FEVER FOUNDATION

MICRO KNOWLEDGE ACADEMY

FEVER-LOOK-ANALYSE-MANAGE

A HANDBOOK FOR PHYSICIANS

Compilation of articles from

FeFCon-2022

5th Annual Fever Foundation Conference 2022, Bengaluru

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FOREWORD

Fever, or pyrexia, is the elevation of an individual's core body temperature above a 'set-point' regulated by the body's thermoregulatory center in the hypothalamus. This increase in the body's 'set-point' temperature is often due to a physiological process brought about by infectious causes or non-infectious causes such as inflammation, malignancy, or autoimmune processes.

The vast majority of fevers are associated with self-limited infections, most commonly of a viral origin, where the cause of the fever is easily identified. A blunted or absent fever response to infections observed in some elderly patients may be due to defects in thermoregulation. These abnormalities in thermoregulation may include impairment of both behavioral and physiologic responses.

The FeFCon 2022 had eminent speakers discussing on the various aspects of Fever. This book is a collection of topics about fever presented at the Fever Foundation National Conference, FeFCon 2022 - virtual held on 5th, 6th of November, 2022 that helps in gaining better understanding about fever and its management.

M. Maiya

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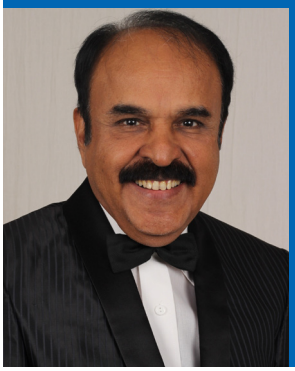
FOREWORD



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

Topics like Emergence of Monkeypox, Haemorrhagic Fevers, Artificial Intelligence in Health Care, Vaccination: Beyond Booster, Emergencies in infectious Diseases, Hyperpyrexia – Causes and Management Newer Drugs in Management of TB, Are we missing typhus, Brucellosis : a diseases of mistakes Fever in intensive care: an open problem, Asymptomatic Bacteruria, Clinico Pathology Cases (CPCs) augurs well.

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

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

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

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

Happy Learning & Happy Learning!

Dr. Muruganathan

Imm. Past Governor American College of Physicians India Chapter,
Dean–Indian College of Physicians (ICP),
Past President Association of Physicians, of India (API)
Organising Chairperson – FeFCon 2022

FOREWORD

Fever or pyrexia is a process where normal body temperature is raised over homeostasis conditions. Although many effects of fever over the immune system have been known for a long time, it has not been until recent studies when these effects have been evaluated in several infection processes. The most frequent causes of fever in acutely ill patients are infection and inflammation, but fever may be caused by one or more of a long list of pathophysiologic processes. The clinician is frequently faced with a situation where, clinical clues are subtle or minimal and a plethora of diagnostic modalities are available, and choosing the best option is a challenge.

The FeFCon 2022 the 5th Annual Conference of fever foundation, was a unique academic conference conducted by the Fever Foundation of India. Highly esteemed and renowned speakers from across India delivered interesting presentations in this academic feast.

This Book is a comprehensive collection of the topics delivered by the esteem faculty. The compilation includes Fever management from pathophysiology of Fever to diagnosis and treatment in different clinical settings.

Hope this FeFCon 2022 book on Fever Management would be helpful in your clinical practice.

Dr. T. S. Ravindra

HOD- Mallige Hospital, Bangalore

Organising Chairperson – FeFCon 2022

PROLOGUE

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 Fifth Annual National conference of Fever Foundation, FeFCon 2022 was held virtually on the 5th and 6th of November, 2022. The theme for the conference was 'Fever Look Analyse Manage'.

The new initiatives in FeFCon 2022 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 2022 Annual Scientific Sessions.

Outstanding presentations were delivered by highly esteemed and renowned faculty during the two days' academic feast of FeFCon 2022.

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.

Sri. G C Surana Oration

Management of Fever: Past, Present, and Future

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Introduction

The meaning, origin and symptoms of fever have changed over time. Based on the duration and severity, several studies have come up with various definitions of fever. Fever management has significantly improved over the years due to the development of newer medications.

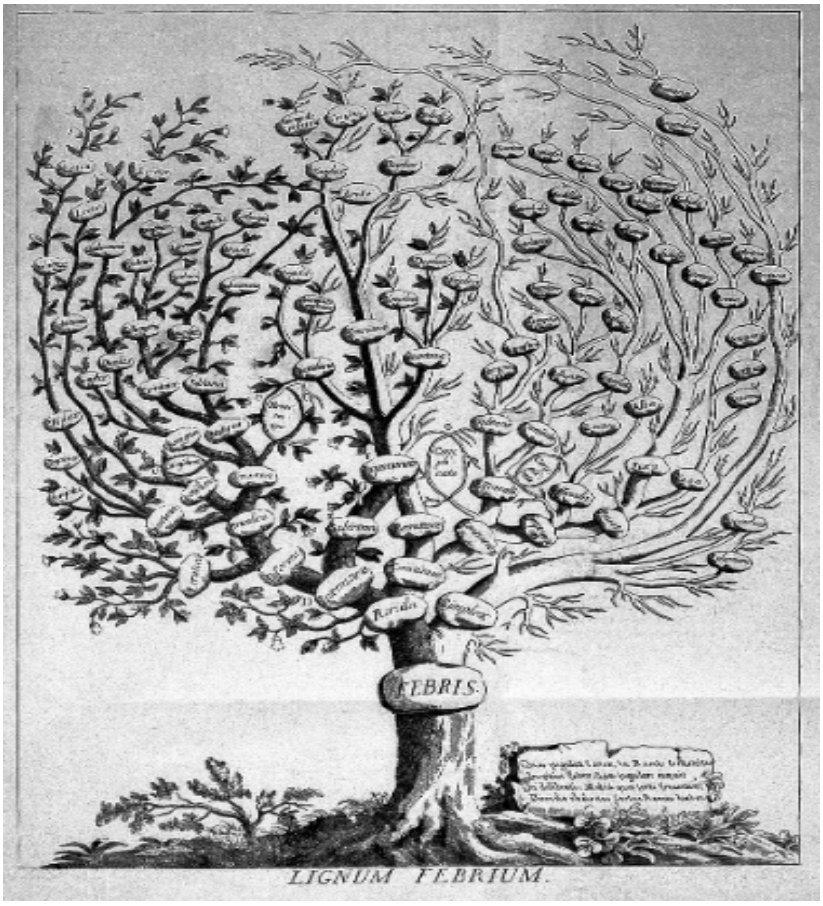
Fever in the past: Philosophy of fever

'Fever phobia', the overconcern or exaggerated misconceptions of parents about fever is prevalent in all socio-economic groups.[1,3] A fever ⩾100.4°F in a one-month-old infant is generally considered a medical emergency. Such young infants are hospitalized and prescribed with several specific investigations and IV antibiotics, before identifying the underlying cause. Nearly one in 25 children suffer from febrile seizures induced by elevated body temperature. Although most kids outgrow febrile seizures without any persisting health problems, they pose major challenges to caregivers. A survey by Eissa et al. observed that a significant number of doctors demonstrated 'lack of knowledge' regarding the nature, dangers, and management of fever in children.[1]

According to an article by LaFrance, an exceptionally high body temperature was considered an indication of the supernatural by the majority of human history. Febris, a Roman goddess of fevers, not only embodied but also guarded against fever and malaria throughout the Roman era. At least three temples in ancient Rome were used to worship a god of fever.[1] As per Hindu tradition, the embodiment of fever is called Jvara, also known as Jvarasura.[2] In the Middle Ages, incantations, elixirs, charms, and exorcisms were used as treatment to get rid of the supernatural aspects of fever.

In the 18th and 19th centuries, the focus was primarily on fever, not on the underlying cause. The newspapers were cluttered with ads of tonics promising to 'cure fever' and stories of people who 'died from fever'. At that time, individuals were treated by inducing vomiting, sweating, or diarrhea. The idea was to get rid of fever by removing bad things through various pores and orifices. In an attempt to link various febrile illnesses, the Italian physician, Francisco Torti created nearly 100 types of fever in a tree structure and published in 1712 (Fig. 1).[1]

Fig. 1: Fever tree by Italian physician Francisco Torti



In the 1970s, doctors still wondered if inciting fever might help to treat an actual infection.[1] Even in the 21st century, philosophies on fever are evolving, and clinicians still debate on the proper treatment for new-born with fever.

Treating fever in the past

Many centuries ago, willow bark was commonly used to treat fever by different civilizations. Ancient Sumerians were the ones who started using willow bark, and Hippocrates and ancient Egyptians recommended the usage.[4] Sushruta Samhita, in an ancient Sanskrit text on medicine and surgery, discusses every aspect of medical art to treat fever. Numerous ingredients including basil, tulsi, onion, raisins, ginger-turmeric, neem tree's flower, green chirayta, mustard oil, apple cider vinegar, garlic, giloy satva, and clove, were recommended as home remedy treatment in children.[5]

Rev Edward Stone discovered that an active ingredient in willow bark can be used as an antipyretic agent. In 1828, Johann Andreas Buschner, a German chemist, isolated salicin from willow bark.[6] In 1850, Raffaele Piria converted salicin into sugar and a second component, which on oxidation

becomes salicylic acid, a major ingredient of aspirin (acetylsalicylic acid).[7] Thomas Maclagan, a Dundee physician, popularly used salicin for treating patients with infectious fevers, especially typhus, typhoid, and smallpox.[8] Friedrich Bayer and Company, UK had subsequently emerged as one of the major manufacturers of aspirin across the world.

In 1877, Harmon Northrop Morse synthesized paracetamol at Johns Hopkins University via the reduction of p-nitrophenol with tin in glacial acetic acid.[9] In 1886, a major medical error of using acetanilide instead of naphthalene demonstrated significant fever reduction in the treated patient. After conducting several investigations, it was marketed as antifebrine to hide its real identity. Further research conducted by Carl Duisberg at Bayer and Company on its by-products led to the discovery of acetophenetidine, an even more powerful antipyretic with fewer side effects. It was marketed as phenacetin.[10]

In 1852, Charles Gerhardt, a French chemist, discovered acetanilide, which was an obscure drug at that time. In 1899, Karl Morner of Germany discovered the relationship between acetaminophen and acetanilide and determined that acetanilide is metabolized into acetaminophen within the body. After ten years, Joseph Freiher con Mering was the first German physician to synthesize acetaminophen. He recommended an extensive investigation into all analgesics and antipyretics, even though his research confirmed the drug's effectiveness against pain and fever. Until 1949, when research on chemically similar medications revived interest in the substance, acetaminophen was neither prescribed nor explored. Modern research techniques and clinical use in England confirmed the effectiveness and safety of the drug as an antipyretic and analgesic.[11]

Biochemists David Lester and Leon Greenberg showed that the body metabolizes phenacetin into acetaminophen, and its effectiveness is comparable to phenacetin. Acetaminophen is not carcinogenic and does not cause methemoglobin. This has led to the wider use of acetaminophen.[12]

Julius Axelrod and Bernard Brodie demonstrated that acetanilide and phenacetin are both metabolized to paracetamol, which is a better-tolerated analgesic. Paracetamol was launched in the US as Tylenol in 1955, and in Britain as Panadol in 1956.[13] In the 1960s, Dr. Stewart Adams discovered ibuprofen, a new potential painkiller, and subsequently launched it as an anti-inflammatory and antipyretic drug in the 1980s.[14]

In 1961, Claude Winder and co-workers from Parke-Davis discovered mefenamic acid, but it has significant side effects and is primarily used as an analgesic. Nimesulide was first launched in Italy as Aulin and Mesulid in 1985. Since several adverse effects had been reported, the Indian Government suspended its use in children <12 years of age from 10 March 2011.[15]

Pathogenesis

Fever is mediated by endogenous pyrogens (cytokines) in response to exogenous pyrogens, which primarily act on thermo-sensitive neurons in the hypothalamus. The body reacts by increasing heat production and decreasing heat loss. Fever, in contrast to hyperthermia, does not increase relentlessly because of the effective control of hypothalamic center. Cytokines play a pivotal role in the immune response. The induction of fever simultaneously with lymphocyte activation provides evidence in favor of the protective role of fever. According to WHO, fever <101°C should be not treated with antipyretic. The protective processes of the immune response are optimal at high temperatures

(around 39.5°C). Certain effects of fever generation such as severe and fulminant infections and septic shock are harmful and lethal. This occurs mainly due to the overproduction of cytokines or imbalance between cytokines and their inhibitors.[16] Humoral, neural, and unrecognized integrated pathways of thermoregulatory circuitry act on the hypothalamic center in the brain to cause fever.[17]

Managing fever in the present

Paracetamol is the drug of choice for treating fever. Although the drug may relieve stuffed or runny noses, it does not affect other symptoms such as sore throat, malaise, sneezing, and cough. It can be used to treat pain and ductal closure in patent ductus arteriosus (PDA).[18] It is available in oral, suppository, and IV forms. Aspirin is contraindicated in pediatric subjects, due to the increased risk for Reye's syndrome. Ibuprofen (10mg/kg/dose) is recommended for children ≥6 months of age, and the duration of action is six to eight hours. It may cause adverse effects like gastritis and gastrointestinal bleeding. The onset of action for oral paracetamol, paracetamol suppositories, and ibuprofen are 30 minutes, 90 minutes, and 15 minutes respectively.

The beneficial role of fever

The human febrile response is a vital component of the immune response and is important to survival to the reproductive age. The hallmark fever response during infection and disease has been maintained for hundreds of millions of years. Febrile temperatures boost the probability of an effective immune response. The pyrogenic cytokine interleukin-6 (IL-6) elevates the core body temperature via thermoregulatory autonomic mechanisms and serves as a thermally sensitive effector molecule that amplifies lymphocyte trafficking into lymphoid organs. There is emerging evidence that adrenergic signaling pathways associated with thermogenesis can greatly influence immune cell function. Thus, the thermal element of fever serves as a systemic alert system that broadly promotes immune surveillance in the setting of infection and disease.[19]

The therapeutic role of fever

There is a hypothesis that fever can have therapeutic value in bacterial infectious diseases like syphilis. Some studies have shown that inducing fever may help in treating cancer patients by the destruction of cancer cells. This research is still in the experimental stage and has not been implemented clinically.[20]

In the omics revolution, different pathways like genomics, transcriptomics, proteomics, lipidomics, metabolomics, and glycomics help in the synthesis of proteins and amino acids. In genomics, different genes help to determine the response to fever. Recently, a study has reported that metabolomics can differentiate between survived and non-survived patients due to COVID-19.[21]

According to a multicentric study by Bhavani et al., temporal compared to oral temperature measurement was associated with lower odds of identifying fever in Black patients, while there was no significant difference in White patients.[22] The origin of different variants associated with familial Mediterranean fever is determined by the machine learning approach.

Pathogenesis of fever-induced febrile seizures

Interleukins (IL-β) transmitted across the blood-brain barrier act on glial cells and disrupt the gamma-

aminobutyric acid (GABA) neurogenic transmission, thereby causing febrile seizures**.** Studies have noted that the overproduction of certain interleukins and their breakdown at the blood-brain barrier may cause seizures in certain children.[23] Hautala et al. reported that serum cytokines in individuals with recurrent febrile seizures were different from individuals with single or no seizures. Researchers are currently investigating the relevance of human virome in febrile illnesses in children.[24]

Technology and fever research

Using a dataset of 4.4 million body temperature measurements and 1.6 million treatment records Choi et al. investigated the effect of antipyretic treatment.[25] Nijman et al. evaluated the potential of a prediction model consisting of clinical signs and symptoms and C-reactive protein (CRP) to identify serious bacterial infections in febrile children.[26]

Non-contact infrared thermometers may not be consistently accurate at all times. The advances in technology have contributed to the development of wearable devices to continuously record vital signs and body temperature to assess and identify infection much faster than conventional methods.[27] With artificial intelligence and machine learning, the costs of the drug discovery process have been significantly reduced by $2 billion, and the process can be completed rapidly, enabling the quicker launch of the drug to the market.[28]

Conclusion

Due to the fever phobia, there has been an increase in the use of antipyretics as the preferred agent for managing fever over the past two decades. The accumulated data have corroborated the protective role of fever in promoting host defense against infection. Recent years have witnessed significant improvement in fever management due to the availability of newer medications. Technology has improved the accessibility for individualized and targeted infection, inflammation, and fever management therapies.

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Review of Poxvirus: Emergence of Monkeypox

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Introduction

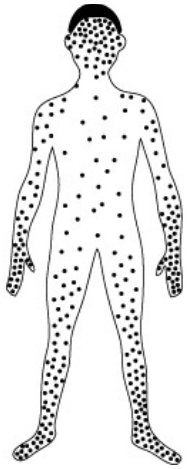
The re-emergence of monkeypox infections in the smallpox post-eradication era poses a major public health challenge, as there are huge knowledge gaps regarding its epidemiology, transmission pattern, and ecology. The present review provides clinical and epidemiological information that may help in effective clinical management and prevention.

When to suspect monkeypox

Monkeypox is a viral zoonosis with the characteristic presentation of monomorphic maculopapular lesions of 2-5 mm in diameter, which often spread in a centrifugal pattern.[1] A proper history collection of the suspected individual should gather details of recent travel, food, medication, and contact with infected patients. It is important to consider whether the patient has traveled to recent outbreak areas.[2]

The disease is endemic in the Democratic Republic of the Congo, and sporadic cases have been reported in Central and West Africa. In May 2022, the cases have been majorly reported in the western part of the world such as Europe and the US.[3,4]

Fig.1: Typical centrifugal rash presentation in monkeypox



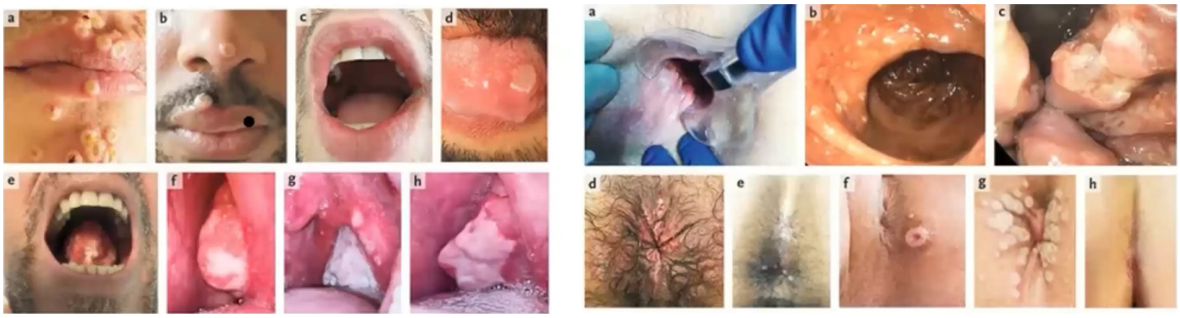
Diagnosis

Polymerase chain reaction (PCR) is the currently preferred technique for diagnosis, as viral culture is time-consuming. The systemic symptoms include rash, fever, joint pain, and lymphadenopathy.[5] The diagnosis should be confirmed by PCR in patients having epidemiological contact, and presenting with centrifugal pattern of monomorphic rash and systemic symptoms.

Monkeypox in 2022

The prodrome of 2022 monkeypox outbreak was different from that of previous outbreaks. The generalized and monomorphic presentation of the rashes was less common in patients and fever was noted only in 50-60% of the cases. Instead of the characteristic centrifugal presentation, the lesions were localized in genital, oral, perioral, and intraoral regions in a pleomorphic pattern (Fig. 1). Increased occurrence of painful vesiculopustular rashes was noted compared to the pleomorphic rashes.[6] Joint pain and lymphadenopathy were noted in certain cases. The outbreak was associated with sexual and intimate contact, especially in men who have sex with men (MSM).[3,4] The transmission was not restricted to the African population, and cases were reported among the general population of US and UK. [3,4] Almost 75-80 countries reported cases of monkeypox.

Fig. 1: Oral, perioral, anal, perianal, and rectal lesions noted in cases reported in 2022



Summary 1: It is important to make a syndromic approach for disease diagnosis. The symptoms and history to be considered for the syndromic approach are listed below:

- Fever, skin rash, and men having sex with men: Monkeypox
- Fever, headache, seizures, and weakness: Meningitis
- Fever, cough, chest pain, and shortness of breath: Pneumonia
- Fever, urgency, dysuria, hematuria, and lower abdominal pain: UTI syndrome
- Fever, diarrhea, dysentery, and vomiting: Acute gastroenteritis syndrome
- Fever and skin rash: Rash syndrome
- Fever, runny nose, sneezing, headache, facial swelling, and throat pain: Rhinitis, pharyngitis, and rhino sinusitis
- Fever, redness, pain, and swelling of the skin: Cellulitis

Route of transmission

Monkeypox virus is a double-stranded DNA virus belonging to the *Orthopoxvirus* genus of the *Poxviridae* family. The disease was first identified in 1958 in research monkeys, and the first human case was reported in 1970. The routes of transmission are respiratory droplets, skin-to-skin, close intimate contact, mucosal surfaces, parenteral (bite or scratch), mother-to-child, and sexual route. [7, 8] HIV- associated immunocompromised individuals are at increased risk of severe disease due to monkeypox. Extended interhuman transmission has also been reported for monkeypox.[9] Since the virus has extended incubation period, post-exposure prophylaxis (PEP) is possible for the disease. The infected patient needs to be in isolation for around 21 days till the lesion crust falls off. [10]

High-risk group

Healthcare workers and MSM are at increased risk of contracting the disease. The risk assessment for the different population categories is summarized in table 1.

Table 1: Monkeypox risk assessment for different population categories

	Persons with multiple sex partners	Broader population	Healthcare professionals			
			Healthcare workers		Laboratory personnel	
			Proper PPE	UE	PP and PPE	UE
Probability	High	Very low	Very low	High	Very low	High
Impact	Low	Low	Low	Low	Low	Moderate
Overall risk	Moderate	Low	Low	Moderate	low	High

MSM: men who have sex with men, UE: unprotected exposure, PP: proper procedure

Summary 2: It is important to know the source of infection, and the route and pattern of transmission. For example, many deaths could have been averted in the recent COVID-19 infection by understanding the transmission dynamics, and other related epidemiological features.

Symptomatic differentiation

The differential diagnoses to be considered for monkeypox are chickenpox, measles, secondary syphilis, and molluscum contagiosum. The classic differentiation between monkeypox and chickenpox is the presentation of rashes. The pattern of lesions is centrifugal for monkeypox, whereas it is centripetal and vesicular in chickenpox (Table 2).[5] Hence adopting a syndromic case management approach is very crucial for the accurate diagnosis of infectious diseases. GeneXpert MPX-specific PCR test helps in concluding the diagnosis and the blood sample can be drawn from vesicular lesions.[11]

Summary 3: It is important to know the ideal diagnostic tests for the accurate diagnosis of infectious diseases. For example, PCR is recommended for monkeypox, malaria, scrub typhus, leptospirosis, and dengue.

Table 2: Symptomatic differentiation of monkeypox, chickenpox, and measles

		Monkeypox	Chickenpox	Measles
Symptoms	Fever	1-3 days before rash	1-2 days before rash	3-5 days before rash
	Rash appearance	Lesions often in one stage of development	Lesions often in multiple stages of development	Lesions often in multiple stages of development
	Rash development	Slow	Rapid	Rapid
	Rash distribution	More dense on face; present on palms and soles	More dense on trunk; Absent on palms and sole	Starts on face and spreads, sometimes reaching hands and feet
	Lymphadenopathy	Present	Absent	Occasional
	Death	Up to 10%	Rare	Varies widely

Summary 4: It is important to include uncommon as well as common diseases in the differential diagnosis.

Management

The risk stratification of the patients such as those with comorbid conditions, severe lesions, and inability to eat helps in effective disease management. Tecovirimat, cidofovir, and immunoglobulins are the preferred anti-viral treatment options for monkeypox.[7,12] JYNNEOS and ACAM2000 are the two currently approved vaccines for the prevention of monkeypox disease. PEP with these vaccines during the incubation period may help in disease prevention.[13]

Summary 5: Prevention through immunization is recommended for infectious diseases such as monkeypox, chickenpox, hepatitis B, meningococcal disease etc. Prevention is also possible even after disease exposure during the incubation period.

Conclusion

In the 2022 monkeypox outbreak, localized lesions with minimal prodromal symptoms were observed, instead of generalized rashes. The classic symptoms of monkeypox include rash, fever, lymphadenopathy, and anogenital pain/ulcer. The differential diagnoses are varicella, molluscum contagiosum, secondary syphilis, and herpes simplex virus infection. The therapy should be symptomatic for stable patients with fewer lesions. PEP should be considered for high-risk individuals. JYNNEOS and ACAM2000 are the two currently available vaccines. However, it is not available in India.

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Hemorrhagic Fevers

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Introduction

Emerging and re-emerging zoonotic diseases, especially hemorrhagic fevers, account for majority of the fevers with exanthem.[1,2] A thorough history collection and clinical examination should be performed while evaluating a child with febrile exanthem for accurate diagnosis. The evaluation should also include local demographic and epidemiological characteristics, particularly exposure to insects, animals, and outbreaks, and examination of rash (point of onset, progression, and distribution).

