factors include neurogenic bladder and poor glycemic control.

Until 1986, clinicians believed that ASB had increased mortality and needed routine treatment.[11] However, the research conducted in 90s concluded that there is no direct association between ASB and mortality, and routine screening and treatment are not required.[12, 13] ASB screening or clinical treatment is not required for pre-menopausal, non-pregnant women; diabetic women; older persons

living in community; elderly institutionalized subjects; persons with spinal cord injury and catheterized patients while the catheter remains *in situ*. Whereas, screening or clinical treatment is required in pregnant women; patients suspected with obstructive uropathy; before TURP, urological interventions and insertion of prosthetic device; and in renal transplant and neutropenic patients.

Antibiotic treatment

The international guidelines recommend a 3-day course for simple acute cystitis. However , it may not be always applicable in Indian scenario and it should be customized as per the hospital antibiotic policy. A 7-day antibiotic course may be required in the following cases: patients requiring hospitalization and instrumentation of the urinary tract, diabetes, immunosuppression failure of previous therapy, >3 infections in the previous year, and symptoms lasting over 7 days.[2] The commonly recommended antibiotic regimens for uncomplicated UTI are given in table 2.

Table 2: Commonly recommended antibiotic regimens for uncomplicated UTI

Suggested Antimicrobial Regimens for Uncomplicated UTI	
Lower Tract Infection	**Regimen**
Trimethoprim-sulfamethoxazole	1 double-strength tablet bid for 3-7 days
Ciprofloxacin	250 mg bid for 3-7 days
Levofloxacin	250 mg qid for 3-7 days
Nitrofurantoin	100 mg qid for 7 days
	100 mg bid (sustained-release) for 7 days
Upper Tract Infection	**Regimen**
Ciprofloxacin	500 mg bid for 14 days
Levofloxacin	250 mg qd for 14 days
Trimethoprim-sulfamethoxazole	1 double-strength tablet bid for 14 days
Ceftriaxone	1 gram IV qd (can complete 14-day course with oral regimen)

The common adverse effects and drug interactions associated with antibiotics used for treating UTIs are given in table 3.

Table 3: common adverse effects and drug interactions associated with antibiotics used for treating UTIs

Common Side Effects and Drug Interactions Associated with Antimicrobials Used to Treat UTIs		
Antibiotic	**Side Effects**	**Drug Interaction**
Trimethoprim-sutfamethoxazole	Rash, bone marrow suppression, increased creatinine, hyperkalemia	Warfarin (prolonged prothrombin time), phenytoin, methotrexate (increased levels)
Fluoroquinolones	Mental status changes, gastrointestinal upset, tendon rupture	Iron supplements, antacids, sucralfate (decreased absorption); theophylline (increased level with some fluoroquinolones)

Nitrofurantoin	Pulmonary fibrosis (with chronic use); peripheral neuropathy (patients with renal failure)	Antacids (decreased absorption); probenecid (increased nitrofurantoin levels)
Aminoglycosides	Nephrotoxicity, ototoxicity	Loop diuretics (increased nephrotoxicity and ototoxicity)

Catheter-associated UTI

The incidences of catheter-associated UTI (CAUTI) below and above 65 years of age were 27% and 52% respectively. Around 10-15% of hospitalized patients with indwelling catheter develop bacteriuria and it is mainly due to gram negative bacteria. Patients with CAUTI have shown greater antimicrobial resistance and no treatment is required if the symptoms are absent. Third generation cephalosporins and/or ciprofloxacin or levofloxacin are recommended for treating gram negative bacilli; and for treating gram positive, vancomycin can be used.14

The guidelines by Infectious Diseases Society of America (IDSA) do not recommend the routine change of Foley catheter. If CAUTI is suspected, it is preferred to change the catheter and decide the treatment based on the culture obtained from clean catch urine from the newly exchanged catheter.[15] Antimicrobial-coated catheters can be considered. However, there are contradictory findings on the effectiveness of different types of such catheters in preventing symptomatic UTI.[16]

Prophylactic measures

Cranberry juice inhibits adherence of uropathogens to uroepithelial cells, thus preventing pathogenic colonization. However, there is no evidence that cranberry juice or tablets are effective for treating an acute infection.[17] Clinical research shows that cranberry juice or capsules 400 mg twice a day for 6 months may reduce UTIs in elderly women compared to placebo.[18] Cephalexin is very effective for long-term prophylaxis. Studies have shown that topical vaginally applied estrogens may assist in normalizing the vaginal flora by increasing *lactobacilli* and decreasing the *E. coli* colonization.[19]

Conclusion

UTI and ASB are highly prevalent in elderly and distinguishing symptomatic UTI from ASB is one of the major challenges faced by the clinicians. Overutilization of antibiotics for ASB remains a significant problem, especially in long-term care facilities. Treating asymptomatic patients only on the basis of urine bacteriuria and urine cultures is not recommended. Frequent changing of Foley catheters in catheterized patients is not advocated. There is no role for frequent bladder wash or prophylactic antibiotics in long-term catheterized patients.

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Post-operative fever: Clinical approach and management

Prof (Dr.) Channaraya V
Senior consulting physician,
Sagar hospital, Banashankari
Ex-prof and HOD medicine, KIMS

Introduction

Post-operative fever is the presence of temperature >38°C (>100.4°F) for 2 consecutive post-operative days or >39°C on any post-operative day. Proper identification and appropriate management of fever associated with sepsis are paramount to reduce mortality rates. Knowledge of differential diagnosis and adoption of a systematic approach are crucial for proper management.[1]

The study by Garibaldi et al., involving 871 general surgery patients, has found that 72% of fevers within the 48hrs after surgery were non-infectious.[2] Fever is the most common presentation in 1/3 of the infections. The probable cause for fever on day 1 or 2 post surgery could be intraoperative tissue trauma and subsequent release of endogenous pyrogens into the bloodstream. Whereas, the fever after 48 hours could be due to wound, urinary tract, and respiratory infections.

Unwanted investigations and empiric antibiotic treatment should be contraindicated in patients with fever within 48 hours post-surgery, if no specific diagnosis has been concluded even after thorough evaluation. Continuing perioperative prophylactic antibiotics does not confer any benefit in preventing infection. The pathophysiology of post-operative fever is closely associated with the production of IL-6 in response to fever stimuli.

Causes of post-operative fever

The causes of post-operative fever can be categorized as infectious as on-infectious, as given in table1.[3]

Table 1: Infectious and non-infectious causes of post-operative fever

Infectious	Non-infectious
• Pneumonia	• Atelectasis Hematoma
• UTI	• Transfusion related
• Surgical site infection	• Deep vein thromboses
• Abscess	• Acute myocardial infarction
• Blood stream infection	• Pulmonary thromboembolism
• Endocarditis	• Subarachnoid hemorrhage
• Meningitis	• Alcohol/drug withdrawal
• *Clostridium difficile*	• Thyrotoxicosis
	• Drug related

Drug fever

The incidence of drug fever is around 2-3% of all post-operative fevers. Antibiotics are the most common cause for drug-related fever and the fever often subsides after the withdrawal of the offending agent. The occurrence of malignant hyperthermia and neuroleptic malignant syndrome has also been reported in drug-related fever. The common causes of drug fever include: antimicrobials (macrolides, ampicillin, Isoniazid, cotrimoxazole, vancomycin, gentamicin), CNS drugs (methyldopa, barbiturate, anticholinergics), anesthetics (halothane, enflurane, succinylcholine), anti-neoplastic agents (doxorubicin, chlorambucil, cisplatin) and CVS drugs (hydralazine, captopril, procainamide, quinidine).[4]

Infectious causes

If the surgery is performed for controlling infection, the fever is expected to settle within 72 hours. New or persistent fever for >3 days post surgery should raise a strong suspicion of persistent sepsis or a new complication.[5]

Device-related infections often arise due to the use of IV drips, ET-tube, tracheostomy tube, NG tube, urinary catheters and drains. The incidence of nosocomial infection in the first 48 hours after operation is very rare. Nosocomial chest infection commonly occurs after 3rd day of surgery and the risk factors include prolonged mechanical ventilation; cardiothoracic, neurosurgical, and trauma operations; and major head and neck/gastrointestinal surgeries. Purulent sputum, fever, high WCC count, and abnormal chest X-ray are suggestive of underlying nosocomial infection.[6]

Most important risk factor for developing post-operative fever due to UTI is prolonged use of catheters. The catheter should be monitored daily, and in suspected cases, it should be removed at the earliest opportunity. Infection can also occur through central or peripheral lines and percutaneously placed catheter should be removed in suspected cases. Nosocomial infections not associated with devices include wound infections, necrotizing fasciitis, pseudomembranous colitis and acalculous cholecystitis.

Approach to post-operative fever

Individual approach is essential while managing post-operative fever. Uncommon diagnoses should

not be considered, until the exclusion of more common causes. It is important to differentiate the fever due to infection from that of inflammatory response.[7]

Based on the time of onset, the post-operative management can be divided as follows:

Day 1

Atelectasis is the most common cause for day 1 post-operative fever.[8] Bacteremia should be suspected, if high-grade fever (40°C) occurs 30-40 min after the surgery (e.g. urinary instrumentation). The fever on day 1 can also occur due to persistent sepsis, if the procedure was done for controlling infection. The rare causes of day 1 fever are thyroid crisis, transfusion reaction, drug fever and malignant hyperthermia

Day 2 to day 5

The probable common causes for fever between day 2 and 5 are drip site infection, chest infection and UTI. The rare causes are antibiotics-induced colitis, acute acalculous cholecystitis, hematoma, tissue necrosis (e.g. flap) and gout.

Day >5 to day 7

The common causes of day >5 - Day 7 fever include wound infection, anastomotic leak, intra-abdominal abscess / collection, deep venous thrombosis, and pulmonary embolism.

Between 1-4 weeks (Subacute fever)

The subacute fever could be due to deep infection (pelvic or abdominal abscess). In such patients, digital rectal exam should be carried out to rule out pelvic abscess and CT scan to locate abscess. Radiologically-guided percutaneous drainage needs to be carried out in necessary cases. In patients having rash and peripheral eosinophilia, further investigations should be performed to exclude drug fever.[1]

After >4 weeks (Delayed fever)

The probable causes of delayed fever after 4 weeks are skin and soft tissue infections (SSTI), and viral infections.

The following case scenarios may help in better understanding the management of post-operative fever.

Case scenario 1

Mr. X who had undergone laparoscopic cholecystectomy was discharged on 3rd day post surgery. The patient returned to emergency department with the complaints of fever, abdominal distension, and BP of 90/60. The patient was referred to physician for evaluation of sepsis and shock. The lab findings indicated CBC of around 23,000 and ultrasound revealed no collection. The patient was initiated with antibiotics and vasopressors. Further consultation with surgeon confirmed it as a wound infection, which required debridement. In patients presenting with pos-operative fever, it is preferred to seek surgeon's opinion to rule out the possibility of wound infections.

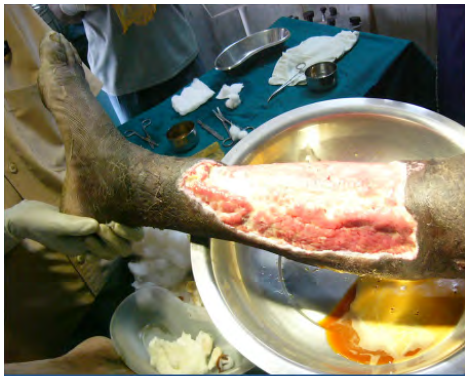
Case scenario 2

Following a lower segment Caesarean section, a patient developed psychosis and was referred to consult psychiatrist. She was initiated on antipsychotics, but developed fever on day 3. She was referred to physician on 6th day post surgery, as the patient did not show any improvement. The results of routine examination were insignificant, but the Widal test was positive. The diagnosis was concluded as typhoid and she was started with antibiotics and was instructed to stop antipsychotics. The patient recovered well within a short period. In post-operative period, it is important to consider the common infections also as a cause for post-operative fever.

