FEVER FOUNDATION

Vision

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

Mission

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

Objectives of Fever Foundation

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

MICRO KNOWLEDGE ACADEMY

A HANDBOOK FOR PHYSICIAN

MICRO KNOWLEDGE ACADEMY

FEVER FOUNDATION

FEVER IN INDIA OPPORTUNITIES & CHALLENGES

Compilation of articles from

FeFCon-2019

2nd Annual Fever Foundation Conference 2019, Bengaluru

FEVER FOUNDATION

FEVER

IN INDIA

OPPORTUNITIES & CHALLENGES

This book has been made possible by a grant from MICRO LABS LIMITED, as a service to the medical profession.

Published by:

MICRO LABS LIMITED

31, Race Course Road, Bengaluru - 560001

For free distribution to doctors under the aegis of Micro Knowledge Academy.

Disclaimer:

The editors have checked the information provided in this publication to the best of their knowledge. However in view of possibility of human errors and changes in medical science, neither the authors nor the publisher or any other person/s who has/have been involved in the preparations of this work warrants that the information contained herein is in every respect accurate or complete and therefore disclaim all the responsibility for any errors or omissions or for the results that may be obtained from use of the information contained in this publication.

FOREWORD

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. The decision to reduce fever with antipyretics assumes that there is no diagnostic benefit of allowing the fever to persist. However, there are rare clinical situations in which observation of the pattern of fever can be helpful diagnostically.

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. The decision to reduce fever with antipyretics assumes that there is no diagnostic benefit of allowing the fever to persist.

Recognizing symptom patterns can provide crucial clues and, thus, lead to the initiation of targeted specific diagnostic tests and therapies

There is some debate as to whether fever should be routinely treated. However, people with a high fever generally feel much better when the fever is treated

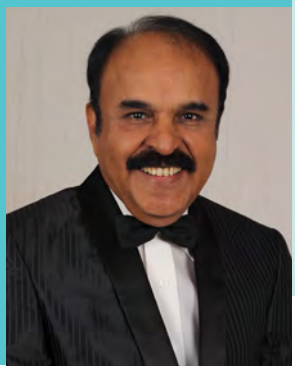
Fever can be tricky in older people because the body may not respond the way it would in younger people.

The ability to develop fever in older adults is impaired, and baseline temperature in older adults is lower than in younger adults. Thus, older adult patients with severe infections may only display a modest fever.

This fever book provides the comprehensive information about the fever , its approach and management

Dr Maiya M MBBS (Mys), FRCP (lond), FRCP (Edin), FRCP (Glasg), FICP (Ind), FICC (Ind)
Chief patron, Fever foundation of India, Bangalore
Former professor of Medicine , Karmanataka medical service
Senior physician, Rangadore Memorial hospital, Bangalore

FOREWORD



Fever is one of the body's most effective ways of fighting infection. Fever is a prominent feature of disease since antiquity. It is the balance in the interactions between pyrogens and cyrogens that determine the severity and duration of the febrile response to any immune challenge.

In view of its integral role in the pathogenesis of diseases, fever will remain a cardinal manifestation of old, new and emerging diseases, whether infectious and non-infectious disease. It is therefore imperative for clinicians to continue to harness and expand knowledge gained so far in the understanding of the febrile response in order to improve on the diagnosis, prevention and management of the numerous diseases characterised by fever.

Optimal management of fever is contingent on meticulous patient assessment, with implementation of appropriate treatment interventions as befits patient-determined goals of care. Treatment options include antipyretic therapy and primary approaches targeted at contributing etiologies and pathophysiologic mechanisms.

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. A. Muruganathan
Chairman- Fever foundation CME committee
Governor – American College of Physicians
Past Dean – Indian Collegeof Physicians of India
Past President – Association of Physicians of India
Past president- Hypertension society of India

FOREWORD

Fever in children is a common concern for parents and one of the most frequent presenting complaints. Although the incidence of serious infections has decreased after the introduction of conjugate vaccines, fever remains a major cause of laboratory investigation and hospital admissions.

Fever plays a physiologic role in response to infection, inhibiting bacterial growth and viral replication, and enhancing the immune response

Fever itself is not dangerous, antipyretic treatment should be reserved for distressed children, aiming at improving the child's wellbeing rather than achieving normothermia. Antipyretic treatment has not been shown to prevent recurrence of febrile seizures and should therefore not be recommended for this purpose.

Appropriate counseling on the management of fever begins by helping parents understand that fever, in and of itself, is not known to endanger a generally healthy child

Response to antipyretics cannot predict the severity of the underlying illness, since children with bacterial and viral illnesses have a similar response to antipyretics.

A primary goal of treating the febrile child should be to improve the child's overall comfort. The desire to improve the overall comfort of the febrile child must be balanced against the desire to simply lower the body temperature.

Pediatricians should focus instead on monitoring for signs/symptoms of serious illness, improving the child's comfort by maintaining hydration, and educating parents on the appropriate use of antipyretics.

The fever foundation provides scientific data on various aspects of fever for better understanding, care of the child.

This book provides the updates on the latest advances in diagnosis and management of fever in the children

Dr. Jagdish Chinnappa
Eminent Paediatrician – Senior consultant
Department of Paediatrics
Manipal Hospital, Child Central clinic Bangalore
jagchin@gmail.com

PROLOGUE

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

The second Annual National conference of Fever foundation, FeFCon 2019 was held on 16th and 17th November at Hotel Shangri -La, Bengaluru. Mind opening presentations by highly esteemed and renowned speakers were delivered in the two days academic feast.

This book is the brief capture of important sessions on fever and its management which can be of great help in day to day practice.

Happy Reading,

Dr. Manjula S
Organizing Secretary,
FeFCon 2019

Index

Index

An overview of fever : A lifespan approach

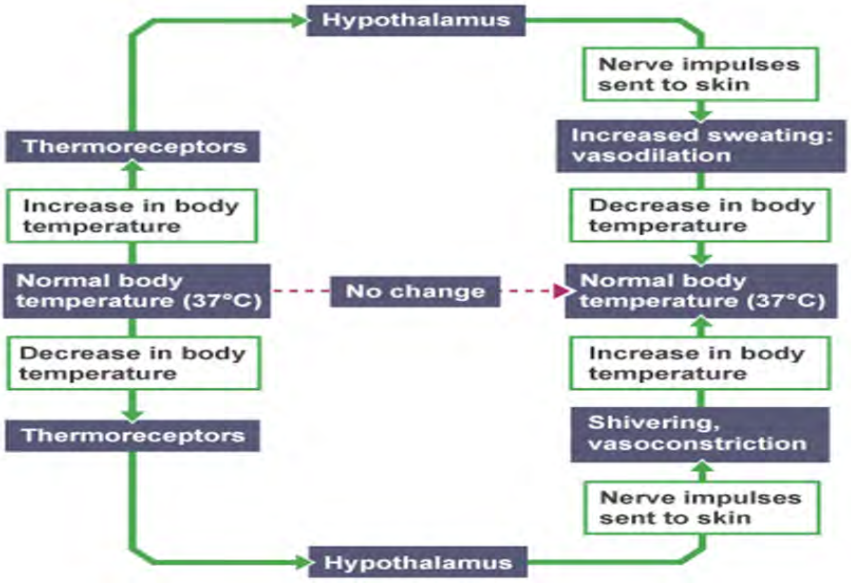
Dr. S. Balasubramanian MD, DCH, FIAP, FRCPCH (UK)
Medical Director, HOD PEDIATRICS
Course Coordinator- IAP IDC PID Fellowship
Kanchi Kamakoti CHILDS Trust Hospital,
Honorary pediatrician, Southern Railway Headquarters Hospital
CHENNAI

Basics of fever

Humanity has three great enemies: fever, famine and war, of these by far the greatest, by far the most terrible is fever- William Osler.[1]

Fever is a well-planned response by the human body against any pathogenic invasion, wherein the hypothalamus serves as the regulatory center. Impulses generated from any part of the body, due to the presence of a microbe, cytokine or endotoxin, instruct the hypothalamus to increase the body temperature. Once the temperature has increased to the desired level, the built-in thermostatic safety mechanism is activated to stop further increase in the temperature. This is followed by increased sweating and vasodilation (Fig 1).[2]

Fig. 1: Pathophysiology of fever



Accurate measurement of temperature

Temperature is measured using various methods including rectal, oral, axillary, infrared thermometers and smart phones. The various kinds of thermometers include ear thermometer, forehead thermometer, wireless thermometer, infrared thermometer and digital thermometer. In infants <4 weeks, axillary temperature should be measured with an electronic thermometer. In children aged between 4 weeks to 5 years, body temperature should be measured by an electronic thermometer or chemical dot thermometer in the axilla or infra-red tympanic thermometer.[3] Although rectal measurement is considered as gold standard, it is not preferred in neutropenic patients due to increased risk of infection. Moreover, it is uncomfortable, unacceptable and has increased risk for rectal perforation.[4] Forehead chemical thermometers are unreliable and should not be used by healthcare professionals.

Defining the term fever

Fever is an abnormal elevation of body temperature that occurs as part of a specific biologic response. This is mediated and controlled by the central nervous system. The temperature elevation that is considered 'abnormal' depends upon the age of the child and the site of measurement. As per the standard definition, an a.m. temperature of >37.2°C (>98.9°F) or a p.m. temperature of >37.7°C (>99.9°F) would define a fever.[5]

- In a healthy neonate (0 to 28 to 30 days of age) or young infant (1 to 3 months of age), rectal temperature ≥38.0°C (100.4°F) is generally defined as a fever of concern.
- In children 3 to 36 months, fever is generally defined by rectal temperature ranging from ≥38.0°C to 39.0°C (100.4 to 102.2°F) and fever of concern by rectal temperature ≥39.0°C (102.2°F), if there is no focus of infection on examination.
- In older children and adults, fever may be defined by oral temperature ranging from ≥37.8 to 39.4°C

(100.0 to 103.0°F) and fever of concern by oral temperature ≥39.5°C (103.1°F).[6]

Teng et al. have reported that parental perception of a fever should be considered valid and taken seriously by healthcare professionals[7] even in the absence of documentation of fever.

Treating fever: Concepts and a rational approach

Although fever is a symptom of concern for parents and caregivers, the prevalence of serious infections in children is very less. It is estimated to be around <1% in primary care settings in industrialized countries.[8] However, the figure may increase up to 25% in emergency departments.[9]

Fever is an energy-dependent, leukocyte-based amplification mechanism that facilitates motility of leukocytes, lymphocyte response to mitogens, production of interferon, and immune response to viral antigens. The warning signs of fever include difficulty in swallowing/ breathing, lethargy, rash, and distressed mood and parents should be educated regarding these signs for seeking medical consultation.[10]

According to the NICE guidelines, antipyretic agents should not be used in routine practice with the sole purpose of reducing body temperature. Either paracetamol or ibuprofen should be considered for the management of fever in children who appear distressed with fever.[11] The American academy of pediatrics (AAP) has noted increased pediatric hospitalization due to wrong dosage of acetaminophen-paracetamol. AAP appealed and removed all multi-strength preparations of paracetamol from the US drug market and has transitioned to a single strength of 160 mg to improve dosing compliance and reduce medication errors.[12]

A retrospective study conducted at the pediatric emergency of Kanchi Kamakoti CHILDS Trust Hospital, Chennai has reported that 13% of all poisonings was due to paracetamol. Around 37% of the infants with toxicity belonged to < 1yr of age and 80% were administered with wrong dosage of the drug. Based on this study, the institution has banned selling of 250 mg/500 mg strength liquid preparations through the pharmacy.[13]

In India, paracetamol is available as different formulations of varying strengths such as syrup, suspension, drops, tablets, injection, and rectal suppositories (120/125/150/250 and 500 mg/5 mL). The usual cause of paracetamol overdose is frequent administration of the drug round the clock by an anxious parent who considers fever as a potentially dangerous event and as a trigger for febrile seizures. In addition, wrong prescription by a doctor is also an important cause of paracetamol toxicity in Indian setttings.[14]

IM preparations of paracetamol are painful and poorly absorbed, and rectal preparation (suppository) is used rarely in postoperative cases. IV paracetamol is generally safe, but it is not used for treating fever, except in surgical wards and pediatric ICU. In order to reduce such incidences of overdosing, all the medical fraternities are requested to prescribe only 120 mg/5 ml preparations in liquid form.

Ibuprofen as antipyretic is approved as OTC abroad and should be avoided during dengue season in India. A dosage of 5 mg/kg at an interval of 6 hours is effective but should be avoided in infants <6 months of age. Combining ibuprofen with paracetamol is irrational. The use of ibuprofen in febrile children with a history of asthma has been reported to be safe. However, it should not be used in

children with known hypersensitivity to NSAIDs.[15]

Mefenamic acid is another commonly used antipyretic agent in India and one of the past issues of the journal Indian Pediatrics had published an advertisement on the drug with the tag line, 'The preferred antipyretic'. However, the drug use is associated with frank colitis in patients with no known predisposing factors and overdosing can induce generalized tonic clonic seizures. It can also cause mucosal damage due to impaired local prostaglandin synthesis and imbalance in the equilibrium between the cyclo- and lipoxygenase pathways of arachidonic acid metabolism. Literature evidence for the past 15 years has reported increased occurrence of acute renal failure and other side effects due to use of mefenamic acid.[16] Mefenamic acid should not be used as antipyretic in children because of concerns of safety.

Paracetamol is intestinal friendly and can be used for managing fever in children. Paracetamol is comparatively safer to manage fever as well as pain in children at a dosage of 15mg/kg/dose. However, the use of >5 doses per day should be avoided. Its use in neonates and as a prophylactic drug is also contraindicated.

A medication for fever should be considered only if the axillary temperature is >101° F. Tepid sponging is not recommended for the treatment of fever, as it makes the child feel more uncomfortable.[18] The use of antipyretics or treating the fever does not decrease the risk of having recurrent febrile seizures. In children with increased risk for febrile seizure, it is ideal to conduct screening for iron deficiency, preferably after 1 week of fever resolution. Intranasal midazolam may be prescribed if the febrile seizures lasts >5 mins, and oral clonazepam 0.01mg/kg 8 hourly (max 1.5 mg/day) for managing frequently recurring seizures.[19] Parents should be counselled regarding the treatment and dosages while managing children with febrile seizures.

Fever without focus: Overview

Fever without focus is an acute onset of fever (rectal ≥38°C [100.4°F] or more) without identifiable cause even after completing a thorough history and physical examination.[20] Such fevers are not managed appropriately in pediatric subjects. The terms 'fever without localizing signs' and 'fever of unknown origin (FUO)' are considered as subcategories of fever without a focus.

Case 1

A 20-days-old neonate with a body weight of 2.2 kg, born through normal vaginal delivery, had fever for 2 hours with axillary temperature 100.6°F. The Chennai weather was 105°F and the baby was wrapped in 2 sweaters. They had no A/C at home.

In neonates, it is challenging to clinically distinguish a serious bacterial infection (SBI) or viral (herpes simplex virus [HSV]) infection from self-limited viral illnesses. Fever recorded at home by a reliable parent should be considered to corroborate the febrile status of the neonate. The elevation in body

temperature could be due to environmental conditions. If false elevation in temperature is suspected, removing the clothing and reassessing the child are necessary. Oral antibiotics should not be recommended to neonates. The initial management strategies include culturing of blood, stool, CSF and urine, and conducting PCR to conclude the diagnosis, and initiation of empirical IV antibiotics. Acyclovir can be used if HSV infection is suspected due to seizures, hypotension, transaminase elevation, CSF pleocytosis or known maternal history of genital HSV, especially at the time of delivery.

In neonates having a fever without focus and a temperature >101°F, urine routine analysis is the simple relevant test to be carried out, as UTI is the common cause of fever in such infants. The indications for full sepsis evaluation for febrile young infants are as follows: any ill appearing infant <28 days old, 29 to 60 days old infant with rectal temp >38.6°C, congenital or chromosomal defects, history of receiving antibiotics within the prior 3 to 7 days, and focal infections. The indications for conducting lumbar puncture to rule out meningitis in infants having fever without focus are listed in table 1.

Table 1: Indications for lumbar puncture in infants having fever without focus

Preferred
• TC <5000/mcL >15000/mcL
• ABC >1500
• Immature to mature neutrophil ratio >0.2
• CRP >20 mg/dL
• X-ray suggestive of pneumonia

In recently immunized infants having fever without focus, close follow-up is needed to ensure that the fever resolves within 48 hours of vaccination. If the fever persists after 48 hours, urine analysis and other tests need to be carried out. Toxemia should be assessed using clinical clues such as altered mental status, poor eye contact, inappropriate response to stimuli, abnormal vital signs, poor skin perfusion, cyanosis and grunting.

A single CRP level is neither sensitive nor specific enough to identify SBI in children. However, a raised CRP suggests the need for further assessment. CRP levels that persist or continue to rise after 48 hrs of antibiotic therapy indicate treatment failure.[21] In infants with suspected neonatal sepsis, two CRP measurements of 24 h apart and having values <10 mg/L are useful in excluding sepsis.[22]

Procalcitonin should not be used as a 'rule-out' test for sepsis, suspected SBI or invasive bacterial infections (IBI) in febrile infants and children. Although it can aid in decision-making, a low serum procalcitonin does not exclude the possibility of bacterial meningitis or bacteremia. A raised serum procalcitonin level (>0.3 ng/mL) may therefore be useful to support a diagnosis of suspected IBI with a good level of sensitivity.[23]

Summary

- Parent education on fever should be routinely carried out routinely in office practice.
- Treating fever without thermometer readings is unscientific.
- Parents should be educated that the cause of fever is a concern rather than fever per se.
- Paracetamol is comparatively safer as pediatric antipyretic medication, even though avoidable errors continue to occur in dosage.
- Adequate lab/clinical investigations need to be carried out, prior to prescribing antibiotics, in infants with fever without focus.
- Triaging the fever in pediatric patients based on the following queries assist in effective management:
    - Whether the fever is serious?
    - Whether lab tests are required?
    - Whether the child should be admitted or treated as outpatient?
    - Whether antibiotic should be prescribed?

