FEVER FOUNDATION

MICRO KNOWLEDGE ACADEMY

Fever: Bench to Bedside

HANDBOOK FOR PHYSICIANS

Compilation of articles from

FeFCon-2023

6th Annual Fever Foundation Conference 2023 - Virtual

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FOREWORD

Dear Colleagues

Greetings!!

The fever response, a natural reaction that evolved over millions of years in warm-blooded organisms, serves as a protective mechanism against infections. Higher body temperature activates immune surveillance through various cell types, further contributing to the body's defense against infections. Throughout history, fever has been a significant feature in various diseases, with the central nervous system orchestrating the fever response through endocrine, neurological, immunological, and behavioral mechanisms. Beyond the regulated temperature rise, fever is often accompanied by diverse sickness behaviors, changes in metabolic and physiological characteristics, and alterations in immune responses. Consequently, fever and its associated response play crucial roles in the development, clinical manifestation, and outcomes of numerous illnesses and diseases.

As quoted by Sir William Osler, "Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever". Though Fever is a common manifestation of most of the disease, surprisingly we do not have associations/ bodies on Fever providing academic support.

Fever Foundation is an Independent, non commercial foundation supporting the educational/ academic activities to address the unmet needs in fever management.

The Fever Foundation National Conference (FeFCon) 2023, which took place virtually on November 17th, 18th, and 19th, was a groundbreaking event that united prominent experts and thought leaders in fever research and management. The conference covered a spectrum of topics, including the latest advancements in diagnostic approaches, treatment modalities, and the broader impact of fever on public health. Distinguished speakers shared profound discussions, innovative research findings, and practical insights, highlighting the Fever Foundation's dedication to advancing the comprehension of fever. This book stands as a remarkable tribute, acknowledging the exceptional contributions made during FeFCon 2023.

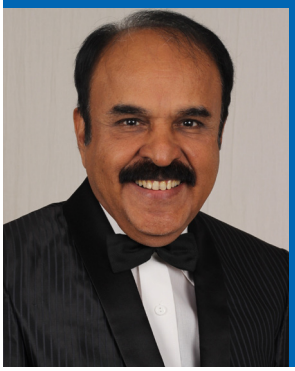
I hope this book serves as a source of inspiration for those committed to advancing knowledge and improving healthcare practices in the realm of fever.

M. Maiya

Dr. M. Maiya

Chief Patron, Fever Foundation of India, Bangalore
Former Professor of Medicine, Karnataka Medical Service
Senior Physician, Rangadore Memorial Hospital, Bangalore

FOREWORD



Dear Colleagues,

Greetings!

In the dynamic realm of healthcare, unraveling the intricacies of fever remains crucial for clinicians globally. The sixth annual National Conference of the Fever Foundation of India (FeFCon 2023) provided an exceptional platform for the exchange of knowledge, and the culmination of that collective expertise is presented in this volume of the FeFCon book.

The articles within this book offer a thorough exploration of fever, covering its associations with fungal infections to its manifestations in emergency rooms. Esteemed clinicians and researchers from across India, recognized for their contributions to the field, have shared their insights on fever in various clinical scenarios. Whether decoding red flags, mastering diagnostics, or engaging in insightful discussions on the duration of antibiotic therapy, the content herein reflects the collaborative efforts of experts committed to advancing our comprehension of fever.

Incorporating topics such as 'Fever, Diet, and Fluids' and 'Fever in the Elderly' acknowledges the diverse challenges clinicians face in fever management. Furthermore, the exploration of clinical pathology cases provides a practical perspective, bridging the gap between theory and real-world scenarios. A highlight of this compendium is the panel discussion on 'Non-Infective Causes of Fever,' a subject often overshadowed in broader discussions. This debate encourages readers to ponder the intricate web of factors contributing to fever beyond infectious etiologies, challenging conventional perspectives, and expanding our diagnostic acumen.

FeFCon 2023 brought together experts for enlightening discussions and a conducive learning environment. The insights shared by our respected speakers guide clinicians in navigating the complexities of fever. As we transition from bench to bedside, this knowledge compendium delves into multifaceted dimensions, addressing diverse aspects of fever and its clinical implications. I am sure this book will help the practitioners in their day to day practice.

Best Wishes,

Dr. Muruganathan

Director Elect - Physician Research Foundation [API]
Immediate Past Governor, American College of Physicians India Chapter
Past Dean–Indian College of Physicians (ICP)
Past President, Association of Physicians of India (API)
Organizing Chairperson – FeFCon 2023.

FOREWORD

Dear Friends

Greetings!!

Exploring fever is essential for unraveling the complexities of various diseases, guiding clinical decisions, and advancing medical knowledge. It has far-reaching implications for diagnosis, treatment, and public health strategies, making it a subject of ongoing research and clinical importance.

The Fever Foundation National Conference (FeFCon) 2023, conducted virtually on November 17th, 18th, and 19th, marked a significant milestone in the field of fever research and management. The conference provided a unique platform for professionals in the field to share and discuss their expertise, innovative research findings, and practical insights. By bringing together distinguished speakers, FeFCon 2023 facilitated a vibrant intellectual environment, contributing to the advancement of understanding in fever-related matters.

The virtual format allowed participants from diverse geographical locations to connect, creating a truly global network of professionals dedicated to the study and management of fever. The shared discussions and findings not only reflected the current state of the field but also projected a vision for its future development.

The insights shared during FeFCon 2023, as highlighted in this book, stand as a testament to the exceptional contributions made by the participants. The outcomes of these conferences, compiled as articles in the book, contribute not only to the current state of knowledge but also lay the groundwork for future research initiatives, ultimately shaping the trajectory of fever research and healthcare practices.

Dr. T. S. Ravindra

HOD- Mallige Hospital, Bangalore

Organising Chairperson – FeFCon 2023

PROLOGUE

Dear Doctors,

Greetings from Fever Foundation of India!

Fever Foundation is a non-commercial, independent foundation supporting the educational / academic activities to address the unmet needs in fever management. Fever Foundation is committed to conceptualize, invigorate programs and develop scientific initiatives aimed at providing evidence based updates to health care professionals.

The Sixth Annual National conference of Fever Foundation, FeFCon 2023 was held virtually on the 17th, 18th and 19th of November, 2023. The theme for the conference was "Fever: Bench to Bedside"

The FeFCon 2023 conference included the Poster Presentations from the PGs of Internal Medicine and Paediatrics. The Zonal level PG quiz was conducted which culminated as Grand Finale in the background of FeFCon 2023 Annual Scientific Sessions.

Outstanding presentations were delivered by highly esteemed and renowned faculty during the three days' academic feast of FeFCon 2023.

This book is the brief capture of sessions that helps in gaining better understanding about fever and its inculcation in routine clinical practice.

Manjula S

Dr. Manjula S

Convener

Fever Foundation of India.

Enigma of Pyrexia in Systemic Lupus Erythematosus

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Medical College & Super Speciality Hospital Hyderabad,
Past President of Indian Rheumatology Association Former Dean ICP / API,
Founder Member Fever Foundation of India

Introduction

Fever is a common symptom seen in patients and can significantly impact their quality of life and, in some cases, may even lead to fatal outcomes. Fever is generally defined as a morning oral temperature reading of more than 37.2°C (99.9°F) or an afternoon temperature of more than 37.7°C (99.9°F).[1] Normal body temperature is regulated by the thermoregulatory center located in the anterior hypothalamus. The febrile response is mediated by prostaglandin E2 (PGE2), and during fever, shivering occurs to reach the new febrile set point quickly.[2] Evaluating fever in Systemic Lupus Erythematosus is highly challenging, as it may mimic features of infectious diseases, adding complexity to the diagnostic process.

Pathophysiology of fever

Fever is initiated by pyrogens that stimulate cells to produce endogenous pyrogens, which are then transmitted to the hypothalamus, raising the thermostatic set point. In SLE, a cascade of events occurs, mediating the neuroendocrine mechanism and altering the hypothalamus set point, leading to severe fever that decreases through vasodilation and sweating.[3,4.]

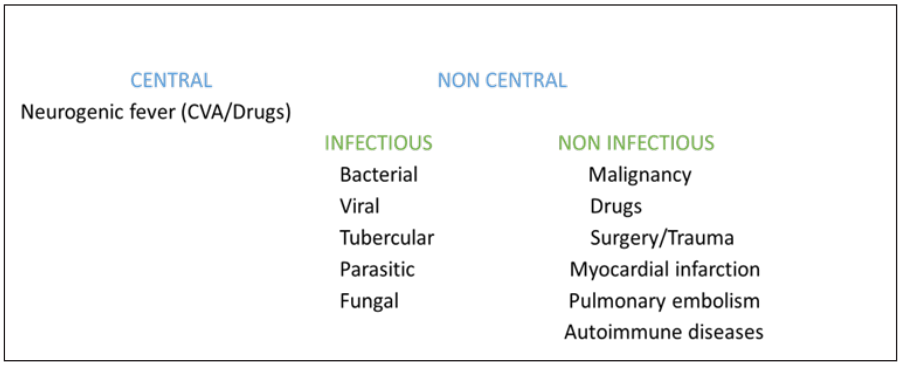
During fever, the hypothalamic thermostat becomes set at a higher temperature. The mechanisms for temperature elevation (endogenous and pyrogens) come into action, contributing to initial pallor and shivering. As fever decreases, the set temperature is lowered, and warm skin and sweating represent heat loss mechanisms.[2]

Endogenous pyrogens are substances produced within the body that can cause fever by affecting the hypothalamic thermoregulatory center. Interleukin-1 (IL-1), tumor necrosis factor (TNF), and interferon (INF) are examples of endogenous pyrogens. Additionally, a decrease in the levels of albumin and transferrin can also induce fever.[3]

Etiology of fever

The etiology of fever, or the underlying causes, can be diverse and may vary depending on the context (Fig. 1).

Fig. 1: Etiology of fever



Prevalence of fever in children and adults

Most acute fevers in infants and young children result from infections, with the common culprits being viral respiratory or gastrointestinal infections and certain bacterial infections such as otitis media, pneumonia, and urinary tract infections. The prevalence of specific symptoms varies, with diarrhea alone at 5.5%, cough and diarrhea at 2.5%, cough alone at 9.5%, and fever alone at 7% in children under 5 years of age.[5]

According to a multicenter study in India led by Morch et.al, the leading causes of fever among hospitalized patients with acute undifferentiated fever included malaria (17%), dengue (8%), bacteremia (8%), scrub typhus (10%), leptospirosis (7%), and chikungunya (6%).[6] Another study by Wangdi et al. identified dengue as the most common cause of acute undifferentiated febrile illness (11.8%), followed by leptospirosis (4.4%), typhoid (4%), scrub typhus (4%), and influenza other than H1N1 (3.1%).[7]

The enigma of fever in adult lupus patients

In rheumatological practice, fever is a prevalent phenomenon among patients with SLE, significantly contributing to morbidity and, at times, mortality. Various factors can contribute to fever in SLE patients. Commonly used drugs for SLE treatment, like NSAIDs and corticosteroids, may obscure the clinical signs and symptoms of fever, and certain medications may even induce fever. Additionally, fever can be a presenting feature of various infectious diseases that mimic SLE, making it challenging for rheumatologists to determine its root cause.[8]

Fever is a common manifestation of SLE, occurring in 36-86% of patients. In some cases, fever may be the only presenting symptom of SLE, and among patients initially diagnosed with fever of unknown origin (FUO), up to 5% are eventually diagnosed with SLE. Assessing lupus patients with fever is a crucial diagnostic challenge, as the initial clinical presentation of a patient with lupus may mimic to the acute febrile phase of an infection.[2]

Inflammation plays a key role in lupus. Activated macrophages/monocytes produce pyrogenic cytokines such as IL-1β, TNF, IL-6, INF- β, IFN- α, and INF- γ, which act directly on the hypothalamus, triggering a fever response. SLE patients often exhibit elevated IFN-α serum levels, and these levels correlate with disease activity. Additionally, SLE patients show increased IL-17 levels, initiating a positive feedback loop by inducing the secretion of PGE2, GM-CSF, and G-CSF, leading to further IL-17 production.[9,2]

Hyperactive B cells and loss of B-cell tolerance are hallmarks of the disease. Immune complexes containing nucleic acid autoantigens can activate endosomal Toll-like receptors (TLRs) and promote inflammation. Proinflammatory cytokines drive T-cell activation and dendritic cell maturation and can stimulate extramedullary hematopoiesis, leading to the expansion of innate immune cells. Autoantibodies become deposited in tissues, leading to tissue destruction. Factors like genetics, environment, diet, and stress can modify disease course and severity.[10]

Clinical features of fever in lupus

In patients with active SLE without infection, the peek temperature ranges from 38°C to 40°C with an intermittent pattern.[2] The differential diagnoses for fevers in lupus patients include:

- Lupus disease activity
- Infection
- Disease activity and infection
- Malignancy
- Drug-induced

Clinical identification of lupus fever

Typically, chills and rigors are absent in patients with lupus fever. Rovin et al. defined SLE fever with three criteria:[11]

1. Absence of infection despite extensive testing
2. Presence of an illness typical of active SLE accompanying the fever
3. No evidence for infection despite escalation of immunosuppression.

It is important to differentiate lupus fever from infections as management varies and infections remain a major cause of mortality in newly diagnosed lupus patients.

Study on fever in adult lupus patients in South India

Our team conducted a prospective cohort study at the Department of Clinical Immunology and Rheumatology in a tertiary care center in South India. The study, carried out from April 2022 to August 2023, included adult patients meeting the 2019 ACR/EULAR classification criteria who were presented with fever in the outpatient department (OPD) or were admitted.

The study gathered demographic data and assessed the etiology of fever in adult lupus patients by analyzing markers such as the systemic lupus erythematosus disease activity index 2000 (SLEDAI2K) and laboratory indicators distinguishing infection from disease flare. Disease activity levels were categorized as follows: No activity (SLEDAI=0), Mild activity (SLEDAI=1 to 5), Moderate activity (SLEDAI=6 to 10), High activity (SLEDAI=>11).

Among 192 patients admitted during the study period with fever, 54 (28.1%) were diagnosed with SLE. Half of the SLE patients (50%) were in the 30 to 39 years age group, and the majority (94.4%) were female. The primary cause of fever in SLE patients was a flare of the underlying disease, observed in 58.8% (28) of patients. Infections accounted for 31.4%, with urinary tract infections (UTI) being the most common at 16.6%. Additionally, 16.6% of patients experienced both disease flares and infection. Drug non-adherence was identified as the leading cause of disease flare (Table 1).

Table 1: Etiology of fever in SLE patients

SLE Etiology	Frequency	Percentage
DISEASE FLARE	28	51.8%
UTI	9	16.6%
RESPIRATORY TRACT INFECTION	6	11.1%
ACUTE G.E	4	7.4%
DENGUE	3	5.5%
CELLULITIS	3	5.5%
HZV	2	3.7%
TB PERICARDITIS	1	1.85%

SLE	INFECTION	DISEASE FLARE (SLEDAI2K)	BOTH
TOTAL NUMBER	19	28	9

The study revealed a significant elevation in c-reactive protein (CRP) levels among SLE patients with infections compared to those experiencing disease flares, consistent with prior research ($P < 0.00012$). In contrast to earlier findings, the neutrophil-lymphocyte ratio (NLR) was elevated in patients with both SLE disease flare and those presenting with evidence of infection, indicating its limited reliability as a marker to differentiate between infection and disease flare in SLE patients with fever. However, procalcitonin levels were notably elevated in SLE patients with infection ($P < 0.001$).

The study has concluded that fever is a common finding in SLE patients, with infections and disease flares being the main causes. High disease activity and poor drug compliance increase the risk of infections. A thorough evaluation is necessary to identify the cause of fever, as it guides management. CRP and procalcitonin are useful markers in differentiating infection from disease flare, while NLR is not useful.

Infections in SLE patients

Infections are the most prevalent cause of death and mortality in patients with SLE. Factors associated with increased risk of infections in SLE patients include:

- High disease activity
- High dsDNA levels
- Low complement levels and leukopenia

- Lupus Nephritis
- Prednisone or equivalent dose >7.5mg/day
- Methylprednisolone Pulse Therapy
- Cyclophosphamide high-dose regimens

Studies indicate that the respiratory tract (12–54%), urinary tract (8–36.4%), skin and mucosa (5–33.6%), and sepsis (1–15.9%) account for the majority of infections in SLE. The most prevalent microorganisms include bacteria (65–97%), viruses (7–27%), and fungi (3–20.6%).[12]

Laboratory markers of SLE

Commonly used laboratory markers in SLE include:[13]

- Anti-dsDNA antibodies
- Complement (C3 and C4)
- Erythrocyte Sedimentation Rate (ESR)
- C-Reactive Protein (CRP)
- Anti-C1q antibodies
- Activity on urinary sediment

Parameters that differentiate the diagnosis of SLE fever over infection include:

- Leukopenia
- Normal or slightly elevated CRP
- Low C3 and C4
- Elevated anti-dsDNA

Measures to prevent infections in SLE

1. Vaccination:

- A vaccination history should include protection against *H. influenzae B*, hepatitis A, hepatitis B, human papillomavirus (HPV), influenza, *N. meningitides*, *S. pneumonia*, and tetanus.
- Inactivated live vaccines should be avoided in patients receiving immunosuppressive agents, including glucocorticoids at daily doses over 20 mg.

2. Hydroxychloroquine:

- Hydroxychloroquine (HCQ) has antibacterial, antifungal as well and antiviral effects beyond its well-known antiparasitic activity.
- The first two effects are exerted by pH-dependent iron deprivation and by increasing lysosomal pH, leading to growth inhibition of intracellular organisms.

3. SLE remission or low disease activity:

With the help of judicious use of steroids and other immunosuppressants, control of lupus disease activity is essential to prevent infections.

Conclusion

Fever in SLE presents a diagnostic challenge due to its diverse etiologies, including disease flares and infections. Effective management necessitates a thorough evaluation, considering markers like CRP and procalcitonin for differentiating infection from disease flare. As fever significantly impacts the quality of life for SLE patients, understanding its multifaceted nature is crucial for tailored and timely interventions for improving patient outcomes.

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Cytokine Release Syndrome: Physician Perspective

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President-Indian Rheumatology Association

Introduction

The severe acute respiratory syndrome COVID-19 pandemic underscores the critical role of an effective host immune response and the devastating effects of immune dysregulation. It has also brought attention to an already existing terminology, known as cytokine release syndrome or cytokine storm. The common feature shared by these conditions is a massive release of cytokines due to excessive activation of immune cells, and this dysregulates inflammatory response. The term cytokine storm was initially introduced by James L. Ferrara in 1993 to characterize acute graft-versus-host disease (GvHD) in the context of engraftment syndrome following allogeneic stem-cell transplantation.[1, 2] From a historical perspective, cytokine storm was previously denoted as an influenza-like syndrome occurring after systemic infections such as sepsis and immunotherapies like Coley's toxins. Cytokine storm or cytokine release syndrome represents a life-threatening systemic inflammatory syndrome involving elevated levels of circulating cytokines and immune cell hyperactivation that can be triggered by various therapies, pathogens, cancers, autoimmune conditions, and monogenic disorders.[3]

Cytokine storm occurs frequently in the background of certain diseases, syndromes, and therapies such as anaphylaxis, graft-versus-host disease, primary and secondary hemophagocytic lymph histiocytosis (HLH), acute respiratory distress syndrome (ARDS), and systemic inflammatory response syndrome (SIRS). Additionally, it is associated with chimeric antigen receptor-T (CAR-T) cell therapy and sepsis, the latter accounting for up to 19.7% of all deaths worldwide.[2]

Cause of cytokine storm

Cytokine storm is not exclusively a diagnosable condition. Instead, it can complicate diverse inflammatory disease states, including infections, rheumatic illnesses, and hematologic malignancies. Owing to the myriad underlying conditions linked to cytokine storm, various diagnostic criteria and classifications exist for the distinct entities falling under the cytokine storm umbrella.[4] Different conditions, which can trigger cytokine storms, can be classified into primary or genetic conditions like familial HLH, related performance pathways, genetic defects, or X-linked lymphoproliferative disorders due to a deficiency of a variety of genes. Cytokine storms are characterized by constitutional symptoms, systemic inflammation, and multi-organ dysfunction, and targeted interventions can help alleviate the illness.[4]

It can also be triggered by immunodeficiency conditions, infections like herpesvirus family (e.g., EBV, CMV, HHV6, HSV1/2), influenza strains (e.g., H1N1, H5N1) and severe acute respiratory syndrome (SARS)-COVID 19. Similarly, cytokine storms can be triggered by bacteria, parasites, fungi, and sepsis. Additionally, they are associated with rheumatological conditions such as systemic lupus erythematosus (SLE), Still's disease, Kawasaki disease, and various other conditions that can induce cytokine storms.[4]

Clinical presentation of cytokine storm

Cytokine storms, characterized by flu-like symptoms, systemic inflammation, and multi-organ dysfunction, can be triggered by various factors, including infections and autoimmune conditions. Patients are also at higher risk of spontaneous hemorrhage. Severe cases may lead to renal failure, liver injury, cardiomyopathy, capillary leak syndrome, and anasarca.[3] Immune effector cell-associated neurotoxicity syndrome (ICANS) or cytokine release syndrome-associated encephalopathy (CRES) is the neurologic toxicity associated with T-cell immunotherapy. The onset of neurologic toxic effects is often delayed and developing several days after the onset of the cytokine storm.[5]

Pathophysiological features of cytokine storm

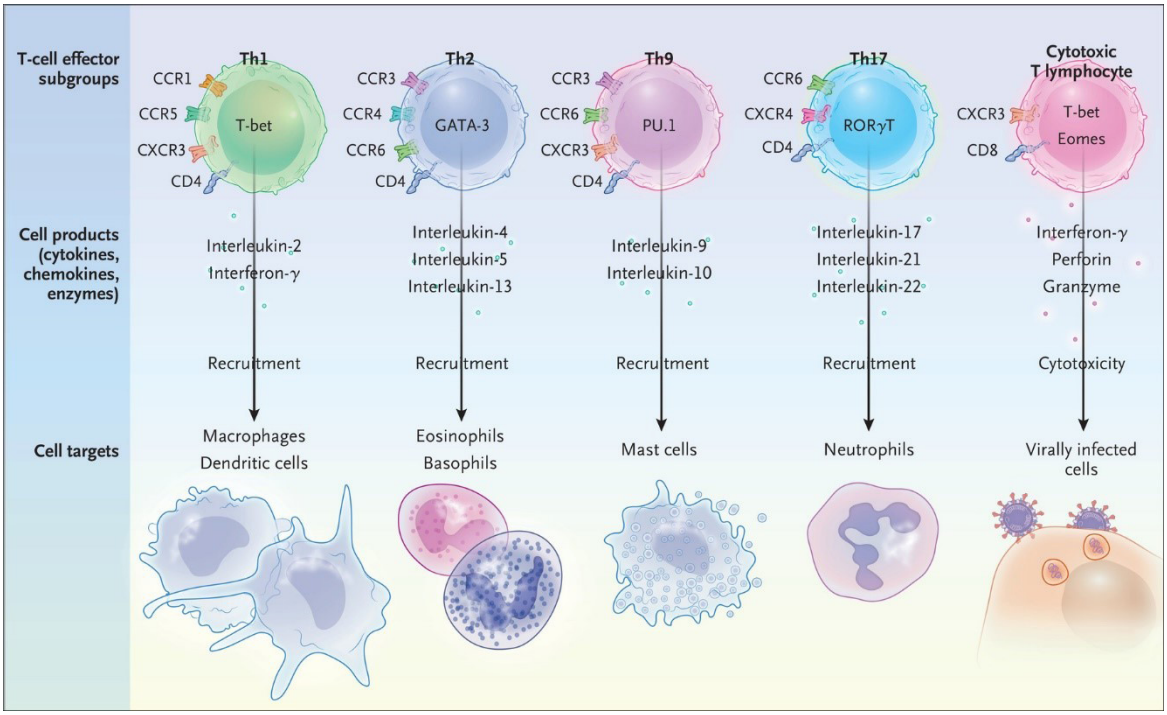
Inflammation represents a natural mechanism intrinsic to multicellular organisms, facilitating the activation of the immune system. The maintenance of balanced cytokine production is pivotal for effectively eradicating pathogens while preventing an unwarranted inflammatory overreaction. Cytokines play a significant role in coordinating antimicrobial effector cells and regulating the immune response. However, elevated levels of cytokines can have harmful systemic effects and even damage vital organ systems.[2]

Inappropriate recognition in hypersensitivity or ineffective recognition with immune evasion of Epstein-Barr virus (EBV) associated HLH can lead to cytokine storm. Similarly, an exaggerated effector response and cytokine production in chimeric antigen receptor (CAR) T-cell therapy or an inadequate response due to immune evasion in sepsis can also precipitate this condition. Additionally, the failure to restore homeostasis in HLH can result in persistent hyperinflammation. Certain drugs have the capacity to inhibit signaling pathways. In all these scenarios, malfunctioning negative feedback mechanisms contribute to the prevention of hyperinflammation and the overproduction of inflammatory cytokines and soluble mediators. This excessive production leads to hyperinflammation and multiorgan failure. Regulatory cell types, decoy receptors for proinflammatory cytokines like IL1RA, and anti-inflammatory cytokines such as interleukin-10 play a crucial role in counteracting inflammatory cell populations and preventing immune hyperactivity.[6]

Cytokine storm cell types

The cytokine storm primarily involves innate cells, including neutrophils, macrophages, and NK cells, and can also be triggered by B and T cells of the adaptive immune system. These cells differentiate into subsets, each with distinct functions capable of initiating a cytokine storm. An exaggerated Th1-type inflammatory response often serves as the catalyst for cytokine storm, with T cells also demonstrating the capacity to initiate it. Some instances of cytokine storm are attributed to impaired granule-mediated killing by cytotoxic T lymphocytes (CTLs). Additionally, both TH17 cells and B cells can independently induce cytokine storm (Fig. 1).[3, 7]

Fig. 1: T-cell effector subgroups that are involved in a cytokine storm[3]



Source: Fajgenbaum DC, June CH. Cytokine Storm. New England Journal of Medicine. 2020 Dec 3;383(23):2255–73.