Case scenario 3

A patient who was operated for diabetic foot (Fig.1) developed fever on day 1 due to cellulitis. He was initiated with antibiotics, and was on continuous debridement and wound care. During the course, the patient had persistent greenish exudate and ongoing infection. The culture demonstrated the presence of pseudomonas resistant to most of the drug, except ciprofloxacin. The antibiotics were changed to ciprofloxacin, linezolid, and meropenem. The patient subsequently developed acute dyspnea, increased urea and creatinine, decreased urine output, and fall in SpO2 to 85%. The patient was admitted in ICU.

Fig. 1: operated diabetic foot



X-ray and other investigations revealed that the patient had acute renal failure and acute respiratory distress syndrome due to sepsis. He was improved on treatment with furosemide and O2 4L/min, but the fever persisted. Further investigations including lung perfusion scan, Doppler, ECHO, bone marrow analysis and liver biopsy did not show any abnormal findings.

Chest X-ray showed right lower zone haziness and CT of chest revealed bilateral pleural effusion (Fig. 2) and subjacent consolidation of lung. Pleural fluid analysis revealed: protein-2.9 gm%, sugar-96 mg%, cell count-950 cells/cmm and cell type-L90%,10%. The patient was initiated with anti-tuberculosis regimen and he had become afebrile within 3 days of treatment. Skin grafting done after 1 month and the patient recovered.

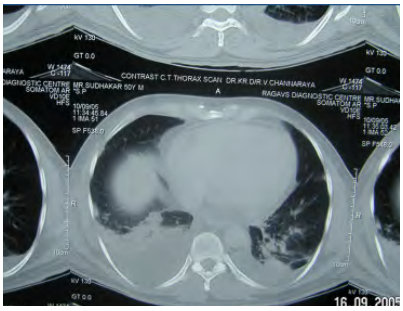


Fig. 2: CT showing bilateral pleural effusion

Approach to post-operative fever

Careful review of history should comprise of premorbid condition, indication of surgery and nature of operation. Physical examination should evaluate vital signs and possible source of infection. CBC, culture of blood, sputum and urine, chest X-ray, USG abdomen, CT scan, CRP, and procalcitonin can be considered, based on the requirement. Empiric antibiotics need to be started in necessary cases. In patients with type 7 stools, *Clostridium difficile* enterocolitis should be ruled out.

Prognosis

In most cases, the cause of post-operative fever is benign and resolves faster with treatment. Patients with atelectasis recuperate quickly following incentive spirometry and /or chest physiotherapy. Similarly, subjects with deep vein thrombosis and pulmonary thromboembolism have low-grade fever and recovers quickly with treatment. However, the prognosis is poor in patients with anastomotic leak or bowel obstruction.[1]

Conclusion

Post-operative fever is frequently a normal response to surgery, which needs a systemic and logical approach. The underlying cause could be infectious or on-infectious in origin. The work-up may depend on multiple factors and patient presentation.

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Case presentations on fever

Dr. Dipankar Pal
Faculty, Department of Tropical Medicine
School of Tropical Medicine
Kolkata

Introduction

Awareness regarding the clinical presentation and a high level of clinical suspicion are integral for early diagnosis, especially in immunocompromised patients. The cases on fever, discussed in this paper, highlight the need of early detection of underlying cause to reduce the mortality and morbidity.

Case scenario 1: Young male with acute shortness of breath

A 36-year-old male, migratory worker presented with the complaints of intermittent fever and loose motion for one month, and non-productive cough and progressive shortness of breath for the past 15 days. He had received anti-tubercular medications for pulmonary tuberculosis around 7 years before. Around 3 weeks back, he was found to be positive for HIV1. The patient was a non-smoker. Physical examination revealed: oropharyngeal candidiasis, tachypnoea-40/min, pulse-104/min, BP-120/80, SpO2-90%, and diminishing of breath sound in right infra axillary area.

The sputum was AFB negative, but the culture was positive for *Streptococcus pneumoniae*. The patient was initiated with moist O2, oral co-amoxiclav and fluconazole based on the aforementioned finding. Subsequent investigation revealed a CD cell count of 47 per cubic millimetre. Microscopic evaluation of sputum obtained on hypertonic saline nebulization revealed *Pnemocystis jirovecii* cysts on Giemsa stained smear (Fig. 1).

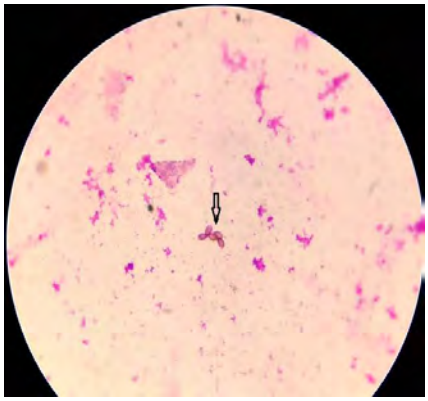

Fig. 1: Sputum microscopy showing Pnemocystis jirovecii cysts

The patient was started with cotrimoxazole and prednisone. His cyanosis disappeared on day 3 and his condition improved gradually. On day 10, he presented again with sudden increase in shortness of breath at rest and cyanosis. Subcutaneous emphysema was noted on both sides of neck (Fig.2) and slight diminution of vesicular breath sound bilaterally. He was shifted to critical care unit (CCU). The X-ray (Fig. 2) and CT scan confirmed the diagnosis as pneumothorax with pneumomediastinum (Fig.3).

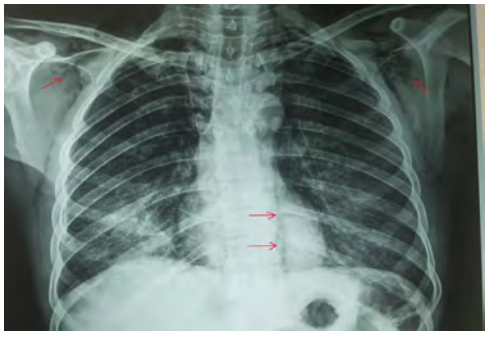

Fig. 2: X-ray showing subcutaneous emphysema and pneumomediastinum

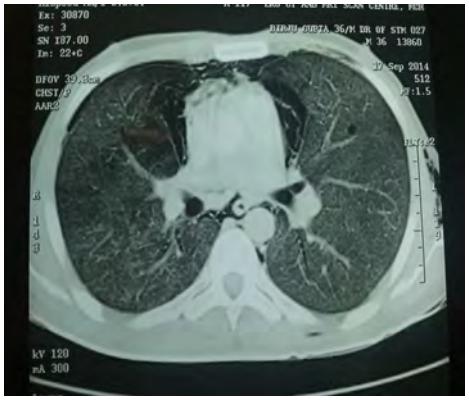

Fig.3: CT scan showing pneumomediastinum on both sides

Conservative management with high flow O2 was continued in CCU. Air was absorbed from the pneumothorax with pneumomediastinum for around 2 weeks. Antiretroviral therapy was initiated and the patient condition improved. He was discharged on co-trimoxazole prophylaxis.

Case scenario 2: Trouble never comes alone

Case history

A 30-years-old female from rural Bengal was admitted with complaints of high-grade intermittent fever and cough with expectoration for 10 days. She subsequently developed jaundice. She had paraesthesia in lower limbs and sacral area, and progressive weakness of both lower limbs for last 1 week. The patient also complained of no girdle-like sensation over trunk, difficulty in passing urine, absence of bowel involvement and dimness of vision of right eye. The patient did not have any history of tuberculosis or medical/ surgical intervention. She had a CD4 cell count of 27/µL. Seropositive HIV was diagnosed a couple of months ago and she was on anti-retroviral therapy (ART) with tenofovir, lamivudine and efavirenz (TDF+ 3TC+EFV) for one month before the presentation of current illness.

Physical examination revealed that the patient was conscious, alert, co-operative, febrile, pale and icteric; pulse 110/min; BP 110/76 mm of Hg, crepitations on both lung bases, and hepatomegaly. Patchy sensory impairment in lower limbs and sacral area was noted. Power in lower limbs bilaterally was 3/5. Abnormal clinical investigations noted were pancytopenia, hyperbilirubinemia, hypoalbuminemia, raised liver enzymes, and presence of *Pseudomonas aeruginosa* in sputum culture.

Ophthalmological examination revealed features suggestive of cytomegalovirus (CMV) retinitis. CT of brain and MRI of spine could not be done, as the patient was very sick. CSF analysis indicated decreased glucose, and markedly elevated proteins with polymorphonuclear leucocytosis.

Differential diagnosis

Based on the findings, distal sensory polyneuropathy, acute inflammatory demyelinating polyneuropathy (AIDP) and mononeuritis multiplex were ruled out and initial diagnosis of CMV polyradiculopathy was made. Further investigation of CSF sample using DNA PCR confirmed the presence of CMV. Biochemical tests revealed elevated levels of triglyceride (327 mg/dl) and serum ferritin (4238.6 ng/ml). Histopathology of bone marrow showed the presence of hemophagocytes. Based on the aforementioned clinical and lab investigations, the final diagnosis was concluded as hemophagocytic lymphohistiocytosis (HLH). The patient met the following criteria of HLH: fever pancytopenia, hypertriglyceridemia, hyperferritinemia and bone marrow evidence of hemophagocytosis.[1]

Treatment

The patient was administered with dexamethasone injection 10mg/m^2 for 1st 3 weeks, which was tapered off over next 5 weeks as per HLH-94 protocol. Injections ganciclovir 5mg/kg and G-CSF were also given for treating CMV disease and pancytopenia respectively.

Treatment response

Rapid improvement in the patient's condition was noted with subsidence of fever and improvement of all laboratory parameters in couple of weeks. Lower limb motor weakness improved gradually with physiotherapy. The patient was discharged after 1 month of her admission in an ambulatory state. Early diagnosis and treatment are paramount in managing HLH. The possibility of hemophagocytic

syndrome should be considered while managing critically ill patients with variety of pertinent symptoms.

Case scenario 3: A lady with fever and cough

A 44-year-old lady from West Bengal presented with low-grade intermittent fever, dry cough, fatigue and deterioration of general health. She was non-diabetic and non-hypertensive. Routine examination showed anaemia and ESR of 66 mm/1st hour. Chest X-ray and CT scan revealed homogenous rounded opacity over the left aperture. The patient subsequently developed hemoptysis along with pain over left upper chest. CT-guided FNAC revealed granulomatous lesion and she was initiated with anti-tubercular drugs. However, the patient developed drug-induced hepatotoxicity within 6 weeks of treatment and the medications were changed to liver friendly anti-tubercular drugs.

After 1 month, she presented again with dull aching pain over right upper abdomen. Further evaluation detected gallbladder cancer involving cystic duct and neck of gallbladder. Radical cholecystectomy with extrahepatic bile duct excision and hepaticojejunostomy were performed. A small, skin coloured, slightly painful nodule was also noticed just above the elbow joint. The nodule gradually increased in size over next 6 months and turned to a fungating lesion of about 3 cms. The nodule was excised for skin biopsy.

The patient was referred to a specialist and had undergone CSF analysis, brain imaging and sputum culture. The skin biopsy report showed thick walled budding yeasts, and sputum culture and sputum on Indian ink revealed *Cryptococcus* (Fig. 4). In addition, the cryptococcal antigen in CSF was detected to be positive with titre 1:160. The review of previous slides of lung SOL biopsy showed chronic inflammatory lesion showing large population of capsulated yeast cells morphologically mimicking *Cryptococcus* (Fig. 5).

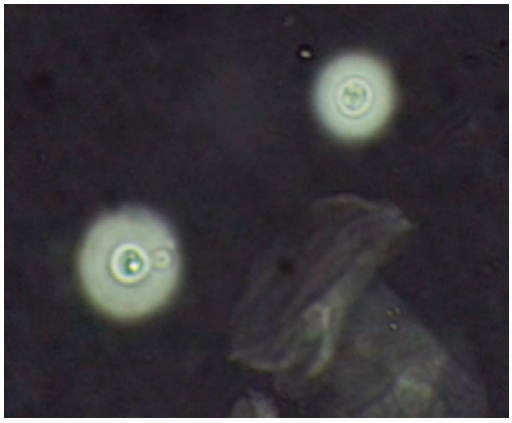

Fig. 4: Sputum on Indian ink showing *Cryptococcus*

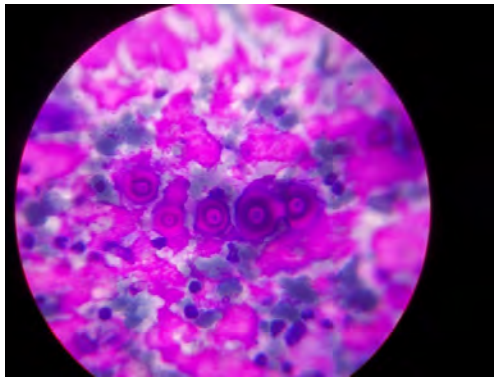

Fig.5: Previous SOL biopsy showing large population of capsulated yeast cells

As per the 2010 clinical practice guidelines for the management of cryptococcal disease, the patient was treated with IV amphotericin-B(1 mg/kg BW)+ tab flucytosine (100 mg/kg BW) in 4 divided doses for 6 weeks, followed by tab fluconazole 400 mg for 1 year.[2] The 5 months of treatment had significantly improved the patient's condition including the healing of skin lesion and reduction of SOL size in chest X-ray.

