MICRO KNOWLEDGE ACADEMY

FEVER FOUNDATION

FEVER-BEYOND BASICS

A Handbook for Physicians

Compilation of articles from

FeFCon 2021 VIRTUAL CONFERENCE

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FOREWORD

Fever is an active yet nonspecific response of the body to infections and other insults that cause immune cells to release cytokines, resulting in a brain prostanoid-mediated rise in body temperature. Physicians use fever as a clinical sign for diagnoses and prognoses, but "fevers of unknown origin" continue to be problematic.

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 2021 had eminent speakers discussing on the various aspects of Fever. This book is a collection of topics about fever presented at the FeFCon 2021 virtual conference held on 19th, 20th, and 21st of November, 2021 that helps in gaining better understanding about fever and its management.

M. Maiya

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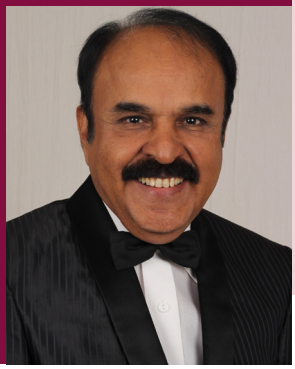
FOREWORD



Fever is a prominent feature of disease since antiquity. The febrile response is orchestrated by the central nervous system through endocrine, neurological, immunological and behavioural mechanisms.

Other than a regulated rise in body temperature, fever is often accompanied by various sickness behaviours, changes in metabolic and physiological characteristics of body systems and alterations in immune responses.

Fever and the febrile response, therefore, remain significant contributors to the pathogenesis, clinical presentation and outcome of many illnesses and diseases.

The fourth annual conference of FeFCon is held on 19th, 20th, and 21st of November 2021 virtually, addressed various aspects of fever, in the midst of COVID 19 pandemic. Exclusive lectures rendered by experts on its approach and management

This fever book is a valuable for the practising physicians to overcome the challenges in fever management in day to day practice.

I hope this book helps in giving insight of fever in normal and special circumstances.

Dr. Muruganathan
Chairman- Fever foundation CME committee
Imm. Past Governor – American College of Physicians, India Chapter
Past Dean – Indian College of Physicians of India
Past President – Association of Physicians of India
Past president- Hypertension society of India

FOREWORD

Greetings!

Fever is a host defence response that provides a sign of an ongoing process related to infection, inflammation, drug reactions, neoplasms, autoimmune diseases, and vascular disorders. 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 2021 the 4th annual conference of fever foundation, was a unique academic conference conducted by the Fever Foundation of India. It was conducted on virtual platform due to ongoing COVID-19 pandemic. 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 2021 book on Fever Management would be helpful in your clinical practice.

Happy Reading!

Dr. T. S. Ravindra
Organizing Chairperson
FeFCon 2021

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.

Due to the pandemic, The Fourth Annual National conference of Fever Foundation, was conducted using the digital platforms. The theme for the conference was 'Fever Beyond Basics'.

FeFCon 2021 Virtual conference was held on the 19th, 20th, and 21st of November, 2021. Outstanding presentations were delivered by highly esteemed and renowned faculty during the three days' academic feast.

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

Happy Reading,

Manjula S

Dr. Manjula S,
Convener,
Fever Foundation of India.

INDEX

Sri. G C Surana ORATION

Love yourself, Improve wellness & Reduce burnout

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Introduction

The present paper deals with self-love, comparison between stress and burnout, healthcare professional's wellness and burnout, and the approaches at the personal and organizational level to mitigate burnout and achieve wellness.

According to Dr. Steve Maraboli, in order to love yourself, it is necessary to create an environment conducive for your nourishment and personal growth. Cultivating a vibrant environment, and avoiding negative thoughts, individuals and situations help in great expression of a person's unique beauty and purpose.[1]

"You yourself, as much as anybody in the entire universe, deserve your love and affection" - Buddha

"To fall in love with yourself is the first secret of happiness" - Robert Morley

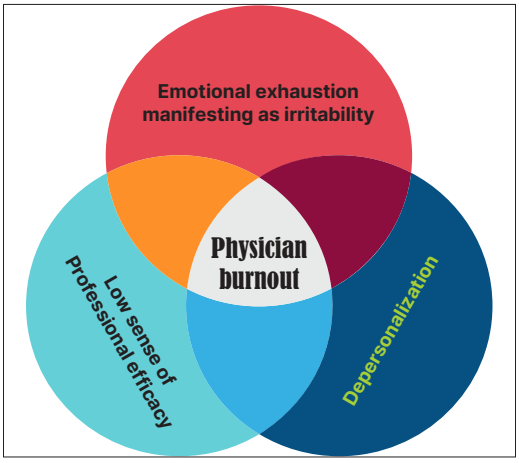
Stress and the organ system

Stress and anxiety affect the entire body systems including the musculoskeletal, respiratory, cardiovascular, endocrine, gastrointestinal, nervous, and reproductive. Unnecessary emotional stress, overworking and straining have serious adverse effects on the body.[2] Good self-care facilitates overall quality of life and it involves emotional, psychological and physical care. For self-care, it is paramount to understand that thoughts and emotions can affect a person's health.[3]

Burnout

Burnout is defined as the physical, emotional and mental exhaustion caused due to interpersonal workplace stressors and emotionally demanding situations. This term was first coined by Herbert Freudenberger in 1974 to describe the emotional fatigue associated with the mismatch of resources to the needs of patients.[4] The 3 major dimensions of burnout in healthcare are emotional exhaustion, feeling low personal accomplishment and depersonalization (Fig. 1). It takes a toll on treating physicians, their patients and medical practice. The contributing factors of burnout are professional isolation, working with a difficult population, long working hours with limited resources, ambiguous success, unreciprocated giving, failure to live up to one's own expectations and personality variables.[5]

Fig. 1: Components of burnout



The adverse effects of the 3 major components of burnout are briefed in table 1.[6, 7]

Table 1: Adverse effects of the 3 major components of burnout

Emotional exhaustion	Fatigue, insomnia, loss of motivation impaired concentration, repeated illness, appetite loss, somatic symptoms, anxiety, depression and anger
Reduced personal accomplishment	Pessimism, isolation, detachment and loss of enjoyment
Depersonalization	Apathy, irritability and lack of productivity

Characteristics of burnout

The following are the major characteristics of burnout:[5]

- Diminished mood, loss of motivation, feeling of guilt or worthlessness persisting for ⩾ 2 weeks
- Persistent social isolation, changes in relationships
- Life interfering anxiety symptoms
- Use of non-prescribed medications, alcohol and illicit substances
- Sustained decline in function
- Changes in eating patterns or weight loss/gain
- Suicidal thoughts or self-harming behaviours

Impact of burnout on clinical practice

Burnout among clinicians may result in suboptimal patient care practices, such as early admission or discharging, prescribing more tests, improper treatment of patients' pain, not communicating important handsoff, options and answers to patient queries, and not discussing plans with staff. Burnout is also a risk factor for higher rates of patient safety errors, medical errors, and mortality ratios among hospitalized patients.[8] Professional consequences include increased medical errors and malpractice, failure of interpersonal relationships, and limited patient satisfaction, quality of care and patient outcomes.[5] A study of emergency physicians showed that stress is the greatest predictor of career burnout arising from uncertainty, risk of poor outcomes and the anxiety due to high-stakes environments in routine practice. Short visits, complicated cases, inability to work, stress due to electronic health records and poor work-life balance can compel the clinicians to quit clinical practice, this inturn result in shortage of primary care clinicians.[9]

Physicians' burnout and COVID-19

The negative emotions experienced by clinicians in routine practice during this pandemic could be attributed to various patient factors (abusive behaviours, unpredictability and entitlement), hospital-level concerns (understaffing, overcrowding, and limited resources), and system-level issues (lack of community resources and time constraints). Such emotions adversely impair the clinician's wellbeing through increase depression, anxiety and burnout.[10]

An interview-based survey conducted by Medscape involving 7,500 physicians globally has noted that 64% of the clinicians in the US had experienced intense burnout due to COVID pandemic, among them 50% had treated COVID patients. The 2 major sources of stress reported by the physicians were: 1) Treating patients with high mortality risk and 2) Exposure to COVID due to improper personal protective equipment (PPE). The strategies adopted by these clinicians to cope with the COVID-related stress were: 1) binge eating (29%) 2) alcohol consumption and 3) receiving prescription stimulants and medications (2%). Feeling of loneliness and experiencing at least one symptom of burnout were reported by 46% of the clinicians. Only 49% of the clinicians were satisfied by their work-life balance.[11]

Stress vs. burnout

Comparison between stress and burnout is provided in table 2.

Table 2: Comparison between stress and burnout

Stress	**Burnout**
Characterized by over engagement	Characterized by disengagement
Emotions are overreactive	Emotions are blunted
Leads to urgency and hyperactivity	Leads to detachment and depression
Primary damage is physical	Primary damage is emotional
May lead to premature death	May feel like life is worthless

Wellbeing

The 3 major dimensions of wellbeing are subjective (values, perceptions and experience), material (practical welfare and standard of living) and relational (personal and social relations).[13]

COVID and Physicians' wellbeing

COVID pandemic poses a major risk to clinicians' mental, physical, spiritual and emotional well-being. Physicians are working in most unprecedented conditions to provide optimal patient care, despite the challenges. They have been working for long shifts and sleeping in hospitals or vehicles, without meeting their families and receiving salaries. They are fighting as true leaders to diagnose and treat suspected/ confirmed COVID patients in India and across the globe. They are frontline COVID-19 warriors and some of them had even sacrificed their life. It is paramount to monitor the physicians' wellness and address the concerns related to their family's safety, to ensure the well-being and resilience throughout the pandemic.[14]

Some of the key measures to improve physicians' wellness during COVID pandemic are as follows:[12]

- Addressing the shortages of PPE and lifesaving medical supplies
- Improving working conditions and schedules
- Implementing well-defined protocols and measures for clear communication
- Encouraging open discussion on anxieties, stress and other issues
- Support from peers, families and mental health resources.

The strategies that can be implemented at micro level to prevent burnout in day-to-day practice are practicing mindfulness, self-connect to understand unreasonable emotional and mental burden, and practicing breathing exercise and name to tame it strategy (name the emotion that is experiencing).[13]

Wellness

According to WHO, *wellness is a state of complete physical, mental, spiritual, environmental, occupational, intellectual and social well-being and not merely the absence of disease or infirmity.* Wellness is related to a person's activity, emotions and wellbeing.[15] It is important to achieve optimal wellness to subdue stress and risk of illness, and ensure positive interactions.[16]

The 10 commandments of physician wellness are listed below:[17]

- Thou shall not expect someone else to reduce your stress
- Thou shall not resist change
- Thou shall not take thyself in vain

- Remember what is holy to thee.
- Honour thy limits.
- Thou shall not work alone.
- Thou shall not kill or take it out on others.
- Thou shall not work harder. Thou shall work smarter.
- Seek to find joy and mastery in thy work.
- Thou shall continue to learn.

The 8 dimensions of wellness are emotional, environmental, occupational, intellectual, financial, social, physical, and spiritual. The following are the ways to achieve all these 8 dimensions.[18]

- Emotional wellness: Learning to accept is the key to transform a person's life and achieve peace.
- Occupational wellness: The career should be pursued for passion and not for financial gains and one should strive to achieve realistic career goals. Physicians should learn to treat patients with detached attachment.
- Intellectual wellness: Having an open mind to opportunities, engaging in research and habitual reading, active listening, learning newer dimension in life and practicing cognitive exercise daily.
- Environmental wellness: Spending time with nature, reducing carbon footprints, and digital detoxicity.
- Financial wellness: Setting budget goals and plans, avoid unplanned and non-emergency buys, and starting savings at an early life for best returns.
- Social wellness: Participating in group discussion and active listening, working with social organizations and volunteering community services.
- Physical exercise: Physical exercises and activities, healthy diet, and practicing sleep hygiene.
- Spiritual wellness: Travelling and exploring other cultures, exploring inner self and practicing mindfulness.

Conclusion

A person's thoughts and emotions play a crucial role in all aspects of health. Optimal psychological wellbeing can be achieved through a balance of mind, body and environment. Physician's burnout can have serious and wide-ranging implications. In the face of unprecedented challenges like COVID pandemic, clinician's well-being requires sustained attention and support at the organizational, state, and national levels.

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FeFCon 2021 Inauguration and Keynote address

COVID 19: Lessons learned and improving pandemic preparedness

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Introduction

According to Walter Cronkite, an American broadcast journalist, *"America's health care system is neither healthy, caring, nor a system."*[1] American college of physicians has issued organizational commitment to be anti-racist, diverse, equitable and inclusive to improve the transparency and accountability.[2] It is important to understand the difference between equality and equity in healthcare sector to remove systemic and structural barrier.

Determinants of health

The US tops the list in terms of medical and social complexities, and healthcare cost. However, total healthcare investment, access to care, equity, administrative efficiency, and healthcare outcomes are significantly lower when compared to Other Economic Co-operation and Development (OECD) countries.[3,4]

In a position paper from the American College of Physicians, Ryan et al., has reported that the exponential growth of corporate interest and their influence in healthcare sector have resulted in the emergence of a more business-oriented healthcare system in the US.[5]

According to a data derived from Bureau of Labor Statistics, the National Center for Health Statistics, and the United States Census Bureau's Current Population Survey, the rate of growth in number of healthcare administrators outpaced the number of physicians between 1975 and 2010 (Fig. 1).[6] According to 2015 data, the age-adjusted major causes of mortality per 100,000 population was found to be higher in the US than in other countries (Fig. 2).[7]

Fig. 1: The rate of growth in number of physicians and healthcare administrators (1975-2010)

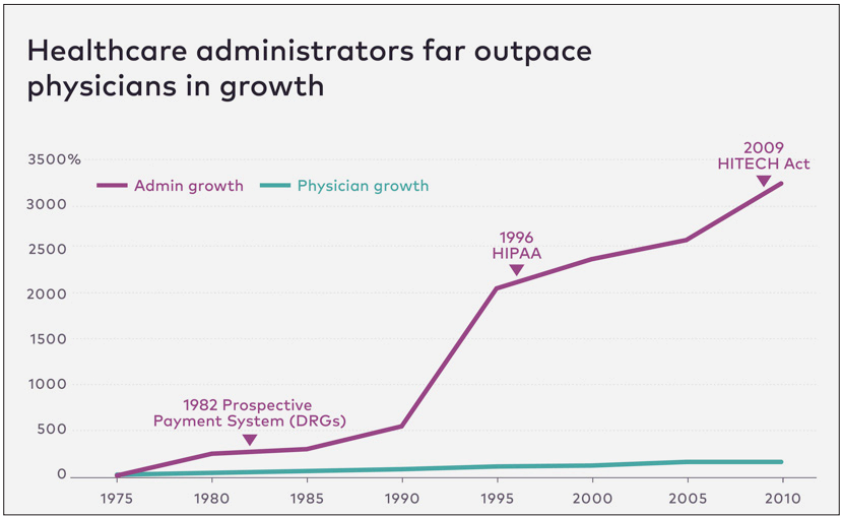
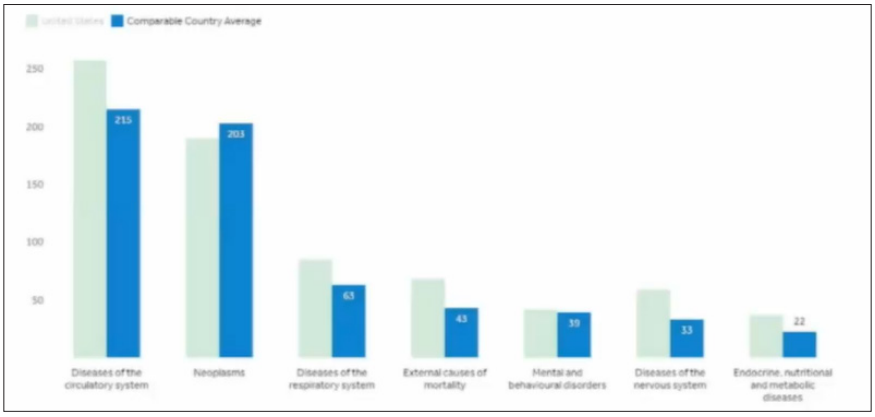


Fig. 2: Age-adjusted major causes of mortality per 100,000 population, 2015



COVID-19

The COVID-19 pandemic has further ripped the US healthcare system. As per World Health organization (WHO) 2019 reports, the 10 threats to global health are air pollution, climate change, non-communicable diseases, global influenza pandemic, fragile and vulnerable settings, antimicrobial resistance, Ebola and other high threat pathogens, weak primary healthcare, vaccine hesitancy, and dengue and human immunodeficiency virus (HIV).[8] COVID has been identified as the third leading cause of death in the US in 2020 after heart disease and cancer.[9] There was tremendous disparities in terms of delivering optimal healthcare services. Studies have noted that race/ethnicity was a major determinant of the risk for COVID-19 and it was found to be higher in American Indians or Alaska native, non-Hispanic persons; Asian, non-

Hispanic person; Black or African, non-Hispanic persons; and Hispanic or Latino persons (Table 1).[10]

Table 1: Risk for COVID-19 by race/ethnicity (updated on July 16, 2021)

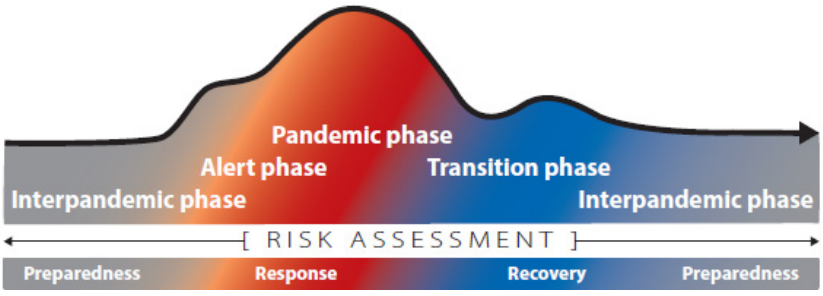
Rate ratios compared to white, non-Hispanic persons	American Indian or Alaska native, non-Hispanic persons	Asian, non-Hispanic persons	Black or African, non-Hispanic persons	Hispanic or Latino persons
Cases	1.7x	0.7x	1.1x	1.9x
Hospitalization	3.4x	1.0x	2.8x	2.8x
Death	2.4x	1.0x	2.0x	2.3x

As per the Centers for Disease Control and Prevention (CDC) 2020 data, COVID-19 was the second most common cause for death in India, replacing chronic obstructive pulmonary disease.[11] According to the ministry of Health, India holds the topmost position in terms of the number of people who received at least one dose of COVID-19 vaccine and those who have completed the vaccination schedule.[12]

Pandemic preparedness

The pandemic has unleashed the lacunae in public health structure, post-acute sequelae of COVID-19, exacerbations of existing inequities in healthcare professionals and patients, and professional dissatisfaction and devastation of the healthcare workforce. In addition, the pandemic has revealed the inequality in accessing healthcare services, especially among individuals who lacked health insurance.[13] The American college of Physicians' (ACP) vision for the U.S. healthcare system, published in Annals of International Medicine, has addressed the issues related to healthcare coverage and cost, payment and delivery systems, barriers in healthcare and social determinants of health.[14] The lessons from the COVID pandemic highlight the significance to prepare, respond, recover and repeat (Fig. 3).[15]

Fig. 3: Continuum of pandemic phases



An article published in the September 2021 issue of *The Atlantic* by Ed Young titled *We're already barrelling toward the next pandemic* has clarified the reasons that led to the deterioration of the pandemic scenario. The article has reported that learning from the

mishandling of the original SARS-CoV-2 virus would have helped the country to better prepare to handle the variant that was already spreading in India. Some experts have suggested that the failure in handling COVID-19 could be due to the country's modern inexperience with infectious disease.[16]

Following the devastation of typhus in Europe, Rudolph Virchow has noted that epidemics were tied to poverty, overcrowding, squalor, and hazardous working conditions. The economic downturn due to the 2008 recession had resulted in the loss of 55,000 jobs in the US local public health department. The subsequent increase in zoonotic diseases and failure was due to impaired contact tracing, testing, communication and vaccination, human encroachment to remote regions, climate changes, disruptions of natural areas and their ecosystems, and global migration. The COVID-19 pandemic may end up costing $16 trillion in US, in addition to lives lost and the morbidity of post-acute symptoms of COVID-19.[16]

The future pandemic preparedness strategy should be driven by scientific evidence. In addition, educating the population, especially those with comorbidities such as obesity, hypertension, and diabetes, increasing the resilience of health systems, improving public health capacity, and understanding governance failure are paramount for pandemic preparedness.[17]

An editorial paper by Wenham et al., published in British Medical Journal, has reported that government must prioritize and build global platforms for equitable access to diagnostics, vaccines, and treatments worldwide. Moreover, there is a need to establish a high-level global council with participants from all countries and adopt a legally binding pandemic treaty. WHO and other global health governance should get more power and money.[18]

Countries with good primary care services have better population health outcomes and equitable access to care, and reduced health disparities and costs.[19] Improved density of primary care physicians in the US has helped in reducing the mortality associated with COVID-19. Even though primary care accounts for majority of the outpatient services, the infrastructure facilities have been severely affected by COVID pandemic. Moreover, the increased workload of the clinicians during the pandemic has increased the risk of adverse mental health effects. Adoption of strategies and improved accessibility to resources may help to enhance the mental well-being of practicing clinicians. American College of Physician has introduced a platform called I.M Emotional support hub to tackle daily burdens, stress, and depression among physicians.[20] The use of telehealth during the pandemic has helped to improve the provision of health services and it has also helped to keep both the patients and health providers safe.[21]

Conclusion

Provision of scientific advice, preparedness, procurement and the accountability of political leaders need to be considered to ensure the quality of healthcare system. It is important to address the existing inequities, structural barriers, and racism and to organize or collaborate with other stakeholders and communities through global platforms. The present pandemic has also underscored the need to devote more political capital and economic resources to mitigate the gap in global and domestic vulnerabilities.

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Rapid diagnosis of Infectious Diseases

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Introduction

Shorter turnaround time and providing accurate results with high sensitivity and specificity are crucial for a microbiological laboratory.

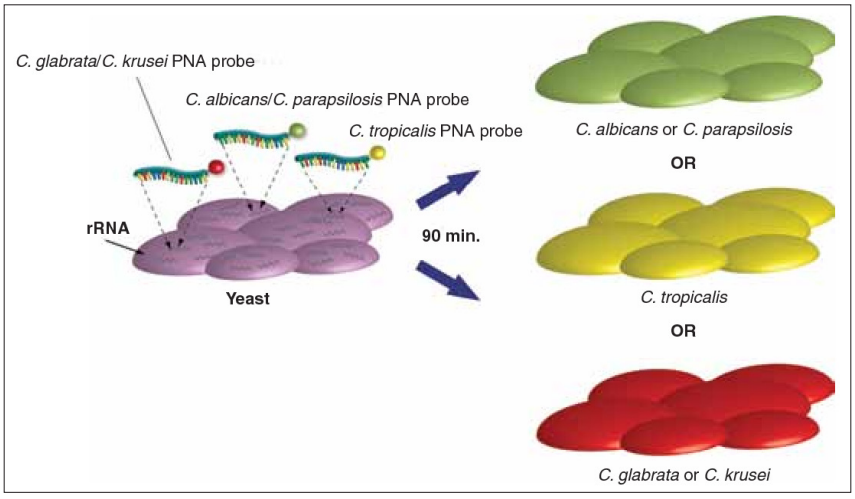
Several rapid pathogen identification methods used for microbial diagnosis include peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH), quick fluorescence *in situ* hybridization (FISH), Verigene, matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF), GeneXpert, and Biofire.[1]

Rapid microbial detection methods used are transmitted light drop analyser (TLDA), Roche light cycler-septifast, VYOO, Magicplex, and T2 Candida.

Peptide nucleic acid fluorescence *in situ* hybridisation (PNA FISH)

PNA FISH is a rapid molecular diagnostic method for identification of microbes directly from supernatant of bacterial culture.[2] PNA-FISH can identify microorganisms and label them into different colours as shown in fig 1.[3] The five most important microorganisms identified by FISH are *S. aureus*, *Coagulase-negative staphylococci* (CoNS), *P. aeruginosa, K. pneumonaie,* and *E .coli*. [4]

Fig. 1: Labelling process with the peptide nucleic acid fluorescence in situ hybridization (PNA FISH) 3



Source: Emily et al, 2012, *American Journal of Health-System Pharmacy*

Accelerate pheno system: The fully automated system has revolutionized the diagnostic armamentarium, as it assists in detecting microorganisms within 2 hours and conducting antimicrobial susceptibility testing in 7 hours.