Therapeutic approaches

Various anti-inflammatory therapies have been employed to mitigate the elevated levels of cytokines, aiming to alleviate morbidity and mortality associated with cytokine storms. However, none of the current treatment approaches have demonstrated the desired effectiveness, and consensus is yet to be reached regarding the ideal timing, duration, and type of regimen. Cytokine storms emerge when circulating cytokine levels are elevated and commonly associated with infections. Targeting specific pro-inflammatory cytokines stands out as a potential therapeutic approach with minimal harm to the host.[8]

Reasons for failure of treatment of cytokine storms

Understanding the challenges in treating cytokine storms is essential for refining therapeutic strategies. Some of them are listed below:

- Delayed interventions may render the treatment of cytokine storms ineffective, while early intervention can pose dangers.
- The optimal point for managing a cytokine storm remains unclear.
- The current manifestations and profiles of cytokines are insufficient guides, contributing to uncertainty in the treatment process.

Conclusion

The overall approach to treating cytokine storm involves providing supportive care to sustain vital organ function, addressing the underlying disease, eliminating factors that trigger an abnormal immune response, and using targeted immunomodulation or nonspecific immunosuppression to reduce overactive immune response. Despite the complexity of the treatment process, its effectiveness has been demonstrated in managing monogenic diseases and acute respiratory distress syndrome.

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Cytokine Release Syndrome: Pediatrician Perspective

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Introduction

Cytokine release syndrome (CRS), a subset of disorders associated with dysregulation of the immune system, has garnered increased attention due to its potential to trigger multiorgan failure when not effectively managed. It is characterized by systemic inflammation, constitutional symptoms, and multiorgan dysfunction. This set of disorders shares similarities with cytokine storm syndrome, a family of syndromes that induce hyperinflammation and multiorgan disease through the excessive release of cytokines from uncontrolled immune activation.[1, 2]

Clinical presentation of CRS

CRS can manifest itself in various ways, ranging from mild flu-like symptoms to severe, life-threatening manifestations of the overshooting inflammatory response. Patients with mild CRS typically experience symptoms such as fever, fatigue, headache, rash, arthralgia, and myalgia. On the other hand, severe CRS cases are characterized by hypotension and high fever, and can progress to an uncontrolled systemic inflammatory response, resulting in vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure.

Patients with CRS typically exhibit laboratory abnormalities such as cytopenia, elevated creatinine and liver enzymes, deranged coagulation parameters, and a high c-reactive protein. Respiratory symptoms are also common in patients with CRS. Mild cases may display cough and tachypnea, but the condition can progress to acute respiratory distress syndrome, characterized by dyspnea, hypoxemia, and bilateral opacities.[3]

Therapeutic approaches

In cases of sepsis refractory to antibiotics, the consideration of immunomodulatory drugs is warranted. A small proportion of Epstein–Barr virus (EBV)-associated hemophagocytic lymphohistiocytosis (HLH) patients may develop hemophagocytic syndrome. For this group, rituximab and steroids can be both curative and lifesaving. For human herpesvirus 8 (HHV-8)-associated multicentric Castleman disease (MCD), B cell-depleting therapy, and sometimes interleukin (IL)-6-based therapies can be considered. However, rituximab, which depletes B cells, might be a more effective option, even for idiopathic MCD. In the case of COVID-19 patients, steroids and baricitinib can be lifesaving treatments.

For primary HLH, the treatment approach may involve T-cell inhibition or ablation, interferon-γ inhibitor, or glucocorticoids. On the other hand, for secondary HLH, treating the underlying cause, along with T-cell inhibition or ablation, IL-1β inhibitor, Janus kinase (JAK) 1 and JAK2 inhibitors, and glucocorticoids can be beneficial.[1]

Pathophysiological mechanisms of CRS

Chimeric antigen receptor (CAR) T cells are infused into patients to recognize and kill tumor cells, triggering cytokine production and immune cell activation. This process leads to a systemic inflammatory response and tissue damage, even in the central nervous system. Ultimately, T cell death results in decreased cytokine levels and the resolution of symptoms.[4]

Though several individuals are exposed to dengue, only a few become significantly ill. The underlying cause may be a defective immune system in cases of life-threatening diseases such as dengue or other bacterial, viral, and parasitic triggers. Cytokines are released to combat the infection; however, unregulated release can occur when the immune system perceives persistent antigenic stimulation, leading to an exaggerated release of cytokines. In such cases, it is not the infection that causes death but the immune response. IL-1 inhibition with anakinra can be a lifesaving intervention for this group of patients.

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a hyperinflammatory state that can occur in various conditions, including systemic juvenile idiopathic arthritis (sJIA), Adult-onset Still disease (AOSD), connective tissue diseases, sepsis, infection, cancers, and cancer immunotherapy. The development of MAS is influenced by a complex interplay of genetics, immunodeficiency, infectious triggers, and innate immune effector responses.

In the pediatric arena, MAS is characterized as a form of secondary HLH. Primary HLH is a potentially fatal autosomal-recessive condition that is genetically and functionally defined by immunodeficiency of natural killer (NK) cells and cytotoxic T cells. The failure to efficiently kill target cells leads to prolonged immunological synapse formation, resulting in high levels of interferon (IFN)γ production and subsequent macrophage activation with hemophagocytosis.[5]

MAS can manifest as an autoinflammatory condition within a broader immune response. The spectrum of MAS disorders can be viewed as a continuum of immunological diseases involving inflammation against oneself, resulting in changes in function and loss of function. Anti-IL-6 therapy is effective for MAS associated with cancer immunotherapy, but not for Systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still Disease (AOSD). IL-1Ra is effective for MAS in sJIA and AOSD, while IFNγ antagonism has shown some efficacy in sJIA-associated MAS. Corticosteroids and JAK inhibitors may have a broad impact.[5]

Diagnostic criteria for HLH

The HLH 2004 criteria for diagnosis require either a molecular diagnosis or the presence of five or more of the following eight criteria:[6]

1. Fever

2. Splenomegaly

3. At least 2 of: (i) Hemoglobin <90 g/L; (ii) Platelets <100 x 109 /L; (iii) Neutrophils <1 x 109 /L

4. Either of: (i) Fasting triglycerides ≥265 mg/dL (3.0 mmol/L), OR (ii) Fibrinogen ≤1.5 g/L

5. Ferritin ≥ 500 μg/L

6. Tissue hemophagocytosis

7. Decreased NK cell function

8. Soluble CD25 (i.e. IL 2 receptor) ≥2400 U/ml

The role of ferritin levels in HLH diagnosis

A retrospective study conducted by Sen et al. at eight UK centers analyzed patients aged ≤16 years with a serum ferritin level exceeding 10,000 mg/L between April 1, 2014, and March 31, 2017, utilizing biochemistry databases. Data were collected using a standardized proforma, and cases were assessed against the 2004 HLH criteria. Of the 94 identified patients, 14 (14.9%) met ≥5/8 criteria, leading to a diagnosis of HLH by the treating team. Additionally, 33 patients (35.1%) met ≥4/5 criteria, with 17 (51.5%) of these diagnosed with HLH by clinicians. Notably, HLH was not considered in the differential diagnosis for 11 patients (33.3%).

The overall mortality rate was 33.0% (31/94), but it decreased to 17.2% (5/29) in patients diagnosed with HLH during their admission. The study suggests that HLH may not be adequately considered in the differential diagnosis for many patients with ferritin levels >10,000 μg/L. Mortality rates appeared lower in patients diagnosed with HLH by the treating team compared to the entire group. Thus, the study emphasizes the importance of considering or excluding hyperinflammation when faced with markedly elevated ferritin levels, which are highly specific for HLH.[7]

Children presenting with fever, cytopenia, and coagulopathy, and refractory to antibiotics, should be evaluated for HLH/sepsis and undergo serum ferritin level assessment. If the serum ferritin level is less than 500 μg/L, the likelihood of HLH is low. However, if it exceeds 10,000 μg/L, the likelihood of HLH is higher, and consideration of immunomodulatory treatment is crucial. HLH may still occur when ferritin levels are in the range of 500–10,000 μg/L; however, confirmation requires examination of other biomarkers.[8]

Study on IL-1 inhibitor treatment in sepsis patients

In a study by Shakoory et al., involving the reanalysis of phase 3 data from a randomized controlled trial of anakinra in sepsis, participants were categorized into two groups: those with hepatobiliary dysfunction (HBD) + disseminated intravascular coagulation (DIC) vs. those with HBD or DIC or neither. A total of 763 adults were randomized to receive anakinra or a placebo. Among them, 43 patients (5.6% of the total, aged 18–75; 47% women) exhibited concurrent HBD/DIC.

The 28-day survival rate was comparable in both anakinra and placebo-treated non-HBD/DIC patients (71.4% vs. 70.8%, P = 0.88). However, treatment with anakinra demonstrated a significant improvement in the 28-day survival rate among HBD/DIC patients (65.4% anakinra vs. 35.3% placebo), with a hazard ratio for death of 0.28 (0.11–0.71, P = 0.0071).[9]

Conclusion

CRS is a condition in which the body's immune system responds to inflammation caused by various factors, such as infections and certain drugs. Distinguishing between HLH and systemic sepsis can be challenging; however, specific criteria exist for the diagnosis and classification of HLH and MAS. A serum ferritin level exceeding 10,000 µg/L strongly supports the diagnosis of HLH. In children presenting with fever, cytopenia, and multi-organ involvement, checking ferritin levels and evaluating for HLH is crucial. HLH can be life-threatening and should be considered early in any patient with fever, multi-organ failure, and cytopenia. While infection is a key trigger for HLH, it also poses a challenge for clinicians in administering the required immunosuppression to stop the cytokine storm.

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Newer Diagnostics in Infectious Diseases

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Introduction

The clinical microbiology laboratory is in a perpetual state of evolution, advancement and transition due to the integration of cutting-edge technologies that revolutionize the characterization and diagnosis of pathogens. Optimal microbiology testing necessitates meticulous collection of samples and the rapid, accurate, and cost-effective delivery of results. Optimization of these factors contributes to the ongoing refinement and optimization of diagnostic methodologies in the field of clinical microbiology.[1,2]

Diagnostic options for detecting pathogens

Both direct demonstration and supportive evidence contribute to a comprehensive diagnostic approach, offering different perspectives on pathogen detection and aiding clinicians in tailoring appropriate treatment strategies.

A. Direct demonstration

Utilizing smear microscopy involves directly observing the pathogens under a microscope, allowing for visual identification and classification.[3]

B. Supportive evidence

Antigen (Ag) or Antibody (Ab)/biomarkers tests provide supportive evidence of the presence of pathogens by detecting specific components or the body's immune response to them. They contribute to a more comprehensive understanding of the infection dynamics especially when cultures are either negative due to prior antibiotic administration or due to fastidious organisms that fail to grow[3]

Some of the advanced antigen/antibody detection methods for various infections are listed below:

- Pneumonia: Binax urinary antigen for *S. pneumoniae* and *L. pneumophila*
- Meningitis: Latex agglutination for rapid detection of 5 principal pathogens as Grp B Streptococci and Ecoli for neonates and *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*. The BinaxNow pneumococcal cerebrospinal fluid (CSF) antigen exhibits high sensitivity (95-100%) and specificity (100%) in diagnosing meningitis due to *S pneumoniae*.

- *C. neoformans* (cryptococcal infections): The CrAg lateral flow assay provides rapid and easy detection of cryptococcus antigen, requiring no specimen pretreatment. It offers room temperature stability and demonstrates exceptional sensitivity and specificity (>99%) across all four serotypes.
- Malaria: Rapid diagnostic tests (RDT) include parasitic antigens as histidine rich protein (*hrp 2)* and parasite lactate dehydrogenase (*pLDH)*
- Dengue: NS1, IgM, and IgG assays
- Chikungunya: IgM assay
- Kala-azar: rK39
- Scrub typhus: IgM assay
- SARS CoV2: Lateral flow assay (LFA)

Specific newer Biomarker immunoassays

- **3-β-d-glucan for invasive fungal infections:** During invasive fungal infections (IFI), 3-β-d-glucan (BDG) emerges as a biomarker in serum, serving as a diagnostic indicator for conditions like invasive aspergillosis (IA) and invasive candidiasis (IC). Additionally, it serves as a reliable test for diagnosing Pneumocystis pneumonia (PCP). Therefore, its significance as a diagnostic tool in the ICU cannot be overstated especially as a rule out test.[4,5]
- **Galactomannan for invasive aspergillosis:** Galactomannan (GM), a constituent of the cell wall polysaccharide in hyphae forms of *Aspergillus spp*., is released during tissue invasion. Detectable in serum, bronchoalveolar lavage (BAL), biopsies, urine, CSF, pericardial fluid, and pleural fluid, GM serves as a valuable diagnostic tool, especially in monitoring neutropenic patients. However, GM values may not exhibit the same diagnostic efficacy in non-neutropenic patients, with potential for false positives due to cross-reactivity with other fungal species (*Penicillium spp., Alternaria spp., Paecilomyces spp., and Cryptococcus spp*.), antibiotic treatments (piperacillin-tazobactam, amoxicillin-clavulanic acid), and neonatal colonization *by Bifidobacterium spp*.[6,7]
- **Immunochromatographic lateral flow test for carbapenemases:**

  Immunochromatographic lateral flow test (ICT) assays target carbapenemase-specific epitopes, providing rapid results in approximately 15 minutes. They exhibit good sensitivity and specificity across various carbapenemase variants NDM, VIM, KPC, IMI & OXA 48 in Enterobacterales . These ICTs hold promise for significantly enhancing both the efficiency and speed of detection within routine microbiology laboratories. This is particularly significant considering the expense and limited accessibility of more expensive molecular assays as PCR or next-generation sequencing for detecting carbapenemases in many laboratory settings.[8]

- **Biomarkers of sepsis:** C-reactive protein (CRP) and procalcitonin are produced as a response to infection and inflammation. They serve as indicators of neutrophil and monocyte activation and are the most frequently used biomarkers.[9] CRP, as a point-of-care test, is cost-effective and surpasses procalcitonin in utility. It is evolving into a highly valuable tool within the antimicrobial stewardship program, guiding antibiotic initiation, determining duration, and facilitating de-escalation.

C. Successful Isolation

Culture and Drug Susceptibility Testing (DST): It aims to grow and isolate pathogens successfully in controlled laboratory conditions. DST assists in determining the drugs that would effectively treat the pathogen.

- **Blood cultures:** This is of paramount importance for individuals presenting with fever. Automated methods are preferable over manual ones due to their avoidance of issues such as routine culture and contamination. The recommended blood culture procedure involves at least two (preferably three) sets of 2 bottles each (aerobic and anaerobic) and not solitary cultures. Increasing the volume of blood to 40-60 ml of blood enhances isolation chances and aids in distinguishing important isolates from contaminants.[10] According to a study by Cockerill et al., analyzing 163 bloodstream infections, the first blood culture detected 65.1%, the first two detected 80.4%, and the first three detected 95.7% of cases.[11] Absolute blood culture is essential in cases of severe sepsis/septic shock and infections linked to a high or intermediate risk of bacteremia. Repeated blood cultures are necessary to document the clearance of *S. aureus or S. lugdunensis* bacteremia and *Candida* bacteremia, identifying organisms suspected to cause infective endocarditis/endovascular infections, addressing concerns regarding persistent bacteremia, and distinguishing between contamination and genuine bacteremia.[12]

Recommended pediatric blood culture volumes based on weight are listed in table 1.[13]

Table 1: Recommended pediatric blood culture volumes based on weight

Weight (lbs)	Recommended blood volume/culture (ml)	Volume of blood collected = 1% of total volume (ml)
<18	1	2
18-30	3	6-10
30-60	5	10-20
60-90	10	20-30
90-120	15	30-40
120	20	>40

Newer diagnostic technologies in Identification of microorganisms

Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS): It has revolutionized the rapid identification of bacteria, fungi, and mycobacteria by significantly reducing the test frequency and turn around time from 24 hours to a mere 20 minutes. Ongoing research is exploring potential applications for susceptibility testing. During MALDI-TOF analysis, the m/z ratio of an ion is measured by evaluating the time taken to traverse the length of the flight tube.

Some TOF analyzers incorporate an ion mirror at the end of the flight tube, effectively reflecting ions through the tube to a detector. This extends the length of the flight tube and corrects minor differences in ion energy. Using this TOF data, a distinct spectrum, known as the Peptide Mass Fingerprint (PMF), is generated for analytes in the sample.[14,15] In contrast to traditional diagnostic methods that need an overnight incubation, MALDI-TOF MS identification can be conducted rapidly for bacterial, fungal and mycobacterial species [16]

T2 Magnetic Resonance assay (T2MR): It is an expensive method that is not currently available in India. It represents a significant advancement as it allows direct testing from patient samples such as blood, urine, and CSF. It employs magnetic biosensor technology to measure the reactions of water molecules in magnetic fields and utilizes nanoparticles with magnetic properties to enhance the magnetic resonance signals of specific targets.[17,18]

Drawbacks of current diagnostic methods

Blood cultures might fail to indicate positivity, potentially resulting in inappropriate therapy due to the detection of contaminants. Approximately 40% of sputum culture cases either cannot generate sputum or provide samples of poor quality, making it challenging to identify the true pathogen once antibiotic treatment has commenced. Collection and transportation issues significantly affect urine culture samples, often leading to the inappropriate treatment of asymptomatic bacteriuria.[19-21]

D. Molecular methods

These techniques involve amplifying the genetic material of the pathogen, enabling accurate identification and sometimes quantification.[3]

Modern tools for rapid Antimicrobial Susceptibility Testing (AST)

Approaches that leverage Nucleic Acid Amplification Test (NAAT), nucleic acid hybridization, or immunodiagnostics have the potential to utilize non-purified polymicrobial clinical samples. By subjecting these samples to brief cultivation with a predetermined antibiotic load, followed by NAAT (such as isothermal amplification), the presence of antimicrobial resistance can be identified (Table 2). Antimicrobial Resistance determinant is a term that includes both resistance genes and resistance mutations that give a microbe the ability to resist the effects of one or more drug[25,26] This process offers a rough estimate of the minimal inhibitory concentration for the antibiotics under test. While many swift growth-based AST methods focus solely on endpoint analysis, others depend on frequent sampling from the cultivation chamber.[22]

Table 2: NAAT-Based Methods in Sepsis

Assays	Sample	Technology	Pathogens	Resistance genes	Turn-around time
SeptiFast (Roche Molecular System, Switzerland)	Whole blood	Real-time PCR	25 bacteria and fungi	None	4.5 hours
SepsiTestTM (Molzym, Germany)	Whole blood	Broad-range PCR sequencing	345 bacteria and fungi	None	8-12 hours
Vyoo (SIRS-Lab, Jena, Germany)	Whole blood	PCR+ Electrophoresis	39 bacteria and fungi	mecA, vanA, vanB, vanC, and blaSHV genes	7 hours
Magicplex™ Sepsis Real-time Test (SeeGene, Korea)	Whole blood and CSF	Real-time PCR	73 gram-positive+12 gram-negative bacteria+6 fungi	mecA, vanA, vanB	3-4 hours

Blood culture identification 2 panel

The blood culture identification 2 panel (BCID2) is an advanced *in vitro* diagnostic tool that utilizes NAAT to rapidly detect and characterize prevalent pathogens and potential contaminants present in blood cultures. This closed, multiplex PCR system is equipped for automated sample preparation, amplification, detection, and analysis. It simultaneously screens for 27 targets, covering a spectrum from gram-positive and gram-negative bacteria to yeast and antimicrobial resistance genes. The process involves a quick ~2-minute hands-on procedure, requiring the addition of 200 µl of a sample from a positive blood culture bottle to a sample buffer within a single pouch. Subsequently, this pouch is loaded into the film array system for analysis.[23,24]

Syndrome multiplex panels

They have revolutionized clinical microbiology laboratories by facilitating the rapid identification of bacteria, viruses, fungi, and parasites. Seamlessly integrated into the routine testing protocols of numerous clinical laboratories, these panels offer minimal hands-on sample preparation, high automation, and rapid outcomes, representing a significant advancement in testing practices.[27] They can simultaneously detect multiple pathogens, ensuring rapid, sensitive, and specific results. This technology not only provides a more efficient diagnosis but also aids in rapidly and accurately identifying patients who will benefit from antibiotic treatment. However, it is essential to acknowledge certain disadvantages associated with these panels, including limitations to the predefined panel, high costs, proprietary nature, and the possibility of not influencing patient management.[23]

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) panels for Tropical Fevers

RT-PCR panels typically include a multiplex set of assays, allowing for simultaneous detection of multiple pathogens in real time . The commonly used multiplex tropical fever panels are listed below:[28-30]

- *Plasmodium spp*
- *Chikungunya virus*
- *Rickettsia spp*
- *Dengue virus*
- *Zika virus*
- *Salmonella spp*
- *Leptospira spp*
- *West Nile virus*

Additionally, a multiplex panel is available specifically for *Mycobacterium tuberculosis* and non-tuberculous mycobacteria in sputum specimens, utilizing the Universal Lateral Flow Assay (ULFA).

Multiplex fungal panels

Multiplex fungal panels cover a spectrum of pathogens with detailed resistance targets. Examples are given below:

- *Aspergillus spp: A fumigatus, Aspergillus terreus* with multiplex resistance targets L98H, Tandem repeat 34, T289A, Y121F.
- Mucor: *Pan-Mucormycetes*, *Rhizopus spp, Mucor spp, Lichtheimia spp, cunninghamella spp, Rhizomucor spp*

Current diagnostics for enteric fever, such as culture-based techniques, demonstrate high specificity but are hindered by low sensitivity and relatively lengthy processing times. PCR-based NAATs provide a faster alternative; however, the challenge in enteric fever lies in accurately identifying the appropriate nucleic acid amplification target amid the array of available target antigens.[31] Furthermore, the lower bacterial load in enteric fever, which requires the detection of a minimum of 5 colony-forming units (CFU)/ml, necessitates the optimization of detection methods.

Multiplex platforms for respiratory pathogens

Multiplex assays exhibit significantly greater sensitivity and specificity when compared to rapid immunochromatographic tests and immunofluorescence assays. However, due to their ability to detect both viable and non-viable viruses and bacteria, the results are debatable. While a virus may act as an etiologic agent, it can also be asymptomatically carried or shed for several weeks after the infection has been cured. Consequently, viruses may be identified during the asymptomatic incubation period without necessarily playing a role in the disease. The prolonged shedding of viruses post-infection can further compromise the effectiveness of multiplex platforms in accurately identifying the disease etiology. The complexity is increased by the detection of co-infections,

making it practically impossible to establish which agent is the true causative factor. All these factors contribute to the challenges in identifying the etiologic agent using multiplex platforms.[32]

Influenza RT panel

It covers a comprehensive spectrum of the following viruses: [33]

- Influenza A
- Influenza B
- H1N1
- H3N2
- RSV

The Xpert Xpress panel extends its coverage comprehensively to include COV2, influenza, and RSV.[34] The imminent arrival of an era where microchips can detect up to 500 pathogens by 2026 is on the horizon.