Hemorrhagic fever and vasculitis

Most of the hemorrhagic fevers are arboviral infections and they are characterized by sudden onset of muscle and joint pain, fever, and bleeding from orifices and internal organs. Dengue, Crimean-Congo hemorrhagic fever, chikungunya, and Ebola are the common viral hemorrhagic fevers.[3] Leptospirosis, rickettsia, and malaria are endemic in many parts of India.[4] Meningococcemia is endemic in north India and the last outbreak was reported in 2010-2012.[5] Clinically recognizable viral hemorrhagic fever needs to be confirmed through rapid diagnostic tests, or molecular or serological diagnosis.

Case study 1

There are many non-infectious causes for fever with hemorrhagic rash such as vasculitis.[6] Vasculitis is an end-stage organ damage pathogenesis that causes inflammation of the blood vessels.[7] It may involve small to big vessels, causing damage to the endothelium or intima. Underlying vasculitis is the hallmark of hemorrhagic rash in immune-mediated diseases such as dengue, COVID-19, rickettsia, and autoimmune and chronic inflammatory disorders. Chronic inflammation of medium and large vessels is mediated through cytokine signaling dependent on JAK3 and JAK1.[7,8] Irrespective of the infectious or non-infectious causes, a however hemorrhagic rash in the ear is always suggestive of vasculitis.

Case study 1

An 11-year-old boy presented with high fever for 4 days, abdominal pain, erythroderma, and petechial rash. Lab findings revealed disproportionate hemoglobin and hematocrit levels, and associated thrombocytopenia. Such dengue-like presentations could be seen in Zika, chikungunya, and Crimean-

Congo hemorrhagic fever. In such cases, it should be noted that musculoskeletal manifestations are more specific for Zika and Chikungunya, and hemoconcentration and thrombocytopenia are exclusive to dengue infection.[9] Non-structural protein 1 (NS1) is a highly sensitive and specific diagnostic test for dengue, and PCR for chikungunya.[10]

Crimean-Congo hemorrhagic fever

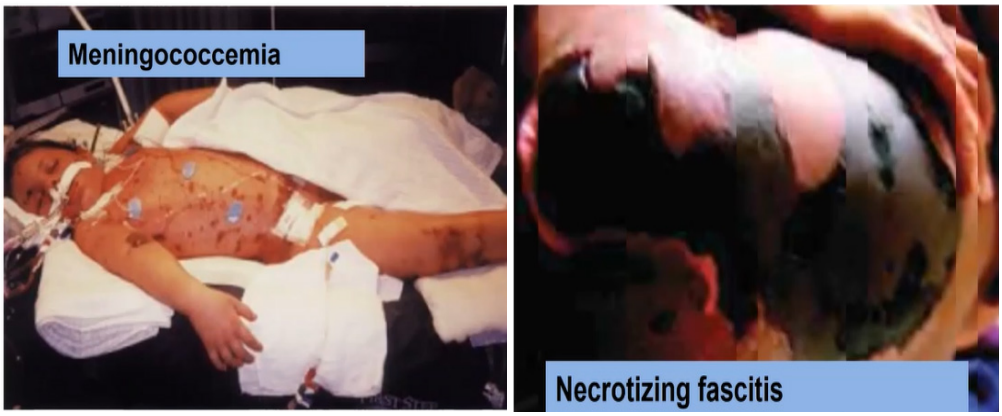
Nearly 80-90% of Crimean-Congo hemorrhagic fever in humans is transmitted through tick bites or direct contact with blood/tissue of livestock or infected wild animals. The disease is predominant in Africa and the first confirmed case in India was reported in 2011 in Ahmadabad, Gujarat. Secondary human-to-human transmission occurs through direct contact with the blood, secretions, organs, or other body fluids of infected persons.[11] It is similar to a dengue-like illness with major bleeding manifestations accompanied by thrombocytopenia and leukopenia.

Case study 2

A 14-year-old boy presented with a short-duration fever, non-specific abdominal pain, vomiting, and respiratory problem. The patient was admitted due to rapid deterioration of vasomotor collapse. His history revealed an initial presentation of diffused erythroderma rash with progression to ecchymosis. Since the patient was admitted during the first COVID-19 wave breakout, multisystem inflammatory syndrome (MIS) related to COVID-19 was suspected. The RT-PCR test for COVID-19, and NS1 and serology tests for dengue were negative; however, the patient had high COVID-19 antibodies. Lab investigations revealed a pro-coagulation state with high D-dimer levels and inflammatory markers. Although multiorgan involvement, LV dysfunction, and prominent coronaries were observed, Z score for the Kawasaki presentation was not qualified. The patient achieved normalcy after 2 weeks of treatment and supportive care. MIS should be suspected in patients presenting with undifferentiated fever with rash, coagulopathy, and no evidence of sepsis.

Meningococcemia and necrotizing fasciitis are the two life-threatening bacterial hemorrhagic fevers that require immediate medical intervention (Fig. 1).[12,13]

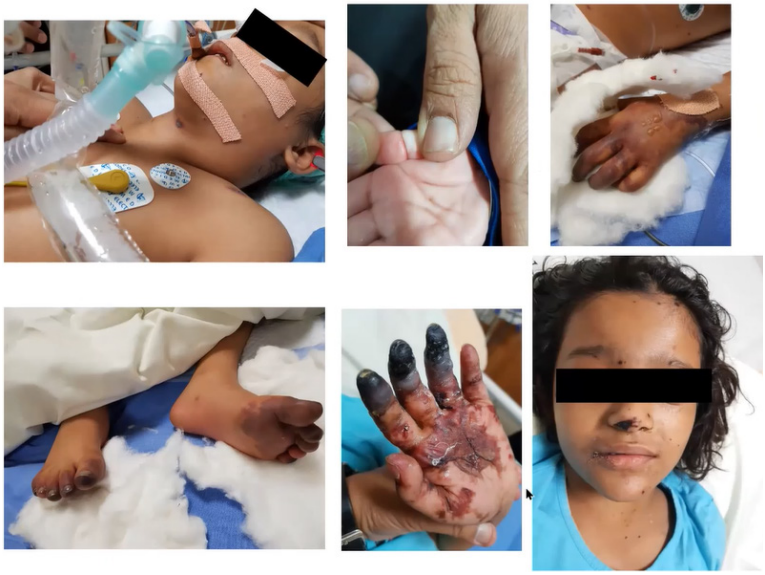
Fig. 1: Meningococcemia and necrotizing fasciitis



Case study 3

A 7-year-old girl who presented with a high fever for 5 days and chills was admitted during the post-monsoon period before the COVID-19 outbreak. Routine investigations were unremarkable, ruling out the possibility of tropical fever. She had persistent fever, altered sensorium, and vesicular lesions appearing on the lymph and face, which progressed to peripheral ecchymosis and gangrenous patches on hands and feet (Fig. 2). Gram-negative sepsis or necrotizing fasciitis with toxic shock rickettsia was suspected. However, the child developed multiorgan involvement and multiple brain infarcts. All the microbiological investigations were negative, except Weil-Felix test for rickettsial infection. The child responded well to doxycycline treatment.

Fig. 2: Presence of vesicular lesions, peripheral ecchymosis and gangrenous patches



In pediatric patients presenting with continuous fever for 4-5 days, myalgia with no lymph node involvement, and exanthem indicative of vasculitis and pleomorphic palmoplantar rash; laboratory investigations should focus on thrombocytopenia, elevated inflammatory markers, hyponatremia, hypoalbuminemia, and rickettsia. Leptospirosis should be suspected in patients with abrupt onset of fever and chills, sepsis-like presentation, conjunctival suffusion, pulmonary hemorrhage, and thrombocytopenia with bleeding manifestations. The diagnosis should be confirmed by Faine's criteria and microscopic agglutination (MAT) test.[14]

Conclusion

The emergence and re-emergence of viral hemorrhagic fevers is a growing concern across the globe due to high case-fatality rates. Due to the differential presentation of hemorrhagic fever, careful evaluation and accurate diagnosis are important for proper intervention. Developing standardized clinical protocols for disease management that integrate infection control measures with comprehensive care for patients is the need of the hour.

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Artificial Intelligence in Healthcare

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Introduction

Healthcare systems in emerging countries like India witness various key challenges such as lack of awareness, inadequate infrastructure, and skilled personnel, limited accessibility, increased cost and unequal distribution of medical care, delay in early diagnosis, and increased prevalence of chronic diseases.[1] The conventional approaches alone may not be sufficient in addressing these challenges and in such scenarios exponential technologies come into play.[1]

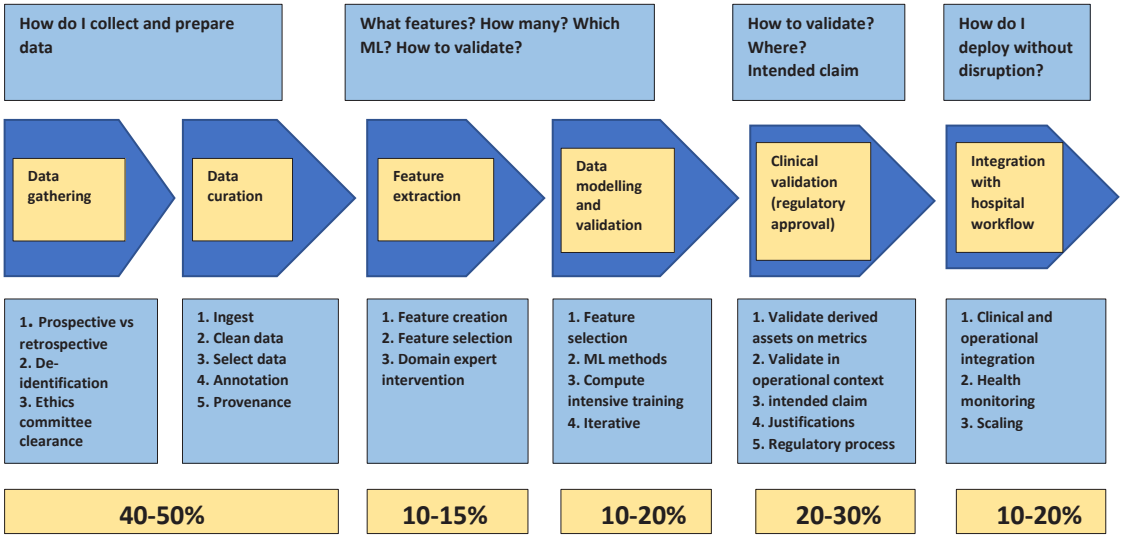
Artificial intelligence assets

Artificial intelligence (AI) is a collection of technologies, which can bring greater transformation to various aspects of patient care. The field of AI research defines itself as the study of 'intelligent agents', any device that perceives its environment and takes action that maximizes its chance of success at some goal.[2] The common AI assets that can be used in the healthcare system are imaging data, waveform data such as the electrocardiogram (ECG), clinical notes and prescriptions, critical care monitoring data, and pathology data such as genomic and molecular information.[3]

Lifecycle of an AI model

The first step in developing an AI algorithm is data collection, preparation, and curation. The second step of feature extraction involves feature creation and selection, and clinical domain expert intervention. The subsequent step of data modeling and validation involves machine learning, deep learning, and compute-intensive and iterative training. Post-development, the model is clinically validated by the concerned regulatory authorities. If the model complies with all the regulatory requirements, it will be integrated into the hospital workflow to assist the doctors and caregivers (Fig. 1).[4] During the development of the model, cleaning, and preparation of data take around 40-50% of the turnaround time, followed by 20-30% in data validation, and around 10% in integration.

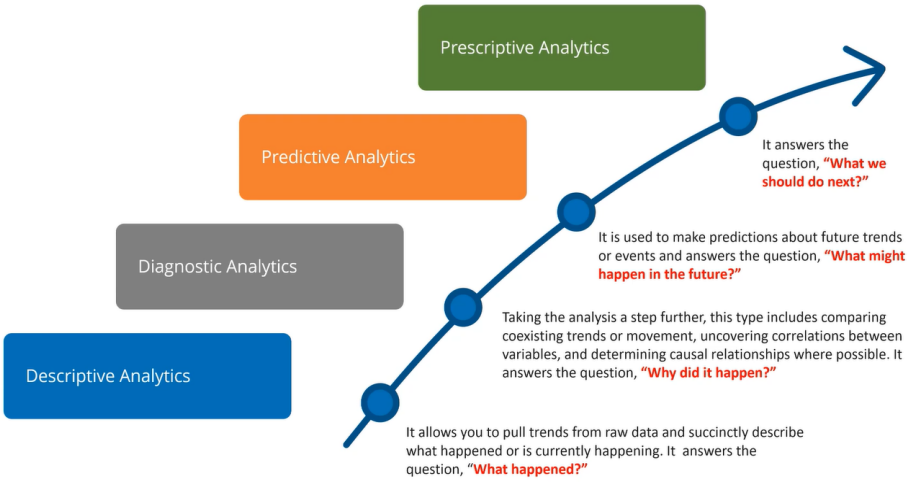
Fig. 1: Lifecycle of an AI model



Types of AI solutions

The commonly used AI solutions in healthcare include descriptive analytics, diagnostic analytics, predictive analytics, and prescriptive analytics (Fig. 2). Descriptive analytics allows the extraction of raw data and succinct analysis of current trends and happening. Diagnostic analytics assists in comparing coexisting trends or movements, uncovering correlations between variables, and determining casual relationships. Predictive analytics employs statistics and modeling techniques to predict future trends and outcomes, and forecast potential scenarios, which may help in strategic decision-making. The prescriptive analysis also helps in data-driven decision-making by considering all the relevant factors.[5]

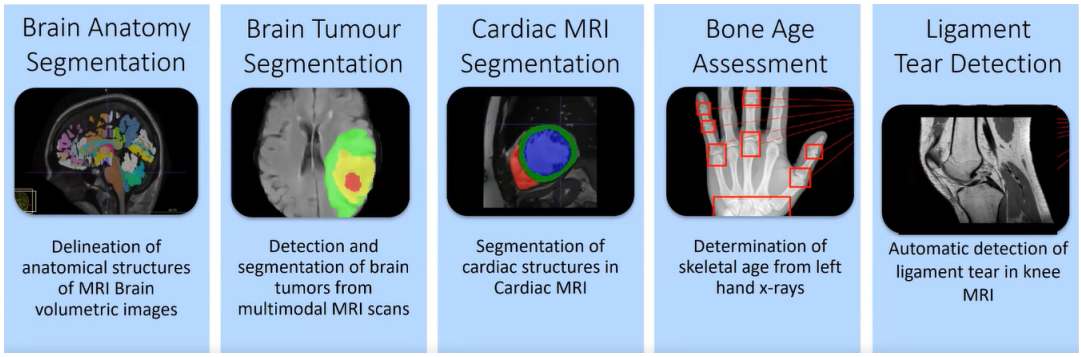
Fig. 2: Types of AI solutions



AI-enabled precision medicine

The implementation of AI in the diagnostic field helps in obtaining more precise images of magnetic resonance imaging (MRI) and computerized tomography (CT) scans, and quicker identification of variations and disease patterns (Fig. 3). AI adoption helps in the analysis of healthcare management at the population level through the interpretation of dense data and conducting risk stratification to implement preventative health programs. Pattern recognition via machine learning can be performed for the interpretation of immense data, and this can be applicable for in-home monitoring as well as ambulatory care in ICU. The convergence of AI and precision medicine facilitates personalized diagnosis and prognostication through real-time monitoring and analysis of vast amounts of untapped data. Evolving sensor technology based on wearable devices helps in detecting abnormalities at a very early stage and also to screen for disease relapse.[6]

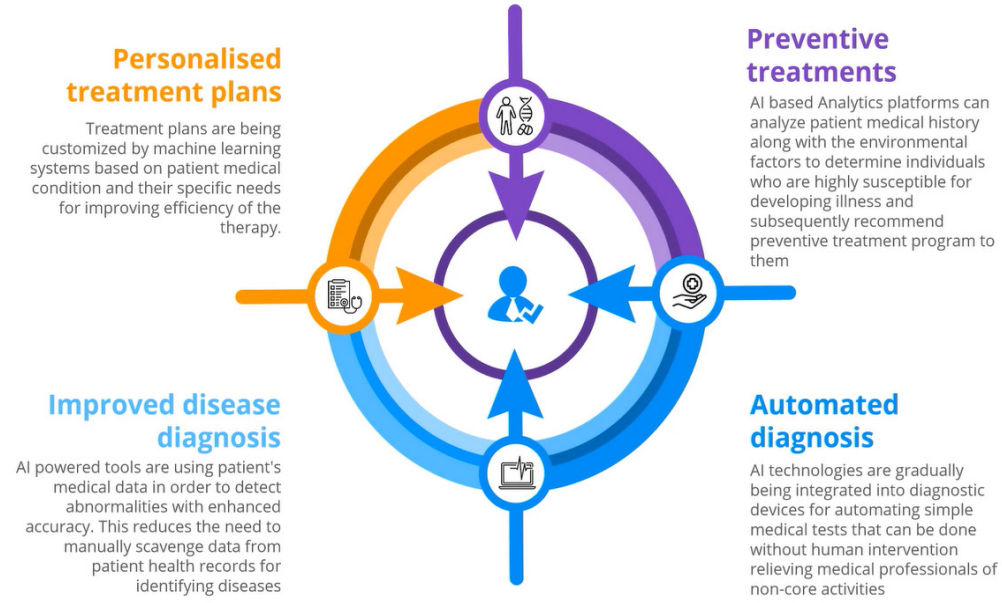
Fig. 3: Uses of AI-enabled products in disease diagnostics



AI trends in the medical device industry

Machine learning algorithms help in customizing the treatment plan based on the patients' medical condition and addressing their specific needs for improving the therapeutic response. AI-powered tools can be used to detect abnormalities with enhanced accuracy, thereby reducing manual efforts related to patient health record screening. AI-based analytic platforms are also used to analyze patient medical history and the associated environmental factors to identify highly susceptible individuals and to recommend customized preventive programs. AI technologies are increasingly being integrated into diagnostic devices for automating simple medical tests (Fig. 4). This in turn helps to reduce human interventions and associated errors and relieve medical professionals from non-core activities.[7,8]

Fig. 4: AI trends in the medical device industry



The iron triangle of healthcare has 3 competing priorities namely cost, quality, and access.[9] Enhancing the quality of care increases the cost and limits patient accessibility; on the other hand, reducing the cost of care improves accessibility, but may impact the quality. The use of cloud-based AI tools in the field of virtual radiology helps in accessing high-quality diagnostic images that can be reviewed by radiologists anywhere across the world, thus enabling access to care for the underserved patient population. The adoption of AI-based self-assessment tools has helped to significantly reduce healthcare costs and eliminate unnecessary interpersonal doctor visits.[10] AI platforms help healthcare providers in identifying patients at higher risk for hospital readmission and treatment decision-making.

Philips has developed an algorithm detection that can be used by type 1 and 2 diabetics to track their consumption, insulin level, activity level, and nutrition, which may help the clinician to customize the treatment plan.[11] The tracking system has helped to reduce the cost of care by 26% and readmissions by 52%.

Adaptive intelligence and population health management

Adaptive intelligence has various uses in diagnostic care such as optimizing speed through intelligent exam setup, enhancing the patient experience through intelligent patient workflow, performing more confident diagnoses and clinically intelligent interpretation, and driving operational efficiency. It has wider applicability in turning communities and homes into care settings, empowering healthcare workers, and improving primary care to decrease the pressure on hospitals. Large-scale clinical, behavioral, and operational data analysis helps in stratifying patients and individuals at high risk to receive timely appropriate treatment intervention.[10,12]

Biophysical modeling

The future of personalized healthcare relies on timely access to appropriate care for every individual in a proper clinical setting. Integration of computational biophysical modeling helps in improving precision diagnostics and therapeutics through the adoption of image analysis algorithms and models to understand clinically relevant entities. For example, customizing the treatment strategy is often challenging in the case of individuals diagnosed with atrial fibrillation, despite the increased prevalence of the disease. In such cases, biophysical modeling can help in creating a patient-specific biophysical model of virtual heart based on patients' medical data. This biophysical model combined with cloud data allows the clinician to select the ideal treatment strategy based on the best possible predicted outcomes. The clinician can carefully plan the procedure by simulating various possible scenarios on the patient's virtual heart model and select the appropriate one that shows the optimal computed result.[13] All unforeseen situations that can occur during any medical procedure can be simulated using the biophysical model to obtain real-time intervention guidance. Thus, biophysical modeling helps in offering patient-centric care through personalized diagnosis, treatment selection, procedure planning, and guidance.

Conclusion

AI-powered healthcare solutions are revolutionizing the healthcare system by providing more accurate tools for early disease prediction, patient risk stratification, and identifying proactive therapeutic course of action. AI thus helps in prioritizing all the 3 components of the iron triangle of healthcare.

However, AI cannot substitute the role of a healthcare provider due to the reasons such as empathy and compassion, the non-linear working method of a clinician, and the requirement of experts' competence to handle complex digital health solutions. Both human skills and technology should work hand in hand to provide optimal patient care.

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Vaccination: Beyond Booster

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Introduction

COVID-19, first reported in Wuhan, China, in December 2019, has highlighted countries' lack of preparedness to fight pandemics.[1] Over the past 2 and a half years, it has infected at least 634 million people worldwide and caused >6.6 million deaths. India has suffered three pandemic waves of COVID, and the second wave was highly devastating.

INDIA COVID-19 timeline

India has the second-highest documented COVID cases (4.46 crore) and the third-highest documented mortality (5.29 lakh) in the world.[2] The first case in India was reported on January 30, 2020, affecting three medical students who had returned from China to Kerala. On 25th March 2020, a nationwide lockdown was imposed to curb the spread of COVID-19. The peak of the first wave of COVID-19 in India was seen in September 2020 with over 90000 cases/day.[3] On 16th January 2021, the COVID-19 vaccination program was launched initially among healthcare workers. The COVID-19 second wave, caused by the delta strain, peaked at 400000 cases per day from March to May 2021. India's first Omicron variant case was reported on 2nd December 2021.[4] The 3rd wave of the pandemic was caused by the Omicron variant in January-February 2022. The Omicron variant cases are still being reported, but with low hospitalization and mortality.

COVID-19 vaccines: Principles and evidence

Over 60 COVID-19 candidate vaccines have been evaluated in human trials, and over 180 in preclinical trials.[5] Following vaccination, the transmission of the disease has been significantly reduced with a decrease in the number of infected subjects and shorter duration of infectivity. The different types of vaccines include inactivated vaccines, live attenuated vaccines, viral vector vaccines (replicating, non-replicating), nucleic acid vaccines (RNA, DNA vaccines), and protein-based vaccines (protein subunit, virus-like particle).[6]

In weakened live-attenuated vaccines, a virus is conventionally weakened by passing through animal or human cells, until it picks up mutations that make it less infectious to cause disease. In inactivated vaccines, the virus is rendered uninfectious using chemicals such as formaldehyde or heat. E.g., Covaxin, Sinovac.[6]

In nucleic acid vaccines, nucleic acid is inserted into a bacteria-derived plasmid, which subsequently produces copies of the virus protein. The spike protein of the virus is encoded in most of these vaccines. The production of RNA- and DNA-based vaccinations is simple and safe. Production of nuclear vaccine requires only the genetic material and not the entire virus. Examples of COVID RNA vaccines are Pfizer-BioNTech and the Moderna COVID-19, and DNA vaccine is ZyCov-D (Zydus Cadilla, DBT India).[6] ChAdOx1 is a non-replicating viral vector vaccine (Covishield) that uses chimpanzee adenovirus (viral vector), and Sputnik (Gamaleya) is a human adenovirus vector vaccine.[6]

Protein subunit vaccines comprise the virus's spike protein or a key part of it called the receptor binding domain. These vaccines might require adjuvants as well as multiple doses for their action. A protein subunit vaccination known as Cobrevax is currently available.[6]

COVID-19 clinical trials

A preclinical study is conducted on animals/primates to assess safety and immunogenicity. Phase 1 is performed on <100 healthy volunteers for dose-ranging, safety, and immunogenicity. Phase II is conducted on 100-1000 volunteers to study immunogenicity and safety. Phase III involves >10000 participants to assess vaccine efficacy in preventing laboratory-confirmed infection and safety. In the traditional paradigm, it takes multiple years for vaccine development, as various phase trials are performed in a step-by-step manner. COVID-19 vaccines became available within <1 year of the pandemic due to the huge investment and rapid simultaneous completion of clinical trials.[7]

The vaccine efficacy is calculated using the following formula:

Vaccine efficacy = (attack rate in the unvaccinated -attack rate in the vaccinated)÷attack rate in the unvaccinated) ×100

Each clinical trial targets a pre-specified number of detected cases for efficacy assessment. US FDA and WHO have provided the following minimal efficacy criteria for licensure: vaccine efficacy should be ⩾ 50% and the lower bound of the 95% confidence interval should be ⩾ 30%. Studies should also assess severe COVID-19 as an additional endpoint.[8]

COVID-19 vaccines roll out in India

In April 2020, the National Expert Group on Vaccination Administration for COVID-19 (NEGVAC) was formed. In October 2020, state-level mechanisms for vaccine programs including cold chains were set up. In November 2020, COVID Suraksha Mission was launched and Rs 900 crores were granted to the Department of Biotechnology (DBT) for the development of the COVID vaccines.[9] In the 2021 budget, 35000 crores were allocated to vaccine procurement.[10] In January 2021, the COVID-19 vaccination program with Covaxin and Covishield has been launched.