Each reagent cartridge is equipped with gel electro filtration stations and FISH probes. For microscopy-based, single-cell analysis of antimicrobial susceptibility testing, the Accelerate Pheno system uses an automated sample preparation and bacterial immobilization technique.[5]

Biofire filmarray pneumonia panel: This FDA-approved panel is useful for the identification respiratory viral and bacterial pathogens, and antimicrobial resistance genes from sputum or bronchial alveolar lavage (BAL) (Table 1)[6] However, it is not preferred for identifying fungal infection. The panel quantifies the levels of organism in genome copies/mL. The difference between real-time amplification of the quantified standard material and the amplification of a target is used to extrapolate the genome copies/mL. Values calculated below 10^{5-7} copies/mL are reported as 'not detected.[7]

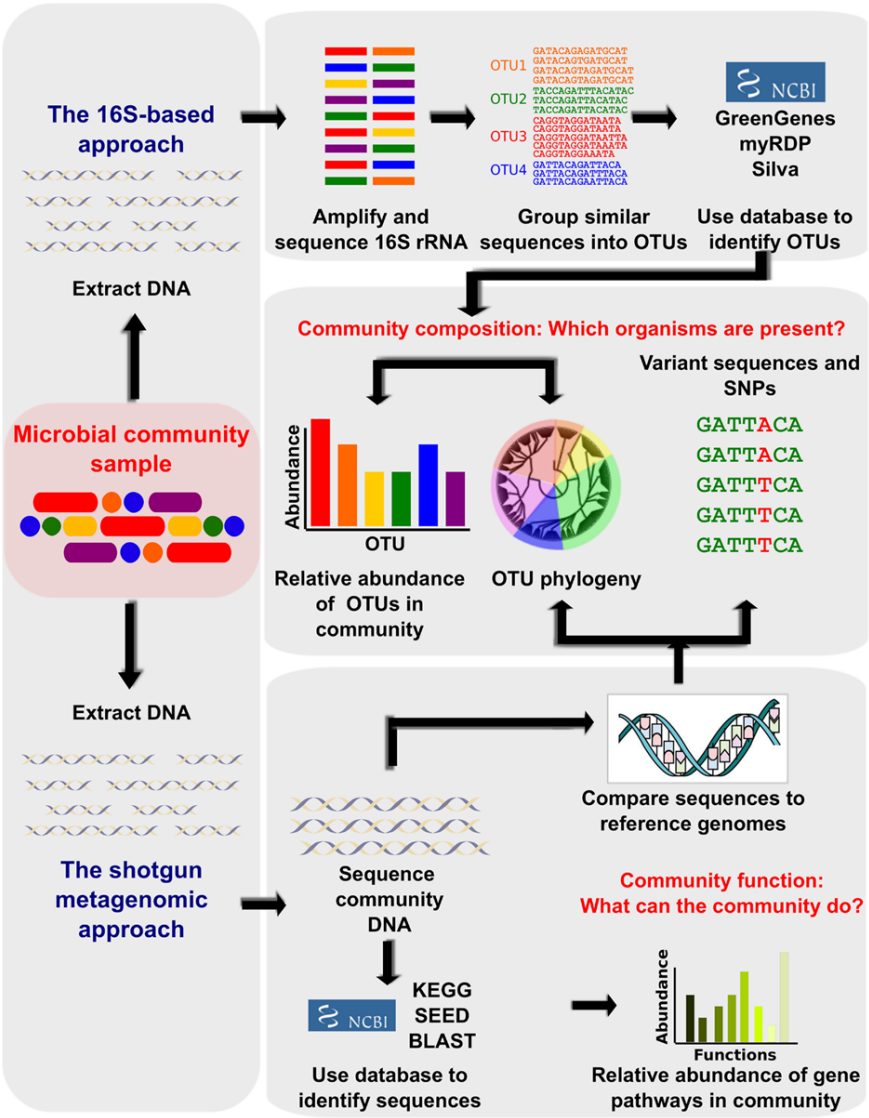
Table 1: Pathogens and genes identified by Biofire film array pneumonia panel [7]

Bacteria	Virus	AMR genes
Acinetobacter calcoaceticus-baumannii	Adenovirus	mecA/C - MREJ (methicillin resistance)
Enterobacter cloacae complex	Coronavirus	ctx-M extended spectrum beta-lactamases (ESBL)
Escherichia. Coli	Human rhinovirus/ enterovirus Human metapneumovirus	Carbapenemases:
Haemophilus influenzae	Influenza A	Klebsiella pneumoniae carbapenemase (KPC)
Klebsiella pneumoniae group	Influenza B	New Delhi metallo-ß-lactamase (NDM)
Klebsiella aerogenes	Parainfluenza virus	Oxacillin-hydrolyzing beta-lactamase (OXA-48-like)
Klebsiella oxytoca	Respiratory syncytial virus	Verona integron-encoded metallo-ß-lactamase (VIM)
Moraxella catarrhalis		IMP-type ß-lactamases (IMP)
Proteus spp		
Pseudomonas aeruginosa		
Serratia marcescens		
Staphylococcus aureus		
Streptococcus pneumonia		
Streptococcus agalactiae		
Streptococcus pyogenes Streptococcus		
Atypical bacteria		
Chlamydia pneumoniae		
Legionella pneumophila		
Mycoplosma pneumoniae		

16s rRNA vs. Shotgun metagenomic sequencing

16s rRNA metagenomics only targets 16s rRNA and identify microbial and taxonomic composition of bacterial species. It is not useful for functional analysis and is limited to only bacteria. Whereas, shotgun metagenomics can identify microbiome, whole genome sequencing and taxonomic composition of bacteria, fungi, and virus. The functional analysis such as antimicrobial resistance, virulence gene, and metabolic pathways can be carried out using shotgun metagenomic sequencing.[8]

Fig. 2: General differences between 16s rRNA and shotgun metagenomic sequencing[8]



Source: Morgan et al, 2012, PLoS Computational Biology

Rapid detection of carbapenemases

Detection of antimicrobial resistance in India is highly challenging, as it is noted in both Gram-positive and Gram-negative species.9 Nearly 90% of the E. coli resistance could be attributed to New Delhi metallo-beta-lactamase (NDM) and remaining 10% due to oxa-48. In Klebsiella species, 50-60% of resistance is due to both NDM and oxa-48, 30% due to OXA-48, and the remaining 5-10% due to NDM. Among both the organisms, NDM is responsible for majority of resistance and there is no proper antibiotic to tackle the same. In Pseudomonas aeruginosa, 60-70% resistance is due to NDM and in Acinetobacter baumannii, 70-80% is due to carbapenem resistance either OXA 23/24 or NDM. The most common rapid carbapenemase methods of detection is listed in table 2.

Table 2: *Rapid* carbapenemase detection method

Test	Enzymes	TAT	Sensitivity (%)	Specificity (%)
Xpert carba R v2/cepheid	blaKPC, blaNDM, blaVIM, blaOXA-48, blaMP	<1 hour	100	99
Check direct CPD for BD max	blaKPC, blaNDM, blaVIM, blaOXA-48	3 hours	100	100
Rapidec Carba NP/bioMerieux	KPC,NDM-1, VIM, OXA, IMP	30 minutes to 2 hours	96	96
ß carba/Bio-rad	KPC,NDM, VIM, OXA, IMP,SPM	24-48 hours	97	100
Neo- rapid carb test/ROSCO	KPC,NDM, VIM, OXA, IMP	30 minutes to 2 hours	96	100
NEW resist/Coris Bioconcept	KPC,NDM, VIM, OXA	< 5 minutes	98	100

Xpert carba-R is the most commonly and routinely used kit in India and worldwide to detect all variants of KPCs (1-23), NDM-1 (1-16), VIMs, OXA-48 like, IMP-1 like, and NDMs within 1 hour. OXA-23 K-SeT, a novel immunochromatography assay is available for rapid detection of OXA-23. It also prevents cross-reactivity with OXA 24, OXA 72, OXA 58, OXA 143, OXA 48, and OXA 198.

Synergy testing

All NDM-positive bacteria are highly susceptible to simultaneous administration of ceftazidime/avibactam with aztreonam. Although the treatment is found to be superior to colistin, the limitations are hepatotoxicity, poor lung penetration, PBP3 insertion and efflux. There are no reports of OXA 48-like resistance for ceftazidime/avibactam.

Target therapy

Target therapy for E. coli and Klebsiella species is listed in table 3.

Table 3: Target therapy for E. coli and Klebsiella species

E. coli	*Klebsiella spp*
NDM Ceftazidime/avibactam with aztreonam	**OXA 48 like (OXA-181 and OXA-232)** Ceftazidime/avibactam
OXA 48 like Ceftazidime/avibactam	**NDM+ OXA 48 like+ompK35/36** Ceftazidime/avibactam with aztreonam Cefiderocol Tigecycline/colistin
NDM+ OXA 48 like+PBP3 insert Ceftazidime/Avibactam with aztreonam Cefiderocol Tigecycline/colistin	

For the management of *Pseudomonas aeruginosa* with resistance mechanisms of porin loss, hyper efflux and NDM, the preferred drug combination is colistin with carbapenem. ß-lactamase inhibitors (BLI) are not preferred in such cases.

Treatment options for the management of *Acinetobacter baumannii* is listed in table 4.[10]

Table 4: Treatment options available for the management of Acinetobacter baumannii

Infection site	Preferred	Alternatives, including colistin/polymyxin-sparing regimens	Therapies to avoid when alternatives exist
Bacteremia, primary or line-related	Meropenem + polymyxin B ± ampicillin–sulbactam	Meropenem + Minocycline ± Ampicillin–sulbactam OR Cefiderocol in combination	Tigecycline, Eravacycline
Pneumonia	Meropenem + polymyxin B ± ampicillin–sulbactam	Meropenem + minocycline OR Cefiderocol in combination	Monotherapy with any agent
Intra-abdominal infection	Tigecycline ± meropenem	Eravacycline ± meropenem	Aminoglycosides

Infection site	Preferred	Alternatives, including colistin/polymyxin-sparing regimens	Therapies to avoid when alternatives exist
Osteomyelitis	Minocycline ± meropenem	Eravacycline ± meropenem	
UTI-pyelonephritis	Amikacin OR colistin	Gentamicin Tobramycin Cefiderocol	Tigecycline, eravacycline
UTI-cystitis	Amikacin OR colistin	Gentamicin Tobramycin Cefiderocol	Tigecycline, eravacycline
Central nervous system	Meropenem + polymyxin B + ampicillin–sulbactam	Meropenem + tigecycline + ampicillin–sulbactam	Aminoglycosides

Conclusion

Newer diagnostic assays are much easier to adopt to a clinical microbiology laboratory workflow with the prime objective of decreasing the turnaround time for microbial identification in a cost-effective manner. Antimicrobial susceptibility testing is key for the prescription of appropriate treatment regimen. However, the emergence of newer mechanisms of resistance warrants a constant vigilance on the ability of each testing method to accurately detect resistance.

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Experience in Detecting an Unknown Bug

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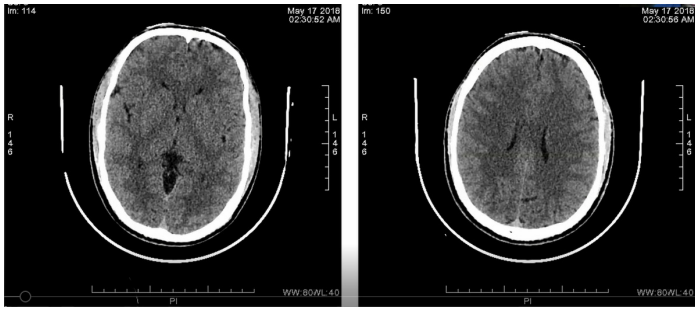
Introduction

In 2018, isolated cases of Nipah virus disease were reported in Kozhikode district, Kerala, India. The challenges and concerns witnessed while conducting the emergency preparedness and response for the containment of Nipah outbreak in southern India are shared in this chapter.

Challenges in diagnosis

A 26-year-old male, who was electrician by profession, presented with 3 days of fever, vomiting, breathing difficulty, and altered sensorium. He was admitted to medical ICU. CT of head revealed diffused brain edema (Fig.1). He did not have any travel history and physical examination revealed hypertension (200/110), hypoxia (SpO_2 86, RR 36/min), tachypnea and tachycardia. The patient was conscious, disoriented, and restless with no signs of wheezing, movement limitation, meningeal irritation, focal neurological deficit, and palpable organomegaly.

Fig. 1: CT of brain

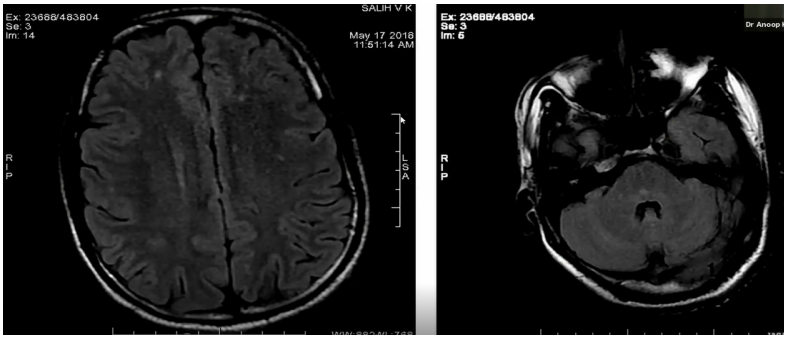


The arterial blood gases (ABG) test was normal with mild hypoxia. Screening ultrasound and ECHO revealed normal LV function and absence of hepatosplenomegaly, pleural effusion and ascites. Routine CBC showed mild hemoconcentration and thrombocytopenia and elevated procalcitonin level (13ng/mL). Renal and liver function tests were unremarkable. The patient was on ventilator support and empirical treatment was initiated with anti-oedema measures.

Family history revealed that the patient's brother had succumbed to death almost 2 weeks before with similar symptoms, eliciting the suspicion of infectious or communicable disease. Three close relatives of the current patient also had recent history of fever, which resolved with

medications. The patient demonstrated hypertensive response, persistent tachycardia, ptosis, segmental myoclonus, myocarditis and segmental sweating. MRI (Fig. 2) and CSF analysis were unremarkable. The possibility of dengue encephalitis was ruled out through PCR test.

Fig.2: MRI of brain



The diagnostic criteria to be considered for encephalitis and encephalopathy in patents with presumed infectious or autoimmune aetiology have been provided in table 1. CSF leucocytosis may not be seen in all cases of early encephalitis. Unusual clinical features pertaining to meningoencephalitis were observed in the present cluster of cases. Based on the clinical and lab investigations, the possibility of an unusual viral syndrome was considered.

Table 1. Diagnostic criteria for encephalitis and encephalopathy of presumed infectious or autoimmune aetiology[1]

Major criterion (required):

- Patients presenting with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified

Minor Criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis):

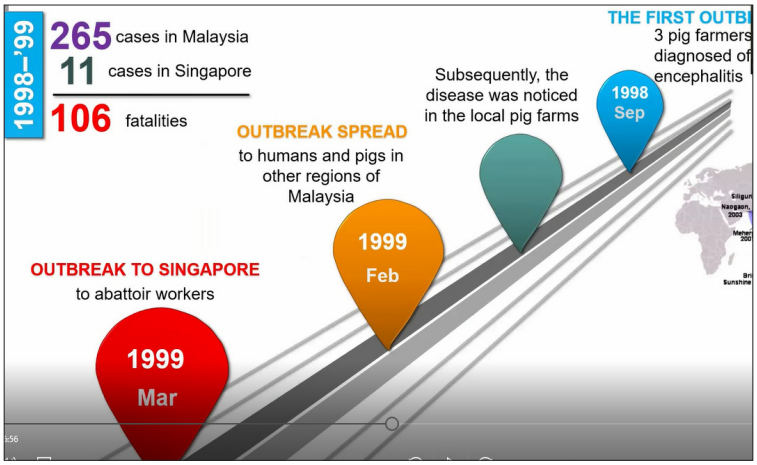
- Documented fever ≥38° C (100.4°F) within the 72 h before or after presentation
- Generalized or partial seizures not fully attributable to a preexisting seizure disorder
- New onset of focal neurologic findings
- CSF WBC count ≥5/cubic mmd
- Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
- Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

Source: international encephalitis consortium. Clin Infect Dis. 2013 Oct;57(8):1114-28

Dr. Arun Kumar, Chief of Virology, Manipal Virology Centre was consulted for expert opinion and as per his instruction, throat swab, CSF, urine and blood samples were collected from all the patients at Manipal Virology Centre. Samples were also sent for toxicology analysis to rule out toxic encephalopathy. Following a bedside discussion with critical care, neurology and internal medicine team members, Nipah virus was considered as one of the possibilities.

Nipah outbreak was first reported in 1998 among pig farmers in Malaysia and patients were diagnosed with encephalitis. In 1999 and 2002, Singapore and Bangladesh had witnessed outbreaks respectively. In Bangladesh, contamination of date palm sap by bat secretions and human-to-human transmission were the routes of outbreak. The disease had also been periodically reported in eastern and southern India (Fig. 3).

Fig. 3: History of outbreak of Nipah



In the current cluster, the subjects did not have any contact with the pigs; however, they had consumed mangos grown in their farm land and some of them were partially eaten by the birds. Moreover, the trees and wells in land were habitat of bats, indicating the viral transmission through bats. A 2000 study by Goh et al. has reported tachycardia, hypertension, segmental myoclonus and bilateral ptosis as prominent clinical features of Nipah virus encephalitis and this was in concurrence with the symptoms noted in all the current patients.[2]

The current patient succumbed to death on day 5 of admission due to severe myocarditis, acute respiratory distress syndrome (ARDS) and circulatory failure. Pathological autopsy was needed to conclude the diagnosis. The team at Manipal Virology Institute isolated a deadly virus with high transmission and mortality rate from the samples.

Caregivers were subsequently alerted and the patients were isolated. Government officials were informed and they had opened a control centre in the district. The medical team had to deal with various challenges and concerns such as dealing with viral exposure of ICU team and 60 other hospital contacts, managing patients admitted in the ICU, and triaging of febrile patients. The immediate measures adopted to contain further viral transmission were as follows:

- Infection control strategies
- Triaging of febrile patients
- Dedicated ward and ICU for suspected cases
- Counselling and emotional support for exposed staff members
- Conducting training classes
- Adoption of SARS-COV-1 gudielines for disease surveillance and management[3]

The final report from National Virology Institute, Pune had concluded the virus as Nipah, and further measures were taken such as contact tracing, implementation of quarantine and funeral protocols and procurement of necessary drugs.

At the same time period, another patient got admitted with similar features such as hypertension, tachycardia, fever, tiredness, vomiting, thrombocytopenia, hemoconcentration and encephalopathy. He was residing around 100 km away from the patient who succumbed to death, indicating the probability of another source of viral transmission. Another case was admitted with loose stools, vomiting, oral ulcer, ataxia, severe hypertension, and tachycardia. Although initial viral screening was negative, repeated evaluation had concluded the case as Nipah positive. Contact tracing had revealed that all the positive cases were interconnected and from the index case, 15 patients contracted the infection. Through stringent infection control measures, it was possible to significantly reduce the viral transmission. Ribavirin along with supportive treatment was used initially to manage the infected patients. Recent literature evidence suggests the use of remdesivir along with monoclonal antibodies for effective disease management.

Containment strategies

Risk communication strategies and public advertisement campaign adopted by the government of Kerala were widely acknowledged. WHO has also commented on the emergency preparedness and response measures adopted by the government and the Baby Memorial Hospital for the containment of Nipah virus outbreak in India.

Observations suggestive of Nipah infection

The following observations were suggestive of Nipah infection:

- All the CSF samples screened through PCR was negative for Nipah virus. Hence, it is recommended to conclude the diagnosis through urine, blood and throat swab specimens.
- Multiple discrete lesions in MRI of brain.
- Encephalitis with ARDs was noted in 37% of the infected patients.
- Common presentation of primary neurological syndrome (84%).

Conclusion

Recent outbreaks happened in Kerala shows that Nipah is emerging as a deadly zoonotic disease in India and the early disease surveillance and interventions helped to contain the disease as only a local occurrence limited to two districts. It also highlights the possibility of spill over events and the need to strengthen the surveillance systems for effective prevention of transmission.

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Emerging and Re-emerging Infectious Diseases

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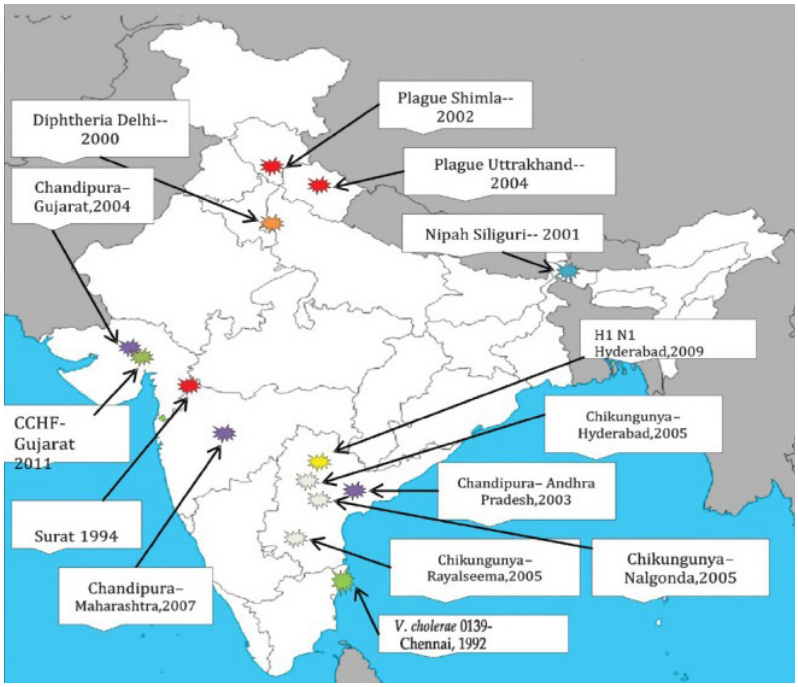
Introduction

Emerging infectious diseases are newly identified and previously unknown infectious disease, which can cause major public health problems. Remerging infectious diseases are those infectious diseases, which were considered earlier as not public health problems due to lower incidence, but are now showing upward trends in incidence or prevalence worldwide.

The emerging and remerging infections in the southeast Asian region include anthrax, avian influenza, AIDS, cholera, diphtheria, dengue, dengue hemorrhagic fever, hand, foot, and mouth disease (HFMD), Japanese encephalitis, leptospirosis, malaria, measles, meningitis, Nipah, rabies and scrub typhus.[1] For the past few years, India is witnessing the re-emergence of several infections including diphtheria, cholera, and plaque, and recently Nipah and zika have been added to the list (Fig. 1).[2] Nearly 70% of the newly recognized emerging pathogens are zoonotic, whereas 23% are vector borne.