Metagenomics

Metagenomics has emerged as a powerful tool for diagnosing various febrile illnesses. This innovative approach involves the study of microorganisms within a specific environment through functional gene screening or sequencing analysis. Metagenomic investigations focus on exploring microbial diversity, community composition, genetic and evolutionary connections, functional behaviors, and intricate interactions within the environment.[35,36]

Conclusion

The evolution of molecular techniques offers a promising alternative to slower conventional blood culture platforms, allowing for rapid and direct identification of bacterial pathogens. This advancement has the potential to revolutionize clinical decision-making and antimicrobial treatment, complementing traditional diagnostics and stewardship programs. Integrating molecular methods with blood culture diagnostics optimizes infection management, enabling rapid identification of pathogens and relevant antimicrobial resistance genes. Early detection is crucial for prompt initiation of appropriate therapy, guided by factors such as patient severity, symptom duration, co morbidities, and immune status. While accuracy, efficacy, and cost-effectiveness are essential considerations in test selection, effective communication and collaboration with clinicians remain pivotal for maximizing the impact of these diagnostic advancements.

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Mastering Diagnostics: Clinicians' Dilemma

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Introduction

Infectious disease professionals are well-positioned to advocate for the judicious use of antibiotics and other antimicrobials, leading to improved patient health, lower healthcare costs, and the prolonged efficacy of these treatments.[1] However, non-specific symptoms and the diagnostic challenges associated with pyrexia of unknown origin (PUO) present a complex scenario for healthcare professionals. PUO can be caused by a wide range of conditions, including infectious diseases, inflammatory disorders, neoplasms (tumors), and autoimmune conditions. The current paper explores common diagnostic tests, with a particular focus on serological assessments, along with an examination of sampling procedures and optimal timing within routine clinical practice.

Mastering the skill of diagnosis

If a patient is in a state of septic shock or experiencing shock, prioritizing stabilization is paramount before proceeding with the diagnostic procedures. This approach optimizes the chances of a positive outcome, as it addresses immediate life-threatening issues. Collecting a comprehensive medical history and closely monitoring vital signs, oxygen saturation, urine output, and other relevant parameters are essential during the initial investigation. In cases where the patient is stable, healthcare providers may recommend a wait-and-watch approach for 5-7 days. This period allows for the observation of the patient's condition and helps rule out the possibility of viral infections, which may present with similar initial symptoms.

Patients presenting with meningoencephalitis, neutropenia, or immunocompromised status warrant immediate and thorough clinical investigations. This clinical scenario raises concerns about potentially severe and life-threatening conditions, and prompt assessment is crucial. However, there are scenarios where investigations can be bypassed, and treatment can be initiated based on clinical suspicion. These scenarios include suspected cases of leptospirosis, scrub typhus, bacterial pneumonia, cellulitis, acute gastroenteritis with dysentery, and syndromes related to sexually transmitted diseases (STDs). In instances where access to PCR testing is limited, a pragmatic approach involves relying on clinical acumen to guide early treatment interventions in these specific conditions.

Malaria and diagnostic challenges

Discouraging the presumptive antimalarial use in clinical practice signifies a notable shift in medical guidelines and treatment strategies for malaria. Until 2010, the National Drug Policy in India allowed

clinicians to prescribe presumptive chloroquine for managing malaria, contingent on confirming the diagnosis through smear examination. However, the government of India subsequently withdrew the recommendation for presumptive chloroquine, aligning with evolving global practices that prioritize accurate diagnosis.[2] With advancements in diagnostic tools and a greater understanding of the importance of accurate diagnosis, the strategy of presumptive antimalarial use has become less common. Indiscriminate use of antimalarial drugs can contribute to the development of drug resistance in malaria parasites. Using these drugs only when a confirmed diagnosis helps preserve their efficacy.

Clinical effectiveness in suspecting malaria based on symptoms like chills, intermittent fever, splenomegaly, nausea, vomiting, and rigor is reported to be merely 50%. Chandramohan et al. highlighted that clinical algorithms lack the necessary precision to determine whether antimalarial drugs should be administered to children with febrile illnesses.[3] The World Health Organization (WHO) does not recognize clinical malaria as a distinct diagnostic entity. Instead, the WHO emphasizes the importance of laboratory confirmation for accurate malaria diagnosis. Clinical symptoms alone, such as fever and other nonspecific manifestations, are considered insufficient for a definitive diagnosis. Laboratory tests, including rapid diagnostic tests (RDTs) or microscopic examination of blood smears, are recommended to confirm the presence of the malaria parasite. This approach ensures more precise identification of malaria cases, allowing for targeted and effective treatment while minimizing the risk of over diagnosis and unnecessary antimalarial drug administration.[4]

In the context of suspected malaria, a thorough physical examination is crucial before considering additional diagnostic modalities. This examination is essential to rule out other potential causes of febrile illness and provides valuable insights into the patient's overall condition. A comprehensive head-to-toe examination is considered mandatory for all febrile patients before initiating any specific diagnostic tests. While laboratory tests, such as RDTs or microscopic examination of blood smears, are fundamental for confirming malaria, the importance of the initial physical examination should not be understated.

Interpreting Widal agglutination test

The Widal test, introduced over a century ago as a serologic method for detecting typhoid fever, remains entangled in controversies related to the quality of antigens used and result interpretation, especially in areas where the disease is endemic. While interpreting Widal test results, it is crucial to consider the broader clinical context, potential confounding factors, and the limitations of the test. Confirmation through additional diagnostic methods may be necessary for accurate diagnosis, especially in regions with a high prevalence of infectious diseases.[5] The causes of negative and positive Widal agglutination tests are listed below:

Causes of negative Widal agglutination tests

- Absence of *S. Typhi* Infection
- Individuals in a chronic carrier state
- Inadequate bacterial antigen inoculum
- Technical errors or test conducting challenges:
- Previous antibiotic treatment
- Variability in commercial antigen preparation

Causes of positive Widal agglutination tests

- Typhoid fever Infection
- Previous immunization with *Salmonella* antigen
- Cross-reaction with non-typhoidal *Salmonella*
- Inconsistencies and poor standardization in the preparation of antigens
- Infections with other organisms, including malaria and certain enterobacteria
- Diseases like dengue, which share some symptoms with typhoid fever

Due to the aforementioned limitations, Widal is not preferred in clinical practice. The WHO also advises against the routine use of the Widal test due to its inherent challenges and lack of specificity. In endemic regions, a single Widal test is considered to have limited diagnostic significance. The test's reliance on antibody detection and its susceptibility to cross-reactivity with other infections make it less reliable compared to more modern and specific diagnostic methods. As a result, healthcare professionals are encouraged to utilize more accurate and specific diagnostic tools, such as blood cultures, molecular methods, and RDTs, for the diagnosis of typhoid fever.[6]

Potential of Typhi-dot

Typhidot, an ELISA-based method, typically becomes positive within 2-3 days of infection. This test has demonstrated a sensitivity of 100% and specificity of 80% in bacteremic patients. It proves to be a valuable complementary diagnostic tool making it an accessible option for laboratories with limited resources. While Typhidot is a useful addition to the diagnostic arsenal for typhoid fever, it should be noted that it is not effective for diagnosing infections caused by *Salmonella Paratyphi*.[7]

Serologic markers of tropical fever

The differential diagnosis of tropical fevers often involves the use of serological markers to identify specific pathogens. The patterns of common serological markers that aid in the differential diagnosis of tropical fever are illustrated in figure 1.

Fig. 1: patterns of common serological markers for tropical fever

	Dengue	**Typhoid**	**Lepto/Scrub**	**Malaria**
HB	↑ HB	Normal	Normal	Normal/↓
TC	Normal/↓	Normal/↓	Leucocytosis	Normal
DC	Normal	Eosinopenia	Neutrophilic	Normal, Monocytosis
Platelets	Normal/↓	Normal	Normal/↓	Normal/↓
SGOT, SGPT Alk, GGTP	SGOT/PT↑	SGOT/PT↑	Alk Pho, GGTP ↑	Alk Pho, GGTP ↑
TB/DB/IDB	Normal ↑ TB/DB	Normal	↑ TB/DB	↑ TB/DB

While a low eosinophil count is not specific to typhoid and can be observed in various infectious and inflammatory conditions, its absence can prompt healthcare professionals to consider typhoid fever in the differential diagnosis. The absolute eosinophil count is often considered alongside other laboratory parameters and clinical symptoms to build a comprehensive diagnostic picture. A retrospective chart review of enteric fever in Mumbai by Jog et al. reported the incidence of absolute eosinopenia in 77% of the subjects.[8]

Biomarkers in ICU

Procalcitonin is a useful biomarker in the ICU settings, particularly for the management of sepsis and bacterial infections. Procalcitonin levels tend to rise early in response to bacterial infections, often before clinical symptoms become apparent. Elevated procalcitonin levels have been associated with increased morbidity and mortality in critically ill patients. Its integration into clinical decision-making processes can help optimize patient care, reduce unnecessary antibiotic use, and contribute to more individualized treatment strategies in critically ill patients.[9]

A prevalent example of indiscriminate culture collection in mechanically ventilated patients is the implementation of a 'pan-culture' workup in cases of new fever or leukocytosis. This approach lacks clinical relevance in ICU settings. Respiratory cultures are routinely obtained as part of a comprehensive workup for infection, even in the absence of clear radiographic or clinical evidence of pneumonia. It is crucial to acknowledge that recovering bacteria from the respiratory tract under these circumstances is unlikely to indicate pneumonia. However, this practice may inadvertently prompt unwarranted antibiotic treatment based on positive culture results, especially in patients who do not exhibit localizing pulmonary features of infection.[10]

Conclusion

The selection of appropriate tests for acute fever may depend on the day of illness and the patient's condition, emphasizing a tailored approach for optimal diagnostic accuracy. The practice of 'pan culture,' involving indiscriminate collection of cultures without clear clinical indications, is discouraged. The interpretation of diagnostic tests should be closely correlated with the patient's clinical presentation, emphasizing a comprehensive evaluation that considers medical history, physical examination, and other relevant diagnostic findings. This individualized approach helps ensure that tests are relevant and contribute to accurate diagnosis and effective management while aligning with antibiotic stewardship principles to prevent unnecessary antibiotic use and minimize the risk of antibiotic resistance.

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Mastering Diagnostics: Clinicians' Dilemma

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Introduction

Clinicians navigate through a myriad of diagnostic challenges and each patient represents a unique puzzle that requires careful consideration of the delicate balance between comprehensive diagnostic assessments and practical, patient-centered care. This paper delves into the intricacies of diagnostic decision-making through real-world examples, emphasizing the importance of judiciously utilizing diagnostic investigations.

Significance of judicious early investigations

The significance of early investigations cannot be overstated, yet it is crucial to approach them with a thoughtful and discerning mindset. While the reflex to request investigations is understandable, it is essential to recognize that investigations should complement rather than replace clinical diagnosis. Therefore, the initial step is to systematically narrow down possibilities through clinical evaluation before resorting to tests. Decision-making regarding which tests to request is a critical aspect, emphasizing the importance of a targeted and tailored approach.[1]

Contrary to a common misconception, early tests may not always accelerate the diagnostic process and can be of limited value if performed too hastily. Instead, investigations should be strategically employed to confirm clinically suspected diagnoses. It is also imperative to acknowledge the inherent limitations of investigations. Positive test results may not necessarily indicate active disease, as observed in tests like tuberculin or serological tests. In addition, commonly used tests might uncover minor abnormalities that may not be directly relevant to the clinical condition under investigation.

A noteworthy consideration is that certain test abnormalities might signify a general phenomenon, such as inflammation (e.g., elevated ESR). To extract meaningful insights from test results, it is essential to correlate them meticulously with the overall clinical profile. While investigations play a crucial role in medical practice, their utility is maximized when integrated judiciously into a comprehensive clinical assessment, ensuring a more accurate and clinically meaningful diagnosis.[2]

Scenarios requiring clinical management without lab investigations

Some of the clinical scenarios where judgment and immediate intervention are required over waiting for lab results are listed below:

- Acute life-threatening situations
- Clinical diagnosis is evident
- Time-critical conditions
- Resource constraints
- Clinical monitoring is adequate

Case 1: Cautious interpretation of CBC

A 4-year-old boy presented with a persistent high fever unresponsive to paracetamol. Concerned about a potential bacterial infection, a complete blood count (CBC) was ordered, revealing mild elevations, prompting the initiation of antibiotic therapy by the family physician. The next day, he presented with new symptoms, a running nose and cough, indicative of a potential viral component. Despite the antibiotic intervention, the fever persisted, leading to a re-evaluation of the initial diagnosis. Over the next 2-3 days, the fever gradually subsided, highlighting the dynamic nature of febrile illnesses.

The case shows that ordering a CBC within the first two to three days of illness may not provide conclusive diagnostic information. Neutrophilic leukocytosis, a common finding in CBC, is not synonymous with acute bacterial infection. Viral infections, categorized as 'acute,' can also elicit a neutrophilic response, especially in the early stages. Importantly, the absence of neutrophilic leukocytosis does not rule out all bacterial infections; it simply signifies acute stress, which can occur in various conditions such as asthma or burns and even in the early stages of viral fevers. Conditions like acute bacterial infections, including typhoid, may present with leucopenia, further emphasizing the limitations of CBC in specific diagnoses. Notably, CBC is not a reliable tool for diagnosing chronic infections like tuberculosis. Clinicians should exercise caution in interpreting CBC results and consider the broader clinical context for accurate diagnostic assessments.[3]

Case 2: Appropriate use of throat culture and antibiotic

A 1-year-6-month-old male child presented with a history of fever, cough with rhinorrhea for two days, red eyes, and diarrhea. There was no exanthema, but a notable family history revealed a similar case. The ideal option considered in such case is a symptomatic management and follow-up since the provisional diagnosis indicates a viral infection. Clinical diagnosis of viral infections could typically be made based on clinical manifestations alone, often obviating the need for investigations and warranting symptomatic treatment. Viral infections, especially common ones, tend to show a declining trend by day 3 or 4.

However, due to the persistence of symptoms, a throat swab culture was sent, and the child was initiated on amoxicillin. After 2 days, there was slight improvement, but the throat culture revealed β-hemolytic streptococci, resistant to penicillin. Consequently, the antibiotic was changed to co-amoxiclav.

A throat culture is considered the gold standard or rule-out test for diagnosing strep pharyngitis. Although a negative result has a very high negative predictive value, false-negative rates range from 5% to 10%. On the other hand, a positive result does not distinguish acute streptococcal pharyngitis from asymptomatic carriage.[4] Throat cultures are typically sent only for clinically suspected streptococcal pharyngitis. While there is a delay of 18-48 hours for results, it is deemed necessary for

guiding appropriate antibiotic therapy, and this delay, up to 9 days, does not compromise the ability to prevent rheumatic fever. The case underscores the importance of clinical judgment, considering both symptomatic management and diagnostic investigations in specific clinical scenarios.

Case 3: Interpretation of stool analysis

A 10-month-old child presented with a two-day history of illness characterized by frequent vomiting (6-7 times a day), fever, and a high frequency of watery stools (12-15 times a day) with large quantities. The child was on a combination of breastfeeding and a weaning diet. Due to the severity of symptoms, the child was admitted and treated with intravenous fluids, inj. amikacin, and inj. metronidazole. Stool examination revealed 5-6 WBCs, 2-3 RBCs, and cysts of *Entamoeba histolytica*. The presence of *E. histolytica* cysts alone is not necessarily an indication for anti-amoebic treatment, as these cysts can be seen as commensals. To confirm amoebic infection, it is crucial to demonstrate trophozoites in a fresh stool sample.[5]

Furthermore, the case highlighted the perspective that routine stool examination may not be required in a child with diarrhea, as the majority of cases are viral. In such instances, the focus should be on assessing and managing the child's hydration status rather than solely relying on stool examination. This underscores the importance of a targeted and clinically guided approach in the management of pediatric diarrheal illnesses.

Case 4: Significance of blood culture in outpatient settings

A 5-year-old child presented with a history of fever persisting for five days, with a rising trend in temperature. The CBC results showed a normal range, with Hb at 12.3 gm%, TLC at 6100/mm^3, and a differential count of N 53%, L 43%, M 2%, E 0%, and B 2%. Urine routine microscopy yielded normal results. However, the ELISA test was negative. Typhidot IgG was positive, while IgM was negative. Blood culture results were awaited at this point.

The interpretation of Typhidot results revealed the limitations of this serologic test. The classical Typhidot measures both IgG and IgM against a 50 KD outer membrane protein, with a sensitivity ranging from 70-100% and specificity from 43-90%.[6] The child's Typhidot result (IgG+ve & IgM–ve) raised challenges in differentiation between acute and convalescent infection, considering factors like endemicity, past infection, and current reinfection. Widal test, a widely used serologic diagnostic method for typhoid fever, has several limitations. One notable drawback is its poor specificity and reproducibility, posing challenges in accurate diagnosis. Approximately 30% of cases that are culture-positive for typhoid may yield negative results. Moreover, the test tends to become positive only after the first week of illness, limiting its utility in the early stages. To enhance reliability, titers greater than 1/160 or rising titers are considered more indicative. The tube test is preferred over the slide test for improved accuracy.[7]

Upon awaiting the blood culture reports, the child was initiated on empirical oral cefixime therapy. Subsequently, the 48-hour culture report revealed the presence of *Salmonella Typhi*. The treatment plan was then adjusted based on the sensitivity pattern derived from the culture results.

Salmonella Typhi and *Paratyphi* are recognized as among the most prevalent bacterial pathogens, known for causing enteric fever. Their ability to grow easily makes them common targets for detection through blood culture. It is considered ideal to perform blood culture before initiating antibiotic therapy,

as this enhances the chances of isolating and identifying the causative microorganism accurately. Even in cases where a patient has been exposed to antibiotics earlier, conducting a blood culture is still imperative. This practice helps overcome the potential interference of prior antibiotic treatment, ensuring a more reliable diagnosis.

Factors influencing blood culture sensitivity

Blood culture, a crucial diagnostic tool, requires meticulous precautions to ensure accurate results. The factors influencing the blood culture specificity and sensitivity are listed below:[8]

- **Timing of collection:** Sensitivity is highest during the first week of illness (approximately 90%), underlining the importance of timely collection to maximize diagnostic accuracy.
- **Volume of blood drawn**: Adequate blood volume, such as 5ml in children and 10ml in adults, is crucial for enhancing the sensitivity and reliability of blood culture results.
- **Number of blood culture sets:** Utilizing multiple sets of blood cultures increases the chances of isolating and identifying pathogens, contributing to higher sensitivity.
- **Site of blood collection:** The site chosen for blood collection can impact the success of the culture. Appropriate selection enhances the accuracy of the results.
- **Collection procedure:** Proper techniques during the blood collection procedure are essential for maintaining the integrity of the specimen and optimizing the sensitivity of blood culture.
- **Patient's antibiotic status:** The patient's history of antibiotic therapy significantly influences blood culture results. Collection before antibiotic exposure is imperative for accurate diagnosis.
- **Blood-to-broth ratio:** Maintaining an optimal ratio of blood to broth (1:5 to 1:10) is crucial for supporting microbial growth and improving the sensitivity of blood culture.
- **Immediate inoculation:** Inoculating the collected blood into the culture media immediately after collection is essential for preserving the viability of microorganisms and obtaining reliable results.
- **Transport conditions:** Proper transportation of the culture bottle at room temperature is necessary to prevent changes in the microbial composition and maintain the accuracy of results.
- **Nalidixic acid sensitivity:** Checking for nalidixic acid sensitivity is important for enhancing the specificity of blood culture results, especially in regions with antibiotic-resistant strains.

Case 5: Significance of urine culture in UTI

A 3-year-old child presented with a 4-day history of undifferentiated fever, lacking localizing signs, and exhibiting a normal physical examination. Clinical evaluations included a CBC and a test for malarial parasites, both of which returned negative results. However, due to the ongoing fever and to explore potential causes, a urine routine examination was conducted, revealing 10 pus cells/cumm.

Subsequent urine culture showed the growth of *E. coli* with a colony count exceeding 10^5 CFU/ml. and appropriate antibiotic therapy was promptly initiated.

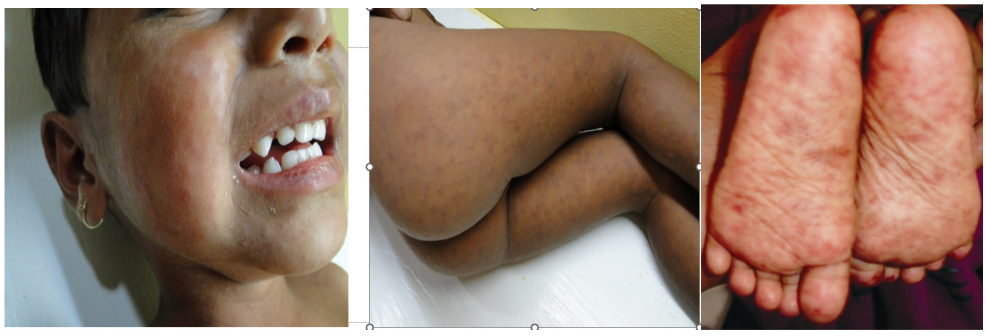
Prior to urine culture, bedside tests such as the nitrite test and leucocyte esterase test can be performed to aid in UTI diagnosis. The nitrite test, which is based on the reduction of nitrate to nitrite by the nitrate reductase enzyme, demonstrates a sensitivity and specificity of 53% and 98%, respectively. It is important to note that sensitivity is lower in infants and less reliable in young boys due to the presence of bacteria in the preputial area. The leucocyte esterase test, utilizing the chloro-acetate stain, reacts with the leukocyte esterase enzyme, demonstrating a sensitivity of 83% and specificity of 78%. This test is considered more accurate than microscopy, as the enzyme activity persists even after white cells have disintegrated.[9]

Regarding urine collection methods, the clean catch midstream approach is commonly favored as the best method. Suprapubic aspiration is an alternative for newborns and infants, while urethral catheterization is another option. However, bag collection, although less desirable, is associated with higher rates of false positivity. Choosing the appropriate method is crucial for accurate UTI diagnosis.[10]

Case 6: Appropriate timing of mycoplasma testing

A 5-year-old girl presented with an 8-day history of fever, a rash that developed over the past 4 days, irritability persisting for 4 days, and leg pain emerging 2 days ago. The child had been administered co-amoxiclav for 5 days, received anti-malarial treatment for 3 days, and was given paracetamol. Upon investigation, the hemoglobin level was found to be 9.2 g/dL, WBC count was 14,500/cu.mm with a differential of P68, L32, and platelet count was 146,000/cu.mm. The Widal test was negative, and urine routine showed no abnormalities. The child hailed from a rural area, had a history of contact with animals, and no reported insect bites. On examination, the child was febrile with a temperature of 102°F. A maculopapular rash was observed over the extremities, trunk, face, palms, and soles, accompanied by leg edema (Fig. 1). Due to urticarial rash after three doses of vancomycin, the child was shifted to tertiary care for further management.

Fig.1: Presence of maculopapular rash over the extremities, trunk, face, palms, and soles

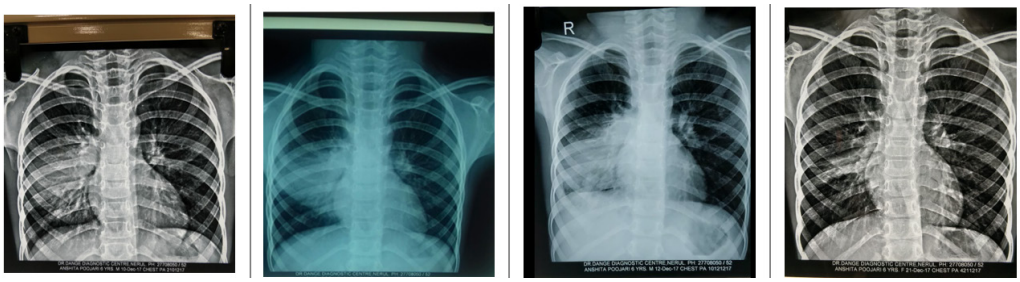


Abdominal examination revealed a 2 cm liver and a 1 cm spleen. Malarial antigen and dengue NS1 antigen tests were negative, and Leptospira IgM test was also negative. Blood culture showed no growth, but USG abdomen indicated moderate hepatosplenomegaly.

Further serological tests revealed a positive ELISA for spotted fever and a positive Immunofluorescence assay for *Rickettsia conorii* (>640). Hyponatremia during the first 10 days was noted, consistent with rickettsial fever. Serological tests for rickettsia were based on IgM antibodies, and a significant increase in IgG antibodies between two consecutive samples taken 1-4 weeks apart was observed.

Intravenous ceftriaxone was initiated, but persistent fever after 72 hours led to the addition of vancomycin and azithromycin. The diagnosis was confirmed by a CT scan, and mycoplasma IgM became positive. The child was subsequently initiated on macrolides, and X-rays (Fig. 2) showed significant improvement.