References

1. *Osler W. The study of the fevers of the south. JAMA. 1896 May 23;XXVI(21):999–1004.*
2. *Osilla EV, Sharma S. Physiology, Temperature Regulation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Dec 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507838/*
3. *Measuring body temperature in babies and young children [Internet]. [cited 2019 Dec 24]. Available from: https://www.healthprofessionalacademy.co.uk/docs/default-source/clinical-reviews/measuring-body-temperature-review.pdf?sfvrsn=86121622_2*
4. *Batra P, Saha A, Faridi MM. Thermometry in children. J Emerg Trauma Shock. 2012 Jul;5(3):246-9*
5. *Harrison's Manual of Medicine, 19e | AccessMedicine | McGraw-Hill Medical [Internet]. [cited 2019 Dec 24]. Available from: https://accessmedicine.mhmedical.com/book.aspx?bookID=1820*
6. *Fever that precious ally. [Internet]. [cited 2019 Dec 24]. Available from: http://www.oplelibrary.com/Handler/downloadDocument.ashx?fId=12917*
7. *Teng CL, Ng CJ, Nik-Sherina H, Zailinawati AH, Tong SF. The accuracy of mother's touch to detect fever in children: a systematic review. J Trop Pediatr. 2008 Feb;54(1):70–3.*
8. *Van den Bruel A, Aertgeerts B, Bruyninckx R, Aerts M, Buntinx F. Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary care. Br J Gen Pract. 2007 Jul 1;57(540):538–46.*
9. *Nijman RG, Vergouwe Y, Thompson M, van Veen M, van Meurs AHJ, van der Lei J, et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ. 2013 Apr 2;346:f1706.*
10. *Kluger MJ. Fever in acute disease--beneficial or harmful? Wien Klin Wochenschr. 2002 Feb 15;114(3):73–5.*
11. *Fever in under 5s: assessment and initial management | Guidance | NICE [Internet]. [cited 2019 Dec 24]. Available from: https://www.nice.org.uk/guidance/cg160*
12. *Hegland A. Pediatric acetaminophen solid products transitioning to single strength. AAP News [Internet]. 2019 Dec 23 [cited 2019 Dec 24]; Available from: https://www.aappublications.org/news/2017/03/10/Acetaminophen031017*
13. *Lakshmi.M, Radhika. R.Analysis of Acetaminophen Toxicity in Children in a Tertiary Care Setting Indian Journal of Trauma and Emergency Pediatrics.vol.5 No1.2013*
14. *Balasubramanian S, Ramesh V. Paracetamol--high strength formulations and toxicity. Indian Pediatr. 2014 Oct;51(10):839.*
15. *A Kader, T Hildebrandt, C Powell. How safe is ibuprofen in febrile asthmatic children? Arch Dis Child 2004;89:881–886*
16. *Balasubramanian S, Sumanth A. Mefanamic acid-role as antipyretic. Indian pediatrics. 2010. 47:453*
17. *Barbi E, Marzuillo P, Neri E, Naviglio S, Krauss BS. Fever in Children: Pearls and Pitfalls. Children (Basel). 2017 Sep; 4(9): 81.*
18. *Havinga W. NICE guidelines on fever in children. Br J Gen Pract. 2007 Oct 1;57(543):835.*
19. *Nelson Textbook of Pediatrics, 2-Volume Set - 21st Edition [Internet]. [cited 2019 Dec 24]. Available from: https://www.elsevier.com/books/nelson-textbook-of-pediatrics-2-volume-set/kliegman/978-0-323-52950-1*
20. *Niehues T. The Febrile Child: Diagnosis and Treatment. Dtsch Arztebl Int. 2013 Nov;110(45):764–74.*
21. *McWilliam S, Riordan A. How to use: C-reactive protein. Arch Dis Child Educ Pract Ed. 2010 Apr;95(2):55–8.*
22. *Beltempo M, Viel-Thériault I, Thibeault R, Julien A-S, Piedboeuf B. C-reactive protein for late-onset sepsis diagnosis in very low birth weight infants. BMC Pediatr. 2018 30;18(1):16.*
23. *Robinson P, De SK. How to use. Procalcitonin. Arch Dis Child Educ Pract Ed. 2018;103(5):257–62.*

Surveillance of fever with rash; on the path towards measles and rubella elimination

Dr. Asish Kumar Satapathy
Regional Team Leader-South
WHO Country Office for India (NPSP), Bangalore

Introduction

Measles is one of the leading causes of death among young children, even though a safe and cost-effective vaccine is available. As per available data in 2015, 1.35 lakh measles deaths occurred globally, about 367 deaths every day or 15 deaths every hour.[1] Measles vaccination resulted in a 79% drop in measles deaths between 2000 and 2015 worldwide. There is a resurgence of measles in various regions of the world including United States, Venezuela, Brazil, Ukraine, Yemen, Madagascar, France, Thailand, Sudan, Serbia and Philippines.[2]

Measles-Rubella (MR) elimination

Background

The total population of WHO South-East Asia region (SEAR) is estimated to be around 1.8 billion with an annual birth cohort of over 37 million.[3] In September 2013, all countries of SEAR adopted the goal of measles elimination and rubella/ congenital rubella syndrome (CRS) control by 2020.[4]

Target for 2020 is to achieve 95% reduction in rubella and CRS cases, as compared to 2008 baseline. It is also aimed at achieving the absence of endemic measles transmission for ≥12 months in the presence of a well-performing surveillance system.[5]

Strategic objectives

The following strategic plan has been developed to achieve the elimination of measles and control of rubella/ CRS in SEAR:

1. Immunization: 95% coverage with two doses of measles- and rubella-containing vaccine (MRCV).
2. Surveillance: Sensitive, case-based MR surveillance where the non-measles and non-rubella discarded rate should be >2 for 100 thousand population.
3. Laboratory network should be WHO accredited and meet the global standards.
4. Support and linkages with other child life programs for advocacy, mobilization and outbreak preparedness and response, measles in emergency, and research and development.

Regional progress

The regional progress in the SEAR from the year 2000 to 2018 for measles shows that the overall coverage in this region for MCV1 was 86% and MCV2 was 69%. In India, the respective rates were 82% and 70-72%.[5] The coverage of regional progress in the SEAR from the year 2005-2018 for rubella cases was around 85%, and in India, it was a little lower (70%). Additionally, the case load also came down to around 4000-4500 cases/year by the end of 2018.

India and Indonesia contribute the highest with regard to the number of under-vaccinated children for measles in SEAR. The missing rates of MCV1 and MCV2 dosages in India and Indonesia were 2.9 million and 1.2 million.[7]

The key surveillance indicators for eradication are non-measles and non-rubella discard rates, which should be >2 per 100,000 population. However, it is concerning to note that India and the overall SEAR have discard rates of 0.46 and 0.87 respectively till 2018, which is <2. However, 5 countries (Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste) of SEAR have been successful in eliminating the indigenous measles transmission. Moreover, 6 SEAR countries (Bangladesh, Bhutan, Maldives, Nepal, Sri Lanka and Timor-Leste) have controlled rubella/CRS. In the 72nd session of the WHO regional committee for SEAR meeting, the goal of 'measles and rubella elimination by 2023' has been revised and a draft on 'strategic plan to achieve and maintain measles and rubella has been prepared.[8]

MR surveillance

Measles is an acute viral infection that spreads through respiratory secretions or aerosols. The classic manifestations include maculopapular rash, fever, cough, coryza or conjunctivitis and Koplik's spot.[8] Complications and mortality are mostly seen in children <2 years and in adults. The case fatality ratio (CFR) ranges between 0.1%-10%.[9] In emergency situations like floods, the CFR may rise even more. The mortality associated with measles is high due to complications such as corneal scarring (causing blindness), encephalitis, pneumonia and diarrhea due to secondary infections.[10]

On the other hand, rubella is a mild, self-limiting viral disease and CRS may result in spontaneous abortion, still birth and serious birth defects. Hence, it is a public health concern owing to the teratogenic potential. High CRS burden is seen in countries not using rubella vaccine. The various complications of rubella include lymphadenopathy, arthritis, thrombocytopenic purpura, Forchheimer spots (petechiae on the soft palate), and encephalitis. The complications associated with CRS include hearing impairment, cataracts/ glaucoma, heart defects, microcephaly, developmental delay, mental retardation, hematological disorder, and liver and spleen damage.[11] A good surveillance system will helpfast track the elimination of measles and rubella from the SEAR.

Evolution over the past years

MR surveillance in India uses acute flaccid paralysis surveillance platform for strengthening MR reporting. It is supported by the WHO accredited laboratory network. It involves investigation of suspected measles cases and outbreaks and detection of areas of transmission. It generates evidence on age distribution, immunization status and other indicators. It helps in identifying under-immunized areas and inform policy decisions. MR surveillance started in 2005 in Tamil Nadu and gradually expanded to other South-Indian states. By 2015, every state of the country was performing MR surveillance.[12] The history of the surveillance system is depicted in Fig. 1.

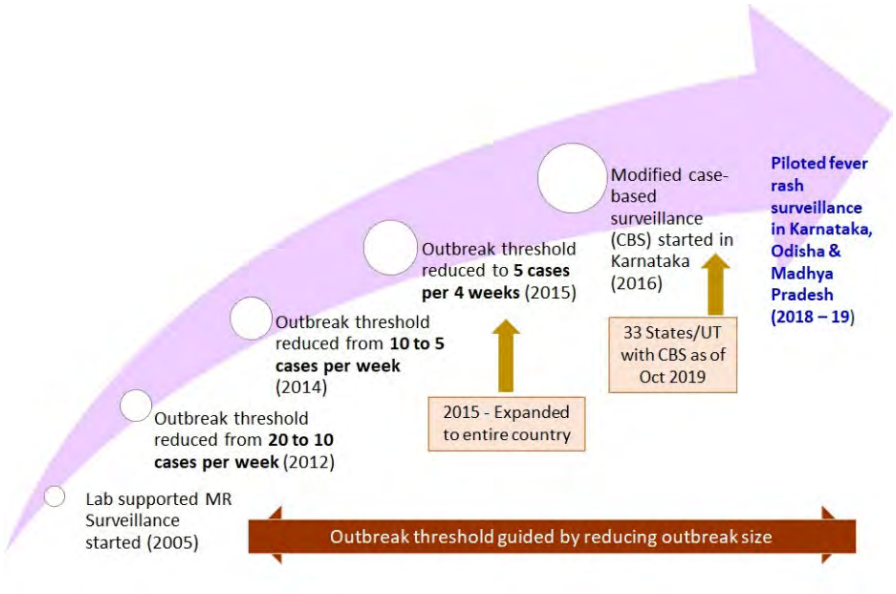


Fig.1: The history of the surveillance system

In 2005, the lab-supported MR surveillance system in India was purely an outbreak-based surveillance system. However, by 2015, the outbreak threshold reduced to 5 cases per 4 weeks. The case-based surveillance pilot started in Karnataka in 2016, now majority of states in India have shifted to CBS system. Presently, a pilot of fever rash surveillance has been started in Karnataka, Odisha and Madhya Pradesh.[13]

Case definition and protocol

Case definition- Any person with fever and maculopapular rash with cough or coryza (running nose) or conjunctivitis (red eyes) or any person in whom a clinician suspects measles/rubella infection.

Once any suspected case arrives, it is investigated by the trained medical officer and a case investigation form is filled. The samples are collected subsequently. Serum samples of 0.5 ml are collected, maintained in a cold chain and send to the WHO-accredited lab for classification. If it is

reported within 7 days of onset of rash, then throat swabs or urine samples are also collected for doing a culture to identify the genotype of measles detected.[14-15] The figure 2 represents the modified case-based MR surveillance algorithm.

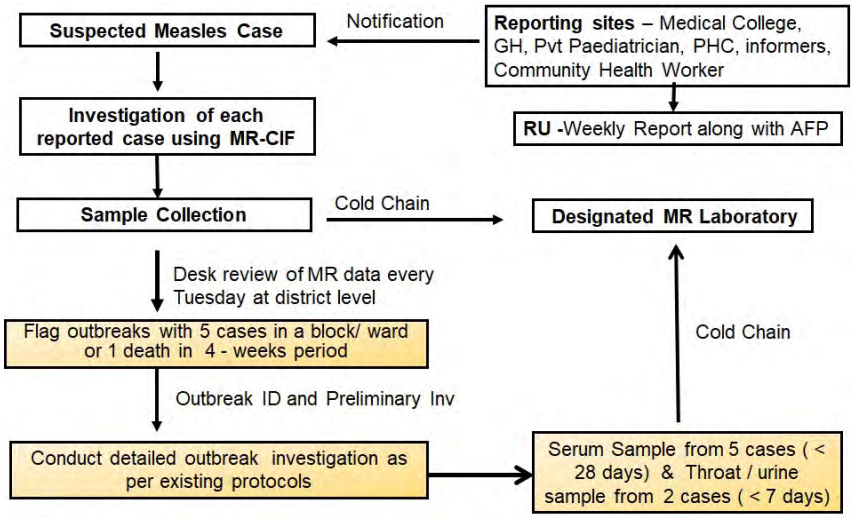


Fig.2: The modified case-based MR surveillance algorithm

The serum samples are first tested for measles, and negative ones are checked for rubella. If it is negative again, it is tested for dengue, chikungunya and scrub typhus in states piloting fever rash surveillance.

Measles and Rubella surveillance

In India, a total of 52308 suspected cases of measles were reported in 2018 and 24136 in 2019 through the ongoing outbreak and case based surveillance. The corresponding lab-confirmed outbreaks of measles reported in the country in 2017, 2018 and 2019 were 717, 952, and 206. The overall lab-confirmed cases for measles and rubella reported in 2018 and 2019 were 19064 and 6421, and 2306 and 2664 respectively. It is evident from the available surveillance data that both measles and rubella mostly affect children less than 15 years of age. The most prevalent genotype of rubella seen in India is 2B and for measles, it is B3, D4 and D8. The non-measles non-rubella discard rate has improved from last year; and, intensification process is in progress.

Karnataka experience

After the introduction of the fever and rash surveillance system in Karnataka, there is increase in the number of cases reported (Fig. 3). As more non-measles non-rubella cases get reported, the discard rate will increase to >2 cases per 100,000 population. As per available data In Karnataka, only 16% of fever cases are due to measles and 7% due to rubella, 8% dengue, 16% chikungunya and 3% scrub typhus. The implementation of fever rash surveillance from Jan 2019 onwards in Karnataka, along with concerted efforts to increase the vaccination coverage with MR vaccine will accelerate progress towards elimination of measles and rubella.

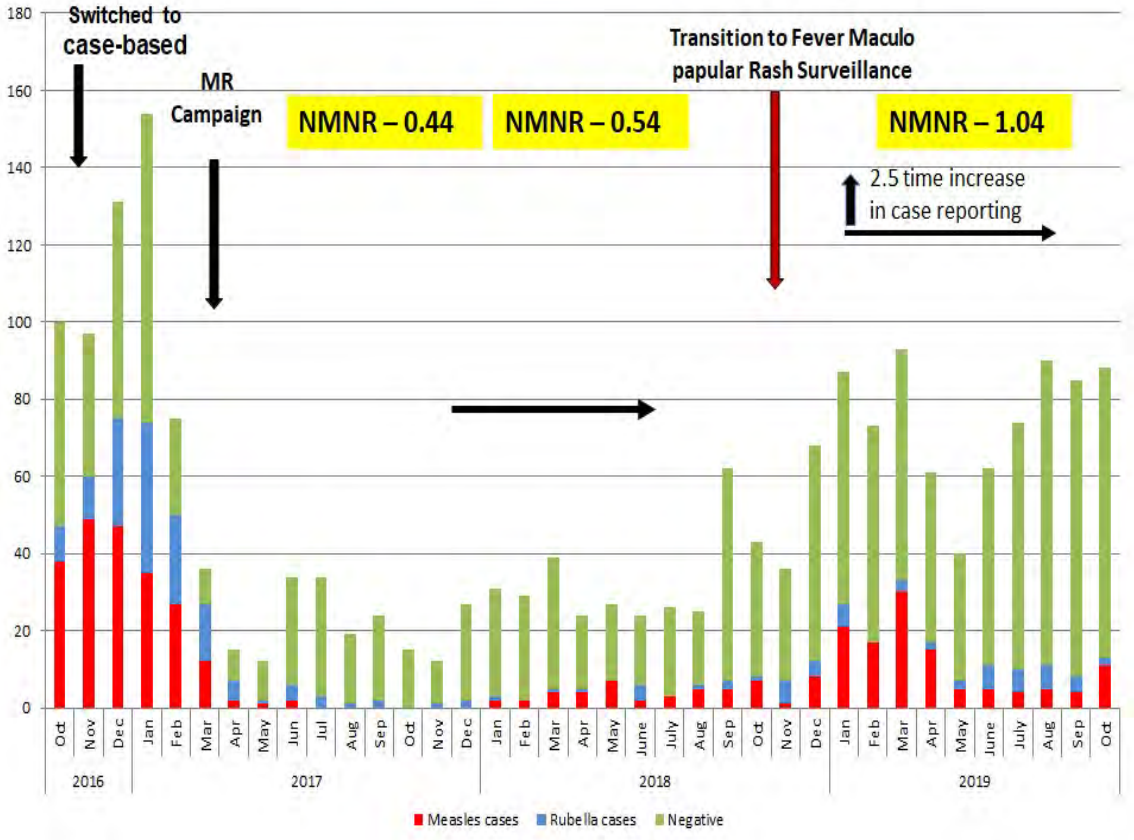


Fig. 3: Fever and rash surveillance system in Karnataka

Way forward

India has committed to the SEAR goal of MR elimination by 2023. Recent efforts to improve population immunity through wide age range vaccination campaign with MR vaccine is a step in the right direction. Efforts have been intensified to improve MR surveillance sensitivity by the phased transitioning to modified case-based surveillance. However, non-measles non-rubella discard rate remains sub-optimal at national and sub-national levels. Evidence generated from the piloting of fever rash MR surveillance in the state of Karnataka (and other states) will guide policy decisions at the national level. Strategies and efforts required to eliminate measles will help to get rid of rubella. Global experience has shown that rubella is much easier to eliminate than measles.

References

1. *Measles [Internet]. WHO | Regional Office for Africa. [cited 2019 Dec 3]. Available from: https://www.afro.who.int/health-topics/measles*
2. *Alarming global surge of measles cases a growing threat to children – UNICEF [Internet]. [cited 2019 Dec 3]. Available from: https://www.unicef.org/press-releases/alarming-global-surge-measles-cases-growing-threat-children-unicef-0*
3. *Dhillon PK, Jeemon P, Arora NK, Mathur P, Maskey M, Sukirna RD, et al. Status of epidemiology in the WHO South-East Asia region: burden of disease, determinants of health and epidemiological research, workforce and training capacity. Int J Epidemiol. 2012 Jun;41(3): 847–60.*
4. *World Health Organization, editor. Strategic plan for measles elimination and rubella and congenital rubella syndrome control in the South-East Asia region, 2014-2020. New Delhi: World Health Organization, Regional Office for South-East Asia; 2015. 77 p.*
5. *Patel MK, Dumolard L, Nedelec Y, Sodha SV, Steulet C, Gacic-Dobo M et al. Progress Toward Regional Measles Elimination - Worldwide, 2000-2018 MMWR Morb Mortal Wkly Rep. 2019 Dec 6;68(48):1105-1111.*
6. *3_Measles_and_Rubella_Regional_Progress_Updates.pdf [Internet]. [cited 2019 Dec 3]. Available from: https://www.who.int/immunization/sage/meetings/2016/october/3_Measles_and_Rubella_Regional_Progress_Updates.pdf*
7. *3_GVAP_SecReport2017.pdf [Internet]. [cited 2019 Dec 3]. Available from: https://www.who.int/immunization/sage/meetings/2017/october/3_GVAP_SecReport2017.pdf*
8. *Eliminating measles and rubella - Framework for the verification process in the WHO European Region. :28. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/247356/Eliminating-measles-and-rubella-Framework-for-the-verification-process-in-the-WHO-European-Region.pdf*
9. *Kondamudi NP, Waymack JR. Measles. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Dec 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK448068/*
10. *Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. International Journal of Epidemiology. 2009 Feb 1;38(1):192–205.*
11. *Perry RT, Halsey NA. The Clinical Significance of Measles: A Review. J Infect Dis. 2004 May 1;189(Supplement_1):S4–16.*
12. *Wassilak SGF, Williams CL, Murrill CS, Dahl BA, Ohuabunwo C, Tangermann RH. Using Acute Flaccid Paralysis Surveillance as a Platform for Vaccine-Preventable Disease Surveillance. J Infect Dis. 2017 Jul 1;216(Suppl 1):S293–8.*
13. *Shrivastava SR, Shrivastava PS, Ramasamy J. Measles in India: Challenges & recent developments. Infect Ecol Epidemiol [Internet]. 2015 May 25 [cited 2019 Dec 19];5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444763/*
14. *Measles | Specimen Collection, Storage, and Shipment | Lab Tools | CDC [Internet]. 2019 [cited 2019 Dec 19]. Available from: https://www.cdc.gov/measles/lab-tools/rt-pcr.html*
15. *Rubella | Specimen Collection, Storage and Shipment | CDC [Internet]. 2019 [cited 2019 Dec 19]. Available from: https://www.cdc.gov/rubella/lab/specimen-collection-shipment.html*

Causes of Fever in Healthcare professionals

Dr. Pratik Patil
MBBS, DNB (General Medicine), FNB (Infectious Diseases)
Consultant, Infectious Diseases
Fortis Hospitals

Background

Healthcare workers (HCWs) possess an increased risk for contracting infectious diseases. The excess death rate in US researchers due to occupation-specific infections is estimated to be around 9-29 per one million HCWs.[1] The famous WHO physician Dr. Carlo Urbani, who had identified SARS as a dangerously contagious disease, died contracting the same disease at the age of 46. During the SARS outbreak, out of the 8,096 individuals affected globally, 21% were HCWs.[2] In the recent Nipah outbreak happened in Kerala, 3 out of 23 cases were HCWs; and the mortality reported among HCW was 2 out of 21.

In order to protect the HCWs, the Needlestick Safety and Prevention Act (NSPA) was enacted in the USA in 2000. In 2007, the WHO developed the Global plan of action on Workers' Health. In India, new biomedical waste management rules have been established in 2016, which mandates the reporting of needlestick injuries (NSI). An amendment to these rules has been published in 2018. The Joint Commission International (JCI) and the National Accreditation Board for Hospitals & Healthcare Providers (NABH) accreditations mandate reporting of both NSI as well as blood and body fluid exposure.

Fever in HCW can be either due to community-acquired infections or occupational infections.

Occupational infections (OI)

Occupational infections mainly include blood-borne infections, droplet/ air-borne infections, infections spread by contact transmission and vector-borne infections. Blood-borne infections are caused mainly through blood and body fluid exposure and NSI. The blood-borne viruses include HIV, HBV, HCV. Nipah, Ebola and Marburg are spread by close contact with host through body fluids, respiratory droplets. Other common droplet/air-borne infections include diseases like TB, varicella and influenza-like illness including influenza, MERS-CoV and SARS. Contact transmission in HCWs happens through direct contact with patients suffering from infections caused by H. influenza, Methicillin-resistant Staphylococcus aureus (MRSA) and Gram-negative bacilli (GNB). Whereas, vector-borne infections like dengue may or may not be occupational.