Fig. 1: Emerging and remerging infections in India



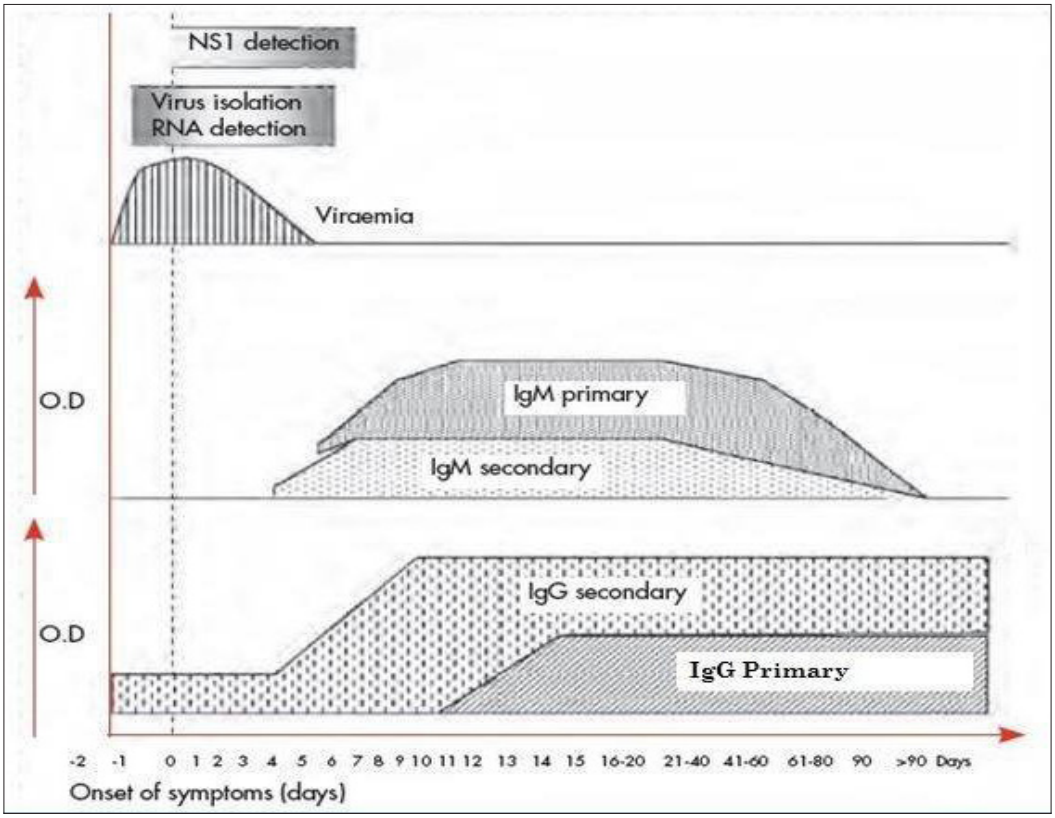
Some of the key reasons for the emergence/ re-emergence of infectious diseases are listed below:

- Increased demand for the animal proteins, change in farming practices and animal consumption of animal products
- Mutation and recombination in microbial genes
- Human behavioral changes, change in eating habits, food processing and storage techniques, deforestation and shortfall in public health and infrastructure policies due to poor funding of scientific studies
- Antibiotic abuse, bioterrorism, blood transfusion, impaired public health measures
- Good documentation of research on prevalence/ incidence, improved diagnostic techniques, monitoring and surveillance
- Mixed farming, occupational exposure, recreational activities, road construction, trade and transportation, travel and tourism, urbanization, war, water control projects, and increase in population.[3]

Re-emerging disease in India

The last 15 years have witnessed exponential increase in dengue cases, accounting for around 50-100 million cases annually.[4] Studies have shown that dengue is not a cause for pyrexia of unknown origin, as the fever generally resolves within 14 days. If a person had visited an endemic area and developed the fever after 14 days of return of travel or the fever persisted beyond 14 days, the probability of dengue is unlikely.[5] The detection of NS1 antigen in 2-3 days and IgM after 5 days is indicative of dengue (Fig. 2). Platelet transfusion is very rarely needed for managing dengue and it is recommended only if the platelet count falls below 10,000/μl.[7]

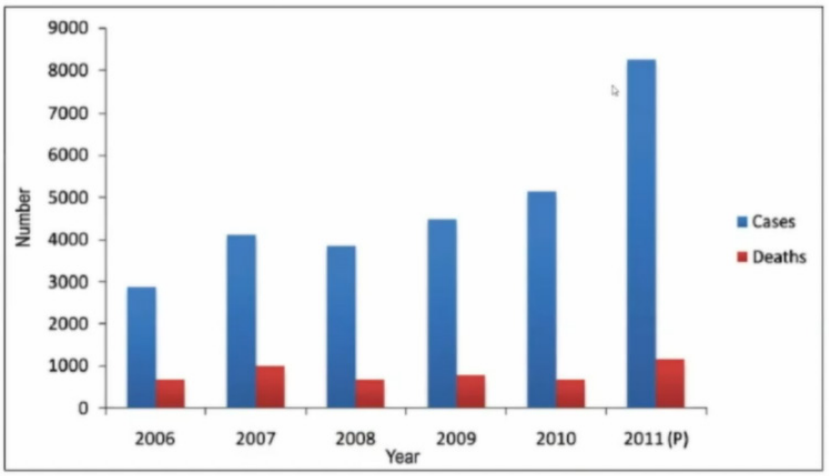
Fig. 2: Diagnostic methods for dengue virus infections.6



Chikungunya, transmitted by Aedes mosquito, is another endemic disease that remerged after 15 years in India. It was first reported in Kolkata in 1963 and in Chennai in 1964. The outbreak occurred in 2005-2006 almost reached a pandemic status and it was due to increased susceptibility of non-immune population and mutation in chikungunya strain.[8]

Japanese encephalitis is another mosquito borne zoonotic viral disease remerging in India and its increased incidence rate could also be attributed to improved diagnostic modalities. The availability of vaccine against Japanese encephalitis virus in India has contributed to effective disease management. The cases and deaths due to Japanese encephalitis occurred in India between 2006-2011 is depicted in figure 3.

Fig. 3: Cases and deaths due to Japanese encephalitis



The serological and molecular evidence of hantavirus infections in human and rodents has also been reported in India. Hanta virus, a zoonotic rodent borne virus belonging to Bunyaviridae family, is reported in some parts of southeast Asia and southeast Europe. The presentation could be either in the form of hemorrhagic fever with renal syndrome or Hanta virus cardiopulmonary syndrome (more common among Americans). The transmission is through aerosols generated from virus-contaminated rodent urine, or saliva and also through bites and scratches of infected rodent and the symptoms may depend on the serotype.[9] The diagnoses is mainly through polymerase chain reaction (PCR) or serology. Thottapalayam virus is the indigenous isolate of the virus from India, and a non-rodent shrew a species of insectivores is believed to be the carrier.[10] There is no definite treatment and ribavirin has been reported to be beneficial for Hantavirus hemorrhagic fever with renal syndrome (HFRS), but not for Hantavirus cardiopulmonary syndrome.[9]

Nipah virus infection was first reported in Malaysia in 1998. Pteropus bat species are the primary reservoirs of Nipah, and pigs, cats, dog, and horses are the intermediate hosts. Nipah virus, a paramyxovirus related to Hendra virus, is generally transmitted through infected aerosols or contaminated fruits.[11] Many cases have been reported in Kerala in recent years and even back in Siliguri, West Bengal in 2001.[12,13] Person-to-person transmission also occurs through body fluids. The incubation period is 5-20 days, and the common symptoms are fever, headache, myalgia, altered sensorium, seizures, tachypnoea, and respiratory distress.[11] In Malaysia, the transmission was mainly through pig, whereas in Bangladesh and India, it was through date palm sap, domestic animals, and direct contact.[14] Severe respiratory disease was more predominant in India as opposed to Malaysia (65% versus 14%). Case fatality rate was 73% in India versus 39% in Malaysia, and more patient required mechanical ventilation.

Chandipura virus, has emerged as an encephalitic pathogen in various parts of Maharashtra and outbreaks had been reported in Gujrat (2004) and Andhra Pradesh (2003).[15] It typically causes epidemic brain attack in children and young adults. The typical symptoms include fever, myalgia, arthralgia, and altered sensorium and case fatality rate is estimated to be around 55%.[16] Lack of specific diagnostic modalities is hampering the timely and accurate diagnosis and treatment of Chandipura virus.

Ebola virus is predominantly seen in African regions. The infection is typically a hemorrhagic fever, characterized by headache, conjunctivitis, fever, lack of appetite, internal bleeding, myositis, diarrhea, skin rash, abdominal symptoms, sore throat, and dyspnea.[17] The use of personal protective equipment is mandatory while handling this cases, and vaccine is available for prevention.[18]

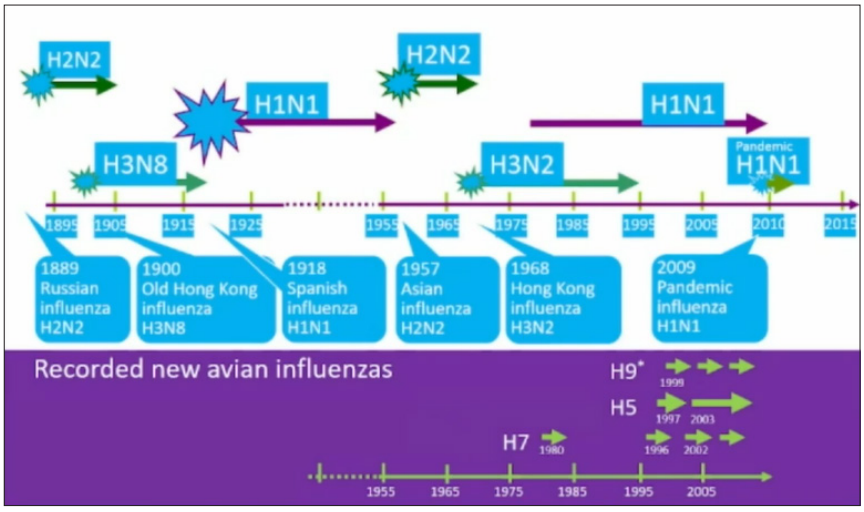
Other viral infections that have been reported in India are Crimean-Congo hemorrhagic fever in Gujrat (2010-2012) and Kyasanur Forest Disease in Shimoga, Karnataka (2011-12). [19, 20] West Nile fever, cholera, plague and acute encephalitis syndrome are the other diseases that has emerged recently in India.[21] However there is lack of diagnostic modalities to identify these viruses in India.

The first pandemic due to influenza virus was reported in the Central Asian city of Bukhara in May 1889. Subsequently, several outbreaks had been reported globally (Fig. 4).[22] Spanish influenza, occurred in 1918, was one of the worst outbreaks causing the death of 50 million people.[23]

The outbreak of severe acute respiratory syndrome (*SARS*), a potentially fatal respiratory illness, was first reported in 2002. These outbreaks have led to the widespread usage of mask in east countries.[24] The H1N1 influenza virus outbreak in 2009 was probably caused due to proximity of humans with animals. The gastrointestinal symptoms such as diarrhea, nausea, and vomiting are more prominent in H1N1 than other conventional viral epidemics.[25]

Middle east respiratory syndrome was first reported in Saudi Arabia in September 2012. The disease is associated with high mortality rate and common symptoms include fever, cough and shortness of breath.[26] COVID-19, caused by the SARS-CoV-2 virus, is an ongoing global pandemic started in 2019. The preventive measures comprise of vaccine, sanitization, wearing mask and social distancing. According to a recent article, wearing mask, social distancing, and hand hygiene help to reduce the incidence of COVID by 53%, 25% and 53% respectively.[27, 28]

Fig. 4: Timeline of pandemics due to influenza virus



Scrub typhus, is another a life-threatening infectious disease, that shows a of period re-emergence. The resurgence of diphtheria in recent years could be attributed to poor immunization practices. The re-emergence of other parasitic diseases such as cryptosporidiosis, microsporidiosis, cyclosporiasis, trichinellosis, toxoplasmosis, cysticercosis, leishmaniasis, and echinococcus have also been reported in various parts of the world.

Conclusion

In order to combat the emergence/resurgence of infectious diseases, it is paramount to strengthen the surveillance and rapid response mechanisms, complying with international health regulations. It is also important to facilitate epidemiology research, laboratory networks, research and development and information sharing and partnerships.

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Monoclonal Antibodies and Their Application in Management of Infectious Disease/Fever

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Introduction

The immune system is a complex network of various cells and proteins, which mediates various biochemical, cellular, and vascular mechanisms for defending the invasion of various microbial pathogens. The present chapter discusses the timeline of evolution of monoclonal antibodies and their use in managing various diseases.

Basic notions of immune response

The diverse microbial pathogens confronted by the immune system are equipped with danger associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which are crucial for eliciting innate immunity and recognition of pathogens of cellular injury. These repetitive biochemical entities are recognized by the sentinels of the immune system namely the antigen presenting cells (APCs), which are heterogeneous group of immune cells comprising of macrophages, Langerhans cells, B cells, and dendritic cells.[1] Toll-like receptors (TLRs) or pattern recognition receptors (PRRs) present in these cells initiate the first line of defence, namely innate immune response, by recognizing potentially harmful pathogens.

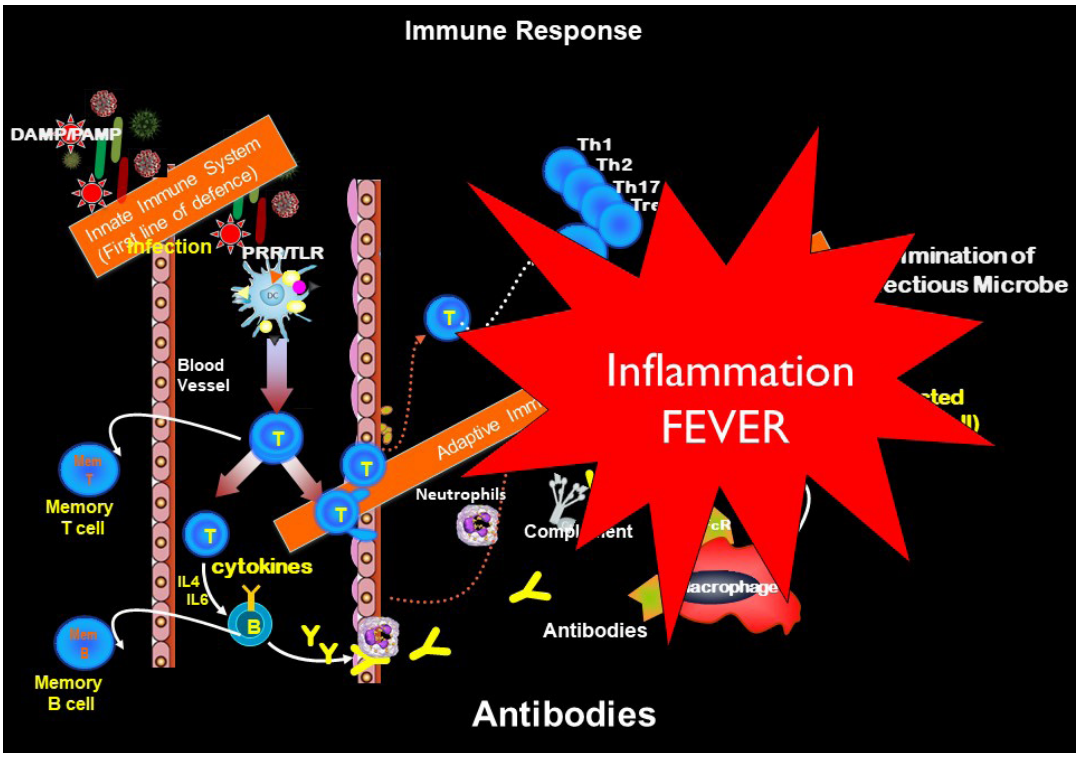
In scenarios where the innate immune response is inadequate to manage the pathogenic overload or virulence, the adaptive immune response sets in. In adaptive immune response, the various APCs present the small antigenic peptides to the T lymphocytes through the class 1 or 2 molecules. The co-stimulatory signal between the APCs and T cells and their subsequent activation contributes to the production of cytokines and other molecules. The differentiation and polarization of T lymphocytes into subtypes is dependent on the nature of the pathogen and the microenvironment. If the pathogen has already reached the target organ, the T-lymphocytes secrete other cytokines namely IL4 and IL6, which in turn contribute to the differentiation of B cells to plasma cells secreting antibodies. The recognition of pathogens by the antibodies leads to a series of biochemical reactions.[2]

The antigen combining site of the antibody molecule helps in the recognition of a specific part of the antigen, whereas the constant region attaches to the fragment crystallizable (Fc) receptors present in the macrophages. The macrophages and the recruited neutrophils from various reserve pools mediate various antimicrobial effector mechanisms for the elimination of the pathogens.[3] The antigen-antibody reaction also mediates the activation of complement system, which in turn contributes to the recruitment and activation of immune cells from both the innate and adaptive arms of the immune system.[4]

The differentiation of T cells into various inflammatory effector populations namely Th1, Th2, and Th17 also elicit specific immune responses based on the type of the pathogen present; whereas

the regulatory T (Treg) cells control or prevent the excessive or inappropriate inflammatory immune responses.[5] Cytotoxic T cells, also known as CD8+ T cells, are effector cells involved in the destruction of virus-infected cells and tumour cells.

Fig. 1: Pathways of immune response



Inflammation, induced by various cellular responses and chemical mediators, occur due to the invasion of the physical barriers by the pathogens. However, inflammation is necessary for the recruitment of the cellular defence components for the elimination of the pathogens.[5]

Timeline of antibodies

Emil Adolf von Behring, a German physiologist, received the 1901 Nobel Prize in Medicine for showing that the antibodies could be transferred from one person to another by means of blood plasma or serum. During the period 1900-1940, the Behring's antibodies were the main focus of research for the immunologists with regard to their functional and therapeutic aspects, and structural and binding properties. Following the discovery of clinical use of these antibodies against diphtheria, several immunologists and clinicians were successful in developing antiserum against various diseases and started with a new era of passive immunotherapies. These antibodies helped in saving lives of thousands during World War II.

In 1943, Edwin Cohn standardized the process of purifying plasma proteins including the antibodies and albumin. In 1950, Col. Bruton was successful in treating a male child with

agammaglobulinemia by administering immunoglobulin, this paved the way for a revolution in treatment for primary immunodeficiency. The Nobel prize in 1984 was awarded to Niels Jerne and Kohler-Milstein for their discovery of production of monoclonal antibodies. Niels Jerne has identified different antigenic determinants of immunoglobulin.

Development of monoclonal antibodies

Inflammation is well recognized as the hallmark of autoimmune diseases. Dissecting the anti-inflammatory effects of immunoglobulin has found that the polyclonal IV immunoglobulin has the potential to block complement activation (C3, C% and C9 complex) and interfere with the cytokine network, Th1 and Th17 cells to re-establish the immune balance. A study by Ravetch et al. in 2001 demonstrated that the Fc portion of the immunoglobulin is sufficient to confer the anti-inflammatory effect, and this has contributed to the development of therapeutic humanized monoclonal antibodies.[6]

Newer therapeutic advances have led to the development of plethora of engineered antibody fragments. Zuercher et al. (2019) has reported the initial promising results of recombinant fragment crystallisable (rFc) multimers primarily target Fcγ receptors (FcγRs) for the management of autoimmune diseases.[7] Monoclonal antibodies are currently used for the management of diverse diseases (Table 1).

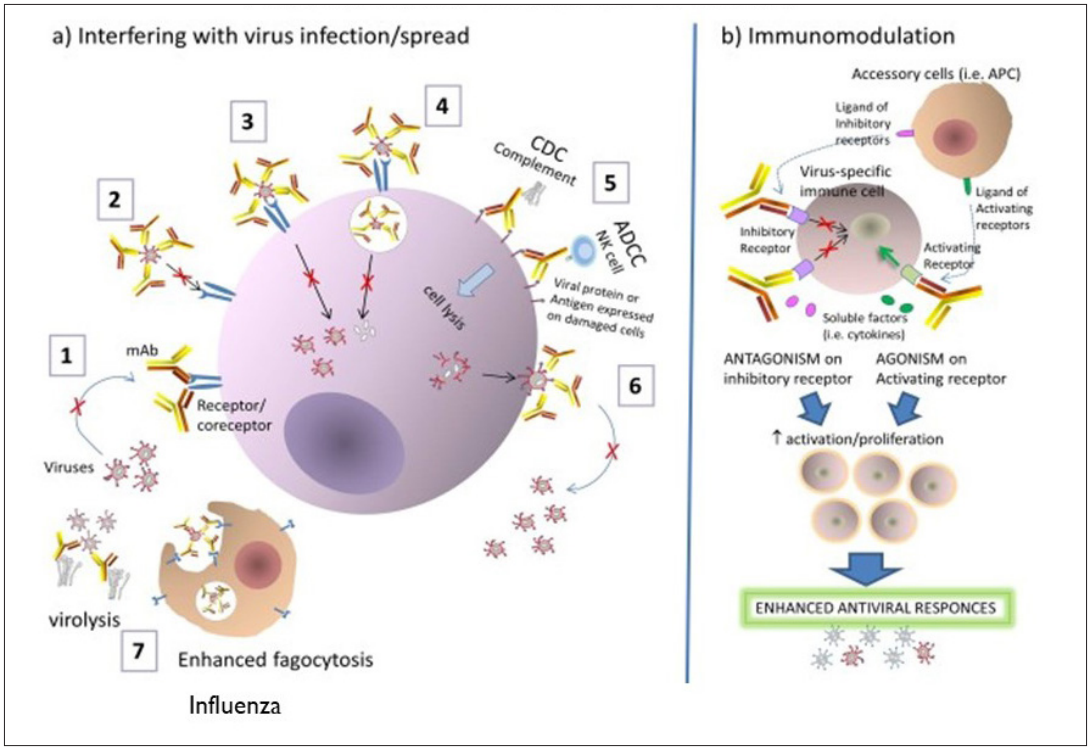
Table 1: Diseases that can be treated with monoclonal antibodies

Cancers	Inflammatory diseases	Infectious diseases	Other diseases
▪ Neuro/glioblastoma ▪ Colorectal, ovarian ▪ prostate, testicular ▪ breast, non-small cell lung, renal, bladder, pancreatic, endometrial and gastroesophageal cancers ▪ Melanoma, ▪ Multiple myeloma ▪ Squamous cell carcinoma ▪ Leukemia ▪ Hodgkin's ▪ Hepatocellular carcinoma ▪ Angiosarcoma	▪ Rheumatic disease ▪ Inflammatory bowel disease Crohn's ▪ Psoriasis ▪ Arthritis Spondylitis ▪ Multiple sclerosis ▪ Sepsis ▪ SLE ▪ Asthma, allergies ▪ Atopic dermatitis ▪ Duchenne muscular dystrophy ▪ Scleroderma ▪ Macular degeneration ▪ Immune thrombocytopenia ▪ Diabetes	▪ *C. difficile* colitis ▪ Sepsis ▪ Ebola ▪ COVID-19 ▪ Flu ▪ Anthrax ▪ Rabies ▪ Infections with Pseudomonas ▪ *S. aureus* ▪ *E. coli* ▪ Varicella-zoster ▪ Cytomegalovirus ▪ Respiratory syncytial virus ▪ HIV ▪ Hepatitis B virus	▪ Platelet aggregation Thrombosis ▪ Hemolytic disease of new born ▪ Hypercholesterolemia ▪ Osteoporosis ▪ Dyslipidemia ▪ Amyloidosis ▪ Alzheimer's ▪ Haemophilia ▪ Migraine, ▪ Sciatica ▪ Diabetic nephropathy ▪ Parkinson's

Mechanisms of action of monoclonal antibodies

The key mechanisms of action of monoclonal antibodies are opsonization of the bacteria or virus, modulation of receptors/co-receptors, Fc-, complement-, NK cell- and antibody-dependent cellular cytotoxicity (ADCC)-mediated cell lysis and neutralization of replicated virus.[8] Monoclonal antibodies can also enhance the antiviral responses through agonistic and antagonistic action of inhibitory receptors (Fig. 2).

Fig. 2: Mechanisms of action of monoclonal antibodies



Conclusion

Monoclonal antibodies are homogenous, consistent, highly reproducible and specific with regard to their mechanisms of actions. However, several grey areas are still persisting with regard to the direct, indirect and antibiotic sparing effects, and cocktail use of monoclonal antibodies. The advances in antibody technology may help in developing cost-effective and long-lasting novel therapeutic options based on monoclonal antibodies.

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Fever in Geriatrics

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Introduction

Fever in elderly is the only clinical presentation that may assist clinician in suspecting an underlying disease such as infection. Similar to all other illnesses, infections in geriatric patients are associated with a variety of nonspecific, atypical and, unusual manifestations. However, infections in elderly are underreported, as many of the symptoms are attributed to ageing. In addition, the presence of multiple comorbidities such as diabetes, hypertension, congestive cardiac failure, and benign prostatic hypertrophy may mask the underlying infection.[1]

Despite a serious underlying infection, fever may be absent in 20%-30% of elderly patients. The criterion to be considered for fever in elderly subjects include an elevation of body temperature by 2°F from baseline values.[2] Fever of unknown origin occurring in majority of the cases are due to infections (30%-35%), followed by connective tissue diseases (25%-30%), and malignancies (15%-20%). Unexplained change in functional capacity, weakness and fatigue, worsening of mental status, weight loss or failure to thrive, and generalized pain are some of the clues that may assist clinician in suspecting infection in an elderly.[2]

Factors contributing to increased susceptibility to infections in elderly

Immunoscenescence refers to changes in the immune status due to aging and this may lead to decrease in the number and activity of NK cells, CD4 cells production and efficiency of B cells, impaired proliferation of T cells and increased autoantibodies in circulation.[3] It has been well documented that the development of anergy can lead to reactivation of several dormant infections. Poor response to immunization (influenza and Hep B vaccine) in the form of delayed and lower peak titres and rapid reduction from previous titre levels has often been noted.