Covishield and Covaxin are the two initially approved vaccines in India. Other approved vaccines are Sputnik V, Johnson & Johnson's ZyCov-D, and Corbevax. Corbevax is a protein subunit vaccine that contains a version of the receptor binding domain (RBD) of the SARS-CoV-2 spike protein together with adjuvants. It was initially developed by Texas Children's Hospital and Baylor College of Medicine (USA) and licensed to the Indian company Biological E. Limited.[11] On 28 December 2021, India approved the vaccine for emergency use, and subsequently for pediatric subjects. As per current COVID-19 vaccine statistics in India, over 2.19 billion doses of vaccines have been administered and 70% of

the population is fully vaccinated.[12]

Voysey et al. reported the efficacy of ChAdOx1 nCoV-19 vaccine as 70% and the occurrence of two transverse myelitis cases.[13] Ella et al. estimated the efficacy of an inactivated SARS-CoV-2 vaccine (BBV152) as 77.8%.[14] A test-negative case-control study by Desai et al. reported the adjusted effectiveness of BBV152 against symptomatic COVID-19 after two doses as 50%. These findings support the ongoing roll-out of vaccines for effective disease prevention.[15] Malhotra et al. assessed the reinfection rate of SARS-CoV-2 and the effectiveness of inactivated whole virion vaccine BBV152 against reinfection. The vaccine administration conferred 86% protection against reinfection.[16]

Indian SARS-CoV-2 Genomics Consortia (INSACOG), which was initially established with 10 national laboratories, has expanded to 50 laboratories to study genome sequencing and assess SARS-CoV-2 virus variants in Indian patients. It provides continuous genomic surveillance linked with epidemiological surveillance and clinical correlation.[17] On 12th March 2021, INCASOG reported the discovery of the B.1.617 lineage of SARS-CoV-2. It is called a double mutant, as it combines the mutations at sites E484 and L452 in the same virus. On 11th May 2021, WHO declared a variant belonging to this lineage, the B.1.617.2 (Delta variant), as 'Variant of Concern' considering its increased transmissibility and mortality risk.[18]

Challenges related to waning vaccine effectiveness and emergence of variants

Progressive waning of vaccine protection against SARS-CoV-2 infection over time is a major concern. Gradually decline in the degree of protection against hospitalization and mortality has also been reported, but lesser than the degree of protection against infection. A recent study of state-wide data in North Carolina involving over 10 million adults has also corroborated the waning of protection with time, particularly against infection (Table 1).[19]

Table 1: Findings of analysis of North Carolina state-wide data on vaccine protection and outcomes

Vaccine effectiveness	Against infection	Against hospitalization	Against death
At 7 months	54-70%	86-90%	90-93%
At 12 months	38-47%	60-65%	70-75%

Majority of SARS-CoV-2 genome mutations do not affect viral function. Certain variants have generated widespread attention because of increased transmissibility and disease severity. B.1.1.7 lineage (alpha variant), B.1.351 lineage (beta variant), P.1 lineage (gamma variant), and B.1.617.2 (delta variant) are some of the variants of concern first detected in the United Kingdom, South Africa, Japan/ Brazil, and India respectively.[18] B.1.1.529 Omicron (a variant of concern), which has over 30 mutations in the spike protein including mutations that have been found in other variants of concern, is associated with increased transmissibility and decreased susceptibility to neutralizing antibodies. The COVID-19 vaccinations are still effective in reducing the risk for severe disease with the Omicron variant and its sub-lineages (BA.1, BA.2, BA.2.12.1, BA.4, and BA.5), but their efficacy in preventing symptomatic infection has been diminished.[20]

A case-control study by Andrews et al. has reported that immunity to the omicron variant, 20 weeks after the second vaccine dose, was very low and less than that to the delta variant, regardless of the vaccine type. The study also concluded that a booster dose of mRNA vaccine improved vaccine effectiveness to 65%, but the protection waned over 10 weeks.[21]

Tweaking vaccines to cover new variants

Immunologists are concerned about the emergence of newer variants, which could render the existing vaccines less effective. It is possible to 'tweak' current vaccines to keep up with virus alterations. Tweaking DNA/RNA virus vaccines is simpler and faster than inactivated influenza vaccine, as it requires only modifying the nucleic acid template. Tweaking viral vector vaccine is also possible, however, the host may develop immunity against the vector. Hence, the vector may need to be modified in subsequent immunization.[22] According to Chalkias et al., in contrast to monovalent booster doses, booster doses with bivalent vaccinations that contained the BA.1 spike protein elicited higher levels of neutralizing antibodies against omicron subvariants as well as other variations of concern.[23]

All subjects aged 5 years and older who have finished the primary COVID-19 vaccination series, including those who have already received booster doses with monovalent vaccines, are now advised by the CDC to get one dose of one of the bivalent vaccines at least two months after finishing the primary vaccination series.[24]

Vaccine delivery and vaccine hesitancy

Equitable distribution of vaccines to rich and poor countries is very important to avoid hoarding of vaccines by wealthy nations. However, many countries in Africa have still not vaccinated even 10% of their population.

Around 70% of the population of India is fully vaccinated, and Lazarus et al. have reported that 75% of the Indian population is ready to receive COVID vaccine if proven to be safe and effective. [25] WHO has rated vaccine hesitancy as one of the top 10 global health threats in 2019 and the main reasons are concerns related to side effects and safety, and lack of trust in the process.[26,27] It presents a major obstacle in achieving the intended vaccination coverage and herd immunity. This must be addressed by healthcare providers by making direct recommendations for vaccination, identifying concerns, educating patients on vaccine risks and benefits, and dispelling misconceptions about the disease and the vaccine.[28]

Conclusion

Studies have proven the efficacy and safety of COVID-19 vaccines in preventing infections, hospitalizations, and deaths. However, waning of vaccine protection with time and the emergence of new variants are major concerns. Bivalent vaccines that induce antibodies against newer variants may provide better protection. Global commitment is necessary for equitable vaccine coverage, tackling vaccine hesitancy, and preparing the world for future outbreaks.

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Infectious Disease Emergencies

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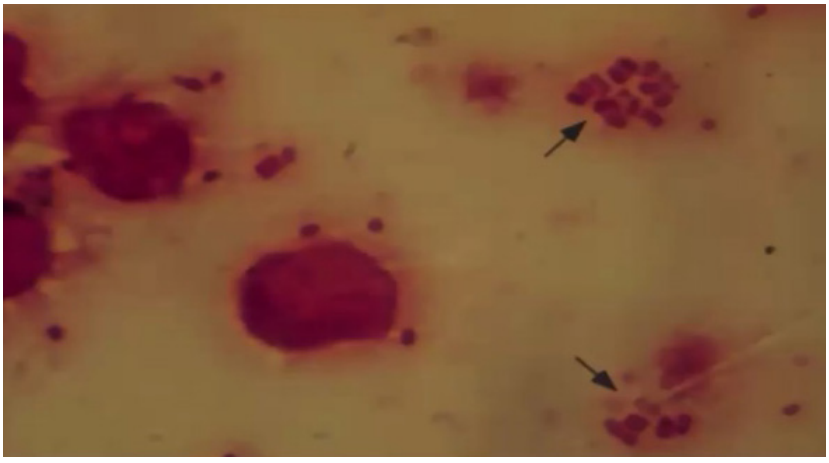
Introduction

The severity of an infectious disease is largely determined by the host's response to the virulence factors of the invading pathogen. Rapid initiation of appropriate antibiotic therapy and controlling the source of infection are the two key critical determinants of host survival. A team-based approach is vital for the effective management of achieving value-based care goals. The present paper discusses some of the challenging cases on infectious disease emergencies.

Case 1

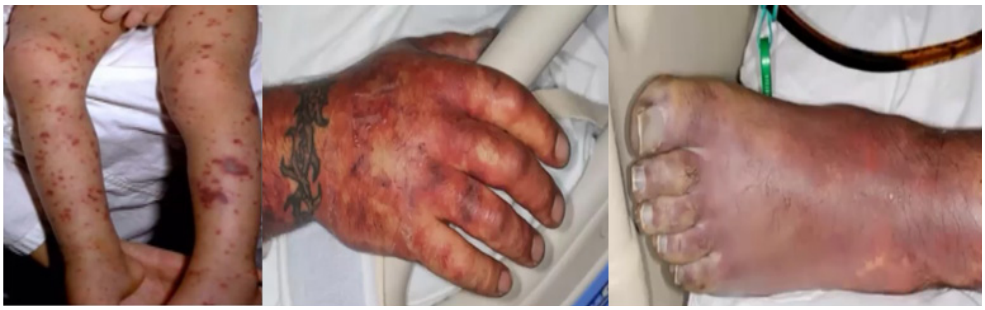
A 23-year-old woman presented to the emergency department with headache, sore throat, and rapid progression of petechial skin lesions over 5 to 10 hours. The patient required emergency intubation, however, she succumbed to death on the following day of admission. Persistence of sub-conjunctival hemorrhage was noted, and Gram stain of the cerebrospinal fluid showed inflammatory cells and kidney-shaped gram-negative diplococci (Fig. 1).

Fig. 1: Gram stain of the cerebrospinal fluid showing inflammatory cells and kidney-shaped gram-negative diplococci



The diagnosis was concluded as life-threatening acute meningitis. Rapid diagnosis, determination of etiology, and institution of therapy are essential to decrease the associated mortality and morbidity. ICU care and rapid administration of antibiotics are the recommended line of management. Typical signs and symptoms include severe headache, photophobia, fever, and neck stiffness, which may progress to delirium and seizure. Petechial lesions or purpura fulminans accompanied by hemorrhagic skin necrosis and inter-vascular thrombosis are often noted (Fig. 2). Delay in antibiotic therapy increases the mortality rate in such cases.[1]

Fig. 2: Petechial lesions and purpura fulminans noted in meningitis



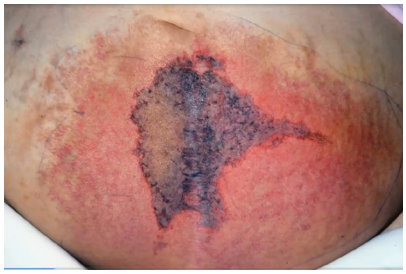
The common bacterial causes of community-acquired infections are *Streptococcus pneumoniae*, *Hemophilus influenza type B*, *Neisseria meningitides Listeria monocytogenes*, *Mycobacterium tuberculosis*, and spirochetes. The viral causes are enterovirus, herpes virus, HIV, arthropod-borne viruses, and measles, mumps and rubella infections. Cerebrospinal fluid analysis (CNS) assists in concluding the diagnosis. Droplet precautions should be instituted in patients suspected with meningitis until treatment has been administered for 48 hours. Close household or school contacts of confirmed cases should receive chemoprophylaxis. Healthcare workers with no close contact with the respiratory secretions of the source patient do not require chemoprophylaxis involving rifampicin 600 mg twice a day for 2 days or single 500-mg dose of ciprofloxacin.

Centre for Disease Control and Prevention recommends the use of meningococcal vaccines for all preteens and teens. The use of meningococcal conjugate (MenACWY) vaccine and serogroup B meningococcal (MenB) vaccines are recommended in certain patient subsets.[2]

Case 2

A 70-year-old female who was admitted for exploratory laparotomy for small bowel obstruction was shifted to surgical ICU postoperatively due to the persistence of hypotension requiring high doses of medications. She had intermittent fever, but her culture findings were negative. On postoperative day 7, a gradually enlarging dark-colored necrosis in the abdominal area was noted (Fig. 3).

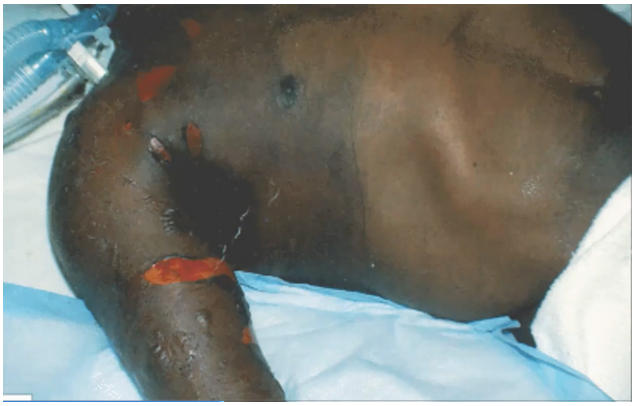
Fig 3: Gangrene (myonecrosis)



Further explorative evaluation concluded the diagnosis as gangrene (myonecrosis) and necrotizing fasciitis. Infection and necrosis of superficial fascia, and subcutaneous fat and deep fascia involving vasculature are often noted. Cellulitis typically shows poorly defined margins, rapid progression, and systemic toxicity. Fournier's gangrene is a type of necrotizing fasciitis that typically affects male genitalia, female perineum, or perianal region. Patients with diabetes mellitus, alcohol abuse, intravenous drug abuse, cirrhosis, and immunosuppression are at increased risk for contracting the disease. The recommended treatment involves immediate wound debridement, intravenous broad-spectrum antibiotics, and hyperbaric oxygen therapy. Treatment delay can cause hemolysis, renal impairment, and death.[3]

Clostridial myonecrosis (Fig. 3) is a life-threatening fulminant clostridial infection of muscle tissue, commonly caused by *Clostridium perfringens*. Rapid worsening and marked systemic toxicity are often noted. Treatment involved urgent surgical debridement and aggressive management using antibiotics.

Fig. 3 Clostridial gas gangrene



Animal bites

Animal bites account for 1% of emergency department visits and the history collection should include type of animal, circumstances of attack, time and location of bite, and health status of animal and patient. The presence of purulence, necrosis, edema, depth and extent of the wound, and neurovascular compromise should be evaluated during physical examination.[4]

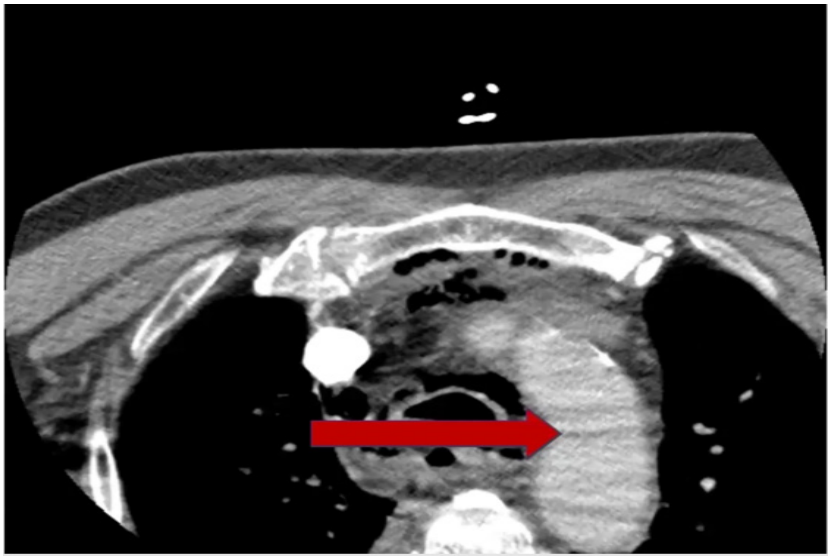
Management measures to be adopted are as follows:[4]

- Prompt wound irrigation
- Removal of any foreign body and debridement of necrotic tissue
- Imaging if fracture is suspected
- Surgical consultation upon hand involvement
- Administration of rabies and tetanus vaccinations in necessary cases
- Administration of prophylactic antibiotics

Case 3

A 65-year-old man with hypertension presented with a three-day history of sore throat, dysphagia, and chest pain. Initial examination showed that he was afebrile without any visible mass. The patient returned the very next day with progressive swelling of the left side of the neck, and drooling/inability to clear his secretions. Lab investigations revealed 26,000 segmented neutrophils and 12,000 bands. CT of neck revealed large abscess and gas in the mediastinum and in the neck, with airway compression and displacement (Fig.4). Postoperative diagnosis showed respiratory obstruction and retropharyngeal abscess with extension into pretracheal and paraesophageal planes, and anterior and middle mediastinum. Culture results were positive for *Beta-hemolytic streptococcus*, group A and anaerobic species.

Fig. 4: CT of neck revealing large abscess and gas in the mediastinum



Extensive exploration and debridement of neck and mediastinum were performed. He was initiated with IV vancomycin, piperacillin/tazobactam, and fluconazole. However, the patient did not survive, despite aggressive surgical management and appropriate antibiotic therapy.

Case 4

A 79-year-old male patient with fever and cough was admitted to the ICU due to suspected sepsis. After a transient period of stabilization, he demonstrated decrease in platelet count and development of necrotic infection on face and extremities. Blood and sputum cultures were positive for *Streptococcus pneumoniae.* The patient was initiated with ceftriaxone 2 gm once daily for 2 weeks. With proper antibiotic use, the necrotic areas on the patient's nose and extremities reversed and his mental status improved.

At least two blood cultures should be obtained before the initiation of antimicrobial therapy in patients with sepsis and associated organ dysfunction.[5] Other cultures such as urine, cerebrospinal fluid, wounds, respiratory secretions, and other body fluids should be obtained based on the clinical requirement. Imaging and sampling should be performed promptly to determine the source and causative organism.[6]

IV antibiotic therapy should be started within the first hour of recognition of severe sepsis after obtaining appropriate cultures. Presumptive choice of antimicrobials should include one or more drugs with activity against probable pathogens, both bacterial and/or fungal, and should be guided by the susceptibility patterns prevalent in the community setting. The broad-spectrum therapy should be continued, until the causative organism and its susceptibilities are defined.[7,8,9] The major causative organisms and presumptive antibiotic choices based on the site of infection are briefed in table 1.

Table 1: Major causative organisms and presumptive antibiotic choices based on the site of infection

	LUNG	ABDOMEN	SKIN SOFT TISSUE	URINARY TRACT	MENINGES
Major CA organisms	*Streptococcus pneumoniae, Hemophilus, Legionella, chlamydia*	E.Coli Bacteroides	S.Aureus S.Pyogenes Mixed	E.Coli Klebsiella Proteus Enterococcus, Enterobacter	S.Pneumo H.Influ Neisseria Listeria
Presumptive abx choices	levofloxacin ceftriaxone	Pip-Tazo, carbapenem	Vancomycin Pip/Tazo	Levofloxacin/ cipro Amp/Gent	Vancomycin, amp, ceftriaxone
Nosocomial organisms	Aerobic GNR	Candida Anaerobes Aerobic GNR	MRSA, Aerobic GNR	Aerobic GNR Enterococci	Aerobic GNR
Presumptive antibiotic choices	Carbapenem, cefepime	Carbapenem cefepime	Vancomycin+ carbapenem/cefepime	Vancomycin+ carbapenem/cefepime	Vancomycin+ carbapenem/cefepime

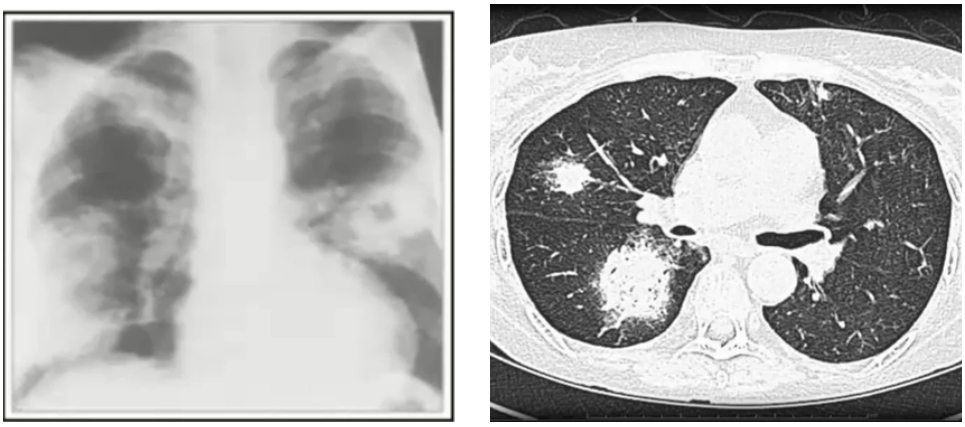
Neutropenic fever

Severe neutropenia, defined as an absolute neutrophil count (ANC) <500 cells/mm^3, is associated with significantly elevated risk for infection and neutropenic fever. Following immediate evaluation, risk assessment, and blood culturing, treatment should start with broad-spectrum empiric antibiotic therapy. Antipseudomonal beta-lactam agents are preferred in Gram-negative infection due to increased morbidity and mortality risk. A fungal infection should be suspected in cases with immunosuppression, and persistent fever and neutropenia for >4–7 days, despite empiric antibiotic therapy.[10]

Aspergillosis

Invasive aspergillosis usually affects immunocompromised individuals, such as those who had recent organ transplantation, patients having prolonged neutropenia, and those on long-term steroids. Invasive aspergillosis most commonly affects the lungs, and may radiologically present with a 'Halo' or ring sign (Fig. 5).[11] Voriconazole and isavuconazole are the first-line drugs indicated for the treatment of aspergillosis.[12]

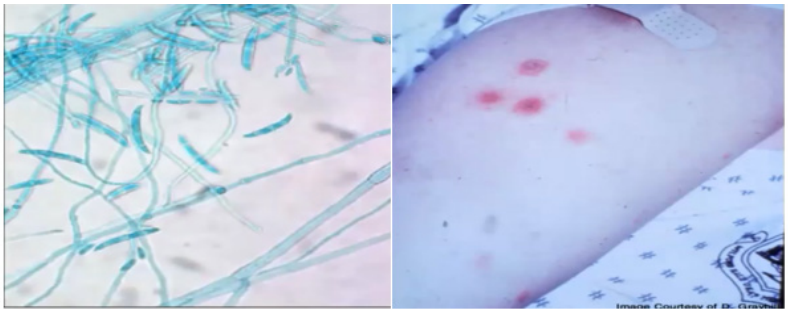
Fig. 5: Radiological findings suggestive of aspergillosis



Case 5

A 36-year-old male diagnosed with acute myeloid leukemia presented with fever and multiple lesions on extremities. Histopathology of the skin lesions revealed acute branching septate hypha and 2 blood cultures performed were positive for fusarium (Fig. 6).

Fig. 6: Findings suggestive of fusariosis



Characteristics presentation of fusarium in histopathology is the septated, nonpigmented hyphae and sickle or canoe-shaped macroconidia with 3-5 internal segments. Four major clinical presentations noted in immunocompromised subjects with invasive fusariosis are pneumonia, disseminated skin lesions, fever and positive blood culture, and superficial infection in the feet and associated lymphangitis. Surgical debridement, and combination antifungal therapy with amphotericin B and voriconazole are the treatment recommendations.[13]

Other infectious ED emergencies

Candida ophthalmitis often poses a diagnostic challenge due to its overlap with other ocular pathologies and highly variable clinical presentations. Mild cases with minimal retinal or vitreous involvement can be managed with systemic antifungal treatment and it is ideal to refer moderate to severe cases to a uveitis specialist.[14] HIV-related opportunistic infections commonly noted in emergency department include pneumonia, histoplasmosis, candidiasis, toxoplasmosis, tuberculosis, coccidioidomycosis, cytomegalovirus infection, and cryptosporidiosis.[15] Management of such infections should be tailored according to the causative organisms.[16] The differential diagnosis to be considered in an international traveler with fever is broad, and high index of suspicion is paramount for accurate diagnosis. Some of the common travel-related infectious diseases reported in an emergency setting include, African tick bite fever, African trypanosomiasis, avian flu, malaria chikungunya, cholera, COVID-19, typhoid, Crimean Congo hemorrhagic fever, dengue, diphtheria, Ebola, HIV and hand, foot, and mouth disease.[17]

Conclusion

The evolution of human history has also witnessed the rapid emergence and mutations that render the infectious pathogens to spread across national and international borders. The development of rapid and accurate antigen detection tests has contributed to the development of pathogen-specific treatment approach over empirical therapy. Emergency clinicians should be aware of current infectious disease outbreaks and the updates from the CDC, WHO, and other international organizations. Complete travel history collection, understanding the full spectrum and course of each disease and appropriate screening and testing are critical to identify and manage infectious diseases in an emergency setting.

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K(No)w antibiotics in OP: When to start? What to start? Why not start?

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Introduction

According to the 2010-2011 National Ambulatory Medical Care Survey published in the *Journal of American Medical Association*, the annual antibiotic prescription rate is 506 per 1000 population, among these only 353 antibiotic prescriptions are estimated to be appropriate. Fleming et al. reported that 1 in 2 patients in the outpatient settings is prescribed with antibiotics. Respiratory infections are the commonest reasons for prescribing medicines and most of the prescriptions are inappropriate. In addition, respiratory tract infections have been identified as the leading cause for prescribing antibiotics and nearly half of these prescriptions have been found to be unnecessary.[1] The present paper focuses on the need for outpatient antibiotic stewardship to prevent the inappropriate prescription practice.