The possibility of *Cryptococcosis* should be considered in patients with non-healing lung and skin lesions, especially in endemic countries. In all cases of pulmonary/cutaneous *Cryptococcosis*, CNS involvement should be evaluated, even in asymptomatic patients.

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Tropical fevers

Dr Ramesh Aggarwal
Associate Professor
Department of Medicine
Lady Hardinge Medical College
New Delhi, India.

Introduction

Tropical infections, which are prevalent and unique to tropical and subtropical regions, causes one-quarter to one-third of the mortality of young adults, especially in Sub-Saharan Africa.[1] The commonly prevalent infections include malaria, dengue, scrub typhus, leptospirosis, typhoid, Japanese B encephalitis, HSV, hanta virus, Lymes, leishmaniasis and brucellosis.

Syndromic approach for managing tropic fever

Syndromic approach refers to the treatment of signs and symptoms based on the causative organisms for each syndrome.[2] This approach for the tropical infections can be classified as follows:[3]

1. **Fever with rash / thrombocytopenia:** In patients presenting with acute onset fever with a transient skin rash or exanthema, with or without thrombocytopenia (platelet count <100,000/mL), the differential diagnosis to be considered are malaria (falciparum), measles, rubella, dengue, leptospirosis, scrub typhus, meningococcal infections, and other viral exanthems. The type of rash helps in concluding the diagnosis.
2. **Fever with acute onset fever with respiratory distress (ARDS):** ARDS in the form of SpO2 <90% at room air or frank ARDS with PaO2/FiO2 ratio <200 is often noted in falciparum malaria, dengue, scrub typhus, influenza (including H1N1), and H1N1.
3. **Acute febrile encephalopathy / acute encephalitic syndrome**: In patients presenting with meningeal or CNS complications, the probable diagnosis could be scrub typhus, cerebral malaria, typhoid fever, Japanese B encephalitis, and leptospirosis.

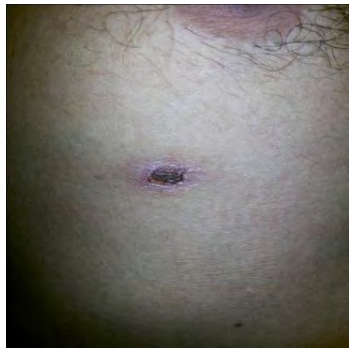
4. **Fever with multiple organ dysfunction syndrome (MODS):** The differential diagnoses for fever with MODS include bacterial sepsis, falciparum malaria, leptospirosis, scrub typhus, dengue, hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome.
5. **Acute undifferentiated fever:** Such patients typically have acute onset fever without any localizing signs. The probable diagnoses can be malaria, dengue, leptospirosis, scrub typhus, typhoid, other common viral infections.

Scrub typhus

The term 'typhus', derived from Greek, means 'fever with stupor' or smoke. The causative organism for scrub typhus is *Orientia tsutsugamushi* ('Tsutsuga' means small and dangerous and 'mushi' means insect or mite). The disease is found to be more predominant in the Tsutsugamushi triangle, which comprises of various countries such as tropical Australia, India, Japan, China, Philippines, Pakistan, Tibet, Afghanistan, and southern parts of the USSR in the north.[4] In India, the epidemic has been reported in the sub-Himalayan belt, and in eastern and southern Indian regions. The disease damages the vasular endothelium, resulting in multi-organ manifestations comprising of skin, liver, kidneys, meninges and brain. The disease accounts for 6% of the death in untreated patients and 1.5% in treated subjects.[5]

The clinical features include fever, headache, myalgia, breathing difficulty, delirium, vomiting, cough, and jaundice. The occurrence of eschar in neck, axillae, chest, abdomen, axilla, scrotum, perianal region, or in groin is a pathognomonic sign of scrub typhus.[6] Eschar is a painless, punched out ulcers (up to 1 cm in width) with a black necrotic centre and erythematous margin (Fig. 1). The complications of the disease include pneumonia with ARDS, hepatitis, aseptic meningitis and myocarditis.

Fig. 1: Eschar noted in typhus



PCR is both sensitive and specific in diagnosing scrub typhus. Indirect fluorescent antibody is considered as gold standard with a sensitivity and specificity of >90. IgM antibody titers are generally noted by the end of 1st week. Whereas, IgG appears positive only by the end of 2nd week. Weil-Felix has variable sensitivity and specificity, but it is commonly used due to the ease of availability. The common antibiotics used are doxycycline (100 mg BD for 7 days), azithromycin and chloramphenicol.

Leptospirosis

It is a spirochetal disease caused by 2 species of leptospira: *L. interrogans*, (pathogenic, responsible for leptospirosis) and *L. Biflexa* (non-pathogenic leptospires). It is transmitted through direct contact

of skin or mucosa with water contaminated with urine or body fluid of an infected animal. Peak incidence has been reported during the rainy season, especially in southern, western and eastern part of India.

The pathophysiology involves multiplication of leptospires in the small blood vessel endothelium, resulting in vasculitis and clinical manifestations. They may settle in the convoluted tubules of the kidneys and shed through urine for a few weeks to several months.[7] The disease has biphasic clinical presentation as mentioned below:

1. Septicaemic/leptospiremic phase: The organism may be present in the urine, blood, CSF and most tissues. This phase is characterized by non-specific presentations such as by fever, chills, weakness, and myalgias primarily affecting the calves, back, and abdomen. Jaundice may develop at the end of first stage. The patient may also have sore throat, cough, chest pain, hemoptysis, rash, frontal headache, photophobia, mental confusion, and other symptoms of meningitis.[8]
2. Immune/leptospiruric phase: It is marked by the recurrence of fever after a brief asymptomatic period. It occurs due to the body's immunologic response to infection and the circulating antibodies may be detected. However, the organism may not be recoverable from blood or CSF. The disease manifestations involve meninges, liver, lungs (ARDS), kidneys, and eyes (subconjunctival hemorrhage, uveitis, iridocyclitis and chorioretinitis).

Microscopic agglutination test (MAT) becomes positive after 7-10 days of illness and may persist at high levels for many years. The IgM EIA is useful in making an early diagnosis and it is extremely sensitive and specific (93%).[9] CPK helps in distinguishing leptospirosis from viral hepatitis. Penicillin G (1.5 MU (IV) 6 hourly for 7 days), cephalosporins, and oral doxycycline are the common treatments of choice.

Dengue fever

The disease is caused mainly by the 4 serotypes of dengue virus namely DENV-1, DENV-2, DENV-3 and DENV-4. Secondary infection with another serotype or multiple infections with different serotypes lead to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[10] Since the vector, *Ae. aegypt*i is a nervous feeder (bites more than one host to complete one blood meal) and a discordant species (needs more than one feed for the completion of the gonotrophic cycle), it results in the generation of multiple cases and the clustering of dengue cases in cities. Studies conducted in Thailand have revealed that the DENV-1/DENV-2 sequences of infection were associated with a 500-fold risk of DHF compared to the primary infection.[11]

The WHO has coined the term 'expanded dengue syndrome' to describe the cases that do not belong to either DSS or DHF.[12] This has several atypical findings of dengue, which do not depend on the falling hematocrit or the plasma leakage. The unusual manifestations of CNS, gastrointestinal and CVS noted in expanded dengue syndrome are listed in table 1.

Table 1: The unusual manifestations of CNS, gastrointestinal and CVS notes in expanded dengue syndrome

CNS	Gastrointestinal	CVS
• Intra-cerebral hemorrhage • Encephalitis • Aseptic meningitis • ADEM • Cerebral infarct • Cortical venous thrombosis • Myelitis • Hypokalemic periodic paralysis • G.B. syndrome • Opsoclonus myoclonus • Optic neuropathy • Myalgia cruris • Rhabdomyolysis • Dysarthria clumsy-hand syndrome	• Hepatic dysfunction (without ALF) • Acalculus cholecystitis • Fulminant hepatic failure • Acute pancreatitis • Diffuse peritonitis • Acute appendicitis • Acute parotitis • Spleen rupture	• Asymptomatic myocarditis • Symptomatic myocarditis • Pericarditis • Myocardial infarction • S-A nodal block • A-V nodal block • Acute atrial fibrillation • Cardiomyopathy

A relative lymphocytosis with increased atypical lymphocytes is a commonly observed lab finding by the end of the febrile phase and in convalescence. A sudden decrease in platelet count to <100 000 /mL is often noted by the end of the febrile phase prior to the onset of shock or subsidence of fever, and the level correlates with the severity of DHF.[13] Increase in hematocrit, by 20% from the baseline, is considered as the objective evidence of plasma leakage. Other significant clinical investigations include the presence of hypoproteinemia, albuminemia, hyponatremia, elevated serum aspartate aminotransferase levels (≤200 U/L), hypocalcemia and metabolic acidosis.

NS1 antigen, assists in early diagnosis, as it is noticeable by day 1 after the onset of the fever and declines to undetectable levels by 5-6 days. The IgM/IgG ratio is used to distinguish primary from secondary dengue infection. If the capture IgM/IgG ratio is >1.2, it is defined as primary; and secondary, if the ratio is <1.2.

In order to manage prolonged/profound shock, 10 ml/kg of bolus fluid should be administered ideally within 10 to 15 minutes. If shock is not reversible, a repeat bolus of 10 ml/kg and laboratory findings should be pursued immediately and blood transfusion should be considered as the next step.[14]

Malaria

Causative organisms of malaria are *P. falciparum, P. vivax, P. malariae,* and *P ovale,* and the vector is anopheles mosquito. The disease occurs in 5 out of 6 WHO regions (except Europe). The cases reported from 15 countries account for 80% of all malaria cases worldwide. The prevalence is highest in Nigeria (27%), followed by the Democratic Republic of the Congo (10%), India (6%) and Mozambique (4%).[15]

Man is the intermediate host for malaria. The sporozoites enter humans from infested mosquito and initiate the former phase of the cycle from the liver and the latter within the red blood cell. This in

turn results in the various clinical manifestations of the disease. In *P. falciparum* infection, membrane protuberances appear on the red blood cell and these cells get attached to the capillary endothelium causing cytoadherence. In addition, the adherence of infected red cells to uninfected red cells leads to the formation of rosettes. The formation of aggregates and intra-vascular sequestration of red cells in the major organs like brain and heart are key to the pathogenesis of malaria.[16]

Malaria can be transmitted through blood transmission. However, the risk of transmission is extremely low for plasma, plasma components, and derivatives devoid of intact red cells. Needle stick injury and congenital malaria are the other modes of malaria transmission. Cerebral malaria, severe anemia, hypoglycemia, metabolic acidosis, acute renal failure, ARDS and shock are the common manifestations of malaria.

Well-stained peripheral smear currently remains as the gold standard for malaria diagnosis. The sensitivity of thick smears is 20-40 times more when compared to thin smears for screening of plasmodium parasites with a detection limit of 10-50 trophozoites/µl.[17] Thin smear is preferred for the identification of the species. The rapid diagnostic tests for malarial antigens are histidine-rich protein 2 for *P. falciparum*, pan-malarial plasmodium aldolase and parasite specific lactate dehydrogenase for diagnosing other malarial species. The major disadvantage of rapid test is that they may remain positive even after the initiation of treatment due to the persistence of antigens.