Fig. 2: Improvement in X-rays noted following macrolide treatment



Testing for mycoplasma is indicated in various scenarios, including cases of pneumonia, especially in hospitalized children. It is particularly considered when there is presumed viral pneumonia not responding to supportive treatment or bacterial pneumonia not responding to beta-lactam antibiotics. Additionally, testing is recommended in cases with extra-pulmonary manifestations. However, in the outpatient setting for community-acquired pneumonia, empirical treatment is often initiated without specific testing.[11]

Different testing methods available for mycoplasma are as follows:[12]

Polymerase chain reaction (PCR): Highly sensitive but may not reliably distinguish active *M. pneumoniae* infection from coinfection with other pathogens or from asymptomatic carriage.

IgM testing: Used as an adjunct to PCR or as an alternative. IgM titers typically rise around 7 to 9 days after infection, peak at 3 to 6 weeks, and can persist for months. A significant diagnostic factor is a four-fold or greater increase in titer in paired sera separated by 4 weeks.

Cold agglutinin testing: Non-specific and has low sensitivity. It's important to note that cold agglutinins can also occur in other conditions, such as Epstein-Barr virus (EBV) infections.

Case 7: Relevance of respiratory panels

A 4-year-old child presented with a high fever and cough persisting for two days. On examination, congested eyes, tachypnea, and bilateral wheezing were noted, with a saturation level of 88%. Initial blood work revealed a hemoglobin level of 11.8 g%, WBC count of 5460 /cu.mm, and platelet count of 2 lakhs/cu.mm. The CRP level was elevated at 16, prompting the initiation of oseltamivir.

A respiratory multiplex PCR panel was conducted, revealing the presence of adenovirus. Consequently, oseltamivir was discontinued as it does not act on adenovirus infections. The PCR panel also detected *Streptococcus pneumonia,* raising the question of coinfection. However, it is important to note that approximately 30% of healthy children may carry *Streptococcus pneumonia* in their upper respiratory tracts without causing infection. Lower respiratory tract samples are considered more reliable for bacterial identification. While respiratory panels offer rapid and broad-spectrum detection of respiratory pathogens, clinicians must be aware of the following limitations:[13]

- Panels can only detect targets for which specific PCR primers exist. Organisms without established primers, such as *Stenotrophomonas maltophilia*, may go undetected.
- The presence of a resistance gene does not necessarily correlate with the organism detected, complicating the interpretation of results.
- Unlike cultures, respiratory panels cannot provide a comprehensive antibiogram, limiting their utility in guiding antibiotic therapy.
- Distinguishing between colonizing organisms and true pathogens, especially for bacteria like *Streptococcus pneumonia, Hemophilus influenzae* type b (Hib), *Moraxella*, etc., can be challenging.
- Panels can only detect the presence of nucleic acid, making it impossible to differentiate between living and dead organisms.

Conclusion

Establishing a provisional diagnosis can be achieved even in the absence of physical signs by carefully analyzing the fever pattern and documenting relevant information. Adopting a systematic approach, incorporating focused examinations, and employing structured analysis significantly contribute to formulating a probable diagnosis. A shift towards advising relevant laboratory tests solely to confirm a diagnosis is crucial. This approach not only instills confidence in medical decision-making but also diminishes over dependency on extensive laboratory investigations. It is essential to recognize that investigations serve as valuable 'assistants' in the diagnostic and management process, while clinicians remain the ultimate 'masters' who make the final decisions.

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Fever and Fungal Infections

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Introduction

Candida species are prevalent among opportunistic fungal infections and often lead to bloodstream infections. These infections typically respond well to antifungal medications such as fluconazole or echinocandins. On the other hand, *Aspergillus* species commonly cause invasive mold infections, particularly in older adults. These infections primarily manifest as pulmonary and sinus infections, carrying a high risk of mortality.[1, 2] To effectively manage complex fungal infections, it is essential to focus on collecting comprehensive patient history, considering radiological and diagnostic features, and formulating appropriate management strategies. The present paper aims to highlight the relevance of these aspects in the early identification and successful treatment of fungal infections.

Importance of taking history in fungal infections

Risk factors play a pivotal role in medical assessments, particularly when dealing with invasive fungal diseases. Collecting a comprehensive patient history holds immense significance as it serves as the cornerstone for understanding individual risk factors. These factors are significant in tailoring the risk assessment for each patient. Typical risk factors for invasive fungal diseases include:[3]

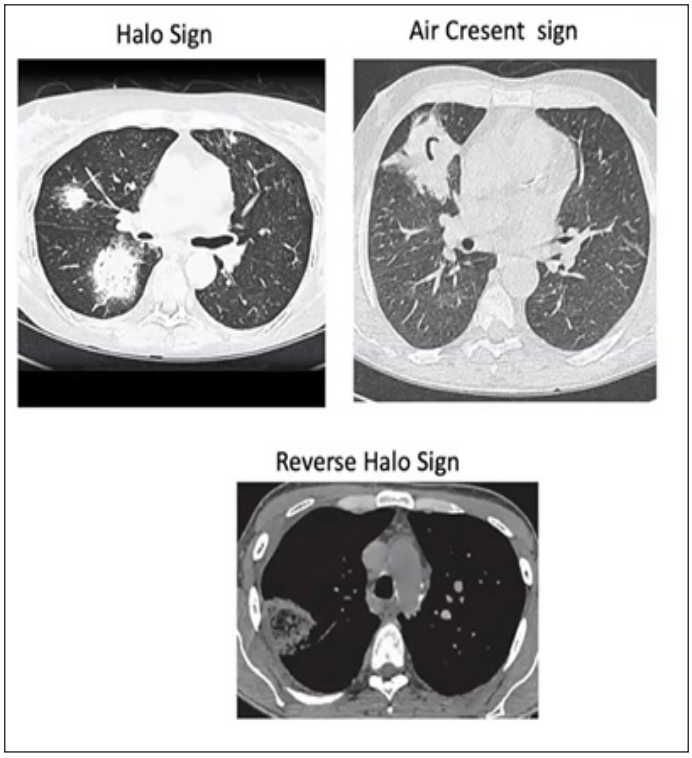
- Recent history of neutropenia
- Hematologic malignancy
- Allogeneic stem cell transplant
- Solid organ transplant
- Prolonged use of corticosteroids
- Treatment with immunosuppressants
- Acute graft versus host disease

Radiological features

Radiological imaging, especially CT scans, is integral in identifying and managing potentially severe conditions and in subsequent monitoring. One specific radiological sign to note is the halo sign, characterized by a ground-glass opacity surrounding a nodule, mass, or consolidation in the lungs.

This sign typically suggests invasive pulmonary fungal infections, notably aspergillosis, although various non-fungal infections can also produce similar manifestations. Other signs that can also indicate invasive fungal infection include air crescent and reversed halo signs.[4] The reversed halo sign is frequently associated with pulmonary mucormycosis. An air crescent signifies a nodular opacity within the lung that has undergone infarction, resulting in retracted lung tissue forming crescent-shaped or circular cavitations. This characteristic can sometimes be observed on chest radio-graphs as a crescent-shaped or circumferential area of radiolucency within a parenchymal consolidation or nodular opacity (Fig. 1).[5]

Fig. 1: Radiological features in CT scan indicating halo, air crescent, and reversed halo signs



Diagnostic significance of culturing molds and microscopic identification in respiratory specimens

Culturing molds like *Aspergillus, Fusarium, Scedosporium species, or Mucorales* from samples such as sputum, bronchoalveolar lavage, bronchial brushings, or aspirates serve as significant diagnostic indicators. Additionally, the microscopic identification of fungal elements in these samples points toward the presence of molds. These findings are crucial in diagnosing fungal infections and can substantially contribute to the identification of specific mold species causing respiratory or pulmonary infections. Such detailed analyses of respiratory specimens are important in providing a comprehensive understanding of the fungal pathogens present, aiding in accurate diagnosis and targeted treatment strategies.[3]

Detecting a positive culture holds significant importance in identifying invasive fungal infections. However, in individuals predisposed to such infections, the presence of a cultured fungus in samples like bronchoalveolar lavage (BAL) or sputum does not invariably indicate an invasive fungal infection. It could merely signify colonization within the respiratory tract. Hence, it is crucial to assess the patient's medical history, predisposing factors, and any underlying immunocompromising conditions for a comprehensive diagnosis.

Galactomannan

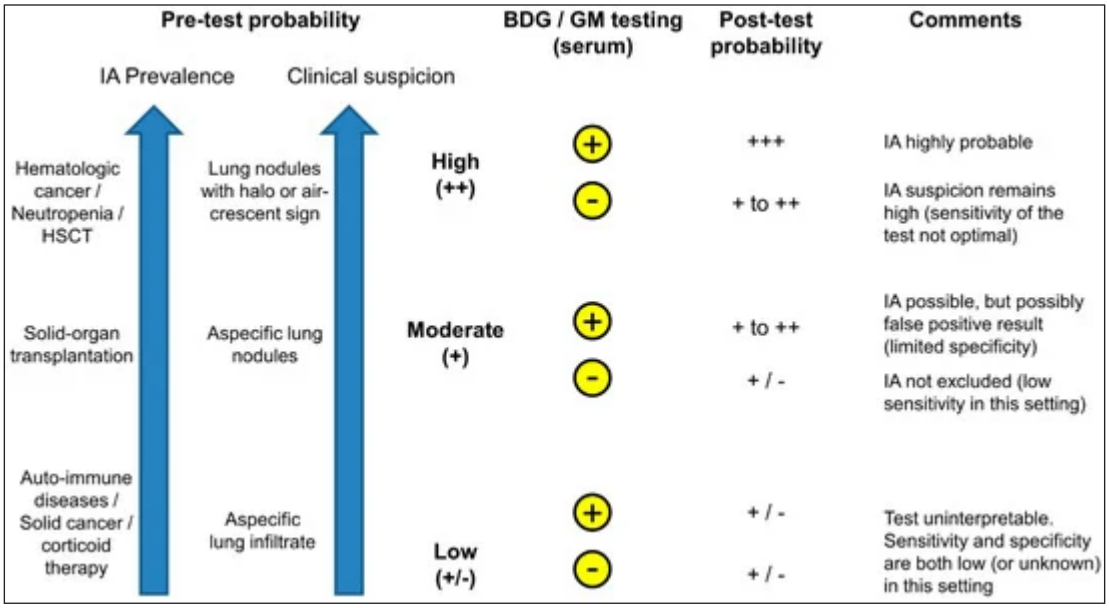
The identification of serum galactomannan (GM) serves as a pivotal microbiological diagnostic criterion for fungal infections, especially in neutropenic patients. This diagnostic approach aligns with the guidelines set forth by the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG). In standard practice, the cutoff value for serum GM detection is typically established around 0.5. Furthermore, the guidelines from 2016 issued by the Infectious Diseases Society of America advocate the utilization of bronchoalveolar lavage fluid (BALF) GM detection. This testing method provides substantial and high-quality evidence, especially in the context of neutropenic patients.[6]

β-D-glucan

The detection of fungal antigens in bodily fluids, such as *Cryptococcus* capsular polysaccharide, *Histoplasma* antigen, GM, and β-D-glucan (BDG), holds significant clinical value, particularly for presumptive diagnoses of invasive fungal infections. BDG, in particular, is an appealing antigen due to its presence across a wide spectrum of fungal agents, including commonly encountered ones like *Candida spp., Aspergillus spp*., and *Pneumocystis jirovecii.* BDG constitutes a key element of the surface structure of *P. jirovecii* and has emerged as a potential marker for identifying *Pneumocystis* pneumonia.[7]

Both galactomannan and BDG tests are valuable; however, they have limitations such as significant false positives, cross-reactivity, and potential instances of false negatives. The interpretation of fungal biomarkers heavily relies on the clinical context, often termed pre-test probability. Before requesting galactomannan or BDG testing, the physician should assess the likelihood of invasive aspergillosis (IA) based on the prevalence of IA in the patient population and the specific clinical signs and symptoms exhibited by the individual. This evaluation aids in establishing a more accurate interpretation of test results (Fig. 2).[8]

Fig. 2: Recommended algorithm outlining the utilization of GM and BDG testing in diagnosing IA in clinical practice



Source: Lamoth F. Galactomannan and 1,3-β-d-Glucan Testing for the Diagnosis of Invasive Aspergillosis. Journal of Fungi. 2016 Sep;2(3):22.

Overview of antifungal agents in clinical practice

The three primary classes of antifungal agents commonly used in clinical practice are azoles, polyenes, and echinocandins. Azoles encompass fluconazole, voriconazole, posaconazole, itraconazole, and isavuconazonium. Fluconazole demonstrates efficacy against *Candida* species but lacks activity against *Aspergillus* and *Mucormycosis*. Itraconazole is effective against many *Candida* strains and displays activity against Aspergillus but not against fungi like *Mucormycosis*. Voriconazole exhibits activity against various *Candida* and *Aspergillus* species but not against *mucormycosis*. Newer azoles such as posaconazole and isavuconazole show activity against a broad spectrum of *Candida* strains, *Aspergillus*, and *Mucormycosis*.

The polyenes class includes amphotericin B deoxycholate, liposomal amphotericin B, and amphotericin B lipid complex. These agents are effective against numerous *Candida* species, *Aspergillus*, and *Mucormycosis*. Echinocandins, such as anidulafungin, caspofungin, and micafungin, exhibit potent activity against *Candida* and *Aspergillus* species but lack efficacy against Mucormycosis.[9] The drug of choice for treating *Aspergillus* is voriconazole, while isavuconazole is an alternative option.

Candidiasis

Candidiasis encompasses a spectrum of manifestations, from colonization in the respiratory and gastrointestinal tracts to mucosal diseases like oral and vaginal infections. While colonization commonly occurs in these anatomical sites, leading to asymptomatic carriage, mucosal disease manifests as localized infections. However, in certain scenarios, *Candida* can breach barriers, causing invasive

candidiasis characterized by the presence of infected thrombi, particularly in cases of endocarditis or vascular access devices. In severe cases, candidemia occurs, signified by positive blood cultures, indicating the dissemination of *Candida* species within the bloodstream, often associated with systemic symptoms and potential complications.

Factors predisposing individuals to disseminated candidiasis encompass a range of contributors. These include exposure to broad-spectrum antibiotics, the presence of indwelling intravenous catheters, the use of hyperalimentation fluids, a history of gastrointestinal or thoracic surgeries, neutropenia, low birth weight in neonates, patients undergoing burn care, individuals utilizing intravenous heroin, and those who have undergone solid organ transplantation while on immunosuppressive therapy.[10]

Spectrum of Candida infections

Candida is responsible for various mucous membrane infections like thrush, vaginitis, esophagitis, balanitis, and gastrointestinal candidiasis. Skin issues include diaper rash, folliculitis, and signs of widespread candidiasis. Identifying these infections through clinical examination based on their appearance is crucial. One of the most commonly diagnosed severe infections in hospitalized patients is candidemia. This infection can seriously impact multiple organs such as the blood, heart, brain, eyes, bones, and more. Deep-seated candidiasis affects organs profoundly, including the central nervous system (like meningitis or abscesses), extremely rare cases of pneumonia, endocarditis, hepatosplenic candidiasis, peritoneal candidiasis (seen in surgical patients), bone and joint infections, pyelonephritis, and ocular complications. Diagnosing these often requires invasive sampling methods.[11,12]

Indicators of candidemia

The indicators of candidemia are as follows:

- Prolonged hospital stay
- Exposure to broad-spectrum antibiotics
- Presence of lines
- Recent surgery involving the gastrointestinal tract in some way
- Neutropenia
- High colonization

Presentation

- Fever with major localization
- Septic shock with any of the above risk factors, negative procalcitonin; negative cultures and not improving on anti-bacterial cover

Diagnosis of candidiasis

Blood cultures

The gold standard for blood cultures involves utilizing the conventional bacterial antigen testing and culture (BACTEC) system with standard and fungal culture bottles. It is crucial to emphasize the significance of the blood volume submitted for culture. Specifically, sending 40 ml of blood is recommended, even though the yield may not surpass 50%.[13]

Non-culture-based methods

Various non-culture diagnostic methods for invasive candidiasis serve as supplementary tools to traditional cultures. Tests like Mannan and anti-Mannan IgG, BDG, T2*Candida* nanodiagnostic panel, and PCR are now accessible for clinical purposes. BDG, while indicating positivity in *Candida, Aspergillus*, and pneumocystis pneumonia, requires at least two tests in intensive care patients to detect candidemia effectively. Despite being a reliable test, BDG is comparatively costlier and necessitates repeated administration for early identification of candidemia.[14] The pros and cons of culture-based, and non-culture-based diagnostic methods are listed in table 1.

Table 1: Pros and Cons of culture-based, and non-culture-based diagnostic methods

Culture-based	Non-culture based
Pros • Gold standard • Identify the species	**Pros** • Rapid • Result available in a few hours
Cons • Turnaround time of 2-5 days • Low yield	**Cons** • Not accurate • Data is still in the making • Does not identify species (Except T2 *Candida*) • Expensive

Management of Candidemia

The recommended initial therapy is echinocandin. However, for individuals not in critical condition and considered unlikely to have fluconazole-resistant *Candida,* an acceptable alternative consists of fluconazole administered intravenously or orally at a daily dose of 800 mg (12 mg/kg). It is advisable to transition from an echinocandin to fluconazole, usually within a 5 to 7-day window, for patients exhibiting clinical stability. This transition is recommended for those with isolates susceptible to fluconazole and negative repeat blood cultures. Treatment duration spans two weeks for negative cultures. For candidemia lacking metastatic complications, the recommended minimum duration extends to two weeks after confirming the elimination of *Candida* from the bloodstream, given that neutropenia has resolved along with symptoms associated with candidemia.[15]

The distinguishing features of *Candida* from other culture types are listed below:

Candida's presence should be disregarded in cultures if:

- *Candida* positivity in respiratory cultures (such as sputum, tracheal tube, or endotracheal secretions), including BAL.
- *Candida* identified in urine cultures.

Candida's presence should not be overlooked in cultures if:

- *Candida* is present in blood cultures.
- The presence of *Candida* in otherwise sterile fluids like CSF, ascitic fluid, and pleural fluid.
- Detection of *Candida* in pus samples.

When to suspect endemic fungi?

The likely presentations to suspect endemic mycoses are:

- Fever of unknown origin
- Chronic pneumonia
- Subacute to chronic meningitis
- Cutaneous findings
- Lymphadenopathy

Dimorphic fungi, including *Histoplasma capsulatum, Coccidioides spp., Paracoccidioides spp., Blastomyces dermatitidis, Sporothrix schenckii, Talaromyces (Penicillium) marneffei, and Emmonsia* spp., are limited to specific geographic regions and are responsible for endemic mycoses. Therefore, it is crucial to gather travel history, as it significantly aids in identifying the particular type of endemic mycosis.[16] In India, three primary types of endemic mycosis infections are predominant namely histoplasmosis, penicilliosis, and sporotrichosis. Histoplasmosis is primarily reported in the northeastern region, notably in Assam and Tripura. Other states where cases have been identified include West Bengal, Jharkhand, and Tamil Nadu.

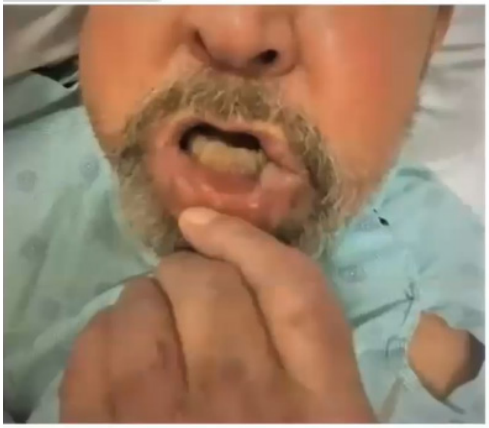
Diverse causes of granulomas beyond tuberculosis

Not all granulomas signify TB. Even if a biopsy reveals a granuloma, it does not necessarily indicate TB. Various infections, including TB, leprosy, fungal infections like *histoplasmosis, cryptococcosis, sporotrichosis, non-TB mycobacteria, Brucella*, cat scratch disease, as well as non-infective conditions such as sarcoidosis, Crohn's disease, vasculitis, Kikuchi disease, hypersensitivity pneumonitis, foreign body reactions, and Whipple's disease, can generate granulomas.

Histoplasmosis is not exclusive to immunocompromised individuals. It is caused by inhaling spores of *Histoplasma capsulatum* found in soil, especially in areas with bird or bat droppings. While those with weakened immune systems are more susceptible to severe forms of the infection, even immunocompetent individuals can contract histoplasmosis if they inhale sufficient amount of spores.

However, their symptoms are typically milder, and the infection may resolve on its own without specific treatment. Signs and symptoms indicative of histoplasmosis are listed in table 2.

Table 2: Signs and symptoms indicative of histoplasmosis



Symptoms and signs
Fever >100°F
Weight loss
Hepatosplenomegaly
Oral ulcers
Cough
Lymphadenopathy
Skin hyperpigmentation
Splenomegaly
Skin lesions (papules, nodules)

Histoplasmosis is diagnosed through either culture testing or the identification of typical histopathological features. Another valuable diagnostic tool is the detection of *histoplasma* antigen in urine or serum. Following the implementation of the antigen test, there was an almost threefold rise in accurate diagnoses.[17] *Histoplasma* treatment is initially started with amphotericin B and later three to six months of itraconazole.

Sporotrichosis

Sporotrichosis, cause by the dimorphic fungus *Sporothrix schenckii*, has a global presence, particularly in tropical and subtropical regions. Infection commonly arises from accidental introduction of the fungus via soil, plants, or organic matter. Activities like floriculture, agriculture, mining, and woodwork are frequently linked to this fungal infection. While zoonotic transmission has been sporadically documented, it mostly occurs in isolated cases or small outbreaks.[18] The diagnosis involves culturing the affected area and performing a biopsy. For cutaneous sporotrichosis, treatment typically comprises a 2-4 week course of itraconazole. In contrast, extracutaneous sporotrichosis necessitates initial treatment with amphotericin B followed by a regimen of itraconazole for a minimum duration of one year.

Talaromycosis

Talaromycosis (also known as penicilliosis) emerges as an opportunistic fungal infection, often observed in immuno-compromised individuals. This infection, caused by fungus *Talaromyces marneffei*, is recognized as an invasive mycosis endemic to tropical and subtropical regions in Asia. It prevails across Southeastern and Eastern Asia, encompassing countries such as Thailand, Northeast India, China, Cambodia, Myanmar, and Nepal. The symptoms manifest as fever, general discomfort, weight loss, cough, swollen lymph nodes, difficulty breathing, liver and spleen swelling, diarrhea, abdominal pain and skin lesions The primary antifungal agents employed for treatment are amphotericin B and itraconazole.[19,20]

Conclusion

The recognition that not all granulomas necessarily indicate tuberculosis emphasizes the need to explore alternative etiologies. This underscores the importance of maintaining a broad clinical perspective, particularly in immunocompromised individuals. In cases of chronic meningitis, considering cryptococcal meningitis as a differential diagnosis is crucial. Additionally, a cautious interpretation of fungal biomarkers is essential, requiring thorough scrutiny and acknowledgment of potential limitations. These biomarkers should be assessed in conjunction with clinical findings, imaging, and other diagnostic modalities for accurate diagnosis and appropriate treatment decisions. Obtaining information about the patient's travel history provides valuable insights into potential exposures, aiding in the identification of specific pathogens and guiding a more targeted diagnostic approach.

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Fever in the Emergency Room: Diagnosis, Red flags, and Management

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Introduction

Fever accounts for approximately 15% of emergency visits among the elderly and around 5% among adults.[1] In the emergency room, fever often emerges from various infectious sources, with tropical infections leading the list. These are followed by pneumonia, abdominal infections, meningitis, urosepsis, infective endocarditis, and cases involving immunocompromised patients. Alongside infectious causes, noninfectious contributors such as heat stroke, thrombotic thrombocytopenic purpura, immune thrombocytopenia, disseminated intravascular coagulation, macrophage activation syndrome, massive transfusion, liver diseases, malignant hypothermia, pancreatitis, poisoning, neuroleptic malignant syndrome, and stroke can also play significant roles. In India, prevalent tropical infections include malaria, dengue fever, scrub typhus, enteric fever, leptospirosis, and influenza.[1,2]

Challenges encountered by clinicians

In the high-stakes environment of the emergency room, clinicians face unique challenges, particularly the symptom overlaps among tropical infections, which complicate rapid and accurate identification during the initial presentation. This uncertainty often leads to the initiation of empiric therapy as a preemptive measure, adopting a 'hit wide and hit early' approach. The urgency to begin treatment rapidly is crucial, aiming to cover a broad spectrum of potential pathogens until a definitive diagnosis is confirmed. Once the specific infection is identified, clinicians must promptly de-escalate treatment to target the precise pathogen, mitigating the risks associated with prolonged broad-spectrum therapies. Achieving this delicate balance demands optimal clinical judgment and access to rapid diagnostic tools. The absence of these resources can impede timely and targeted interventions, emphasizing the critical need for enhanced resources and streamlined protocols in emergency settings to optimize patient outcomes.