Inappropriate use of antibiotics in OPD settings

The period between the 1950s and 1970s is noted as the golden era of antibiotics, and the *Times* Magazine in 1966 reported a rapid jump in life expectancy by 7 years between 1944-1972. However, the subsequent years have witnessed the emergence of antibiotic-resistant strains.[3] Prolonged exposure to antibiotics allows bacteria to acquire resistance through natural evolutionary processes and/or genetic mutations.[2] India is one of the worst-hit countries, and antibiotic-resistant neonatal infections in the country account for nearly 60,000 neonatal deaths annually.[3] Nowadays, antibiotic resistance among gram-negative bacteria is growing exponentially and powerful broad-spectrum antibiotics like meropenem or imipenem are not sufficient to treat even milder urinary tract infections.[4]

Misuse and overuse of antibiotics in OPD settings have contributed to the emergence of newer antibiotic-resistant strains. During COVID-pandemic, several OPD patients with little supporting evidence of bacterial infection were prescribed antibiotics like azithromycin, doxycycline etc.[5] Infections with antibiotic-resistant strains are associated with severe illness, elevated mortality rates, and increased risk for complications and hospital admission. [2] Antibiotic audits conducted for OPD patients diagnosed with dengue in Indian settings have shown unnecessary use of antibiotics and frequent platelet transfusions (17.33%), despite good platelet count (95%) and good clinical outcome (98%). Implementation of antibiotic supervision programs is warranted to reduce the inappropriate use of antibiotics.

Adverse drug events due to irrational antibiotic use in OPD

Irrational antibiotic prescriptions in OPD settings could be attributed to inadequate patient education, inappropriate prescription practice, self-medication, limited diagnostic facilities, and lack of aggressive marketing.[6] Allergic reactions account for majority of the emergency department visits for antibiotic-associated adverse events (78.7%). Nearly 50% of adverse drug events are linked to the use of penicillin and cephalosporin, among these around 6% require hospitalization.[7] Even antibiotic resistance is observed in neonatal patients with no prior antibiotic exposure.

Some of the reasons noted for antibiotic overuse in OPD practice have been listed below:[8]

- Misconception of increased risk for mortality if immediate treatment is not provided in certain infections
- Difficulty in bacterial culturing or obtaining negative culture result
- Myths, beliefs, and fears linked to routine practice
- Lack of control over aggressive marketing
- Self-medication and non-compliance

Practicing appropriate antibiotic therapy

Some of the important recommendations to practice appropriate antibiotic therapy in an OPD setting are the following:[9, 10]

- A proper diagnosis is the key to choosing appropriate antibiotic therapy, and it is important to define the infection anatomically and microbiologically.
- Antibiotic prescription should be based on culture results.
- Use of imaging, rapid diagnostics, and special procedures during the early course of infection is advocated.
- Therapeutic decisions should be based on recommended guidelines and criteria, and not solely on treatment response
- Empiric therapy should be reassessed 48-72 hours after the initiation of treatment.
- Evaluation of vital parameters, proper localization, and anatomical assessment of the infection is very important.

Four hypothetical scenarios incorporating the moments of antibiotic decision-making in daily practice are listed in table 1.[11]

Table 1: Hypothetical scenarios incorporating the moments of antibiotic decision-making in daily practice

Moments	Scenarios	Patients and symptom descriptions	Decision
1	Does this patient have an infection that requires antibiotics?	The patient is a 34-year-old previously healthy woman with dysuria, fever, hypotension, and flank pain.	The patient has signs and symptoms suggestive of pyelonephritis.
2	Have I ordered appropriate cultures before starting antibiotics? What empirical antibiotic therapy should I initiate?	Urine dipstick indicates pyuria and bacteriuria	◆ Urine and blood cultures are obtained prior to the administration of antibiotic therapy. ◆ Ceftriaxone is prescribed as empirical therapy for pyelonephritis. ◆ Broader therapy is not indicated because the patient has no risk factors for pseudomonal or antibiotic-resistant infection. ◆ Vancomycin is not administered because methicillin-resistant *Staphylococcus aureus* is not a common cause of pyelonephritis.
3	A day or more has passed. Whether antibiotics can be stopped or narrow therapy is preferred? Whether the patient can be shifted from intravenous to oral therapy?	◆ The patient has an appropriate response to therapy ◆ Urine cultures grow *E coli* resistant to trimethoprim and sulfamethoxazole but susceptible to ciprofloxacin.	◆ Because *E Coli* has oral treatment options, ceftriaxone is stopped and ciprofloxacin is initiated. ◆ The patient tolerated oral therapy and showed clinical improvement. Hence, the patient is switched from intravenous to oral therapy.
4	What is the duration of antibiotic therapy needed for this patient?	The patient is on day 3 of therapy and is ready to be discharged home.	◆ Treatment with ciprofloxacin for 7 days has been shown to be effective for pyelonephritis. ◆ The patient is discharged to complete additional 4 days of antibiotic therapy.

Some of the probable diagnoses and suggested investigations for commonly noted signs and symptoms in OPD settings are briefed in table 2.

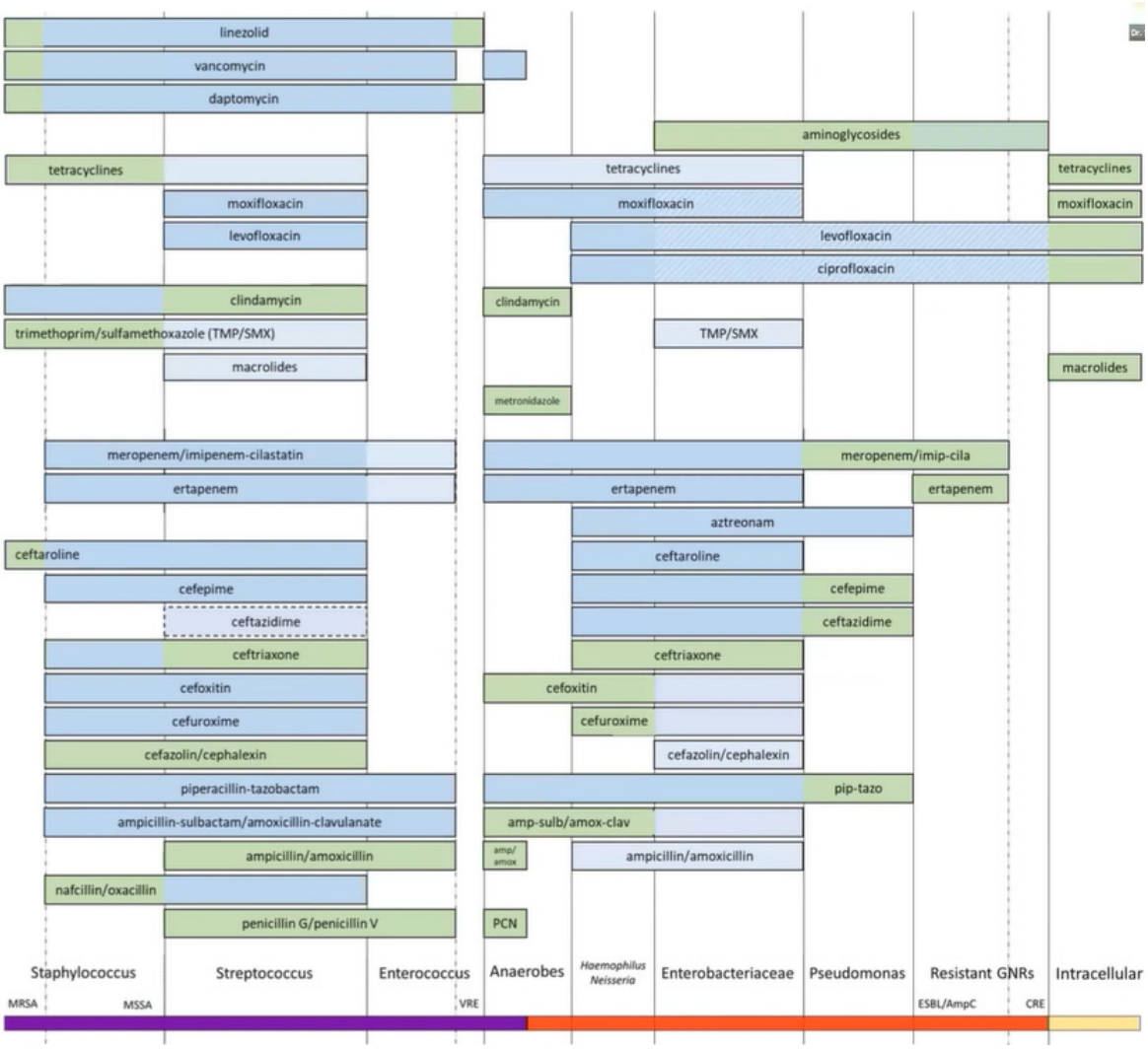
Table 2: Probable diagnoses and suggested investigations for commonly noted signs and symptoms

Minimum think some syndrome

Signs and symptoms	Disease	Investigations
Dyspnoe, cough, SOB, pleuritic pain, discoloured sputum	CAP	Chest X-ray, sputum culture, Throat swab
Severe sore throat/ Fever, Nose block	Pharyngitis/tonsillitis, Sinusitis	Centor score
Frequency, dysuria, loin pain	UTI	U/a, urine culture
Headache, neck stiffness	Meningitis	LP, Imaging, Blood C & S
Ear secretion, headache	Otitis media/ externa	Tissue/ pus culture
Diarrhea/ Vomiting, Abdominal pain	AGE	Symptomatic treatment
Pain & swelling at a joint	Septic arthritis	Joint aspiration, imaging
Bone pain (worse at night)	Osteomyelitis	X-ray, CT, Aspiration
Cutaneous inflammation	erysipelas, cellulitis	Culture, Drainage

Appropriate antibiotic should be chosen from multiple choices after weighing the pros and cons associated with each drug (Fig. 1). Physicians' knowledge of the antibiotic spectrum and sufficient patient education is also paramount for appropriate antibiotic therapy. Antibiotic delay is acceptable in certain infections like acute bronchitis, otitis media with effusion, upper respiratory infection, acute pharyngitis, and rhinosinusitis.[12] Spurling et al. have noted that a delayed antibiotics strategy, instead of an immediate prescription, helped to significantly reduce unnecessary antibiotic use for respiratory tract infections and associated antibiotic resistance, without compromising patient satisfaction and safety.[13] Short-term antibiotic therapy also helps to reduce antibiotic resistance.

Fig. 1: Choice of appropriate antibiotic therapy based on the organisms involved



UTI and antibiotic therapy

UTI is one of the most common infections reported in community and inpatient settings. The disease accounts for 8.6 million visits (84% females) and associated cost of $ 1.6 billion annually.[14] The antibiotic resistance pattern of Indian patients is entirely different from that of Europe or US subjects. Accurate and timely diagnosis with proper symptoms like fever, dysuria, and hematuria is important to prescribe appropriate treatment. Common signs and symptoms that help in distinguishing lower and upper UTIs are briefed in table 3.

Table 3: Common signs and symptoms to distinguish lower and upper UTIs

Lower UTI	Upper UTI
Dysuria	Flank pain
Frequency	Fever
Urgency	Chills
Hematuria	Malaise
Suprapubic discomfort	Nausea, vomiting
Incontinence	Costovertebral angle tenderness
Nocturia	

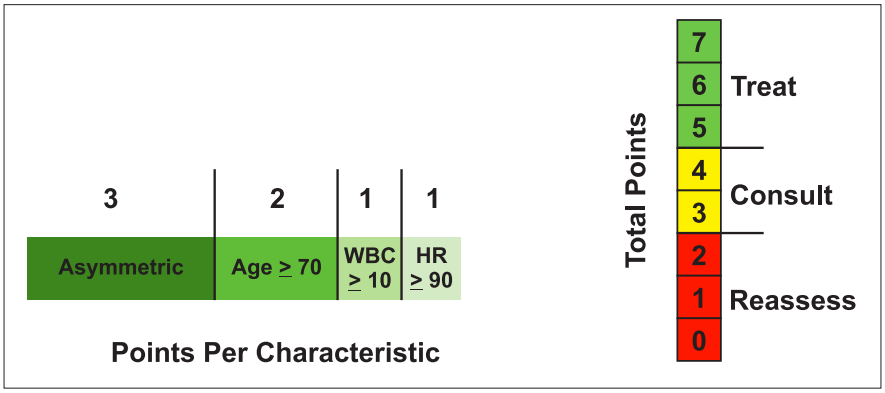
The absence of pyuria may be useful to exclude urinary infection, but the presence of pyuria may not confirm bacteriuria or differentiate symptomatic UTI from asymptomatic bacteriuria. Antibiotic prophylaxis should be prescribed for 48 hours in patients with asymptomatic bacteriuria (pus cells $>10^5$) scheduled for invasive urinary procedures. Urinary culture should be prescribed only in the presence of symptoms and positive urine routine results, as unnecessary culturing may lead to inappropriate antibiotic use. Ofloxacin, levofloxacin ciprofloxacin and nitrofurantoin are commonly used antibiotics for treating lower UTI. Some of the therapeutic advantages of nitrofurantoin are as follows:[15]

- Sufficient antimicrobial activity against *E. coli* and other enterobacteria for treating uncomplicated UTI.
- Lesser drug resistance by uropathogens (*E. coli* <2%)
- Ideal for the empiric treatment of uncomplicated cystitis
- No cross-resistance with commonly prescribed antimicrobial agents.
- No blood, prostate or kidney penetration

Co-trimoxazole is also indicated for the management of UTI; however, the treatment is associated with serious adverse effects like bone marrow suppression, hypokalemia, hypoglycemia, etc. Hence, potassium, creatinine, and blood counts should be monitored prior to and during the co-trimoxazole treatment.[16]

Asymmetry, leukocytosis, tachycardia, and age are clinical variables scored by the ALT-70 predictive model to identify leg cellulitis (Fig. 2).[17] Antibiotics can be prescribed to patients fulfilling these criteria.

Fig. 2: ALT-70 score predictive model to identify leg cellulitis



Intestinal infections and antibiotics

Distinguishing diarrhea from dysentery is paramount to prescribing the appropriate antibiotic therapy. The pathophysiology that may help to differentiate them is briefed in table 4.

Table 4: Pathophysiology distinguishing diarrhea and dysentery

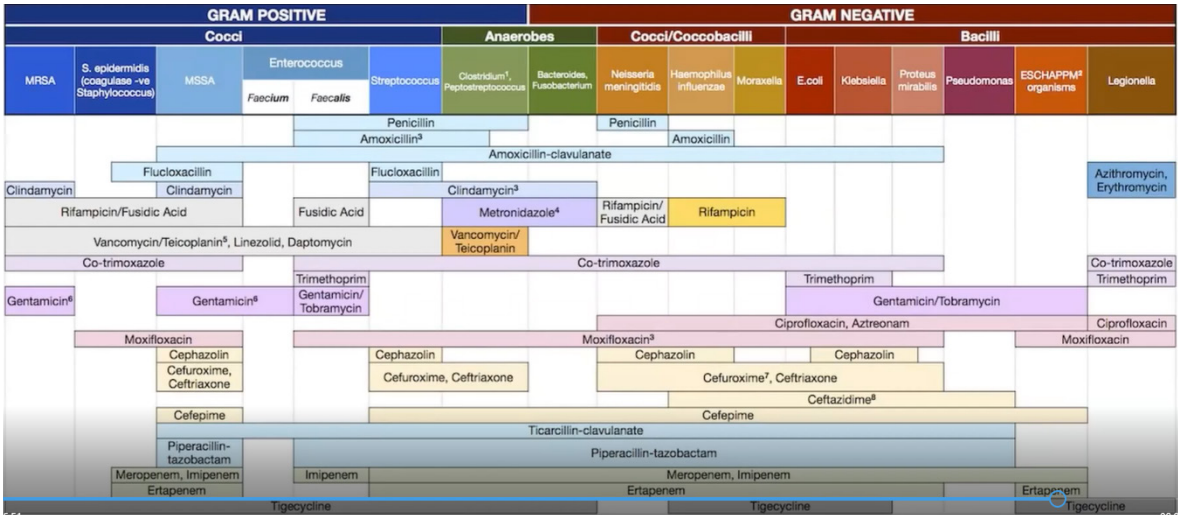
Diarrhea	Dysentery
Proxima small bowel infection enterotoxin/adherence/superficial invasion	Colon infection Invasion/cytotoxin
No fecal WBC Minimal or no lactoferrin	Fecal WBC (+) High lactoferrin
Large volume, less frequent stools, no blood or mucus	Small volume, frequent stools, blood/mucus (+)

Less frequency of bowel movement, absence of fever, and watery stools are mostly suggestive of viral etiology for diarrhea, which does not require antibiotic treatment. Rifaximin is ideal for the treatment of gastrointestinal diseases due to broad-spectrum antimicrobial activity, high fecal concentrations, low systemic absorption, and fewer concerns regarding the development of resistance by extraintestinal flora.[18] Fluoroquinolones and rifaximin are not generally effective for the treatment of Campylobacter diarrhea due to the expected antimicrobial resistance patterns.[18]

Single-dose azithromycin is recommended as empirical therapy for traveler's diarrhea in Thailand.[20] Azithromycin is a reasonable first-line option for the empirical management of visitors to high-risk destinations.

It is important to determine the antibiotic spectrum, whether the antibiotic will cover, Gram-positive, Gram-negative, anaerobes, Pseudomonas, and Methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. 1).

Fig. 3: Choice of appropriate antibiotic therapy based on the organisms involved



Prescribing the optimal dose

Optimization of antibiotic dosing helps in minimizing the resistance emergence. The recommended adult and pediatric doses of some of the commonly used antibiotics are listed in table 4.[21]

Table 4: Recommended adult and pediatric doses of some of the commonly used antibiotics

Antibiotic	Adult Dose	Pediatric Dose	Common Side Effects
Penicillin G (IV)	12-24 million units in a day given either q 4th hourly to 6th hourly doses	50,000 units/kg dose q 6th hourly	Hypersensitivity and anaphylaxis reactions
Amoxicillin - Clavulanic acid	625 mg q 8th hourly to 1 g twice daily	45-90 mg/kg/day in 2-3 divided doses	Rash, diarrhea, AST, ALT elevations
Cephalexin	500-750 mg q 8th hourly	30-40 mg/kg/day in three divided doses	Rash, transient neutropenia, arthralgia
Cefixime	400 mg q 8-12 hourly	15-20 mg/kg/day in two divided doses	Diarrhea, rash, leukopenia, and elevated AST/ALT
Ceftriaxone	1-2 g IV q 12-24 hourly	50-100 mg/kg/day in 1-2 divided doses	Gall bladder sledging, liver enzyme elevation and renal toxicity
Cefotaxime	2 g IV q 6-8th hourly	100-200 mg/kg/day in 4-6 divided doses	Arrythmias, transient elevation in liver enzymes and renal toxicity
Cefazolin	2 g q 6-8th hourly	100 mg/kg/day in 3-4 divided doses	Rash, elevated liver enzymes, eosinophilia, renal toxicity
Cefuroxime	750 mg - 1.5kg 8th hourly	75-100 mg/kg/day in three divided doses	Rash, leukopenia, allergic reactions

Conclusion

Misuse and overuse of antibiotics are major public health challenges that account for the emergence and spreading of newer antibiotic-resistant strains globally. It is imperative that all healthcare professionals should use communication technologies for the exchange of valid information regarding diagnosis, treatment, and prevention of diseases. Conducting telemedicine-based training and mentoring programs helps to raise clinicians' awareness regarding appropriate antibiotic therapy, thereby to optimize clinical outcomes. Coordinated medicine policy implementation is also warranted to promote the prudent use of antibiotic drugs.

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Hyperpyrexia: Causes and Management

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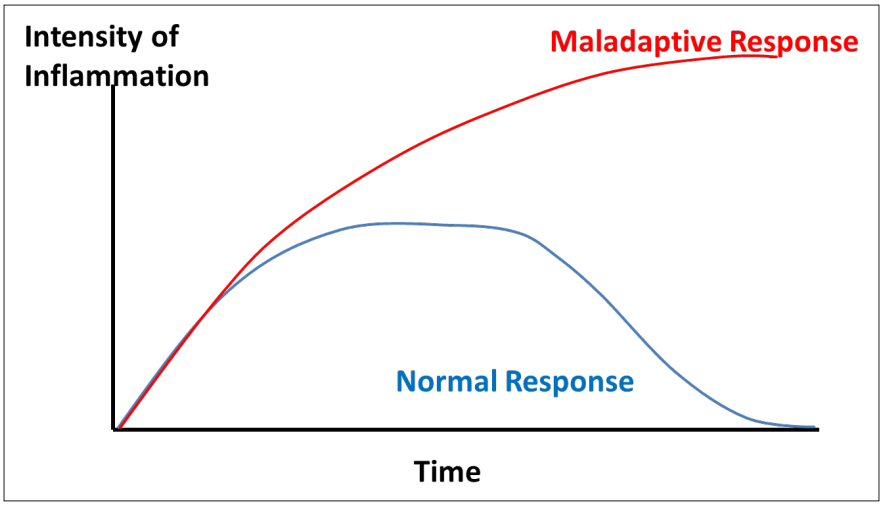
Introduction

Although hyperpyrexia has been recognized as one of the oldest vital signs indicative of an underlying pathology, it is still poorly understood. There are no well-defined criteria as well as technology for recording, assessment, and interpretation of hyperpyrexia.

Fever and maladaptive response

The inflammatory cues delivered by the thermal component are crucial for the stimulation of both innate and adaptive immune responses. The well-coordinated interplay between the innate immune system and neuronal circuitry regulates the induction and maintenance of fever during infection. Normal phase of innate immune response reaches a plateau level with time and this well-coordinated response is important for the proper activation cascade of multiple cellular and humoral elements. However, an uncontrolled maladaptive response can lead to excessive activation and recruitment of immune cells, which may have deleterious effects on the host including organ failure (Fig. 1).

Fig. 1: Maladaptive response of immune system



Hyperthermia, fever, and hyperpyrexia

Fever is a pyrogen-mediated rise in the hypothalamus set point resulting in the elevation of body temperature. In hyperthermia, the temperature set point is not altered and the temperature is elevated by external or internal mechanisms.[1] It is important to understand the underlying mechanism to customize the treatment. Hyperpyrexia is a medical emergency, which can result in organ damage and death, if left untreated. The term hyperpyrexia is exclusively reserved for defining uncontrolled febrile response to pyrogen that exceeds a particular threshold, i.e. 106°F (41°C) in infections.[2] The functional definition of hyperpyrexia is defined as a state in which the internal temperature of the body is so high as to interfere with the physiological mechanisms regulating the body temperature.[3] However, in clinical practice, the treatment should be based on medical judgment, and it is not always necessary to wait to reach 106°F to initiate the treatment.

Shivering

Shivering is a thermoregulatory reflex induced by the core temperature lower than the hypothalamic set point. It imposes significant metabolic burden and discomfort on the host than a steady state of elevated body temperature. If shivering is not controlled by external cooling, it can cause a rise rather than a fall in oxygen consumption, which increases energy demand and may exacerbate hypoxemia.[4]

Core vs. surface temperature

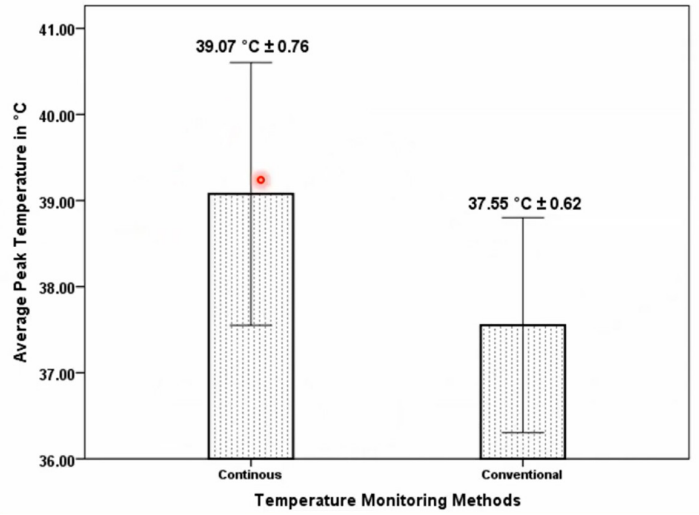
Core body temperature is the ideal indicator of a person's health status and studies have reported that surface temperature measurement cannot accurately predict core temperature in hyperthermic conditions. In hyperpyrexia, core temperature should always be considered rather than the surface temperature. The ideal sites for measurement are tympanic sites and rectal measurements; however, oral measurements can be inaccurate at high temperatures.[1,5,6]

Temperature recording

A study by Mahabala et al. comparing sublignual and tympanic temperature recordings reported that at steady state, the difference between the temperatures was 0.50°C and it increased to 1.5°C at temperatures >39°C.[7] Hence if the oral temperature is 39°C, the core temperature could have already reached 41°C. Mazerolle et al. upon comparing oral and rectal temperatures reported that oral temperature lagged behind rectal temperature by about 1.5°C at temperatures >39°C.[6] Hence It is very important to measure core temperature in hyperpyrexia.