The preferred treatment options based on the type of infections are briefed in table 2.[18]

Table 2: Treatment options for malaria based on the type of infections

Type of infection	Suppressive Treatment	Radical Treatment
P. vivax* and *P. ovale	Chloroquine 25 mg of salt/kg over 36-48 hours	Primaquine for 14 days.
P. falciparum	**Treatment depends on severity and sensitivity** Artesunate + pyrimethamine - sulphadoxine or other ACTs, or quinine plus tetracycline	Primaquine 0.75mg/kg in single dose as gametocytocidal
Mixed (*P. vivax* + *P. falciparum*)	ACT as for *P. falciparum*	Primaquine as for *P. vivax*

Enteric fever

The causative organisms are *Salmonella typhi*, and *Salmonella paratyphi A, B* and *C*. The transmission is mainly through fecal contaminated food and water. The bacteria spread throughout the reticulo-endothelial system and in areas of increased macrophage concentration such as the Peyer's patches. The clinical features include fever, headache, relative bradycardia, abdominal pain, diarrhea, constipation, hepatosplenomegaly, encephalopathy, intestinal bleeding etc. Blood culture remains as the gold standard for diagnosing enteric fever. Typhidot is the rapid test for diagnosing enteric fever and it becomes positive by the end of first week of fever. Widal test, though non-specific, it is used widely due to the easy of availability.[19]

After the development of multidrug-resistant typhoid, ciprofloxacin became the drug of choice. However, point mutations in the quinolone resistance determining region (QRDR) of DNA gyrase

gave raise to decreased ciprofloxacin susceptibility (DCS). Most clinicians prefer azithromycin for uncomplicated disease and ceftriaxone for patients requiring IV therapy.

Japanese encephalitis

The viral disease is prevalent in southern, central and north-eastern Indian states such as Uttar Pradesh, Haryana, Bihar, Maharashtra, Andhra Pradesh and Tamil Nadu. The treatment is conservative including supportive-airway management, seizure control and management of raised intracranial pressure.[20]

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Hyperpyrexia

Dr. N K Soni M.D., F.R.C.P. (Glasgow), F.A.C.P. (USA), F.I.C.P, F.I.A.C.M
Senior Physician Consultant & HOD - Deptt. of Internal Medicine,
Yashoda Super Speciality Hospital & Heart Institute,
Ghaziabad

Introduction

Fevers, including very high fevers, are never illnesses or the cause of illnesses. Instead, they are symptoms of other underlying problems such as an infection or injury. Fever can be due to infectious or non-infectious etiology such as viral, bacterial or malarial infection, intracranial hemorrhage, autoimmune disorders, medications, thyroid storm, heat stroke, malignancy etc. Hyperpyrexia or very high fever is the presence of a running body temperature of >106.7°F or 41.5°C. It should also be noted that the terms fever, hyperthermia, and hyperpyrexia are not synonymous, as they differ with respect to causative factors, pathophysiology and treatment modalities.

What is hyperpyrexia?

Hyperpyrexia is the occurrence of extraordinarily high fever of ≥106.7 °F/>41.5°C. This can be observed in patients with severe infections and in those with central nervous system hemorrhages. Burn injury results in the release of proinflammatory cytokines and catecholamines, causing a hypermetabolic state, which may lead to hyperpyrexia. Hyperpyrexia is a medical emergency and is usually fatal, if not treated promptly.[1, 2]

Differences between hyperpyrexia and hyperthermia

Hyperpyrexia is defined as the occurrence of severely elevated core body temperature, secondary to an increased hypothalamic set thermo-regulatory threshold. The most common cause of hyperpyrexia is brain dysfunction like intracranial hemorrhage. Whereas, hyperthermia is an elevation in core body

temperature beyond the normal hypothalamic set thermoregulatory threshold. In contrast to other fever, the brain is not regulating the rise in temperature in hyperthermia. It usually occurs secondary to an exogenous stimulus like heat stroke or secondary to adverse drug reactions like malignant neuroleptic syndrome and malignant hyperthermia.[3]

Causes of hyperpyrexia and hyperthermia

The hyperpyrexia, seen in neurologic trauma or infection, is mainly due to the presence of CNS pyrogens and cytokines. Exogenous pyrogens are mainly microbes or their toxins. Lipopolysaccharide endotoxin produced by all gram-negative bacteria, belonging to toll-like receptor (TLR) ligands, and *Staphylococcus aureus* enterotoxins are examples of pyrogens. The activation of TLR stimulates the production of specific pyogenic cytokines such as IL-1, IL-2, IL-4, IL-6, TNF, and ciliary neurotrophic factor. These cytokines trigger the hypothalamus to raise the set-point to febrile levels.[1,2]

Apart from common causes of hyperpyrexia, the causative factors of hyperthermia are briefed below:[2]

- Heat exposure/heat stroke
- Neuroleptic malignant syndrome
- Malignant hyperthermia
- Serotonin syndrome
- Intracranial hemorrhage
- Thyroid storm
- Anticholinergic toxidrome (e.g. tricyclic antidepressants)
- Sympathomimetic toxidrome (e.g. amphetamines, cocaine)

Intracranial hemorrhage

In some cases, intracranial hemorrhage causes hyperpyrexia. Accidents or other traumas and strokes are the most likely cause of intracranial hemorrhage. The bleeding in the brain can affect the hypothalamus, which is responsible for regulating the body's temperature.

Sepsis

In rare cases, hyperpyrexia may result from sepsis. The overwhelming immune system response, triggered by the sepsis, may cause organ damage or failure.

Anesthesia

Hyperpyrexia may also occur as a direct side effect of general anesthesia, if there is an underlying muscular disease. In such cases, the body temperature increases rapidly while under anesthesia, and the physician should take necessary measures to regulate the temperature.[4]

Hyperpyrexia in children

Another potential cause of hyperpyrexia is Kawasaki syndrome. It causes inflammation to the medium-sized arteries.[4]

Hussein et al. have noted that hyperpyrexia may appear as the presenting symptom of intracranial hypotension, secondary to hypothalamic dysfunction. Sometimes spontaneous intracranial hypotension might be difficult to diagnose due to presence of only non-classical symptoms like

fever. In such cases, understanding this association may help physicians to decide the management strategies.[3]

Similarly, Erich et al. reported that hyperpyrexia may present as a symptom of life-threatening CNS infection. In such cases, Damage Associated Molecular Pattern (mechanisms) (DAMP) plays a paramount role in causing hyperthermia. This involves a different upregulation of immune responses induced by largely damaged neuronal cells. In such cases, 'aggressive' administration of antipyretics along with antibiotic therapy should be started within 24-72 hours.[5]

Interesting case reports on hyperpyrexia

Shah et al. from the Richmond University Medical Center reported a case of extreme hyperpyrexia of uncertain origin. The researchers noted that the young paraplegic had an extreme hyperpyrexia of 42.8°C (109°F), the highest human temperature recorded in the recent medical literature. They suspected that the traumatic spinal cord injuries from T-6 would have impaired the thermoregulatory mechanisms and neuronal pathways associated with the hypothalamus.[6]

Akçakaya et al. reported a case of life-threatening parkinsonism-hyperpyrexia syndrome following bilateral deep brain stimulation (DBS) of the subthalamic nucleus. Parkinsonism-hyperpyrexia syndrome has many similar characteristics to that of neuroleptic malignant syndrome. It is a neurophysiologic reaction to the acute withdrawal/decrease of central dopamine levels. The patient was treated with fluid replacement, administration of dopamine agonists, and activation of DBS.[7]

Ilhan et al., for the first time in the medical history, reported a case of anicteric leptospirosis, which presented with rectal bleeding and hyperpyrexia.[8] Steele et al. reported a case of malignant hyperpyrexia in a cervical spine-injured patient. The characteristic features of malignant hyperpyrexia are similar to the hemorrhagic shock and encephalopathy syndrome.[9]

Neurosurgical procedures and hyperpyrexia

Post-neurosurgical hyperpyrexia may arise due to both infective and non-infective causes. New onset post-neurosurgical fever, occurring after hemispherotomy, can be caused due to intracranial hemorrhage, operative site infection, blood transfusion, vascular injury, meningitis or extensive tissue damage.[10]

Managing hyperpyrexia

The key objective of the management is to reduce the increased set-point of the hypothalamus, thereby to enhance the heat loss. Along with reduction in elevated temperature, treating the underlying cause is also important.[1] The use of antipyretics like acetaminophen and paracetamol is preferred. Whereas, hyperthermia does not respond to typical antipyretics, since there are no pyrogenic molecules involved.

Peripheral cooling measures that can be adopted include use of cooling blankets, cool water sponging and ice packs. However, such methods can be counterproductive in the absence of antipyretics, since cold receptors in the skin may induce reactive vasoconstriction, thus impairing the heat loss

mechanisms.[11]

Thermoregulatory effectors

The two major mechanisms by which heat loss can be enhanced are sweating and peripheral vasodilation. The peripheral cooling methods are used mainly on axilla, forehead, soles and palms.

The cooling sweat glands are maximum in the axilla and produce milky sweat rich in carbohydrate and protein. The eccrine glands producing 'thermal sweats' are concentrated more on palms, soles and forehead. Hence, using peripheral cooling measures in these parts are more effective in reducing the temperature.

Continuous veno-venous hemo-diafiltration (CVVHDF) can be used to regulate hyperpyrexia in burn patients. CVVHDF acts by reducing the circulating cytokines.[12]

Conclusion

Hyperpyrexia is an emergency that needs immediate medical attention. It can be life threatening, if left untreated. Intracranial bleed, viral, bacterial and fungal infections are common causes of hyperpyrexia. Viruses that can cause hyperpyrexia include enterovirus infection, roseola, rubeola etc. The outlook for hyperpyrexia depends on the underlying condition causing the state of very high fever and the promptness of treatment. Treating the underlying cause and rational use of antipyretics are the corner stones of managing hyperpyrexia.

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Viral hemorrhagic fever

Dr. GhanShyam Pangtey
Prof. of Medicine
LHMC and Associated Hospital, N Delhi-1

Dr Ayush Bansal
Senior Resident
Dept. of medicine, LHMC and associated Hospital, N Delhi-1

Introduction

The term 'viral hemorrhagic fevers' (VHFs) depicts a group of diseases that are caused by several distinct families of viruses. In general, it is used to describe a severe multisystem syndrome.[1] The fever is mainly caused by 5 distinct families of RNA viruses *Arenaviridae* (lassa), *Filoviridae* (ebola), *Bunyaviridae* (Crimean-Congo hemorrhagic fever, CCHF), *Flaviviridae* (dengue), and *Paramyxoviridae* (nipah).

Though VHF viruses spread in a variety of ways, they share some common pathogenic features. They have the potential for aerosol dissemination via respiratory route (except dengue), but they are dependent on an animal or insect host for survival. However, these viruses are geographically restricted to the place of domicile of the host species. After the accidental transmission from the host, human-human transmission is possible in some viruses. VHF may impair the blood clotting ability and can also damage the walls of tiny blood vessels.[2] The mortality rate of viral hemorrhagic fever ranges between 0.5-90%, depending on the pathologic agent.[3] The VHF outbreaks cannot be easily predicted, as they are sporadic and irregular.

VHF: Clinical identification of suspected cases

According to the clinical criteria put forth by WHO, a persistent temperature of 101° F (38.3° C) for <3 weeks is often noted. The presence of any of the following 2 or more of symptoms may assist in concluding the diagnosis: hemorrhagic or purple rash, epistaxis, hematemesis, hemoptysis, blood in stools, other hemorrhagic symptoms, and no alternative diagnosis.[4]

The predominant signs and symptoms noted in common VHFs are listed in table 1.[5]

Table 1: predominant signs and symptoms noted in common VHFs

Disease	Signs and symptoms
Ebola Virus Disease	Fever. headache. muscle pain. fatigue. weakness, diarrhea. vomiting. abdominal pain. conjunctival injection. chest pain. hemorrhage
Marburg Virus Disease	Fever, chills headache, muscle pain, maculopapular, rash, nausea, vomiting, chest pain, sore throat, abdominal pain, diarrhea, jaundice, hemorrhage
Lassa Fever	Fever, nausea, vomiting diarrhea, retrosternal chest Pa., sore throat. muscle P.. enlarged cervical lymph nodes. abdominal pain, bleeding, maculopapular rash. conjunctivitis. headache
Crimean-Congo Hemorrhagic Fever	Fever, headache. back pain, join pain, abdominal pain, vomiting, conjunctival injection. facial tlushing, petechial rash, jaundice. bleeding. photophobia, sore throat

Ebola virus disease

Ebola virus disease (EVD) is a rare, but deadly disease commonly affecting humans and non-human primates. The EVD viruses are mainly located in sub-Saharan Africa and their periodic emergence has caused several outbreaks in African countries. The EVD gets transmitted to humans through direct contact with an infected animal (bat or nonhuman primate) or a sick or dead person infected with the virus. Ebola virus was first described in 1976 near the Ebola River, which currently belongs to the Democratic Republic of Congo.