Mode of presentation in the emergency room

The common mode of presentation in the emergency room is acute undifferentiated febrile illness (AUFI), multiple organ dysfunction syndrome, fever with acute respiratory distress syndrome (ARDS), fever with thrombocytopenia, fever with jaundice, fever with altered sensorium and fever with renal failure.

AUFI

AUFI, typically lasting <14 days, presents as an unclassified fever with an oral temperature of ⩾101ºF. According to Thangarasu et al., among fever patients, most cases were nonspecific, and the exact cause of fever remained undetermined in the majority of instances.[3] Common causes of AUFI include malaria, typhoid, human immunodeficiency virus (HIV), dengue, leptospirosis, rickettsia, relapsing fever, and various viral illnesses.[4]

Fever with ARDS

The common causes of fever with ARDS can be divided into infectious and noninfectious, as listed below:[5,6]

Infectious	Noninfectious
Bacterial, Fungal, Viral, Parasitic: ◆ Community-acquired pneumonia ◆ Aspiration pneumonia ◆ Sepsis ◆ Malaria ◆ Dengue ◆ Typhoid ◆ Leptospirosis ◆ Scrub typhus ◆ Influenza (H1N1) ◆ COVID-19	**Pulmonary:** ◆ Pulmonary embolism ◆ Diffuse alveolar hemorrhage ◆ Idiopathic interstitial pneumonia ◆ Acute hypersensitive pneumonia ◆ Acute eosinophilic pneumonia ◆ Pulmonary renal syndrome **Non-pulmonary:** ◆ Transfusion-related acute lung injury ◆ Trauma ◆ Fat embolism ◆ Amniotic fluid embolism ◆ Acute pancreatitis ◆ Poisonous gases and burns

The timing of disease onset helps in differentiating the etiology of tropical infections in ARDS, malaria typically manifests as a late feature. Leptospirosis, scrub typhus, and dengue emerge in the second week of illness. However, with H1N1, fever occurs in the first week of illness, often leading to ARDS in patients.[5]

Fever with thrombocytopenia

The infectious and noninfectious causes of fever with thrombocytopenia are listed in table 1:[7,8]

Table 1: Infectious and noninfectious causes of fever with thrombocytopenia

Infectious	Noninfectious
Bacterial, Fungal, Viral, Parasitic: ◆ Sepsis ◆ Dengue ◆ Complicated malaria ◆ Leptospirosis ◆ Rickettsia ◆ Zoonotic and tropical illnesses ◆ Opportunistic infections	**Hematological:** ◆ Thrombocytopenic purpura/hemolytic uremic syndrome, immune thrombocytopenia ◆ Disseminated intravascular coagulation, hemolysis, elevated liver enzymes, and low platelets ◆ Macrophage activation syndrome ◆ Massive transfusion **Non-hematological:** ◆ Liver diseases, pancreatitis, hemolysis, elevated liver enzymes and low platelets ◆ Fat embolism, poisoning ◆ Rheumatological diseases

Fever with altered sensorium

The infectious and noninfectious fever with altered sensorium seizure are listed in table 2:[9]

Table 2: Infectious and noninfectious of fever with altered sensorium seizure

Infectious	Noninfectious
Bacterial, Fungal, Viral, Parasitic: ◆ Sepsis ◆ Bacterial (Pneumococcal, meningococcal) ◆ Tubercular ◆ Complicated malaria ◆ Leptospira ◆ Rickettsia ◆ Zoonotic and tropical illness opportunistic infections viral like Japanese encephalitis virus, dengue, and herpes	**Local:** ◆ Stroke, acute disseminated encephalomyelitis, Benign/malignant lesion ◆ Cerebral venous thrombosis, local bleed **Systemic:** ◆ Toxic, metabolic, drugs ◆ Rheumatological ◆ Neuroleptic ◆ Malignant syndrome and hyperthermia ◆ Heatstroke

When encountering fever accompanied by altered sensorium, if the altered sensorium precedes the onset of fever, it may indicate a likelihood of stroke, warranting consideration for a CT scan. Conversely, if fever precedes the altered sensorium, exploring infectious causes through appropriate investigations becomes a priority.[10]

Fever with jaundice/liver failure

The infectious and noninfectious causes of fever with thrombocytopenia are listed in table 3.[11,12]

Table 3: The infectious and noninfectious causes of fever with thrombocytopenia

Infectious	Noninfectious
Bacterial, Fungal, Viral, Parasitic:	**Local + systemic:**
◆ Sepsis, bacterial sepsis	◆ Toxic
◆ Hepatotropic viruses A or E	◆ Metabolic
◆ Malaria	◆ Drugs
◆ Leptospirosis	◆ Autoimmune
◆ Typhoid fever	◆ Malignant
◆ Scrub typhus and other rickettsial infection	◆ Heatstroke
◆ Dengue/dengue shock syndrome	◆ Ischemic
◆ Hemorrhagic fever	
◆ Amoebiasis	

Diagnosis of tropical fever

A detailed history and examination are crucial aspects of diagnosis, helping to narrow down unnecessary investigations. In the case of malaria, clinical features include fever with chills and rigors, altered sensorium without focal signs, jaundice, and breathlessness, often accompanied by metabolic acidosis. Dengue fever is characterized by saddle fever, and investigations may reveal hemoconcentration, petechiae, and a decrease in platelet count. Scrub typhus, being endemic, should always be considered in cases of fever with rash, resembling enteric fever; eschar is present in approximately 40% of cases. In instances of differential organ involvement, malaria may affect all organs, while dengue tends to impact the liver and platelets predominantly. Leptospirosis involves the lungs, liver, and kidneys, and in typhoid, the liver is predominantly affected.[13]

Lab diagnosis of tropical fever

Various laboratory tests include full blood counts, blood smears, liver function tests (LFT), renal function tests (RFT), arterial blood gas (ABG) analysis, cerebrospinal fluid (CSF) examination, and diverse culture assessments (such as sputum and urine), as well as serological investigations, rapid diagnostic tests (RDTs), malaria-specific antigens (malarial Ag), NS1, IgM, molecular methods, procalcitonin analysis, ultrasound, CT scans, and invasive procedures.[13]

Rapid diagnostic tests (RDTs) for malaria commonly utilize histidine-rich protein and lactate dehydrogenase antigens through immune-chromatography, offering high sensitivity and specificity. To exclude malaria, two negative RDTs and three negative smears respectively serve as indicators. For enteric fever, culture testing, whether blood, bone, urine, or stool, takes precedence over serology due to its comparatively higher sensitivity and specificity.[14,15] In scrub typhus diagnosis, assessments such as eschar identification, Weil-Felix testing, indirect fluorescent antibody (considered the gold standard), and ELISA for IgG and IgM antibodies are instrumental.[16]

In cases of dengue, patients presenting within the initial week of fever onset should undergo diagnostic testing for the dengue virus. This may involve testing for the virus itself (via rRT-PCR or NS1) and IgM detection. For patients arriving more than a week after fever onset, detecting IgM is most effective, although NS1 has shown positivity up to 12 days post-fever onset. Leptospirosis manifests seasonally, characterized by severe myalgia, increased creatinine phosphokinase levels, and symptoms like conjunctival suffusion or hemorrhage, often leading to multiorgan failure. Laboratory diagnosis involves positive results in IgM-based immune assays, PCR tests, microscopic agglutination tests (MAT), and culture assessments in blood, urine, and CSF, along with elevated creatinine phosphokinase levels.[13]

Management

A recent study by Franceschi et al. highlights paracetamol 1,000 mg as the primary recommendation for managing fever in the emergency department. For malaria treatment, artesunate is the preferred medication, while clindamycin is the choice for pregnant women. In cases of dengue, supportive care is primarily employed, focusing on patient resuscitation, shock management, appropriate fluid administration, and, if necessary, platelet transfusions based on specific indications.[18] The drugs of choice for tropical fever are listed in table 4.

Table 4: The drug of choice for tropical fever

Scrub typhus	**Doxycycline** (100mg bid orally or iv form for 7- 15 days, **Azithromycin** (500mg orally or IV for 3days)
Leptospira	**Penicillin's** (Amoxicillin/ampicillin 500 mg tid), **Ceftriaxone** (1-2gm/day) **Doxycycline** (200mg orally or IV Day) *All treatment for 5-7days
Dengue	**Paracetamol & Fluids**
Typhoid	**3rd generation cephalosporins** (ceftriaxone 2- 4 gm/day for 7-14 days) **Azithromycin** (1gm/day for 5days) **Quinolones** (Ciprofloxacin 400mg IV bid for 5-7days)

Approach to diagnosis and management of tropical fever

When a patient presents with fever in the emergency setting, the initial focus should be on assessing and stabilizing the airway, breathing, and circulation. Simultaneously, gathering the patient's medical history is crucial. Red flag indicators include hypo tension, inability to maintain airway and oxygenation, necessitating immediate attention. Following a thorough history and examination to identify the focus of infection, if sepsis is recognized, treatment should adhere to sepsis guidelines. Subsequently, after determining the probable causative organism, select the appropriate antibiotic accordingly. For all patients with infectious fever, obtaining blood cultures is imperative.

In cases where the focus of infection remains elusive but the clinical syndrome is discernible, consider risk factors, geographical location, seasonal factors, and associated symptoms such as rash, thrombocytopenia, fever with jaundice, and ARDS. In such instances, conduct essential investigations, including blood cultures and other relevant blood tests. If the diagnosis remains unclear, it is prudent to test for malaria, dengue, leptospirosis, and H1N1 if prevalent based on the number of days. If rapid tests provide a diagnosis, tailor the fever management accordingly. If a tropical fever is suspected without a definitive diagnosis, empiric coverage is warranted (Fig. 1). An ideal combination in such cases includes ceftriaxone, doxycycline, and azithromycin.[19] Recommended management interventions for fever with thrombocytopenia, jaundice, renal failure, encephalopathy, and respiratory distress are listed in figure 2.

Fig. 1: Algorithm for the diagnosis and management of tropical infections

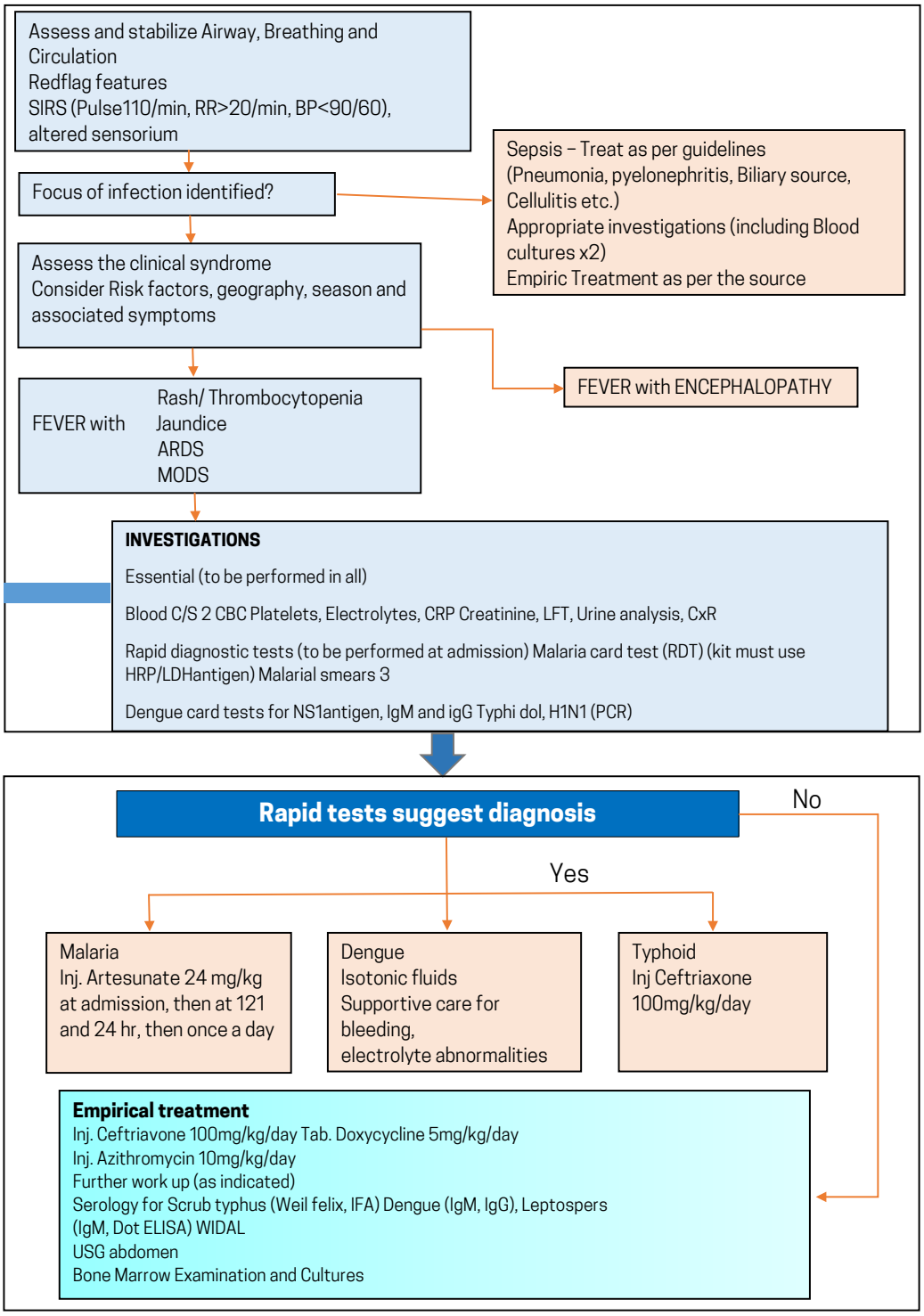

Fig. 2: Management of fever with thrombocytopenia, jaundice, renal failure, encephalopathy and respiratory distress

Thrombocytopenia	• Give fluids • Avoid aspirin/anticoagulants • Watch for bleeding, dyspnea, shock • Platelet transfusion if the platelet count <10,000 or clinical bleeding • No role of sterioid
Jaundice	• Ceftriaxone • Doxycycline • Watch for urine output, seizures, encephalopathy, bleeding • Fresh frozen plasma/cryoprecipitate for bleeding
Renal failure	• Ceftriaxone • Doxycycline • Watch for encephalopathy, bleeding, seizures • Renal replacement therapy if required
Encephalopathy	• Acyclovir • Ceftriaxone • Steroids • Mannitol for raised intracranial pressure
Respiratory distress	• Ceftriaxone • Azithromycin • Oseltamivir, if H1N1 is a possibility • Watch for impending respiratory failure, shock, renal failure, alveolar hemorrhage

Conclusion

A multitude of medical conditions can manifest in the emergency department. Comprehensive history-taking and thorough examinations stand as pivotal steps. Maintaining a high level of suspicion is vital, guiding the selection of the most suitable diagnostic tests tailored to each patient. Employing various diagnostic tests and modalities becomes necessary. An assertive and proactive approach to managing the disease process and underlying pathology is essential. While guidelines offer valuable guidance, individual patient assessment should always prioritize the most suitable course of action. The appropriateness of a treatment or diagnostic pathway should be determined based on the unique presentation and needs of the patient.

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Emerging and Re-emerging Viral Infections

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Introduction

In the current decade, the emergence of new human pathogens and the resurgence of certain diseases are prominent concerns. Emerging infections are characterized by an increased incidence in recent decades or the potential for escalation in the future. These infections often result from the detection and spread of pathogens into new regions, the identification of diseases that previously existed within a population but remained undetected, or the recognition of an infectious cause within established diseases.[1]

Numerous emerging and re-emerging viral infections have been documented, underscoring the importance for clinicians to familiarize themselves with the clinical characteristics and diagnostic methodologies associated with these diseases.

Zika

Zika virus (ZIKV), a typically mild Flavivirus infection transmitted primarily by Aedes mosquitoes, can lead to significant complications such as microcephaly, other congenital malformations, and Guillain-Barre Syndrome. Apart from mosquito transmission (primarily *Aedes aegypti* and *Aedes albopictus*), the virus can also spread through sexual contact and other routes like transfusion, laboratory contamination, and perinatal transmission.[2]

Aedes aegypti, known for transmitting several impactful viruses that affect human health, such as the yellow fever virus (YFV), dengue fever (DENV), chikungunya, and ZIKV, typically takes 5-8 days to progress from eggs to larvae and then pupae, maturing into adults in an additional 3 days. If an adult mosquito carrying ZIKV bites an infected primate, the mosquito acquires the virus from the animal's blood. Subsequently, the virus infects and replicates in the mosquito's epithelial cells, circulates in its bloodstream, and is released in saliva. Infected mosquitoes then transmit ZIKV to other non-human primates or humans, contributing to the spread of the infection and potentially causing outbreaks or epidemics.[2]

The signs and symptoms of the Zika virus include:[3]

- Mild fever
- Skin rashes

- Conjunctivitis
- Muscle and joint pain
- Malaise or headache

ZIKV infection during pregnancy can lead to congenital microcephaly and other significant complications in infants born to infected women. Screening for the ZIKV becomes crucial in identifying and managing potential risks to the developing fetus. In cases where Guillain-Barré syndrome (GBS) occurs after a febrile illness, considering the possibility of ZIKV infection becomes paramount.[3]

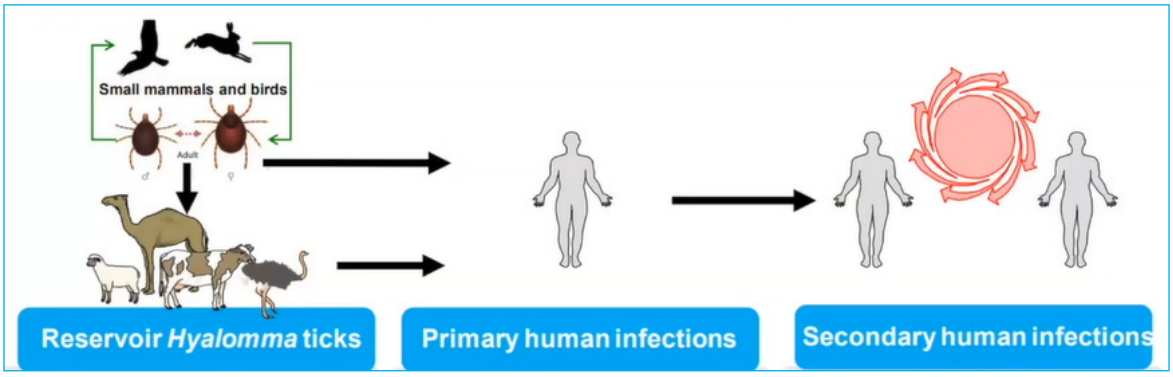
Diagnosis and treatment of Zika virus

The diagnosis of Zika virus involves laboratory examinations of blood and various bodily fluids like urine, saliva, and semen. During the acute phase of the disease, polymerase chain reaction (PCR) testing is employed. Serology testing through the plaque reduction neutralization test (PRNT) is also employed. The management of ZIKV disease focuses on ensuring adequate fluid intake, ample rest, and the use of common medications to alleviate fever and pain. However, there is currently no specific cure for ZIKV infection.[2]

Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) is a frequently fatal viral infection documented in approximately 30 countries, showcasing one of the broadest geographic distributions among medically significant tick-borne viral diseases. This distribution closely aligns with the known global spread of *Hyalomma spp* ticks. In natural settings, the CCHF virus perpetuates itself through a cycle involving ticks and vertebrates. While most animals exhibit no symptoms, 80-90% of human infections occur through tick bites or direct contact with infected tick blood, as well as through contact with blood or tissues of infected wild animals and livestock. Secondary transmission among humans arises from direct contact with the blood, secretions, organs, or other bodily fluids of infected individuals. The highest risk of transmission occurs during direct patient care or when handling deceased bodies (Fig.1).[4]

Fig.1: Transmission of CCHF



Clinical features of CCHF

The incubation period spans between 2 to 14 days. Around 88% of infections are estimated to be subclinical, while the case fatality ratio can peak at 15% among hospitalized patients with severe manifestations. Prominent symptoms typically involve abdominal pain, arthralgia, bleeding manifestations, bradycardia, and thrombocytopenia. The clinical progression of CCHF follows distinct phases: an initial infection and incubation phase (lasting 1-9 days), followed by a pre-hemorrhagic phase (1-7 days), a subsequent hemorrhagic phase (2-3 days or potentially longer), and finally, a convalescence phase.[4]

Various drugs including ribavirin, favipiravir, molnupiravir, and monoclonal antibodies have been explored for treating CCHF. Steroids have also been considered in cases where patients exhibit severe inflammatory responses.

Yellow fever

Yellow fever (YF) is an acute viral hemorrhagic fever predominantly found in tropical regions of Africa and the Americas. Primarily affecting humans and monkeys, it is transmitted by *Aedes aegypti* mosquitoes. It primarily spreads to humans through bites from infected *Aedes or Haemagogus* species mosquitoes. These mosquitoes acquire the virus by feeding on infected primates, be it humans or non-human, and subsequently transmit the virus to other primates of the same category. The urban cycle of transmission involves the virus moving between humans and urban mosquitoes, primarily the *Aedes aegypti* species. Typically, the virus enters the urban setting via a viremic human who contracted the infection in jungle or savannah areas.[5]

Primary symptoms of YF encompass fever, headache, bleeding, vomiting, declining renal function, abdominal pain, and jaundice. The disease progresses through distinct phases: an initial phase of infection, followed by a remission period, and then an intoxication phase. Approximately 88% of patients remain asymptomatic, while up to 10% develop fever. Mortality rates are notably low.[6]

Kaysanur forest disease

Kyasanur Forest Disease (KFD) stands as a life-threatening viral infection transmitted by ticks, endemic to South Asia, and has claimed numerous lives annually over the past decade. The ecology of the KFD virus (KFDV) contributes significantly to disease spread. In its enzootic phase, KFDV disseminates among small mammals including rodents, shrews, and ground birds. When monkeys and these small mammals encounter infected ticks, they become infected and propagate the disease. Human transmission commonly occurs when individuals venture into forests for activities such as collecting firewood, grass, or other forest resources, leading to potential bites from infected nymphs of the tick species *Haemaphysalis spinigera*. Furthermore, individuals residing near forest areas face the risk of infection through tick bites. This establishes a cycle of infection circulation among humans.[7]

The pathogenesis model of KFD involves a sequence of events. Initially, the virus enters the body through tick bites or contact with infected animals, targeting macrophages and dendritic cells. This leads to viral multiplication, causing high viremia and systemic spread to sites like the spleen and liver, triggering disease symptoms. Infected antigen-presenting cells (APCs) release pro-inflammatory cytokines and modulate the host immune response by initiating type 1 interferon production. Activated T cells and B cells contribute to the immune response, producing antibodies and inducing an antiviral state, potentially leading to uncontrolled viral replication. A pro-inflammatory cytokine storm may exacerbate the disease, inducing immunosuppression, disseminated intravascular coagulation (DIC),

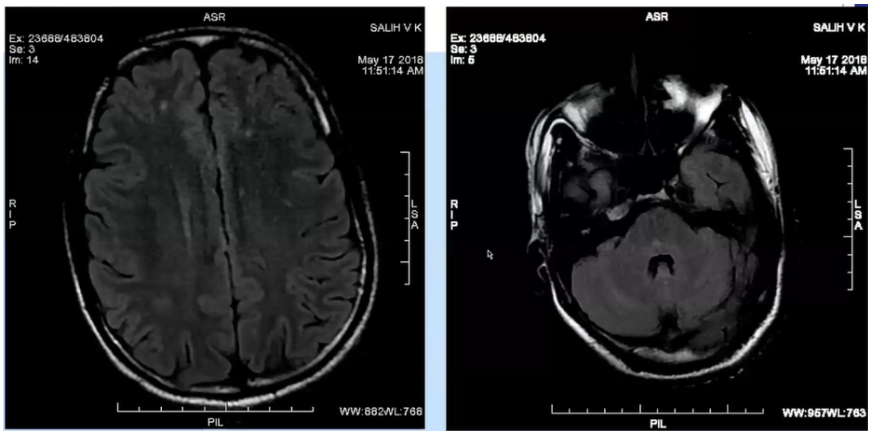
neurological complications, vascular dysfunction, hemorrhagic manifestations, multi-organ failure, and shock, ultimately resulting in death.[8] KFD cases have been reported in Karnataka, Kerela, Goa and Maharashtra.[9] Routine PCR screening is essential in patients hailing from KFD-prone regions, and those residing in forest areas. Macrophage activation is recognized as a significant complication, and needs steroid treatment.