A study by Dakappa et al. comparing conventional axillary temperature and continuous tympanic temperature recordings reported that in one-third of the patients who genuinely experienced intermittent fever, continuous temperature recording was able to provide the true nature of the condition over the conventional technique. In addition, there was a 1.52°C statistically significant and clinically meaningful difference between the average peak temperatures measured using the two distinct techniques (Fig 2).[7] These findings have corroborated the fact that axillary, tympanic, and sublingual temperature recordings may not be appropriate while managing patients having very high temperature.

Fig. 2: Difference in average peak temperature between tympani and axillary recordings[7]



Causes of hyperpyrexia

The causes of hyperpyrexia are majorly non-infectious such as intracerebral hemorrhage (ICH), thalamic involvement, and trauma. Infectious causes include malaria, tetanus, and other tropical fevers. Central nervous system infection, enteroviral infections, and COVID-19 are associated with hyperpyrexia of increased severity. Thyrotoxicosis and a variety of drugs including anesthetic agents can also cause hyperpyrexia.[1,8,9]

COVID-19 and hyperpyrexia

COVID-19 may cause hyperpyrexia due to cytokine storm, direct brain injury from SAR-COV-2, or vascular thrombosis. Studies have reported that hyperpyrexia may adversely impact the treatment outcomes and mortality in patients with COVID-19.[10] Hence it is important to measure the core temperature in COVID patients.

Hyperthermia vs. hyperpyrexia

The clinical differentiation between hyperpyrexia and hyperthermia is challenging, as both have almost similar presentations. Circumstances leading to high temperature provide the clue. Antipyretics act by reducing the setpoint of the hypothalamus, hence they are not beneficial in reducing the temperature in hyperthermia. Physical measures are found to be effective in reducing the temperature in both hyperpyrexia and hyperthermia.[3,11]

Symptoms of hyperpyrexia

The symptoms include fatigue, altered sensorium, hypotension, hemoconcentration, disseminated intravascular coagulation (DIC), and organ damage. Hyperpyrexia should be suspected in cases with dry skin, cold-exposed skin, unexposed areas having elevated temperature on touching, and rapid shallow respiration.[3,8] It should be immediately confirmed by checking core temperature either by the rectal or tympanic method.

Treatment for hyperpyrexia

Antipyretics and physical cooling are the preferred interventions for managing hyperpyrexia. Physical measures help in reducing hyperpyrexia in 30 minutes, whereas antipyretics have delayed, but sustained effects. The combined use of both interventions may help in achieving optimal result. Frequent administration of fluid and temperature monitoring are essential. IV paracetamol is useful in reducing the temperature, and other NSAIDs can also be used. The physical method includes sponging with tepid water, application of ice-packs or cooling blankets, and exposure to circulating air with sponging.[8,9] Cooling is required in hyperthermia; whereas for hyperpyrexia, heat dissipation is important. Caution should be exercised while administering IV paracetamol in patients with decreased muscle mass, depleted glutathione stores, prolonged fasting or malnutrition, several renal, hepatic, or cardiac impairments, dehydration and chronic alcohol intake, hypotension, and infusion site reaction.

Drug-induced hyperpyrexia

Anesthetic agents can induce hyperpyrexia.[12] Drug-induced hyperpyrexia is seen in patients with dyskinesia-hyperpyrexia syndrome, parkinsonism-hyperpyrexia syndrome, neuroleptic malignant syndrome, and serotonin syndrome.[13-16] Gil-Navarro and Grandas (2010) first described the occurrence of dyskinesia associated with hyperpyrexia in a 68-year-old patient with advanced Parkinson's disease. Severe dyskinesia, rhabdomyolysis, acute renal failure, respiratory distress, and hyperpyrexia are often noted in such patients.[17] Dantrolene is found to be effective for treating dyskinesia-hyperpyrexia syndrome. Parkinsonism-hyperpyrexia syndrome is frequently triggered by the withdrawal or sudden dose reduction of antiparkinsonian drugs. It is a rare potentially fatal complication of Parkinson's disease.[14] Hyperthermia, autonomic dysfunction, altered level of consciousness, muscle rigidity, and increased serum creatinine phosphokinase levels are often noted in such patients. The resumption of dopaminergic drugs can help in disease management.

Conclusion

Hyperpyrexia, beyond a certain threshold point, may impart deleterious effects. It causes direct damage and high metabolic cost. The physical measures combined with antipyretics are ideal for managing hyperpyrexia. Core temperature measurement is preferred over surface temperature for accurate monitoring. A tympanic measurement is an emerging non-invasive method for accurate temperature measurement. Identification of the source of elevated temperature is paramount for earlier diagnosis and improved treatment outcomes.

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Newer Drugs in the Management of Tuberculosis

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Introduction

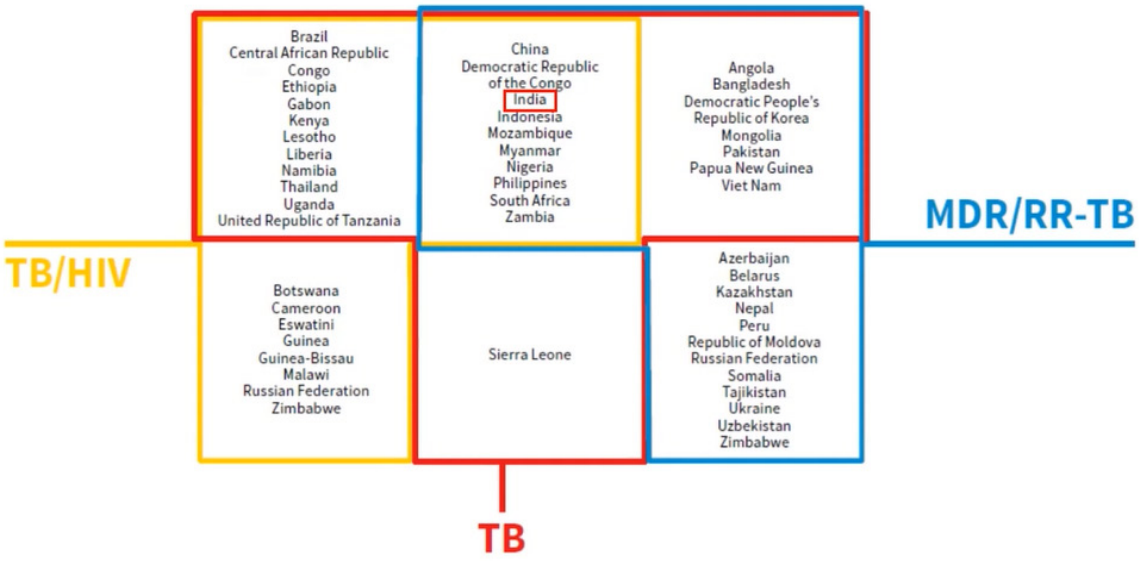
Although access to free tuberculosis (TB) care has expanded substantially in the past 2 decades, many patients and families are still facing the burden, which could be attributed to impaired quality of life, lack of social support, income loss, financial hardship, and impoverishment. The 2021 global tuberculosis report states that India accounts for about 28% of all TB cases globally and has the greatest cases of HIV-TB and multi-drug resistant TB. A comparison global TB cases with India has been provided in table 1.[1,2]

Table 1: Comparison of the global TB cases with India

Year 2021	Global	India
Incident cases	10.6 million	2.95 million
HIV-neg deaths	14,00,000	4,94,000
MDR-/RR-TB	4,50,000	1,19,000
HIV-TB (rate/100,000)	8.9	3.9

Despite the implementation of several eradication strategies and aggressive treatment approaches, India continues to have a high incidence of TB, HIV-TB, and multidrug-resistant tuberculosis (MDR-TB)/ rifampicin-resistant TB (RR-TB). The global high-burden countries lists for TB, TB/HIV and MDR/RR-TB released by WHO for the period 2021-2025 are provided in fig. 1.[3,4]

Fig. 1: High-burden countries for TB, HIV-TB, and MDR/RR-TB as per WHO reports



Countries in the TB list are those within the red T-shaped border. Countries in the TB/HIV list are within the yellow border. Countries in the MDR/RR-TB list are within the blue border:

Newer approach in anti-TB drug development

From the mid-1940s to 1963, p-aminosalicylic acid, streptomycin, isoniazid pyrazinamide, ethambutol, and rifamycin were used as effective anti-TB drugs.[5] However, late 1970s witnessed a resurgence of the disease due to increased HIV prevalence, atypical TB presentation, and development of drug-resistant strains. The present decade has seen newer developments in TB drug research such as clinical validation of drug through multi-arm, multi-stage (MAMS) trials, re-engineering of old drugs, and drug repositioning/repurposing.

MAMS trials aim to answer multiple questions simultaneously under the same regulatory framework rather than conducting a series of separate phase II/III MAMS trials. Such trials also allow the comparison of multiple treatment options simultaneously against a control arm within a single study.[6]

Re-engineering old drugs allows the development of new drugs from old drugs. Rifapentine and rifabutin are the modified versions developed by re-engineering the rifampicin drug. SQ109 is the modified version of ethambutol.[7]

Drug repositioning /repurposing is a strategy for investigating existing or old drugs for treating other diseases. Clofazimine, econazole, meropenem, metronidazole, moxifloxacin, linezolid, and ciprofloxacin are some of the repurposed drugs.[7,8]

The progress in anti-TB drug discovery contributed to the discovery of bedaquiline (2012), delamanid (2014), and pretomanid (2019).

Anti-TB drugs

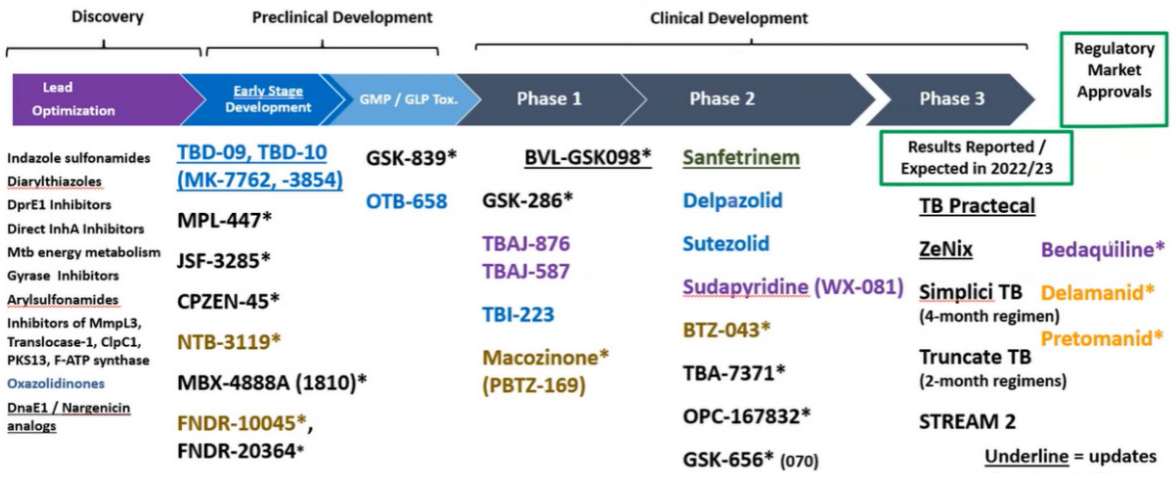
Isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin are the first-line anti-TB drugs.[9] Drugs used for drug-resistant TB are classified into 3 groups (Table 1).[10]

Table 1: Classification of drugs for drug-resistant TB

Groups	Drugs
Group A	Levofloxacin, moxifloxacin, bedaquiline, linezolid
Group B	Clofazimine, cycloserine, terizidone
Group C	Ethambutol, delamanid, pyrazinamide, penems, amikacin, ethionamide, and para-amino salicylic acid (PAS)

Some of the anti-TB drugs that are being investigated under different clinical trial phases are oxazolidinones, nitroimidazoles, benzothiazinone, diarylquinolones, riminophenazines, ethylene diamines, azaindole, and imidazopyridine.[11] As per the latest 2022 global new TB drug pipeline, only bedaquiline, delamanid, and pretomanid have gained marketing approval. (Fig. 2)[12]

Fig. 2-:2022 Global new TB drug pipeline



Bedaquiline, the first specific anti-TB agent developed over 40 years, has been approved by US FDA for the treatment of multidrug-resistant TB in late 2012. The other key features of the drug include extended half-life of up to 5.5 months, high volume of distribution, extensive tissue distribution, and increased binding affinity to plasma proteins. It specifically targets mycobacterial ATP synthase, an enzyme that supplies energy to *Mycobacterium tuberculosis*. The drug has shown significant time-to-culture conversation in MDR-TB patients, and bactericidal and sterilizing activities.[13]

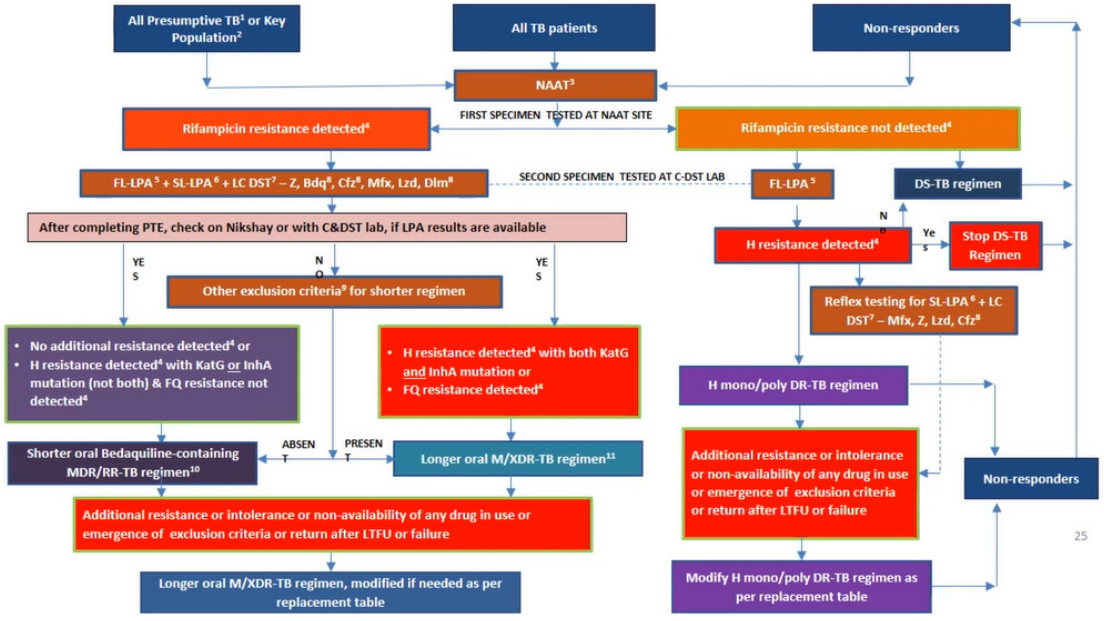
Delamanid is the first nitro-dihydro-imidazo-oxazole class drug approved for the MDR-TB treatment. It is a bactericidal drug with a half-life of 36 hours. It acts by two different mechanisms i.e., blocking the synthesis of mycolic acids and poisoning the bacilli with nitric oxide.[14] As per WHO recommendation,

the risk-benefit considerations for the use of bedaquiline in 6-7 years old patients and delamanid in 3-5 years old patients are comparable to that in adults.[10]

Pretomanid is a bicyclic subsidiary of nitroimidazole that has potent anti-TB activity and drug sensitivity against MDR-TB. It is a prodrug converted to an active form by nitroreductase enzyme, which hinders the amalgamation of cell wall lipids and proteins. It mainly inhibits *M. TB* through intracellular ATP exhaustion by functioning as a nitric oxide donor and by preventing the synthesis of mycolic acid, the essential component of the bacterial cell wall.[15]

The recommended diagnosis and treatment algorithm for integrated DR-TB is briefed in figure 3.

Fig. 3: Integrated DR-TB diagnosis and treatment algorithm



In the past, regimes were based on previous drug intake history and the severity of illness/infectivity. Nowadays, wider access to technology and new diagnostics have significantly improved the drug susceptibility-resistance testing. Studies are being conducted to design newer drug delivery methods such as self-nano emulsifying drug delivery system, lipopolysaccharide polyelectrolyte complex, halloysite nanotubes, nanocage, nanocomposites, nano-lipomer, nanosphere, niosomes, and the vesicles.[16]

Conclusion

Appropriate anti-TB regimen should be chosen based on drug-susceptibility results, coexisting medical conditions, and possible drug-drug interactions. Short-term regimens help in improving treatment compliance. Management of antimicrobial resistance requires an integrated and practical approach based on available treatment guidelines and national policies.

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Are We Missing Typhus?

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Introduction

Scrub typhus, an acute febrile illness caused by *Orientia tsutsugamushi*, is often misdiagnosed due to the presentation of non-specific acute febrile symptoms and signs such as stupor, rash, hepatosplenomegaly, thrombocytopenia, shock, capillary leak syndrome, and multi-organ failures. The differential diagnoses include dengue, malaria, typhoid, and brucellosis. Co-infection of scrub typhus with these diseases has also been reported.[1-4]

Presentation of painless papules known as eschar, subconjunctival hemorrhage, and positive Weil-Felix test may assist in diagnosis; however, they are not confirmatory. [2] Disease confirmation is important for early initiation of treatment.[5] The median mortality rate noted in untreated and treated patients is around 6% in and 1.45% respectively. Mortality is even more higher in patients with complications; for example, around 14% in brain infections and 24% in patients with multiple organ dysfunction.[5]

History

Hippocrates in 460 BC used the term 'typhus' to describe a 'confused state of the intellect' associated with fever. The first book by Hippocrates titled 'L'epidemion', described typhus as a febrile and exanthematic illness associated with the nervous system. The disease was reported during war periods such as civil wars in Granada (1492) and Siege Warfare (1494). During the 14th century from 1485-1551, five epidemics were reported in the UK. In 1546, Fracastoro in his book titled 'Contagione' has given an extensive description of the disease and distinguished it from plague. Around 42-fold increase in the reported cases of typhus was noted during 1812. In 1909, Charles Nicole discovered that *Pediculus corporis* (body louse) serves a vector of epidemic typhus. In 1910, Howard Taylor Rickets discovered rickettsial organisms in the blood of typhus patients and in infected lice and their feces. The famous researchers Howard Taylor Rickets and Stanislaus von Prowazek contracted the disease and succumbed to death during the research. The disease was more prevalent during the second world war (1942-1945).[6,7] Burning clothes, changing bedding, and crude quarantine methods were adopted at that time to reduce mortality in armies, ships, and prisons. In 19th century, based on clinical distinctions, the ill-defined entity was further divided into trials of typhus, typhoid, and relapsing fever.

Rickettsiae, the causative organism, is a small gram-negative bacillus found in the alimentary canal of arthropod vectors such as lice, fleas, ticks, and mites. In vertebrates, including humans, they infect the vascular endothelium and reticuloendothelial cells.[8] Scrub typhus is also called chigger-borne typhus or tsutsugamushi fever. It is transmitted through trombiculid (chigger) mites. Rodents are usually infected, while humans are accidental hosts. It was first described in Japan in 1899. The disease is also called *tsutsugamushi,* as 'Tsutsuga' means dangerous and 'Mushi' means insects or mites. The term scrub is used because of the type of vegetation that harbors the vectors. Scrub typhus is endemic to a region known as 'Tsutsugamushi triangle'. India is one of the countries affected by scrub typhus.[9] The estimated global incidence is around 1 million cases annually and 1 billion subjects are at risk. The case fatality rate in the untreated case varies from 1-60% according to the area, the strain of infectious agent, and previous exposure to disease. Increased preponderance of the disease has been noted in elderly subjects.[10]

Scrub typhus in India

Scrub typhus in India is a re-emerging infectious disease and one of the most underdiagnosed and underreported febrile illnesses. There is no specific epidemiologic data available for the country, however, outbreaks have been reported in Vellore, Rajasthan, and the areas located in the sub-Himalayan belt from Jammu Kashmir to Nagaland.[11,12] There was a resurgence of the disease amongst troops during World War II in West Bengal and Assam, and 1965 Indo-Pak war.[13]

Characteristics feature of a scrub typhus outbreak

It is commonly associated with hilly and forest-laden terrain that commonly harbors the vector. A large percentage of susceptible people may be infected simultaneously within a short period of exposure. The period of the epidemic is influenced by the activities of mites. It occurs more frequently in the rainy season; however, outbreaks have been reported during the winter season in southern India. Areas such as forest clearings, riverbanks, and grassy regions provide optimal conditions for the infected mites to thrive.[14]

Vector and mode of transmission

The vector, called chigger mites are approximately 0.2 mm in size, and they often inhabit sharply demarcated areas in the soil where the micro-ecosystem is favorable. Mite islands are established either in forest vegetation or secondary vegetation after clearance of the forest and on grasses and herbs. Human beings are infected when they trespass into mite islands and are bitten by the mite larvae or chiggers. The mite feeds on the serum of warm-blooded animals only once during its cycle of development.[14]

Risk factors, clinical signs, and symptoms

Scrub typhus is essentially an occupational disease among rural residents in the Asia- specific regions. An increase in the prevalence of scrub typhus has been reported in some Asian countries, which coincides with urbanization in rural areas.[15] The chigger bite is painless and may be noticed as a transient localized itch, often found on the groin, armpits, genitalia, or neck. A papule develops at the site of inoculation. The papule ulcerates and eventually heals with the development of black eschar.[16] Sudden shaking chills, high-grade fever, severe headache, photophobia, myalgia, apathy, and swelling of the lymph nodes are also seen. Complications may include pneumonia, meningoencephalitis, and myocarditis. [15,16]

Diagnosis of scrub typhus

The diagnostic methods include indirect immunofluorescent antibody (IFA), indirect immunoperoxidase (IIP), Weil-Felix testing, enzyme-linked immunosorbent assays (ELISA), polymerase chain reaction (PCR), chest radiographs, and isolation of the organism. The list of differential diagnoses includes other rickettsial diseases, malaria, dengue, chikungunya, leptospirosis, relapsing fever, typhoid, meningococcal disease, and viral fevers.[16] The commonest antibodies detected by Weil-Felix testing are OX19, OX2, and OXK. OXK is highly suggestive of scrub typhus, and OX19 is suggestive of both epidemic and endemic types.[17] OX 2 is suggestive of Indian tick typhus.

Treatment of scrub typhus

Doxycycline is the most commonly used drug of choice and is generally administered at 100 mg twice a day for 7-15 days. Combination therapy with doxycycline and rifampicin is preferred in areas where there is poor response to doxycycline alone. Azithromycin or chloramphenicol is useful for treating infections in children or pregnant women. There are no commercially available vaccines for scrub typhus. [16]

Prevention and Control

In endemic areas, individuals should wear full-length clothing, socks, and shoes, and avoid walking barefoot to prevent chigger bites. Insect repellents containing dibutyl phthalate, benzyl benzoate, and diethyltoluamide (DEET) should be used, and sitting or lying on bare ground or grass should be avoided. In community settings, rapid case identification by healthcare workers can help provide prompt treatment. Public education on case recognition and personal protection will help in the identification and prompt treatment of cases. Rodent control and improved living conditions help prevent the spread of the disease. Clearing vegetation and chemical treatment of the soil help break the cycle of transmission.[16,18]

Epidemic typhus

Epidemic typhus is a classic form of typhus rarely reported in India with endemic spot in Kashmir. The causative agent of epidemic typhus is *R. prowazekii* and the human body louse, *Pediculus humanus corporis* is the vector. The rickettsiae multiply in the gut of the lice and appear in the feces in 3-5 days. Lice succumb to the infection within 2-4. The incubation period is 5- 15 days. Clinical presentation includes a characteristic rash that appears on the fourth or fifth day. Towards the second week, the patient will develop stuporous and delirious typhus infection.[19] The case fatality is around 40% and it increases with age.[20] The rickettsiae may remain latent in the lymphoid tissues or organs for years in certain recovered subjects. Such latent infection may, at times, be reactivated leading to recrudescent typhus or Brill-Zinsser disease.[19]

Endemic typhus

Murine (endemic) typhus is clinically similar, but milder disease than epidemic typhus. In India, endemic typhus has been reported in Pune, Lucknow, Mysore, Kolkata, Golkunda, Karnal, and Kashmir. It is caused by *R. typhi* and transmitted by the rat flea.[21] Clinical presentation includes headache, fever, rash, nausea, vomiting, diarrhea, abdominal pain suggestive of gastrointestinal diseases, and cough and abnormal chest radiograph indicating pneumonia or bronchitis. Severe illnesses including seizures, coma, renal insufficiency, and respiratory failure are seen, and only 1% of cases are fatal.[22]

Spotted fever group

Spotted fevers group (SFG) comprises a large group of tick- and mite-borne zoonotic diseases that are caused by closely related rickettsiae. Indian tick typhus (ITT), caused by *R. conori*, is an SFG prevalent in India. The brown dog tick sp. *Rhipicephalus sanguineus* is the most important vector of the causative agent. Some species of *Haemaphysalis* and *Hyalomma* ticks may also transmit the infection.[23]

Conclusion

Typhus is often undiagnosed or misdiagnosed due to several reasons, and it is an overlooked public health problem in India. Early diagnosis and prompt treatment can significantly reduce the associated complications and mortality. A heightened index of suspicion is needed in patients who present with fever during the monsoon season and from tropical rural areas.