Senile changes that may predispose to common infections are thinning of skin, enlarged prostate, diminished cough reflex, estrogen deficiency, atrophy of genital mucosa, mucociliary dysfunction, visual defects and other anatomic or physiologic accompaniments of aging. Malnutrition may occur due to food deprivation, restrictive meals, poor dentition, defective deglutition, alcoholism, bereavement, depression and dementia. The use of certain drugs and anorexia due to illness can also lead to malnutrition.[4]

Neuromuscular or osteoarticular diseases limiting the mobility, incontinence or dysphagia, and the increased use of certain drugs like analgesics, steroids and other hormones, anticholinergics, H_2 receptor blockers, PPI inhibitors, anti-depressants, and neuroleptics may increase the susceptibility. Prolonged hospital stay, poor ventilation, contact with staff or visitors having infections, inadequate infection control practices may also increase the risk of contracting infections. Outbreaks associated with healthcare settings such as respiratory infections and gastroenteritis occur commonly in elderly subjects.[5]

Diagnostic dilemma

Diagnosing a disease is often challenging in elderly, as opposed to young patients, as multiple factors need to be considered for concluding the diagnosis.[6] For example, the presence of anemia, fever, retinal embolism and heart murmur are indicative of infective endocarditis. Whereas, in elderly, the occurrence of anemia, retinal embolism and heart murmur could be due to aspirin-induced blood loss, cholesterol embolus and calcified valve respectively. Similarly, an elderly patient with pneumonia or urinary tract infection (UTI) may present only with delirium, and hypoglycemia may be the prominent feature in a patient with gastrointestinal infection.[7]

Causes of fever in elderly

The common causes of geriatric fever are listed in table 1.

Table 1: Common causes of geriatric fever

Categories	Causes
Infections	Viral, bacterial, parasitic, tuberculosis, abdominal/pelvic abscesses, endocarditis, infected implants
Non-infectious inflammatory diseases	Temporal arteritis, polymyalgia rheumatica
Tumors	Lymphoma, renal cell carcinoma, atrial myxoma, hepatoma, colon carcinoma
Miscellaneous	Pulmonary embolism, subacute thyroiditis, hyperthyroidism, drug-induced fever

Features of fever in elderly

Although all types of manifestations are noted in elderly, certain presentations are baffling. The common manifestations noted in many infections are functional decline or anorexia, malaise, slight increase or decrease in respiratory rate. Absence or modifications in the cell-mediated immunity may reduce the intensity of manifestations in many illnesses. Some of the key features of fever in elderly are as follows:[8]

- Fever may be absent in certain serious infections, due to the poorer body temperature response. Fever >38.3°C often indicate severe life-threatening infections and hypothermia is considered as an emergency in the elderly.[9]
- Acute confusion and/or delirium, disorientation may occur. Although delirium is potentially reversible, it may lead to death.
- Leukocytosis may be replaced with falling WBC count due to changes in marrow functioning.
- The warning signs of infections noted in elderly are listed below:[8]
    - Fever≥ 103°F

- Vomiting
- Difficulty in breathing
- Extreme sleepiness
- Irritability
- Delirium
- Seizures
- Sudden rash
- Swelling or inflammation
- Headache
- Painful urination and foul-smelling urine
- Chest or abdominal pain
- Confusion and disorientation

Respiratory infections

Elderly is more susceptible to respiratory tract infections. The reduced cough and airway patency noted in elderly could be attributed to alteration in pulmonary reserve, poorer ventilation and decreased mucociliary transport, cough reflex, and elasticity of alveoli.[8] The age-related alterations noted in organ-specific defenses are briefed in table 2.

Table 2: Age-related alterations in respiratory system compromising the organ-specific defenses

Organs affected	Impact	Implications
Lungs	Reduced expiratory flow rate and vital capacity	Diminished clearance of infection and alveolar macrophage function
Bronchi	Sluggish mucociliary transport	Diminished clearance of infection
Pharynx	Abnormal swallowing mechanism and impaired cough reflux	Aspiration

Community-acquired pneumonia is very common in the elderly. *S. pneumoniae and H. influenzae* are the causative pathogens of these infections.[10] Chlamydia and respiratory syncytial viruses are the common pathogens noted in institutional settings. Doxycycline, macrolides or fluoroquinolones can be used to manage Gram-negative infections.[11] In a seriously ill patient, a third-generation cephalosporin is considered appropriate.

For managing hospital-acquired infections in general wards, an extended-spectrum cephalosporin with a macrolide or a beta-lactam/beta-lactamase inhibitor combined with a macrolide is preferred. In ICU settings, antipseudomonal penicillin, carbapenem or cefepime-fluroquinolone combination is preferred for managing structural disease of lungs.[12] Adequate hydration and oxygenation must

be ensured for successful treatment outcome. Elderly with respiratory infections may require longer treatment regimens.

Respiratory Syncytial Virus (RSV) infections

Clinical manifestations of RSV infection in elderly are highly variable, ranging from mild cold to severe respiratory distress. It typically presents with nasal congestion and discharge, and nonproductive cough. Fever is noted in nearly half of the patients with infection.[13] Signs of lower respiratory tract involvement, such as rales and wheezing are common, can help differentiate RSV infection from influenza. Clinical presentations and chest radiographs assist in diagnosis. Symptomatic treatment/supportive measures such as fluid, oxygen and antipyretics administration are recommended. Bacterial infection may complicate 10-30% of RSV infections, and antibiotics should be considered in patients with purulent sputum and those demonstrating dense infiltrates on chest radiographs.

The measures that could be adopted for preventing respiratory infections are as follows:

- Immunization with pneumococcal polysaccharide vaccine and influenza vaccine.[14]
- Adoption of infection control strategies such as hand washing to prevent nosocomial infections.
- Avoiding contact of persons having risk of harboring organisms.

Tuberculosis

Tuberculosis should be suspected in subjects having unexplained infection/fever, poor health and repeated opportunistic infections, and the diagnosis is always a challenge. It is also paramount to differentiate reactivation from reinfection for suggesting appropriate treatment strategies.

Urinary Tract Infections (UTI) and bacteriuria

Increase in vaginal pH due to postmenopausal estrogen depletion and incomplete emptying of bladder are the common reasons for increased female preponderance noted for UTI.[15] Moreover, age-related alterations also increase the risk of contracting UTI in elderly (Table 3).

Table 3: Age-related alterations in excretory systems compromising organ-specific defenses

Organs affected	Impact	Implications
Kidney	Inability to maintain osmolarity, pH, concentration of organic acid, urea and Tamm-Horsfall protein	Bacterial colonization, bacteriuria and UTI
Ureters	Inadequate peristalsis and incompetent vesico-ureteric valve	Reflex, ascending infection
Bladder	Impaired emptying capacity and defective surface mucin	Reflex, ascending infection

Increased prevalence of bacteriuria has been noted in men with advancement of age, especially after 50 years.[16] The factors that may contribute to bacterial colonization and subsequent development of asymptomatic bacteriuria and UTI in elderly are as follows:[17]

- Urethral or condom catheters
- Neurogenic bladders with increase residual urine
- Prostate enlargement in men

Common pathogenic organisms causing bacteriuria and UTI in residents of nursing homes and long-term care facilities include *E-coli* and Gram-positive cocci.[18] However, many episodes are polymicrobial in origin. While, fluoroquinolones are recommended for empiric therapy on both genders, specific treatment choices require consideration of antibiotic safety profiles and bacterial resistance patterns.[19]

Catheter-related UTI is the most common nosocomial infection noted in elderly >65 years of age, who are at risk for bacteremia. Symptomatic UTI requiring treatment should be differentiated from asymptomatic bacteriuria.[16] Proper hydration to ensure good urine flow is a major step in preventing UTI. Urine culture and antibiotic sensitivity studies are a must in all patients. Intermittent self-catheterization and the use of silver- and antibiotic-impregnating catheters help to ensure safety of catheterization process.[20] Long-term prophylactic antibiotic use is not recommended.

Skin infections

Ageing is associated with significant atrophy of dermis/ epidermis and flattening of the dermoepidermal interface. Reduced resistance to external injury and slower epidermal turnover time facilitate delayed wound healing.[21] Diminished water binding capacity and reduced secretion of eccrine and sweat glands lead to dry skin, pruritus, and breaching of epithelial integrity.

Erysipelas and cellulitis are common infections noted in elderly and systemic signs of fever, chills

and tachycardia are often seen. The lesions may spread rapidly and may develop as severe tissue necrosis, if not diagnosed and treated promptly. Herpes Simplex Virus (HSV) infection in elderly causes herpes genitalis, herpes labialis and rarely systemic dissemination.[22] Buschke-Lowenstein tumor is a papillomavirus-induced lesion seen in elderly. It presents as large warty nodules n the anogenital area and is similar in appearance to slow-growing, well-differentiated squamous cell carcinoma. This type of lesion is considered as invasive and the recommended treatment intervention include cryosurgery and surgical excision.[23]

Pressure sores complicate the management of many illnesses in elderly and the contributing factors are listed below:[24]

- Comatose or semi-comatose state of the patient
- Rubbing of skin surfaces
- Urinary and bowel incontinence
- Frequent, prolonged or constant exposure to moisture, particularly irritant secretions related to incontinence
- Sever peripheral vascular disease contributing to poor circulation
- Decreased sensory perception
- Diabetes, severe congestive pulmonary diseases
- Immobility, limited mobility or difficulty in moving without assistance
- Hemiplegia, quadriplegia or paraplegia
- A full body cast
- Terminal cancer, chronic or end stage renal, liver or heart disease/ drug -related immune problems
- Steroid, radiation and chemotherapies
- Dialysis
- Head of the bed elevated in majority of the day
- Poor nutrition, malnutrition, dehydration or poor liquid intake
- Weight loss or being overweight
- Friction caused by improper movement of the bedridden patient

Frequent changing of the patient's position, avoiding wetting of the bed, proper skin care, use of antibiotics as per the culture, local cleansing and good nutrition are the recommended measures to prevent / treat pressure sores.[25]

Infective endocarditis

Recent years have witnessed significant increase in elderly patients having prosthetic valves and prevalence of hospital-acquired bacteremia. About 30% of the elderly subjects with endocarditis

have rheumatic lesions, 25% have calcified valves and 5% have mitral prolapse.[26] Nearly, 40% have unidentified or no valvular lesions. Staphylococcus infections account for nearly 20%-30% of all cases of endocarditis in elderly and *Staphylococcus aureus* often causes nosocomial endocarditis.[27] Large emboli obstructing large arteries, such as the external iliac, superficial femoral and brachial arteries are characteristics of endocarditis caused by fungi or HACEK organisms (*Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae*).[28]

The devastating complications of infective endocarditis include cerebral embolism and rupture of an intracranial mycotic aneurysm. The increased mortality noted in elderly is due to higher incidence of comorbidities. Anemia, raised ESR, albuminuria, microscopic hematuria, and Doppler finding of vegetations assist in diagnosis. Antibiotic treatment and prophylaxis are paramount in managing/preventing endocarditis. Valve replacement and surgical debridement may be considered in selected cases.[29]

Gastrointestinal infections

Deaths due to unresponsive diarrhea and gastroenteritis have been reported in India. An elderly with compromised renal function may develop severe insufficiency followed by a single bout of diarrhea. *C. difficile* infection should be suspected as a cause of GI infection in elderly, who are already receiving antibiotics.[30] Cephalosporins, ampicillin, amoxicillin and clindamycin are the common antibiotics implicated in *C. difficile* infection.[31] The less commonly implicated antibiotics are macrolides and penicillin. Treatment is not indicated in asymptomatic carriers and mild cases require cessation of causative antibiotics.

HIV infections

The changes in demographic patterns and social norms increase the risk for HIV in elderly. Blood transfusions, sexual activity, other STDs and drug use are the factors contributing to HIV disease in elderly. Apart from HIV, comorbidities, late diagnosis, inadequate treatment, and decreased antiretroviral treatment adherence may play a role in the prognosis in elderly.[32]

Conclusion

Antibiotics should be judiciously used for the management of geriatric fever. Moreover, geriatric disease management should focus on lifestyle, early detection, appropriate therapy, nutrition, hydration, control of comorbidities and preventive strategies.

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Social media and Pandemic

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Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a global health crisis and had a major impact on individuals' perception and everyday lives. Social media has played a positive role during the pandemic by promoting effective strategies for helping individuals in dealing with social and physical distancing and reducing stigma, prejudice, discrimination, and inequalities.[1] Technology advancements and social media have also helped to keep people safe, informed and connected. The present chapter discusses the influence of social media and their advantages and limitations pertaining to the management of pandemic crisis.

Influence of social media during pandemic

Although social and mass media (broadcast and digital) have the ability to convey a sense of unity by reaching large number audience/users, it may also provide grounds for misinformation and discrimination. Social media and other digital platforms have amplified the spread of information, and at the same time the same tools jeopardize the measures to control pandemic.[2]

The government can advertise through mass media to refrain from posting unauthenticated information through social media. Public health personnel, teachers, religious and political leaders can also spread awareness.

During pandemic, people rely on social media and online resources for news and health information. Government has launched a country-wide remote mental health telephonic service to tackle mental health wellbeing.[4] In December 2020, the telephonic service gathered the data of 43,000 individuals and found that 9% of people had anxiety symptoms, 4% had depression, and more than 12% of individuals reported stress-related to the health crisis posed by the COVID-19 pandemic.[5]

The emergence of the COVID-19 outbreak has changed the life patterns and individuals' approach to disease prevention. Awareness through social media has helped to promote behavioral changes such as maintaining social distancing, using sanitizer, wearing masks, and washing hands.[6]

Role of different social media platforms

Social media such as Twitter, WhatsApp, Facebook and Instagram have become primary sources of information during pandemic. YouTube and Snapchat have helped in sharing health awareness videos, WhatsApp to send text messages and voice messages, and share images, documents. LinkedIn has helped in hosting webinars on COVID/health-related topics.[7]

On contrary, the pandemic has also witnessed, 'infodemic', i. e., spreading of false or misleading information through digital and physical media.[8] The messages and texts hold a similar pattern i.e., featuring a physician, nurse, surgeon, or other authority for sharing information (e.g., holding breath as a COVID-19 confirmation test, or taking vitamins to decrease the possibility of infection). Since there are no set protocols for checking the authenticity of such information, they have promoted self-treatment, reluctance in seeking medical care on time, and delay in diagnosis.

Myths and facts

The social media has promoted several myths related to COVID-19. Some of them are discussed below:

Myth: *Viruses may spread through 5G mobile networks and radio waves.*

Fact: Virus is spreading through respiratory droplets produced when an infected person coughs, sneezes or speaks. People also get infected by touching contaminated surface and then their eyes, nose or mouth.[9]

Myth: *A person who had COVID-19 is already protected against reinfection.*

Fact: A person who already had COVID-19 can contract reinfection, and vaccination is recommended to prevent the risk of reinfection.[10]

Myths and facts related to vaccine are presented in table 1.

Table 1: Myths and facts related to vaccine

Myths	Facts
It is too soon to know whether vaccines are safe and effective.	All vaccines are thoroughly tested and studied to meet the safety and effectiveness requirements.
No need to wear a mask after vaccination.	Vaccinated person can still carry and spread virus to subjects who haven't vaccinated yet.
Vaccine can cause infertility in women.	Vaccine does not interact with a woman's reproductive system and there is no evidence to support the influence of vaccine on fertility.
The vaccines cause COVID-19.	None of the vaccines use any part of the corona virus and they do not cause COVID-19.
The mRNA technology is new and changes the DNA.	The mRNA technology has been extensively studied for the past 20 years and it does not interfere with DNA.

Good aspects of social media

Governments and healthcare authorities can use social media to spread updates, news, and

scientific discoveries about COVID-19. Social media platforms can also provide helpful direction during this crisis. For example, Facebook redirects users to World Health Organization (WHO) websites where trustworthy information can be obtained. Social media can be used for educating and increasing awareness among people and allied medical professionals. Physicians are hosting webinars to conduct discussions on COVID-19 and other medical topics. Information on symptoms, interactions, and travel routes can all be used to fight the virus and understand how it spreads.

Bad aspects of social media

Social media are major sources for spreading misinformation, disinformation and fake news People are inclined to share such misinformation, which in turn spreads fear, anxiety and paranoia related to COVID-19 among society. In addition, social media is the source for several conspiracy theories related to the origin of COVID-19 and some of them suggest it as a part of biological warfare.[11] Such social medial platforms are also spreading misinformation on remedies that are not scientifically proven e.g., drinks containing mint, herbal products, and spices like saffron offer cure against COVID-19.[12]

Fake news related to COVID-19 is also creating racism and xenophobia. In Japan, discrimination against Chinese nationals became rampant and the Japanese citizens besieged pharmacies to buy surgical masks and sanitizers.[13]

Conclusion

Due to the overflow of information, stringent measures are needed to spread authentic and good information, and to prevent social media infodemic. Information from reliable sources should be promoted and unreliable information should not be circulated before evaluating the sources and their conflicts of interest.

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Panel Discussion: Comprehensive COVID Care

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Case 1

A 54-year-old clinician, who was working in the hospital till afternoon, developed fever by evening. His family included wife and children of 16- and 18-years of age. He tested positive by next day and self-isolated even before taking the test.

Q.1: What is the importance of infectious period and incubation period? Is there any role for early CT in diagnosis? Whether all the people who are in contact with doctor in last 48 hours should be quarantined and tested?

Dr. Nitin Bansal: Infection period starts 3 days before the onset of symptoms and persists till the patient become afebrile or respiratory symptoms reduce. Infectious period remains for around 10 days from the onset of symptoms. In the present case, the infectious stage would have started before the onset of fever and would have already spread to his colleagues and household members. The median incubation period for SARS-CoV is generally 4-5 days. The testing of household can be done anytime from the date of last exposure. Early CT is unnecessary to make a diagnosis, and RT-PCR is ideal for the current situation. The incubation period of around 5 days needs to be considered for testing. Ideally for testing, the suspected individual should wait till the 5th day of exposure or till the first day of onset of symptoms. So, the exposed person should remain under quarantine for 10-14 days if tested positive.

Q2. Whether the patient can present with extrapulmonary manifestations other than respiratory symptom in COVID-19?

Dr. Swati Gohel: The commonly seen extrapulmonary manifestations, apart from pulmonary symptoms, are fever without any cough and cold, severe body ache, and myalgia. Some patients can present with complications such as stroke, myocardial infraction and any syndrome related to hypercoagulability. The extrapulmonary manifestations noted in children are rashes, joint pain, severe throat congestion, and conjunctivitis.

Q3. Is there any correlation between comorbidity and COVID-19 mortality?

Dr. Venkat Ramesh: Age is a major risk factor for COVID-19, and it increases the mortality rate in elderly. As per the Centre for Disease Control and Prevention (CDC) data, 5-18 years age group has lowest mortality rate, and the mortality rate and risk of complications increase with age. The major comorbidities and factors that may increase the morbidity and mortality risk in COIVD-19 patients are age, diabetes, cardiovascular disease, neurological disease such as stroke, chronic kidney disease, chronic lung disease, excessive smoking and alcohol intake, use of immunosuppressives or steroids, advanced HIV/AIDS, and organ transplantation.

Case 2

A 70-year-old male, who had been scheduled to undergo glaucoma surgery, was tested positive for COVID.

Q4. What are the various tests to be done in the current patient?

Dr. Deepak Kumar: The most commonly used confirmatory test is RT-PCR, however, it is very time consuming. Many rapid antigen tests with good sensitivity and specificity are also available. Tests for bronchoalveolar lavage fluid, sputum and faeces are also available. However, they are not clinically significant.

Case 3

A 78-year-old woman, who had been scheduled to undergo cataract surgery, tested positive for COVID and was symptomatic.

Q5. Is it safe to carry out the scheduled surgery? When the testing should be done after the onset of symptoms?

Dr. Nitin Bansal: In the present case, it is important to consider the infection as well as the safety aspects of the patient.

Proceeding with the scheduled surgery may expose healthcare workers and other people in the hospital to infection. Hence, it is recommended to wait till the patient recovers or 10 days from testing positive or onset of symptoms. Considering the safety of patient, conducting surgery may increase the complications related to COVID-19. The testing should be done on the first day of onset of symptoms itself.

Q6. After 28 days, the infection still persists and the patient tests positive again for COVID? How to interpret the test results?

Dr. Swati Gohel: According to CDC, if the patient is immune competent and has mild or moderate disease, she/he may not transmit the infection and practically becomes non-infectious by day 10-12. There is no need of repetitive testing and patients with mild illness generally recover from infection within 2 weeks. In case of severe disease, the patient might be shedding virus for a longer period compared to those with mild to moderate disease. There is no need of repeated testing on day 28 and the patient can be discharged after 3 weeks. In general, 3 weeks are sufficient to clear the infection and in the current case, the patient can be considered as non-infectious, irrespective of the positive PCR test.

Q7. What is the correlation between cycle threshold and severity of COVID-19?

Dr. Venkat Ramesh: It is largely a myth. Although there are a few papers stating that the lower the cycle threshold the greater the severity of infection. However, in fact, there is no correlation between the two.

Case 4

A 46-year-old male presented with a history of fever and cough for 9 days. His father passed away due to COVID-19, and 2-times his RT-PCR results were negative. Chest X-ray revealed pulmonary opacity.

Q8. How to manage the current case?

Dr. Deepak Kumar: All the tests have their own limitations. In the current case, if the patient is symptomatic and has a history of close contact with COVID-19 positive cases, the patient should be treated as a case of COVID-19. CT scan is also recommended.

Q9: When the signs of COVID-19 are obvious in a CT scan?

Dr. Deepak Kumar: CT scan is not recommended in case of mild disease and CT changes appear after the 2nd week of disease. CT is recommended if the patient's condition is deteriorating and there is requirement for oxygen.

Case 5

A 67-year-old man presented with fever up to 102°F, myalgia for 2 days, cough for 1 day duration, and mild sore throat. He did not have hypertension, other comorbidities, or any addictions and not hailing from a hotspot or contaminant zone. On examination, his temperature was 100.6° F, heart rate 108/min, blood pressure 130/80 mm of Hg, and SPO_2 was 99% on air.

Q10. What are the lab investigations to be performed?

Dr. Nitin Bansal: Routine tests such as complete blood count (CBC), kidney function test, D-dimer test, and neutrophil-to-lymphocyte count ratio can help in determining the progression and stage of disease.

Q11. Whether favipiravir, remdesivir, and monoclonal antibody cocktail can be used in COVID-19 treatment?

Dr. Nitin Bansal: There is no clinical evidence to support the use of favipiravir in COVID-19, although some studies suggest the use of favipiravir in viral outcome. However, there is no proven clinical benefit. Remdesivir can be given for managing early disease, and it helps in decreasing the disease transmission, duration and complications of COVID-19. However, there is no overall mortality benefit. For monoclonal antibodies, it is important to understand the vaccination and serology status of the patient. If the serology status is negative and the individual is not vaccinated, and ready to afford the treatment cost, monoclonal antibody cocktail can be considered as a treatment option.

Case 6

A 43-year-old female contracts COVID-19 and she stays with her 76-year-old mother who is on home oxygen therapy for interstitial lung disease (ILD).

Q12. Is there any role for monoclonal antibody therapy in post exposure prophylaxis?

Dr. Swati Gohel: Yes, monoclonal antibody therapy can be considered in such cases. The current patient belongs to high-risk category and if she develops COVID-19, she is likely to have moderate to severe disease and a prolonged course. Hence, she can be a candidate for monoclonal antibody therapy. However, it is important to consider the vaccination status of the patient. When considering monoclonal antibody therapy for moderate disease under emergency use authorization, baseline serology should be performed.

Case 7

A 39-year-old male with no comorbidities presented with a fever 101°F on day 6, with no breathlessness and other systemic complaints. Saturation was 98% and laboratory investigations were normal. It was a mild illness; however, there was persistence of fever.

Q13. Whether the patient should be under observation or should be treated with baricitinib, favipiravir, remdesivir or monoclonal antibody?

Dr. Venkat Ramesh: Although the patient was febrile on day 6, he did not have any warning signs, hence hospital admission is not necessary. The patient should be kept under observation and if there is persistence of fever beyond a week or 10 days, admission should be considered. The role of remdesivir is only studied in hospitalized patients and does not have any mortality benefit. There is also lack of data for favipiravir in terms of reducing the duration of symptoms. Baricitinib has only been studied in patients who were hospitalized with moderate COVID-19. Steroids should be considered only in patients who are febrile after day 10, in such cases low-dose steroids can be prescribed. Monoclonal antibody is not required in low-risk vaccinated patients. If the patient is not vaccinated, it can be administered on days 8-10.

Case 8

A staff nurse who had been admitted to a government hospital was shifted to a private hospital after 11 days. Her oxygen requirement increased from 4 litres to 6 litres, SpO_2 was 98% and she

was tested positive for nucleocapsid antibody. Her pO2 level was 77 mmHg, and CRP was 68.2 mg/L.

Q14. What are the roles of remdesivir, steroids, tocilizumab, convalescent plasma, and monoclonal antibody in managing the current patient?

Dr. Deepak Kumar: Remdesivir can be considered in the current case. Steroid are preferred for managing patients with moderate to severe disease. If the patient's condition is deteriorating within 24-48 hours of hospitalization and CRP level is high, tocilizumab can be considered. Recent studies suggest that convalescent plasma is not useful for COVID-19 treatment. High-dose monoclonal antibodies can be used in seronegative patients having moderate illness with a low flow of oxygen.