Case studies on Nipah

Case 1: In 2018, a 26-year-old man presented with symptoms persisting for three days, including fever, vomiting, breathing difficulties, and altered mental state. Notably, he had no recent travel history. Further investigation revealed a concerning history: his brother (the Index patient) had passed away two weeks prior, displaying similar symptoms. Additionally, his father, aunt, and fiancée initially presented with mild fever upon admission but later developed encephalitis-like symptoms characterized by severe neurological manifestations such as rapid heartbeat, high blood pressure, abnormal pupils, specific muscle jerking, drooping eyelids, localized sweating, speech difficulties, seizures, and signs of cerebellar dysfunction.

Subsequently, the patient underwent MRI and cerebrospinal fluid (CSF) analysis. The distinctive clinical features—rapid heartbeat, high blood pressure, abnormal pupils, specific muscle jerking, drooping eyelids, localized sweating, speech difficulties, seizures, and cerebellar signs—are crucial indicators. In patients with respiratory and encephalitis symptoms, it is essential to consider screening for the Nipah virus in such cases. Although the CSF analysis showed normal patterns in all patients, it is important to note that even in prior Nipah cases, normal CSF findings have been reported. Thus, a normal CSF analysis does not exclude the possibility of Nipah virus infection and may not differentiate it from other viral encephalitis cases. Samples were sent to a virology institute and yielded negative CSF results for all cases. Therefore, in suspected Nipah cases, it is advisable to test throat swabs, blood, and urine. MRI findings highlighted T2 hyperintensity, a characteristic feature in these cases (Fig. 2)

Fig. 2: Characteristic MRI finding highlighting T2 hyperintensity



During that period, one patient transmitted the disease to approximately 10 individuals within a local hospital, which included three of his family members. Subsequently, at another medical college where

the index patient was admitted, the contagion spread to an additional 13 cases. In total, there were 23 cases, with only two survivors while the remaining individuals succumbed to the illness. Given the frequent occurrence of hospital-based transmissions, stringent precautions must be exercised when suspecting Nipah virus or managing cases involving encephalitis.

Case 2: A 21-year-old man presented with fever and altered sensorium of 12 days of duration. MRI of brain showed small areas where blood flow was limited in both the cerebral and cerebellar hemispheres, potentially indicating small strokes or clusters of infected material carried through the bloodstream. CSF examination confirmed the presence of the Nipah virus, and he received antiviral medication.

Case 3: In 2021, a 12-year-old child arrived with fever, focal seizures, and autonomic dysfunction. Initial CSF examination showed nearly normal results. However, upon observing T2 hyperintensity in an MRI scan, the clinicians began considering the likelihood of Nipah virus infection. Subsequently, another CSF sample was obtained and confirmed the diagnosis of Nipah virus infection.

Case 4: In 2023, a concerning medical scenario unfolded when four individuals from a single family displayed respiratory symptoms, drawing attention due to the recent demise of one family member. The deceased initially presented with fever and respiratory distress, later progressing to multiorgan failure. Further inquiry revealed that the initial patient had exhibited slurred speech and double vision. Subsequently, a child admitted with similar symptoms progressed to seizures and signs of encephalitis. Notably, these cases occurred in close proximity to the outbreak's epicenter, raising suspicion of Nipah virus infection.

The child displaying encephalitis symptoms had ventilatory support. MRI findings unveiled multiple areas of heightened signal intensity in T2/fluid attenuated inversion recovery (FLAIR) sequences, primarily affecting bilateral subcortical and periventricular white matter, as well as the midline pons. Additional hyperintensities were observed in the cerebral white matter and pons. The child remained on ventilation for approximately seven days, receiving ribavirin treatment. Notably, the child continued to show no neurological impairments post-treatment. This case exemplifies the transmission of Nipah virus from one index patient to five additional individuals within the family, resulting in a total of six cases. Unfortunately, two individuals succumbed to the infection.

Key diagnostic insights from Kerala Nipah outbreaks

The diagnostic landscape of Nipah virus outbreaks in Kerala has revealed pivotal trends over recent years. In 2018, the outbreak began with the clustering of cases exhibiting atypical clinical features. Subsequent years have unveiled distinctive diagnostic markers: in 2019, cerebellar signs and a comprehensive cerebrospinal fluid (CSF) panel; in 2021, the significance of MRI findings coupled with detailed CSF analysis was highlighted. Presently, the focus remains on case clustering and unusual clinical presentations, especially in proximity to the outbreak's epicenter.

Crucial clinical indicators encompass case clustering and a spectrum of symptoms, such as adrenergic responses, myocarditis, stress cardiomyopathy, brain stem manifestations, cerebellar signs, and myoclonus, often accompanied by characteristic MRI findings. Additionally, patients might initially manifest symptoms similar to influenza-like illness or acute respiratory distress syndrome (ARDS). Therefore, if routine virus screenings yield negative results for ARDS, considering Nipah screening becomes imperative. Nipah virus prevalence spans across all regions of India except certain areas in Kashmir, rendering every state susceptible to potential outbreaks. Consequently, implementing

comprehensive Nipah virus screening protocols holds paramount importance in disease surveillance and management across the nation.

Ebola

Ebola virus disease (EVD), previously known as Ebola hemorrhagic fever (EHF), stands as one of the most severe viral hemorrhagic fevers. Its onset is often abrupt, marked by high fever, profound fatigue, muscle pain, headaches, throat discomfort, vomiting, diarrhea, skin rash, and impaired kidney and liver functions. In certain cases, both internal and external bleeding may occur. This highly threatening virus primarily spreads from wild animals, including fruit bats, porcupines, and non-human primates, before transmitting to humans. Human-to-human transmission happens through direct contact with infected blood, bodily secretions, organs, or other fluids. Surfaces and materials contaminated with these fluids, such as bedding and clothing, also pose a risk of transmission within the human population.[10,11]

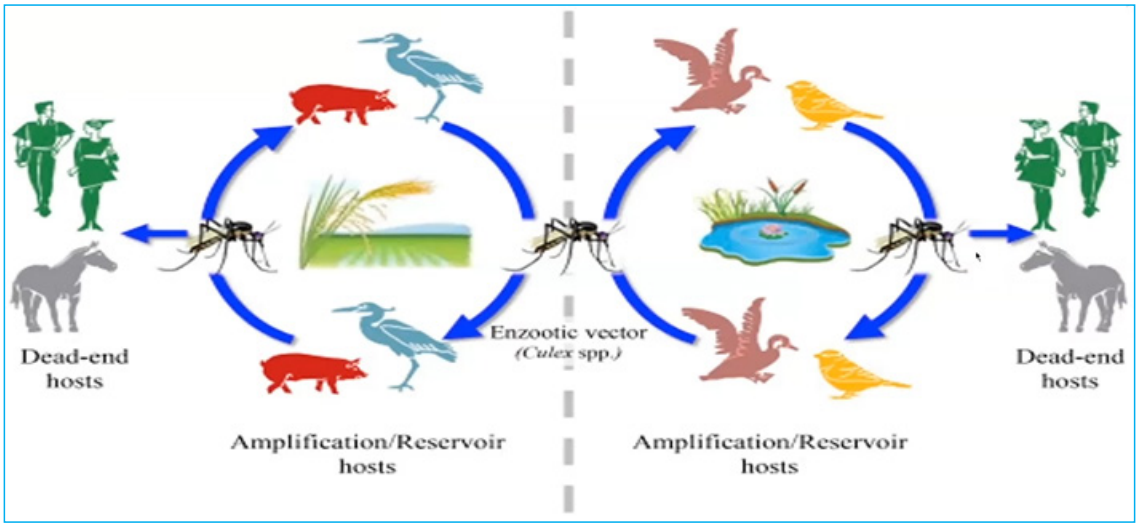
West Nile encephalitis

West Nile encephalitis, an emerging concern across various regions in India, is caused by the West Nile virus (WNV), an arthropod-borne pathogen that first appeared in the country back in 1952. Presently, it is resurfacing, demanding increased attention within public health spheres. WNV is a single-stranded RNA virus belonging to the Flaviviridae family and categorized within the Japanese encephalitis antigenic serocomplex. While it maintains a natural cycle between Culex mosquitoes and avian hosts, it can induce illness in humans, horses, and other vertebrates (Fig. 3). In the majority of cases, human WNV infection remains asymptomatic, displaying acute systemic febrile symptoms in only a small fraction of those infected. However, the mortality rate tends to be notably higher among vulnerable individuals, such as the elderly, immunocompromised individuals, and those with chronic health conditions.

Common symptoms include fever, swollen lymph nodes, nausea or vomiting, muscle and joint aches, as well as skin rash. Additionally, WNV may manifest as non-neuroinvasive disease, posing challenges in diagnosis. Neuroinvasive disease, experienced by <1% of infected individuals, presents as encephalitis, meningitis, or acute flaccid paralysis mimicking acute poliomyelitis.[12]

Diagnosing WNV infection involves detecting WNV-specific IgM in blood or CSF, indicating recent infection. However, these antibodies might arise due to cross-reactivity post-infection with other flaviviruses or non-specific immune reactions. Employing PRNTs becomes crucial to determine the specific flavivirus-causing infection. Additionally, confirming acute infection involves observing a significant fourfold or greater change in WNV-specific neutralizing antibody titers between serum samples collected during the acute and recovery phases, typically taken 2 to 3 weeks apart.[13]

Fig. 3: Transmission of Japanese encephalitis virus and West Nile virus



Conclusion

The ongoing cycle of infectious disease emergence highlights the need for proactive measures. Failure to effectively control these outbreaks could lead to catastrophic human tolls. Urgent action is required for enhanced surveillance and comprehensive assessments of disease burdens within the country. It is imperative to educate clinical microbiologists and virologists on existing outbreak reporting systems, designated laboratories for managing outbreak samples, and to equip them with the necessary skills for identifying emerging pathogens.

India's diverse geography and climate pose a constant threat of emerging and recurring viral infections, underscoring the need to enhance disease surveillance. Further understanding epidemiology, disease burden, and vector biology is warranted to develop target and efficient management and prevention strategies.

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Panel Discussion

Non-infective causes of fever

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Fever often prompts extensive investigations to identify its origin. While infections are frequently implicated, a myriad of non-infective factors can also contribute to elevated body temperature, presenting a diagnostic challenge for healthcare professionals. The present panel discussion focuses on the non-infectious causes of fever.

Dr. Anupam Prakash: What are the common causes of non-infective fever? How common is it?

Dr. K. Shankar: Fever in hospitalized patients is typically infectious, with non-infective causes accounting for 2-3%. Factors like seasonal changes, vascular problems, or endocrine disorders may also play a part in causing fever. It is common for patients to feel anxious about a slight temperature change, even if it is not significant. Therefore, clinicians must first eliminate the possibility of an infection, and consider medication-induced fever caused by steroids or autoimmune drugs. To provide tailored treatment and counseling, it is essential to accurately diagnose the root cause of the fever through a comprehensive assessment of the patient's temperature and medical history.

Dr. Saliha Saleem: In the United States, the prevalence of non-infectious fever varies across medical settings. Whether in an intensive care unit (ICU) or non-ICU environment, there is a possibility that fever may not be attributed to an infection. Therefore, a thorough diagnosis is essential to rule out infection before exploring non-infectious causes when assessing patients with fever. After excluding infection, non-infectious causes can be considered. It is crucial to consider numerous factors that can lead to fever, necessitating consideration of all signs and symptoms by infectious specialists or general physicians.

Non-infectious causes of fever can arise from inflammatory processes, encompassing conditions such as acute pancreatitis, calculus colitis, and ischemic syndromes. Underlying malignancies, including leukemia and tumors, autoimmune diseases such as rheumatoid arthritis, and drug-induced fever can also induce fever. Although drug fever is an uncommon cause and is regarded as a diagnosis of exclusion, it is important to note that certain drugs, such as beta-lactams, tetracyclines, sulfonamides, and nitrofurantoin, among other antimicrobials, can provoke fever.

Dr. Anirban H. Choudhuri: In the ICU, assessing fever involves considering several factors. Firstly, the nature of the fever is examined to determine whether it is continuous or exhibits variations over time (waxing and waning). Typically, non-infectious fevers are continuous, often low-grade, and infrequently high-grade, and they are generally not accompanied by an elevated leukocyte count. Another key consideration is temperature and heart rate dissociation, where a 1°F rise in temperature correlates with approximately ten additional beats per minute in heart rate. This dissociation is more commonly observed in non-infectious fevers. Additionally, assessing the patient's hemodynamic stability is crucial; unstable hemodynamics may suggest a non-infectious fever. However, there are exceptions, such as acute pancreatitis, a non-infectious disease, which may exhibit a high total leukocyte count (TLC). In cases like deep vein thrombosis (DVT), very low-grade fevers of shorter duration may be observed in contrast to other non-infectious fevers. Physical examination plays a vital role, with attention to lymph nodes and mucous membranes providing insights into potential coexisting diseases and aiding in the clinical ruling out of infectious diseases.

Dr. Anupam Prakash: Which are the common autoimmune conditions that can cause Fever?

Dr. K Shankar: Autoimmune diseases like rheumatoid arthritis, ankylosing spondylitis, and chronic conditions such as SLE may manifest with fever, despite the absence of infection. Identifying the specific disease, considering medications and their regular usage is crucial in such cases. Autoimmune patients often experience depression and fever phobia, typically presenting with low-grade, non-persistent fever. Advising patients to monitor fever in the morning and evening can help assess the situation. Trauma-induced inflammation can also lead to fever. While autoimmune fevers are common, a thorough inquiry into the patient's history and medication usage allows for ruling out infectious causes and providing appropriate advice and counseling.

Dr. Anupam Prakash: What is the mechanism of fever in various malignancies?

Dr. Saliha Saleem: Fever in malignancies, particularly lymphoma and leukemia, is primarily attributed to a robust interleukin response and the release of immunomodulators and cytokines. In any malignancy, not limited to leukemia and lymphoma, the interaction of these factors is responsible for inducing fever. In essence, the fever associated with malignancies is driven by an interleukin and cytokine response.

Dr. Anupam Prakash: Which are the non-infectious central nervous system (CNS) causes that can present as fever?

Dr. Ashit V. Hegde: Post-neurosurgery, patients may develop non-infectious fevers, often mistaken for meningitis, leading to unnecessary antibiotics. In the neuro ICU, common causes include subarachnoid hemorrhage, intraventricular hemorrhage, traumatic brain injury, and brain tumors causing paroxysmal

autonomic hyperactivity. Recognizing these fevers is crucial to avoid inappropriate antibiotic use, as fever can worsen the condition. Central fever, common in hemorrhagic cases, is consistently high, lacks fluctuations, and shows specific characteristics. Paroxysmal autonomic hyperactivity, prevalent in younger traumatic brain injury patients, presents as a continuous, less sweaty fever with distinctive features aiding identification.

Dr. Anupam Prakash: Which drugs could contribute to drug fever?

Dr. Anirban H Choudhuri: Commonly, β-lactam antibiotics, specifically piperacillin, tazobactam, cefoperazone, and sulbactam, are frequently implicated in drug fever. While the literature mentions minocycline as an inducer, its occurrence is relatively uncommon. Additionally, drugs affecting the central nervous system, such as haloperidol and amiodarone, as well as less common medications can also lead to drug-induced fever like furosemide.

Dr. Anupam Prakash: Factitious fevers: When to suspect, how to diagnose, and how to manage?

Dr. K Shankar: Factitious fevers pose significant challenges for physicians. Thoroughly investigating the history and systematically addressing common complaints and symptoms is crucial, especially in general outpatient settings. Factitious fever tends to be persistent and not of low grade. Properly scrutinizing history, symptoms, and medications helps rule out infectious causes. Thorough examination plays a pivotal role in identifying factitious fever.

Dr. Saliha Saleem: In the context of factitious fever, it is crucial to correlate information from the patient's history and examination. When assessing a patient with a fever, it becomes essential to examine the frequency and intensity of the fever. Additionally, meticulous attention should be given to ensure that the fever is accurately and appropriately documented.

Dr. Anupam Prakash: What roles do pulmonary thromboembolism (PTE) and venous thrombosis play as causes of fever?

Dr. Anirban H Choudhuri: The diagnosis of venous thrombosis and PTE has become more accessible with contemporary ultrasound technology, facilitating prompt identification. However, individuals with elevated body weight, obesity, reduced mobility, sedentary behavior, and underlying comorbidities pose challenges. The manifestation of pain, redness around cannulation sites, alterations in skin coloration, and signs of plebitis indicate an increased risk of deep vein thrombosis (DVT), often accompanied by fever. This fever typically exhibits a short-duration, continuous pattern and demonstrates favorable responsiveness to DVT treatment upon initiation of anticoagulation. In instances where anticoagulation is delayed or not initiated, the fever may subside without medication. Despite advancements in early thrombosis profiling, some cases persist, necessitating scrutiny of D-dimer values for appropriate therapeutic decisions, including potential adjustments in drug selection or dosage escalation.

Dr. K Shankar: The easiest method to ascertain PTE is by reviewing the patient's history, particularly focusing on those with a complaint of recurrence and an extended history of DVT. This historical context serves to eliminate alternative causes of fever. Therefore, a comprehensive approach to treating PTE involves a thorough examination of the patient's history, a detailed physical examination, and appropriate medication.

Dr. Anupam Prakash: What are the endocrine causes of fever?

Dr. Ashit V. Hegde: The most frequent cause of non-infectious pyrexia of unknown origin (PUO) is likely thyrotoxicosis. Patients presenting with PUO typically undergo a CT scan of the chest and abdomen. Specific attention is given to the thyroid tenderness, classically indicative of subacute thyroiditis. These patients may also exhibit signs of thyrotoxicosis. In addition to subacute thyroiditis, other endocrine causes of fever are thyroid storm, pheochromocytoma crisis, and, occasionally, adrenal insufficiency.

It is important to understand that what may seem like a fever can sometimes be hypothermia caused by an increased hypothalamic set point, which is similar to a fever. In such cases, the elevated temperature is a result of heat production due to increased metabolism, rather than a change in the set point. Both thyrotoxic storm and pheochromocytomas may induce sympathetic activity, making it challenging to distinguish between them. However, certain clinical indicators can aid in differentiation. For instance, the thyrotoxic storm is characterized by higher systolic pressure than diastolic pressure, accompanied by symptoms such as tachycardia, hypertension, sweating, pupil dilation, and elevated blood pressure. In contrast, pheochromocytomas can manifest as an increase in both systolic and diastolic pressure, resulting in a wide pulse pressure due to norepinephrine release.

Distinguishing features also include the warmth of extremities, which is generally present in thyrotoxicosis, and sweating, which is common in both conditions. Additionally, in thyrotoxicosis, the extremities tend to be warm, while in pheochromocytomas, they may not exhibit the same warmth. These distinctions aid in the separation of symptoms between pheochromocytomas and thyrotoxic storm. Several differential diagnoses can further assist in the differentiation of these conditions.

Another endocrine cause of fever is adrenal crisis, which can mimic septic shock with fever and hypotension. Patients with adrenal crisis may experience abdominal pain, vomiting, diarrhea, hyperpigmentation, hyponatremia, hypokalemia, hypercalcemia, normocytic normochromic anemia, lymphocytosis, and eosinophilia. Although these symptoms can be suggestive of infection, negative cultures, and a lack of improvement with antibiotics should prompt consideration of adrenal crisis.

Dr. K Shankar: Occasionally, pituitary adenomas may contribute to endocrine fever by affecting the space between the hypothalamus and the brain. This can disrupt the fever cycle, leading to direct fever manifestations. In neurosurgical settings, particularly in cases of apoplexy, pituitary adenomas may be associated with rheumatoid fever.

Conclusion

Non-infectious fever encompasses a spectrum of conditions, including autoimmune disorders, malignancies, drug reactions, factitious fevers, and endocrine-related fevers. Addressing the diagnostic complexity requires a meticulous clinical evaluation along with targeted diagnostic tests. Unraveling the diverse etiologies is crucial for accurate identification, guiding clinicians toward effective management strategies for individuals presenting with non-infectious fever.

Fever Diet and Fluids

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Introduction

The pathophysiology of fever typically involves exogenous pyrogens, such as bacteria, viruses, or toxins, triggering fever within approximately 2 hours of exposure. These agents interact with macrophages or monocytes, initiating cytokine production.[1] Fevers can be categorized into acute (lasting <7 days), subacute (up to 2 weeks), and chronic (>2 weeks), each requiring specific dietary adjustments. The present paper explores the role of nutritional status fever management as it can influence the body's immune response, energy requirements, and overall recovery.

Management of fever

The management of fever through home remedies involves ensuring adequate rest, sufficient fluid intake to prevent dehydration, and the consumption of clean, boiled water and easily digestible foods. Caution is advised when considering treatment options, as fevers may not invariably require antibiotics or antipyretics due to potential side effects such as kidney damage, sedation, and contraindications. Steroids should be avoided unless deemed essential. Furthermore, alternative interventions, such as administering antipyretics through injection or rectal methods, along with employing physical cooling techniques, are viable choices.[2-4]

How do fevers due to infections affect nutrition

Infections significantly impact the body's nutritional balance. Fever escalates the body's energy requirements, and nutrient absorption from food diminishes during an infection. The body's increased energy needs persist for extended periods (from several days to months), coupled with increased breakdown and excretion of proteins. Symptoms like sweating, nausea, vomiting, and diarrhea further exacerbate nutrient depletion. Even mild infections reduce nutrient intake disrupting the normal nutritional balance. A diet rich in nutrients can expedite recovery and improve the body's defense mechanisms.[5]

Fluid deficit in fever

Fluid deficit is induced by increased catabolism, fever-induced perspiration, coughing, breathing, vomiting, diarrhea, reduced fluid intake due to poor appetite, and decreased gastrointestinal absorption. The general guideline is to encourage oral intake as long as the patient can consume sufficient fluids. However, when oral intake becomes inadequate, parenteral supplementation is crucial, and clinicians must be vigilant about accompanying health conditions. For instance, patients with an ejection fraction of 12-18% or 25-30% require tailored fluid management. Fever is more prevalent in immunocompromised individuals, those with renal dysfunction, COPD, etc., Hence fluid management in such cases should be adjusted to account for catabolic processes, sweating, vomiting, and diarrhea.[6,7]

Fluid and electrolyte balance in fever

Maintaining fluid and electrolyte balance during fever is crucial for supporting the body's physiological functions. Some of the key considerations for effective management are as follows:[7]

- **Fluid-electrolyte balance:** Ensure and maintain a fluid-electrolyte equilibrium for optimal health. The goal is to maintain an equilibrium where intake offsets the net output.
- **Monitor fluids to aid feeding:** This is done by calculating the sum of the last 24-hour fluid output. Add 500 ml if edema is absent or 300 ml if edema is present.
- **Sodium regulation:** Restrict sodium intake based on urinary excretion, aiming for 2400 mg per day (equivalent to one leveled teaspoon) to maintain fluid-electrolyte equilibrium.
- **Potassium regulation:** Customize potassium intake based on individual serum levels for optimal management of fluid and electrolyte balance.

In a pilot study conducted by Nasir et al., the viability and impact of employing a fluid chart to enhance oral fluid intake among suspected dengue fever patients in primary care were examined. The intervention group received a strict 24-hour fluid chart to enhance oral fluid consumption. The findings revealed a decrease in hospital admissions and reduced need for hospitalization among those in the intervention group compared to the control. This straightforward and cost-effective fluid chart shows promise in potentially lowering hospitalization rates and decreasing the need for intravenous fluid administration in acute cases such as dengue patients.[8]

Cycle of nutrition and disease

Reduced food intake results in weight loss, subsequently compromising immunity and elevating susceptibility to infectious illnesses. This decrease in appetite and nutrient loss exacerbates the situation, creating a cycle of mutual exacerbation.[9]

Nutritional requirement

Carbohydrate

The body's increased metabolic rate during fever amplifies the need for calories. However, diminished appetite and potential digestion issues may arise. Hence, increasing carbohydrate intake could be beneficial. Prolonged high fever may necessitate a nearly 50% increase in energy intake. Patients can be provided with fruit juices and sugary liquids as they are readily absorbed. Easily digestible carbohydrates such as rice, simple porridge, fruit juice, and nutritional supplements are advisable choices.[5]

Protein

In the recovery phase of most infections, it is advisable to increase protein intake by about 20-25%. Patients recovering from infections, especially severe ones, should be provided with a high-protein diet, delivering approximately 1.25-1.5 grams of protein per kilogram of body weight per day. Sources of high-quality protein include fish, poultry, lean red meat, eggs, dairy products, nuts, dried beans, peas, lentils, and soy. Additionally, protein supplements can assist in meeting the escalated protein demand during recovery.[5,10]

Vitamin requirements

During infections, there is an elevated need for vitamins. In cases such as tuberculosis, vitamins A (retinol) and C (ascorbic acid) are recommended to expedite recovery and promote faster tissue regeneration. The intake of B-complex vitamins, particularly vitamin B9 (folic acid), should be increased. Meeting the increased vitamin requirements can be achieved by incorporating a diverse range of fruits and vegetables into the diet.[5]

Minerals

Infections often lead to significant loss of two crucial minerals: sodium and potassium, necessitating their replenishment. Sodium can be sourced from salt incorporated into soups, curries, or broths. Meanwhile, potassium is naturally found in fruit juices and milk.[5]

Developing a dietary schedule with five small, evenly distributed meals throughout the day totaling 1800-2000 calories is recommended. As the body burns more calories during fever, prioritizing nutrient-dense foods becomes crucial to supply the energy necessary for the immune system to function effectively.