In 1995, an outbreak of Ebola hemorrhagic fever affected >300 people in and around the city of Kikwit, Democratic Republic of the Congo (formerly Zaire). The outbreak caused the death of approximately 80% of the patients and more than one-fourth of all the patients were healthcare workers.[6] The 2014-16 outbreak of EBV caused a mortality rate of up to 80%-90%, and the death of many healthcare workers were due to human-to-human infection.[7] On March 23, 2014, the World Health Organization (WHO) reported the EBV disease in the forested rural region of southeastern Guinea. It was the beginning of the West Africa Ebola epidemic, the largest in history. On August 8, 2014, WHO declared the Public Health Emergency of International Concern (PHEIC), which is designated only for events with a risk of potential international spread or that require a coordinated international response.[7] Over the duration of the epidemic, the disease had spread to seven more countries: Italy, Mali, Nigeria, Senegal, Spain, UK, and the US.

EBV: Ecology and transmission

Humans get initially infected with EBV through contact with an infected animal, such as a fruit bat or non-human primate. This is called a spillover event. After the spill over event, the virus can spread from person to person through the following routes.

- Direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth)
- Blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with or has died from EVD
- Objects (such as needles and syringes) contaminated with body fluids from a person sick with

EVD or the body of a person who died from EVD
- Infected fruit bats or non-human primates (such as apes and monkeys)
- Semen from a man who recovered from EVD (through oral, vaginal or anal sex)
- Handling and consumption of bushmeat (wild animals hunted for food)

There is no treatment for EBV and only supportive management can be adopted. Ebola survivors mostly complaints of myalgia and muscle pain even after treatment.

Dengue fever

Dengue fever, the most important mosquito-borne viral disease with global epidemic potential, occurs mainly in tropical and subtropical areas of the world. The virus is transmitted to humans through the bites of infected female mosquitoes of the species *Aedes aegypti*.[8] It is a mild to fatal disease with no cure and only palliative care. The factors that have contributed to the emergence of dengue as the classic disease of 21st century are the following: urbanization, increase in travel/trade, highly efficient and adaptive vectors, thriving of larvae and adults in urban areas, inability to avoid day biting of *Aedes* vectors, and difficulty in effectively implementing environmental vector control.

A 30-fold increase in the dengue cases has been recorded globally during the past 50 years, and it is associated with substantial social and economic burden.[9] An average dengue episode results in a loss of 14.8 days for ambulatory patients, at an average cost of USD 514. However, the mortality rate is less than 0.5% and it is asymptomatic in nearly 80% of the subjects.

The first evidence of occurrence in India was reported in 1956 from Vellore district in Tamil Nadu. In 1996, one of the most severe outbreaks of dengue fever occurred in Delhi, with 10252 reported cases and 423 deaths. In 2006, the country witnessed an outbreak of dengue fever with 12317 cases and 184 deaths. During 2014, a total of 40571 cases were reported, which increased to 129166 in 2016 and 188401 in 2017.

Clinical presentation

The clinical presentation of dengue progresses through the following 3 phases:
- Febrile phase (4-7 days after exposure): Headache, eye pain, nausea/vomiting, myalgias, arthralgias, and macular rash
- Critical phase (may develop following resolution of febrile phase, lasts 24-48 hours): Shock, hemorrhage, organ failure, and ARDS
- Recovery phase: Clinical stabilization, may develop confluent rash

Diagnosis and management

Initial diagnosis may be established by clinical suspicion. Serum RT-PCR or viral antigen testing within first week of illness, followed by ELISA, may assist in concluding the diagnosis.

The 2014 revised guidelines for clinical management of dengue advocate bolus fluid regimen for dengue patients who are in shock (20 ml/Kg), and frequent monitoring and optimum fluid therapy in moderate/severe dengue (Fig. 1).[11]

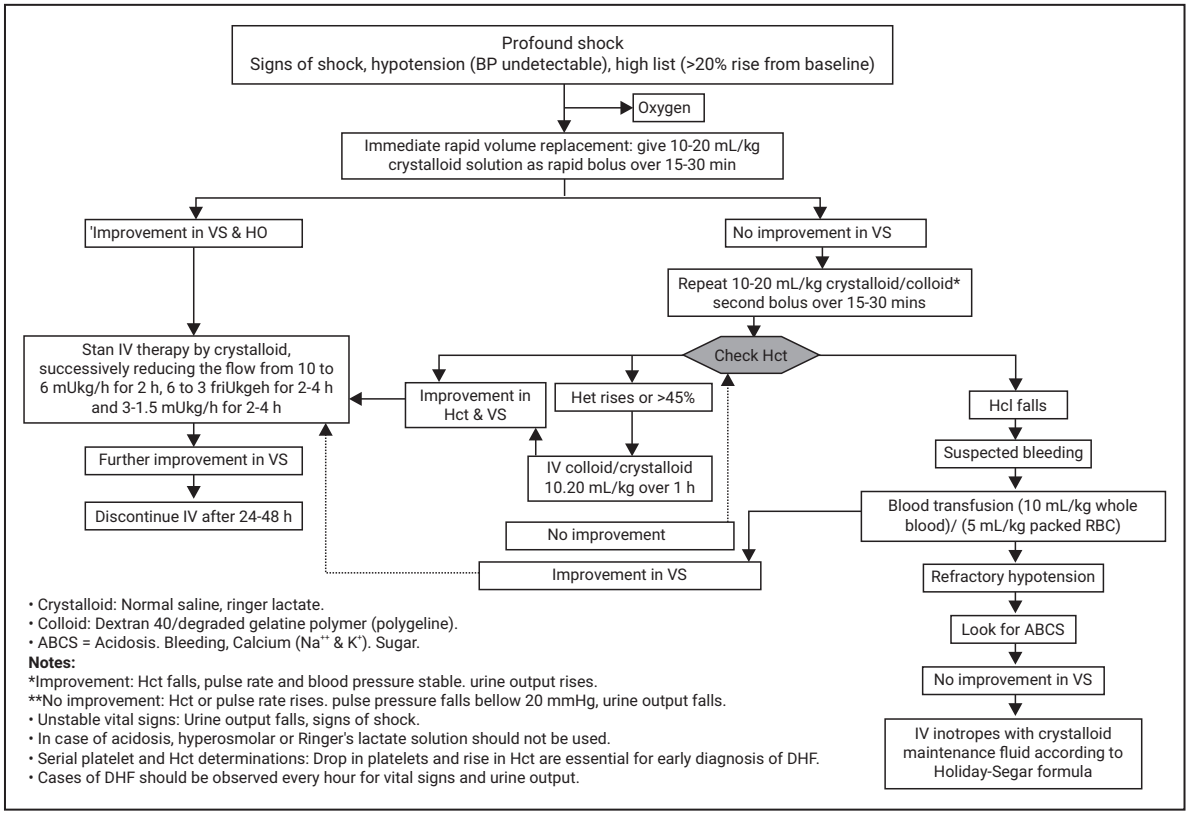

Fig. 1: Volume replacement algorithm for patient with dengue fever11

Chikungunya fever

Chikungunya virus is a self-remitting febrile viral illness transmitted through the bite of infected mosquito Ae. Aegypti.11 The clinical presentation includes acute infection, high-grade fever, polyarthralgia (typically bilateral/symmetric, distal>proximal joints), and macular rash. The severe complications are meningoencephalitis, respiratory failure, renal failure, hepatitis, hemorrhagic, and heart failure/cardiomyopathy. The disease can be diagnosed by RT-PCR or serology. Testing for dengue and zika can also be considered. Management includes supportive care and fluid therapy. Aspirin and other non-steroidal anti-inflammatory drugs should be avoided to reduce the risk of hemorrhage, until patient is afebrile for 48 hours and there are no additional warning signs for dengue.

Zika virus infection

Zika virus is spread mostly through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*). Common symptoms of zika infection include fever, pruritic rash, and arthralgia.[12] The severe complications of the disease are Guillain-Barre syndrome and neurologic complications including encephalitis and transverse myelitis. The recent ongoing outbreak in Madhya Pradesh and Rajasthan (Oct-Nov 2018) has claimed two lives. Diagnosis and management strategies are similar to that of dengue and chikungunya.

Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) is caused by a tick-borne virus (Nairovirus) belonging to the family *Bunyaviridae*. The disease is usually seen in Crimea, Africa, Europe and Asia; and human-to-human transmission occurs through direct contact with infectious blood/ body fluids. In India, the first confirmed case of CCHF was reported during a nosocomial outbreak in Ahmadabad, Gujarat, in January 2011.The outbreak claimed the death of 3 healthcare workers due to multiple organ failure, specifically failure of the liver and kidney. During the period of 2012-2015, several outbreaks of CCHF infections were reported in the states of Gujarat and Rajasthan.[13]

Kyasanur forest disease

Kyasanur forest disease (KFD) virus was first identified in 1957 when it was isolated from a sick monkey from the Kyasanur forest in Karnataka (formerly Mysore) state, India. Since then, around 400-500 human cases per year have been reported. KFDV is a member of the virus family *Flaviviridae*. Hard ticks (*Hemaphysalis spinigera*) are the reservoir and rodents, shrews, and monkeys are common hosts for KFDV. The disease is endemic to South Asia and the human transmission may occur after a tick bite or contact with an infected animal. No person-to-person transmission has been reported.

The disease begins with chills, fever, and headache. Severe muscle pain with vomiting, gastrointestinal symptoms and bleeding problems may occur 3-4 days after initial onset of symptoms. Patients may experience abnormally low BP, low platelets and red blood cells, and leucopenia. After 1-2 weeks of symptoms, some patients recover without complications.

Nipah infection

Nipah virus (NiV) infection is an emerging zoonotic disease of public health importance in the WHO South-East Asia region. The possible routes of transmission include consumption of fruit contaminated by the saliva of infected bats, from direct contact with infected bats or their feces/urine. NiV was first recognized in 1998-1999 during an outbreak among pig farmers in Malaysia and Singapore, and it was first recognized in India and Bangladesh in 2001. In July 2018, a total of 19 NiV cases, including 17 deaths, were reported from two districts in Kerala state (Kozhikode and Malappuram).[14]

Management of VHF

The blood, urine, vomitus, pus, stool, semen and saliva from the VHF patient are infectious. Barrier nursing practices (such as wearing protective clothing) help in reducing the risk of transmission to healthcare workers.

No specific treatment, except supportive care, is available. Correct coagulopathies are needed. Antiplatelet drugs and IM injections are contraindicated due to the risk of hemorrhage. Investigational treatment approaches include ribavirin for 10 days for *arenaviridae* and *bunyaviridae*, and convalescent plasma within 8 days of onset for alkhurma hemorrhagic fever. Upon percutaneous/mucocutaneous exposure to infected blood or body fluids, wash thoroughly with soap and water, and irrigate mucous membranes with water or saline. Medical surveillance for all potentially exposed persons is needed for 21 days. The surveillance measures include: reporting hemorrhagic symptoms, recording fever 2x/day, reporting temperatures ≥101°F (38.3°C), and initiating presumptive ribavirin therapy.

Viral hemorrhagic infection can be prevented using N-95 mask or powered air purifying respirator

(PAPR). Keeping the patient in negative pressure room and using personal protective equipment (PPE) while handling the patient are essential. The healthcare workers should be trained on the use of PPE (Fig. 2).