Case 9

A 43-year-old man presented with moderate-to-high grade fever for 4 days, dry cough for 3 days, sore throat, diarrhoea, worsening of breathless , SpO_2 level 92%. Chest radiograph showed bilateral patchy consolidation and the patient was already on non-invasive ventilation (*NIV*).

Q15. What are the roles of remdesivir, steroids, tocilizumab, and monoclonal antibody in managing the current case?

Dr. Nitin Bansal: It is imperative to start the therapy with steroids. As the patient is already at high risk and tocilizumab can be administered immediately.

Q16. How long does the vaccine work? Whether booster dose is required? Will the vaccine work against emerging strains of SARS-CoV-2? Whether a patient with a history of allergic reaction can receive the vaccine?

Dr. Nitin Bansal: The duration of the vaccine effectiveness may depend on the ongoing epidemiology and the future circumstances. It has been noted that if the patient has already been infected, he/she may require only one dose of vaccine. If the patient is fully vaccinated with two doses of COVID-19 vaccine, the subsequent infection may not be that severe. With regard to duration of vaccine effectiveness, if a healthy individual has received influenza vaccine, he/she may not show good immune response to respective vaccine strain after 6-8 months. If the same logic is implied in case of COVID-19, booster doses might be needed in future. The effectiveness of the current vaccines against emerging strain of SARS-CoV-2 may depend on the type of strain. if the spike protein of emergent strain matches with the vaccine vector, some cross immunity can be expected. It has been seen that the strains emerged in African countries did not show any good response to certain vaccines developed in India and some other countries. It cannot be predicted whether a person with a history of allergic reaction may develop allergic reaction to vaccine preparation also. If a person has history of allergic reaction, he/she can take vaccine under medical supervision.

Q17. Whether immunocompromised patients can receive the vaccine? Whether pregnant or breast-feeding women should receive the vaccine? Is there any minimum or maximum age to receive the vaccine?

Dr. Venkat Ramesh: Immunocompromised patients are at high risk for severe COVID-19; hence

they should be vaccinated. There may need to change the schedule of their immunosuppressive regimen. For example, sometimes it is recommended to postpone the methotrexate dose or to skip the dose by one week. In certain scenarios like post organ transplantation or even in the immediate hemopoietic stem cell transplantation, immunocompromised patients should receive the vaccine immediately. Pregnant or breast-feeding women should receive the vaccine. It has been proven to be safe and efficacious during pregnancy, and the transfer of maternal antibodies to the infant is another benefit. There is no maximum age for patient to receive the vaccine. Covishield, the adenovirus-based vaccines of AstraZeneca, is licensed only for >18 years of age. COVAXIN is approved for use in 12-18 years of age.

Q18. Whether a patient who had been exposed to COVID-19 should receive the vaccine to prevent the diseases? Whether a patient recovered from COVID-19 should receive the vaccine?

Dr. Deepak Kumar: No, a patient should not receive the vaccine immediately after the exposure to COVID-19 to prevent the disease. Vaccine administration may lead to antigen enhancement effect, thereby causing worsening of the disease. Patient who had recovered from COVID-19 should receive the vaccine one month after the recovery.

Q19. Whether a patient who is diagnosed with COVID-19, shortly after the first dose, should receive the second dose also?

Dr. Nitin Bansal: Patient can take the second dose in 1 or 3 months after the recovery.

Q20: What were the reasons behind the development of fungal infections during second wave of COVID-19?

Dr. Swati Gohel: During the first wave, the number of infected patients, use of steroids, and the availability of IL-6 inhibitors were not as high as in second wave. Due to the high patient burden in the hospitals, infection control measures were not strictly followed at that time. Apart from these, routine factors such as hyperglycemia, high level of steroids use, and high level of immunosuppressants use contributed to the development of fungal infections.

Dr. Deepak Kumar: Risk factors include poor infection control, hyperglycemia, and high level of steroids use. There should be specific guidelines for the use of steroids in COVID patients, and the monitoring of blood sugar, even if patient is not diabetic, should be done, as control of blood glucose could reduce risk of *mucormycosis*.

Dr. Venkat Ramesh: COVID-19 itself is a risk factor for developing m*ucormycosis. Data suggest that 15-20% of patients diagnosed with mucormycosis disease in India had only mild disease and did not receive any steroids, and did not have diabetes or any other immunosuppressive condition. Exact molecular mechanism is yet to be determined. Since, mucormycosis is more prevalent among diabetic and chronic kidney disease patients in India compared to western countries, the role of environmental factors needs to be explored.*

Approach to Fever in a Less Resource Setting

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Introduction

A health system that does not meet the accepted norms is termed as low-resource setting (LRS) and managing fever-related illnesses in such settings is highly challenging.[1] The present chapter deals with strategies for managing fever in a low-resource setting, while confronting various clinical scenarios.

Fever is an elevation in body temperature that exceeds the normal daily range and occurs in conjunction with an increase in the hypothalamic set point. In contrast, hyperthermia reflects the body's inability to lower temperature by the usual mechanisms.[2] In a low-resource setting various etiologies of fever needs to be managed, some of it is listed below: [3]

- Bacterial Infection: Typhoid fever, tuberculosis, brucellosis, pneumonia, pyelonephritis, and meningitis
- Viral infections such as hepatitis A and B
- Parasitic infections such as malaria and fungal infections
- Malignancies such as leukemia, lymphoma, hepatoma, and nephroblastoma
- Autoimmune conditions and joint/connective tissue diseases such as rheumatoid arthritis, rheumatic fever, systemic lupus erythematous, vasculitis
- Other causes such as drug induced fever and factitious fever

Clinicians in low-resource setting should be aware of the atypical features of diseases seen in routine practice (Table 1).

Table 1: Atypical features of diseases seen in routine practice

Atypical features	**Suspected diseases/scenarios**
Relative bradycardia (decrease in heart rate <5min/min for each 1°C rise)	Typhoid, brucellosis, leptospirosis, factitious fever
Relative tachycardia (increase in heart rate >15/min for each 1°C rise)	Myocarditis, rheumatic fever
Reversed diurnal pattern (evening temperature is more than morning temperature)	Typhoid, disseminated TB
Failure to have fever	Elderly, patients having Chronic Renal Failure (CRF) and those receiving steroids

The pattern of fever can be broadly classified as continuous, remittent, intermittent and relapsing. The intermittent fever is further divided into quotidian, tertian and quartan.[4]

Approach to the patient caveats

The etiology of the fever is clinically obvious in many cases, on the other hand, fever can be the initial manifestation of an elusive illness. Elderly, immunocompromised, or those receiving steroids may not mount a fever, even in the presence of underlying severe infection. The degree of fever is not predictive of the severity of an underlying illness. Hypothermia may also indicate an overwhelming infection and require thorough evaluation.[5]

History collection

The initial step of history collection should gather details such as grade, duration, pattern severity, relieving and aggravating factors of the fever, presence of rigors, interference of fever with sleep and usual activities, treatment received and the outcome, and associated symptoms. Clinician should conduct a complete review of upper and lower respiratory tract infection, gastrointestinal tract symptoms, skin lesions and musculoskeletal pain. Excessive sweating should raise the suspicion of tuberculosis, brucellosis, endocarditis, or lymphoma.[5]

Gathering drug and allergy history is important, certain group of drugs such as penicillin, phenytoin and some cardiac drugs may cause fever, and this is apparent when the fever subsides after withdrawal of the drugs. It is paramount to collect the history of blood transfusion, immunization and vaccination. Considering the present pandemic scenario, collecting the details of COVID-19 vaccination is important, as the vaccination may elicit fever for one or two days.[5]

Personal and social history should include smoking and alcohol consumption, occupation, home conditions such as water supply and sanitization, exposure to animals in the form of avian flu, toxoplasmosis, brucellosis, rabies, or birds in the form of psittacosis; consumption of unpasteurized milk or milk products, sexual history of unprotected exposure to sexual partner ,and illicit drug use. Travel history should collect the following details: travel to an area known to be endemic for certain disease, name of the area, duration of stay, and onset of illness. if the patient has travelled to an endemic area, the possibility of malaria, typhoid fever, or viral hepatitis should be considered.[5]

Top to bottom approach

This approach is very important for all the clinicians to have a quick review of fever to determine the underlying cause. Signs and symptoms often elicit suspicion for certain diseases. The characteristic signs and symptoms of some of the diseases confronted in low-resource setting are listed in table 2. [5]

Table2: characteristic signs and symptoms of some of the diseases confronted in low-resource setting

Typical signs and symptoms/ procedures	Suspected diseases/indications
Headache, neck stiffness and photophobia	Meningitis
Sinus tenderness	Sinusitis
Ear pain	Otitis
Pharyngitis	Sore throat
Cough, pleurisy and dyspnea	Pneumonia
Recent dental or other invasive gastrointestinal or genitourinary procedures, back pain, new skin lesions	endocarditis
Pain, change in bowel habits, nausea, vomiting	Abdominal infection
Dysuria, increased frequency of micturition, suprapubic, or costovertebral angle tenderness	Urinary tract infection or pyelonephritis
Discharge and dysuria	Pelvic infection
Lower abdominal pain and tender prostate	prostatitis
Pain, tenderness, and swelling	perirectal abscess
Erythema, pain, and swelling	Cellulitis
Pain, warmth, and swelling	Joint infections
Pain and pus	Local intravenous catheter site infection

Clinician should identify whether the fever is associated with lymphadenopathy, jaundice, pulmonary involvement such as influenza, pneumonia, and severe acute respiratory syndrome (SARS). It is also important to identify the exanthem in case of chicken pox, scarlet fever, typhus, typhoid, Koplik spots in measles (Fig. 1) and Forchheimer spots in rubella (Fig. 2).

Fig.1: Koplik spots in measles

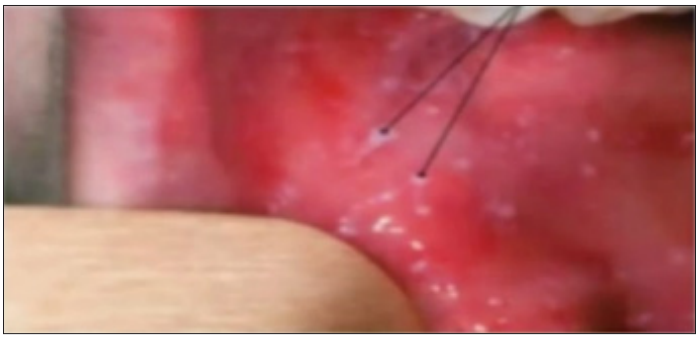
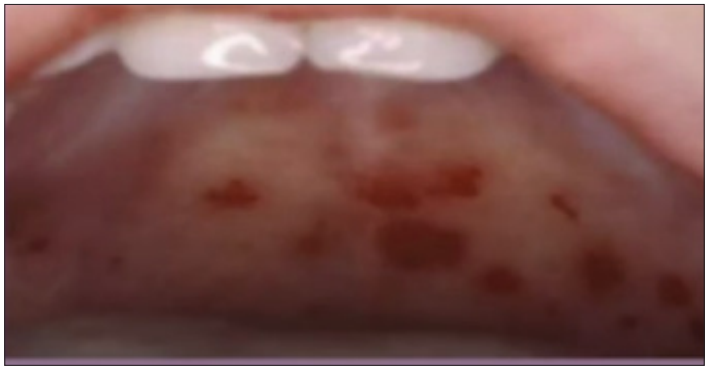


Fig. 2: Forchheimer spots in rubella



Investigations

Some of the common lab investigations recommended for low-resource settings are the following:

- Toxic granulation and band form: bacterial infection
- Neutropenia, lymphocytosis, and atypical lymphocytes: Viral infection
- Monocytosis: Eosinophilia
- Blood film: malaria

Other commonly prescribed biochemical investigations are urea, electrolytes, liver function test, sputum culture and microscopy for mycobacteria, culture of blood/urine, and inflammatory markers such as erythrocyte sedimentation rate (ESR), C - Reactive Protein (CRP) and autoantibodies. Chest X-ray, abdominal ultrasound, echocardiogram, computed tomography, and magnetic resonance are the preferred imaging techniques. Rapid diagnostic tests are available for malaria, dengue, kala-azar, typhoid, influenza, COVID-19 infection, and tuberculosis.

Fever with non-specific laboratory findings

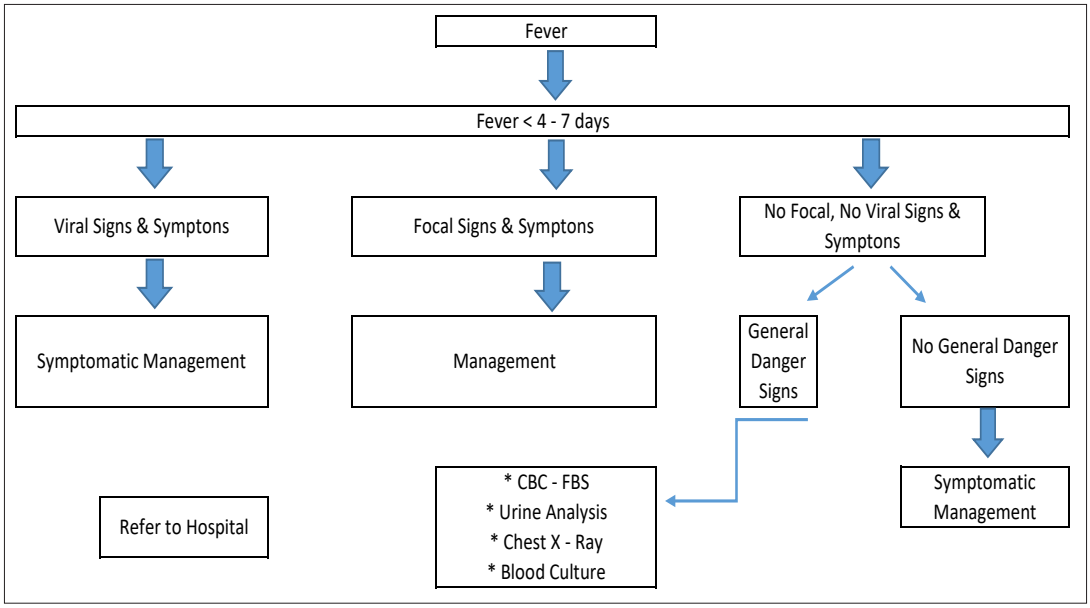
Fever with lymphocytosis is suggestive of pertussis, mononucleosis, cytomegalovirus infection, respiratory syncytial virus, viral hepatitis, chronic lymphocytic leukemia, HIV, or tuberculosis. Fever with monocytosis is indicative of infective endocarditis, tuberculosis, solid tumors, Hodgkin's disease, sarcoidosis, or malaria. Bandemia is noted in severe typhoid fever, malaria, severe viral infection and hemorrhagic fever. Fever with leukopenia is indicative of malaria, tuberculosis, typhoid fever, Kala-azar, brucellosis or severe sepsis.; fever with ESR more than 100mm/hr in sepsis, abscess, kala-azar, lymphoma and collagen vascular diseases.

Some ancillary studies such as computed tomography, and bone marrow/ liver biopsies also can be done, if the facilities are available.

Approach of the fever

The recommended algorithm for managing fever in low-resource settings is depicted in fig. 3.

Fig.3: Recommended algorithm for managing fever in low-resource settings



Clinicians should consider the typical incubation period for various infectious diseases upon presentation of fever in returned travelers, and the treatment should be decided accordingly.

Fever with underlying disease

Fever in alcoholic patients can be due to alcohol withdrawal, delirium tremens, hepatitis, pancreatitis, subarachnoid hemorrhage, pneumonia, tuberculosis, spontaneous bacterial peritonitis, vibrio vulnificus sepsis, or spontaneous bacteremia.

In case of life-threating infections associated with diabetes, *rhinocerebral* mucormycosis, malignant otitis externa, emphysematous cholecystitis, emphysematous pyelonephritis, necrotizing fasciitis and sepsis can be the causes of fever.

HIV, viral hepatitis, infective endocarditis, pneumonia, cellulites at injection sites, tetanus, septic pulmonary emboli, Tuberculosis, pyrogenic reaction can be the causes of fever in intravenous drug users.

Approach of patients with febrile neutropenia

Neutropenia can be defined as an absolute neutrophil count of either <500 cells/mm^3 or <1000 cells/mm^3 with a predictable decline to <500 cells/mm^3 in 24-48 hours. The duration of neutropenia is important in determining the risk of infection.[6] The common sites of infections in patients with cancer are respiratory tract, lungs, blood stream, urinary tract, skin and soft tissue, hepato-biliary and gastrointestinal tract.[7] The clinician should choose the antibiotics according to the location of the infection. Scoring of the neutropenic patients can assist in treatment decision.

Pyrexia of unknown origin

Pyrexia of Unknown Origin (PUO) is defined as a temperature persistently above 38°C for >3 weeks without diagnosis, despite initial investigation during 3 days of inpatient care or after 3 outpatient visit or more.[8] Collecting a detailed history and conducting careful physical examination (including ENT examination) are mandatory for evaluating PUO.

Conclusion

Fever management in low-resource settings may depend on clinical approach of physician and minimal investigations conducted including rapid diagnostic tests. Clinicians should have in depth knowledge and hands-on experience in managing different kinds of fever to arrive at the correct diagnosis and management. Red flag signs of fever should be properly evaluated for on spot management and prompt referral to high-resource setting.

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Emergencies in Infectious Diseases

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Introduction

Nancy M Khardori, the renowned author of the book titled *'Emergencies of the infectious diseases: From head to toe'*, quoted that the course of human history has been altered frequently by the capability of infectious agents to spread and cross national/international borders. The common infection disease emergencies include fever with rash, airway/neck space infections, fever with neurologic symptoms such as central nervous system emergencies, fever with spreading soft tissue infection, septicemia/bacteremia/endocarditis, fever in neutropenic patients, infections in immunocompromised patients including *AIDS and fever in returning travellers.*[1]

Fever with rash

Case 1

A 23-year-old woman presented with headache and sore throat and petechial skin lesions that progressed over 10 hours of ecchymotic lesions. The patient subsequently Presented with shock due to Waterhouse-Friderichsen syndrome (WFS)Though the patient had undergone emergency intubation, she succumbed to death on the following day.

Gram stain of the cerebrospinal fluid revealed inflammatory cells and kidney shaped, Gram-negative diplococci. The organism was identified as *Neisseria meningitidis* and the diagnosis was concluded as fulminant meningococcal disease. Blood culture was carried out, as further investigations and treatment options considered were penicillin G and ceftriaxone. Post-exposure prophylaxis to be considered in such cases is intramuscular administration of rifampin, ciprofloxacin, or ceftriaxone. This disease mainly affects young adults and disease spectrum varies across individuals. Bivalent and quadrivalent vaccines are available in India for disease prevention. The mortality rate due to the disease is estimated to be around 15%, and timely and appropriate antibiotic administration is lifesaving.

Case 2

An 18-year-old female presented with fever and generalized blanching rash, preceded by sore throat for 3 days. The patient had a history of travel, a trip to South Carolina where she walked barefoot on the beach and would have probably sustained a spider bite. She had severe watery diarrhoea, decreased urine output, somnolent with confusion and agitation, hypotension requiring vasopressors, cyanosis, and edema of the extremities, elevated liver enzymes and acute renal failure. Clinical criteria for staphylococcal toxic syndrome put forth by the Centre for Disease Control and Prevention include the presence of fever, hypotension, rash, desquamation and multisystem involvement such as gastrointestinal, muscular, renal, hepatic, hematologic, and

central nervous systems.[2] Since the involvement of renal, hepatic and central nervous systems were noted, the diagnosis was concluded as staphylococcal toxic syndrome.

Case 3

A 36-year-old missionary, who returned from Sierra Leone 10 days ago, presented to the emergency room with vomiting for 2 days, fever for 3 days, and blisters on his hands.

Dengue haemorrhagic fever should be suspected in travellers who return from the epidemic area.

Fever with airway compromise

Case 4

A 65-year-old man, with a history of hypertension, presented with three days of sore throat, dysphagia, and chest pain. The patient returned with no improvement, despite receiving antibiotics, progressive swelling of the left side of the neck, and drooling and inability to clear his secretions. The presence of retropharyngeal abscess was noted in CT scan, and group A streptococcus (GAS) and group B streptococcus (group B strep, GBS) in culture. He had undergone surgery and was prescribed with broad spectrum antibiotics. However, the patient succumbed to death.

Case 5

A 53-year-old woman presented with a 3 days history of sore throat, fever, chills, and odynophagia. Suspecting pharyngitis, the patient was treated with penicillin V potassium. However, the patient presented with stridor and respiratory distress in 10 hours. Epiglottis inflammation was noted in the X-ray and the organism responsible was found to be *Haemophilus influenza*.

Case 6

A 38-year-old man presented with one-week history of tooth pain treated with ciprofloxacin. However, the patient returned with massive swelling of submandibular space and was corrected through emergency surgical intervention.

Case 7

A 19-year-old footballer presented with pain and swelling in the right side of neck. The CT scan revealed that the patient had suppurative jugular thrombophlebitis, also known as Lemierre disease. The cardinal clinical features of parapharyngeal space infections are trismus, induration and swelling below the angle of the mandible, medial bulging of the pharyngeal wall, and systemic toxicity with fevers and rigors.

Fever with neurologic symptoms

Case 8

A 59-year-old male with history of hypertension and alcohol abuse, presented to the emergency department with a 2-day history of fever, nausea, vomiting, and severe headache. The patient became delirious and unresponsive, and was intubated for airway protection. Physical examination revealed fever, nuchal rigidity, tachycardia and no response to verbal and tactile

stimuli. Other systemic examinations were unremarkable. A lumber puncture was performed, CSF analysis showed WBC cell count of 1056/mm^3, comprising of 78% polymorphs, 10% bands, 2% lymphocytes, and 10% monocytes. Gram stain showed the presence of diplococci.

According to the recommendations of Advisory Committee on Immunization Practices (ACIP), a person should receive pneumococcal vaccines PCV15 and PPV23 or PCV 20 (recommended in ≥65 years of age), if the following risk factors are present: cerebrospinal fluid leak, cochlear implant, functional or anatomic asplenia, sickle cell anemia, other hemoglobinopathies, congenital asplenia, acquired asplenia, immunocompromised conditions such as congenital or acquired immunodeficiency, HIV infection, hematologic malignancy, solid organ transplant, iatrogenic immunosuppression including long-term systemic glucocorticoids or radiation, chronic renal failure, and nephrotic syndrome. ACIP recommends the use of the 23-valent pneumococcal polysaccharide vaccine in individuals with cirrhosis or a history of alcohol abuse, for the prevention of invasive pneumococcal disease.[3]

Fever with spreading soft tissue infection

Gas gangrene and necrotizing fasciitis are the two important soft tissue infections showing fever as one of the common manifestations. Necrotizing infections of the skin can be caused mixed streptococcal and staphylococcus infections, mixed aerobic and anaerobic infections, gram negative infections, post-surgical gangrene and infections due to group A streptococci, or *Staphylococcus aureus*. Imaging and blood culture before antibiotic therapy, and gas in soft tissue by palpation or X-ray are suggestive of soft tissue infection.

The occurrence of clostridial gas gangrene can be traumatic, spontaneous or recurrent. Traumatic gangrene is caused by *C. Perfringens, C. Septicum or C. histolyticum* and the trauma is usually associated with crush injury or compromised blood supply. Spontaneous gangrene is caused by *C. Septicum*, and it is associated with metastatic seeding. Predisposing factors are abdominal tumor, acute leukemia, neutropenia, cancer chemotherapy, and radiation therapy.[4] In recurrent gangrene, there is more than one episode of gas gangrene and retention of a foreign body.

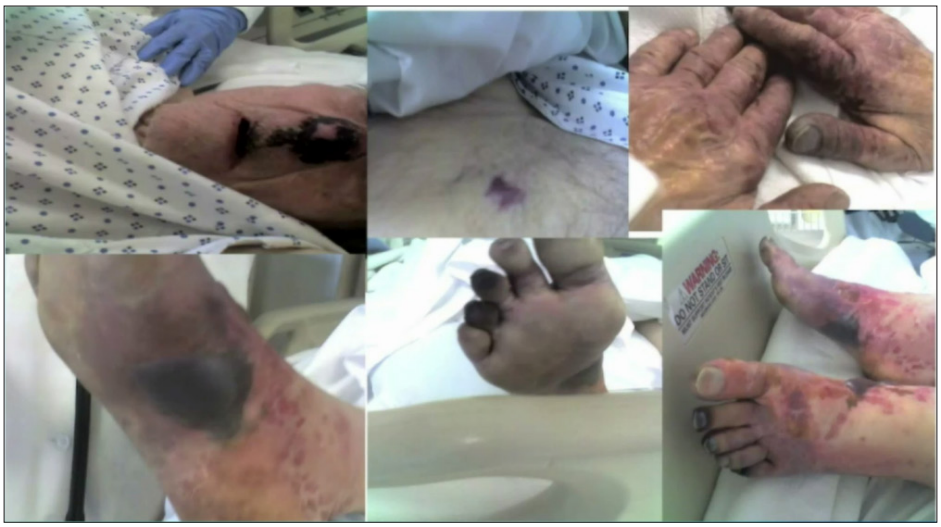
Rapid diagnosis and early wide debridement are key in managing gas gangrene and necrotizing fasciitis. For managing severe pain, surgical intervention and hyperbaric oxygen therapy can be considered. Supportive care, appropriate presumptive antibiotics such as clindamycin and penicillin, intravenous fluids, and surgery are the preferred strategies for managing necrotizing fasciitis.