Blood-borne viral infections: Diagnosis and prevention

The average risks of transmission of HIV, HCV and HBV following NSI are 0.3%, 1.8% and 18% respectively. Risk factors for HIV seroconversion includes deep injury, injury by device with visible blood contamination, NSI, and terminal illness in the source.[3]

HBV can also be transmitted in the absence of visible blood and remains infectious on environmental surfaces for at least 7 days. If the source is both HBsAg and HBeAg positive, then almost 1/3rd of the patients may develop clinical hepatitis and the remaining 2/3rd may show seroconversion to HBV (i.e., HBsAg positive). Whereas, if source is HBsAg positive and HBeAg is negative, then only 1-6% may develop clinical hepatitis and around 1/3rd of the patients may show seroconversion to HBV in future.

The acute infections with HBV and HCV usually present with symptoms of acute viral hepatitis (fever, anorexia); whereas, detection of chronic hepatitis may be incidental and may progress to liver cirrhosis, which can be first clinical presentation. The incubation period for hepatitis B is 30-180 days and hepatitis C is 15-160 days. The acute HBV infection can be easily diagnosed in patients with clinical features, as both HBsAg and HBV DNA may appear positive simultaneously. Whereas, for HCV infection, only HCV RNA may appear positive initially and not anti-HCV antibodies (detectable within 12 weeks).

HIV may have an acute HIV syndrome/acute retroviral syndrome after initial transmission and 10 to 60% may remain asymptomatic. The common symptoms of acute HIV syndrome include fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, diarrhea, weight loss, and headache. The incubation period is 3 to 6 weeks. However, some patients may not show any initial manifestations and progress to advanced HIV after 8-10 years of acute infection and may present with opportunistic infections. The diagnostic test to check the HIV positivity depends on the approximate time since infection (Fig. 1). If ELISA is performed, it is better to perform the 4th generation test, as IgM, IgG antibody and p24 antigen positivity are seen within 15-20 days from time to positivity. Western blot is not required for confirmation as per recent recommendations. The HIV viral load test/ PCR is also not recommended for diagonisis of HIV.

Fig. 1: Time to positivity for HIV tests

Time to positivity of HIV diagnostic tests

Test	Target of detection	Approximate time to positivity (days)
Enzyme-linked immunoassay		
First generation	IgG antibody	35 to 45
Second generation	IgG antibody	25 to 35
Third generation	IgM and IgG antibody	20 to 30
Fourth generation	IgM and IgG antibody and p24 antigen	15 to 20
Western blot		
	IgM and IgG antibody	35 to 50 (indeterminate)
		45 to 60 (positive)
HIV viral load test		
Sensitivity cutoff 50 copies/mL	RNA	10 to 15
Ultrasensitive cutoff 1 to 5 copies/mL	RNA	5

Source: UpToDate-*last accessed on 10th Nov. 2019*

Timely Hep B immunoglobulin and vaccination are effective by >90% in preventing transmission. Initiation of post-exposure prophylaxis (PEP) within 24 hours for HIV reduces the risk to almost zero. If the source patient was HIV positive, then one should perform follow-up testing after 3 months and 4th generation ELISA testing should be used. If 3rd generation testing is used, then repeat testing at 6 months after the exposure is recommended. If the source patient was HBsAg positive or if the status could not be obtained, one should perform follow-up testing with anti-HBc and HBsAg six months after the exposure. If the initial anti-HCV returns negative, HCW should have HCV RNA testing at least 3 weeks after the exposure. Alternatively, anti-HCV testing can be performed at least 6 months after the exposure, and HCV RNA testing can be performed if positive.

Tuberculosis (TB)

HCW are at increased risk of tuberculosis than normal population. The meta-analysis by Menzies et al. have stated that the median annual incidence of TB infection among HCW was 5.8% (0–11%) in low to middle-income countries and 1.1% (0.2–12%) in high income countries. Rates of active TB in HCWs were consistently higher when compared to the general population in all countries.[2]

Occupational risk factors for contracting TB infection include working in internal or respiratory

medicine department, and more years of work in healthcare. Direct indicators of TB exposure include TB admissions and the percentage of patients with TB. The risk is highest if there are higher number of cases with poor infection control, and low when there are few TB patients or pediatric TB patients, or a moderate number of cases, but adequate infection control measures.[5]

Influenza

Influenza-like illness is the most common infection contracted by HCW and the symptoms mainly include fever, cough, sore throat, running nose and myalgia with history of contact.

Chemoprophylaxis should not be given to asymptomatic healthy adults. Chemoprophylaxis should be given to persons who are at high risk of complications associated with influenza. They include children <5 years of age (especially <2 years), adults aged ≥65 years, persons with immunosuppression (including HIV infected persons), chronic pulmonary, cardiac, hepatic, rena, hematological conditions and metabolic disorders, pregnant women, persons with extreme obesity and residents of nursing homes and chronic care facilities. Chemoprophylaxis, when indicated, should be given as soon as possible after exposure, ideally within 48 hours of exposure (A-III). Moreover, once daily post-exposure antiviral chemoprophylaxis should not be administrated if >48 hours has elapsed since exposure.

The infection control measures to be taken in the hospital include droplet and contact precautions, which include providing private room or isolating the patient at risk/carrying the infection, use of surgical mask/gloves by HCW, hand hygiene and continuing the precautionary measures for 7 days or for 24h after resolution of fever and respiratory symptoms. Children and immune compromised need isolation for longer period.

Air-borne precautions (negative pressure rooms, N95 masks etc.) are not routinely needed. However, N95 mask should be worn by those performing bronchoscopy, tracheal suctioning and intubation. It should be discarded immediately during the following scenarios: after aerosol generating procedures; contaminated with blood, respiratory or nasal secretions, or other bodily fluids from patients, and during close contact with, or exit from, the care area of any patient co-infected with an infectious disease requiring contact precautions. The manufacturer's maximum number of donning should be followed (up to five if the manufacturer does not provide a recommendation). Hand hygiene with soap and water or an alcohol-based hand sanitizer should be performed before and after touching or adjusting the respirator. N95 respirator is not a one-time use device and can be used as long as a good seal is ensured. The mask should be labelled on the strap and it should not be bent, crushed or mutilated. It should be kept clean in a ziplock bag and the original shape should be maintained to ensure that the respirator can be worn multiple times.

Varicella

It is not a very common infection affecting the HCW. The symptoms include fever and generalized vesicular rash with centripetal distribution. Acyclovir/valacyclovir is generally used for treatment. PEP include vaccination of the non-immune healthy non-pregnant hosts and administration of immunoglobulins to immunocompromised patients, persons with neoplastic disease, persons on immunosuppressive therapies, neonates and pregnant women with significant exposure (household contact). Additionally, in the absence of both VariZIG and IVIG, some experts recommend prophylaxis with acyclovir for people without evidence of immunity against varicella and with contraindications for varicella vaccination. However, it is not indicated for routine pre-emptive use among healthy children, adolescents and adults after exposure to varicella.[7]

MRSA

It is a bacterial infection, which is not very common in India. It causes purulent skin and soft tissue infections, pneumonia, bacteremia, osteomyelitis and endocarditis. Safdar et al. have concluded that nasal carriage of S. aureus has been associated with an increased risk of infection for the colonized individual.6 Albrich et al. have shown that approximately 5% of colonized HCWs develop clinical infections. In addition, symptomatic MRSA infections among HCWs have been described in several case reports.[6] MRSA screening is not routinely recommended. However, it should be conducted during epidemiological outbreaks and after each contact with MRSA-positive patients.

Infections due to Gram Negative Bacteria (GNB)

No data are available regarding Occuptional infections due to GNB in HCW. But infections with multidrug-resistant GNB are more common in patients who are initially colonized with the organism.

Dengue

There have been rare reports of dengue virus transmission via the mucosal route, vertical transmission during the intrapartum period and transmission via blood transfusion.10-12 A study conducted at Thammasat University Hospital has reported an attack rate of 13 cases per 1000 HCWs, compared to an incidence of 6.3–13.1 cases per 100,000 population in Thailand. Four-pronged vector-control program involving restriction of water sources, use of insecticides in standing water sources, field-based insecticide applications on the hospital grounds, and ongoing active surveillance was performed for 2 years within the hospital. After the implementation of this control program, there were no cases of dengue virus infection in HCWs (attack rate, 0 cases per 1000 HCWs; P<.001), although the regional incidence of dengue virus infection remained constant.[13]

Prevention

Standard precautions (hand hygiene, PPE) should be ensured to prevent infections among HCWs. Specific transmission-based precautions (droplet, airborne, contact precautions) for infections like TB, MRSA, influenza, etc. should be followed. Vaccination for hepatitis B, influenza, and varicella should be given. NSI/blood body fluid exposure reporting should be strengthened, and appropriate PEP should be followed.

Take home message

Occupational infections are common in HCW and can be life threatening. Most common infections include influenza-like illness, HBV, HIV, HCV, and TB. They can be easily prevented by following standard precautions; appropriate use of personal protective equipment (PPE); transmission-based precautions; appropriate handling of sharps; vaccination against HBV, influenza, and varicella; appropriate follow-up for early diagnosis to prevent advanced infection; and MRSA screening and decolonization.

References

1. *Nienhaus A. Infections in Healthcare Workers in Germany—22-Year Time Trends. International Journal of Environmental Research and Public Health. 2018 Dec;15(12):2656.*
2. *Johnston LB, Conly JM. Severe acute respiratory syndrome: What have we learned two years later? Can J Infect Dis Med Microbiol. 2004;15(6):309–12.*
3. *Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med. 1997 Nov 20;337(21):1485–90.*
4. *Centers for Disease Control and Prevention (U.S.), Bernard M. B, Association of Public Health Laboratorie, S. Michele O, Laura G. W, Berry B, et al. Laboratory testing for the diagnosis of HIV infection : updated recommendations [Internet]. Centers for Disease Control and Prevention; 2014 Jun [cited 2019 Dec 18]. Available from:* http://stacks.cdc.gov/view/cdc/23447
5. *Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis. 2007 Jun;11(6):593–605.*
6. *Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis. 2019 Mar 5;68(6):e1–47.*
7. *Varicella (Chickenpox) - Chapter 4 - 2020 Yellow Book | Travelers' Health | CDC [Internet]. [cited 2019 Dec 4]. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/varicella-chickenpox*
8. *Safdar N, Bradley EA. The risk of infection after nasal colonization with Staphylococcus aureus. Am J Med. 2008 Apr;121(4):310–5.*
9. *Albrich WC, Harbarth S. Health-care workers: source, vector, or victim of MRSA? Lancet Infect Dis. 2008 May;8(5):289–301.*
10. *Kuno G. Dengue transmission without involvement of mosquito vector. Clin Infect Dis. 2005 Mar 1;40(5):774–5.*
11. *de Wazières B, Gil H, Vuitton DA, Dupond JL. Nosocomial transmission of dengue from a needlestick injury. Lancet. 1998 Feb 14;351(9101):498.*
12. *Chye JK, Lim CT, Ng KB, Lim JMH, George R, Lam SK. Vertical Transmission of Dengue. Clin Infect Dis. 1997 Dec 1;25(6):1374–7.*
13. *Apisarnthanarak A, Mundy LM. Is dengue virus infection an occupational health problem? Clin Infect Dis. 2009 Jan 1;48(1):135–7.*

Update on tropical fevers

Prof. Bibhuti Saha

Head, Department of Tropical Medicine
Dean of students' affairs
School of Tropical Medicine, Kolkata

Introduction

Tropical fevers are defined as infections prevalent in and unique to tropical and subtropical regions. Some of these occur throughout the year and some are seasonal. Dengue, malaria, rickettsial infections/scrub typhus, typhoid, Leptospirosis, and influenza are some of the important tropical fevers.

Typhoid

Enteric fever (typhoid) is the commonest bacterial bloodstream infection in South Asia. It is caused by *Salmonella enterica* serovars *Typhi* and *Paratyphi A*. The incidence is estimated to be over 100 per 100,000 population. Around 7 million people are affected every year in South Asia and the mortality is around 75,000.[1] The mortality from untreated typhoid has been estimated to be ≥10%. It can develop into life-threatening complications such as intestinal perforation, gastrointestinal bleeding, and less commonly, encephalopathy and shock. Inadequate treatment can cause relapse and chronic fecal carriage. The various diagnostic tests for typhoid include blood culture, Widal test, Typhidot M, Typhirapid IgM and IgG IgM(combo) and Tubex TF. The specificity and sensitivity noted for these tests are listed in table 1.[2]

Table 1: Sensitivity and specificity of various tests used for typhoid diagnosis

Diagnostic Tests	Principle	Sensitivity	Specificity
Non-immunodiagnostic Methods			
Blood Culture	Based on the ability of viable cell to grow on culture medium	15.38–51.8%	100%
Stool Culture		<50%	93%
PCR (without enrichment in blood culture)	Relies on amplification of gene of interest	90–100%	100%
Immunodiagnostic Methods			
TPTest	Measures *S.* Typhi membrane preparation (MP)-specific IgA responses in peripheral blood mononuclear cell culture secretions	96.0%	96.6%
Tube Widal	Measures agglutinating antibodies against O and H antigens of *Salmonella* Typhi and *Salmonella* Paratyphi A; uses a tube or slide	65.38%	89.83%
Typhidot	Measures IgM and IgG antibodies against a 50-kDa outer membrane protein of *Salmonella* Typhi in an immunodot test format	67–98%	58–100%
Typhidot M	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of *Salmonella* Typhi in a dot blot format	47–98%	65–93%
TyphiRapid IgM and IgG IgM (Combo)	Measures IgM antibodies, after removal of IgG antibodies, against a 50-kDa outer membrane protein of *Salmonella* Typhi in an ICT LFA*a* cassette format	89–100%	85–89%
Tubex TF	Detects antibody against *Salmonella* Typhi LPS with an inhibition assay format and a visual result readout	56–100%	58–100%
Enterocheck-WB	Dipstick detecting anti-LPS IgM antibodies	89%	97%
Multi-Test-Dip-S-Ticks	Dipstick detecting anti-LPS IgG and IgM	89%	53%
PanBio	ELISA detecting anti-LPS IgG and IgM	78%	80%

Blood culture is considered as gold standard for diagnosis with suboptimal sensitivity and the test requires reliable laboratory facilities. The sensitivity increases from 51% to 65% with increase in specimen volume from 2 ml to 10 ml. Previous antimicrobial use and specimen collection beyond first week reduced sensitivity by 30%.[1] Widal test shows cross reactivity with other infectious agents resulting in false positive results and over diagnosis of typhoid fever.[3] Rapid diagnostic tests like TUBEX, Typhidot and KIT test are currently used in practice. But a Cochrane review in 2017 stated that current tests are not sufficiently accurate to replace blood culture as a diagnostic test for enteric fever.[4]

First antimicrobial resistance reports of chloramphenicol in *S. Typhi* was reported in the 1970s. Multidrug resistance (resistance to chloramphenicol, amoxicillin, and co-trimoxazole) was found in many areas of South Asia. This was associated with numerous outbreaks in the late 1980s and

early 1990s. Subsequently, fluroquinolones emerged as the treatment of choice. Widespread use of quinolones led to decreased susceptibility of organisms across the Indian subcontinent.[5] After 2010, complete fluoroquinolone resistance, including resistance to the newer generation fluoroquinolone, gatifloxacin, has emerged and has been associated with treatment failures and prolonged fever.[6] Recent data from Pakistan, published as part of the surveillance for enteric fever in Asia project (SEAP), has shown that over half of all *S. Typhi* isolates were multidrug resistant. The fluoroquinolone resistance was noted in nearly 90% of *S. Typhi* and *S. Paratyphi* isolates.[7] A longitudinal study of typhoid fever trends at three large hospitals in India showed a fall in resistance rates for ampicillin, chloramphenicol, and co-trimoxazole between 2000 and 2014; as resistance to more widely used antibiotics has increased.[8] Near universal resistance to ciprofloxacin has been observed in recent isolates from India.[9]

Although azithromycin remains an effective oral option, there is concern about potential emergence of resistant strains. Third generation cephalosporins such as ceftriaxone and cefixime are increasingly used, with recent reports showing very low resistance to these drugs. Since 2016, outbreaks of *S. Typhi* strains that are resistant to ceftriaxone and cefixime have been reported in parts of Pakistan.[10-11]

Short fever clearance time and low relapse rate have been reported with oral azithromycin, and it may be an effective treatment. Third generation cephalosporins (parenteral ceftriaxone and oral cefixime) are reliable choice for suspected typhoid, particularly in regions with known resistance, due to the absence of resistance against *S. Typhi* and *S. Paratyphi*.[12] Potential antimicrobials for extensively drug resistant strains, include piperacillin-tazobactam, ceftazidime- avibactam, carbapenems (such as meropenem, imipenem, or ertapenem), tigecycline, fosfomycin, and colistin (limited experience and evidence). The ICMR guidelines for managing typhoid fever are provided in table 2.

Table 2: The ICMR guidelines for managing typhoid fever

	Type of disease	Organisms	Initial Treatment/ Preferred	Alternatives	Comments
1	Typhoid fever	*Salmonella* Typhi, *Salmonella* Paratyphi A	Oral: co-trimoxazole (1ds tab bd) or azithromycin (10 mg/kg/day) Parenteral: ceftriaxone 2 g IV od	Cefixime (20 mg/kg/day) or chloramphenicol 500 mg qid or ciprofloxacin 750 mg bd	Change empiric regimen based on susceptibility testing. Duration of treatment: 10-14 days.

Approximately 2-5% of patients progress to a state of carriage within one year of recovery, instead of complete elimination of the infection.[13] The permissive niche in humans is primarily the biliary tract and gallbladder. Salmonella persists in biofilms on gallstones and the gallbladder epithelium.

The shedding of bacilli post-infection through faeces occurs between 3 weeks to 3 months in convalescent carriers, 3 to 12 months in temporary carriers, and > 1 year in chronic carriers. Standard practice is followed for examining serial stool and urine samples. Anti-Vi antibody may be present either in chronic carriers or repetitively infected individuals in endemic zones. YncE (STY1479), an uncharacterized protein with ATP and DNA-binding domains, is beneficial in detection. Elevated IgG serum responses against YncE has been noted in *S. Typhi* carriers, but not in individuals at the acute or convalescent phase of disease, and not in healthy endemic zone controls.

Fluoroquinolones are now considered as the drug of choice for typhoid. The recommended treatments include 28-day course of norfloxacin (400 mg twice daily) and ciprofloxacin (500 mg or 750 mg BD) for 14 to 28 days. In the presence of severe cholelithiasis, antimicrobial therapy plus cholecystectomy may be required.[13]

A carrier patient should not attend a child-care facility and should not participate in occupations involving food handling, direct patient care, and care of young children or elderly persons until 3 consecutive stool specimens are salmonella free, collected not <24 hours apart and not sooner than 48 hours after discontinuation of antibiotics.[14]

The 2 currently available vaccines are:

- Oral vaccine (Ty21a vaccine) supplied in enteric coated capsules taken once daily for three days
- Injectable Vi polysaccharide vaccine (ViCPS vaccine) given intramuscularly in a single dose

Protective efficacy of vaccines wanes over time and revaccination is recommended every 3 years. It is not recommended in children <2 years. In January 2018, WHO has prequalified the first conjugated Vi polysaccharide vaccine named Typbar-TCV. It has longer and higher levels of immunogenicity and is safe to use in infants > 6 months. SAGE recommends a single dose in children aged 6-23 months, and for catch-up vaccination in children aged 2-15 years. It does not protect against *S. Paratyphi A*.[15]

Malaria

As per the CDC recommendation, blood smears in nonimmune individuals should be repeated every 12 to 24 hours for a total of 3 evaluations before ruling out malaria. Rapid diagnostic tests detect either histidine-rich protein 2 (HRP2), which is a *P. falciparum*-specific antigen, or the pan-species antigen plasmodium lactate dehydrogenase, and have a similar sensitivity to good microscopy. The use of rapid diagnostic tests is associated with certain pitfalls. HRP2 tests can remain positive several weeks after treatment, so it not useful for conducting follow-up. It has been noted that parasites with HRP2 deletions (mainly in Amazonian basin) evade detection by RDT. Additionally, RDT sensitivity for detecting malaria in pregnant women may be decreased, possibly due to sequestration of antigens in the placental circulation. The 18S small subunit rRNA gene is the commonly used target for amplification and detection. It is more sensitive over other methods, with reported detection thresholds of <10 parasites/µl.