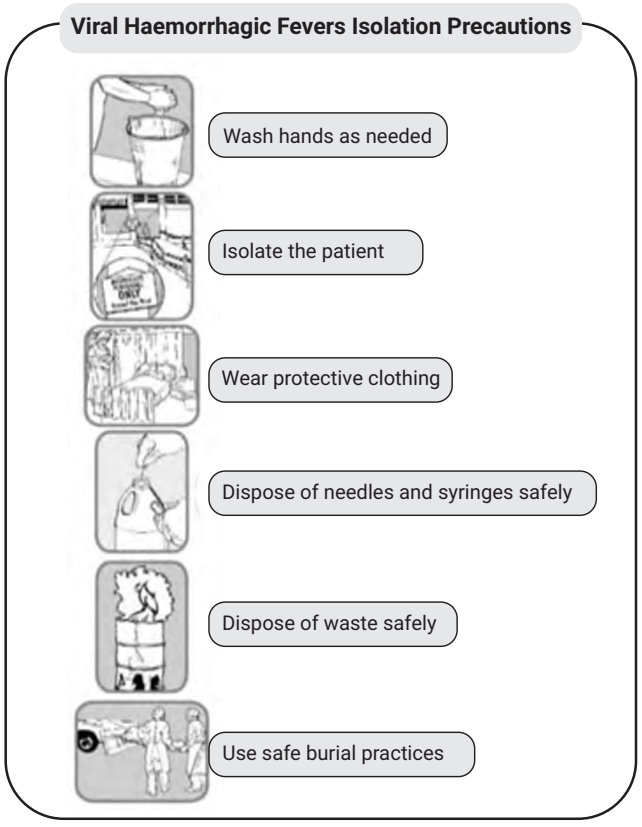

Fig.2: VHF isolation precautions[15]

Assessment for VHF risk

The following CALM (Consider, Act, Laboratory, Monitor) algorithm is used to assess the risk of VHF infection in travelers:

- Consider -Travelers return from a region endemic for and/or currently experiencing VHF outbreaks are considered infected.
- Act - Isolate the patient. Limit the healthcare workers who enter the room. Appropriate PPE should be worn by all personnel entering the patient's room. Immediately notify your state/local health department.
- Laboratory - Inform the laboratory. Decision to test for VHF should be made in consultation with relevant health department/CDC viral special pathogens branch.
- Monitor contacts - Facilities should maintain a log of all the persons entering the patient's room, including full name and contact information.

Conclusion

VHF is a diverse group of illnesses caused by RNA viruses belonging to 5 virus families. Though, the diseases differ by geographic occurrence and vectors/reservoirs, they share some common clinical features. The diseases are considered as having international health risk due to their potential for aerosol dissemination and human-to-human transmission. Management is only through supportive treatment. Infection control in healthcare workers and relatives is of utmost importance. Surveillance of returning travelers by CALM algorithm is important to prevent any outbreak in other geographic area.

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Fever- As a marker of sepsis

Dr. Hemant P. Thacker
Consultant Physician & Cardio Metabolic Specialist,
Mumbai

Introduction

Sepsis, a potentially life-threatening complication of an infection, occurs due to the generation of a cascade of inflammatory responses that can damage to multiple organ systems. Progression of sepsis to septic shock causes decrease in blood pressure, which may lead to death. Any individual with infection is prone to develop sepsis, but it may be dangerous in elderly and subjects with compromised immune system. The primary goal of sepsis management is providing early treatment, usually with antibiotics and large amounts of IV fluids, to increase the chances for survival.[1]

Sepsis, sever sepsis and septic shock: Signs and symptoms

The most common infections that may lead to sepsis include pneumonia, bacteremia, and abdominal and kidney infections. In order to conclude sepsis, the patient should have two of the following signs, along with a probable or confirmed infection:[1]

- Body temperature >101°F (38.3°C) or <96.8 F (36°C)
- Heart rate > 90 beats/ minute
- Respiratory rate > 20 breaths/minute

The presence of at least one of the following signs and symptoms indicates sever sepsis and increased risk for organ failure:[1]

- Significantly decreased urine output
- Change in mental status

- Reduced platelet count
- Difficulty in breathing
- Abnormal heart pumping
- Abdominal pain

In order to diagnose septic shock, a person should demonstrate the signs and symptoms of severe sepsis, in addition to extremely low blood pressure (not adequately responding to fluid replacement therapy). Young and Bellomo have reported the potential of hypothermia as a marker of disease severity or as a marked of defective immune response or both.[2]

Fever: A sepsis marker

Sepsis has been identified as the cause for 74% of fever in hospitalised patients and the remaining is constituted by malignancy, tissue ischemia, and drug reactions.[3] Fever is one of the major criteria for defining septic shock. Some people believe fever as harmful to the body and needs to be controlled. In fact, fever is body's natural response to infection caused by the increased production of cytokines and centrally induced prostaglandin E2 and PGF2. The subsequent changes contribute to the resetting of the hypothalamic temperature control centre.[4]

Launey et al. have highlighted fever as the most prominent diagnostic sign, which assists in early initiation of appropriate therapy and understanding the course of infection.[5] Acute febrile illnesses are more prevalent in children <5 years of age and the probable underlying cause is mostly viral. It has also been reported as the single most common indication seen by primary care clinician and emergency physicians. Nearly 20% of children of <3 years of age experience an acute febrile episode with no apparent source.[6]

During life threatening conditions like sepsis, the high energy cost attributed to fever may impose an additional physiological challenge to patients. Study on temperature variations in ICU shows that 30% -60% of patients with fever have infections. Pyrogenic fever is one of the common immunological responses noted in critically ill subjects.[7] Lipopolysaccharide (LPS) endotoxin, produced by gram-negative bacteria, is the most common exogenous pyrogen eliciting immune response in fever.[7]The generation of fever is due to interaction of exogenous pyrogens/endogenous pyrogens with the organum vasculosum of the lamina terminalis (OVLT), which is one of the seven predominantly cellular structures in the anterior hypothalamus within the lamina terminalis. The neural-mediated fever pathways, including the LPS-mediated, may result in the rapid onset of fever. Whereas the cytokine release account for the maintenance of fever rather than intiation.[3]

A clinical review by Launey et al. has reported that evaluating the balance of benefit to harm of fever in septic ICU patients is highly challenging. The researchers have also summarized the beneficial and adverse effects of fever (Table 1).[8]

Table 1: Beneficial and adverse effects of fever

Beneficial effects	Detrimental effects
On invading microorganism • Reduction in growth/prolonged growth time • Enhancement of antibiotic sensitivity/reduced minimal inhibitory concentration **Effect on immune response** • Increased mobility of polymorphonuclear cells, phagocytosis, and T-helper cell adherence • Elevation of heat shock protein causing a decrease of NF-κB • Inhibition of the lymphocyte cell reduction	• Increased oxygen consumption and metabolic demand • May cause patient discomfort • Seizure in children? (Controversial) • Collagen tissue damage

Fever: A beneficial response to infection

Data based on a retrospective analysis have shown that patients with infection who had elevated temperature in the first 24 h of ICU admission demonstrated a better outcome compared to normothermia or hyperthermia >40°C. The temperature between 37.5°C and 39.4°C was noted to favour the improved outcome compared to normothermia.[3] Elderly patients with community-acquired pneumonia who lacked fever (29%) had increased mortality rate than subjects who demonstrated a febrile response (4 %).[9] A temperature > 38.2 °C has also been found to have a protective role against invasive fungal infections in the ICU. A multicenter, prospective, observational study in France has found that a temperature >38.2°C had conferred a protective role against invasive fungal infections in the ICU.[10]

The elevated temperature is purported to confer protection through the following mechanisms:

- An elevated host temperature inhibits the replication of the infective pathogens.
- Increase in the temperature from 35°C to 41.5°C *in vitro* enhances the antimicrobial activity.
- Rise in temperature augments the innate immunity associated with the destruction of pathogens.

However, in acute sepsis with a temperature > 40°C, the adverse effects of fever on organ and cellular function outweigh any benefit conferred by the increase in temperature.[3]

A review by Russell has underscored the following potential benefits of controlling fever in septic shock patients: reduction in global oxygen demand and the subsequent risk of oxygen supply/demand mismatch, and decrease in metabolic rate and risk of septic encephalopathy.[4] However, the potential benefits of fever in sepsis are under estimated. A survey of current practice, conducted across ICU units in UK, has found that one survey of fever monitoring in sepsis from UK ICUs, around 76% of ICU clinicans would be concerned about a temperature between 38-39°C, and nearly 66% would start active cooling measures for these temperature range.[11] However, a non-pyrogenic fever does not confer any such teleological benefits. A meta-analysis by Zhang et al. has noted that the use of steroids for fever control in H1N1-infected patients increased the morality.[12]

Implementation of effective fever control measures should be promoted in patients with septic shock. The measures include adequate fluid resuscitation, diagnosis and control of infection, continuous

infusion of vasopressors, mechanical ventilation, and the use of automatic cooling blanket with a target temperature between 36.5°C-37°C. The conditions put forth by Schortgen for obtaining the optimal risk/benefit ratio of fever control in sepsis have been listed in table 2.[7]

Table 2: The conditions for obtaining the optimal risk/benefit ratio of fever control in sepsis

Potential risks	Conditions	Goals
Increased bacterial growth	Start after initiating appropriate antibiotics and control of infection	Enhance infection control
Shivering	Select severely ill patients who already require sedation	Reduce shivering threshold. Exposure to additional 'unnecessary' sedation should be avoided.
Impaired host defences	Maintain body temperature within the normal range using a blanket with an internal feedback loop	Avoid hypothermia
Early ICU-acquired infection	Reinforce prophylaxis diagnosis, and treatment of nosocomial infection	Allow early detection / decrease the risk of ICU-acquired infection

Conclusion

A mild increase in core temperature is beneficial in patients with sepsis. The damage in sepsis occurs through various local and systemic mechanisms, and the beneficial effects of pyrexia may assist in balancing these adverse factors. Hyperthermia >40°C is associated with high mortality, irrespective of the cause. Early recognition, and adoption of immediate cooling measures and organ support are integral for managing hyperthermia >40°C.

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Fever in adult malignancy

Dr. Sameer Khatri
Director and head,
Medical oncology
Clearmedi hospitals

Introduction

Fever of unknown origin (FUO) remains a perplexing challenge to clinicians in daily clinical practice. Determining the underlying cause is paramount for providing appropriate treatment on time, thereby to reduce the associated morbidity and mortality. FUO can be due to infectious or non-infectious causes. Non-infectious causes of fever include alterations of oral mucosa, drug use, blood transfusions, radiation, endocrine disturbances, surgery, and tumor fever. Cancer has been reported as the cause of fever in 15% to 20% of patients with FUO.[1]

Causes of pyrexia in patients with malignancy

The common causes of pyrexia in patients with malignancy are listed in table 1.[2]

Table 1: Causes of pyrexia in patients with malignancy

Tumor	Lymphoma, leukemia, myeloblastic syndrome, renal cell carcinoma, hepatoma, atrial myxoma
Treatment	
Chemotherapy	Bleomycin, interferon, interleukin, granulocyte macrophage colony stimulating factor
Antimicrobials	Beta lactam fever, amphotericin
Radiation	Pneumonitis, cystitis

Blood transfusion reaction	
Indirectly related to tumor	Bronchial obstruction, pneumonia, common bile duct obstruction, ascending cholangitis, ureteric obstruction, pyelonephritis, general depressed immunity-coincident infection
Miscellaneous	Pulmonary emboli, factitious, intracerebral bleed, connective tissue disease

Mechanisms of fever in cancer patients

Tumor obstruction of tubular or hollow structure and subsequent infection is one of the common mechanisms of fever in malignancy. The examples include: bronchus: post-obstructive pneumonia, eustachian tube: otitis media, hepatobiliary system: cholangitis, parotid duct: bacterial parotiditis, sinuses: bacterial or fungal sinusitis, ureter: pyelonephritis, and urethra: cystitis and pyelonephritis. Venous thrombosis/thrombophlebitis is another common mechanism in fever-related malignancy. Though rare, hypothalamic metastases (altered thermoregulation) has been identified as a mechanism of fever in breast/ lung cancer patients. Allergic reaction and idiosyncratic reaction can also cause fever in malignancy.[3]

Infection-related fever in cancer patients: Risk factors

The use of venous catheters is associated with significant risk for blood stream infection, especially with staphylococcal species. Implanted surgical ports, central venous line, and peripherally inserted central catheters (PICCs) also elevate the risk of infection.[4]

Chemotherapy-induced mucositis: Rapidly proliferating cells of the oral and alimentary mucosa are susceptible to chemotherapy, resulting in mucositis. This may subsequently lead to bacterial translocation, especially with Gram-negative bacilli and microaerophilic streptococci.[5] The prosthesis and implants used in bone sarcoma patients are also linked to elevated infection risk.