Fever and sepsis

A 50-year-old man presented with black nose, black toes, and black fingers (Fig.). He was diagnosed with purpura fulminans. The disease is marked by microvascular thrombosis in the dermis with subsequent perivascular hemorrhage, necrosis, and minimal inflammation. The differential diagnoses considered were staphylococcal toxic shock syndrome, streptococcal toxic shock syndrome, and infections due to *Listeria monocytogenes*, *Clostridium perfringens,* Capnocytophaga, Neisseria, and Hemophilus. Blood culture revealed the presence of *Streptococcus pneumoniae*. He was treated with antibiotics.

Purpura fulminans is one of the presenting symptoms of protein C deficiency process associated with high case fatality rate. The management includes antibiotics, fluid resuscitation, surgical debridement with skin grafting and active protein C replacement.[5]

Fig. : Presentation of black nose, black toes, and black fingers



Sepsis syndrome

Sepsis syndrome comprises of cellular, complement, coagulation and the cytokine components. Sepsis is a balance between proinflammatory and anti-inflammatory cytokines. So, early initiation of antibiotic therapy is important. Every one-hour delay in antibiotic therapy increases the mortality by 7%.[6] The antibiotic choice should be based on the organ affected and etiology. The antimicrobial therapy should be reassessed after 48-72 hours to narrow the spectrum of antibiotic therapy. The duration of therapy should typically be 7-10 days and guided by clinical response.[7] It is important to evaluate whether the infectious sources are amenable to surgical source control measures and must weigh the benefits and risks of the specific intervention.

Infective causes of neutropenia

Fever in a neutropenic patient should be considered as a medical emergency and early initiation of broad-spectrum antibiotics is vital. Infective causes include Gram-negative infections, port infections, pneumonia, and viral and fungal infections. Depending on the level of immunosuppression; antibiotic, antiviral/antifungal prophylaxis are prescribed to neutropenic patients. In transplant recipients, the timing of infection provides clue to the type of infection.

Cases

A 36-year-old male with *acute myeloid leukemia* presented with fever and multiple skin lesions on her extremities. Histopathology of the skin lesions revealed acute branching septate hyphae and blood culture demonstrated the presence of Fusarium. Fusarium infections are often noted in the blood cultures of almost half of the severely immuno compromised patients.

A 66-year-old diabetic male presented with nasal mass, black discoloration of the skin overlying the maxillary sinus, and regional pain and inability to open eyes. Opacification of the sinuses was seen in sinus CT scan and the biopsy of the lesion demonstrated broad, ribbon-like, aseptate hyphae in the tissue and a rapidly growing mold was isolated in culture and it was diagnosed as Rhizopus.

A 36-year-old woman developed fever and new bilateral pulmonary infiltrates subsequent to *bone marrow transplant*ation. Bronchoscopy was performed, and silver stain of the lung tissue and microscopic morphology of the cultured mould revealed the presence of Aspergillus. The halo sign or ring sign noted in radiological diagnosis helped in concluding the diagnosis.

An 18-year-old with lupus nephritis was on mycophenolate and tacrolimus post kidney transplant. The patient history revealed bat exposure. Due to the worsening of creatinine levels septic shock, and unresponsiveness; the patient was intubated and bronchoscopy was performed. The diagnosis was concluded as histoplasmosis.

Travel-related infections

The infections to be suspected in returned travellers include dengue hemorrhagic fever, yellow fever, Zika virus, Ebola, meningococcal disease, Japanese encephalitis, and rabies. Epidemiology and incubation period play an important role in diagnosing these diseases.

Infections in HIV

The presentation, epidemiology, and outcome of opportunistic infections in immunocompromised patients are significantly different from that caused by HIV infection. Serious opportunistic infection noted in HIV patients include pneumocystis, toxoplasmosis, histoplasmosis, candidiasis, coccidioidomycosis, cryptococcosis, and infections due to Mycobacterium avium complex, Cytomegalovirus (CMV), and cryptosporidium.

Conclusion

The identification and isolation of potentially infectious patients is impaired by increased work burden, unavailability of adequate isolation procedures or areas, or lack of specific training and skills. Timely identification of such infections and management are paramount for reducing the associated complications and morbidities.

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Fever in Pregnancy

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Introduction

Pyrexia, the Greek word for fever is derived from the word pyros, which means 'fire'. According to Roman mythology, the goddess Febris ('fever') protected people against fever and malaria and once there was a dedicated temple for Febris on the palatine hill of Rome. According to Palldino (650 BC), *"fever is a pretenatural heat, which begins in the heart, and is diffused by the arteries over the whole body, injuring the functions of the body".*

Hippocrates in the 5th century BC has reported that persistent headaches with fever were fatal. Herophilus in 335 BC was the first to relate a change in pulse rate with fever. Wunderlich in 1868 recorded 1 million temperature measurements in 25000 patients over a period of 16 years. He subsequently conceptualized fever curves and published the results in Manual of Medical Thermometry.[1]

Fever

Fever is defined as an elevation in morning body temperature of >37.2°C (>98.9°F) or an evening temperature of >37.7°C (>99.9°F). The lower esophageal temperatures closely reflect the core body temperature, and during menstruation, the body temperature rises by 0.6°C (1°F) with ovulation.[2] An elevation temperature >41.5°C (>106.7°F) is called hyperpyrexia.[3]

Fever in pregnancy

Royal College of obstetricians and Gynaecologists (RCOG) has defined maternal pyrexia as a temperature of 38°C once or 37.5°C on two occasions of 2 hours apart. Following spontaneous vaginal delivery, 6-9% of the patients may experience a temperature of ⩾38°C, and in one third of the cases, it could be due to microbial infection.[4] Postpartum fever is defined as a temperature of ⩾38.7°C (101.6°F) for the first 24 hours or >38.0°C (100.4°F) on any two of the first 10 days postpartum. A temperature of >39.5°C (>103°F) during the first trimester increases the risk of spontaneous abortion, fetal brain or spinal cord defects, oligohydramnios, and intrauterine growth retardation.[5]

Fever in the late trimester of pregnancy increases the risk of the preterm labor and meconium-stained amniotic fluid and fetal distress. A temperature of 41.4°C in the first 24 hours of labor can lead to convulsions. Irreversible brain damage occurs at 42.2°C and a temperature of 45.5°C may increase the risk of fetal mortality.

The most common causes of fever in pregnancy are Urinary Tract Infection (UTI), dengue, COVID-19, upper respiratory tract infection (URTI), malaria and typhoid. UTIs are frequently encountered in pregnant women and 3.5% antepartum admissions are due to UTI. Pyelonephritis is the most common cause of septic shock in pregnant women. It is most often right sided and may be bilateral in around 25%.

Predisposing factors for UTI in pregnancy

The predisposing factors for UTI in pregnancy are listed below: [6]

- Changes of the urinary tract during pregnancy
- Dilatation of the ureter and renal cycles due to progesterone-related smooth muscle relaxation and urethral compression from the gravid uterus
- Decreased bladder capacity resulting in urinary frequency
- Increased vesicoureteral reflux
- Frequent catheterizations during labor
- Changes in bladder sensitivity and bladder overdistension in postpartum period
- Association of asymptomatic bacteriuria (ASB) with pregnancy

Association of Asymptomatic Bacteriuria (ASB)

ASB is defined as >100,000 organisms/ml on a clean catch urinalysis obtained from an asymptomatic patient. Untreated ASB in pregnancy causes UTI in approximately 25% of patients. Hence all pregnant women must be screened and treated for ASB at the first prenatal visit. Treatment of ASB decreases the rate of clinical infection by 3% to 4%. Risk factors for ASB in pregnancy are low socioeconomic status, carriers for sickle cell trait and multiparous women.[7]

The major organisms responsible for causing UTI during pregnancy are *Escherichia coli, Klebsiella Pneumoniae, Enterococcus faecalis, Staphylococcus saprophyticus, group B Streptococcus, Proteus mirabilis, and Pseudomonas aeruginosa*. In pregnant women, 82.5% cases of pyelonephritis are caused due to *Escherichia coli*.[8]

Management and treatment of UTI

The tests that assist in UTI diagnosis during pregnancy include

- urine analysis,
- clean catch urine culture,
- renal ultrasound,
- complete blood count,
- renal function tests evaluating creatinine, serum electrolytes and lactic acid, and
- blood cultures in sepsis

It is important to tailor the investigations appropriately to eliminate other causes of patient's symptoms.

Fluoroquinolones are not the first line drugs to be used due to teratogenic effects, however, it is prescribed for managing resistant or recurrent infections. In subjects with G6PD deficiency and during the first trimester of pregnancy, the use of sulfa derivative and nitrofurantoin should

be avoided. In addition, the use of trimethoprim and sulfamethoxazole should be avoided in late third trimester due to the potential risk of developing of kernicterus post-delivery in infants.

Patients with pyelonephritis should be hospitalized and treated with antibiotics such as cephalosporin's, ampicillin, gentamicin, or other broad-spectrum antibiotics. Intravenous therapy is preferred to maintain adequate output of urine, and acetaminophen and cooling blankets are used to manage fever.[7]

Complications

UTI relapse/recurrence occurs due to the infection with the same organism within 2-3 weeks, if it is not eradicated, despite appropriate antimicrobial treatment. The reinfection occurs within 12 weeks of treatment due to a new organism, and superinfection due to a newer pathogen while receiving treatment for the other. The complications of UTI include sepsis, pyelonephritis, pulmonary complications, anemia and preterm labor. In patients with UTI, tocolytics should be prescribed with utmost caution, as it can lead to pulmonary edema and precipitation.[7] Some of the commonly prescribed prophylactic antibiotics in obstetrical conditions are given in table 1.[9]

Table 1: Prophylactic antibiotics recommended in obstetrical conditions

Obstetrical procedure or condition	Recommended antibiotics and dosage
Caesarean section (elective and emergency) Manual removal of placenta Placement of uterine balloon tamponade	Single dose of antibiotics (ampicillin or first-generation cephalosporin) Ampicillin 2g Intravenous (IV); OR Cefazolin 1g IV
Repair of third- and fourth-degree lacerations	Single dose of antibiotics: Ampicillin 500 mg
Preterm premature rupture of membranes (PPROM)	Oral erythromycin 250 mg every 6 hours for 10 days (or until birth); or ampicillin 2g IV every 6 hours

Prophylactic antibiotics are not recommended in uncomplicated vaginal birth, episiotomy, and first- or second-degree lacerations.[9]

Dengue

Dengue fever, the viral illness transmitted through the bite of an infected *Aedes aegypti*, has an epidemic potential and it is the most rapidly spreading mosquito-borne viral illness.[10] It is endemic in tropical countries and worldwide it affects 50-100 million annually. Dengue cases requiring hospitalization is estimated to be around 5,00,000 cases with 20,000 deaths reported annually. The corresponding rates of mortality were estimated to be around 20% and <1% in untreated and treated cases.

World Health Organization (WHO) 1997 has classified dengue as dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome.[11] WHO 2009 classified dengue into dengue without warning signs, and with warning signs such as abdominal pain, persistent vomiting, mucosal bleeding, increased hematocrit level, decreased platelet count, and atypical manifestation.[12]

Dengue in pregnancy

Dengue infection in pregnancy is often under diagnosed and under reported. The available literature is ambiguous regarding the rate of maternal and fetal morbidity due to dengue. The early diagnosis is often difficult due to ambiguity in clinical findings and physiological changes associated with pregnancy. Recent studies have reported mother-to-child transmission of dengue and associated severity.[13] It can clinically present with pain in abdomen and it is often mistaken as uterine contraction and labor. Plasma leakage is difficult to diagnose during pregnancy and hence it is important to carry out early ultrasound of thorax and abdomen. Plasma leakage is a unique sign of severity and hepatic changes can occur in majority of patients.

The risks of exposure to dengue during pregnancy were estimated to be 1% and 2.5% in endemic and hyperendemic settings respectively.[14,15] The maternal complications due to dengue include spontaneous abortions, oligohydramnios, preterm birth, and antepartum hemorrhage (APH). The fetal complications in pregnancy include low birth weight, prematurity, intrauterine growth restriction (IUGR), fetal malformations, fetal distress, meconium-stained amniotic fluid, still birth, and fetal loss. Neonatal outcomes include neonatal ICU admissions and neonatal thrombocytopenia, and mortality in new born could be attributed to hyaline membrane disease and neonatal sepsis.

In neonatal dengue, the rate of vertical transmission varies from 1.6% to 10.5%. Predominant circulating serotype for vertical transmission is serotype-2, and increased vascular permeability and endothelial damage in DHF may disrupt the placental barrier and contribute to the vertical transmission. The neonatal outcome may depend on the severity of maternal dengue, time interval between infection and birth, and early transfusion in severe thrombocytopenia. Low birth weight can occur due to placental damage caused by dengue and preexisting placental pathology may prevent passage of protective antibody to the fetus.

The decline in maternal protective antibody production in late trimester can lead to serious dengue in newborns. Moreover, increased dengue susceptibility can be due to physiological and immunological changes occurring in mid and late pregnancies. Breast feeding is protective and studies showed that majority of the maternal dengue-specific antibodies are acquired through breastfeeding.[16] The differential diagnoses to be considered for dengue in pregnancy are hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, Leukopenia and thrombocytopaenia with or without bleeding, Platelet disorders.[17]

Dengue hemorrhagic fever

The increase in the risk of maternal mortality due to dengue is around 3 times and due to DHF is around 450 times. A secondary infection with different serotype is a risk factor for DHF. The phases of infections in DHF are febrile phase (fever for 2-7 days), critical phase (plasma leakage for 24-48 hours) and convalescence phase (reabsorption for 2-4 days).[18]

Increased white blood cells and tendency for coagulation, low platelets and hematocrit, transaminitis and blunting of normal febrile response are often noted in pregnant subjects with DHF. Hemodilution is associated with normal pregnancy and may mask hemoconcentration associated with plasma leakage in DHF. The causes of underdiagnosis of dengue in pregnancy can be due to physiological changes during pregnancy, hemodilution, coagulation, thrombocytopenia, leucopenia, hematocrit and transaminitis.[18]

Management

Currently, there are no specific antiviral drugs for managing dengue, and only supportive treatment and judicious monitoring of intravascular volume replacement are advocated.[19] Hospital admission is required in patients with warning signs, comorbid conditions, dengue shock syndrome with plasma leakage, acute respiratory distress syndrome (ARDS) with pulmonary edema, severe organ dysfunction, and those requiring emergency treatment and fluid resuscitation. In patients with decreased hematocrit, whole blood transfusion is recommended.[20]

The bleeding manifestations in dengue could be due to thrombocytopenia, coagulopathy and vasculopathy. Bone marrow changes and repeated platelet transfusions may cause immune-related bleeding. According to WHO, platelet administration is needed only if there is significant bleeding due to thrombocytopenia or massive bleeding, which is not controlled by whole blood or *fresh frozen plasma*. Prophylactic transfusion is needed in afebrile patients with platelet count <10,000_/uL and <20,000/uL in febrile patients. Therapeutic transfusion is needed if there is active bleeding with count <50,000/uL.[21]

COVID-19 infection

The overall risk of severe infection is low in pregnant women; however, it is more when compared to non-pregnant women. The risk factors for severe COVID in pregnant women are ethnicity (Black or Hispanic), comorbidities such as diabetes mellitus and hypertension, age >35 years and BMI >35. COVID infection increases the risk of preterm birth, cesarean delivery, pregnancy loss, still birth due to respiratory distress and preeclampsia.[22-24]

A study conducted among 441 pregnant women who acquired COVID-19 has noted that 21% of the subjects had preterm labor, 9% had fetal distress and 8% had premature rupture of membrane. The commonest symptom of COVID reported was pneumonia (96%), and still births and neonatal deaths were reported among 8% of the newborns. The incidence of hospitalization, intensive care, and mechanical ventilation was more in pregnant subjects with severe infection.[25]

The vertical transmission of COVID-19 is very rare, however, the possibilities of intrapartum viral exposure cannot be ruled out. Hence, it is recommended to decrease the length of exposure during cesarian sections.[26]

The leading cause of death in COVID pregnancy is viral pneumonia. The clinical and radiological characteristics of COVID-19 pneumonia are comparable in pregnant and non-pregnant women. The major complications include ARDS, disseminated intravascular coagulation, acute renal failure, secondary bacterial pneumonia and sepsis.[27] COVID in pregnancy leads to increase in maternal morbidity and mortality, increased duration of hospital/ICU admission, elevated risk for preterm birth, neonatal ICU admission and neonatal death.[28]

Conclusion

Fever in pregnancy perse is teratogenic, hence it is necessary to evaluate, diagnose and initiate specific management at the earliest to prevent adverse fetal/maternal complications and pregnancy loss. Further research is warranted to understand the association between maternal fever and birth outcomes.

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Endocrine Fevers

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Introduction

Fever can be the presenting manifestation of endocrine disorders, most commonly seen with hyperthyroidism and subacute thyroiditis. Rarely, primary or secondary adrenocortical insufficiency, thyroid storm, and hyperparathyroidism may also cause fever. In pyrexia of unknown origin, it is important to consider non-infective conditions as the underlying cause.

A study conducted by Simon and Daniels in 1979 monitored 6 patients hospitalized due to fever. Endocrine fever had been reported in all the patients and the causes identified were triiodothyronine (T3) toxicosis, 'masked' thyrotoxicosis, subacute thyroiditis, primary adrenal insufficiency, secondary adrenal insufficiency and pheochromocytoma. The researchers also noted the development of extreme pyrexia in another patient (7th case), which was attributed to thyroid storm.[1]

The present chapter discusses the role of hyperthermia and fever as presenting manifestations of endocrine disorders.

Sub-Acute Thyroiditis (SAT)

SAT also called granulomatous thyroiditis or de Quervain's thyroiditis is an inflammatory thyroid disease, triggered probably by a preceding viral infection (occurring approximately 2-6 weeks earlier).[2] The increased prevalence of SAT in women is estimated to be 4-7 times higher, especially in younger and middle-aged groups. In India, the disease is more predominant in subjects belonging to their third decade of life. In 1895, Mygind in 1895 first described the disease in 18 cases and named it as 'thyroiditis acuta simplex'. He considered it to be distinct from suppurative thyroiditis.[3] It is an acute, inflammatory thyroid disorder occurring in nearly 5% of patients with clinical thyroid disease.

Presentation and diagnosis

The etiology of SAT is not known; however, it is presumed to be caused by viral infection. The self-limited inflammatory condition causes damage to the thyroid follicular cells. Stored thyroid hormone is released into the blood circulation, which results in thyrotoxicosis with suppressed TSH levels.

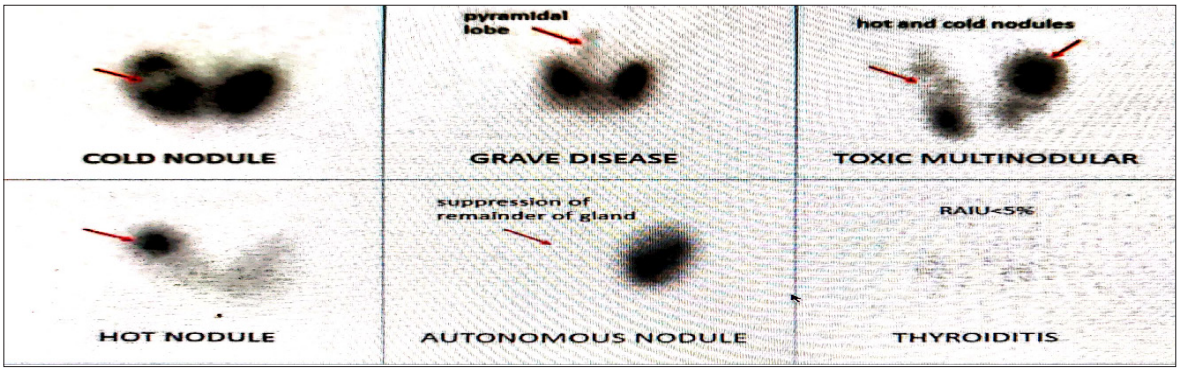
The most common complaint of patients with SAT is pain over thyroid gland, typically radiating ipsilaterally up to the jaw and ear and to the upper mediastinum. Fever occurs in the majority of cases, with frequent elevation >39 °C, especially at night. The initial symptoms may be accompanied by muscle pain, fatigue and malaise. Careful history and clinical examination of

the neck are paramount for diagnosis. The thyroid may be diffusely enlarged and tender (painful thyroiditis).

SAT usually presents as low-grade fever of short duration, neck pain, a tender goiter, and low TSH and elevated or normal free T3 and free T4. Dysphagia is also reported by some patients, along with increased sweating, tremor, and weight loss. Neck pain shifts from side to side and may settle in one area, frequently radiating to the jaw and ears. In rare cases, they dominate the clinical presentation, with a history of weight loss, tremor and palpitations. Nearly 50% of patients with SAT demonstrate symptoms of thyrotoxicosis, and most common differential diagnosis is Graves' thyrotoxicosis.[4]

Erythrocyte sedimentation rate (ESR) and c-reactive protein are elevated in majority of the patients. Procalcitonin seems to be the most helpful laboratory marker for the differentiation autoimmune and autoinflammatory conditions. Nuclear scan with Tc-99m or radioactive iodine uptake usually shows reduced uptake of Tcm 99/ radio- iodine (<1% to 2%) in the thyroid gland during the acute phase of the disease. The difference in iodine intake during the hyperthyroid and hypothyroid phases helps in differentiating SAT from Graves' disease.[5]

Fig. 1: Differences in iodine intake during the hyperthyroid and hypothyroid phases during the Grave's disease and thyroiditis



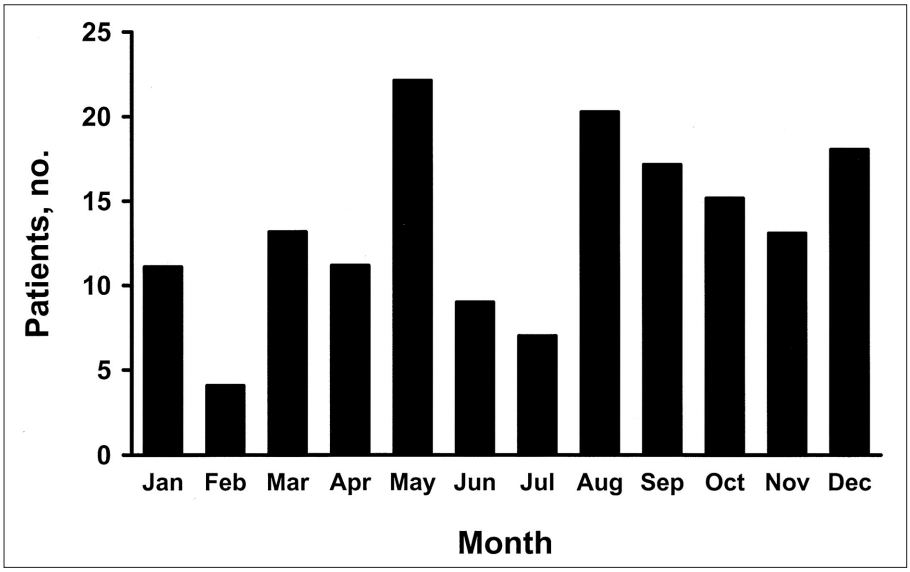
Color-flow Doppler ultrasonography may also help in distinguishing the disease. In Graves' disease the thyroid gland is hyper-vascular, whereas in patients with painful subacute thyroiditis, the gland is hypoechogenic and has low-to-normal vascularity.[6] In majority of cases, the disease is self-limiting and resolves in 8-12 weeks. The thyroid function normalizes spontaneously in 95% of the patients over a period of 6 to 12 months; however, permanent hypothyroidism persists in 5% of the cases.