There are two drug resistance genes that can be present in *P. falciparum*, namely *Plasmodium falciparum* chloroquine resistance transporter (*Pfcrt*) gene and *Plasmodium falciparum* multi-drug resistance gene 1 *(Pfmdr1*) gene. The *Pfcrt* gene, located on a 36 kb segment of chromosome 7,

is associated with chloroquine resistance. *P. falciparum* multidrug resistance 1 (*Pfmdr1*) located on chromosome 5 encoding P glycoprotein homologue 1 has also been linked to the chloroquine resistance, but its association with the resistance could not be substantiated. Haplotypes (amino acid residues) of these two molecular markers determine the status of CQ resistance. In the case of *Pfcrt,* mutations at K76T of 72–76 residues are associated with the CQ resistance. Mutations at N86Y, Y184F, S1034C, N1042D and D1246Y of *Pfmdr1* gene are generally linked to the resistance. In the *Pfcrt* gene, four main haplotypes CVIET (old world), CVMNT, CVMET and SVMNT (new world) are indicators of resistance, and CVMNK is a wild variant (susceptible).

In north east region of India, two *P. falciparum* field isolates from Chirang district, Assam had shown up to 7 mutations: 1 in *Pfcrt*, 3 in *Plasmodium falciparum* dihydrofolate reductase (*Pfdhfr*) and 3 in *Plasmodium falciparum* dihydropteroate synthase (*Pfdhps*) genes. Two cases in Miao (Changlang, Arunachal) had 8 mutations-one each in in *Pfcrt* and *Plasmodium falciparum* adenosine triphosphatase-6 (*PfATPase6)* genes and three each in *Pfdhfr* and *Pfdhps* genes. One case in Miao had mutations in *Pfcrt* (1), *Pfdhfr* (4) and *Pfdhps* (3) genes.[16] In Chhattisgarh, 78% of the samples found to have a *Pfcrt* mutation (53% double, 24% triple and 1% single), and 59% of *Pfmdr1* genes were found to have an *N86Y* mutation. Double mutations in *pfdhfr* gene recorded in 76%. However, there was no mutation found in the K-13 propeller gene. Only one sample showed a mutant genotype for *PfATPase6* gene.[17] However, sequencing of propeller region of K13 gene in 51 isolates from urban Kolkata and sequenced propeller region did not find any. In all isolates studied, there was no sign of emergence of resistance against artemisinin, as evidenced by wild genotype of K13 gene.[18]

P. knowlesi malaria

It is a zoonosis usually infecting long-tailed macaques. It has been increasingly recognized in parts of SE Asia, especially in Malaysia. Although microscopy is sensitive for the diagnosis, the mature trophozoites and schizonts of *P. knowlesi* resemble those of *P. malariae*. Molecular methods such as PCR are required to confirm the diagnosis of knowlesi malaria. IV artesunate is the preferred treatment for severe knowlesi malaria and moderately high parasitemia. For uncomplicated knowlesi malaria, both chloroquine and artemisinin-based combination treatments (ACTs) can be used . There is faster parasite clearance times and lower anemia rate with ACT. Vidhya et al. showed the presence of *P. knowlesi* in the *Anopheles sundaicus* in Andaman and Nicobar Islands.[19]

P. vivax malaria relapse

Usually parasite strains in temperate and subtropical regions exhibit longer dormant period between the primary infection and relapse (8–10 months or longer). Those in tropical regions generally exhibit shorter relapse intervals (around 3–6 weeks). Walter Taylor and his colleagues showed that in 4 countries (Afghanistan, Ethiopia, Indonesia, and Vietnam,) 7-day course of primaquine at a higher dose (1·0 mg/kg per day) proved non inferior to 14-day course of primaquine (0·5 mg/kg per day). A single dose of tafenoquine is another recently developed treatment option for relapse in *P. vivax*. However, G6PD deficiency is a contraindication.[20]

Resistance to chloroquine and failure of primaquine as anti-relapse drug for *P. vivax* malaria have also been reported in some parts of Southwestern and Northeastern regions of India.[21-22] The *P. vivax* multidrug resistance (*Pvmdr*) and putative transporter protein (Pvcrt-o), have been identified as chloroquine resistance markers in *P. vivax*. There are reports suggesting that genotypic variations *in P. vivax* dihydrofolate reductase gene (*Pvdhfr*) and dihyropteroate synthetase (*Pvdhps*) have been associated with drug resistance. A Kokata-based study by Ganguly et al. found that no specific mutation pattern was recorded in the *pvcrt-o* gene. The researchers also identified 3 novel nonsynonymous mutations in the *pvmdr1* gene. However, *Y976F* mutation was not detected in any isolate.[23]

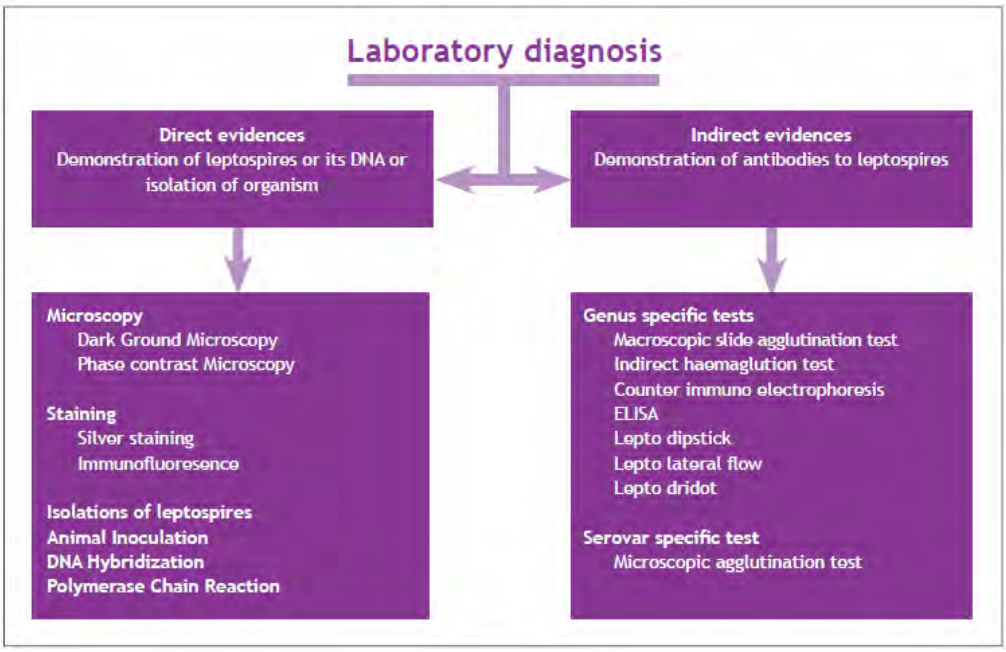
Severe *P. vivax* malaria

An autopsy study in acute respiratory distress syndrome (ARDS) due *P. vivax* malaria, prior to antimalarial drugs, showed heavy infiltrates of intravascular mononuclear cells, endothelial and alveolar damages, and absence of parasite sequestration in the pulmonary vasculature. Another autopsy study demonstrated infiltration of neutrophils in alveolar capillaries even after parasites cleared from peripheral blood by treatment. In such cases, inflammatory mediators might be the possible cause for ARDS.[24]Recommended treatment is IV artesunate followed by ACT(non sulfadoxypyrimethamine based).

Leptospirosis

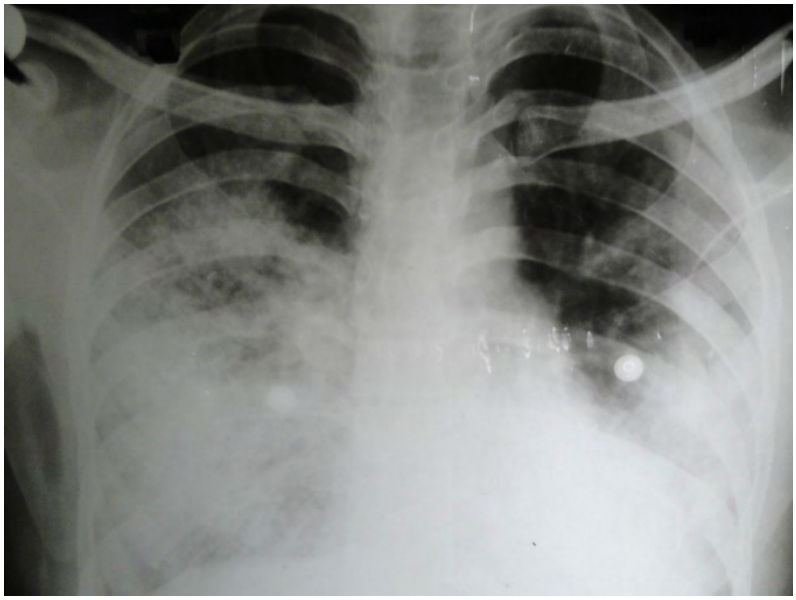
It is considered as the most widespread zoonosis in world. Numerous leptospirosis outbreaks have occurred during the past few years in India. A multi-centric study in India showed that it accounts for about 12.7% of cases of acute febrile illness attending hospitals.[25-29] The various forms of leptospirosis include anicteric febrile illness, icteric leptospirosis (Weil's Disease), hemorrhagic pneumonitis and aseptic meningitis. Diagnosis can be either based on direct or indirect evidence. Direct diagnosis is based on demonstration of leptospira or its DNA by microscopy, staining or isolation of leptospirosis. Indirect diagnosis is based on demonstration of antibiotics to leptospirosis by genus-specific tests like ELISA, lepto dipstick, lepto dri dot etc. (Fig.1). The complications include myocarditis, hemorrhage, hypotension and uveitis. The general treatment given for leptospirosis include penicillin G (20 lakhs IV q4h), doxycycline (100 mg po or IV bd), or ceftriaxone (2g IV od) for 7 days.

Fig. 1: Diagnosis of leptospirosis



Pulmonary involvement in leptospirosis has increased in recent years and ranges from 20% to 70%.[30] The recommended treatment for severe pulmonary form of leptospirosis is bolus methylprednisolone 1 g/day for three days followed by 1 mg/kg/day of oral prednisolone for seven days (Fig. 2).[31]

Fig. 2: Pulmonary involvement in leptospirosis



Dengue management

Intravenous fluid replacement therapy using NaCl 0.9% (154 mM) may perform better than Ringer's lactate (131 mM). In addition, there are theoretical risks of worsening tissue acidosis and lactate accumulation when large volumes of Ringer's lactate are infused. There is no clear advantage in using colloids in terms of the overall outcome. However, colloids may be the preferred choice for the immediate restoration of BP levels (pulse pressure <10 mmHg) They are effective in faster restoration of cardiac index and hematocrit in patients with intractable shock.[32-34]

Prophylactic platelet transfusion in patients without bleeding, when platelet falls <10–20× 10^9/l, is widely practiced in sepsis. However, there is no clinical evidence to corroborate the same. There is no definite inverse correlation between platelet count and bleeding risk. The two risk factors of severe bleeding are prolonged shock and normal to low hematocrit at the diagnosis of shock.

Current data do not support prophylactic platelet transfusion due to the lack of sustainable and significant benefits. In the event of severe bleeding, transfusion of packed red cells, platelets and fresh frozen plasma may be lifesaving. The risks associated with transfusion include fluid overload, transfusion-associated lung injury, blood-borne infections and allergic reactions.[35-37]

Clinical trial to test the efficacy of ketotifen (mast cell stabilizer) to reduce the degree of vascular leakage is in progress in Singapore. Randomized controlled trials are evaluating the anti-inflammatory, endothelial-stabilizing and antiviral effects of lovastatin (targeting DENV virion assembly) in adult dengue patients in Vietnam.[38]

Scrub typhus

The current evidence suggests that doxycycline resistance in scrub typhus is a misconception. There are alternative valid explanations on difference of AFC-3 and AFSC-4 strains from other studied strains and how these bacterial attributes, along with other host and pharmacological factors, contribute to variations in treatment outcome.[39]

Zika

Four Zika cases reported in 2016–17 in Gujarat could be due to local transmission and the affected individuals did not report travel history in past several months. In late 2018, the corresponding zika virus cases reported in Rajasthan and MP were 159 and 127.[40-41] In December 2018, CDC issued a level 2 alert for travelers to India, recommending enhanced precautions against Zika virus infection and advising pregnant women not to travel to affected areas. In April 2019, the status of India was changed from 'current or past transmission but no current outbreak' from the earlier 'ongoing outbreak'. The Zika virus strain isolated by ICMR from Rajasthan matched with the one in Brazil, which saw a massive outbreak in 2016. Though preliminary studies done on strain in Rajasthan do suggest that the mutation causing birth defects (microcephaly) was absent, further characterization of the strain is required.

H1N1

H1N1 virus is speculated to demonstrate oseltamivir resistance. A study performed by Tandel et al. showed that out of 22 fatal cases, 6 (27.27%) were found to harbour oseltamivir-resistant virus strains. Whereas, the H275Y mutation was not observed among the 20 non-fatal cases.[42] Gohil et al. performed a study in Mumbai and found that resistance to oseltamivir in a single isolate of seasonal Influenza A (H1N1) was sensitive to adamantane.[43] However, molecular characterization of influenza A(H1N1) pdm09 viruses circulating at various geographical locations in India by ICMR in 2017 did not find oseltamivir resistance.[44]

Conclusion

Older diseases are changing their faces and newer diseases are being identified. Concerted effort on part of clinicians, microbiologists, pharmacologists, community medicine, entomology, veterinary experts, basic and social scientists is needed to identify threats and suggest remedial measures.

References

1. *Parry CM, Ribeiro I, Walia K, Rupali P, Baker S, Basnyat B. Multidrug resistant enteric fever in South Asia: unmet medical needs and opportunities. Proc Natl Acad Sci U S A. 2015 Mar 17; 112(11): 3356–3361*
2. *Ajibola O, Mshelia MB, Gulumbe BH, Eze AA. Typhoid Fever Diagnosis in Endemic Countries: A Clog in the Wheel of Progress? Medicina (Kaunas) [Internet]. 2018 Apr 25 [cited 2019 Dec 23];54(2). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6037256/
3. *Parry CM, Hoa NT, Diep TS, Wain J, Chinh NT, Vinh H, et al. Value of a single-tube widal test in diagnosis of typhoid fever in Vietnam. J Clin Microbiol. 1999 Sep;37(9):2882–6.*
4. *Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. Cochrane Database Syst Rev. 2017 26;5:CD008892.*
5. *Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clin Microbiol Rev. 2015 Oct;28(4):901–37.*
6. *Parry CM, Vinh H, Chinh NT, Wain J, Campbell JI, Hien TT, et al. The influence of reduced susceptibility to fluoroquinolones in Salmonella enterica serovar Typhi on the clinical response to ofloxacin therapy. PLoS Negl Trop Dis. 2011 Jun;5(6):e1163.*
7. *Qamar FN, Yousafzai MT, Sultana S, Baig A, Shakoor S, Hirani F, et al. A Retrospective Study of Laboratory-Based Enteric Fever Surveillance, Pakistan, 2012-2014. J Infect Dis. 2018 10;218(suppl_4):S201–5.*
8. *Balaji V, Kapil A, Shastri J, Pragasam AK, Gole G, Choudhari S, et al. Longitudinal Typhoid Fever Trends in India from 2000 to 2015. Am J Trop Med Hyg. 2018;99(3_Suppl):34–40.*
9. *Dahiya S, Sharma P, Kumari B, Pandey S, Malik R, Manral N, et al. Characterisation of antimicrobial resistance in Salmonellae during 2014-2015 from four centres across India: An ICMR antimicrobial resistance surveillance network report. Indian J Med Microbiol. 2017 Mar;35(1):61–8.*
10. *Rai S, Jain S, Prasad KN, Ghoshal U, Dhole TN. Rationale of azithromycin prescribing practices for enteric fever in India. Indian J Med Microbiol. 2012 Mar;30(1):30–3.*
11. *Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. MBio. 2018 20;9(1).*
12. *Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. J Postgrad Med. 2012 Jun;58(2):112–8.*
13. *Gunn JS, Marshall JM, Baker S, Dongol S, Charles RC, Ryan ET. Salmonella chronic carriage: epidemiology, diagnosis, and gallbladder persistence. Trends Microbiol. 2014 Nov;22(11):648–55.*
14. *Ameda IM. Guidelines for the Management of Typhoid. 2011:39.*
15. *Andrews JR, Baker S, Marks F, Alsan M, Garrett D, Gellin BG, et al. Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance. Lancet Infect Dis. 2019 Jan;19(1):e26–30.*
16. *Sharma J, Khan SA, Soni M, Dutta P. Prevalence of multiple drug-resistant Plasmodium falciparum malaria cases in Northeast India. Indian J Med Microbiol. 2017 Mar;35(1):140–2.*
17. *Patel P, Bharti PK, Bansal D, Ali NA, Raman RK, Mohapatra PK, et al. Prevalence of mutations linked to antimalarial resistance in Plasmodium falciparum from Chhattisgarh, Central India: A malaria elimination point of view. Sci Rep. 2017 30;7(1):16690.*
18. *Chatterjee M, Ganguly S, Saha P, Bankura B, Basu N, Das M, et al. No Polymorphism in Plasmodium falciparum K13 Propeller Gene in Clinical Isolates from Kolkata, India. J Pathog. 2015;2015:374354.*
19. *Vidhya PT, Sunish IP, Maile A, Zahid AK. Anopheles sundaicus Mosquitoes as Vector for Plasmodium knowlesi, Andaman and Nicobar Islands, India - Volume 25, Number 4—April 2019 - Emerging Infectious Diseases journal - CDC. [cited 2019 Dec 23]; Available from:* https://wwwnc.cdc.gov/eid/article/25/4/18-1668_article
20. *Rosenthal PJ. A shorter course for anti-relapse therapy against vivax malaria. The Lancet. 2019 Sep 14;394(10202):898–900.*
21. *Garg M, Gopinathan N, Bodhe P, Kshirsagar NA. Vivax malaria resistant to chloroquine: case reports from Bombay. Trans R Soc Trop Med Hyg. 1995 Dec;89(6):656–7.*
22. *Singh RK. Emergence of chloroquine-resistant vivax malaria in south Bihar (India). Trans R Soc Trop Med Hyg. 2000 Jun;94(3):327.*
23. *Ganguly S, Saha P, Guha SK, Das S, Bera DK, Biswas A, et al. In vivo therapeutic efficacy of chloroquine alone or in combination with primaquine against vivax malaria in Kolkata, West Bengal, India, and polymorphism in pvmdr1 and pvcrt-o genes. Antimicrob Agents Chemother. 2013 Mar;57(3):1246–51.*
24. *Tan LKK, Yacoub S, Scott S, Bhagani S, Jacobs M. Acute lung injury and other serious complications of Plasmodium vivax malaria. Lancet Infect Dis. 2008 Jul;8(7):449–54.*
25. *Leptospirosis, India. Report of the investigation of a post-cyclone outbreak in Orissa, November 1999. Wkly Epidemiol Rec. 2000 Jul 7;75(27):217–23.*
26. *Sehgal SC, Sugunan AP, Vijayachari P. Outbreak of leptospirosis after the cyclone in Orissa. Natl Med J India. 2002 Feb;15(1):22–3.*
27. *Karande S, Kulkarni H, Kulkarni M, De A, Varaiya A. Leptospirosis in children in Mumbai slums. Indian journal of pediatrics. 2002 Nov 1;69:855–8.*