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Brucellosis: A Disease of Mistakes

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Introduction

Brucellosis is one of the seven most neglected diseases in the world and the true incidence of the disease is estimated to be 5,000,000 to 12,500,000 cases annually. The current seroprevalence of brucellosis in cattle is around 13.5% in India and it is at a stable endemic equilibrium. The country's serological evidence of human brucellosis ranges between 0.9 and 18.1% with Punjab state being the highest.[1]

Transmission

Brucella organisms can survive up to two days in milk at 8°C, 3 weeks in frozen meat, and 3 months in goat cheese. In damp soil, brucellae shed through animal excretions may remain viable for >40 days. Brucellosis is transmitted from cattle to humans due to the consumption of infected and unpasteurized animal products, contact of skin or mucous membranes with infected animal tissue (such as placenta or miscarriage products), infected animal fluids (such as blood, urine, or milk) or inhalation of infected aerosolized particles. [1,2]

There is a wrong notion that humans can only acquire skin infections from cattle. In contrast, it is one of the most common contagious zoonotic diseases associated with significant morbidity and lifetime sterility. Some of the common practices that increase the risk of disease transmission are as follows:[1]

- Drinking raw milk
- Sleeping in cattle sheds
- Not isolating sick cattle
- Not testing buffaloes for any disease before purchasing
- Applying intrauterine medication with bare hands to buffalo after the abortion of the fetus
- Not cleaning cattle shed with a disinfectant

Due to the lack of knowledge about the disease, animal handlers have a substantially higher risk of exposure to brucella organisms when compared to para-veterinarians and veterinarians.[3]

Clinical presentations

The most common signs and symptoms of brucellosis include fever, malaise, night sweats, arthralgia, hepatomegaly, and splenomegaly. Neurobrucellosis, an important complication of systemic brucellosis, presents with meningoencephalitis, myeloradiculitis, cranial nerve palsies, and peripheral neuropathy. Brucellosis can be presented with uncommon manifestations like acalculous cholecystitis, acute prostatitis, and Guillain-Barre syndrome.[4,5] Some of the brucellosis cases with unusual clinical presentations are discussed below.

Case 1

A 60-year-old lady presented to the orthopedics department with low backache and 3-months of intermittent fever. Her neurological exam and MRI of the spine were normal, whereas her investigations showed a borderline low WBC count and high ESR. She was subsequently referred for the treatment of fever and abnormal ESR. Her blood culture was found to be positive for brucellosis. Anti-tuberculosis treatment helped the patient to recover completely from backache. Most of the brucellosis cases initially present to the orthopedic department due to low backache or other arthralgic manifestations.

Case 2

A 35-year-old female presented with 4 weeks of fever and pancytopenia. Physical examination revealed hepatosplenomegaly and lymphadenopathy. Investigation for hematological malignancy with bone marrow showed reactive changes. Her vitamin B12 levels were normal. Blood culture was negative for all organisms including brucella. The bone marrow culture test helped to conclude the diagnosis as brucellosis.

Case 3

A 35-year-old cattle farmer presented with fever, weight loss, and embolic stroke hemiparesis. Vegetations in aortic value were suggestive of infective endocarditis. Infarcts were found in CT scans. TB, blood culture and tropical infection tests were negative. The result of brucella agglutination was >1:1280. Based on the clinical and lab investigations, the case was diagnosed as brucella endocarditis with embolic stroke. The patient was treated with aminoglycoside, doxycycline, and rifampicin. The aortic valve replacement proved the diagnosis of brucella endocarditis. Titers dropped to 1:320 following the surgery, however; the cultures from the valve tissues were negative. This case signifies the importance of considering brucella endocarditis as one of the differentials in patients presenting with pyrexia of unknown origin (PUO) and central nervous system manifestations.[6]

Case 4

A 55-year-old man was investigated for PUO for 4 weeks. There was no localizing systemic involvement and the hematological report revealed normal total count, low platelets, and anemia. All other tests including blood culture were negative. Negative imaging results ruled out the malignancy. Considering the history of close contact with cattle, a brucella serology test was performed. Based on the positive test result, the diagnosis was concluded as brucellosis.

Laboratory investigations

Typical laboratory findings for brucellosis include elevated alanine aminotransferase, anemia, leukopenia, leukocytosis, relative lymphocytosis, thrombocytopenia, and pancytopenia. Positive culture tests from blood or body fluids, brucella agglutination test > 1:160, or a four-fold rise in titer indicate brucellosis. Microagglutination test (MAT), slide agglutination test (SAT), and immunoglobulin M (IgM) are the serology tests performed to diagnose this condition.[7]

A case on misinterpretation of laboratory tests has been described below.

Case 1

A 45-year-old male, manager by profession, presented with fever and lymphadenopathy. Investigations revealed normal WBC counts, high ESR, and brucella antibody titers 1:320. The lab findings were suggestive of brucellosis, but the lymph node biopsy revealed tuberculosis. In some cases, positive brucella serology may be misinterpreted for the presence of other infections.

Disadvantages of brucellosis tests

Brucellosis serology tests cannot be used for distinguishing present and past infections. The titers may persist for a long time and cross-react with other infections. It may not yield positive results at the early stages of the disease. Blood culture positivity of brucellosis varies from 15 to 70%. Even though the bone marrow culture positivity is 92% accurate, it is not recommended in all cases.[8]

Brucella endocarditis is a diagnostic challenge due to the reduced sensitivity of blood cultures, the time lag between infection and diagnosis, the fastidious nature of the organism, and the interference of previous antibiotic treatment with culturing. Cultures of fluids or tissues, except blood, may take up to three weeks to grow on plated media. The recent introduction of semiautomatic blood culture systems (Bactec and BacTAkert) helped to shorten the detection time considerably (can be detected by the third day of incubation). With the use of automated blood culture systems, it is possible to recover most isolates in one week and there is no need to incubate bottles for more than 2 weeks.[9]

Treatment plan

The key goals of treatment are to alleviate symptoms and prevent complications, recurrence, and chronicity. The possibility of therapeutic failure is around 5-30%. At least two antimicrobial drugs with the following characteristics should be considered for treatment: agents with long-term treatment effects, and those with the ability to enter into macrophages and can stay active in the acidic intracellular environment. The treatment should be planned based on the treatment stages and reported complications. Doxycycline with good intracellular penetration potential is the drug of choice. The other options include rifampin, aminoglycosides, trimethoprim-sulfamethoxazole (TMP-SMX), and ceftriaxone. The minimum duration of treatment is 6 weeks. The available doxycycline-based treatment regimens are as follows:

- Doxycycline 200 mg a day orally in 1 or 2 doses for 6 weeks plus streptomycin 1g intramuscularly or intravenously once a day for the first 2-3 weeks.
- Doxycycline 200 mg a day orally in 1 or 2 doses for 6 weeks plus gentamicin 3-5mg/kg/day I.M/I. V in 1 -3 divided doses for 1-2 weeks.

- Doxycycline 200 mg a day orally in 1 or 2 doses for 6 weeks plus rifampin 600-900 mg a day orally in one dose for 6 weeks.

The first two regimens are considered the gold standard for managing brucellosis, and the third is an alternative regimen. The failure rate of doxycycline+aminoglycoside is estimated to be 1-5%, whereas doxycycline+rifampicin is 19%. The relapse rate of doxycycline + aminoglycosides is estimated to be 5-10%, whereas doxycycline+rifampicin is 15%. The doxycycline-rifampicin combination with extended treatment course for 8 weeks is found to be slightly superior to 6 weeks course. [10,11]

Disease relapse

Disease relapse occurs when the organism manages to evade the human immune system and survives for prolonged periods by inhabiting an acidic vacuole environment. Brucellae invading the macrophage's intracellular compartments are protected from antibiotics due to low therapeutic concentrations. As a result, despite adequate antibiotic treatment, brucella causes chronic disease that manifests as relapse, late reactivation of suppurative processes years or decades after the initial clinical cure, or persistence of clinical manifestations. The original treatment regimen should be repeated to treat relapse, and in refractory cases, an alternative regimen is recommended. Symptomatic treatment should be provided for prolonged and disease chronic brucellosis.[12]

Longer treatment course (12-52 weeks or even longer) is recommended for endocarditis, spondylitis, neurobrucellosis, deep abscesses, infection of prosthetic joints, and therapeutic failure. Triple therapy of doxycycline, rifampicin, and aminoglycosides is preferred in these conditions. The role of steroids in brucellosis is controversial and is recommended only in neurobrucellosis and cytopenia.[13]

Brucellosis in pregnancy

Sulpha drugs can be prescribed during pregnancy, except in the first and last trimesters. Rifampicin and ceftriaxone are the safer drugs in pregnant subjects, whereas doxycycline should be avoided during pregnancy and breastfeeding.[14]

Special conditions

Rifampicin and doxycycline combination is preferred in patients with renal failure, and streptomycin with doxycycline/ quinolone for liver failure. A 3-drug regimen of rifampicin, doxycycline, and ceftriaxone is preferred in neurobrucellosis.[15] In certain cases of brucella endocarditis; along with aminoglycoside-doxycycline-rifampin combination, TMP-SMX is added as a fourth antimicrobial agent. Aminoglycosides should be given for 1 month and other drugs for 3-15 months.[16] Surgery is recommended in conditions like endocarditis, resistant abscess in the spleen, spinal instability, cord compression, severe muscle weakness due to extradural inflammatory mass or progressive collapse, and infection of prosthetic joints.

Conclusion

Several uncommon clinical manifestations are noted in brucellosis patients. Hence high index of suspicion is needed in patients presenting with PUO, pancytopenia, low backache, arthritis, or endocarditis. It is important to conduct follow-up for long period for any complications or relapse of the disease. An integrated approach involving both clinicians and veterinary experts is important to increase awareness regarding the disease and to better understand the disease dynamics at the animal-human interface.

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Fever in Intensive Care: An Open Problem

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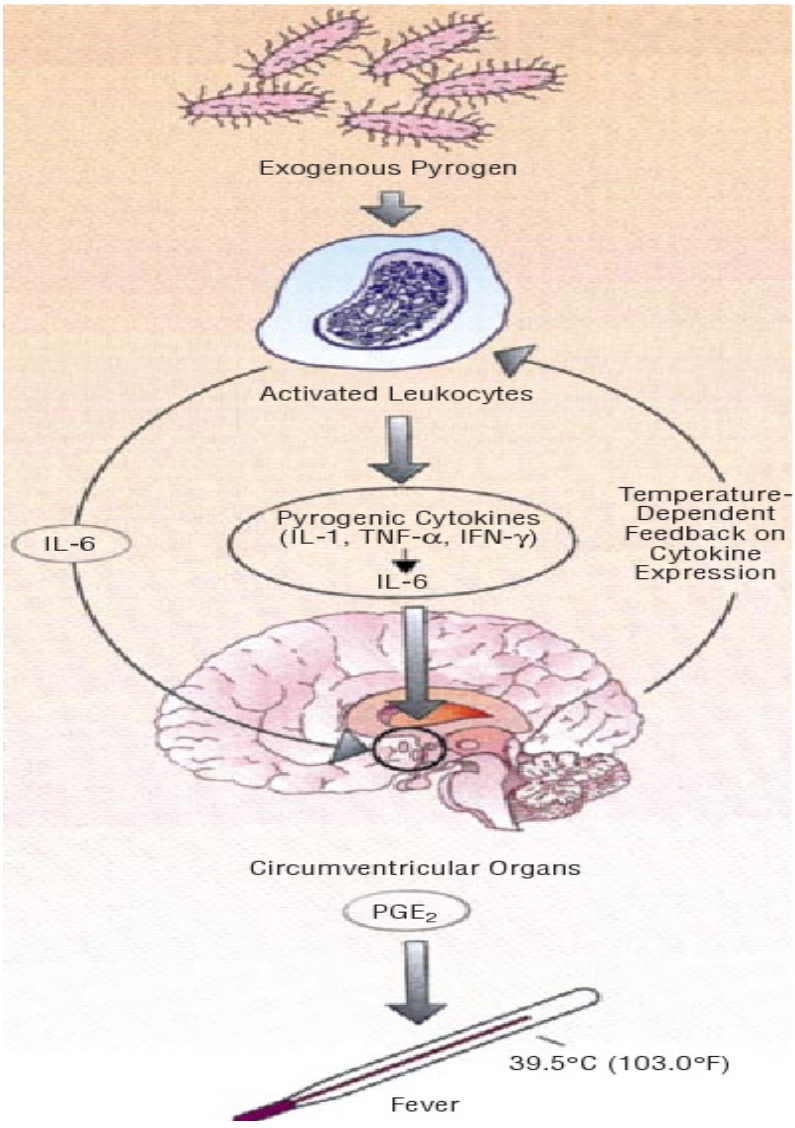
Introduction

Fever is an important vital symptom in ICU and it can be infectious or non-infectious in origin. It is a complex physiologic response that has potential benefits and risks for patients. In patients with infections who are admitted to ICU, fever is independently associated with a decreased risk of in-hospital mortality.[1,2] Even in the absence of infection, low-grade fever appears to be independently associated with reduced mortality risk compared to normothermia.[1]

Pathophysiology of fever

Typically, a fever has three stages namely chill, plateau, and defervescence. The pathophysiology of fever is mediated by the production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. It should also be considered as a reset of the elevated hypothalamic set point. The lowering of the hypothalamic set point makes a person hot and sweaty. Fever is associated with the release of prostaglandin E2 (PGE2) in the hypothalamus, which primarily mediates vasoconstriction, increase in metabolism, and muscle contraction.[3] The febrile response cycle starts with the exogenous pyrogens, which in turn activates leukocytes, and the proliferation of pyrogenic cytokines including IL–1 (IL-1α and IL-1β), TNF-α, IL-6, and interferon-gamma (IFN-γ). It affects the circumventricular organs and releases PGE2, and it has a temperature-dependent feedback loop on cytokine expression (Fig 1).[4,5]

Fig. 1: Hypothetical model of febrile response



Ref: Walter EJ, Hanna-Jumma S, Carraretto M, Forni L. The pathophysiological basis and consequences of fever. Crit Care. 2016 Jul 14;20(1):200.

Mechanisms of damage due to hyperthermia

Fever causes cellular effects such as mitochondrial and DNA damage, stimulation of excitotoxic mechanisms, protein denaturation, and cell death, especially in patients with hyperthermia. It also has local effects such as cytokine stimulation, inflammatory response, and vascular stasis. Systemic effects include endotoxemia and gut bacterial translocation.[6]

Various agents indicated for hyperthermia target different stages of the mechanism. For example, corticosteroids act on pyrogenic cytokines, antipyretics on PGE2, and dantrolene on metabolic heat production.[7]

Benefits of fever

Fever may serve as a good prognostic sign in acutely unwell patients with infection, associated with higher rates of survival.[8] A prospective observational study by Dai et al. involving 502 subjects reported that fever inhibited microbial reproduction and viral replication, as well as accelerated the rate of phagocytosis.[9] Heat-shock proteins (present in fever) are also thought to prevent thermal damage to cells by inhibiting pro-inflammatory-signaling pathways. An individual's ability to mount a febrile response has been shown to be a good prognostic sign in critically unwell patients.[10]

Causes of fever

The non-infectious causes include vascular diseases, neoplasms, autoimmune diseases, trauma, inflammatory conditions, environmental stressors, and drug-induced fever. The diagnostic approach depends on the magnitude of fever elevation, fever pattern, the relationship of pulse to fever, and the presence or absence of localizing signs.

Evaluating fever thresholds is very important. If the temperature is >41.1°C, other causes such as malignant hyperthermia, hypothalamic dysfunction, heat stroke, or drug fevers should be considered along with infection. No prognostic significance has been noted for temperatures between 38.9 and 41.1. The major infectious causes in ICU can be bacteremia, intravascular catheter-related infection, surgical site infection, ventilator-associated pneumonia, and urinary tract infection.[11] Other infectious causes include cellulitis, cholangitis, diverticulitis, empyema, endocarditis, intra-abdominal abscess, meningitis, myonecrosis, necrotizing fasciitis, pseudomembranous colitis, septic arthritis, sinusitis, and suppurative thrombophlebitis.[12]

Causes in terms of inflammatory pathology include trauma, burns, and surgery. The non-infectious causes of fever include pancreatitis, pneumonitis, acute respiratory distress syndrome (ARDS), hypersensitivity reactions, connective tissue diseases, inflammatory bowel disease, hepatitis, myocarditis, vasculitis, neuropathies, myopathies, gout, and granulomatous disease.[13] Infarctions such as myocardial, cerebral, gastrointestinal, and pulmonary are also common causes of fever. The other causes include seizures, hypothalamic stroke, adverse drug reactions, drug withdrawal or overdose of alcohol, anticholinergic, sympathomimetic, and salicylate toxicity, multiple system atrophy, Parkinson's disease with autonomic dysfunction, heat stroke, and factitious fever.[14]

Cooling approach

The physical cooling approaches to reduce body temperature include a cool environment exposure, wet towels, ice packs, cooling blankets, evaporative cooling, cool fluids, body cavity lavage, and extracorporeal. A systematic review and meta-analysis by Dallimore et al. reported that active temperature control in critically ill patients did not have any significant effect on mortality risk. In critically ill adults, physical cooling techniques may be more efficient than pharmaceutical ones when the therapeutic goal is to lower body temperature.[15]

Key studies on fever management in ICU

Laupland et al. reported the development of fever ≥38°C in 44% of ICU admissions, and high fever of >39°C in 8% of the subjects. They noted that high fever is considerably more likely to cause death than low fever, although fever is not related to higher ICU mortality.[16] Young et al. noted the presence of a confirmed or suspected infection in 9% of patients admitted to the ICU with a fever and around 2/3 of the patients with fever received paracetamol on any given day.[17] Lee et al. found that the use of NSAIDs is independently linked to a higher 28-day mortality rate in patients with sepsis.[18] Another study by Laupland et al. reported that 5.7% of the patients had a temperature of ⩽38.3 °C at ICU presentation. They have also observed that hypothermia is an independent predictor of death in medical patients; however, fever is not linked to higher mortality.[19] According to Young et al, in the first 24 hours in the ICU, elevated body temperature is linked to a higher risk of mortality in patients without infections and a lower risk in patients with infections.[20]

A randomized control trial by Bernard et al. observed no significant difference between ibuprofen and placebo in terms of in-hospital mortality rate (18.8% ibuprofen-treated group vs. 42.9 % placebo-treated group).[21] Similarly Morris et al. reported no appreciable differences across the treatment groups with regard to ventilator requirements, duration of stay, or in-hospital mortality (4% placebo, 3% 100 mg ibuprofen, 7% 200 mg ibuprofen, and 6% 400 mg ibuprofen).[22] A randomized controlled trial by Schortgen et al. noted that external cooling drastically lowered body temperature in febrile patients with septic shock. The proportion of patients who experienced a 50% reduction in vasopressor dose after 48 hours was unaffected by external cooling. Day-14 mortality was significantly lower in the patients who received external cooling, but there was no discernible difference between the groups in terms of ICU or in-hospital mortality.[23] A study by Young et al. found that the number of ICU-free days was unaffected by the early treatment of acetaminophen for fever due to infection causes.[24] A meta-analysis study by Young et al. refuted the hypothesis that more active fever control promotes survival in patients with low physiological reserves.[25]

Conclusion

The cornerstone in managing fever in ICU is to seek and treat the underlying cause. There is a certain degree of clinical practice variation in the management of fever in an ICU setting. The patient subsets that need closer attention in ICU are post-surgical and pregnant subjects, and those with neurological conditions, immunosuppression, malignant hyperthermia, and neuroleptic malignant syndrome. A less-is-more approach in the management of fever is entirely appropriate. Active fever management does not improve survival, overall and in those with limited physiological reserve.

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Asymptomatic Bacteriuria

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Introduction

Asymptomatic bacteriuria (ABU) is defined as the presence of bacteria in a noncontaminated urine sample collected from a patient without signs or symptoms related to urinary tract infection (UTI). It is prevalent even in some healthy female subjects and in many women or men with abnormalities of the genitourinary tract that impair voiding.[1]

Criteria for diagnosis

The criteria for diagnosis include the isolation of the same organism from two consecutive voided urine specimens for women and one voided urine specimen for men. It should be $\geq 10^5$ colony-forming units (CFU)/mL in a single catheter urine specimen and without signs or symptoms attributable to UTI.[1]

Prevalence of ABU

The prevalence varies widely across different population subgroups**.** The prevalence is low in children (about 1-2%); whereas, in healthy premenopausal, pregnant, and postmenopausal women, it is up to 5%, 9.5%, and 8.6% respectively. Among diabetic patients, the corresponding prevalence noted in women and men is 16% and 11%. In the case of elderly persons in a long-term facility, the prevalence is 50% in both genders. The prevalence in patients with spinal cord injury is upto 69% in those with intermittent catheters and 57% in those with sphincterotomy or condom catheters. In kidney transplant patients, the prevalence is 24% in the first-month post-transplant, 17% in 1 month to 1 year, and 9% in > 1 year. It is around 5% and 100% in subjects using indwelling catheters for short-term and long-term respectively.[2]

The symptomatic or asymptomatic presentation of bacteriuria is based on the complex interplay of the organism, host, and environmental variables.

Bacterial factors: *Escherichia coli* isolates from symptomatic UTI or asymptomatic bacteriuria, known as uropathogenic *E Coli* (UPEC), are different from gut flora. The potential virulence factors found in UPEC isolates are type 1 fimbriae, P fimbriae, hemolysin, and iron uptake systems. Similar genotypes have been observed for isolates causing symptomatic and asymptomatic infections. However, comparative genomic hybridization demonstrated mutations or minor deletions that can substantially

affect gene function. For example, point mutations in *papG* render its P fimbriae incapable of adhering to their normal uroepithelial target. [3] These findings have concluded that UPEC is not a commensal organism that picked up adaptive genes for survival in the bladder but was originally a pathogenic strain that lost important virulence factors.

Host and environmental factors: Certain polymorphisms in the Toll-like receptor 4 (TLR4) promoter can lead to an attenuated immune response, promoting the asymptomatic carrier state. CXC-chemokine ligand 8 (CXCL-8, also called IL-8) levels were found to be higher in the urine of women with asymptomatic bacteriuria than in women without significant bacteriuria. These observations substantiate the fact that neutrophil activation is required to regulate the colonizing bacteria and prevent symptomatic invasion. The bladder environment may also increase a person's propensity for asymptomatic bacteriuria. The use of indwelling urinary devices such as bladder catheters and impaired bladder voiding are recognized as risk factors for bacteriuria, as both obstruct the bladder's capacity to naturally wash out the germs.[4]

Need for screening and treatment

ABU may serve as a precursor for symptomatic UTI including pyelonephritis and it may lead to chronic kidney disease (CKD) due to renal scarring. The screening can lead to excessive costs, and unnecessary antibiotic use can result in *Clostridium difficile* infection (CDI) and the development of multidrug-resistant strains.[5]

According to the recommendations of the Infectious Disease Society of America (IDSA), screening and treatment for ABU are beneficial in two population groups namely pregnant women and patients who are planning to undergo endourological procedures such as cystoscopy, transurethral resection of the prostate (TURP), and double J-stent placement.[6] Several randomized control trials and observational studies reported that ABU is associated with an increased risk of acute pyelonephritis, preterm delivery, and intrauterine growth restriction (IUGR), and treatment is warranted to decrease the adverse events.[7] However, none of these trials evaluated the incidence of renal scarring. All this evidence is dated back to the late 1960 and 1970s, and considerable progress would have happened in antenatal care in the last few decades.[8-10] Hence, it is important to study the risk of preterm delivery and IUGR in the current era to understand and triage the patients who will be benefited from the treatment.

There is robust evidence to validate that the treatment of ABU before proceeding to any urological procedure reduces the incidence of sepsis and acute pyelonephritis post-procedure. Studies have noted that 3-5 days of treatment before surgery and single-dose therapy are beneficial, however, there are no reports on the long-term outcomes like scarring.[6, 11,12]

Pediatric population: Available evidence did not demonstrate any benefit of screening or treatment in pediatric subjects. In addition, the use of antibiotics in this subgroup is associated with increased treatment costs, adverse effects, and risk for antimicrobial resistance. Future studies involving children with neuromuscular disorders and immunocompromised states are required.[6, 13,]

Non-pregnant women: Evidence did not demonstrate any benefit; paradoxically, the treatment may increase the risk of symptomatic UTI and antibiotic-associated complications including CDI. Hence, no screening or treatment is recommended in this subgroup.[6]

Diabetics: There is robust evidence against conducting screening and treatment of ABU in diabetes patients, as it may increase the risk for symptomatic UTI.[6,14-16]

Elderly patients with impaired cognition: There is paucity of evidence for the treatment of ABU in elderly patients presenting with the non-localizing syndrome. As per IDSA recommendation, in the absence of symptoms or systemic signs of sepsis, this subgroup needs careful evaluation for presentation like falls or delirium, rather than initiation of antimicrobial therapy.[6]

Non-urological surgeries: Available evidence does not favor conducting screening or treatment for ABU in patients scheduled for non-urological surgeries involving prosthetic implants or grafts. Trials have demonstrated more harm than benefit in the treatment group.[6,17]

Miscellaneous conditions: For certain miscellaneous conditions, there is evidence against screening and treatment for ABU such as patients on short-term or long-term urinary catheters, post renal transplant after one month, those who received any other solid organ transplant, patients with spinal cord injury with voiding disturbances, and patients on other urological devices like stents, nephrostomy tubes, etc.[6]

Overtreatment of ABU

The current management of ABU is not as per the recommended evidence-based guidelines and paucity of literature characterizing the appropriate choice of antibiotics adds to the challenges. Published studies on western data have reported about 20% to 50% of the incidence of overtreatment. [6,18,19] The major reasons for overtreatment are lack of knowledge, fear of deleterious consequences, conventional belief that the bladder and the urine are normally sterile, and patients' demand for treatment.