Literature evidence

Epidemiological studies on SAT are very limited. A large community-based study performed in Olmstead County, Minnesota, between 1960 and 1997 has reported the incidence of SAT as 4.9 cases per 100,000 persons per year. The study has noted that the incidence of early transient hypothyroidism was common in patients with SAT and comparatively lesser occurrence

of permanent hypothyroidism. The proportion of subjects receiving T4 therapy after 28 years of follow-up had significantly reduced to 15%. Nearly 36% of the study participants received corticosteroid therapy (Fig. 2).[7]

Fig. 2: Number of patients with SAT reported in Olmsted County, Minnesota, at different months of the year, from 1960 to 1997



Several studies have established the association between SAT and *HLA-B35* allele and this finding has concluded on the genetic predisposition noted in most of the patients with SAT.[8] SAT may also develop secondary to a viral infection such as coxsackievirus, EBV and HIV. However, it has been rarely reported secondary to bacterial infections. Certain recent reports from US have noted the incidence of SAT secondary to COVID.[9]

Benbassat et al. evaluated the clinical characteristics and treatment outcome of 56 consecutive patients diagnosed with subacute thyroiditis between 1999 and 2005. The study noted the presence of anti-thyroid antibodies in 25% of the subjects and 9% with recurrent disease. Ultrasound performed in 35 patients revealed the presence of thyroid nodules in 25 subjects (median size, 17 mm). Ten patients did not receive any treatment, and 43 received either non-steroidal anti-inflammatory drugs (n=25) or glucocorticoids (n=18). The median disease duration was 77 days and hypothyroid phase was documented in 31 patients (remained permanent in 6). Untreated patients had less severe clinical disease than treated patients, but the outcome was comparable. The study has concluded on the unpredictable clinical course of SAT, with no effect of clinical features or treatment.[10]

A study carried out by the author and colleagues for a period of 5 years based on symptoms and technetium (Tc) 99m scan at 5 centres identified 2513 persons with SAT. The study has noted that women were more commonly affected compared to males with sex distribution of 1698 women and 815 men (2:1), and the mean age of women with disease was comparatively lesser

than men (32.5 ± 11.3 years vs. 37.2 ± 12.4 years). The highest number of cases were recorded in the months of June and August.[11]

SAT treatment

Beta blockers, non-steroidal anti-inflammatory agents (NSAIDs) and steroids help in alleviating the pain and may shorten the course of illness. Beta-blockers reduce tremor in hands, palpitation due to tachycardia and excessive sweating during the hyperthyroid phase. Aspirin (2,600 mg per day in divided doses) or ibuprofen (3,200 mg per day in divided doses) is appropriate for alleviating the pain.[12] However, there are no randomized controlled trials comparing doses or agents.

Corticosteroids can be considered, If the neck pain has not improved after 4 days, or if the patient presents with severe neck pain. High doses of glucocorticoids - 40 mg of prednisone per day can provide immediate relief. The doses of steroid should be tapered over a period of four to six weeks. Steroid should be discontinued when the Iodine 131 / Tcm 99 uptake returns to normal. Corticosteroid therapy should be given to improve the symptoms and quality of life. However, the disease recurrence was found to be more frequent in patients who received only steroids as compared to those who received NSAIDs.

Recurrence/ relapse of SAT

There is a higher incidence of transient hypothyroidism in the first year of SAT and life-long T4 therapy is generally not needed in such cases. Recurrent thyroiditis is defined as a repeat attack of SAT and it is seen in 3-14% of the patients. A study by Yamamoto et al. evaluated the recurrence of SAT over 10 years after the first attack in 3 cases. Evaluation of the data for 3,344 patients with SAT between 1970 and 1993 demonstrated the occurrence of 4 recurrent episodes in 3 cases, which were similar to the first episodes of SAT.[13]

Painful Hashimoto's thyroiditis

It is an atypical variant of Hashimoto's thyroiditis characterized by thyroid pain and fever. In patients with this condition, anti-inflammatory agents are not always effective and long-term pain management is highly challenging. A case report of four cases of painful Hashimoto's thyroiditis by Ohye et al. has noted the occurrence of high titers of anti-thyroperoxidase and thyroglobulin antibodies in all the patients. Total thyroidectomy helped in complete resolution of all the symptoms in affected subjects and the study has concluded on the safety and efficacy of treatment in patients with recurrent painful Hashimoto's thyroiditis.[14]

Thyroid storm

Thyroid storm is a life-threatening manifestation of thyrotoxicosis and the mortality associated with the disease is estimated to be 10.7%.[15] A study based on nationwide surveys had estimated the incidence of thyroid storm among hospitalized patients in Japan as 0.20 per 100,000 per year. Multiple organ failure was the most common cause of death, followed by congestive heart failure, respiratory failure, and arrhythmia.[16] The primary treatment of thyroid storm is with inorganic

iodine and antithyroid drugs (propylthiouracil or methimazole) to reduce synthesis and release of thyroid hormone.[17] Beta blockers are often used to reduce the effects of thyroid hormone. High-dose propylthiouracil (PTU) is preferred in severe thyroid storm due to its early onset of action and capacity to inhibit peripheral conversion of T4 to T3. Temperature control and intravenous fluids are also mainstay of management.

Some interesting case studies on endocrine fever

A 36-year-old woman presented with prolonged fever, hypercalcemia, hypercalciuria, and elevated serum parathyroid hormone levels. Surgical excision of the hyperplastic and adenomatous parathyroid glands contributed to reversal of the elevated biochemical parameters as well as temperature.[18]

Choudhary et al. have reported the presence of fever and seizures in an 11-year-old boy with primary adrenal insufficiency. This is an unusual presentation of Addison's disease and the disease completely resolved after the initiation of specific therapy.[19]

A case of disseminated tuberculosis with bilateral adrenal insufficiency was reported by Al-Mamari et al. MRI of brain revealed multiple tuberculomata and CT abdomen revealed lesions in the adrenal gland. The patient responded well to corticosteroid and catgory-1 anti-TB treatment.[20]

Conclusion

Fever in endocrinopathies is often missed and poorly understood. Thyroid storm is a true emergency that often presents with fever. SAT follows an unpredictable clinical course, hardly affected by its clinical features or treatment. Steroids are indicated only when patients have severe pain not responding to NSAIDs.

Adrenal insufficiency should be suspected and steroids empiric therapy should be started in a febrile patient with hypotension unresponsive to fluids and vasopressors. Pheochromocytoma can cause a wide variety of clinical syndromes including multisystem crisis, multisystem organ failure, and vascular lability, and is associated with a high mortality rate. Endocrinologist plays a major role in managing malignant pheochromocytoma and the assessment involves metastasis, control, chemoradiotherapy, and follow-up.

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Importance of Fever clinic: What? Why? How? Worth? Where?

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Introduction

Fever clinics serve as triage center for diagnosis, treatment and specialty care. The present paper discusses the functioning of fever clinic and its relevance in managing COVID pandemic.

Different types of clinics

Clinic is a healthcare facility providing medical care for ambulatory patients, especially who do not require admissions. Some of the different types of clinics are listed below:[1]

- **Fever clinic** helps in diagnosing and managing fever, and also provides care to patients who require isolation.
- **General OPD clinic** offers general diagnoses and treatments to patients who do not require overnight stay.
- **Polyclinic** is a facility where both general and specialist consultations are available for outpatients.
- **Specialty clinics** are dedicated clinics for the diagnosis and treatment of the respective specialty.

Apart from fever clinic, there are dedicated clinics for adult vaccination and wound care.

Need of fever clinic during COVID pandemic

Patients suspected with COVID need to be managed under isolation to break the chain of disease transmission. Moreover, the pandemic has increased the workload of emergency departments and the opening of fever clinics has helped to reduce the burden. Such clinics are also intended to provide emergency care to the COVID patients. A retrospective study conducted in a tertiary hospital in China has noted that the upgraded fever clinics has helped in significantly reducing the burden of ED and new protocol for the use of fever clinic during COVID pandemic has prevented the disease transmission within the hospital.[2]

Requirement of a fever clinic

The standard requirements of a fever clinic put forth by Dubai Health Authority are listed below:[3]

- The clinic should have a direct external access, not requiring the patients to commute through a hospital or a community area.
- The clinic design should provide disease-free environment to the patients and staffs with enough ventilation.
- The staffs should be trained to handle the specialized equipment and should have trained medical experts to handle critical and emergency cases.
- It is necessary to ensure the availability of person in-charge for each working shift.
- The facility should have the basic testing infrastructure and should screen patients for fever and COVID-19 symptoms before entering the clinic.

Fever clinics in India

However, the public sector fever clinics in India, designated for triaging patients, are not following any standard protocol. In such facilities, they generally measure temperature and oxygen saturation and shift the patient requiring hospitalization to nearby public health centers. Some of the fever triage clinics maintained by private entities have no testing facilities, apart from dedicated access to the center.

Certain expanded clinics possess ventilation, oxygenation and testing facilities, and some of them carry out camera surveillance to monitor whether patients have been maintaining social distancing. There is separate registration area with case-less payment and basic screening facilities. Clinical and radiological assessment rooms are equipped with exhaust fans and air conditioners to maintain air quality, and there are dedicated lifts to transfer patients to requiring admission, imaging and emergency care.

Effectiveness of non-contact infrared thermometers

Non-contact infrared thermometers (NCITs) are rampantly used in all public places and healthcare settings for screening and isolating potentially infected subjects with increased temperature. Temperature ⩾38 °C is one of the classic symptoms exhibited by COVID-19 patients.[4] A prospective observational study conducted among 736 healthcare workers between April-December 2020 had conducted 44,836 NCIT screenings and the reported percentage positivity rate was zero. Whereas, the corresponding positivity rates reported for PCR and serology were 9.23% and 39.34%. The study had concluded on the limited efficacy of NCIT in identifying single episode of fever.

Air quality of fever clinics

The air quality of the clinic can be determined by measuring CO_2. If the CO_2 level is <800 PPM, the place is safe for patients; whereas, if it is >800, the patients should spend less time or wear mask while visiting particular clinic.

Staffing

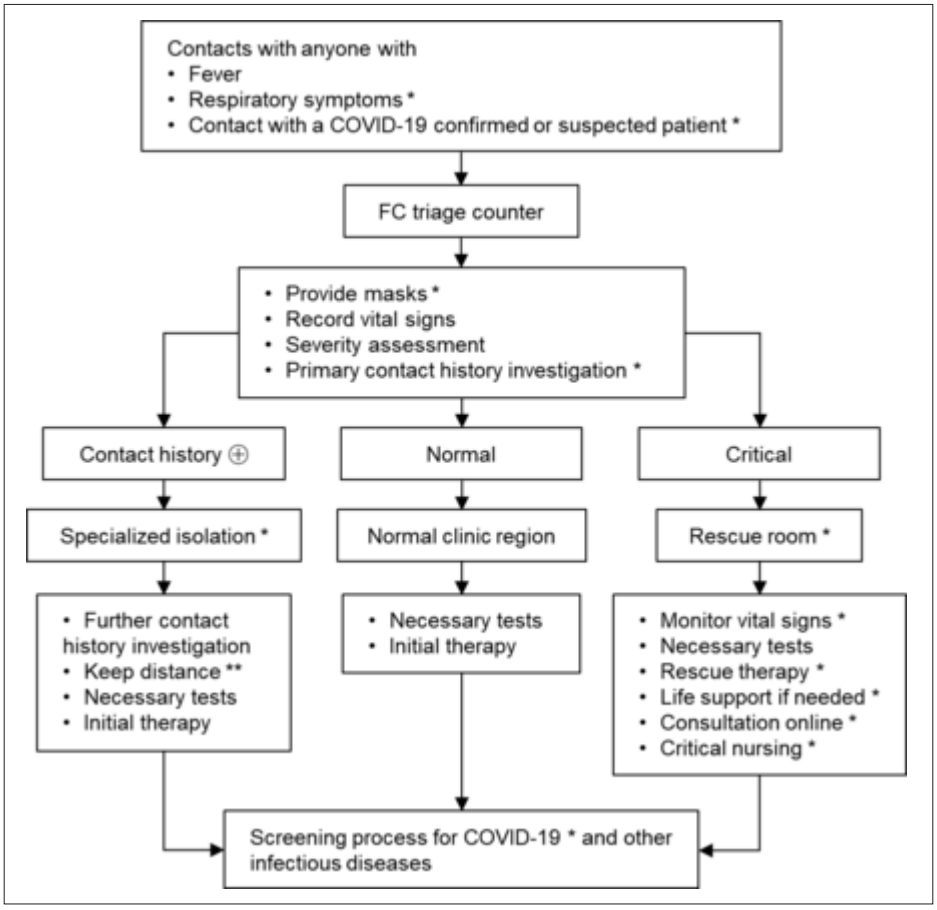
The staff requirement for a fever clinic is listed below:[5]

- Necessary staff for cleaning, sanitization and maintain hygiene.
- Sufficient nursing staffs based on the bed capacity of the center with knowledge on infectious disease prevention and control
- A physician assistant to monitor the vitals and record the patient history.
- The physicians working in fever clinics should have sufficient clinical experience and thorough knowledge on infectious disease, relevant disease characteristics, treatment principles diagnostic criteria, and disease prevention strategies.
- Emergency care personnel, lab technicians and CT scan experts.

Maintaining electronic health record is recommended for ease of reference and further consultation. Several new contactless monitoring devices and apps are available for remotely tracking vital signs such as oxygen saturation, heart rate, respiratory rate and temperature. Now-a-days, apps are available to monitor ECG and HB levels. Adoption of such remote monitoring digital care solutions help to enhance the convenience and safety of both patients and healthcare workers.[6]

A retrospective study by Wang et al. has put forth the algorithm to be followed for the triaging and regional isolation of different patients vising the fever clinic (Fig. 1). As per the algorithm, all the subjects, with fever or respiratory symptoms should undergo the triage process, irrespective of their history of COVID-19 exposure.[7]

Fig. 1: Triage process and regional isolation for different patients in the FC



The COVID treatment guidelines published by the Directorate General of Health Services in May 2020 have recommended the use of only antipyretics and antitussives for patients with mild disease, and no medication or investigation for asymptomatic patients. The guidelines also instructed to effectively dropped te use of azithromycin, doxycycline,ivermectin, zinc, favipiravir and plasma therapy.[8]

Advantages and challenges of fever clinic

A retrospective study involving 1034 febrile patients in China has concluded on the extraordinary role played by the fever clinics in managing a huge crowd of unknown febrile patients.[9] Establishing fever clinics also help to reduce cross-infections and to identify COVID symptoms early for effective triaging. The major challenges confronted in setting-up of fever clinics are having a good facility with necessary infrastructure, availability of trained personnel, and implementation of proper algorithm/ protocol for effective management.

Considering the changing paradigms in COVID-19 and reduction in infection, the current fever clinics can be modified for the administration of cocktail monoclonal antibodies. In addition, the same fever clinics can be converted to COVID/adult vaccine and travel clinics. In a country like India with tropical infections reported through the year, fever clinics can be modified to point of care testing centers with RT-PCR facilities

Way forward

Infectious disease (ID) telehealth clinic is the way forward and it is emerging as a viable alternative to hospitals with no access to infectious disease expertise. Such services will help to improve the compliance of patients and convenience of physicians. Setting up of virtual/ mobile vaccination clinics and point-of-care testing centers can help to improve the healthcare access in rural settings.

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Fever of Unknown Origin: Panel discussion

Panelists

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Case 1

A 66-year-old woman presented with primary complaints of weakness, fever, fatigue, myalgia, symptoms of hypotension and increased urinary frequency. Her medical history revealed hypertension, on medication for hypothyroidism, temporary hearing loss and tinnitus. Two weeks prior to the presentation, the patient had daily fever of 102°F, non-productive cough with pleuritic chest pain, severe body aches and low blood pressure (90 mm of Hg systolic). She had consulted her primary care clinician 3 days prior to the current presentation and was prescribed with amoxicillin presuming it as respiratory infection, but her symptoms worsened in the subsequent days.

The patient revealed a 2-year history of intermittent episodes of bronchitis and hemoptysis, and prescription of multiple courses of antibiotics. Sputum samples were negative for acid fast bacilli and the cultures were negative for tuberculosis (TB). The patient was ultimately treated for community-acquired pneumonia. Radiographic evaluation in an outgoing setting revealed the presence of benign pulmonary nodules. The patient did not have the habit of smoking or alcohol consumption.

Q1. What are the differential diagnoses to be considered in the current case?

Dr. Nagraj: Considering her history of hemoptysis and bronchitis, the probability of TB needs to be considered.

Q2. What is the probability of TB, even though the AFB and cultures are negative?

Considering the increased prevalence of TB in the country, it is important to consider the probability of the disease. The reasons for negative AFB and cultures are reduced (40-60%) sensitivity, bad sampling and inappropriate or partial treatment for TB.

Q3. Considering the history of tinnitus and hearing loss. Which systemic diseases can cause such presentations?

Dr. Hemant Thacker: It could be due to a low-grade ear infection or cerebellopontine angle (CPA) tumor. Pulmonary nodule may be a major clue to suspect any other underlying condition.

Dr. Nagraj: Drug-induced tinnitus, especially due to hydroxychloroquine treatment, or paraneoplastic syndrome should be suspected as causes for tinnitus.

Q4. What are the definitions of fever put forth by World Health Organization (WHO) and Infectious Diseases Society of America (IDSA)? Is the fever definition different for geriatric patients?

Dr Meenakshi Bhattacharya: According to the definitions of WHO, the basic mean temperature is 36.8°C ± 0.4°C. In addition, the measurement of core temperature should be based on circadian rhythm. If the rectal temperature is >38°C and axillary temperature is >37.5°C, it should be considered as fever. Core body temperature is comparatively lower in elderly and temperature >100°F or 37.8°C is considered as fever in geriatric patients. According to IDSA, a single oral temperature of >100°F should be considered as fever.

Q5. What is the significance of thermometer in temperature measurement? Which site should be considered as ideal for temperature measurement?

Dr Meenakshi Bhattacharya: Considering the risk of infectious diseases, measurement of axillary temperature is preferred. However, such results may not be accurate in patients with thick axillary hairs, increased sweating and moisture. The site that provides accurate core temperature reading is rectal, followed by oral and axilla. The pandemic has contributed to the wider adoption of non-contact temperature assessment measures such as thermal scan, especially in western countries.

The findings of systemic examination and measurements of vitals in case 1 are provided in table 1.

Table 1: Findings of systemic examination and measurements of vitals

Vitals	**Findings**
Pulse rate	92/min
Blood pressure	124/67 mmHg
Respiratory rate	23/min
Temperature	Afebrile 96.8°F
Saturation	96% room air
System findings	
Respiratory system	Decreased breathing sounds over the right intrascapular areas
CNS	Normal
CVS	Normal
P/A	Normal

Physical examination revealed pallor and bilateral pedal edema. However, there was no rashes, swollen joints, digital ulcers or loss of digit pulp. Results of clinical investigations are provided in table 2.

Table 2: Results of clinical investigations

Parameters	**Findings**
Hemoglobin	9.1g/dL
WBC	24,000/μL, neutrophils 87%, lymphocytes 4%, monocytes 7%
Platelets	513,000/μL
Troponin	0.11
AST	399 IU/L
ALT	368 IU/L
ALP	131 IU/L
Total bilirubin	0.4 mg/dL
Direct bilirubin	0.1 mg/dL
Albumin	2.5 g/dL
RFT	Normal
Urine routine	Pus cells plenty, presence of *E. coli*

Q6. What are the differential diagnoses to be considered in the present case?

Dr. Hemant Thacker: The patient has urinary tract infection (UTI) and deranged liver enzymes which indicates systemic involvement. Neutrophilic leucocytic infection pattern is noted in the current patient and considering the female gender, the probability of connective tissue disorders also needs to be considered.

Dr Meenakshi Bhattacharya: The possibility of Gram-negative speticemia along with UTI should be considered.

Q7. What are the false-positive conditions that may cause troponin elevation?

Dr. TS Ravindra: The current patient had mild elevation in troponin level. Various conditions can cause false-positive troponin elevation and they include aortic dissection, dilated cardiomyopathy particularly stress-induced cardiomyopathy, cocaine poisoning, renal diseases, and trauma to the chest.

Dr. Hemant Thacker: Troponin level measurement is one of the commonly misused tests in a clinical setting and other tests like ECHO are preferred in a cardiac setting.

Despite appropriate antibiotic therapy, the patient had persistent intermittent febrile illness, accompanied by increasing leucocytosis and neutrophil counts ranging from 80 to 86%. Repeated urine culture was negative and no source of infection was found, despite extensive investigations. Multiple blood cultures were negative. CT of chest demonstrated chronic scarring and architectural distortion of right upper lobe, suspected to be caused due to prior chronic disease.

Q8. How the newer definition of FUO varies from the old one?

As per the old definition, if the patient has fever for >3 weeks and has fever >38.3°C on at least 2 different occasions and the diagnosis is uncertain, despite 1 week of in-patient evaluation, the fever can be classified as FUO. Whereas, the need for in-hospital evaluation has been eliminated from the newer definition of FUO. As per the new definition, the patient should not be an immunocompromised host.

Q9. What are the newer classes of FUO?

The newly identified classes of FUO are as follows:

- Nosocomial FUO
- Classical FUO
- Neutropenic FUO
- HIV-associated FUO

Q10. What are the physical examinations to be carried out in the current patient, apart from the usual history?

Dr. Nagraj: Complete thorough physical examination is needed in the current patient, including the evaluation of skin and lymph nodes and mucous membranes.

Q11. In FUO with headache, which are the organisms to be suspected during the microbial examination of CSF?

Dr. TS Ravindra: The presence of 3 major organisms should be suspected namely HSV 1, *Cryptococcus neoformans* and TB.

Q12. Before conducting further diagnostic tests, is it necessary to stop antibiotics and glucocorticoid treatments?

Dr. Hemant Thacker: Yes, it is necessary to stop these medications before conducting further diagnostic tests. For example, while conducting PET-CT, receiving glucocorticoid impairs the avid-FDG uptake, especially in patients with mixed connective tissue disease (MCTD). Similarly, fluroquinolone may impair the imaging findings in a TB patient.

Further evaluation in the current patient revealed that the echocardiogram was negative for valvular vegetation. CT scan of the abdomen was negative for occult abscess. Pelvic ultrasound did not reveal any gynecologic pathology. MRI of the abdomen was negative for any infectious pathology. Peripheral blood smear examination was interpreted as reactive without signs of any neoplasms.

Q13. What are the first- and second-line investigations to be conducted in FUO?

Dr. TS Ravindra: The first-line investigations are blood culture, repeat CBC, urine routine, FNAC, ophthalmologic evaluation and investigations for common infectious diseases. PET-CT and skin biopsy can be considered as the second-line investigations.

Q14. Can FDG-PET/CT be helpful in the current case? What is the diagnostic yield of CT/MR/FDG-PET-CT?

Dr. TS Ravindra: FDG-PET/CT are helpful in identifying the inflammation, but to detect the exact pathology, it may be necessary to conduct a biopsy. The specificity of PET-CT is generally low, and can miss the diagnosis of certain conditions like temporal arteritis, leukemia and multiple myeloma.

Q15. Can the present case be a culture-negative endocarditis?

Dr. Hemant Thacker: There should have been some evidence of thromboembolic phenomena and cardiac history to suspect culture-negative endocarditis in the current case.

Q16. What are the important clues to be considered with regard to the blood culture for the diagnosis of endocarditis as a cause of FUO?

Dr. Nagraj: Multiple blood samples with appropriate spacing should be taken from different venepuncture sites for culture. Adequate volume of >10 ml should be collected for culturing.

Further evaluation of the present case revealed serum iron 14 mcg/dL, transferrin 105 mg/dL, TIBC 147 mcg/dL, ferritin 452 ng/mL, and reticulocyte count 5.6%. Serological testing was negative for HIV, acute or chronic viral hepatitis, Epstein Barr virus and cytomegalovirus infection. Creatinine gradually increased from 0.9 mg/dL to 3.4 mg/dL. Urine microscopy showed 5-10 red cell casts/LPF and 2-3 coarse granular casts/LPF.

Q17. What are the differential diagnoses to be considered after completing most of the diagnostic work-up? Can HIV cause all the aforementioned symptoms and lab derangement?

Dr. TS Ravindra: The differential diagnoses to be considered are TB, and connective tissue disorders such as SLE and Wegener's granulomatosis. Yes, HIV can cause all the aforementioned symptoms and lab derangement. However, it is necessary to conclude the diagnosis through ELISA or western blots.

Q18. What conditions can produce red-granular casts?

Dr Meenakshi Bhattacharya: Diseases like acute glomerular nephritis, lupus nephritis, Wegener's granulomatosis, renal infarction and renal thrombosis can produce red-granular casts. In the present case, the presence of multisystem disease involving hepatorenal and urinary systems can be suspected.

Markers of inflammation revealed ESR 67 mm/hr and CRP 17.5 mg/dL. ANA was weakly positive (1: 80) and p-ANCA was positive (1: 160) with MPO 115.2 units. All other rheumatological parameters were unremarkable.