28. *Sehgal SC, Murhekar MV, Sugunan AP. Outbreak of leptospirosis with pulmonary involvement in north Andaman. Indian J Med Res. 1995 Jul;102:9–12.*
29. *Sehgal SC, Sugunan AP, Vijayachari P. Leptospirosis disease burden estimation and surveillance networking in India. Southeast Asian J Trop Med Public Health. 2003;34 Suppl 2:170–7.*
30. *Dolhnikoff M, Mauad T, Bethlem EP, Carvalho CRR. Leptospiral pneumonias. Curr Opin Pulm Med. 2007 May;13(3):230–5.*
31. *Shenoy VV, Nagar VS, Chowdhury AA, Bhalgat PS, Juvale NI. Pulmonary leptospirosis: an excellent response to bolus methylprednisolone. Postgrad Med J. 2006 Sep;82(971):602–6.*
32. *Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001 Jan 15;32(2):204–13.*
33. *Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999 Oct;29(4):787–94.*
34. *Kalayanarooj S. Choice of colloidal solutions in dengue hemorrhagic fever patients. J Med Assoc Thai. 2008 Oct;91 Suppl 3:S97-103.*
35. *Lye DC, Lee VJ, Sun Y, Leo YS. Lack of efficacy of prophylactic platelet transfusion for severe thrombocytopenia in adults with acute uncomplicated dengue infection. Clin Infect Dis. 2009 May 1;48(9):1262–5.*
36. *Sellahewa KH, Samaraweera N, Thusita KPGD, Fernando JLIN. Is fresh frozen plasma effective for thrombocytopenia in adults with dengue fever? A prospective randomised double blind controlled study. Ceylon Med J. 2008 Jun;53(2):36–40.*
37. *Khan Assir MZ, Kamran U, Ahmad HI, Bashir S, Mansoor H, Anees SB, et al. Effectiveness of platelet transfusion in dengue Fever: a randomized controlled trial. Transfus Med Hemother. 2013 Oct;40(5):362–8.*
38. *Chan CY, Ooi EE. Dengue: an update on treatment options. Future Microbiology. 2015 Nov 23;10(12):2017–31.*
39. *Wangrangsimakul T, Phuklia W, Newton PN, Richards AL, Day NPJ. Scrub Typhus and the Misconception of Doxycycline Resistance. Clin Infect Dis [Internet]. [cited 2019 Dec 23]; Available from:* https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz972/5579380
40. *Khaiboullina S, Uppal T, Martynova E, Rizvanov A, Baranwal M, Verma SC. History of ZIKV Infections in India and Management of Disease Outbreaks. Front Microbiol [Internet]. 2018 [cited 2019 Dec 23];9. Available from:* https://www.frontiersin.org/articles/10.3389/fmicb.2018.02126/full
41. *Saxena SK, Kumar S, Sharma R, Maurya VK, Dandu HR, Bhatt MLB. Zika virus disease in India - Update October 2018. Travel Med Infect Dis. 2019 Feb;27:121–2.*
42. *Tandel K, Sharma S, Dash PK, Parida M. Oseltamivir-resistant influenza A(H1N1)pdm09 virus associated with high case fatality, India 2015. J Med Virol. 2018;90(5):836–43.*
43. *Gohil D, Kothari S, Shinde P, Chintakrindi A, Meharunkar R, Warke R, et al. Oseltamivir Resistant Influenza A (H1N1) Virus Infection in Mumbai, India. Journal of Antivirals and Antiretrovirals. 2015 Nov 20;7:108–14.*
44. *Potdar V, Vijay N, Gupta N, Arunkumar G, Borkakoty B, Malhotra B, et al. Molecular characterization of influenza A(H1N1)pdm09 viruses circulating at various geographical locations in India, 2017. Indian Journal of Medical Research. 2019 Jun 1;149(6):783.*

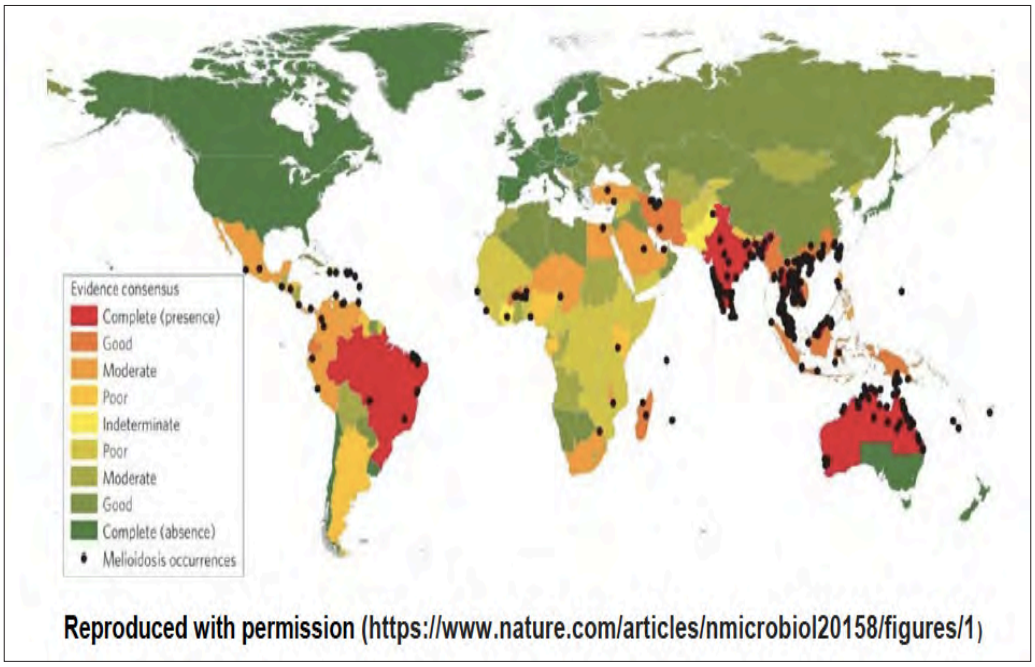
One name, many faces: Melioidosis

Dr. Vinay D MD FNB FRSPH
Consultant Infectious Diseases,
Apollo Hospitals, Bangalore

Epidemiology of melioidosis

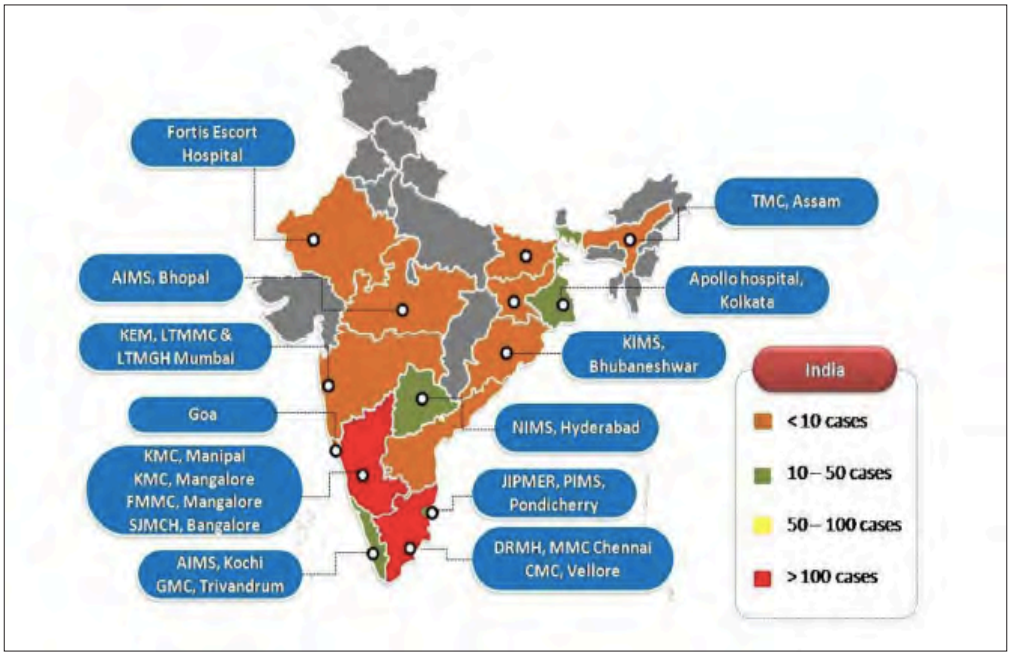
Melioidosis is a condition caused by Gram-negative bacteria named *Burkholderia pseudomallei* (previously *Pseudomonas pseudomallei).* It has a varied spectrum of presentations and the disease should be suspected in patients with both common and uncommon clinical features. It is a lactose non fermenter and shows the characteristic 'safety pin' appearance on Gram staining. On blood agar plate, it grows as non-hemolytic colonies and as glistening colonies on Mac Conkey's agar. The global distribution of *Burkholderia pseudomallei* and the burden of melioidosis are shown in Fig. 1. It is present throughout the world, except in Greenland and in some parts of northern America and Europe.[1] India is one such region showing high prevalence of *Burkholderia*. In India, most of the cases are reported from Karnataka and Tamil Nadu (>100 cases, based on the published reports between 1991-2018) (Fig.2). Global data shows that the disease burden is higher in India with around 20,000-52,000 newer cases reporting annually and estimated mortality of 32,000 per year.[2] It is evident from the prevalence data that the disease is underrecognized, and early diagnosis and management are vital.

Fig 1: Global distribution of *Burkholderia pseudomallei* and burden of melioidosis



Reproduced with permission (https://www.nature.com/articles/nmicrobiol20158/figures/1)

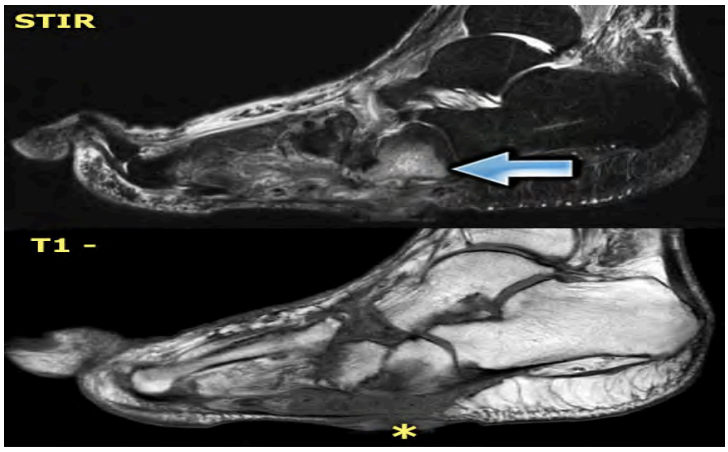
Fig 2: Distribution of *Burkholderia pseudomallei* and burden of melioidosis in India



Case 1

A 64-year-old male, farmer, with a history of diabetes mellitus for 20 years, presented to the hospital with fever and no localizing symptoms for 12 days. A previously performed blood culture showed *Pseudomonas*, which was managed with amikacin. However, his symptoms worsened with low BP of 90/50, and uncontrolled blood glucose. The blood culture was repeated, and he was started on meropenem. A thorough physical examination revealed tenderness over left foot with abscess formation. Both the blood and tissue cultures revealed *Burkholderia pseudomallei,* and the MRI findings indicated osteomyelitis (Fig. 3).

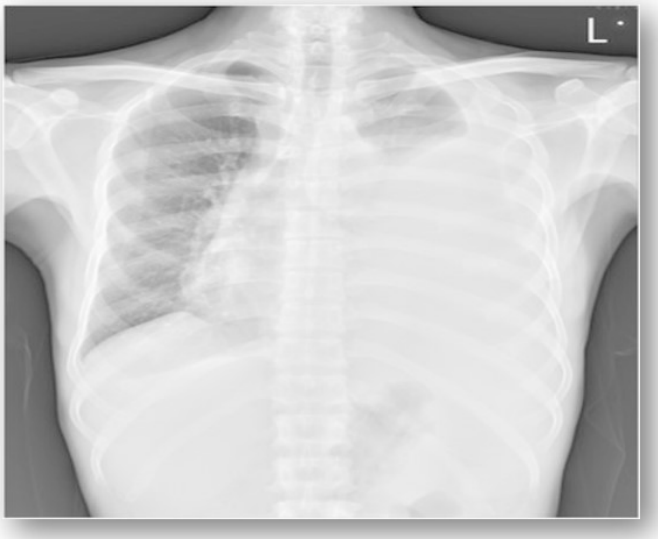
Fig. 3: MRI showing osteomyelitis



Case 2

A 31-year-old male from Krishnagiri, who was contractor by profession and used to perform field work, presented to the hospital with fever for 5 days, productive cough, breathlessness and acute onset left-sided chest pain. He had hypoxia, SPO2 84% on room air, and borderline blood pressure of 90/40 mm Hg. He showed absence of breath sounds over left hemithorax, and chest X-ray revealed massive pleural effusion and underlying consolidation (Fig. 4). Blood, pleural fluid and pleural biopsy cultures were positive for *Burkholderia pseudomallei*. He was found to be diabetic with HbA1c 14. Thoracentesis and other management interventions were adopted, and the patient recovered very well. This case study shows that the presence of diabetes is a major risk factor for contracting melioidosis.

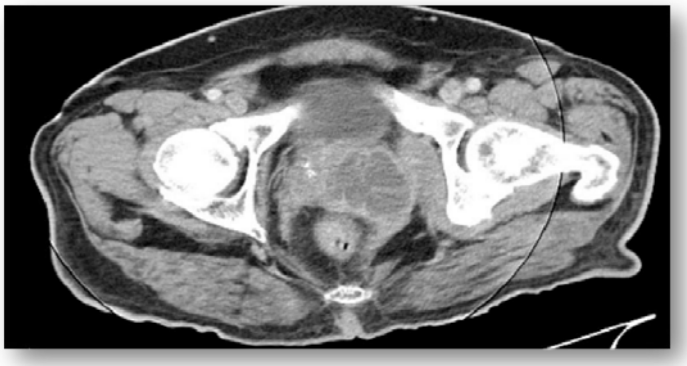
Fig. 4: X-ray revealing massive pleural effusion and underlying consolidation



Case 3

A 39-year-old male presented with fever, dysuria for 5 days and acute abdominal pain. His history revealed chronic kidney disease, alcohol addiction and the use of steroids for managing IgA nephropathy. CT finding revealed prostatic abscess (Fig.5). The blood culture showed the presence of *Burkholderia pseudomallei.* This is a case of melioidosis in a non-diabetic male.

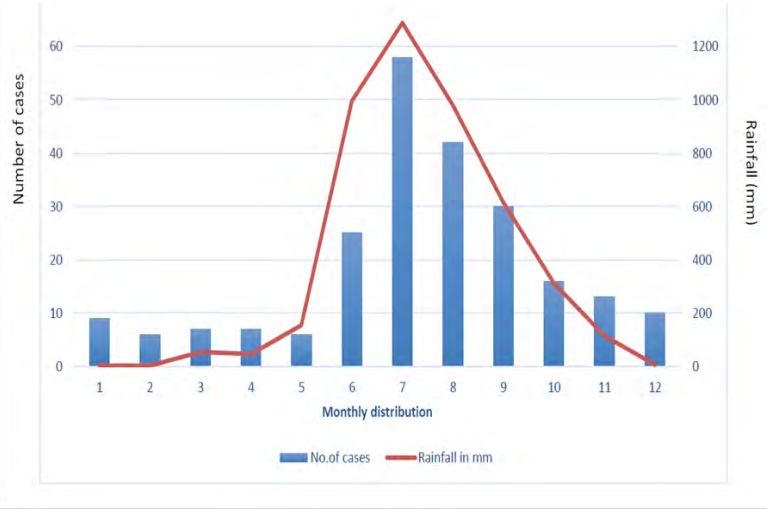
Fig. 5: CT finding showing prostatic abscess



Infectivity

Burkholderia pseudomallei is present in all types of soil, particularly damp and wet soil. Hence agricultural lands have highest risk margin. It probably spreads through direct contact with soil (subcutaneous inoculation), inhalation (prevalence is highest during rainy seasons [Fig.6]) and ingestion (through water contaminated soil).[3]

Fig. 6: Monthly distribution of melioidosis during rainfall



Diabetes mellitus, alcohol abuse, chronic kidney, liver and/ or lung disease, thalassemia and immune suppressed state are the common risk factors for contracting the infection.[4]

Case 4

A 16-year-old female from Assam (Cherrapunji where it rains throughout the year) was admitted with fever for 18 days duration and no clinical localization. ECHO reports showed a tricuspid valve endocarditis, which did not reduce following the administration of antibiotics. Physical examination showed tenderness in her right calf. MRI revealed tibial osteomyelitis with extensive calf abscess. The blood culture was sterile, but the pus culture showed *Burkholderia pseudomallei.* This case did not possess any risk factors, yet had melioidosis due to soil exposure.

Spectrum of clinical presentation of melioidosis

Spectrum of clinical presentation of melioidosis includes pneumonia (most common), pleural effusion, lung abscess, septicemia, osteomyelitis, cellulitis, necrotizing fasciitis, liver abscess, splenic abscess, parotid abscess, prostatic abscess, meningitis, encephalitis, brain abscess, endocarditis, pericardial effusion, parotitis and orbital cellulitis. Since the spectrum of the disease is wide ranging, it is also called as 'the great mimicker'.[5]

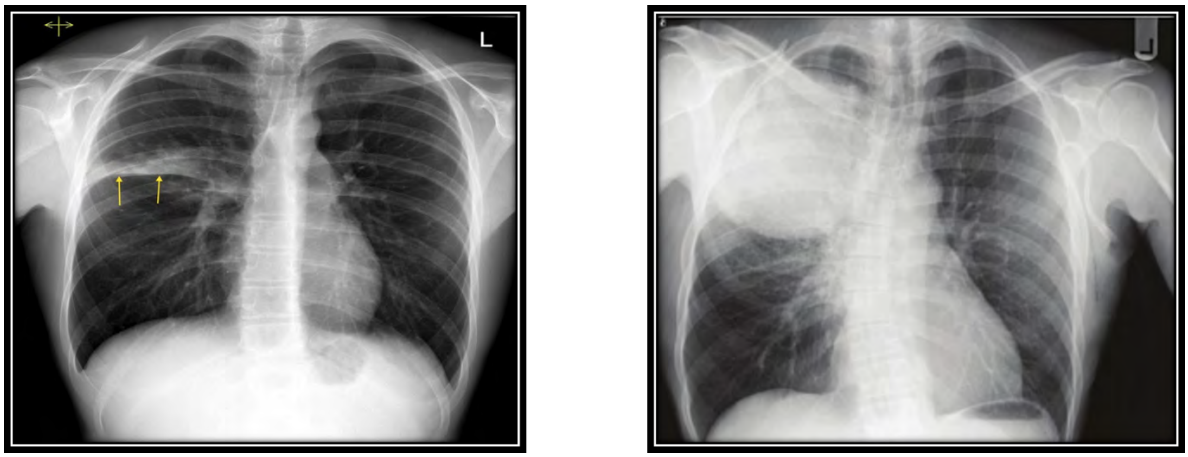
Case 5

A 55-year-old diabetic female presented with progressively enlarging cervical lymphadenopathy. Fine needle aspiration cytology showed granulomas and anti-tubercular treatment was started, suspecting the presence of TB. However, the patient did not show any response over 6 weeks. Therefore, excision biopsy was carried out and the results also indicated necrotizing granulomas. GeneXpert finding was also negative. Culture performed on day 7 revealed *Burkholderia pseudomallei.* This case is an example of chronic presentation of melioidosis.

Case 6

A 75-year-old non-diabetic, ex-service man presented with fever and dry cough for 4 weeks, with no clinical focus. The chest X-ray of 4 weeks showed the presence of a mass-like structure in the right upper zone (Fig. 7). Malignancy or TB was suspected. A CT- guided lung biopsy indicated non-specific inflammatory infiltrate and the culture was found to be positive for *Burkholderia pseudomallei.* This is an example for emergence of the disease after remaining dormant for several years.

Fig. 7: X-ray on week 1 and week 4



Melioidosis: The time bomb

Dubbed as the 'Vietnamese time bomb', the disease received wide attention after the Vietnam War during the 70s. The soldiers got exposed to the hidden pathogens in the soil, as the helicopter blades kicked up the dirt, while transferring the troops to the tropical nation. War veterans presented with symptoms consistent with melioidosis many years after returning from Vietnam (many proven by culture after few years). *Burkholderia pseudomallei* can remain dormant for many years and can emerge with or without risk factors.[6]

Diagnosis

Culture using any body fluids on blood agar/ Mac Conkey Agar is considered as gold standard for diagnosis. A protocol was developed in Brazil for diagnosis of melioidosis, which includes both culture and PCR.[7] PCR is highly specific, but not widely available.

National center for disease control (NCDC) in India has developed another simple diagnostic criterion. Meeting both clinical and epidemiological criteria can be considered as a case of probable melioidosis. The clinical criteria include presence of fever with acute onset sepsis/ community acquired pneumonia/ skin and soft tissue infections/ deep seated abscesses (liver and spleen, parotid, prostate)/ bone and joint infections (osteomyelitis, septic arthritis) and having any of the major risk factors like diabetes, chronic alcoholism, and chronic kidney disease. Epidemiological criterion includes resident of or history of travel to a melioidosis-endemic region or exposure to contaminated soil/ water. Any probable case should be confirmed by culture or PCR.[8]

Treatment

Treatment includes a combination of source reduction and antimicrobial therapy. An intensive phase treatment followed by eradication therapy is recommended in all cases. Ceftazidime can be used for less sicker patients and meropenem for severe cases. The drugs of choices for eradiation phases are trimethoprim and sulfamethoxazole. Doxycycline can be used in patients allergic to sulfamethoxazole and amoxicillin-clavulanate in pregnant subjects (Fig. 8).

Fig. 8: Antibiotic dosing for treatment of melioidosis

Antibiotic dosing for treatment of melioidosis in Australia.

Phase	Antibiotic	Adult Dose
Intensive	Meropenem	1 g intravenously 8-hourly 2 g intravenously 8-hourly [1]
Intensive	Ceftazidime	2 g intravenously 6-hourly
Intensive and eradication	Trimethoprim-sulfamethoxazole	≥60 kg: 320 + 1600 mg orally 12-hourly 40–60 kg: 240 + 1200 mg orally 12-hourly
Eradication	Amoxicillin-clavulanate	20/5 mg/kg orally 8-hourly
Eradication	Doxycycline	100 mg orally 12-hourly

The treatment duration is also very crucial. The intensive phase should not be <2 weeks and longer eradication phase helps in clearing the disease and it varies from 3 to 9 months based on the organ involved. The poor prognostic factors include cases with pneumonia, bacteremia and shock.[9]

Summary

- Melioidosis is truly a 'great mimicker' and the disease should be suspected in any undiagnosed case with a conducive setting for melioidosis.
- The disease is often misdiagnosed as Pseudomonas infection; reconsider the diagnosis if the clinical improvement is not satisfactory.
- Focus on effective diabetes management post discharge.
- Prompt and effective management with appropriate antibiotics is paramount. It is preferred to start meropenem early in sick cases.
- Always suspect the disease in patients having any mass lesion, without conclusive diagnosis.