Optimal foods during fever

The following recommendations can be provided to the patients regarding the selection of beneficial foods during fever:[5]

Hydration-focused options: Prioritize drinking water, hot tea, fresh fruit juices, and fluid-rich foods like poultry broths, thin soups, and coconut water to maintain hydration levels.

Fresh fruits: Opt for vitamin C-rich fruits such as apples, oranges, watermelons, pineapples, and kiwis. These fruits contain antioxidants that can help reduce fever. Bananas are nutrient-rich and easy to digest. Avoid fruits high in added sugars or canned syrup, as excess sugar can hinder the immune system.

Adequate protein intake: Incorporating protein-rich foods like scrambled eggs, low-fat milk smoothies, lentils (dal), chickpeas (chana), or paneer (Indian cottage cheese) into your diet for their beneficial protein content.

Need for a balanced diet during fever

A balanced diet is crucial during fever as it supports proper digestion and assimilation, preventing excessive bodily depletion and providing the necessary strength to combat the disease. However, it is important to avoid overfeeding, as it can have detrimental effects. Overfeeding introduces substances into the digestive system that cannot be properly digested or absorbed, acting as foreign bodies that may trigger vomiting and diarrhea. This, in turn, can lead to elevated temperatures and an increased pulse rate, promoting a tendency toward exudations. Additionally, excessive intake of protein-rich foods can generate toxins that, when absorbed, may either produce symptoms or impose added burdens on the body's excretory functions.

During fever, it is recommended to avoid certain foods to ease the digestive process and minimize discomfort. These include high-fiber foods like whole grains and cereals, as well as pulses with husks. Raw and strongly flavored vegetables such as cabbage, capsicum, turnip, radish, onion, and garlic should also be avoided, along with fried and fatty items. It is also advisable to avoid chemical irritants like condiments, spices, pickles, and chutneys.

On the other hand, certain foods are considered permissible during a fever for their ease on the digestive system. These include plenty of juices, soups, and various beverages, as well as milk and milk-based drinks. Low-fibre foods like refined cereals such as maida and suji, dehusked pulses, well-cooked fruits, soft vegetables, and potatoes are also suitable. Desserts like plain gelatin-based treats, sugar, honey, and jam can be consumed. For protein, options like eggs, soft cheese, tender meat, fish, and poultry are recommended. It is essential to avoid alcohol and smoking during this period. Patients should begin with a liquid diet and gradually progress to a soft diet to ensure the digestive system's comfort and recovery.

List of Do's and Don'ts

Recommending the following dos and don'ts can aid in faster recovery in febrile patients:

Do's:

- Consume a soft, bland diet loaded with immune-boosting foods to strengthen the immune system.
- Include easily digestible and absorbed foods such as cereal and milk, soft fruits (banana, papaya, and orange), mashed khichdi, mashed curd rice, or softly boiled veggies.
- Ensure adequate sleep, reduce stress, and engage in gentle mobilization for quicker recovery.
- Maintain sufficient oral hydration, aiming for a minimum fluid intake of 50 ml/kg of body weight in 24 hours to prevent dehydration.

Don'ts:

- Avoid deep-fried foods, processed foods, alcohol, and tobacco during the fever period.

Conclusion

Fever often accompanies various infections, requiring prompt diagnosis and treatment. It initiates a catabolic process, creating an imbalance between the body's increased energy demand and reduced food intake. The overall nutritional status plays a crucial role in effectively managing fever. Ensuring ample fluid intake is key to dietary management, aiding in maintaining proper hydration levels. Individuals should opt for a nutritious diet comprising easily digestible foods to facilitate recovery during this period.

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Fever in Elderly

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Introduction

Fever in the elderly poses a distinctive set of challenges when compared to fever in adults, requiring a specialized approach in terms of presentation, interpretation, and management. The febrile response in older individuals is characterized by unique features that warrant careful consideration. Healthcare professionals must comprehend these differences to deliver effective care and address the specific needs associated with fever in the elderly population.

Why fever in the elderly is different?

In comparison to the younger population, older individuals exhibit increased vulnerability to infections, facing a substantially elevated risk of morbidity and mortality from various common infections. The increased rates of morbidity and mortality in older patients can be attributed to diminished physiological reserves resulting from age-related biological changes and the frequent presence of comorbid conditions. Age and comorbidity-related declines in host defenses also play a role in influencing morbidity and mortality rates. The elderly are more prone to hospitalization, which can be further complicated by nosocomial infections. Additionally, they encounter an increased risk of adverse drug reactions, often being prescribed multiple medications even with careful consideration in clinical geriatrics. Biological changes associated with aging can also affect the pharmacology of various drug classes, including antibiotics. Furthermore, delays in diagnosis and the initiation of appropriate treatment due to atypical presentations contribute to increased morbidity and mortality.[1]

The prevention, early identification, and prompt initiation of empirical antimicrobial therapy serve as the fundamental pillars in reducing the impact of infectious diseases on older adults. In addition, recognizing and avoiding diagnostic delays poses challenges in this age group due to the common occurrence of atypical presentations of acute diseases. Despite significant infections, nearly 30% of elderly individuals do not exhibit a febrile response or demonstrate fever.[2]

Site of temperature measurement

Normal body temperature varies widely, even in young, healthy individuals, and this diversity extends to the elderly. Limited studies have established normal body temperature for older adults due to factors such as chronic diseases, aging-related biological changes, and medication use. Physiological heterogeneity in the elderly is further complicated by circadian rhythms, measurement sites, and thermometry methods. While rectal temperature is considered a 'gold standard', practicality issues arise in debilitated patients. Oral and tympanic membrane measurements are common, but oral readings can be affected by factors like patient behavior and thermometer type.[1,3]

Febrile response

With age, the fever response in the elderly becomes inadequate and imprecise. This can lead to diagnostic delays in the elderly population, who have a higher risk for morbidity and mortality due to infections. Fever in the elderly is determined by a persistent oral or typmanic temperature of ⩾37.2°C or a persistent rectal temperature of ⩾37.5°C. Additionally, an increase of temperature by ⩾1.3°C from the baseline, regardless of the measuring site or device used, indicates the presence of a fever.[1]

Incidence

The incidence of fever among individuals aged ⩾65 residing at home is 2.5 per 1000 patient days. Research indicates that individuals who are wheelchair-bound or bedridden, as well as those with cognitive impairment and increased dependency, are more prone to fever compared to ambulatory individuals. The primary culprits for fever in this demographic are pneumonia and urinary tract infections (UTIs).[4]

Comparing fever in young

Studies have investigated disparities in the causes of fever between older and younger adults, revealing that the underlying factors contributing to fever differ across these age groups. In older adults, autoimmune disorders, cancer, soft tissue infections, vasculitis, and osteomyelitis are the predominant causes of fever. Concurrently, individuals with diabetes face an elevated risk of bacterial and fungal infections.[5]

Fever in long-term care facilities

In long-term care facilities (LTCFs), infections pose a significant risk to frail, elderly residents who often have multiple comorbidities such as diabetes, hypertension, coronary artery disease, stroke, dystopia, and other health issues. The prevalence of morbidity and mortality resulting from infections is notably high in this vulnerable population. Adding to the complexity, fever, a common indicator of infection, may be absent in up to 50% of those experiencing serious infections in LTCFs. Furthermore, the challenge is increased by the limited availability of staff and facilities on-site for proper evaluation, making detecting and managing infections in this setting particularly intricate and demanding.[6,7]

Fever of unknown origin in older persons

Fever of unknown origin (FUO) is a condition that persists beyond the expected period for self-limited infection and whose cause cannot be ascertained despite considerable diagnostic efforts.

The differential diagnosis is often different in older patients, and the diagnosis of the disease is frequently nonspecific, and symptoms are difficult to comprehend.[8] Multisystem disease emerges as the most common cause of FUO in the elderly, with temporal arteritis being the most frequent specific diagnosis. Some of the common causes of FUO in the elderly are listed below:

- Infections, particularly tuberculosis
- Polymyalgia rheumatic (PMR), Wegener's granulomatosis (WG), rheumatoid arthritis (RA) and sarcoidosis
- Infections like endocarditis and abscess
- Tumors

Geriatric fever score (GFS) prediction model

Assessing elderly individuals with fever poses a time-consuming and complex task. Elevated temperatures in geriatric patients could result from unconventional illnesses, medication side effects, or a combination of various underlying conditions. Consequently, several studies have suggested predictive models based on decision rules to assist emergency department (ED) physicians in making informed decisions regarding the optimal management of geriatric patients experiencing fever. An example of such a model is the GFS, designed to address the intricacies of comprehending, interpreting, and diagnosing fever in the elderly population.[9] Independent mortality scores have been developed. Features associated with mortality are:

- Leukocytosis (WBC > 12,000/μL)
- Severe coma (GCS <8)
- Thrombocytopenia (platelets < 150,000/μL)

Geriatric patients with a high-risk GFS should be considered critically ill and sent to the ICU for advanced treatment. It has been discovered that 30% of these patients would benefit most if managed in an ICU. For individuals with a low-risk score, the options include transferring them to a general ward or providing treatment in the ED. Subsequent discharge, with close follow-up in an outpatient clinic, is determined by the treating physician based on the patient's condition and available medical resources. This approach aims to conserve medical resources for patients with more critical needs. In the long term, the low-mortality group has shown a 4% mortality rate during the hospital stay. Specifically, patients aged >65 years, those with leukocytosis or severe coma, and those predicted to have high mortality based on thrombocytopenia in the GFS can be considered for management in an ICU.[9]

Conclusion

Fever in older individuals is not merely an isolated symptom but serves as one of several clinical indicators that can prompt clinicians to consider the presence of a severe ailment, particularly an infection. In geriatric patients, infections mimicking other medical conditions often exhibit a spectrum of nonspecific, atypical, nonclassical, and unusual symptoms. It is crucial for healthcare providers caring for elderly patients to remain vigilant about these unconventional presentations of infections to conduct assessments for timely and accurate diagnoses.

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Clinicopathology Case Discussion

CPC Protocol

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Dr. Srikant Hegde discussed a challenging clinicopathologic case involving a 58-year-old male with fever. The discussion included subsequent clinical investigations and findings that contributed to an accurate diagnosis.

Case presentation

A 58-year-old male presented with fever for one-week duration, joint pain, and abdominal discomfort. He reported anorexia, fatigue, and limb pain. The initial temperature ranged from 39 to 39.6°C, and testicular swelling developed within two days. Notably, there were no complaints of dysuria, hematuria, lymphadenopathy, or rash. The patient's medical history included past pulmonary tuberculosis (TB), with completed antitubercular treatment, though patient had persistent cough with scanty sputum and negative acid-fast bacillus (AFB) in sputum.

Furthermore, a history of hepatitis B infection diagnosed 12 years ago, with subsequent negative hepatitis B DNA. Regular monitoring of alpha-fetoprotein (AFP) levels and repeated ultrasound examinations over the last 12 years revealed simple hepatic cysts. Three years prior, evaluation for respiratory symptoms revealed a nodular opacity in the right apex on chest X-ray, later identified as a calcified granuloma with bronchiectasis on CT chest imaging. The patient, a chronic smoker for nearly 40 years, consumed moderate alcohol and had no family history of pulmonary, ocular, or rheumatological disorders.

Examination findings

Upon examination, the patient was febrile with stable vitals with stable vitals: blood pressure of 126/68 mmHg, heart rate of 76/min, and 97% oxygen saturation on room air. No signs of anemia, rashes, or jaundice were observed. Lung base faint rales were present, with no murmurs or lymphadenopathy. Throat examination and bowel sounds were unremarkable. Neurological assessment revealed no significant abnormalities. Abdominal evaluation indicated softness, absence of organomegaly, and no distension. However, details of scrotal examination and testes findings were absent.

Clinical investigations

Post-admission investigations revealed persistent chest X-ray opacities and sub-centimetric liver hypodensities identified as simple cysts on abdominal CT. Bilateral small pleural effusion and trace ascites were evident, with subsequent CT showing increased pleural effusions and transudative fluid, negative for Gram stain, AFB, and bacterial/fungal cultures. Continued fever, left scrotum swelling, pain, and tenderness prompted urine examination, revealing 2+ blood and 10-20 RBCs. Scrotal ultrasound displayed engorged testicular vessels suggestive of epididymo-orchitis. ECG findings indicated sinus tachycardia. Findings of lab parameters are detailed in table 1.

Table 1: Findings of laboratory parameters

Laboratory parameters	Results	Laboratory parameters	Results
Troponin I	Normal	Hemoglobin	12.6 g/dL
Creatine kinase	Normal	Total Leukocyte count	19700/cmm
Lipase	Normal	Lymphocyte	7.4%
Lactate dehydrogenase	Normal	Monocyte	11.9%
Prostate-specific antigen	Normal	Eosinophil	2.6%
Thyroid-stimulating hormone	Normal	Platelets	3.63L/cmm
Blood	2+	Hematocrit	34.9
Ketones	Negative	Urea	23 mg/dL
Nitrate	Negative	Creatinine	1.23 mg/dL
Protein	Negative	Plasma glucose	120 mg/dL
Bilirubin	0.5 mg/dL	Albumin	2.7 g/dL
Aspartate aminotransferase	57 IU/L	Alanine transaminase	73 IU/L
Fibrinogen	725 mg/dL (high)	CRP	144 mg/L (high)
Erythrocyte sedimentation rate	93 mm	Haptoglobin	453 mg/dL (high)
Blood culture	No growth	HIV	Negative
Epstein-Barr virus DNA by PCR	Negative	HBsAg	Negative
HBsAb	Negative	HBeAg	Negative
HBeAb	Negative	HBcAb	Positive
HBV DNA	Negative	HCV	Negative
HCV RNA by PCR	Negative	Brucella IgM	Negative
Brucella IgG	Negative	Mumps IgM	<1.2 (considered negative)
Mumps IgG	Positive	Antinuclear antibody	Positive (1:40, 1:160)
Rheumatoid factor	Negative (<30)	Anti-cyclic citrullinated peptide	Negative (<15.6)
Complement tests (C3 and C4)	Normal	Cryoglobulin	Not detected
ANCA	Negative	Serum protein electrophoresis	Normal
Bence Jones protein in urine	Negative	Urine culture	No growth
Stool examination	No ova/parasites detected		

Systemic involvement

The patient exhibited multifaceted system involvement, including genitourinary manifestations such as testicular and epididymal inflammation. Previous TB suggested potential pulmonary engagement, supported by pleural effusion. A history of cough three years ago hints at respiratory involvement, while microscopic hematuria implies renal impairment. Musculoskeletal engagement is evident through nonspecific muscular tenderness and joint pain. Inconclusive indications of gastrointestinal involvement arise from the initial presentation of fever, joint pains, and abdominal discomfort. Despite a mild elevation in liver enzymes, subsequent history and examinations do not strongly support abdominal involvement. This signifies a complex multisystemic condition requiring further evaluation and correlation between clinical findings to ascertain the precise extent of system involvement.

Fever with testicular symptoms

Fever with testicular pain/swelling suggests epididymo-orchitis, characterized by inflammation of the epididymis and testis. This condition is often induced by factors such as infections, vascular issues, trauma, mechanical lesions, and rarely tumors, and presents with localized swelling. Considering the patient's prolonged fever and leukocytosis, infectious etiologies, particularly bacterial infections, could be the cause.

In younger individuals, sexually transmitted diseases (STDs) like gonorrhea or chlamydia are prevalent causes, while in older men with enlarged prostates, *E. coli* infections could be the cause *E. coli* infections are notably frequent in homosexual men. Brucella infections are also a possibility, linked to epididymo-orchitis. Given the patient's history, TB could also cause epididymo-orchitis and systemic infections. Additionally, mumps infection stands out as a potential cause.

Differential diagnoses

1. Epididymo orchitis: Bacterial Infections

In younger individuals, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are common causative agents, while in elderly with enlarged prostates, *E. coli* is the predominant pathogen. Typically, these infections commence with urethritis before progressing to epididymo-orchitis. Classic symptoms encompass urethral discharge, dysuria, and elevated leukocyte counts, often accompanied by increased c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. However, the patient lacked urethral discharge, dysuria, and exhibited no pus cells in the urine. Additionally, urine cultures yielded negative results. Investigations for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were not definitively conducted, likely due to the patient's hospitalization with fever, leukocytosis, and testicular pain.

Considering the hospitalization, it is presumed the patient received antibiotics, but the lack of response, increased testicular pain, and swelling, suggests potential resistance or insufficient efficacy against suspected infections. The lack of response to antibiotics during the hospital stay suggests that the condition may not be responding to standard treatment protocols typically effective for such infections, based on presumptions drawn.

2. Epididymo orchitis: Brucellosis

Testicular and epididymal involvement in brucellosis occurs in approximately 6 to 10% of cases. Orchitis, a common manifestation of brucellosis, can progress to necrotizing orchitis or manifest as

a testicular abscess, occasionally resembling tumor-like masses. However, the patient's tests for Brucella, including IgM and IgG Brucella antibodies, along with blood cultures, yielded negative results.

3. Mumps orchitis

Mumps orchitis typically occurs a few days or weeks after the initial onset of parotid swelling. In rare cases, testicular swelling might precede parotid swelling. However, this patient did not exhibit any parotid swelling either before admission or during the hospital stay. Additionally, tests revealed negative IgM mumps antibodies but positive IgG, indicating a previous infection or vaccination against mumps.

4. Tubercular epididymo-orchitis

Approximately 50% of renal TB cases extend to epididymis and testis. This patient, with a history of TB, ongoing respiratory issues, and elevated ESR and CRP, raises suspicion for tubercular epididymo-orchitis. Typically, subacute, or chronic, it may present with painless enlargement, occasionally exhibiting an acute onset. Despite extensive testing, including negative TB-related tests and cultures, urine analysis ruled out renal TB. While a cartridge-based nucleic acid amplification test (CB-NAAT) for urine could have provided insights into genitourinary TB, it was not conducted. Ultrasonography typically reveals a beaded pattern in the epididymis or hypoechoic areas in the testes, characteristic of tubercular epididymo-orchitis.

In the current patient, there is no indication of reactivated pulmonary TB. Three years ago, computed tomography (CT) scans during evaluation revealed healed granulomas, and in the current admission, both X-ray and CT scans exhibited persistent shadows. Sputum tests returned negative. It is noteworthy that primary tubercular epididymo-orchitis is an infrequent occurrence. Considering the patient's history of prior TB, it is challenging to definitively exclude the possibility of tubercular epididymo-orchitis based solely on clinical grounds. Hence, this remains a plausible consideration in the differential diagnosis for this patient.

5. Trauma/Torsion/Tumor

Torsion typically manifests as a very acute condition demanding immediate surgical intervention. Considering the patient's prolonged symptomatology, the probability of torsion is unlikely. Furthermore, ultrasound findings indicating increased blood flow contradict torsion, which typically presents with decreased or absent blood flow on Doppler imaging.

The absence of trauma in the patient's history allows its exclusion as a causative factor. Although testicular tumors are usually painless, these tumors may cause pain in the presence of hemorrhage or infarction. Diagnostic markers such as elevated beta-human chorionic gonadotropin (hCG) /AFP or specific ultrasound features like heterogeneous enlargement or hypoechoic areas in the testes are typically observed. However, the patient's presentation of painless testicular enlargement accompanied by constitutional symptoms like fever and acute inflammation, adds complexity to the diagnostic landscape. Considering the typical presentation of testicular lymphoma as painless testicular enlargement without constitutional symptoms, it is reasonable to exclude testicular tumors as a differential diagnosis in this case.

6. Vascular etiology: Vasculitis

The testis, a highly vascularized organ, can be implicated in various systemic vasculitis conditions. In this case, the patient's presentations are indicative of a systemic inflammatory condition,

as evidenced by elevated inflammatory markers. Although an extensive investigation for infectious causes yielded no clear leads, the ultrasound evidence displaying engorgement of testicular vessels indicated testicular involvement. Considering these factors, vasculitis emerges as a viable differential diagnosis for this patient, given the suggestive signs of systemic inflammation and potential vascular involvement.

The classification of vasculitis encompasses large vessel vasculitis, medium vessel vasculitis, small vessel vasculitis, and ANCA-associated vasculitis (AAV).

Large vessel vasculitis

Giant cell arteritis: It typically affects the elderly and presents with severe headaches, visual disturbances, and tenderness of the temporal artery. Despite the patient having an elevated ESR, there were no reported symptoms of headaches, visual issues, or indications of temporal artery tenderness during history-taking or examination. Giant cell arteritis usually involves branches of cranial arteries impacting the head and neck, the absence of these hallmark features reasonably excludes the diagnosis in this case.

Takayasu arteritis: It commonly affects younger individuals and primarily involves the aorta and its branches. Clinical manifestations may include claudication, angina, and absent peripheral pulses. However, none of these symptoms align with the presentation of the current patient, allowing for the reasonable exclusion of Takayasu arteritis.

Small vessel vasculitis

IgA vasculitis (Henoch-Schönlein purpura): Henoch-Schönlein purpura typically exhibits a triad of symptoms: rashes, abdominal pain, and arthralgia, commonly observed in children. Testicular involvement can occur, and fever is not a prominent feature. It often presents with mild glomerulonephritis, noted by red blood cell casts in the urine, mild leukocytosis, and elevated IgA levels. However, in the present patient's case, there were no red blood cell casts in the urine. Notably, significant rashes on the lower limbs or other characteristic findings were absent. While the patient reported abdominal pain, further specifics were not available, and there were no typical rashes on the lower limbs, nor any signs of glomerulonephritis with red blood cell casts in the urine. Consequently, vasculitis appears less likely in this.

Cryoglobulinemic vasculitis: It typically manifests with palpable purpura, arthralgia, neuropathy, and glomerulonephritis, often associated with conditions like hepatitis C virus (HCV) infection, myeloma, and connective tissue diseases. However, in the present case, there were no cryoglobulins, HCV test was negative, and the serum protein electrophoresis (SPEP) showed normal findings, ruling out cryoglobulinemic vasculitis.

ANCA-associated vasculitis

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Churg-Strauss, a subtype of small vessel vasculitis, typically presents with peripheral and tissue eosinophilia, asthmatic episodes, skin rashes, and urticaria. Common manifestations include pulmonary infiltrates, mononeuritis multiplex, myocarditis, elevated eosinophil counts, ESR, and CRP, with approximately 50% positive results in ANCA tests. However, in this case, the absence of asthmatic episodes, skin lesions, pulmonary infiltrates, eosinophilia, and negative ANCA test results makes Churg-Strauss vasculitis unlikely.

Granulomatosis with polyangiitis (GPA/Wegener's): It typically features prominent respiratory and renal involvement, characterized by destructive upper airways lesions and lung abnormalities. Around 90% of cases show positive ANCA during active disease phases. Despite stable lung shadows, elevated inflammatory markers, and evidence of prior infections in the patient, there is no indication of destructive lung lesions, upper airway complications, or signs of nephritis. Additionally, the absence of ANCA positivity in this case makes a diagnosis of GPA unlikely.

***Microscopic polyangiitis*:** It involves small and medium-sized arteries, capillaries, and venules, resembling GPA, yet distinct in the absence of upper airway disease and pulmonary nodules. Common features include glomerulonephritis, often presenting as rapidly progressive glomerulonephritis (RPGN), and pulmonary hemorrhages. In approximately 75% of cases, ANCA tests yield positive results. However, in the current case, there is no evidence of pulmonary hemorrhages, glomerulonephritis, or significant respiratory/pulmonary involvement. Additionally, the ANCA test was negative, making the diagnosis of microscopic polyangiitis less probable.

Medium vessel vasculitis

Kawasaki disease: It primarily affects children <5 years of age, often involving coronary arteries, accompanied by mucocutaneous lesions and lymphadenopathy. While typically self-limiting, it can lead to aortic or coronary aneurysms. Considering the patient's age of 58 years, Kawasaki disease can safely be excluded as a diagnosis.

Polyarteritis nodosa (PAN): It affects medium and small-sized arteries, featuring acute necrotizing vasculitis. Early symptoms include fever, myalgia, anorexia, and a general sense of unwellness. While testicular and epididymal pain occurs in approximately 20% of cases, pulmonary involvement is absent, distinguishing it from the current case. Renal complications can lead to hypertension, but typical glomerulonephritis is not observed. PAN is associated with hepatitis B virus (HBV) infection, but the patient's case, with HBV positivity, leukocytosis, elevated ESR, CRP, and negative ANCA tests, presents a more complex scenario.