Q19. How does ESR help in the work-up of FUO? Whether ANA screening or ANA profiling is needed for FUO work-up?

Dr. Nagraj: If the ESR is high, it is necessary to suspect chronic infections such as vasculitis or malignancies, however the test is very non-specific. Low ESR may be indicative of hypofibrinogenemia. If there is a clinical suspicion, ANA profiling will be definitely useful.

Q20. How often ANCA profiling is being conducted during the work-up of FUO?

Dr. TS Ravindra: General testing involves the complement C3 and C4. It should be considered as a part of work-up of FUO, if autoimmune diseases are suspected.

Q21. Considering all the clinical investigations conducted, what may be the final diagnosis in the current case?

Dr. TS Ravindra: The final diagnosis in the current case could be Wegner's granulomatosis with polyangiitis.

Workshop on Basics and Challenges in Infection Control

Part I: Basics and challenges in infection control

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Introduction

World health organization (WHO) defines healthcare-associated infections (HAI) as infections acquired from hospital by a patient who was admitted for a reason other than that infection. These are infections contracted by the patient from a hospital or other healthcare facility in whom the infection was not present or incubating at the time of admission or >48 hours of admission.[1] According to WHO estimates, nearly 1.4 million people are affected with HAI globally. Moreover, the risk of acquiring HAI in developing countries is 2 to 20 times higher when compared to developed countries. Apart from hospitals, other healthcare settings such as nursing homes, ambulances, outpatient Department(OPD), and clinics can become a source of HAI. Such infections are associated with impaired patient life, longer hospital admission and increased economic burden.[2]

Chain of infection

The chain of infection must be completed for the transmission of infection. If one of the links is broken, the transmission of infections is impaired. The chain of infection comprises of person at risk, pathogenic organism, reservoir or source, means of exit, mode of transmission, and portal of entry. The transmission of infection can occur from the source or infectious person via contaminated equipment, medications or hands, and it can be prevented by adopting hand hygiene, environmental cleaning, and wearing p*ersonal protective equipment* (*PPE).* [3]

Centers for Disease Control and Prevention (CDC) recommends the adoption of two tiers of precautions for preventing transmission: [4]

- Standard precautions intended for all patients in all healthcare settings, regardless of suspected infections.
- Transmission-based precautions intended for patients who are known or suspected to be infected or colonized with infectious agents.

Components of standard precautions

Components of standard precautions include hand hygiene, PPE, respiratory hygiene, patient placement, cleaning and disinfection, needle stick injury and sharp injury prevention, safe injection practices, and proper disposal of the waste.[5]

The first route of transmission is contact transmission, it can be direct (where host meets

reservoir) or through skin-to-skin contact. Whereas, in indirect transmission, the disease is carried from reservoir to host contaminated surfaces (e.g., methicillin-resistant Staphylococcus aureus (MRSA), scabies). The droplet infection is the second mode of transmission where pathogen-laden droplets are transmitted during coughing, sneezing, talking or medical procedures (e.g., tracheal intubation, non-invasive ventilation, bronchoscopy). Diseases such as diphtheria, pertussis, meningococcal meningitis, corona virus, and H1N1 are transmitted through droplets. The airborne method is the third route of transmission where very small particles of evaporated droplets with infectious agent may remain in air for longer time, travel further and become aerosolized during procedures.[6]

Transmission-based precautions

Contact precautions can be exercised by following proper hand hygiene, and using gloves and PPE. Droplet precaution, hand hygiene and use of mask are important. Negative pressure rooms and N-95 respirator mask are important components of airborne precautions. The hand hygiene is maintained by washing the hands thoroughly by removing all the hand accessories and applying soap or hand sanitizers. Hand hygiene includes routine hand washing for around one-minute, surgical scrub 5-6 minutes, and use of alcohol rub/gels for 20-30 seconds. For routine washing in clinics, wards, ICU and nursing homes, it is recommended to use normal liquid soap and follow aseptic precaution. For in-between OPD patient care, alcohol-based hand rub consisting of 0.5% chlorhexidine plus 70% w/v ethanol is advocated. Hand wash and hand rub should be easily available and accessible at every point of contact.[6]

The use of negative pressure room for isolating highly infectious disease patient helps to prevent airborne transmission of infections. Whereas, positive pressure room is intended to protect immunocompromised patients.

Case 1

Q1. What should be the isolation strategy to be followed for a child diagnosed with diphtheria?

The strategy should be droplet isolation. Special air handling and ventilation are not required, as the infectious pathogen do not spread over long distances. A single patient room is preferred, and close contacts should wear mask upon room entry and discard the same on room exit. Disinfecting the room during patient stay and discharge, and hand hygiene should be followed.

Case 2

Q2. A 4-year-old girl child was diagnosed with blood culture-positive MRSA. There was no focus sepsis or shock. What precaution strategy should be followed in the current patient?

The isolation strategy to be followed is reverse barrier nursing. Other prevention measures include providing single room to the patient, using surgical gowns, minimizing patient movement, maintain hygienic environment, and disinfecting non-critical equipment such as stethoscope.

Case 3

A 10-year-old male child sustained needle stick injury while walking barefoot on beach. The parents checked the needle and found traces of blood. What is the risk of infection? What are the precautionary measures and PEP to be followed? How to monitor the child?

The corresponding risks of infection noted for various pathogens following infected needle stick injury are 0.3% for human immunodeficiency virus (HIV), 1 to 1.8% for hepatitis C virus (HCV) and 9 to 30% for hepatitis B surface antigen (HBsAG).

Management of needle stick injury and splash includes washing the area with soap and water. It is important to recall the immunization status of the patient, especially for hepatitis B virus (HBV) and tetanus. Putting pricked finger in mouth, squeezing the pricked part and applying antiseptics should be strictly avoided.

The post exposure prophylaxis (PEP) includes first aid, counselling, risk assessment, collecting details of relevant lab investigations, and follow-up. HBV prophylaxis should be started if the child has not been immunized or anti-HBs antibody is negative. If the anti-HBs antibody is positive, there is no need of prophylaxis. if negative but received vaccination, the child can receive hepatitis B vaccine and hepatitis B immunoglobulins. Post-exposure prophylaxis for HCV is not available. PEP along with antiretroviral Therapy (ART) is indicated in the present child, ideally within 1-4 hours of injury, and the duration of prophylaxis is 28 days. PEP cannot be initiated after 72 hours of needle prick injury.[7,8]

The child should be monitored regularly for blood born infections: HIV ELISA at 6 weeks, repeat HIV ELISA and anti-HCV antibody testing at 3 months, and anti-HIV, anti-HCV, HBsAG and anti-Hbs antibody tests at 6 months. If test source is negative, the follow-up testing should include only HIV, HBsAG, and HCV at 1, 3, and 6 months.

Disinfection of medical equipment

The methods to be followed for disinfecting various medical equipment is listed in table 1.

Table 1: Disinfection of medical equipment in clinic

Equipment	Methods
Thermometer	Wash after every use, disinfect with alcohol swab.
Stethoscope	It should be wiped with 70% alcohol, once a day in clinic.
Tongue depressors	Disposables are preferred, metallic should be autoclaved or boiled.
Infant weighing scale	Clean with soap and water, strong disinfectants should be avoided.
Otoscope	Wipe with alcohol.
Non-invasive Blood Pressure (NIBP) cuff	Wash with soap.

Care of nebulisation machine

It is preferable to use disposable mask and tubing for each patient. The mask and T-shaped part should be washed with mild soap and dried using clean cloth. Tubings should not be washed or rinsed. The tubing with the mask/T shaped part should be connected and machine should run for 10-20 seconds to dry the nebuliser. It is preferrable to wear N95 mask when conducting procedures like induced sputum collection of a suspected TB patient.[9]

Measures for neonatal settings

Busy hospital schedule, lack of sufficient staff nurses, unsterilized equipment, over crowding in the nursery and understaffing increase the risk of infections in neonatal ICU. The measures to be followed for prevention of infection in neonatal settings include following standard aseptic, isolation and barrier precautions, use of disposables, disinfection and sterilization of re-useable equipment, bundle approach to invasive procedures, proper waste management and outbreak management.[10]

Some effective prevention measures for neonatal settings are listed below: [11,12]

- Baby linen and blankets must be washed and autoclaved.
- Feeding utensils should be washed and boiled.
- Surgical instruments such as forceps should be autoclaved.
- Laryngoscope must be cleaned with spirit swabs daily.
- Stethoscope, tape, pulse oximeter probe, radiant warmer probe, and thermometer must be cleaned with spirit and cotton.
- Weighing machine and infusion pump must be cleaned with Bacillocid.
- Effective handling and management of biomedical waste are paramount to prevent the occurrence of hospital-acquired infection and reduce the rates of disease transmission. Categories of biomedical waste and its segregation are described in table 2.[13]

Table 2: Categories of biomedical waste and its segregation

Yellow category	
Type of waste	**Type of bag**
Human anatomical waste: Human tissues, organs, body parts, and fetus below the viability period Animal waste	Yellow non-chlorinated plastic bags
Soiled waste: Items contaminated with blood, body fluid like dressings, plaster casts, cotton swabs, and bags containing residual or discarded blood, blood components, cap, and mask	Yellow non-chlorinated plastic bags
Expired or discarded medicines**:** Antibiotics, cytotoxic drugs, including all items contaminated with cytotoxic drugs	Yellow non-chlorinated plastic bags
Chemical waste: Used or discarded disinfectants	Yellow containers or non-chlorinated plastic bags
Chemical liquid waste: Discarded formalin, infected secretions, aspirated body fluids, liquid from laboratories, and floor washing, cleaning, and housekeeping	Separate collection system leading to effluent treatment system
Discarded linen, mattresses, beddings with blood or body fluid	Yellow non-chlorinated plastic bags
Microbiology and laboratory waste: Blood bags, laboratory cultures, stocks of microorganisms, live/attenuated vaccine	Autoclave safe plastic bags or containers
Red category	
Contaminated waste(recyclable)	**Type of container**
Wastes generated from disposable items such as tubing, bottles, intravenous tubes and sets, catheter, urine bags, syringes without needles and fixed needle syringes and vacutainers with their needles cut, and gloves.	Red coloured non chlorinated plastic bags or containers.
White(translucent) category of waste	Type of container
Needles, fixed needle syringes, needles from needle tip cutter, or burner, scalpels, blades, or any other contaminated sharp objects that may cause puncture and cuts. This includes both used, discarded, and contaminated metal sharps.	Puncture proof, Leak proof, tamper proof containers
Blue category	
Glassware: Broken or discarded and contaminated glass including medicines vials, and ampoules except those contaminated with cytotoxic wastes.	Cardboard boxes with blue coloured marking
Metallic implants	Cardboard boxes with blue coloured marking

Symbols such as biohazard, cytotoxic hazard and handle with care should be taken consciously.

Conclusion

The strategy for infection prevention requires strict attention to hand hygiene, prudent antibiotic use, adoption of aseptic techniques, disinfection or sterilization of medical items and equipment, and increasing the awareness of staff regarding infection control. It is also important to keep the environment clean, dry and dust free, and surveillance of nosocomial infection is necessary to identify problem areas and set priorities.

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Part II: Challenges in Infection Control

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Introduction

All the health workers are at risk of contracting infection and further transmission in a hospital setting. Estimates show that the risk of infection is comparatively higher in healthcare workers than patients.[1] The present paper focuses on the challenges in infection control and precautions to be taken during patient care for preventing infections.

PEP for needle stick injury

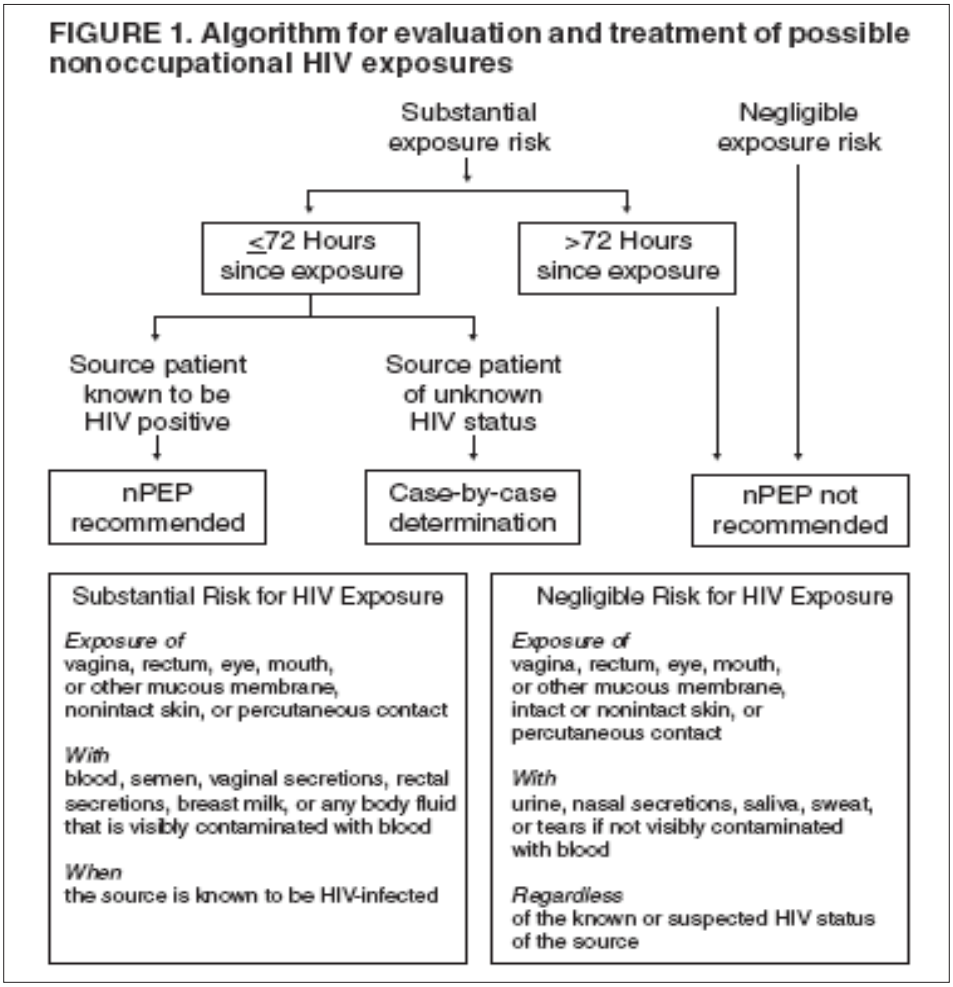
Post-exposure prophylaxis (PEP) is important in both hospital and non-occupational settings. Systemic infection does not occur immediately after pathogenic exposure, thereby presenting a window of opportunity for potential interventions such as immunoglobulin (passive), vaccine (active) and anti-viral/anti-bacterial/anti-parasitic drugs. Early administration of the initial dose is the major determinant of PEP. The PEP is effective up to 7 days for needlestick and perinatal exposures and 14 days after sexual exposures.

Administration of HB vaccine alone, as 3 or 4 schedules within 12 hours after parturition, is found to be effective in 70-95% of perinatal HBV infections in infants born to HBsAg/HBeAg-positive women.[2] The dosage for HB vaccine for passive/active PEP is 0.5 ml for infants and 0.06 ml/kg for adults.

Physicians (51%) possess the highest risk for NSI and are often underreported.[3] Though NSIs are more common in surgeons, the use of gloves and solid needles to some extent protect them from such injuries. This finding highlights the need to wear personal protective equipment (PPE), even during phlebotomy.

Risk assessment is very important in all such incidences of exposure. The risk of exposure due to percutaneous injuries is very minimal; whereas, blood transfusion has the maximum risk. The recommended algorithm for the evaluation and treatment of possible non-occupational HIB exposures is depicted in fig.1.[4]

Fig.1: Algorithm for the evaluation and treatment of possible non-occupational HIB exposures



Source: Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR Recomm Rep. 2005;54(RR-2):1-20.

The preferred and alternative medications indicated for PEP is briefed in table 1.

Table 1: Preferred and alternative mediations indicated for PEP

Age group	Preferred/ alternative	Regimen
Adults and adolescents ⩾13 years including pregnant women with normal renal function (creatinine clearance ⩾60mL/min)	Preferred	A 3-drug regimen comprising of tenofovir DF 300 mg and fixed dose combination of emtricitabine 200 mg once daily with raltegravir 400 mg twice daily or dolutegravir 50mg once daily
	Alternative	A 3-drug regimen comprising of tenofovir DF 300 mg and fixed dose combination of emtricitabine 200 mg once daily with darunavir 800 mg and ritonavir 100 mg once daily

If the exposed person is not vaccinated against hepatitis B, it is important to start immunoglobulin treatment and vaccination protocol. The protocol to be followed based on the vaccination status and antibody response of the exposed subject is briefed in table 2.[5]

Table 2: Recommendation for PEP in patients with hepatitis B exposure

Vaccination and antibody response status of exposed workers	Source HBsAg positive	Source HBsAg negative	Source Unknown or not available for testing
Unvaccinated	HBIG X 1 and initiate Hepatitis B vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated Known responder Known non responder	No treatment HBIG x 1 and initiate revaccination or HBIG x 2	No treatment No treatment	No treatment If known high-risk source, treat as if source was HBsAg positive
Antibody response Unknown	Test exposed person for anti-HBs 1. If adequate, no treatment is necessary. 2. If inadequate, administer HBIG X 1 and vaccine booster.	No treatment	Test exposed person for anti-HBs 1. If adequate, no treatment is necessary. 2. If inadequate, administer vaccine booster and recheck titre in 1-2 months.

Source: Vaid N, Langan K, Maude R. Post-exposure prophylaxis in resource-poor settings: Review and recommendations for pre-departure risk assessment and planning for expatriate healthcare workers. Tropical medicine & international health : TM & IH. 2013 Mar 6;18.

However, PEP is not recommended for hepatitis C. The following symptoms of acute retroviral syndrome or acute mononucleosis and side effects of treatment need to be monitored during the prophylaxis: fever, fatigue, myalgia, skin rash headache, pharyngitis, cervical adenopathy, arthralgia, diarrhoea, and night sweats.

if any health worker sustains NSI in a healthcare setting, it is important to document the same as incident report. This may help to take necessary precautions to prevent such future incidents. Conducting baseline testing of the suspected subjects provides only the status of HIV infection 4 week prior to the current exposure.

Risk for varicella exposure

Risk for contract varicella is high in the following scenarios:

- Living in the same household with a person having active varicella or herpes zoster
- Direct face-to-face contact with a person having active varicella or herpes zoster for at least 5 minutes.
- Being in the same room with an infected person for at least 1 hour

Chickenpox cases are infectious 2 days prior to the appearance of rashes until the crusting of lesions.

Administration of varicella vaccine is recommended as PEP within 5 days of exposure, if there are no contraindications to use. Unvaccinated subjects of ⩾12 months, without evidence of immunity to prevent or modify the disease can receive the vaccine. Protective efficacy has been reported in majority of the children who had undergone vaccination within 3 days of exposure.[6]

VariZIG is recommended in the following subjects:

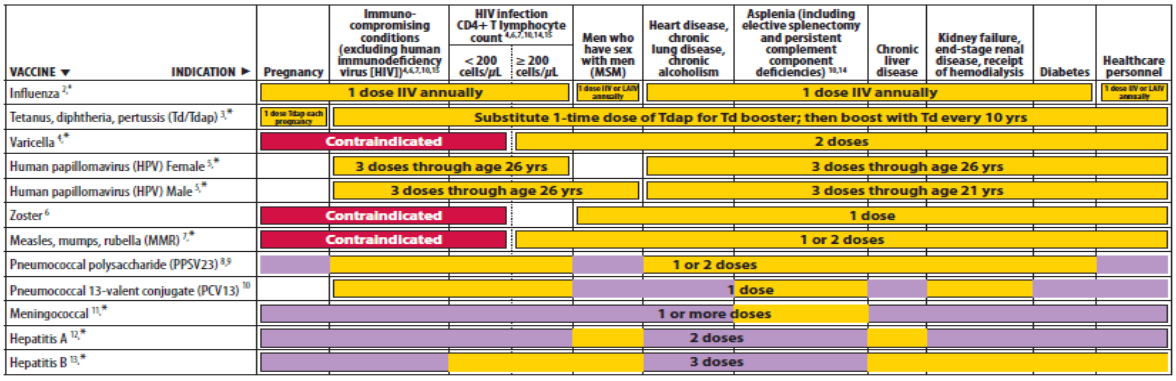
- Immunocompromised subjects
- Pregnant women without evidence of immunity
- Infant with specific indications

Maximum benefit is achieved upon administration of VariZIG immediately after the exposure. It may be effective if administered within 10 days. If VariZIG is not available, intravenous immunoglobulin can be administered within 10 days of exposure.[7] Acyclovir (80 mg/kg/day 4 times daily for 7 days, maximum dose 800 mg, 4 times per day) can be considered in immunocompromised scenarios where immunoglobulin is contraindicated. Systematic selective vaccination of susceptible healthcare workers is paramount to break the chain of annual varicella outbreak in a hospital setting.[8]

Immunzation of healthcare personnel

The immunization schedule recommended by the advisory committee on immunization practices for adults based on medical and other indications is provided in table 3.[9]

Table 3: Immunization schedule advocated by the advisory committee on immunization practices for adults



Source: Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedule for Adults Aged 19 Years and Older — United States, 2013 [Internet]. [cited 2022 Feb 18]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a3.htm

The recommended vaccines for healthcare professionals are provided in table 4.[10]

Table 4: Recommended vaccines for healthcare professionals

Vaccine	Recommendations in brief
Hepatitis B	Give 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). Give IM. Obtain anti-HBs serologic testing 1-2 months after dose #3
Influenza	Give 1 dose of influenza vaccine annually. Give inactivated injectable influenza vaccine intramuscularly or live attenuated influenza vaccine (LAIV) intranasally.
MMR	For healthcare personnel (HCP) without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart.
Varicella (chickenpox)	For HCP who have no serologic proof of immunity, prior vaccination, or history of varicella disease, give 2 doses of varicella vaccine, 4 weeks apart. Give SC.
Tetanus, diphtheria, pertussis	Give a one-time dose of Tdap as soon as feasible to all HCP who have not received Tdap previously. Give Td boosters every 10 years thereafter. Give IM.
Meningococcal	Give 1 dose to microbiologists who are routinely exposed to isolates of N. meningitidis. Give IM or SC.

Source: CDC. Immunization of Health-Care Personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 2011; 60(RR-7).

Policy for HBV, HIV and HCV positive healthcare workers

In HBV-, HIV- and HCV-positive healthcare workers, if the viral load is not detectable in annual screening, they can continue the same job. If the person is not willing to undergo screening, avoid posting in exposure prone areas.

Risk for meningococcal meningitis

The risk for meningococcal meningitis is high in the following scenarios:[11]

- Household, preschool or childcare centre exposure at any time during the 7 days before the onset of illness.
- Persons who had direct exposure to index patient's secretions at any time during the 7 days prior to the onset of illness.
- Person who had resided in the same dwelling as the index patient at any time during the 7 days prior to the onset of illness.
- Airline passengers who shared seat next to the index patient during a flight lasting >8 hours.
- Healthcare workers exposed to respiratory secretions (during unprotected intubation, suctioning and mouth-to-mouth resuscitation)

Chemoprophylaxis in suspected cases should be started within 24 hours after concluding the disease in index patient. Prophylaxis administered after 2 weeks of exposure has no beneficial effect.

PEP for COIVD-19

A recent study by Brien et al. evaluated the potential of subcutaneous REGEN-COV, a combination of casirivimab and imdevimab, in preventing SARS-CoV-2 infection and subsequent COVID-19 in persons at high risk for infection due to household exposure. The researchers have concluded that the vaccine helped in preventing both symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected subjects. Moreover, in infected subjects, the vaccine helped to reduce the duration of the symptomatic disease and viral load.[12]

PEP for COIVD-19 can be recommended to the following subjects:

- Patients who are at high risk for progression to severe COVID-19
- Subjects who are not fully vaccinated or those having inadequate immune response
- Patients who had been exposed to an individual infected with SARS-CoV-2, as per the close contact criteria put forth by CDC
- Subjects who are at high risk of exposure in an institutional setting

Take home message

- Increasing awareness and educating the lab personnel periodically about precautions to be followed while handling the specimens may help in preventing the risk of lab exposures.
- Standard infection control measures need to be strictly followed in a laboratory setting presuming that all the specimens handled are infectious.
- Outbreak investigation is one of the important tools for infection prevention.
- Well-ventilated consultation room, appropriate use of mask and social distancing are important infection control measures.
- Antibiotic stewardship may help in preventing the irrational use of antimicrobials and subsequent development of antibiotic resistance.

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FEVER FOUNDATION

Vision

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

Mission

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

Objectives of Fever Foundation

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

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