References

1. *Limmathurotsakul D, Golding N, Dance DAB, Messina JP, Pigott DM, Moyes CL, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. Nat Microbiol. 2016 Jan 11;1:15008.*
2. *Mukhopadhyay C, Shaw T, Varghese GM, Dance DAB. Melioidosis in South Asia (India, Nepal, Pakistan, Bhutan and Afghanistan). Trop Med Infect Dis [Internet]. 2018 May 22 [cited 2019 Dec 19];3(2). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073985/
3. *Wiersinga WJ, Virk HS, Torres AG, Currie BJ, Peacock SJ, Dance DAB, et al. Melioidosis. Nat Rev Dis Primers. 2018 Feb 1;4:17107.*
4. *Currie B, Jacups S, Cheng A, Fisher D, Anstey N, Huffam S, et al. Melioidosis epidemiology and risk factors from a prospective whole-population study in northern Australia. Tropical medicine & international health : TM & IH. 2004 Nov 1;9:1167–74.*
5. *Singh M, Mahmood M. Melioidosis: the great mimicker. J Community Hosp Intern Med Perspect. 2017 Sep 19;7(4):245–7.*
6. *Rathor N, Khillan V. "Vietnamese time bomb" waiting to explode; Burkholderia pseudomallei, retributing the "rare" tag. An update. Indian Journal of Medical Specialities. 2016 Jul 1;7(3):116–24.*
7. *Inglis TJJ, Rolim DB, Rodriguez JLN. Clinical guideline for diagnosis and management of melioidosis. Revista do Instituto de Medicina Tropical de São Paulo. 2006 Feb;48(1):1–4.*
8. *National Centre for Disease Control. Directorate General of Health Services. Government of India. CD Alert. April 2019. [Available from:* https://ncdc.gov.in/WriteReadData/l892s/6530510401565065401.pdf*]*
9. *Smith S, Hanson J, Currie B. Melioidosis: An Australian Perspective. Tropical Medicine and Infectious Disease. 2018 Mar 1;3:27.*

Cardiac fevers

Dr. S. Natarajan

Professor of Cardiology and Senior Interventional Cardiologist
GKNM Hospital, Coimbatore

Introduction

The cardiogenic causes of fever can be both infective and non-infective. Infectious diseases of heart are with diverse clinical presentations and may affect the endocardium, myocardium, and pericardium.[1] Some of the infective causes for cardiac fever include infective endocarditis, pericarditis and myocarditis. On the other hand; rheumatic fever, post-myocardial infarction fever and Dressler's syndrome are a few non-infective causes.

Infective endocarditis (IE)

The clinical presentation of fever is almost invariable for infective endocarditis. However, it is less remarkable in elderly and immune compromised subjects. The symptoms include chills, malaise, myalgia, polyarthralgia, anorexia and weight loss. IE should be suspected in patients withnew signs of heart failure. The classical cutaneous markers like Osler's nodes, Janeway lesions, and Roth's spots are uncommon in the current post-antibiotic era. Petechiae occur in 20 to 30% of the patients.[2]

Apart from the aforementioned manifestations, IE should be suspected in the following scenarios:[3]

- Previous episode of IE
- Congenital / acquired structural heart disease
- Prosthetic heart valve or cardiac implants
- Recent dental procedures
- Long- term IV access ports

- IV drug abuse
- Any new regurgitant murmurs ,S3, RUB
- Compatible findings in Transthoracic Echocardiogram/Transoesophageal Echocardiogram
- Positive blood culture

Modified Duke's criteria

The modified duke's criteria assist in the clinical diagnosis of IE. The major and minor criteria to be considered are as follows:[4]

Major criteria

1. Microbiological detection of typical pathogen at least 2 blood samples taken 12 hrs apart
2. Imaging like ECHO demonstration of vegetations / complications like ring abscess, intracardiac fistula, valve perforation, newly detected partial dehiscence of prosthetic valve (or) abnormal activity in implanted prosthetic valve in PETscan (after 3 months of implantation) (or) paravalvular lesions in CT scan

Minor criteria

3. Predisposing factors like structural heart lesions (congenital/acquired) and IV drug abuse
4. Fever of > 38°C
5. Vascular phenomena like arterial embolism, septic pulmonary infarction, mycotic aneurysms, intra cerebral hemorrhage, conjunctival bleeding, and Janeway lesions
6. Immunological phenomenon like glomerulonephritis, Osler's nodes, Roth spots, and RA factor
7. Serological evidence (rising titers) of infection by compatible pathogen

Presence of both major criteria, one major and 3 minor criteria, or all 5 minor criteria is required for the definite diagnoses of IE. IE should be suspected in patients with endocarditis risk factors presenting with pyrexia of unknown origin or unexplained hemodynamic worsening. *S. aureus*, *Streptococci* and *Enterococci* account for 80% of IE infections. A six-month evaluation conducted at GKNM Hospital found that *Streptococcus viridans, Enterococcus*, coagulase-negative staphylococci and Gram-negative bacilli are the key pathogenic organisms responsible for causing IE.

Treatment

Administration of antibiotics at appropriate doses and duration by parenteral route is the ideal treatment approach. Around 4-6 weeks of antibiotic therapy along with a combination of drugs with diverse mechanism of action is generally followed. Although studies have evaluated the effect of shortening the duration of parenteral therapy with subsequent oral administration, it has not been clinically accepted. Uncontrollable infection, acute heart failure and large vegetations likely to embolize warrant early surgical intervention.[5]

Myocarditis

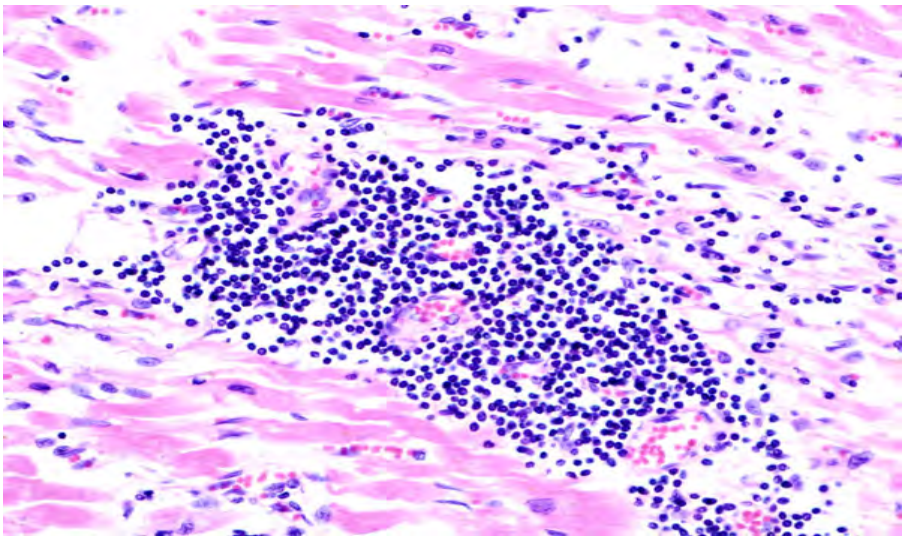
Infective myocarditis

The causes of infective myocarditis are viral, bacterial, spirochetal, fungal, protozoal, parasitic or rickettsial infections. Among these, viral infections are the most common for infective myocarditis. The RNA and DNA viruses responsible for causing infective myocarditis are listed in table 1.[6]

Table 1: The RNA and DNA viruses responsible for causing infective myocarditis

RNA viruses	DNA viruses
Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, yellow fever virus, chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus -1	Adeno viruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus

The common causes of viral myocarditis include Coxsackievirus A and B, echovirus, HIV, and influenza virus. The main histopathological hallmarks of viral myocarditis are collection of lymphocytes infiltrating the cardiac muscles, degeneration of cardiac muscles induced by the virus, and the associated inflammatory process.



Immune-mediated myocarditis

It may be caused due to allergens, alloantigens or autoantigens. Immune-mediated myocarditis is also associated with autoimmune or immune oriented disorders. The common causes are listed in table 2.[6]

Table 2: Common causes of immune-mediated myocarditis

- **Allergens**: Tetanus toxoid, vaccines, serum sickness; drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
- **Alloantigens:** Heart transplant rejection
- **Autoantigens:** Infection-negative lymphocytic, infection negative giant cell
- **Associated with autoimmune or immune-oriented disorders:** Systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)

Toxic myocarditis

Toxic myocarditis is caused due to exposure to certain drugs, heavy metals, animal poisons, hormones and physical agents.[6]

Diagnosis

Myocarditis accounts for 20% of all causes of sudden death in young adults. The diagnosis of myocarditis is challenging due to the heterogeneity of clinical presentations . It ranges from mild symptoms of chest pain and palpitations associated with transient ECG changes to life-threatening cardiogenic shock and ventricular arrhythmia. The signs and symptoms include chest pain (stabbing-kind), CHF, palpitations, fever and symptoms consistent with recent viral infections. Myocarditis is usually associated with pericarditis. Chest X-ray, echocardiogram, cardiovascular magnetic resonance and endomyocardial biopsy are recommended diagnostic tests. elevation in biomarkers such as CK-MB, ESR, CRP, and troponin are suggestive of myocarditis. However, there is no safe and sensitive non-invasive diagnostic test to conclude the diagnosis.[7] though there are risks and it cannot be used for every case Endomyocardial biopsy is considered as gold standard for diagnosing myocarditis.

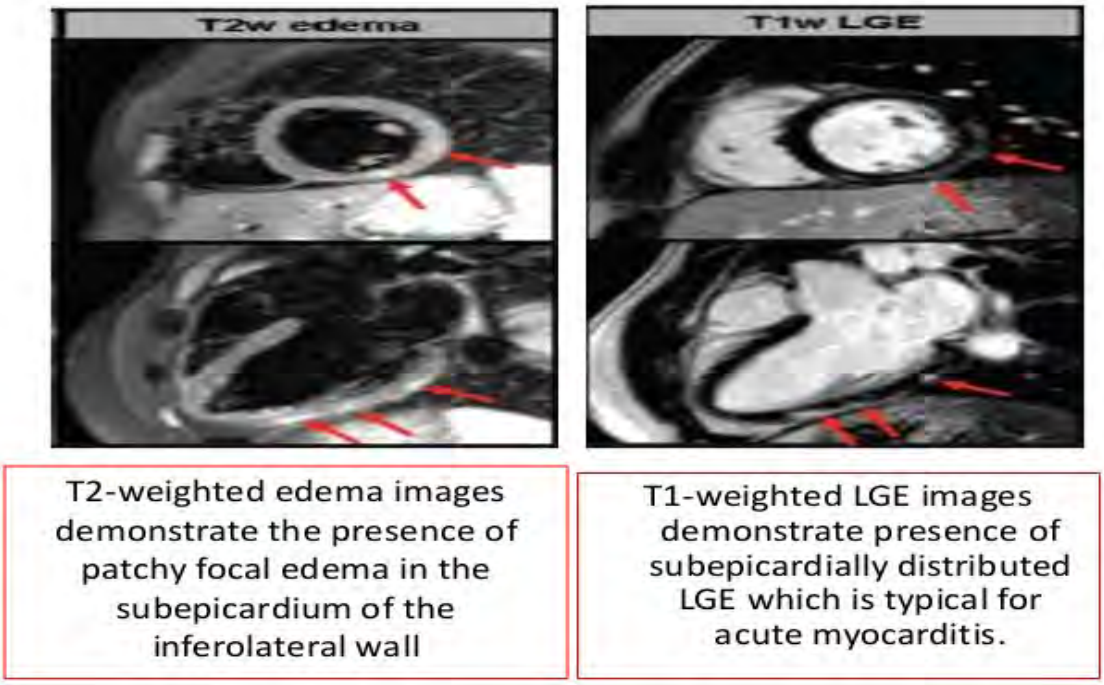
The characteristic ECG changes noted for myocarditis include sinus tachycardia, QRS/ QT prolongation, diffuse T wave inversion, ventricular arrhythmias, AV conduction defects, and features indicative of pericarditis. Myocarditis may mimic acute myocardial infarction, which may occasionally show a pseudo infarct pattern and ischemic changes. ST segment depression, and poor R and Q wave progression are also observed.[8]

Echocardiography helps to rule out non-inflammatory cardiac diseases such as valve disease and to monitor changes in cardiac chamber size, wall thickness, ventricular function and pericardial effusions. Global ventricular dysfunction like wall motion abnormalities and diastolic dysfunction with preserved EF may occur in myocarditis. Histologically proven myocarditis may resemble dilated, hypertrophic and restrictive cardiomyopathy, and ischemic heart disease.[9]

MRI also plays a role in discriminating myocarditis from myocardial infarction, which can help in the evaluation of acute chest pain. In myocarditis, the infiltrates are characteristically located in the mid

wall and tend to spare the sub-endocardium; whereas in infarction, the sub-endocardium is primarily involved.[10] T2-weighted edema and T1-weighted LGE images suggestive of myocarditis are given in fig.1.

Fig. 1: T2-weighted edema and T1-weighted LGE images suggestive of myocarditis



VIRAL PERICARDITIS

It is a combination of fever with sharp pleuritic chest pain and pericardial rub. The ECG shows a ubiquitous ST elevation that cannot be localized to vascular territory with concave ST elevation, PR depression and absence of R wave loss or Q waves. Echo shows pericardial effusion, which is often small. Pericarditis is also associated with myocarditis showing ventricular arrhythmias, reduced LVEF and raised troponin. The etiology is viral in 90% of the cases. Other causes include tuberculosis, uremia, hypothyroidism, autoimmune disease and neoplasia. Non-steroidal anti-inflammatory agent along with colchicine facilitate early resolution.[11]

RHEUMATIC FEVER

It is an acute non-suppurative autoimmune-mediated inflammatory response following pharyngitis caused due to group A beta-hemolytic streptococcus. It affects heart valves, myocardium, pericardium, skin, subcutaneous tissue and brain. The presence of fever is almost invariable, except in rheumatic chorea. Fever starting 2-4 weeks following pharyngitis, persists for 3-4 weeks. It is a significant disease leading to crippling valvular heart disease in India and other developing countries. Jones clinical criteria is generally used for diagnosing rheumatic fever.[12]

Jones criteria

The essential criteria include evidence for recent streptococcal throat infection. Presence of two major or 1 major+2 minor criteria is required for diagnosis.

Major criteria: Polyarthritis (50-70%), pancarditis (30-40%), chorea (10-15%), subcutaneous nodule (< 5%) and erythema marginatum (<5%)

Minor criteria (for endemic areas): Monoarthralgia, fever >38°C, ESR > 30mm/ hour or CRP > 3mg/dl and prolonged PR interval

However, in endemic areas, the recurrences, indolent carditis and rheumatic chorea are considered as only minor criteria, and polyarthralgia is replaced by polyarthritis as a major criterion.[13]

Polyarthritis

In endemic areas (moderate and high-risk population), polyarthritis/mono arthritis and polyarthralgia are considered as major criteria, and migratory polyarthritis as pathognomonic. The disease mainly affects weight-bearing and highly mobile joints. However, hip involvement is minimal. Spine, sacroiliac, temporomandibular and sternoclavicular joints are rarely affected. If the total duration of migratory arthritis exceeds 6 weeks, consider alternate causes like juvenile rheumatoid arthritis, seronegative spondyloarthropathy, lupus erythematosus and gonococcal disease. Arthritis is absent in nearly half the patients with carditis.[14]

Pancarditis

It is responsible for crippling rheumatic valvular heart disease. The endocarditis causes valvulitis leading to mitral regurgitation (apical pan systolic murmur), Carey-Coombs murmur (apical mid diastolic murmur) and aortic regurgitation (early diastolic murmur in LSB). Myocarditis causes disproportionate tachycardia, LV dysfunction , cardiac failure and arrhythmias. Whereas, pericarditis causes pericardial pain, pericardial rub and pericardial effusion.

Rheumatic chorea

Increased female preponderance has been noted. late manifestationsare often afebrile and evidence for recent streptococcal infections may be absent. It is commonly seen with carditis and nodules.

Erythema marginatum

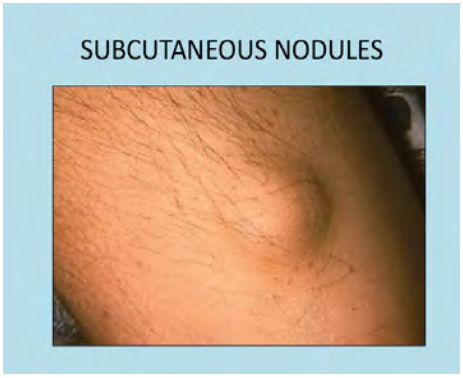
It occurs in about 5% of patients. The red macules enlarge and fade in the center with persistence of redness at the edges (Fig. 5). It is a non-pruritic, painless lesion occurring mainly on the trunk and proximal extremities and not on the face.[15] The lesions disappear within a few hours.

Fig. 5: Red macules noted in erythema marginatum

Subcutaneous nodules

It occurs in <5% of patients. They appear as small (<2 cms), firm, painless nontender nodules attached to underlying bone and tendons with free movement of overlying skin (Fig. 6). They are felt over the bony prominences like skull, galea aponeurotica, spine, extensor surfaces of extremities, scapula and sacrum. It typically appears more than 3 weeks after onset of fever and helps in concluding the diagnosis. It is usually associated with severe carditis.

Fig. 6: Subcutaneous nodules



Post MI fever

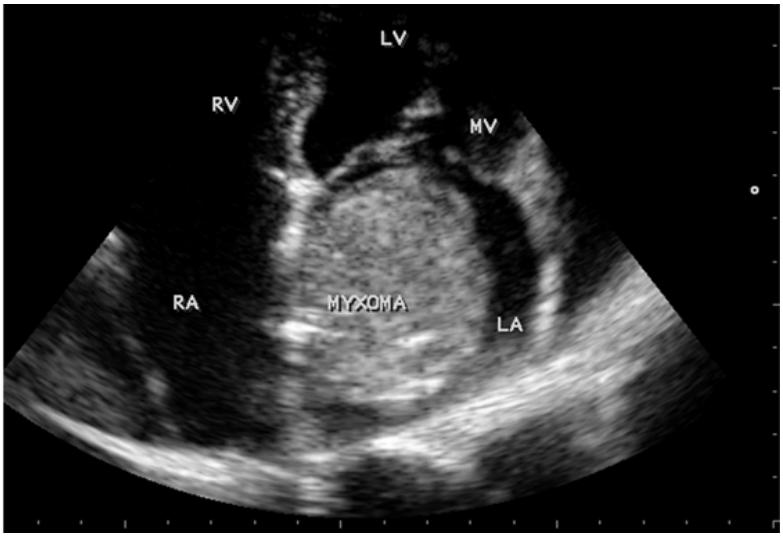
The myocardial necrosis activates inflammatory process leading to influx of macrophages and phagocytosis of dead tissue. Fever often indicates large area of necrosis. The occurrence of elevated temperature of >38°C is associated with reduced LV EF, aneurysm formation and heart failure. It may also occur secondary to thrombolysis following streptokinase therapy. Early administration of beta-blockers helps in fever reduction.[16]

Dressler's syndrome (postpericardiotomy syndrome)

It is an antibody-triggered inflammation of pericardium occurring after heart surgery/ acute myocardial infarction. It occurs after any surgery involving opening of pericardium (including beating heart surgery and minimally invasive surgery). Trauma to mesothelial pericardial cells causes release of cardiac antigens and subsequent production of antibodies. The resulting immune complexes are deposited in pericardium, pleura and lungs and cause inflammatory damage. Previous latent viral infection may also play a role. The clinical presentation is similar to acute pericarditis and the same diagnostic criteria can be used to conclude the diagnosis. It usually occurs 3 weeks to 3 months after surgery. Pericardial tamponade is rare (<2%), unless patient is on long-term anticoagulation. The treatment includes administration of aspirin (600mg 3-4 times/day) or ibuprofen (800 mg tid). Colchicine and steroids are used in necessary cases. It can also result in constrictive pericarditis.[17]

Atrial Myxoma

Myxoma is the common primary heart tumor with left atrium being its common location. Clinical manifestations of LV inflow obstruction – dyspnoea on exertion, syncope, palpitations along with embolic manifestations due to the friable nature of the tumor. Is the commnest mode of presentation. Occasionally constitutional symptoms like weight loss, low grade fever and malice may also dominate the picture. Clinical recognition depends upon symptoms of LV inflow obstruction, elevated jugunal venous pressure with pulmonary hypertension, tumor plop and apical diastolic murmur which varies with position of patients raise the possibility of left atrial myxoma. Echocardiogram is highly diagnostic.