Surgical Procedures: Such procedures induce a reparative and inflammatory response in the body. Surgical procedures in cancer often produce large incisions and empty tissue spaces that can be filled with fluid or blood. This may increase the risk of infection. Patients who have received chemotherapy recently and those with immune dysfunction or neutropenia are more prone to develop fever associated with wound/incision infections. Release of cytokines from migrating leukocytes, at the interface of surgery-induced tissue trauma, is another cause of fever in cancer patients undergoing surgery.[2]

The miscellaneous factors that may increase the risk of infection-related fever in cancer patients include: candidemia caused due to the long-term use of broad-spectrum antibiotics for neutropenic fever, necrotizing fasciitis or Fournier's gangrene, bedridden with subsequent decubiti formation or aspiration pneumonitis and mucormycosis of the nasal cavity. [2]

Non-infectious etiologies of fever in cancer patient

The non-infectious etiologies include:

- Venous thromboembolism/Trousseau's syndrome
- Non-thrombotic ('marantic') endocarditis
- Disseminated intravascular coagulation (DIC)
- Thrombotic microangiopathy

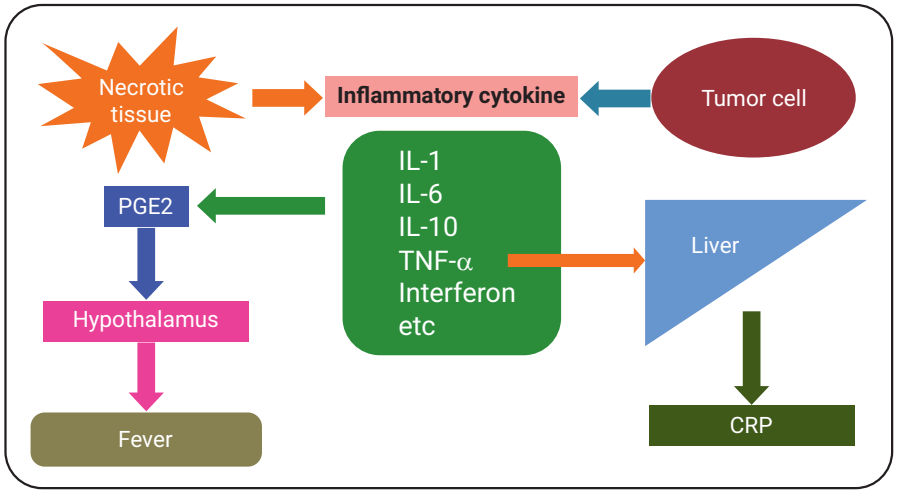
- Tumor-associated/ paraneoplastic
- Drug related (e.g., gemcitabine, mitomycin-C)
- Transfusion reactions
- Neoplasms
- Foreign bodies (e.g., artificial joints, drains, stents)
- Surgical procedures
- Mucositis
- Hematoma
- Medications

Neoplastic fever

Neoplastic fever or tumor fever, is often excluded during diagnosis because such fevers do not have persistent clinical features.[1] The neoplastic fever constitutes 7 to 31% of the incidence of FUO.[6] Among neoplastic febrile patients, tumor fever has been identified as the most common cause of non-infectious pyrexia (41%).[6]

The pathophysiology of tumor fever is still elusive. The cytokines such as IL-1, TNF, IL-2, IL-6, IL-10 and IFN play a paramount role in pathophysiology. These endogenous pyrogens stimulate the secretion of prostaglandin E2, subsequently contributing to an increase in hypothalamic set point and fever (Fig. 1). Tumor-induced inflammation, secondary to ulceration or necrosis, is another possibility.[6]

Fig. 1: Pathophysiology of tumor fever



Diagnostic criteria for neoplastic fever

Extensive investigations and diagnostic studies assist in differentiating neoplastic fever from other fever types. Zell and Chang have put forth the following diagnostic criteria for neoplastic fever.[7]

Fig. 2: Diagnostic criteria for neoplastic fever

I. Temperature over 37.8°C at least once each day

II. Duration of fever over 2 weeks

III. Lack of evidence of infection on

A. Physical examination

B. Laboratory examinations, e.g., sputum smears or cultures, cultures of blood, urine, stool, bone marrow, spinal fluid, pleural fluid, and discharge from local lesions

C. Imaging studies, e.g., chest radiograph and computed tomo-graphic scans of the head, abdomen, and pelvis

IV. Absence of allergic mechanisms, e.g., drug -allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction

V. Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days

VI. Prompt, complete lysis of fever by the naproxen test with sustained normal temperature while receiving naproxen

Non-steroidal anti-inflammatory (NSAID) challenge test

In 1984, Chang et al. proposed the potential use of naproxen in the differential diagnosis of FUO in cancer patients.[8] Naproxen is effective in reducing tumor fever due to its unique ability to suppress tumoral cytokines. However, the test should be interpreted on the basis of clinically-driven assessment.

Drug-induced fever

Not all fever in cancer patients are due to infectious causes. In the absence of underlying conditions, drug-induced fever should be suspected if the fever coincides with the drug administration. Another characteristic feature is subsidence of fever following the withdrawal of offending agent. Studies have noted that drug-induced fever may prolong the length of hospital stay and prompt an average of 5 blood culture draws, 3 radiological studies, and use of unnecessary antibiotics. The mechanisms involved in drug-induced fever are altered thermal regulation, pharmacological action, idiosyncrasy and hypersensitivity.

The drugs that can induce fever include: bleomycin, chlorambucil, daunorubicin, hydroxyurea, vincristine, 6-mercaptupurine, antimicrobials, anticonvulsants, bisphosphonates, immunosuppressants, and antineoplastic agents

As per the literature, the corresponding incidences of drug-induced fever noted in patients who received cladribine and gemcitabine were 70% and 20-40% respectively. Another study has reported that the use of β lactams and piperacillin induced the fever in 13% and 17% of the subjects respectively. The occurrence of eosinophilia was noted in 25% of the subjects with drug-induced fever, secondary to β lactams.[1]

With regard to monoclonal antibodies, the incidence varies from <1% in fully human-derived panitumumab to as high as 60% in rituximab, a genetically engineered, chimeric murine/ human monoclonal antibody.

Fever patterns in cancer patients

There is no specific pattern for fever associated with malignancy. Drenching night sweats with weight loss are frequently noted manifestations.[9] Pel-Ebstein fever, the prototype of fever associated with Hodgkin's lymphoma, has a specific pattern of several days of fever separated by afebrile episodes of similar duration (7 to 14 days). However, this pattern is very uncommon.

Diagnosis

Radiologic methods including MRI and CT play a paramount role in diagnosing the underlying cause of fever associated with malignancy. Fever due to malignancy may manifest in CT as a primary mass lesion, body cavity effusions, metastases, hydronephrosis, pneumonia, biliary dilatation, and lymphadenopathy.[2]

Though limited diagnostic use, MRI assists in delineating pancreatic-biliary neoplasms (with magnetic resonance cholangiopancreatography, MRCP), soft tissue/ muscle tumors, and even bone sarcomas/ osteomyelitis. Brain MRI is very sensitive in diagnosing brain metastasis and gliomas.[10]

Nuclear imaging studies are occasionally useful in evaluating fever in cancer patients. Technetium bone scanning is useful in assessing osseous metastases, especially osteoblastic metastases.[11] Positron emission tomography (PET) scanning is used to identify areas of increased metabolic activity, focal inflammation or infection.

This is no substantial evidence to conclude the role of biomarkers in evaluating fever in malignancy.

Conclusion

Fever in cancer patients is associated with several types of infectious and non-infectious causes. Although infection remains the main etiology of fever in patients with cancer, non-infectious causes should also be considered following the negative results of a thorough work-up for infection. Neoplastic fever, drug-induced fever, and venous thromboembolism are all important causes of fever in malignancy. Future research should focus on the usefulness of acute-phase reactants, along with a nonsteroidal anti-inflammatory drug challenge, as an adjunct tool for investigating fever in cancer.

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Fever in ICU: Infectious causes

Justin Gopaldas
Intensivist
Manipal hospital
Bangalore

Introduction

"Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever"- William Osler.

As per the 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America on the guidelines for the evaluation of new fever in critically ill adult patients "*a new onset of temperature of ≥38.3°c is a reasonable trigger for a clinical assessment but not necessarily a laboratory or radiologic evaluation for infection*".[1]

The incidence of multi-organ failure and mortality is significantly lower and hospital stay is significantly shorter among patients with sepsis in the medical wards compared to the ICU.[2] Bhattacharya et al. have (2016) noted that sepsis and severe sepsis are significantly higher in medical wards, while septic shock was significantly higher in ICU.[2] These findings indicate that ICUs tend to have sicker patients. A survey of current practice across ICU in UK has (2016) reported that the least level of concern was noted at 37°C (normal temperature), and it raised rapidly with higher and lower temperatures.[3] The present review discusses on the management of fever from ICU perspective, and the difference in practice of an intensivist and a physician in managing fever.

Fever in ICU: Implications for practice

The presence of fever in an ICU patient calls for a battery of diagnostic tests including blood cultures, scans and X-rays, which easily escalate the cost of hospitalization, expose the patient to unnecessary

risks, and often produce misleading or inconclusive results. The evaluation of a febrile ICU patient should be performed in a systematic, prudent, clinically appropriate and cost-effective manner. There is increased probability of getting positive result in ICU patients with increase in number of tests. The research over the last decade from ICU shows that the less is more and this is applicable for fluids, oxygen, ventilator, dialysis, antibiotics etc. On a daily basis, judging the likelihood of events as infectious or non-infectious by intensivist plays a paramount role in ICU care.

Though vast literature evidence is available from west, there is very limited studies on ICU septic patients in Indian population. Literature from western population mostly deals with the non-tropical fever, however most of the cases encountered in Indian population are of tropical nature. A retrospective cohort study by Laupland et al. (2008), involving 204 ICU patients, has concluded that fever was not associated with increased mortality.[4] Young et al. (2011) have reported fever in only 9% of the patients admitted to the ICU.[5] Literature evidence also reported increased risk of mortality in patients with non-infection and lower risk in patients with infection.[6] Pyrexia may be beneficial in sepsis and pyrexia and can be harmful, if it is non-infectious.

Fever in ICU: Epidemiology

Divatia et al. (2016), based on a larger single center, 5 year-study conducted on Indian patients, have proven that the organ dysfunction for the septic patients is lesser than expected. Majority of the patients with sepsis and septic shock had infection. The trial also noted that 72.4% of the patients received antibiotics, although only 11% were deemed septic.[7] It seems to be the underrepresentation of the data of patients with infection. Organ-wise documentation of admission reason and sepsis as leading reason have underestimated the incidence of all septic cases. Mixing of primary admission and secondary sepsis data during collection makes the distinction unclear. Moreover, segregation of tropical fever and non-tropical fever as cause of sepsis is not well defined.

Tropical fever in ICU

Singhi et al. (2017) have conducted a large prospective study involving subjects from 36 centers across north India and reported that only 80% of the patients had diagnosis and most of them had tropical fever.[8] Based on the above findings, it can be understood that, as long as pretest probability of tropical fever is high, the likelihood of finding a tropical fever etiology is almost 80%. The guidelines of the Indian Society of Critical Care Medicine suggest the need of clear starting point for the management of infection in terms of antibiotics or supportive care.[9]

Non-tropical fever in ICU

The Extended Prevalence of Infection in Intensive Care (EPIC II) study has reported an ICU mortality of 25% (almost double that of the noninfected patients) and a hospital mortality rate of 33%.[10] The incidence of gram-negative sepsis in the ICU is very high in Indian patients compared to the Western population. The comparison of acute physiology and chronic health evaluation (APACHE) II scores and hospital mortality among Asian and Indian ICU patients has revealed a mortality rate of 45% and 38% for Asian and Indian patients respectively. The corresponding APACHE II scores noted were 23 and 22.[11]

Epidemiology: Issues

Information regarding the following is important: 1) primary pathogens like community acquired bugs, how many infections they probably cause and how different they are from tropical fevers; 2) segregation from the secondary sepsis. If patients presenting with fever are evaluated for the tropical or non-tropical nature of the infection, planning the management strategy in the ICU becomes easier.