In this specific case, the patient initially presented with fever and vague musculoskeletal symptoms, followed by testicular pain and swelling. Laboratory analyses indicated an increased WBC, elevated ESR, and CRP, with absent ANCA. The patient's history includes a prior HBV infection, but current indicators suggest a past infection. Despite the positive core antibody, HBV is not the primary cause of PAN; it appears as a coexisting factor.

Although the patient presents lung shadows and occasional respiratory symptoms, these are not indicative of significant lung involvement. The stability of these shadows, along with consistently negative sputum examinations, suggests a lack of active respiratory disease. Despite microscopic hematuria, the absence of red blood cell casts or proteinuria indicates minimal renal involvement. Negative results in extensive investigations for infectious diseases point toward the likelihood of an inflammatory condition, such as vasculitis, rather than an infectious etiology in this patient.

Diagnosis

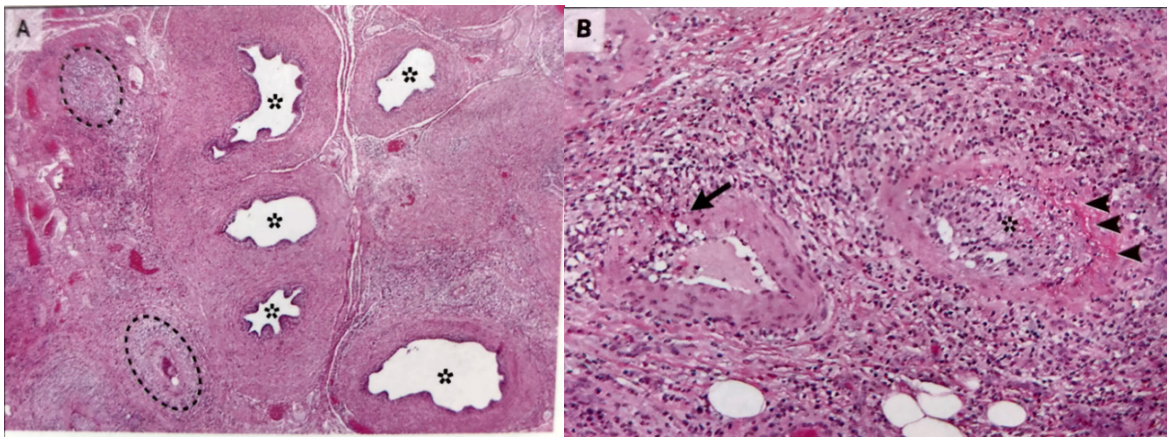
Dr. Srikant Hegde considers PAN as a plausible explanation for various aspects, including testicular involvement resembling epididymo-orchitis. The patient's history of remote HBV infection aligns with this consideration. This historical background becomes crucial due to the risks of TB and hepatitis B

reactivation. To reach a definite diagnosis, the recommended diagnostic procedure is an epididymal and testicular biopsy.

According to Dr. Vijaya Basavaraj, a temporal artery biopsy was initially undertaken due to its accessibility, revealing an inflammation primarily within the outer layer of the arterial wall (adventitia). Sporadic inflammatory cells were noted in the middle (media) and innermost (intima) layers. Verhoeff-Van Gieson (VVG) staining delineated specific areas where disruption of elastic fibers occurred within the inner vascular layer. Additionally, immunohistochemistry (IHC) staining for CD3 and CD163 highlighted the presence of lymphocytes and histiocytes within the inflammatory infiltration, respectively.

The presence of vascular lymphohistiocytic infiltration and disruption of elastic fibers supported a diagnosis of active arteritis. Given that the inflammatory infiltration primarily affected the adventitia rather than the media, the diagnosis leaned towards PAN and ANCA-associated vasculitis. However, the absence of giant cells, as seen in this case, does not entirely exclude giant cell arteritis. A subsequent epididymal biopsy (Fig. 1) revealed significant inflammation surrounding small arteries within fibrovascular connective tissue situated between unremarkable epididymal tubules. These blood vessels exhibited fibrinoid necrosis and were infiltrated by a mixture of inflammatory cells comprising neutrophils, lymphocytes, eosinophils, and histiocytes. The testicular biopsy also indicated necrotizing vasculitis affecting small to medium-sized arteries. These histological observations strongly corroborate a diagnosis of PAN.

Fig.1: Epididymal biopsy showing focal fibrinoid necrosis and transmural inflammation



PAN, first described by Adolph Kussmaul and Rudolph Maier in 1866, primarily targets medium-sized arteries. Unlike antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, PAN usually lacks a known cause. Approximately one-third of PAN cases are linked to chronic hepatitis B, forming HBsAg-HbsAb complexes that deposit in affected vessels. Its clinical impact is due to underlying tissue and organ ischemia, caused by segmental transmural necrotizing inflammation in small to medium-sized arteries, often leading to aneurysms or thrombosis. Kidney, heart, liver, and gastrointestinal vessels are commonly involved, impairing tissue perfusion and causing ulcers, infarctions, or hemorrhages.

While PAN primarily affects young adults, it can occur across all age groups. Its course is often characterized by remitting and episodic patterns, featuring prolonged symptom-free intervals. Due to the scattered nature of vascular involvement, clinical signs and symptoms of PAN can vary significantly. Typical presentations include rapidly escalating hypertension due to renal artery involvement,

abdominal pain, and bloody stools resulting from vascular gastrointestinal lesions, diffuse myalgias, and predominantly motor nerve-related peripheral neuritis. Renal involvement frequently contributes to mortality. Left untreated, PAN tends to be fatal; however, immunosuppressive therapies demonstrate promising outcomes, resulting in remissions or complete recovery in about 90% of cases.

Conclusion

The examination of the small blood vessels in both the testis and epididymis revealed vasculitis features, while the temporal artery displayed signs of active arteritis. Negative findings for ANCAs, cryoglobulins, and infectious diseases, including negative results for *Neisseria* and chlamydia, contribute to the conclusive diagnosis. Clinical investigations and histopathological analysis of the testis and epididymis conclude that the diagnosis is PAN.

Short-course Antibiotics

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Introduction

Recent years have witnessed a significant increase in antibiotic consumption by 36% in Brazil, Russia, India, China, and South Africa (BRICS), which accounts for three-quarters of the overall increase.[1] Short-course antibiotic therapy, aims to achieve optimal therapeutic outcomes while reducing the duration of antibiotic exposure, thereby potentially lowering the risk of resistance development. The present paper provides a brief overview on the safety and efficacy of short-course antibiotic therapy for common bacterial infections.

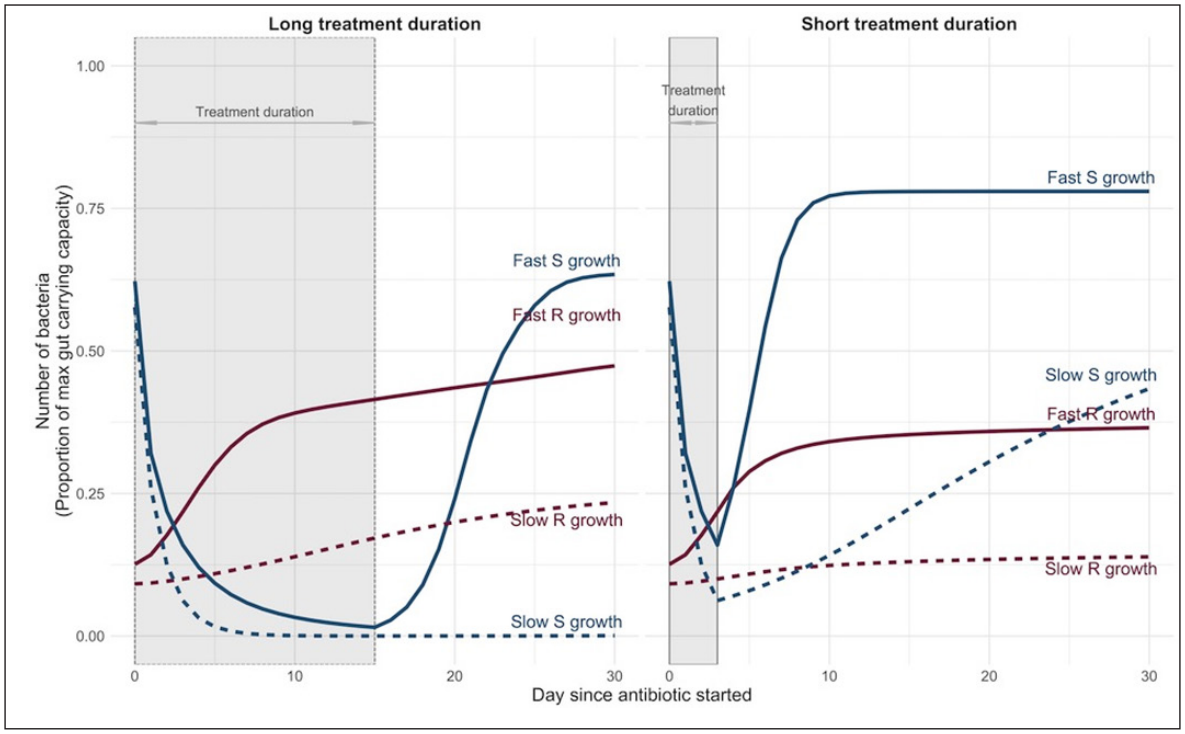
What is adequate antibiotic therapy?

The goals of adequate antibiotic therapy encompass achieving a complete cure of the infection episode, preventing recurrence, minimizing side effects, and avoiding the development of antimicrobial resistance. [2] These objectives collectively contribute to the overall effectiveness and safety of the treatment.[3]

Why shorter course antibiotics?

The overuse of antibiotics, seen in unnecessarily prolonged therapies, contributes to resistance.[4] There is strong evidence supporting the effectiveness of shorter courses of antibiotics, which can be as effective as standard durations. Longer antibiotic treatments can increase the risk of negative effects, such as antibiotic resistance, candidiasis, and *Clostridium difficile* infections, especially in commensal bacteria. Short antibiotic courses work best when resistant bacteria experience rapid growth under antibiotic selection pressure and then decline when treatment stops. However, shortening the treatment duration may increase the presence of resistant bacteria if the antibiotics effectively eliminate colonizing bacteria with a specific resistance phenotype. The rates of bacterial growth and removal without antibiotics are crucial factors linking treatment duration and resistance development, regardless of the antibiotic effectiveness. Longer treatments lead to a higher proportion of resistant bacteria at the end, requiring more time for the resistant population to decrease significantly after treatment termination (Fig. 1).[5]

Fig. 1: Effect of duration of antibiotic exposure on susceptible and resistant bacteria in same host dynamics (15 vs. 3 days)



Source: Mo Y, Oonsivilai M, Lim C, Niehus R, Cooper BS. Implications of reducing antibiotic treatment duration for antimicrobial resistance in hospital settings: A modeling study and meta-analysis. PLOS Medicine. 2023 Jun 15;20(6):e1004013.

Short-course antibiotics for urinary tract infection

Urinary tract infections (UTIs) are common infections that predominantly affect females, leading to over 10.5 million annual medical visits. It is important to start antibiotic treatment promptly in UTI to prevent severe complications such as septic shock and renal scarring in children. However, to address antibiotic resistance, it is important to use antibiotics responsibly and minimize their use for conditions like UTIs.[6] Guidelines recommend short-course antibiotics for lower UTIs without fever, such as nitrofurantoin for 5 days, cotrimoxazole for 3 days, or even a single dose of fosfomycin. However, there is a need for clearer protocols and standardized approaches to address upper UTIs with febrile symptoms.

Supporting the case for short-term antibiotics, a randomized controlled trial (RCT) provides evidence suggesting that discontinuing effective non-fluoroquinolone (FQ) antibiotics on day 7 is sufficient once patients show clinical improvement. This approach is deemed appropriate for hospitalized patients with acute pyelonephritis (APN) who lack severe urosepsis features and underlying urogenital tract abnormalities. Implementing this strategy has the potential to significantly reduce antibiotic usage and shorten hospital stays for these patients.[7]-

Another RCT compared the effectiveness of 7-day and 14-day antibiotic therapy on the resolution of symptoms among men with UTI. The study found that a 7-day course of ciprofloxacin or trimethoprim/sulfamethoxazole provided similar results to a 14-day treatment in resolving symptoms for afebrile men with suspected UTI. For febrile men with UTI, a 2-week treatment duration yielded comparable results to a 4-week regimen. These findings suggest that opting for a 7-day regimen of ciprofloxacin or trimethoprim/sulfamethoxazole could be a suitable alternative to the traditional 14-day course for treating afebrile men with UTI (Table 1).[8]

Table 1: Adverse events of short-term vs. long-term antibiotics in treating UTI in men

Adverse event	**Participants, No./total No. (%)[a]**	
	7-Day antimicrobial + 7-day placebo group (n = 136)	14-Day antimicrobial group (n = 136)
Warfarin dosing affected[b]	2/4 (50)	3/6 (50)
Abnormal blood glucose levels[c]	7/28 (25)	6/36 (17)
Diarrhea	12 (9)	12 (9)
Nausea	8 (6)	9 (7)
Headache	4 (3)	4 (3)
Dizziness	3 (2)	7 (5)
Muscle/joint aches	2 (1)	6 (4)
Tested for Clostridiodes difficile	2 (1)	0
Allergy	0	4 (3)
≥1 Adverse event	28 (21)	33 (24)

[a] The percent values shown in each cell are based on the absolute values in that same cell, not for the number of participants in each study group.

[b] Assessed only in the 10 participants taking warfarin.

[c] Assessed only in the 64 participants with diabetes.

Source: Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men with Urinary Tract Infection: A Randomized Clinical Trial. JAMA. 2021 Jul 27;326(4):324–31.

Short-course antibiotics for pneumonia

Recent studies indicate that short-term antibiotic courses for treating pneumonia are more effective. Moreover, changes in pneumonia treatment guidelines, approved by both the Infectious Diseases Society of America (IDSA) and the Indian Council of Medical Research (ICMR), support this approach. A multicenter cohort study investigated the efficiency and safety of short-course antibiotic therapy in routine clinical settings for patients hospitalized with community-acquired pneumonia (CAP) who exhibit an early clinical response. The study revealed that short-course antibiotic therapy demonstrated

comparable outcomes to prolonged-course therapy in CAP patients with an early clinical response. These findings contribute significantly to the applicability of evidence from RCTs in routine clinical settings, enhancing their relevance.[9]

An RCT assessed whether an 8-day antibiotic treatment is as effective as a 15-day regimen for patients with microbiologically proven ventilator-associated pneumonia (VAP). The study involved 197 patients randomly assigned to an 8-day treatment and 204 to a 15-day regimen, with antibiotic selection guided by the treating physician. For patients receiving appropriate initial empirical therapy, except for those developing nonfermenting Gram-negative bacillus infections, both the 8-day and 15-day treatment regimens demonstrated comparable clinical effectiveness against VAP. Notably, the 8-day group exhibited reduced antibiotic use.[10]

In 2016, IDSA updated the guidelines based on findings from five trials, redefining 'hospital-acquired pneumonia' (HAP) to exclude mechanical ventilation-related cases. To reduce harm and resistance, antibiogram data should be used to limit unnecessary dual antibiotics. Short-course antibiotic therapy is advised for most HAP or VAP patients, regardless of the microbial cause, with a focus on de-escalation.

Short-course antibiotics for bloodstream infections

Bloodstream infections (BSI) pose a significant global threat to morbidity and mortality, arising from either localized infections or being classified as primary when no specific focus is identified. The primary treatment for bacteremia is antibiotic therapy, and efforts should be made to minimize the duration of therapy. Multiple RCTs have shown no significant difference between short and long antibiotic courses in treating severe Gram-negative infections, such as pyelonephritis and complicated intra-abdominal infections. Gram-negative bacteremia is common in these cases, occurring in 10% to 60% of pyelonephritis and <10% to 75% of intra-abdominal infections. Despite guidelines suggesting a broad range of durations (7 to 14 days), the choice often leans towards prolonged treatments due to a lack of data on the appropriate duration.[12] In a recent RCT involving hospitalized patients with Gram-negative bacteremia who were stable and afebrile for at least 48 hours without an ongoing infection focus, a 7-day antibiotic therapy was as effective as a 14-day course. The shorter duration had the added benefits of fewer cumulative antibiotic days within three months and a quicker return to baseline functional capacity.[13]

A systematic review and meta-analysis that supports the use of short-course antibiotics for treating uncomplicated Gram-negative bacteremia found that short-course antibiotics were just as effective as long-course antibiotics. Furthermore, because of the potential for side effects and cost-effectiveness, it may be preferable to use a shorter duration of antibiotic treatment for these patients.[14]

Short-course antibiotics for intra-abdominal infections

Intra-abdominal infections, originating from various sources, can impact any abdominal organ and often require prolonged antibiotic courses due to complex surgeries. Recent suggestions propose that, with sufficient source control, a shorter 3 to 5-day antibiotic course may be effective, reducing the risk of antimicrobial resistance. In line with this finding, a multi-center trial on short-course antimicrobial therapy for intra-abdominal infections revealed that outcomes for patients with adequate source control were similar after a fixed duration (approximately 4 days) or a longer (approximately 8 days)

antibiotic course extending beyond the resolution of physiological abnormalities.[15] A non-inferior RCT reported that the short duration of antibiotics is non-inferior to conventional duration in patients with moderate-to-severe cholangitis in terms of clinical cure, recurrence of cholangitis, and overall mortality.[16]

Short-course antibiotics for skin and soft tissues

Antibiotic treatment for patients with soft tissue encounters challenges, often extending until the reduction of rashes. In the context of necrotizing skin and soft tissue infections (NSTI), a study from a quaternary referral center suggests that a 7-day course of antibiotics following the final operative debridement may suffice. This duration appears effective for NSTI without secondary complicating infections, as clinical characteristics do not seem linked to successful antibiotic discontinuation.[17] Short-course antibiotics offer the advantage of effective treatment with reduced antibiotic exposure, minimizing the risk of antibiotic resistance and potential side effects (Table 2).

Table 2: Advantages of short-course antibiotics over long-term antibiotics in 20 conditions[18]

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9**
Intra-abd Infection	4	8-10	Equal	3
Complex Appendicitis	1-2	5-6	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2Φ
Septic Arthritis	14	28	Equal	1
Bacterial Meningitis (peds)	4-7	7-14	Equal	6
AECB & Sinusitis	≤5	≥7	Equal	>25
Variceal Bleeding	3	7	Equal	1
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	55Ψ
Erythema Migrans (Lyme)	7	14	Equal	1
P. vivax Malaria	7	14	Equal	1
Total: 20 Conditions				>130 RCTs

*Infiltrate on CXR but low CPIS score (≤6), both ventilated and non ventilated, likely CAP, HAP, and VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; Φall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

Source: mysite [Internet]. [cited 2023 Dec 26]. Shorter Is Better. Available from: https://www.bradspellberg.com/shorter-is-better

Conclusion

Shorter courses of antibiotics are proven to be safe and effective in treating common infections among hospitalized patients, including pneumonia, urinary tract infections, and intra-abdominal infections.

These shortened regimens achieve clinical and microbiologic resolution without adverse effects on mortality or recurrence. This approach signifies a significant advancement in antibiotic stewardship, emphasizing targeted and judicious use to minimize adverse effects and address antibiotic resistance concerns. Embracing evidence-based practices is crucial for optimal patient care and preserving the effectiveness of these essential therapeutic agents.

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Long-course of Antibiotics

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Introduction

Prolonged antibiotic course is designed for the complete eradication of pathogens, with the primary objective of preventing the development of antibiotic resistance and reducing the likelihood of recurrence. Determining the optimal duration depends on factors such as the chosen antibiotic, infection severity, and the individual's treatment response. Guidelines, drawn from expert opinions and evidence-based medicine, provide flexibility in selecting short or long courses tailored to individual cases.[1] The present paper discusses literature studies comparing the effectiveness of short vs. long-course antibiotic therapy.

Evidence comparing short- and long-term antibiotics

The primary challenge in the short vs. long-course antibiotics debate is the absence of a specific definition for these terms. The duration that distinguishes short from long remains undefined, leading to confusion about optimal prescription practices. This is further complicated by the absence of established parameters to categorize antibiotics by duration. Additionally, it is unclear whether the same duration should apply universally across clinical conditions or if definitions should vary based on specific medical settings.

Several studies have investigated the superiority of short or long courses of antibiotics. One such study titled 'Short-course vs long-course antibiotic treatment for community-acquired pneumonia (CAP): A literature review', investigated the effectiveness of short-course antibiotics compared to longer courses in treating adults with CAP. Additionally, it explored whether the duration of antibiotic treatment influences the development of resistant bacteria. Out of 4132 screened randomized clinical trial publications, only six were considered relevant. The study defined 5 days as a short course and 7 days as a long course. Critical questions arise regarding the existence of a standardized definition or parameter for determining the appropriate duration. Moreover, there are concerns about the validity of this limited sample size (6 out of 4132 publications) in establishing a definitive duration for antibiotic courses. The study outcome also did not mention the relapse or recurrence of CAP.[2]

The duration of antibiotic treatment has been a longstanding debate in the scientific community, particularly considering the conventional 7-10-day regimen. A study emphasized the need to address other concerns before focusing on the duration of antibiotics. Over prescribing of antibiotics in primary

care significantly contributes to antimicrobial resistance (AMR). A potential strategy to mitigate this issue is addressing inappropriate and repeated antibiotic prescriptions. The study highlights psychosocial drivers behind repeat antibiotic prescriptions and proposes incorporating these drivers into intervention design.[3] Although another study evaluating the effectiveness of antibiotics in adult patients with acute pyelonephritis defined durations ranging from 4 to 14 days for short-course antibiotics and 7 to 42 days for long-course antibiotics, the parameters guiding these durations remain unclear. The systematic review also notes a significantly higher recurrence frequency within 4-6 weeks after short-term therapy, raising questions about the optimal duration.[4]

There is considerable variability in global guidelines on oral antibiotic treatment for infections in outpatient settings. A notable gap exists due to the absence of well-defined guidelines for antibiotic duration for different diseases.[5] The guidelines by Lee et al. for the appropriate use of short-course antibiotics in common infections recommend a 5-day limit for managing COPD exacerbations and acute uncomplicated bronchitis with bacterial signs. For community-acquired pneumonia, they recommend a minimum 5-day antibiotic course, with extension based on validated measures of clinical stability.[6]

The optimal duration for treating bloodstream infections due to Gram-negative bacteremia is unclear. A study comparing short, intermediate, and long courses concluded that short-course therapy yields comparable clinical and microbiological outcomes. However, closer inspection reveals exclusions that may limit generalizability, emphasizing the need for comprehensive baseline guidelines in defining antibiotic durations.[7]

A prospective cohort study reported that antibiotic use across various life stages, particularly during middle and older adulthood, is linked to an elevated risk of future cardiovascular events in elderly women with average risk profiles. The study participants reported their antibiotic usage duration in middle age (40-59) and late adulthood (60 or older), revealing a correlation between prolonged antibiotic exposure and cardiovascular risk. This raises a crucial question: are antibiotics causing adverse outcomes, or are they prolonged due to the severity of the patient's illnesses? The possibility of prolonged inflammation increasing the risks for secondary disease introduces doubts about antibiotics being directly responsible for cardiovascular diseases.[8]

Another study suggested that physicians in the late stages of their careers are more inclined to prescribe prolonged antibiotic courses, underscoring the potential influence of experience. A post-hoc analysis of a sepsis database demonstrated lower 28-day mortality in the short-course group, despite a higher rate of antibiotic re-initiation. However, a discrepancy in the study methodology was observed, as re-initiated antibiotics and hospitalization duration were notably higher in the short-course group.[9,10]

In a comparative study of short versus long-course antibiotic therapy for ventilator-associated pneumonia, a meta-analysis indicated that short courses did not result in more recurrences. However, there was a higher risk of short-term recurrence, a critical aspect overlooked in the analysis. Another meta-analysis favored short-course antibiotics, yet the overall odds ratio for treatment failure was elevated.[11-12] The dilemma arises when dealing with infections like infective endocarditis, deep-seated abscesses, empyema, and enteric fever, where prolonged antibiotic courses are considered necessary.

Conclusion

Defining the proper duration for long and short-course antibiotics is essential for effective treatment. However, current data supporting short-course antibiotics lack clarity, with insufficient explanations for relapse and recurrence risks. Recent studies aim to explore the efficacy and implications of shorter antibiotic treatments, contributing to the ongoing discussions and guiding healthcare professionals in refining prescription practices for optimal patient outcomes.

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