Recurrent pulmonary embolism

Recirrent pulmonary emboli can also manifest as pyrexia of unknown origin. The clinical situation of prolonged immobilisation and other predisposing risk factors, unilateral ankle edema, recurrent unexplained breathlessness,tachycardia and hypoxia are often clinical clues. Estimation of D Dimer and CT pulmonary angiogram confirm the diagnosis.

References

1. *Murillo H, Restrepo CS, Marmol-Velez JA, Vargas D, Ocazionez D, Martinez-Jimenez S, et al. Infectious Diseases of the Heart: Pathophysiology, Clinical and Imaging Overview. RadioGraphics. 2016 Jul 1;36(4):963–83.*
2. *Ashley EA, Niebauer J. Infective endocarditis [Internet]. Remedica; 2004 [cited 2019 Dec 13]. Available from:* https://www.ncbi.nlm.nih.gov/books/NBK2208/
3. *Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG. Infective endocarditis. Nat Rev Dis Primers. 2016 Sep 1;2:16059.*
4. *Topan A, Carstina D, Slavcovici A, Rancea R, Capalneanu R, Lupse M. Assesment of the Duke criteria for the diagnosis of infective endocarditis after twenty-years. An analysis of 241 cases. Clujul Med. 2015;88(3):321–6.*
5. *Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075–128.*
6. *Nussinovitch U. The Heart in Rheumatic, Autoimmune and Inflammatory Diseases: Pathophysiology, Clinical Aspects and Therapeutic Approaches. Academic Press; 2017. 768 p.*
7. *Jeserich M, Konstantinides S, Pavlik G, Bode C, Geibel A. Non-invasive imaging in the diagnosis of acute viral myocarditis. Clin Res Cardiol. 2009 Dec;98(12):753–63.*
8. *Universal Definition of Myocardial Infarction | Circulation [Internet]. [cited 2020 Jan 7]. Available from: https://ahajournals.org/doi/10.1161/circulationaha.107.187397*
9. *Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis. 2010;52(4):274–88.*
10. *Caforio A, Marcolongo R, Basso C, Iliceto S. Clinical presentation and diagnosis of myocarditis. Heart (British Cardiac Society). 2015 Jun 24;101.*
11. *Khandaker MH, Espinosa RE, Nishimura RA, Sinak LJ, Hayes SN, Melduni RM, et al. Pericardial Disease: Diagnosis and Management. Mayo Clin Proc. 2010 Jun;85(6):572–93.*
12. *Cunningham MW. Post-Streptococcal Autoimmune Sequelae: Rheumatic Fever and Beyond. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016 [cited 2019 Dec 13]. Available from:* http://www.ncbi.nlm.nih.gov/books/NBK333434/
13. *Binotto M, Guilherme L, Tanaka A. Rheumatic Fever. Images Paediatr Cardiol. 2002;4(2):12–31.*
14. *Szczygielska I, Hernik E, Kołodziejczyk B, Gazda A, Maślińska M, Gietka P. Rheumatic fever – new diagnostic criteria. Reumatologia. 2018;56(1):37–41.*
15. *Orchard TR. Management of Arthritis in Patients with Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2012 May;8(5):327–9.*
16. *Smid J, Scherner M, Wolfram O, Groscheck T, Wippermann J, C. Braun-Dullaeus R. Cardiogenic Causes of Fever. Dtsch Arztebl Int. 2018 Mar;115(12):193–9.*
17. *Leib AD, Foris LA, Nguyen T, Khaddour K. Dressler Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Dec 13]. Available from:* http://www.ncbi.nlm.nih.gov/books/NBK441988/

Approach to fever with altered consciousness and neurogenic fever

Dr. P. T. Acharya
Professor and Head,
Department of Neurology,
M.S Ramaiah Medical College and Hospital

Introduction

The syndrome of fever and altered sensorium is a relatively common medical emergency seen in all age groups. It poses major diagnostic and management challenges to general practitioners, general physicians, pediatricians, emergency/ICU physicians and neurophysicians. Apart from infective causes, non-infective conditions may present with this syndrome. Immune-mediated disorders are also being increasingly identified.

Fever with altered sensorium presenting in a clinical setting can be classified into 3 groups as show below:

- Fever with brief loss of consciousness
  - Febrile seizures
  - Fever with syncope
  - High fever with delirium

- Fever and loss of consciousness of unrelated etiology
  - Stroke/cranial trauma with aspiration pneumonia; UTI

- Febrile illness with persistent altered sensorium
    - CNS infections/ systemic infection/autoimmune
    - Toxic
    -. Central causes

Infectious causes of fever

The present paper provides a brief overview of febrile illness with persistent altered sensorium. Infection of the CNS is the common cause of fever with altered sensorium. The distinct clinical syndromes related to infections of the CNS in adults include acute bacterial meningitis, viral meningitis/ encephalitis, TB, meningitis, cryptococcal meningitis and brain abscess.[1]

A study from India has noted viral encephalitis, which accounted for around 40% of the cases, as the commonest cause of acute febrile encephalopathy in children <18 years of age. Bacterial meningitis (33.8%), tubercular meningitis (7.9%) and cerebral malaria (5.2%) were more common among the non-viral causes, (Karmarkar et al., 2008).[2]

Encephalitis, meningitis, meningoencephalitis, cerebral malaria, brain abscess, subdural empyema, sepsis associated encephalopathy (SAE) are the causes of fever with altered sensorium. The DNA and RNA viruses responsible for the infections are listed below:[3]

- **DNA viruses**: herpes simplex virus (HSV1, HSV2), other herpes viruses (HHV6, EBV, VZV, cytomegalovirus), and adenovirus.
- **RNA viruses**: influenza virus (serotype A), enterovirus, arboviruses (Japanese B encephalitis), Nipah virus and retrovirus (HIV).

Herpes simplex virus (HSV-1 and 2), varicella and varicella zoster virus (VZV), Epstein-Barr virus (EBV), mumps, measles and enteroviruses, arbovirus (JE), and Nipah virus are responsible for most cases of acute viral encephalitis among immunocompetent individuals. Immunocompromised patients with CMV and those with a history of dog bite may also show febrile illness with persistent altered sensorium. Apart from bacteria causes; rickettsial, fungal and parasitic organisms are also responsible for febrile illness with altered sensorium.

Non-infectious causes of fever

The non-infectious causes associated with overproduction of heat are given below:[3]

- Neuroleptic malignant syndrome (due to acute dopamine deficiency)
- Malignant hyperthermia
- Serotonin syndrome
- Cocaine, amphetamine toxicity
- Ecstasy intoxication
- Salicylate poisoning
- Thyrotoxic encephalopathy
- Convulsive status epilepticus
- Catatonic schizophrenia

Anticholinergic toxicity (e.g. amitryptiline) and heat stroke cause fever due to impaired heat dissipation. Hypothalamic lesion, brain stem lesions (stroke) and intraventricular and subarachnoid

hemorrhage cause fever through impaired thermoregulatory mechanism. The miscellaneous causes include autoimmune encephalitis, SLE, febrile infection-related epilepsy syndrome (FIRES), infectious or post infectious demyelination (ADEM), metastasis/CNS lymphoma and cerebral fat embolism.

Approach to fever with altered consciousness

It is important to address the following queries before deciding on the managing approach:

- Is it a CNS/ systemic infection?
- Is it infective in origin?
- What is the probable pathogen?
- What is the cause in non-infective cases? (inflammatory/ immune mediated/ toxic or drug induced/ heat stroke/ central structural cause with thermoregulatory disturbance)

The steps to be followed for the evaluation of a patient with fever and altered consciousness are mentioned below:

History collection

The following details need to be collected as a part of history collection:[3]

- Fever, headache, vomiting, altered sensorium, seizure, focal neuro deficits, middle ear infection
- CSF rhinorrhea, head trauma, cranial surgery
- Geographical and seasonal factors
- Immune status, asplenia, drug intake
- Contact with animals, dog bite, insect/tick bite
- Recent travel
- Occupation
- Psychosis, cognitive/movement disorder
- Clinical examination

Clinical examination should consider the following:

- Fever, neck stiffness, altered sensorium
- Skin rash and exanthema
- Lymph node, liver, spleen and other sites of concomitant infection
- Neurological examination for level of consciousness, localizing or lateralizing signs
- Papilledema, seizures, brainstem signs and autonomic features

Cryptococcal meningitis should be suspected in patients showing severe headache, though imaging and other lab findings may appear normal.

Lab investigations

The hematological investigations should include complete blood count, routine biochemistry tests, blood culture, MP smear, Widal, VDRL, CD4, and other serology tests for HIV, dengue, rickettsia, leptospira and brucella. CRP and procalcitonin have to be considered in suspected cases of bacterial meningitis and sepsis respectively. Chest X-ray helps to rule out tuberculosis, pneumonia, miliary mottling etc. Urine analysis also needs to be carried out. Thyroid function test, ANA, toxic screening, and auto-immune encephalitis panel may be required in selected cases. It is not safe to perform CSF

examination without imaging in suspected bacterial meningitis. The recommended criteria put forth by the Infectious Diseases Society of America (IDSA) to carry out CT scan before lumbar puncture in adult patients with suspected bacterial meningitis are provided in table 1.[4]

Table 1: The criteria put forth by the Infectious Diseases Society of America (IDSA) to carry out CT scan before lumbar puncture in adult patients with suspected bacterial meningitis

Table Recommended criteria for adult patients with suspected bacterial meningitis, who should undergo CT scan before lumbar puncture

Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy or after transplantation
History of CNS disease	Mass lesion, stroke or focal infection
New-onset seizure	Within 1 week of presentation, some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures
Papilloedema	Presence of venous pulsations suggests absence of increased intracranial pressure
Abnormal level of consciousness	Moderate-to-severe impairment of consciousness Glasgow Coma Scale (GCS <10)
Focal neurological deficit	Dilated non-reactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift

The characteristics observed for various types of meningitis during CSF examination are listed in table 2.

Table 2: Characteristics observed for various types of meningitis during CSF examination

Test	Appearance	Pressure	WBC/μL	Protein mg/dL	Glucose mg/dL	Chloride
Normal CSF	Clear	90 – 180 mm	0-8 lymph.	15-45	50-80	115-130 mEq/L
Acute bacterial meningitis	Turbid	Increased	1000 -10000	100 – 500	< 40	Decreased
Viral meningitis	Clear	Normal to moderate increase	5-300, rarely >1000	Normal to mild increased	Normal	Normal
Tubercular meningitis	Slightly opaque cobweb formation	Increased/ decreased, spinal block	100-600 mixed or lymph.	50-300 due to spinal block	Decreased	Decreased
Fungal meningitis	Clear	Increased	40-400 mixed	50-300	Decreased	Decreased
Acute syphilitic	Clear	Increased	About 500 lymph	Increased but <100	Normal	normal

Electroencephalogram

Electroencephalogram (EEG) is important to rule out a nonconvulsive status in a patient with febrile encephalopathy. It is recommended in any suspected case of acute encephalitis, since it may help distinguishing focal encephalitis from generalized encephalopathy. In the latter, the EEG may show diffuse, bihemispheric slowing, for example, triphasic slow waves in a case of hepatic encephalopathy. The EEG is invariably abnormal in HSE and evolves from a non-specific slowing to more characteristic 2–3 Hz, (PLED) periodic lateralized epileptiform discharges, originating from the temporal lobes.

Treatment

Appropriate antibiotics are recommended bacterial meningitis. Bacterial pathogens causing infections according to the age and recommended guidelines for choosing empiric antibiotic therapy is listed in table 3.[5]

Table 3: Bacterial pathogens causing infections according to the age and recommended guidelines for choosing empiric antibiotic therapy

Bacterial Meningitis		
Age	**Common organisms**	**Antibiotic therapy**
Neonates (< 1 month)	• *E. coli* • Group B strep • *Listeria monocytogenes* • Gram-neg bacilli	Cefotaxime + Ampicillin OR Gentamicin + Ampicillin
Infants (1 - 3 months)	• Neonatal pathogens • *S. pneumoniae* • *N. meningitidis* • *Group B strep* • *H. influenzae*	Cefotaxime + Ampicillin + Vancomycin OR Ceftriaxone + Ampicillin + Vancomycin
Children (3 months - 18 years)	• *S. pneumoniae* • *N. meningitidis* • *H. influenzae*	Ceftriaxone + Vancomycin OR Cefotaxime + Vancomycin
Adults (18 - 50 years)	• *S. pneumoniae* • *N. meningitidis*	Ceftriaxone + Vancomycin
Adults > 50 years and alcoholics	• *S. pneumoniae* • *N. meningitidis* • *Listeria monocytogenes* • Gram-neg bacilli	Ceftriaxone + Vancomycin + Ampicillin

Anti-TB drugs with steroids are indicated for TB meningitis, amphotericin B for fungal meningitis, and acyclovir/ ganciclovir for managing viral meningitis/encephalitis. Tetracyclines can be used for effective management of rickettsial infections and ceftriaxone for salmonellosis. Abscess, subdural empyema and hydrocephalus may require emergency surgical intervention.[6]

Neurogenic fever

It is caused by damage to the hypothalamus due to central nervous system trauma, intracerebral

bleeding, subarachnoid hemorrhage and the use of certain drugs. It is characterized by high temperature resistant to antipyretic therapy and not associated with sweating. Treatment advocated include external cooling, and the use of bromocriptine or dantrolene.

Conclusion

Though syndrome of fever with altered consciousness is a fairly common medical emergency, its diagnosis and management pose a major challenge to clinicians. It is a treatable disorder with favorable outcome, if diagnosed early. Apart from CNS/systemic infections, non-infective causes need to be considered while doing the work-up. Clinical examination should consider the presence of petechiae, rashes, icterus, lymphadenopathy, and hepatosplenomegaly. Middle ear infection and CSF rhinorrhea may be indicative of bacterial meningitis. Brain imaging is useful in diagnosis. Meningitis showing further deterioration may suggest subdural empyema, infarcts or hydrocephalus. It is important to identify conditions requiring surgical interventions. Neurogenic fever is a rare entity, which should be considered in the presence of a serious brain disease when other causes of fever are excluded.

References

1. *Agarwal A, Gutch M, Kumar S, Agrawal S. State of the Globe: Acute Febrile Encephalopathy. J Glob Infect Dis. 2016;8(4):127–8.*
2. *APIINDIA. [cited 2020 Feb 4]. Available from: http://apiindia.org/wp-content/uploads/pdf/monograph_2015_update_on_tropical_fever/front_pages.pdf*
3. *Banerji D, Pauranik A. Emergencies in Neurology. Byword Books Private Limited; 2011. 449 p.*
4. *Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice Guidelines for the Management of Bacterial Meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267–84.*
5. *Hoffman O, Weber RJ. Pathophysiology and Treatment of Bacterial Meningitis. Ther Adv Neurol Disord. 2009 Nov;2(6):1–7.*
6. *Dorsett M, Liang SY. Diagnosis and Treatment of Central Nervous System Infections in the Emergency Department. Emerg Med Clin North Am. 2016 Nov;34(4):917–42.*

Influenza in adults

Dr. M R K Ravi Chandra

Consultant Physician and Pulmonologist
Narayana Health – Mazumdar Shaw Medical Center

We regret very much, the fact, that an influenza virologist is unable to live say 200 years, so that he himself would be able to see what has developed from his earlier assumptions."

J. Mulder and J.F.P Hers, Influenza (1972)

I had a little bird,
Its name was Enza,
I opened up the window and in-flu-enza.

Children's Rhyme from 1918

Demographic trends between 1901-2011 for Indian population shows that there was a drop in the population growth in 1921 to 251 million from 252 million in 1911 and this was mainly due to emergence of the Spanish flu pandemic of 1918. It was the first of the two pandemics involving H1N1 influenza virus and the case fatality rate associated with the flu was around 10% to 20%. Within the span of 1 year, the virus had infected 33% of the world population and the associated mortality rate was around 3- 6% of the entire global population. As per the current estimates, the death toll ranges between 50-100 million. [1,2,3] Direct mortality data were available only for a fraction of the princely states and territories. Extrapolation of the statistical analyses from the Indian subcontinent shows that the mortality was between 15.6 million to 25.5 million.[4]

The 3 landmark papers published by Richard Shope in 1931 established the etiology of 'swine influenza' or 'hog flu', the epizootic disease of pigs that had been first noted during the fall wave of the 1918 influenza pandemic.[5,6,7] The H1N1 influenza virus belongs to the family of *Orthomyxoviridae,* which has 7 genera of viruses. Among these, influenza viruses belong to 3 genera. These are enveloped negative-strand RNA viruses with 8 discrete segmented genomes.[8] Influenza A and B have the propensity to cause pandemic diseases; whereas, influenza C causes sporadic diseases. Each influenza RNA segment is encapsulated by nucleoproteins to form ribonucleotide-nucleoprotein complexes. The viral envelope contains 3 viral transmembrane proteins, hemagglutinin (HA), neuraminidase (NA), and matrix protein 2 (M2). The functions of each genomic segment and coding are listed in table 1.[9]

Table 1: The functions of RNA gene segment and coding

Influenza A virus—genomic segments and coding

RNA segment	Designation	Known and probable functions
4	Hemagglutinin (HA)	Receptor binding; membrane fusion of cell and virus to bring about infection
6	Neuraminidase (NA)	Cleaves cellular neuraminic acid prevents virus aggregation; facilitates release of newly produced virus
7	M1 (matrix)	Interacts with genome and nuclear export factor, assists viral assembly
	M2	Tetrameric ion channel, controls pH in Golgi during HA synthesis and in virion uncoating
5	NP	Nucleoprotein (capsid) and viral synthesis
		Transcriptase complex
1	PB-2	Cap binding subunit, polymerase, virulence determinant
2	PB-1	Catalytic subunit of RNA polymerase
3	PA	Subunit, viral RNA polymerase
8	Non-structural (NS)	
	NS1	Post-transcription RNA control; interferon antagonist
	NEP	Nuclear export of viral RNA, viral assembly

Hemagglutinin and neuraminidase

Researchers have recognized 15 different HA subtypes (phenotypes) numbered 1 to 15, and 9 NA subtypes numbered 1 to 9. However, only three HAs and two NAs were identified among the pandemic and epidemic viruses of human beings in the 20th century. The appearance of a new HA in each pandemic virus typically marks the dominance of the new virus and the disappearance of the previous one.[9]

Variability of hemagglutinin

The variability in HA, resulting from accumulation of molecular changes in the 8 RNA segments, can occur due to the following mechanisms:[10]

(i) Point mutations (antigenic drift)

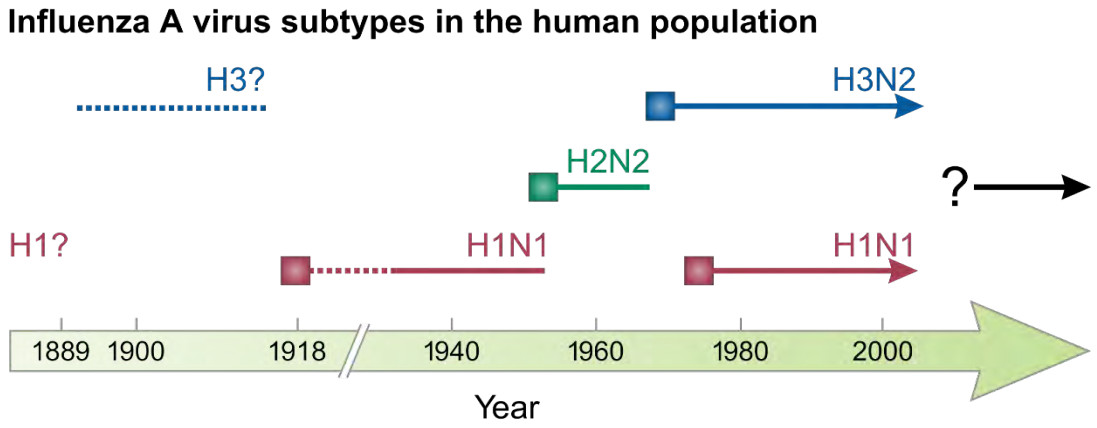
(ii) Gene reassortment (genetic shift)

(iii) Defective-interfering particles

(iv) RNA recombination

Pandemic influenza occurs through a major antigenic change (antigenic shift) of the influenza A virus, which can originate from other hosts, such as birds and swine. Whereas, seasonal influenza causes annual epidemics by the accumulation of antigenic changes (antigenic drift), which allows viruses to evade herd immunity. The retrospective assessment indicates that the 5 major epidemics were caused by different virus subtypes (Fig. 1). Though both 1918 and 2009 pandemics were caused by H1N1 virus subtypes, their genetic constituents were dramatically different.[10, 11]