Secondary sepsis

The patients may develop infection after 48 h or 7 days of admission. Irrespective of the guidelines followed, the presence of infection before or not is a non-significant factor. Moreover, irrespective of the infection before, the secondary infections developed remains same, as the paralysis of the immune system because of the earlier insult depends on the severity of the insult. The predominant top five secondary sepsis or gram-negative causing problems in the ICU are:

- Catheter-related blood stream infections
- Catheter-associated urinary tract infections
- Ventilator-associated Pneumonia
- Post-surgical infections
- Miscellaneous: sinusitis, acalculous cholecystitis, *C. difficile* infections etc.[12]

Fever in ICU

The following investigations are generally performed while starting the work-up for an ICU patient with fever: blood counts, cultures (blood, urine, sputum and others), tropical fever work-up, inflammation or infection markers and organ function test (Liver and renal function test).

Fever in ICU work up: blood count and cultures

Blood cultures and total blood counts seem to differentiate the negative predictive values, but not the positive prediction values. A thumb rule for doing a blood culture is probably the best guide to limit the number of investigations. Several publications are available on the evaluation of inflammatory markers such as CRP, cell count and procalcitonin in ICU patients. They suggest that procalcitonin can differentiate bacterial infection from non-bacterial infection and aids in the proper antibiotics therapy. Procalcitonin levels can indicate the right time for the initiation and termination of antibiotics.[13]

Literature indicates that sicker patients presenting to the ICU, particularly from the Southeast Asia, have similar tropical fever. In such patients, the CRP levels triumph over procalcitonin unlike the evidence suggested by the western literature.[14]

Management

Following guidelines to the block probably is the best and their compliance should extent to every part of the caring including palliative care. The commonly used methodologies for the management of fever include:

- Paracetamol
- NSAIDs
- External cooling
- Extracorporeal measures

- Alpha-2 agents (clonidine and dexmedetomidine)

Sepsis-3 guidelines form the cornerstone of resuscitation and applying strategies including anti-microbial therapy. Tropical disease management guidelines are given out recently by ISCCM for ICU group of patients and could be modified based on local sensitivities pattern.

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Fever in ICU: Non-infectious causes

Pradeep Rangappa
DNB (Int.Med), FJFICM, EDIC, FCICM, PGDipECHO,
MBA (HCS), FICCM, PGDMLE (NLSIU)
Consultant Intensive Care Physician
Columbia Asia Hospitals

Introduction

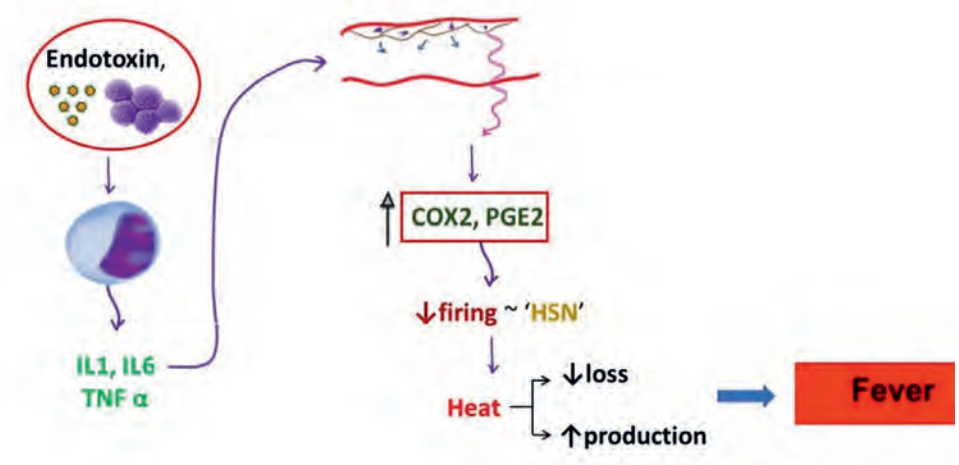
Being India at the forefront of global antibiotic resistance, a cautious approach is needed while using antibiotics in in-patients, especially in ICUs. The key challenge confronted by intensivists is to identify non-infectious cases and limit the unnecessary administration of antibiotics. This paper mainly focuses on the definition and pathogenesis of fever, different non-infectious causes, diagnostic approach and role of antipyretics in fever management.

Fever: Definition and pathogenesis

Fever is defined as a complex physiological response to underlying disease involving a cytokine-mediated rise in core temperature, production of acute-phase reaction, and activation of numerous immunologic and endocrinologic systems.[1]

The endotoxins or exotoxins activate the lymphocytes causing the production of interleukins such as IL1, IL6 and TNFα. The interleukins induce signal transduction from the vascular endothelium contributing to the production of COX2 and PGE2, which are the basic drivers of the fever. This in turn leads to reduced firing of heat sensitive neurons, resulting in reduction in heat loss or increase in the heat production (Fig. 1).[2]

Fig.1: Pathogenesis of fever



The body temperature of 37°C (98.6°F) is considered as normal. According to American College of Critical Care Medicine and the Infectious Diseases Society of America (AACCM/IDSA), a temperature of ~ 38.3°C (101°F) should be considered as a fever.[3] The temperature measurement is broadly classified into two, core temperature and peripheral temperature. Oral, tympanic and axillary measurements are considered as peripheral, while core temperature constitutes the measurement from pulmonary artery, urinary bladder and rectum.

How common is fever in ICU?

A Canadian study by Laupland et al., involving 24,204 ICU admissions, has noted that nearly 44% of the subjects had at least one episode of fever in ICU and 8% had >39.5°C temperature. In addition, the researchers noted that the mortality rate was higher in patients with increased temperature (20% vs. 12%).[4]

Fever evaluation in ICU

In infectious causes, the delay in diagnosis and treatment can lead to worse outcomes. Non-infectious causes are often benign and the prognosis cannot be predicted. Moreover, there are very limited management strategies for non-infectious fevers. The non-infectious causes of fever in ICU patients include: hematoma, thyroid storm, after surgical procedures, drug fever, gout, alcohol withdrawal, acute myocardial infarction, transfusion reaction, ARDS, tumor fever, inflammatory conditions and burns.[5]

Magnitude of fever assists in fever evaluation and it can be classified as:

- Mild: 38.3^0 – 38.8^0C (101°F – 101.8°F)
- Moderate: 38.9°– 41°C (102°F – 105.8°F)
- Severe: > 41.1°C (> 106°F)

Non-infectious mild fever can be excluded with good clinical history and examination. If the fever is >102°F, the most probable cause is infection; whereas, if it is >106°F, it could be non-infectious due to drug fever or endocrine abnormalities.

The non-infectious causes can be classified as with shock and without shock. Endocrine problems such as thyroid storm, adrenal insufficiency, transfusion-related hemolysis, and hemolytic anemia can lead to shock. Drug fever, venous thromboembolism, pancreatitis, cystitis and non-hemolytic reaction due to transfusion are the non-infectious causes without shock.

Non-infectious causes that can be dangerous

Non-hemolytic transfusion reaction

It occurs generally after 1-6 hours after transfusion and the common symptoms are increase in temperature, chills and dyspnea. The reaction is often benign, without any sequalae; but the patient may feel very uncomfortable.

Drug fever

It poses a major diagnostic challenge among ICU patients. The fever (>101°F) commonly occurs after 4-5 days of drug administration and may persist for several days, even after discontinuation of the treatment.[6] The incidence rate of drug fever is unknown and it is a diagnosis of exclusion. Drug fever can occur due to hypersensitivity reaction, altered thermal regulation (anti-Parkinson's drug, phenothiazine, anti-histamines), and local reactions at the site of drug administration. The local reactions generally occur with the drugs like amphotericin B, potassium, sulphonamides, macrolides, and cytotoxic chemotherapy drugs. Drugs like atropine reduces heat loss; whereas, medications like thyroxine increases heat production. The common, uncommon and rare offending agents of drug fever are listed in table 1.

Table 1: Common, uncommon and rare causes of drug fever

	Drug fever
Common offenders	Atropine, Amphotericin B, Asparaginase, Barbiturates, Bleomycin, Methyldopa, Penicillins, Cephalosporins, Phenytoin, Procainamide, Quinidine, Salicylates, Sulfonamides (including sulfa-containing laxatives), Interferon
Uncommon offenders	Allopurinol, Azathioprine, Cimetidine, Hydralazine, Iodides, Isoniazid, Rifampin, Streptokinase, Imipenem, Vancomycin, Nifedipine, NSAIDs
Rare causes	Corticosteroids, Aminoglycosides, Macrolides, Tetracyclines, Clindamycin, Chloramphenicol, Vitamin preparations

Acalculous cholecystitis

It typically presents with non-specific symptoms in ICU patients such as fever >101°F and abdominal discomfort. Palpation of the mass and tenderness in the hypochondriac region are noted in most cases. It is recommended to perform an ultrasound to confirm the diagnosis.[7] The mortality rate due to acalculous cholecystitis is around 30-40%, hence, a high index of suspicion is very essential.[8]

Acute pancreatitis

In obese patients with persistent fever, it is recommended to do a work-up for amylase. It may present without abdominal pain, especially in patients with polytrauma.

Venous thromboembolism

The incidence rate is around 12-33%. High index of suspicion along with local signs may help in the diagnosis.

Adrenal crisis

The condition gets manifested with stress and subnormal production of cortisol, ultimately leading to shock. It typically presents with confusion, comma hypoglycemia and seizures.

Thyroid storm

It is caused due to thyrotoxicosis and usually triggered by iodine overload, post-surgical setting, infection etc. The typical presentations include high-grade fever and neurological manifestations such as comma, confusion and delirium. The patients are at increased risk for acute heart failure due to hyperdynamic circulation.

Acute hemolytic transfusion reaction

It is predominantly caused due to ABO incompatibility and can present with fever, shock, hypotension, and acute kidney injury.

Management and diagnostic approach

Collecting the patient history and carrying out physical examination are extremely important for ascertaining the cause of fever. Even if the cause is non-infectious, it needs to be ruled out through blood culture. The sample has to be cultured under aseptic conditions, and nearly 20-30 ml of blood has to be cultured in 2 sets and the site of collection needs to be cleaned with 1-2% chlorhexidine.[9]

The IV and CVC (central venous catheter) lines have to be closely checked and if there is any sign of infection through lines like erythema, they need to be removed.[10] Empiric antibiotic treatment should be reserved to patients with fever >102°F, neutropenia, shock or with devices like external ventricular drain / ventricular assisting devices. A 2012 study by Lee et al. has concluded that treating fever with antibiotic has different clinical and biologic implications in patents with and without sepsis. The study has noted an independent association between administration of NSAIDs or acetaminophen and 28-day mortality.[11] Whereas, a randomized study, involving 700 ICU patients, has found that early administration of IV acetaminophen to treat suspected infection did not influence the number of ICU-free days.[12]

A randomized controlled trial by Schortgen et al. has reported that fever control using external cooling is safe and very effective and it helped in reducing vasopressor requirements and early mortality in septic shock.[13]

Take home message

- Fever >101°F should be considered as fever.
- The approach to non-infectious causes include collecting history, and conducting physical examination and blood culture to rule out infection.
- Two important management paradigms of non-infectious causes include removing CVC and reserving pending cultures and empiric treatment to patients with fever >102°F, neutropenia, shock or with devices like external ventricular drain / ventricular assisting devices.

- Cooling is the safe and effective method and IV paracetamol should be used judiciously in patients with sepsis.

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FEVER FOUNDATION

Vision

Strive towards imparting knowledge on the unmet needs and provide information on research, education and therapy updates on fever management.

Mission

- Independent, non-commercial foundation supporting the educational / academic activities to address the unmet needs in fever management
- The foundation is committed to conceive, build, and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals.
- To run patient education programs on fever management

Objectives of Fever Foundation

- To address the unmet needs and provide updates on fever management
- To provide access to health care through evidence based programs that can reach to large audience
- To engage eminent doctors for various scientific activities

MICRO KNOWLEDGE ACADEMY

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