Conclusion

ABU is frequently observed in subjects with anatomical or functional anomalies of the urinary system, and inappropriate antibiotic use can cause antibiotic resistance and drug-related adverse events. There is no point-of-care testing to distinguish between asymptomatic bacteriuria and symptomatic UTI, and functional genomics, such as transcriptomics, may provide biomarkers for screening in the future. The magnitude of overtreatment is a serious concern. Hence treatment should be limited to beneficial subjects. Further studies are needed to study the benefits of treatment in elderly individuals with cognitive impairment and to optimize the duration of therapy in benefit groups.

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Clinico Pathologic Case Discussion
Horses or Zebras?

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Introduction

The present paper discusses a clinically challenging case that highlights the need to conduct a comprehensive, reasonable investigation to elucidate the fever etiology and multiple reviews, which can help to arrive at the correct diagnosis.

Case report

A 34-year-old male with no previous comorbidities presented with a low-grade fever for 2 months, decreased appetite and weight loss of about 6 weeks, and vomiting for 7 days. The low-grade fever, decreased appetite, and weight loss clearly indicated the presence of significant systematic illness. The patient also had abdominal pain of unknown etiology, predominantly in the right upper quadrant for 2 months. The pain was insidious in onset, progressive, localized to the right hypochondrium, persistent, and dull with no radiation. It was not associated with food intake or aggravating/ relieving factors.

There was no history of diarrhea or vomiting at the onset, blood in stools, jaundice, clay-colored stools, or pruritus, thereby ruling out obstructive hepatopathy and biliary obstructive lesions. The right upper quadrant pain points towards the possibility of biliary, colonic, hepatic, pulmonary, or renal causes. Biliary causes can be cholecystitis, cholelithiasis, or cholangitis; colonic can be colitis or diverticulitis. The hepatic cause seems to be localized to that particular region and not associated with jaundice, pruritus, or blood in stool and bowel disturbances. Whereas pulmonary and renal causes are unlikely due to the absence of any respiratory and renal symptoms. Epigastric pain can be also considered, however hepatic source of pain is more likely.

The patient had a fever for 2 months, which was undocumented and mostly nocturnal. There was a loss of appetite of 50% and a weight loss of 6 kg over 2 months. These are classic symptoms of tuberculosis but are relatively non-specific. In light of these initial symptoms, the possibility of abdominal tuberculosis or non-tuberculosis abdominal infection needs to be considered. A week before the present consultation, he had pain and redness in the left lower limb from mid-thigh to mid-calf. It may be due to deep vein thrombosis (DVT), cellulitis, or superficial thrombophlebitis.

Physical examination revealed a heart rate of 98 per minute, temperature of 100.2°F, and localized

redness and tenderness on the lateral side of the left leg and thigh. The other findings were relatively normal including saturation and there was no icterus. Right upper quadrant pain with no icterus rules out the possibility of acute hepatitis, sub-acute hepatitis, and any biliary abnormalities. Fever and tachycardia are suggestive of an infection. Systemic examination revealed that the abdomen was apparently normal with umbilicus central, and no visible pulsations, peristalsis, or dilated veins. The liver was palpable 5 cm below the right costal margin, had smooth surface, tender, and had a span of 12 cm.

The causes of tender hepatomegaly, after ruling out concurrent splenomegaly and jaundice, can be infiltrative, congestive, infectious, or inflammatory. Tenderness does not occur in infiltrative conditions; however, it can be due to malignant infiltration such as primary carcinoma. In the present case, the differentials to be considered are primary carcinoma, tuberculosis, bacterial cholangitis, abscess, alcoholic and autoimmune hepatitis, and rarely drug-induced hepatitis and sarcoidosis. Results of clinical and lab investigations are briefed in table 1.

Table 1: Findings of clinical and lab investigations

Hb	11.5 gm%	BU	27 mg/dL
TLC	19900 /cu mm	Creatinine	1.0 mg/dL
DC	N87L8E1M4	TP/Albumin	6.8/3.2 g/dL
Platelet	2.27 lakh	TB/CB	1.3/0.8 mg/dL
PBS	Normocytic, normochromic with neutrophilic leucocytosis, platelets adequate	AST/ALT	72/106 U/L
ESR	20 mm	ALP	227 U/L
PT/INR	17 sec/1.4	GGT	144 U/L
APTT	30 sec	AFP	2.4 U/L
Urine routine	Albumin -Nil, RBC-1, WBC- 2	Na/K	134/4.8 mEq/L
Blood C/S	No growth	HIV/HbSAg/ Anti-HCV	Negative
RT-PCR for SARS CoV2	Negative		

The investigations revealed mild anemia with neutrophilic leukocytosis (total count of almost 20000/cu mm, 87% neutrophils). The liver function showed mild hypoalbuminemia with mildly elevated total and conjugated bilirubin. Prothrombin time and international normalized ratio (PT/INR) and activated partial thromboplastin clotting time (APTT) were significantly abnormal at 17sec/1.4 and 30 seconds respectively. Transaminases, gamma-glutamyl transferase (GGT), and alkaline phosphatases were mildly elevated. The alpha-fetoprotein (AFP) was normal. The serology investigations were negative for hepatitis B, C, and HIV. The findings suggested liver involvement, which appears to be infective in origin with mild anemia. AFP was normal, however, AFP in hepatocellular carcinoma has only 50-70% sensitivity. Hence normal AFP does not rule out the possibility of hepatocellular carcinoma.

Ultrasound sonography (USG) of the abdomen showed hypoechoic lesions in both lobes of the liver, suggestive of pyogenic liver abscesses. USG venous Doppler of bilateral lower limbs showed a left great

saphenous vein (GSV) thrombus extending from the saphenofemoral junction (SJF) to mid-calf. USG and Doppler findings revealed the probability of pyogenic liver abscess than amoebic. Hepatocellular carcinoma cannot be ruled out, and the possibility of superficial venous thrombosis needs to be considered. The contrast-enhanced computed tomography (CECT) was done in three phases: venous, arterial, and porto-venous (Fig. 1. Fig. 2 and Fig. 3). In the venous phase, multiple hypoattenuating liver lesions predominantly involving the left lobe, and larger lower lobe region measuring around 6 cm in two dimensions and extending to other areas of the liver were present. Mild peripheral enhancement and non-enhancing centers such as cysts or abscesses were also seen (Fig. 1).

Fig. 1: CECT abdomen: Venous phase

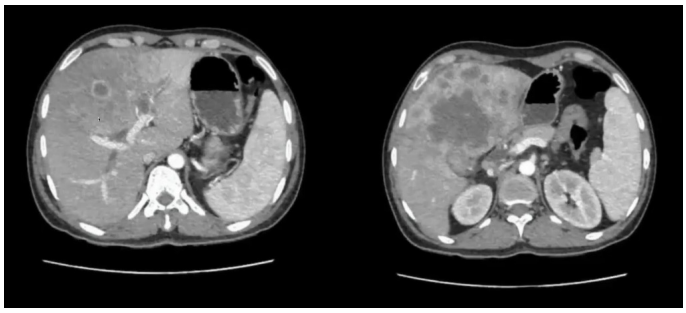


Fig. 2: CECT abdomen: Arterial phase

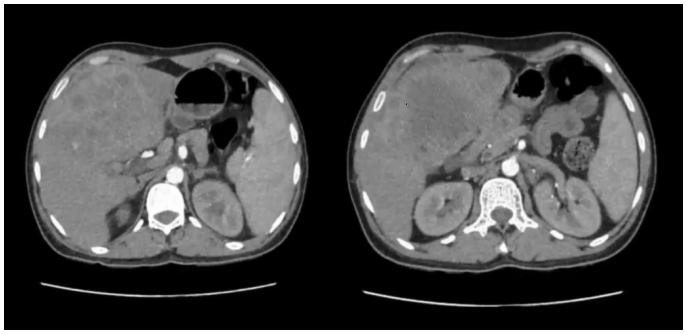
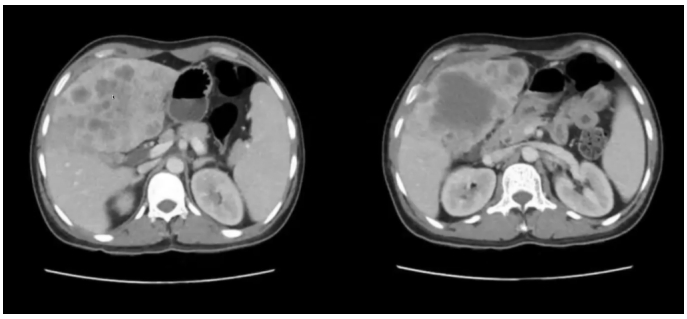


Fig. 3: CECT abdomen: Porto-venous phase



In the arterial phase, there was liver enhancement, without the involvement of the center (Fig. 2). In the porto-venous phase, there was a delayed enhancement and some central pseudo-capsule formation in the center, but there was no spleen enlargement (Fig. 3).

Several well-defined peripherally enhancing thick-walled, cystic (non-enhancing centers) lesions (largest lesion was 6.6 x 6.2 cm) were noted throughout the liver, predominantly in the left lobe compressing the left branch of the portal vein, with no infiltration.

The following details were not available in the present case: history of ethanol/drug use such as anabolic steroids, which increases the risk of hepatocellular carcinoma, any preceding gastrointestinal symptoms, tumor markers such as cancer antigen (CA)-19-9, CA-125, and carcinoembryonic antigen (CEA), and possible aflatoxin exposure.

Differential diagnosis

The common symptoms of a pyrogenic liver abscess are fever and weight loss followed by nausea and anorexia. Pyogenic abscess is more likely if both the liver lobes are affected Lodhi et al. have noted increased likelihood of pyrogenic abscesses in women, elderly, and those with diabetes mellitus, jaundice, and abdominal pain and liver tenderness. White blood cell count is not useful to differentiate between amoebic and pyogenic abscesses.[1]

The present case favored pyogenic abscess. However, low-grade fever, and late central enhancement are unlikely, and FNAC and biopsy are not the investigations of choice for the pyogenic abscess. Other differential diagnoses to be considered are hepatocellular carcinoma and hepatic tuberculosis.

Hepatocellular carcinoma (HCC)

HCC are multifocal and within the liver in nearly 75% of the cases. In CT, it generally appears as a focal nodule with early enhancement on the arterial phase with rapid washout of contrast on the portal venous phase. This was not seen in the present case. HCC typically occurs in elderly with risk factors such as cirrhosis, chronic hepatitis B or C, and alcoholic hepatitis. Whereas none of them were described in the present case study. Neutrophilic leukocytosis and normal AFP were not suggestive of HCC.

Hepatic tuberculosis in isolated lesions: The insidious onset and age favor the possibility of hepatic tuberculosis. However, neutrophilic leukocytosis is unlikely.

The final differential diagnoses considered in the present case are:

- Liver abscess – pyogenic, unlikely to be amoebic
- Hepatocellular carcinoma
- Isolated liver tubercular abscess
- Secondary infection of multiple cysts of various causes

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Hoofbeats- Horses or Zebras? Clinicopathologic Correlation

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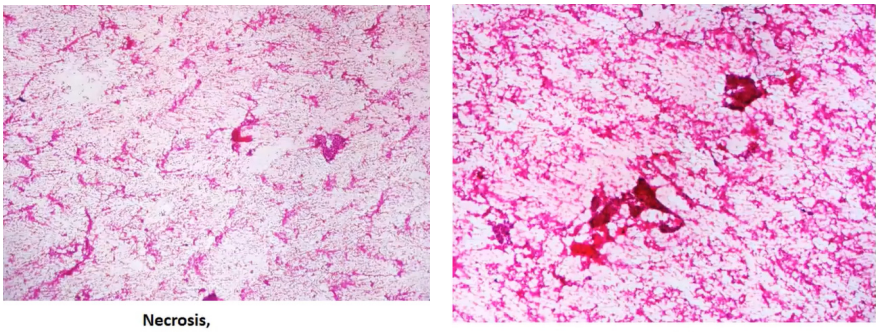
Case summary

The present case is of a relatively healthy non-alcoholic adult man who presented with fever, abdominal pain, hepatomegaly, and multiple liver abscesses. Imaging was suggestive of venous thrombosis and the working diagnosis was that of pyogenic liver abscess. Treatment with antibiotics was unresponsive.

US-guided FNA diagnosis

Ultrasound-guided fine needle aspiration (FNA) revealed a peripherally enhancing, heterogenous, hypoechoic lesion in the left lobe of the liver measuring 6.6 x 6.2 cm. There was no pus on repeated aspirates and cultures were negative. Imaging of the FNA smear showed necrosis and the absence of inflammatory cells. Amorphous eosinophilic background and cellular clusters were also noted (Fig. 1).

Fig. 1: FNA smear imaging showing necrosis and cell clusters

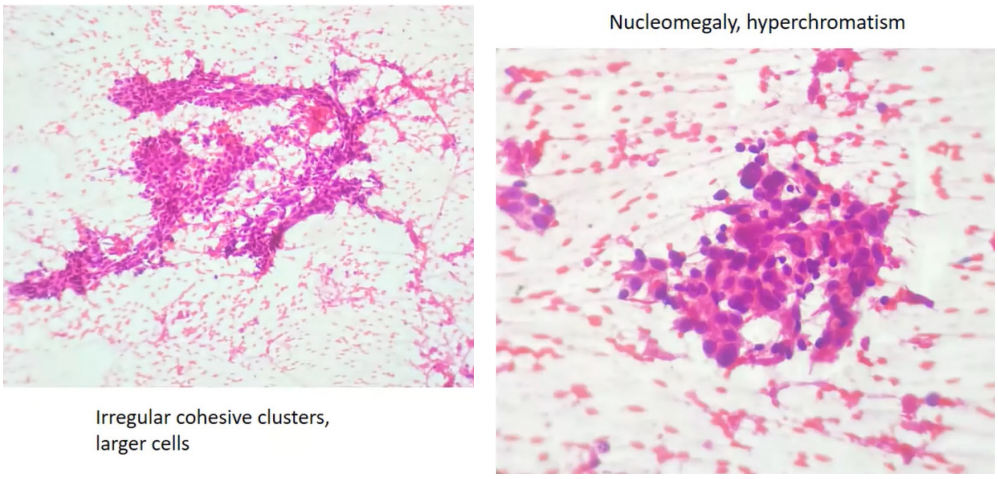


Necrosis, absent inflammatory cells

Cell clusters

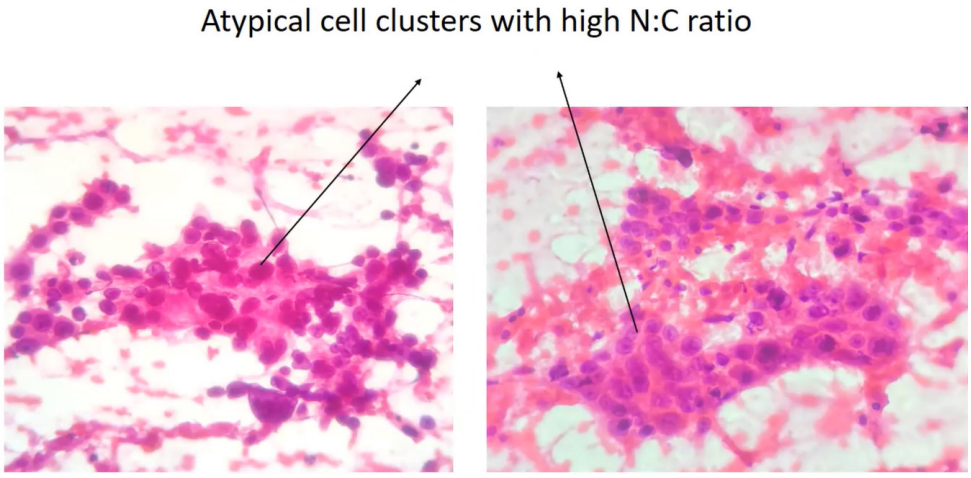
Some of these clusters were normal hepatocytes, thereby ruling out the possibility of hepatocellular carcinoma. However, other clusters showed large, irregular cohesive cells, nucelomegaly, and hyperchromatism (Fig. 2).

Fig. 2: FNA smear imaging showing irregular cohesive cell clusters, nucelomegaly, and hyperchromatism



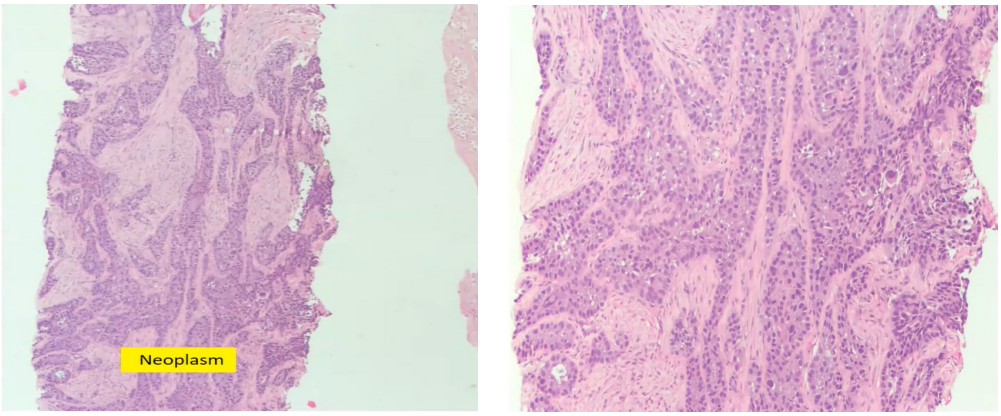
The presence of normal hepatic cells along with atypical cells did not favor the diagnosis of hepatocellular carcinoma (Fig. 3).

Fig. 3: Presence of atypical cell clusters



Malignancy favoring carcinoma of the liver nodule was considered and a core biopsy of the lesion for ancillary testing was recommended considering the amount of necrosis. Images of the biopsy showed two cores, one with necrosis and the other with tumor (Fig. 4). The infiltrating neoplasm was arranged in nests and cords. There was no cirrhosis/hepatitis, or hepatocellular glandular or squamous differentiation (Fig. 7).

Fig. 4: Images of the biopsy



Immunohistochemistry evaluation

Hepatocyte paraffin 1 (HepPar-1), a marker for hepatocellular differentiation, was negative and ruled out the diagnosis of hepatocellular carcinoma. The coordinate expression of cytokeratins (CK)7/CK20 pattern of tumors helps in the diagnosis of differentiation of carcinoma of unknown primary (Table 1).[1] The immunohistochemistry test for CK7 was strongly positive, whereas CK20 was negative (Fig. 5). Negative CK20 excluded the possibility of adenocarcinomas. CDX2, a critical nuclear transcription factor for intestinal development, was also negative. Chromogranin A test, done to exclude neuroendocrine tumor, was negative. TTF1 was also negative. Since CK7 can also be expressed in squamous cell carcinomas (SSC), diffuse nuclear staining of p40 and p63 tests were carried out and turned out to be positive (Fig. 6).

Table 1: Cytokeratins (CK)7/CK20 patterns of tumors that help in the differentiation of carcionma of unknown primary

CK7+/CK20−	CK7+/CK20+	CK7−/CK20+	CK7−/CK20−
Breast carcinoma Lung adenocarcinoma Endometrial adenocarcinoma Endocervical adenocarcinoma Ovarian (serous) carcinoma Cholangiocarcinoma Small cell lung carcinoma Mesothelioma Thyroid carcinoma Salivary gland tumours Kidney (papillary) Urothelial carcinoma (subset) Pancreatic adenocarcinoma Gastric adenocarcinoma	Urothelial carcinoma Pancreatic adenocarcinoma Ovarian mucinous carcinoma Bladder adenocarcinoma Gastric adenocarcinoma Cholangiocarcinoma	Colorectal adenocarcinoma Merkel cell carcinoma Gastric adenocarcinoma	Prostate adenocarcinoma Renal (clear cells) Hepatocellular carcinoma Adrenocortical carcinoma Non-seminoma germ cell tumours Mesothelioma Small cell lung carcinoma Gastric adenocarcinoma

Fig. 5: immunohistochemistry test showing positive CK7 and negative CK20

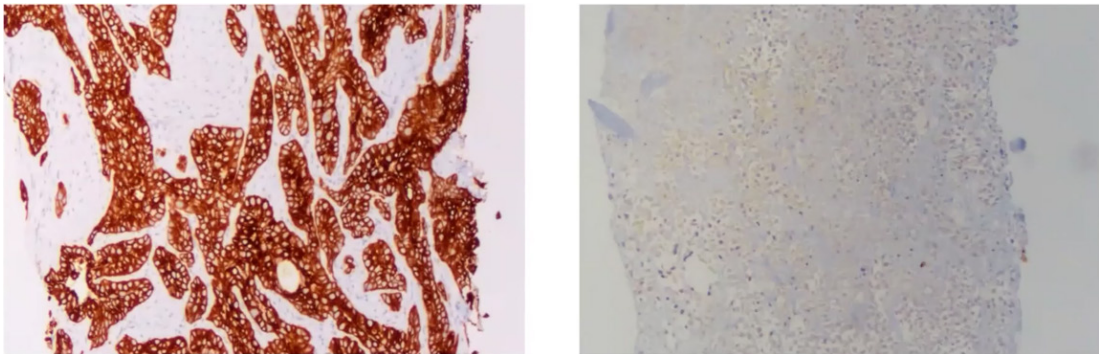
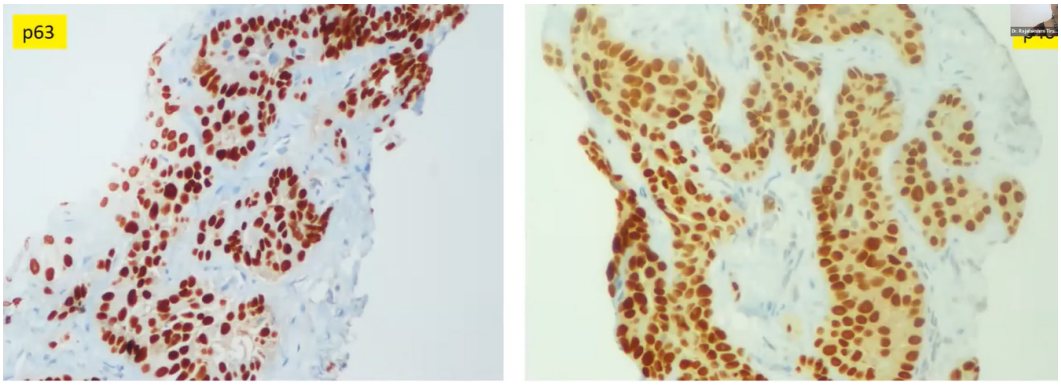


Fig. 6: Positive p63 and p40 suggestive of SSC



The presence of multiple lesions and primary SSC of the liver is extremely rare and usually occurs in the setting of either biliary cysts or long-term cholangitis or calculi. Hence, considering the rarity of lesions, the diagnosis can be concluded as metastatic SSC.

Liver metastases

The liver accounts for 25% of all cancer metastases, and most of them are adenocarcinomas. The common primary sites are colon, pancreas, stomach, breast, esophagus, and genitourinary organs. SSC and neuroendocrine carcinomas are less common. Lung and neuroendocrine carcinomas although small, can give rise to hepatic metastasis. In the case of SSC, there are no site-specific markers, except for p16 as a relevant prognostic factor in oropharyngeal SSC.[2] Possible primary sites of SSC include the esophagus, anorectal, head, neck, or lung. Neither morphology nor immunohistochemistry is site-specific for SCC.[3]

Malignancy mimicking liver abscess

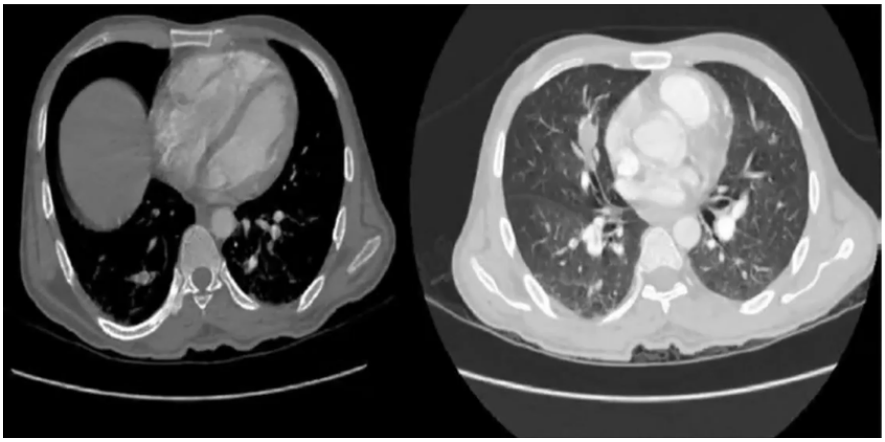
In the present case, there were multiple liver lesions mimicking liver abscesses. Infection in the liver

and tumors like intrahepatic cholangiocarcinoma, hepatic metastasis, and cystic tumors can also present with arterial rim enhancement mimicking liver abscesses. Diffusion-weighted MRI helps in the distinction of abscesses from malignant lesions.

Further clinical course

Subsequent to the biopsy, the patient developed sudden onset of breathlessness. Contrast-enhanced computed tomography (CECT) and pulmonary angiogram showed bilateral pulmonary thromboembolism (Fig. 7), a solitary nodule in the right middle lobe of the liver. Despite adequate anticoagulative measures, the patient succumbed to thromboembolism.

Fig. 7: CECT indicative of bilateral pulmonary thromboembolism



Final diagnosis

Metastatic squamous cell carcinoma of the liver with radiology favoring a lung primary.

Learning points

- Fever in malignancy is uncommon, but it is an important cause of pyrexia of unknown origin.
- Hepatic metastases, though common, can have unusual clinical presentations such as pyogenic liver abscesses.
- Judicious use of immunohistochemistry is helpful in decoding carcinomas of unknown primary.
- Timely reviews and multidisciplinary consultations are paramount for the accurate management of metastasis.

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Pros Cons Debate: Fever in ICU... Not Responding to Antibiotics

Will you add Antifungal without proof?

PROS

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Whether antifungals can be added without proof when a patient in ICU has a fever and not responding to antibiotics?

Yes, antifungals can be added to the patient, the advantages and evidence of adding antifungals are discussed below.

As per the findings of the European ICU project (EUCANDICU), the cumulative incidence of candidemia/ intra-abdominal candidiasis was 7 episodes per 1000 ICU admissions and the crude 30-day mortality rate was 42%. The incidence of candidemia is highest in medical ICUs followed by mixed ICUs and lowest in surgical ICUs.[1] The Extended Prevalence of Infection in Intensive Care (EPIC II) study showed a similar incidence of 7 episodes of candidemia and crude 30-day mortality, which included 1265 ICU in 76 countries. ICU stays for patients with candidemia were 33 days longer than those for patients with gram-positive or gram-negative bacteremia, which were 20-21 days.[2] The burden of candidemia in Indian ICUs is high with early onset after ICU admission, even in patients with less severe physiology score at admission, and 30-day crude and attributable mortality rates were 44.7% and 19.6% respectively.[3] The chance of invasive fungal infection is 20-90% among septic ICU patients with fever while on antibiotics.[4] There is a huge burden of negative blood culture reports. The blood cultures positivity for hematogenous disseminated candidiasis is only <50%, and <20% for intra-abdominal candidiasis.[5]

Empirical therapy should be started in symptomatic patients at risk. The delay in antifungal therapy may increase the mortality rate in patients with fungal infections. The mortality rate in patients who started therapy on day 1 was lower (15%) compared to patients who started therapy on day 3 (41%). The clinicians should consider the clinical evaluation, risk factor assessment, candida scores, and surrogate biomarkers to initiate antifungal treatment before a definite microbiological diagnosis.[6,7] The risk factors for invasive candida infection in critically ill patients include broad-spectrum antibiotics, sepsis, candida colonization, renal replacement therapy, mechanical ventilation, blood transfusion, and diabetes.[8]

The Candida score with sepsis 3.0 criteria of 3 or more in critically ill patients is considered significant, The score is calculated as sepsis: 2 points, total parenteral nutrition: 1 point, surgery: 1 point, and Candida colonization at 2 or more sterile sites: 1 point.[4] There are different scoring systems to

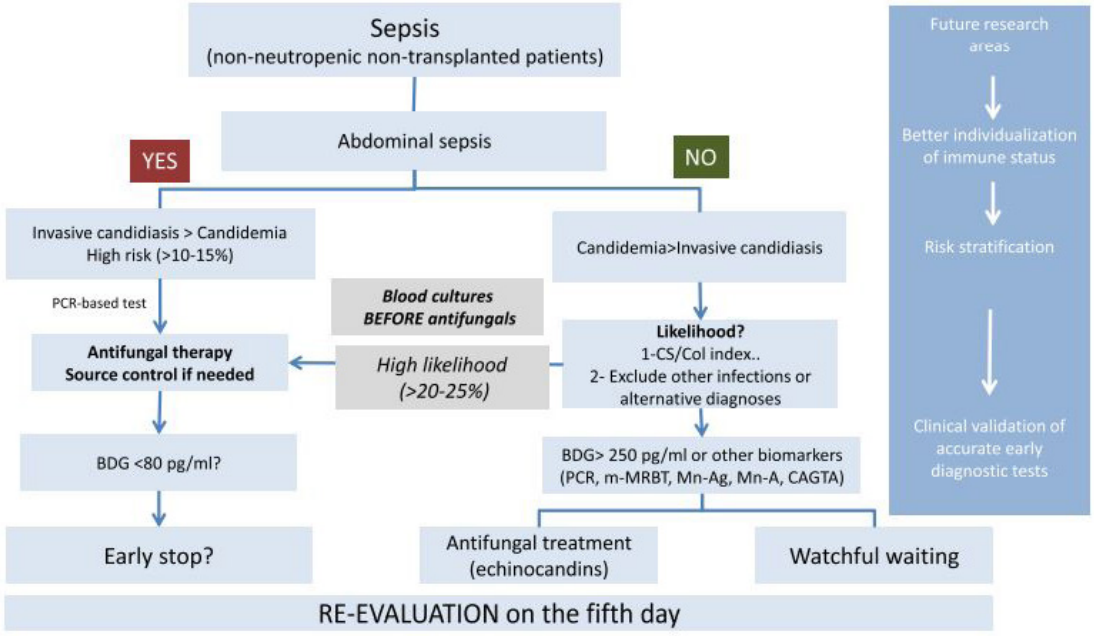
calculate Candida scores and can rely on the biomarkers to initiate empirical therapy.[9] The European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) task force on practical management of invasive candidiasis in critically ill patients have recommended the use of risk prediction models for identifying high-risk patients, because of their simplicity and high negative values.[10]

Infectious Diseases Society of America (IDSA 2016) guidelines – the role of empiric treatment for invasive candidiasis in nonneutropenic patients in the ICU

- Empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from non-sterile sites (strong recommendation with moderate-quality evidence).
- Empirical antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (strong recommendation with moderate-quality evidence).
- The preferred empiric treatment in this situation is an echinocandin and fluconazole is the acceptable alternative choice.
- **De-escalation:** For patients who have no clinical response to empiric antifungal therapy at 4-5 days and who do not have subsequent evidence of invasive candidiasis after the start of empiric therapy or have a negative non-culture diagnostic assay with a high negative predictive value, consideration should be given to stopping antifungal therapy**.** (Strong recommendation with low-quality evidence)[11]

ESICM/ESCMID task force suggests that empirical antifungal therapy might be considered only in patients with septic shock and multi-organ failure (MOF) who have more than 1 extra-digestive site (i.e., urine, throat, upper and lower respiratory tracts, skin folds, drains, operative site) with proven Candida species colonization. ESICM/ESCMID proposed an algorithm for sepsis in non-neutropenic non-transplanted ICU patients at risk for Candidemia and/or invasive candidiasis (IC) patients. (Fig. 1)[10]

Fig. 1: Proposed algorithm for sepsis in non-neutropenic non-transplanted ICU patients at risk for Candidemia and/or IC



BDG, 1-3 β-d-glucan; CS, Candida score; m-MRBT, miniaturized-magnetic resonance-based technology; Mn-Ag, mannan antigen; Mn-Ab, anti-mannan antibody; CAGTA, Candida species germ tube antibody; Col index, colonization index; PCR, polymerase chain reaction; Abdominal sepsis: refers to anastomosis leak, postoperative abscess, repeated surgery for recurrent abdominal sepsis or infected pancreatitis

The secondary observation of the EMPIRICUS trial is that the micafungin group had a significantly lower incidence of newly proven invasive fungal infections. The fragility index of this trial is 3 and not as adequate when compared to 11 for Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial and 48 for the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial. The intervention group had a higher BMI and greater incidence of chronic renal diseases and diabetes, whereas the control group had a greater incidence of chronic respiratory disease, immunosuppressed patients, and septic shock. Nonsignificant improvement in survival was noted among patients with high Sequential Organ Failure Assessment scores (SOFA), which may suggest that certain critically ill patient subgroups may benefit from empirical therapy. Additionally, there was low participation among patients with postoperative gastrointestinal leakage and acute necrotizing pancreatitis, and they had high risk of invasive fungal infection. Previous studies have shown surgical patients may benefit from empirical therapy.[12] Increasing resistance among Candida species is another major challenge. Bruyère et al. showed that the time elapsed from candidemia onset to echinocandin therapy initiation was shortened upon empiric administration.[4]

The survival rate in patients who were administered empirical antifungal therapy (EAFT) showed large variability ranging from 50 to 90%. Two studies from Singapore and China found that EAFT is an independent protective factor that decreases hospital mortality. Three out of twelve studies from

seven countries reported significant survival rates for critically ill ICU-admitted patients who were administered EAFT.[13] A study by Kollef et al. found that delayed EAFT, defined as no antifungal therapy within 24 hours of the onset of septic shock, was independently associated with greater odds of in-hospital mortality when compared to earlier EAFT administration and appropriate source control.[14]

Invasive candidiasis is a common and rather morbid complication of critically ill patients. The diagnosis can be elusive and delayed when relying solely on blood cultures. (1,3)-β-d-glucan (BDG) test has been proposed as a rapid method for the early diagnosis of candidiasis in critically ill patients. The delay in initiating therapy due to the inability to definitively establish the diagnosis results in poorer outcomes. The most recent guidelines by IDSA demonstrated that its applicability is not perfect, but its clarity is very high.[15]

Conclusion

The decision of initiating therapy should be individualized based on clinical assessment, surrogate markers, and culture data demonstrating candida colonization at nonsterile sites. The results should not be generalized to a particular trial. Early empirical therapy will increase the survival rate. De-escalation when appropriate will ensure antifungal stewardship principles.

Clinical scenario

A diabetic and non-oliguric chronic (CKD) patient with creatinine 1.7 mg/dL was admitted with fever for 3 days. He was started on broad-spectrum antibiotics and had persistent spikes in temperature. On day 2, he had mild oliguria and was shifted to ICU. On day 4, he had mild hypotension, which was managed with fluid resuscitation. A central venous catheter was placed. There were no foci of infection identified in cultures. On day 5, the fever was persistent, total count was 13500/mm^3. He was on insulin and was on the verge of hemodialysis.

Pros Cons Debate: Fever in ICU... Not Responding to Antibiotics

Will you add Antifungal without proof?

CONS

Dr. Neha Mishra
Consultant Infectious Diseases, Manipal Hospitals, Bengaluru.

Whether antifungals can be added without proof when a patient in ICU has a fever and not responding to antibiotics?

No, antifungals cannot be added to the patient, the cons and evidence for the same are discussed below.

Introduction

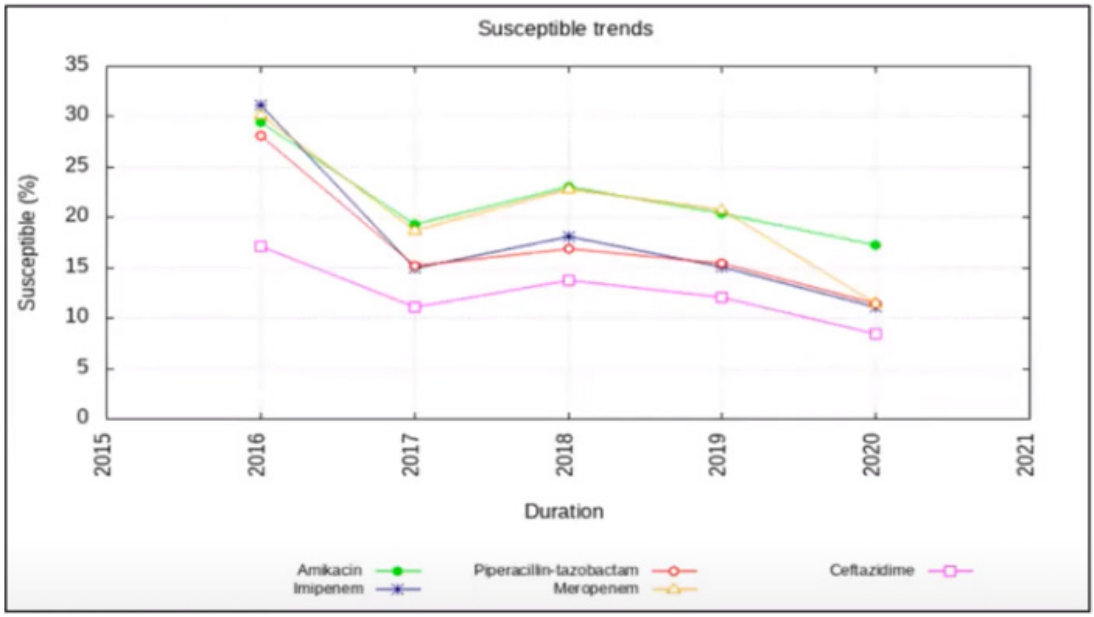
Fever in ICU can be hyperthermia or pyrexia. The causes of pyrexia can be infectious or non-infectious. In most cases, non-infectious causes are compromised.[16] Chakrabarti et al. noted that 1,400 patients contracted ICU- acquired candidemia with approximately 6.51 cases/1000 ICU admissions.[3] Elevated body temperature is detected in approximately 50% of patients admitted to adult ICUs. About 50% of fevers in ICU are due to infectious etiology. This infective etiology includes fungal, bacterial, viral, and parasitic causes where the fungal infection etiology can be <10%.[17] The incidence of infections due to different candida species is <1% in ICU patients. On contrary, the risk of bacterial infections in the ICU is higher than fungal infections. The yearly trends for Candida species isolated from all samples have dropped in 2021 compared to 2016 (Fig. 2). The maximum subgroup of infections is caused by bacteria (50%), and 25% of infections are due to non-fermenting gram-negative bacilli (NFGNB), whereas fungal infections include only 2.5%.[18]

Fig. 2: Yearly trends for Candida species isolated from all samples

Bacteria	Year-2016 (%)	Year-2017 (%)	Year-2018 (%)	Year-2019 (%)	Year-2020 (%)	Year-2021 (%)
Total Candida	432/11604 (3.7)	1498/45521 (3.3)	1704/74295 (2.3)	2403/108465 (2.2)	1869/65561 (2.8)	2605/95728 (2.7)
Candida tropicalis	201/11604 (1.7)	628/45521 (1.38)	494/74295 (0.66)	621/108465 (0.57)	500/65561 (0.76)	796/95728 (0.8)
Candida albicans	145/11604 (1.2)	452/45521 (0.99)	560/74295 (0.75)	652/108465 (0.60)	364/65561 (0.56)	662/95728 (0.7)
Candida glabrata	47/11604 (0.4)	136/45521 (0.30)	179/74295 (0.24)	185/108465 (0.17)	113/65561 (0.17)	314/95728 (0.3)
Candida parapsilosis	25/11604 (0.2)	105/45521 (0.23)	134/74295 (0.18)	232/108465 (0.21)	189/65561 (0.29)	279/95728 (0.3)
Candida auris	0/11604 (0)	17/45521 (0.04)	55/74295 (0.07)	117/108465 (0.11)	121/65561 (0.18)	194/95728 (0.2)

The occurrence of bacterial infections is higher compared to fungal infections. The susceptibility of *Klebsiella pneumoniae* to ertapenem and imipenem in the ICU sector is only 27% and 31% respectively. This demonstrates the possibility of making a poor antibiotic selection. The susceptibility of *A. baumannii* to carbapenems is quite low.[18] A decline in the yearly susceptibility trend of *A. baumannii* isolated from all the samples except feces has been noted (Fig. 3).

Fig. 3: Yearly susceptibility trend of *A. baumannii* isolated from all the samples except feces



Before the addition of EAFT, it is important to consider a low burden of fungal infections, a high risk of bacterial infections, and more resistance to antibiotics. With EAFT in nonneutropenic critically ill patients with sepsis, multiple Candida colonization, and multiple organ failure exposed to broad-spectrum anti-bacterial, there is no significant difference in the rate of survivors without any fungal infection at day 28 between micafungin-treated and placebo-treated groups.[19]

An exploratory, multi-center, randomized, double-blind placebo-controlled study by Knitsch et al. was unable to provide evidence that preemptive administration of an echinocandin was effective in preventing IC in high-risk surgical ICU patients with intra-abdominal infections.[20] In earlier times, when fluconazole was used empirically, there was no benefit of mortality seen in ICU patients.[21] A double-blind placebo-controlled trial by Pelz et al. observed that there is no difference in mortality rate between patients on fluconazole and those on placebo.[22] For adults with sepsis or septic shock at high risk of fungal infection, updated International Guidelines for Management of Sepsis and Septic Shock 2021 suggest using empiric antifungal therapy over no antifungal therapy. For adults with sepsis or septic shock at low risk of fungal infection, it suggests against empiric use of antifungal therapy.[23] These recommendations are weak with low-quality of evidence.

Challenges with empirical therapy

Empirical antifungal treatment may obscure the diagnosis of invasive Candida infections, while it may not influence the development and outcome of invasive disease. Candida colonization and infection are life-threatening in critically ill patients. Hence, Candida colonization and IC may serve as markers of the severity of the primary illness, and consequently, the impact of EAFT may be limited. IC is an uncommon event in the general ICU population, and the number of patients requiring prevention of IC is high.

The risk factors for IC and multidrug-resistant organisms (MDRO) are similar apart for Candida colonization. In such cases, it is important to optimize the use of antibiotics before considering antifungal therapy.[24,25] Sepsis occurring in patients with multiple organ dysfunction and multiple-site colonization in patients receiving broad-spectrum antibacterial agents are rare due to invasive infection.[26,27] BDG levels are not significantly different between Candidemia and patients with Candida colonization.[26,28,29] The isolation rates of candida species are more in the ICU sector compared to OPD and wards.[18] There is no benefit in increasing the inadvertent use of antifungals.

Conclusion

It is paramount to optimize the use of antibiotics before the addition of antifungals. Thorough evaluation should be conducted before planning the treatment with antifungals. De-escalating the treatment should be considered based on the markers and patient's condition.

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Panel Discussion

Non Localizing Fever: Do I give an Antibiotic?

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How to define non-localizing fever?

Dr. Ashutosh Biswas: Understanding the fever localization is very important, as the underlying cause could be infectious or non-infectious. A lack of knowledge of fever localization and prescription based only on clinical acumen can lead to antibiotic abuse and subsequent development of resistance.

Conducting extensive evaluation through basic clinical approaches, lab investigations, molecular diagnostics, and imaging is highly time consuming. Hence it is important to analyze the symptoms and signs, involvement of multiple organs or tissues, immune responses, and inflammatory causes of noninfectious fever during the investigation of the localization. Empirical therapy is recommended if bacterial infection is suspected. Understanding the root of entry of the infected organism and the presence of local infection such as cellulitis or local inflammatory process may help in concluding the fever localization. If there are no signs and symptoms of localization, the fever can be considered as non-localizing.

What are the common causes of non-localizing fever? Do they vary from region to region?

Dr. Jayant K Panda: The cause of fever in tropical areas may primarily depend on the environmental situations and presenting symptoms. For example, heat stroke should be considered as the cause of fever during the hot summer. Similarly, an immunological cause should be suspected in a patient with polyarthralgia. In elderly patients, persistence of fever can be due to the underlying malignancies; likewise, very high leucocyte count without any localizing symptoms in young subjects could be indicative of adult-onset Still's disease. The causes of non-localizing fever are diverse such as malignancies, immunological causes, and metabolic causes like hyperthyroidism presenting with pyrexia of unknown origin.

Immediate antibiotic prescription should be avoided in patients with non-localizing fever. Factors to

be considered while deciding on the cause of fever in such patients include patient's locality, age, environmental conditions, and presenting signs and symptoms. Complete history of patients, and investigations for culture sensitivity and other non-infectious causes should be considered while evaluating non-localizing fever.

How non-localizing fever can be diagnosed? What are the investigations to be conducted and when they should be performed?

Dr. Ramesh Agarwal: Both infectious and noninfectious etiology should be considered while evaluating fever. The non-infectious cause can be autoimmune, malignancies, or drug induced. Stepwise approach is always recommended for evaluating non-localizing fever i.e., from basic to specific investigations. Basic investigations like hemogram, liver function test (LFT), and kidney function test (KFT) provide key information regarding the underlying cause. Hemogram can provide vital clues. For example, immediate antibiotics may not be required in a patient with total leucocyte count of around 13,0000. It is important to explore other non-infectious causes like malignancy, eosinophil examination may give vital clues of parasitic infection, vasculitis or lymphoma.

Hemogram with a peripheral smear should be the first approach while evaluating non-localizing fever. Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) may assist in diagnosing chronic systemic diseases. LFT and KFT are non-specific. Thyroid function test helps in concluding any thyroid dysfunction. Serum ferritin is one of the major inflammatory markers and should be evaluated in patients with undiagnosed fever persisting for 7 to 10 days, despite receiving antibiotics.

Inflammatory markers assist in diagnosing hemophagocytic syndrome, tuberculosis, HIV, and syphilis. Basic urine investigation helps in identifying microhematuria, asymptomatic bacteriuria, and pyuria suggestive of infectious causes. Radiological investigations are not advisable before hematological investigations. Good clinical experience and a high index of suspicion are necessary for accurate diagnosis. For infectious causes, it is meaningful to conduct the primary evaluation for diseases prevalent in that particular area.

What are the treatment options to be considered for non-localizing fever? What is the role of antibiotics in such cases?

Dr. Ahshuthosh Biswas: Definite diagnosis is important for appropriate prescription of medication**.** The inflammatory response can be due to rheumatoid arthritis or joint inflammation. Hence clinical and laboratory investigations should be continued for non-localizing fever. Evidence-based treatment should be provided in such cases, instead of mere antibiotic prescription without identifying the underlying etiology.

Which antibiotics cover atypical infections? What are the causes of non-localizing fever?

Dr. Jayant K Panda: In eastern regions of India, many atypical infections like brucellosis and scrub typhus may present with persistent fever and multi-organ involvement. It is very difficult to locate and treat such infections, and doxycycline has shown very good response. Macrolides are good choices for treating mycoplasma infections. Locating the infections such as anaerobic infection, fungal infection, atypical tuberculosis, and non-mycobacterial infections is important to get optimal treatment

response. Specific investigations should be conducted for non-localizing fever not worked up for 2-3 weeks. For example, blood culture may help to conclude bacterial endocarditis in patients with cardiac lesions and abnormal echocardiographic findings. Similarly, in patients with multiple skin/bone lesions, immunocompromised individuals, and those with foot ulcers/ diabetic foot not responding to treatment for a longer period, pseudomonas has been identified as the cause of infections. Recurrent urinary tract infection is often noted in patients with retention of urine, obstructive uropathy, and those on sodium-glucose cotransporter- 2 inhibitors (SGLT- 2i).

What governs the choice of antibiotics in such situations, especially in non-localized fever?

Dr. Ramesh Agarwal: Deciding the type, dose, and escalation of antibiotic treatment should be based on the diagnosis. It is also important to understand the patient's history and triage the patient based on the disease severity. History should include patient's age, immunocompromised status, hemodynamic status, localized signs and symptoms, drugs taken, other underlying diseases etc. If there are no localized symptoms, the patient should be assessed for hypotension, septicemia, or compromised vital functions. In patients with confusion and altered sensorium, and there is no time to do extensive investigations, empiric antibiotic therapy can be started.

For empiric therapy, broad-spectrum antibiotics covering both Gram-positive and Gram-negative bacterial infections should be used., Fluoroquinolones like ciprofloxacin can be used for treating Gram-negative infections, keftaglan for pseudomonas, and vancomycin, leptomycin, and colistin for Gram-negative infections. The empiric therapy can be customized based on the disease pattern prevalent in a particular geographical area.

Conclusion

Atypical infections and non-infectious diseases are also accompanied by fever, hence conducting proper examinations may help in deciding the treatment. A stepwise approach from basic to specific should be carried out for diagnostic investigations. Initiation of antibiotic treatment depends on the patient's condition, irrespective of the causes. Appropriate use of antimicrobial agents may depend on accurate diagnosis, determining the need for medication, and timing and dosing of antimicrobial therapy.

Notes

FEVER FOUNDATION

Vision

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

Mission

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

Objectives of Fever Foundation

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

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MICRO KNOWLEDGE ACADEMY