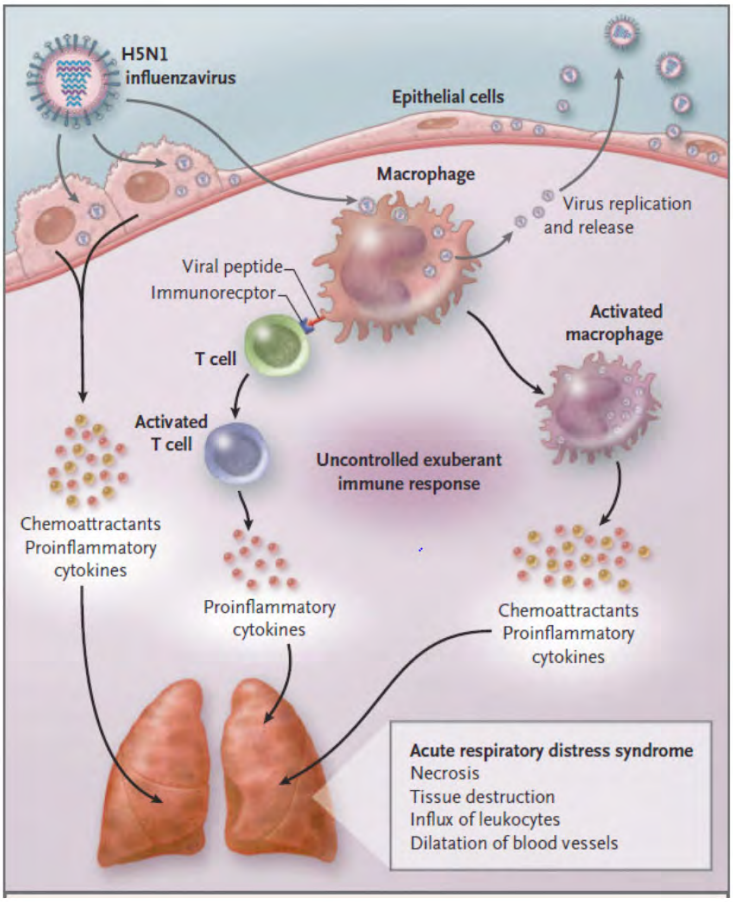
Fig. 1: Influenza A virus subtypes in the human population



Viral fusion and cytokine storm

Hemagglutinin helps in the viral entry by binding to the cell surface receptors. The two coiled-coil domains named 'HRN HRC', present on the hemagglutinin, undergo folding to bring the virus in close proximity to the cells surface. This is followed by dissolving of the cell membrane and fusion of the virus. The respiratory epithelial cells secrete chemoattractants and proinflammatory cytokines as a part of immune response against viral entry. The activated macrophages also release chemokines and proinflammatory cytokines. The activated T-lymphocytes recruited by the macrophages also release proinflammatory cytokines. The cytokine storm ultimately results in necrosis, tissue destruction, influx of leukocytes and dilation of blood vessels (Fig. 2).[12, 13]

Fig. 2: Proposed mechanism of cytokine storm



Histological patterns of injury

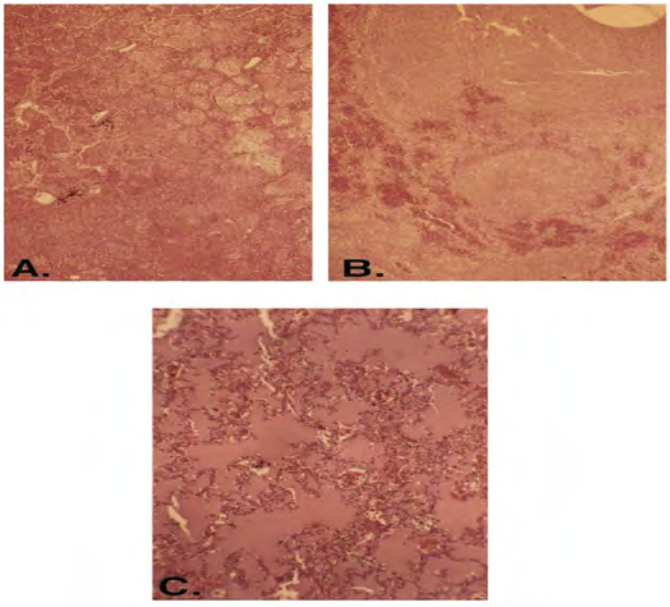
Three distinct patterns of histological presentations noted are as follows (Fig.3):[14]

Pattern 1: Severe and rapidly progressing necrotizing/hemorrhagic bronchopneumonia: Consistent with cytolytic viral damage and secondary bacterial invasion by respiratory-tract pathogens. It may lead to death in very few cases.

Pattern 2: Severe bacterial bronchopneumonia associated with 80% mortality: The extent of secondary bacterial pneumonia, which would have followed primary necrotizing viral pneumonia is unclear, because early signs of viral cytolytic damage had typically been obliterated by the time of autopsy. Culture may show *Streptococcus pneumoniae*, *S. pyogenes*, *Hemophilus influenzae*, or less frequently *Staphylococcus aureus.*

Pattern 3: Similar to acute respiratory distress syndrome (ARDS) with a minority of fatal cases: Patients with this form experience extremely rapid progression of the disease and may have literally drowned because of fluid-filled alveoli, often in the absence of bacteria or inflammatory infiltrate. This pattern was predominant during 2009 pandemic.

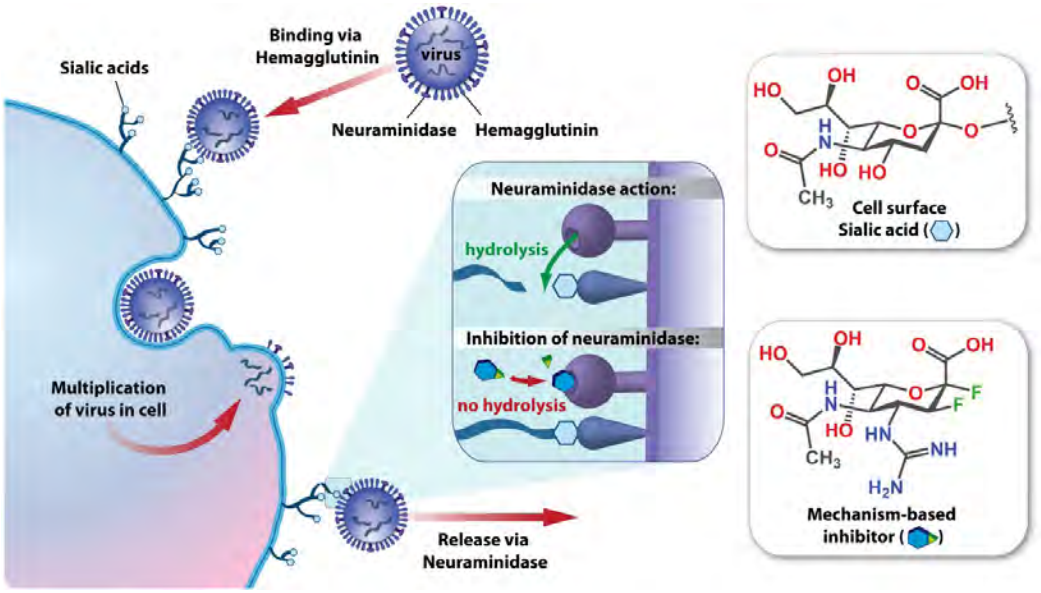
Fig.3: Distinct patterns of histological presentations: A: Pattern 1, B: Pattern 2, and C: Pattern 3



Viral release

The neuraminidase protein helps in the viral release following replication. The hydrolytic enzyme cleaves the sialic acid moiety present on the viral surface, thereby releasing the virus to infect other cells in the host organism (Fig. 4).[15]

Fig.4: Viral release following replication



Clinical presentations

Pregnant women, children <2 years of age, individuals with chronic lung diseases, obese Individuals and individuals with other chronic co-morbid conditions are more prone to contract influenza. Majority of the cases encountered in the outpatient department tend to have uncomplicated influenza. The symptoms of uncomplicated influenza include fever, cough, sore throat, rhinorrhea, headache, muscle pain, malaise, and absence of shortness of breath and dyspnea. The common clinical presentations noted in complicated or severe cases of influenza are as follows:[16]

- Clinical (e.g. shortness of breath/dyspnea, tachypnea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia)
- Central nervous system involvement (e.g. encephalopathy, encephalitis)
- Severe dehydration
- Renal failure
- Multiorgan failure
- Septic shock
- Rhabdomyolysis
- Myocarditis

Symptoms and signs (developing over time) suggesting oxygen impairment or cardiopulmonary insufficiency are indicative of disease progression. These symptoms include shortness of breath (with activity or at rest), difficulty in breathing, blue discoloration, bloody or colored sputum, chest pain and low blood pressure.[16]

Detection and management strategies

Direct detection of virus is possible only through reverse transcriptase PCR (RT-PCR). Throat swab or respiratory secretion is used as the source for isolating RNA. The RNA is used as a template to generate the cDNA. The cDNA is subsequently amplified and the PCR products are analyzed for detecting the virus.[17]

Neuraminidase inhibitors are mainly indicated for the treatment and prevention of seasonal and pandemic influenza. Zanamivir and laninamivir are inhalational agents; whereas, oseltamivir and peramivir are oral drugs. They act by preventing the reproduction and budding of virus from the host cell. Baloxavir marboxil, a cap-dependent endonuclease inhibitor, has been approved in 2018 for the treatment of influenza. It acts by blocking cap-dependent endonuclease (CEN), an essential enzyme in the initiation of mRNA synthesis of influenza viruses.

Oseltamivir is the mainstay of treatment for managing severe or progressive clinical illness and the treatment should be initiated at the earliest. This recommendation applies to all patient groups including pregnant women and young children. In adults, a dose of 150 mg twice daily is sometimes used. However, there is no clinical evidence on the therapeutic outcome. Oxygen therapy with appropriate lung protective ventilatory strategies is advocated in such patients.[16]

In high-resource settings with very specialized intensive care technologies, individual patients with refractory hypoxemia have benefited from negative fluid balance, prone positioning, and advance respiratory support such as nitric oxide, high frequency oscillation (HFO), and/or extracorporeal

membrane oxygenation (ECMO). Such rescue therapies should be considered only if the treating physician/facility has established experience in these modalities. Moreover, it should be noted that such interventions may help only to provide a time frame to heal the lung tissues through the main treatment strategies.[16]

Patients at higher risk of developing severe or complicated illness, but presenting with uncomplicated illness due to influenza, should be treated with oseltamivir or zanamivir. Treatment should be initiated at the earliest following onset of illness. In addition, oximetry and oxygen support should be considered. Patients not considered to be at higher risk of developing severe or complicated illness and who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. They must be monitored for progressive illness and secondary bacterial infections.[16]

Since the influenza viruses constantly evolve with rapid changes in their characteristics, the composition of influenza vaccines is modified annually for the northern and southern hemispheres. Hence, the vaccine available in one hemisphere may offer only partial protection against the infection in the other hemisphere.[18]

Key messages

- H1N1 is a serious illness with propensity to cause high morbidity and mortality.
- Pandemics have the propensity to cause very large numbers of deaths if there is no preparation and anticipation.
- The virus replicates intracellularly causing severe cytolytic damage to respiratory mucosa resulting in hypoxia, shock and death.
- In patients with complicated and progressive disease, especially in high-risk groups, oseltamivir should be initiated early with supportive care and oxygen therapy
- Vaccine is strongly recommended in high-risk groups and helps in reducing assoicated morbidity and mortality.

References

1. *Crosby A. America's forgotten pandemic. Cambridge (UK): Cambridge University Press;1989.*
2. *Patterson KD, Pyle GF. The geography and mortality of the 1918 influenza pandemic. Bull Hist Med. 1991;65:4–21.*
3. *Johnson NPAS, Mueller J. Updating the accounts: global mortality of the 1918–1920 "Spanish" influenza pandemic. Bull Hist Med. 2002;76:105–15.*
4. *Chandra S, Kuljanin G, Wray J (August 2012). "Mortality from the influenza pandemic of 1918-1919: the case of India". Demography.* **49** *(3): 857–65.*
5. *Shope RE. Swine influenza. I. Experimental transmission and pathology. J Exp Med 1931;54:349-59.*
6. *Lewis PA, Shope RE. Swine influenza: II. A hemophilic bacillus from the respiratory tract of infected swine. J Exp Med 1931;54:361-71.*
7. *Shope RE. Swine influenza. III. Filtration experiments and etiology. J Exp Med 1931;54:373-85.*
8. *Palese P, Shaw ML. Orthomyxoviridae: the viruses and their replication. In: Knipe DM, Howley PM, editors. Fields virology. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2007. p. 1647-90.*
9. *Hilleman M (2002). Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. Vaccine, 20(25-26), 3068–3087.*
10. *Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev 1992;56(1):152–79.*
11. *Palese P. Influenza: old and new threats. Nat Med. 2004; 10(12): 82-87.*
12. *Eckert DM, Malashkevich VN, Kim PS. Crystal structure of GCN4-plQl, a trimeric coiled coil with buried polar residues. J Mol Biol 1998;284:859–65*
13. *Osterholm MT. Preparing for the next pandemic. N Engl J Med. 2005;352:1839-184215872196.*
14. *Morens DM, Fauci AS. The 1918 influenza pandemic: insights for the 21st century. J Infect Dis. 2007;195(7):1018-102817330793.*
15. *Smith, B. J.; McKimm-Breshkin, J. L.; McDonald, M.; Fernley, R. T.; Varghese, J. N.; Colman, P. M. . "Structural Studies of the Resistance of Influenza Virus Neuramindase to Inhibitors". J Med Chem. 2002; 45 (11): 2207–12.*
16. *WHO | Clinical management of human infection with pandemic (H1N1) 2009: revised guidance [Internet]. WHO. [cited 2020 Jan 19]. Available from: https://www.who.int/csr/resources/publications/swineflu/clinical_management/en/*
17. *Bachman J. Reverse-transcription PCR (RT-PCR). Methods Enzymol. 2013;530:67–74.*
18. *WHO | Influenza [Internet]. WHO. [cited 2020 Jan 19]. Available from: https://www.who.int/ith/vaccines/si_iAh1n1/en/*

Fever in elderly

Dr. Ananya Das

MBBS, MD Medicine, PGD Geriatric Medicine
Consultant Geriatric Medicine
Manipal Hospitals, Bangalore

Introduction

As per the WHO estimates, the geriatric population (≥65 years old) constituted 6.2% of the world population in 1992 and is projected to reach 22% by 2050.[1] According to the Population Census 2011, nearly 104 million elderly persons are living in India and the number is estimated to rise two-fold by 2050.[2] Studying the geriatric population is important because elderly patients account for 12–24% of all emergency department admissions. About 10% of the elderly paying hospital visits have fever, among them 70-90% will be admitted and 7-10% will succumb to death within a month.[3] Hence the mortality rates are comparatively higher among admitted cases of geriatric subjects.

Measuring fever in elderly

Managing fever in elderly population is challenging, as they show wide variations in normal body temperature. Several factors that may influence the body temperature in elderly are: co-existing chronic diseases, biological changes with normal aging, medications, circadian rhythm, site of measurement and method of thermometry.[4]

Although rectal temperature measurement is considered as gold standard in elderly, it is often impractical in debilitated, non-cooperative patients. Measuring oral temperature is difficult in uncooperative patients and those having dementia, those with tongue tremors, mouth breathing, and variations in the rate/ depth of respiratory patterns, and those following ingestion of hot and cold fluids.[5] Tympanic membrane temperature is more sensitive (86%) and specific (89%).[6] A raised

temperature is not always suggestive of fever. For example, the body temperature increases in a healthy person while exercising. In contrast, a 'normal' temperature of 37.3 °C (99.1 °F) may represent a clinically significant fever in a frail elderly patient due to the impaired ability of the body to generate heat. Hence, it is paramount to have a high degree of clinical suspicion to diagnose fever in elderly.

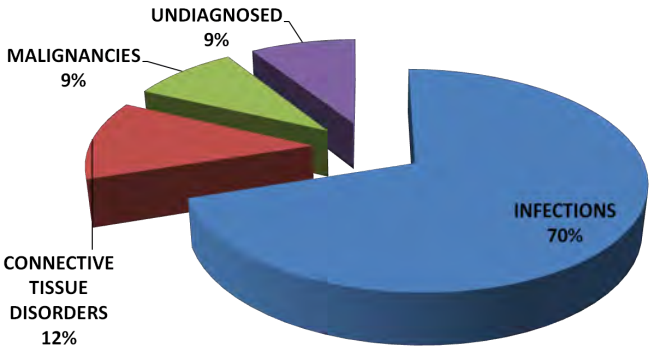
The Infectious Disease Society of America (2008) has put forth the following 4 criteria for classifying fever in elderly: [7]

- Persistent rectal temperature > 37.5°C (99.5°F)
- Persistent oral temperature >37.8°C (100°F)
- Persistent tympanic membrane temperature >37.2°C (99°F)
- An increase over baseline temperature >1.3°C (2°F), independent of the measuring site.

Causes of fever in elderly

The most common causes of fever in elderly are infections (70%), followed by connective tissue disorders (12%), malignancies (9%) and undiagnosed causes (9%) (Fig. 1).[8]

Fig. 1: Causes of fever in elderly



Aging and infectious diseases

Aging and infectious diseases are the important causes of fever in elderly. Increase in age is associated with elevated risk for susceptibility to infection, and significant morbidity and mortality, even in the modern antibiotic era. Altered adaptive immunity, decline in the physiological reserve, coexisting and comorbid illnesses, and treatment effects are the risk factors for increased susceptibility to infections noted in elderly (Fig 2).[9]

Fig. 2: Risk factors for the development of infection in elderly

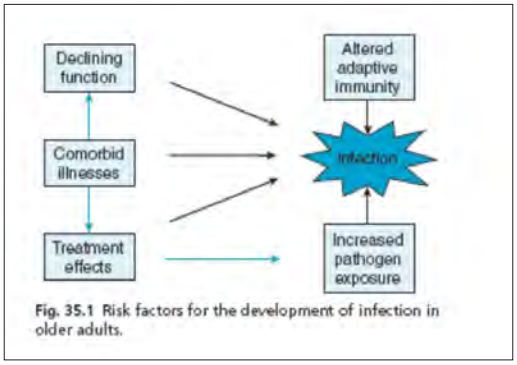


Fig. 35.1 Risk factors for the development of infection in older adults.

a) Immune aging

The decline in cellular immunity is prominent with aging. It includes involution of thymus, which leads to increase in circulating memory T cells and decrease in naïve B cells. There is also a blunted antibody response, resulting in the lack of regulatory control of T cells on B cells.[9] Breakdown of natural mechanical barriers (skin, mucosal surfaces of lung and GIT) is also associated with immune aging, leading to invasion by pathogenic organisms.

b) Diminished physiological reserves

Elderly subjects, especially those with neurological disorders, have decreased cough reflex, which may cause aspiration pneumonia. Cellulitis is a common infection in elderly due to impaired arterial and venous circulation, and compromised wound healing. Malnutrition also plays a role in diminishing the physiological reserves.[10]

c) Co-morbid illness

The comorbid conditions that make elderly prone to infections are as follows:[5]

Diabetes mellitus: Increased susceptibility to UTI, skin and lung infections due to delayed phagocytosis with decreased clearance of yeast and bacteria by neutrophils in diabetic patients.

- CLD: Impairment of complement factor formation and proliferation of cellular immunity.
- COPD: Recurrence of pneumonia due to impaired mucociliary clearance, alveolar macrophage dysfunction, and suppressed cough mechanism
- Frailty: A decline in activities of daily living (ADLs) causes an increase in traumatic falls and injuries that often lead to hospitalization, thus exposing elderly to nosocomial infections.

d) Complications of treatment

Increased susceptibility to infections is noted in the following scenarios:[11]

- Bedridden with invasive devices like indwelling catheter, feeding tubes, IV lines and tracheostomies
- Subjects undergoing chemotherapy/immunosuppressant treatment
- Those having drug-resistant microbes due to recurrent hospitalizations and/or multiple antibiotics

Diagnostic challenges

Fever, the cardinal sign of infection, may be absent or blunted (30%-50% of the times) in elderly because the basal body temperature of such subjects is comparatively lesser than that of standard normal body temperature of younger adults. Fever in the geriatric patient is an indication of serious viral or bacterial infection. Therefore, it is important to assess the change in temperature from the individual patient's baseline rather than the absolute temperature value.

Fever response in elderly is blunted due to diminished thermoregulatory response (sudomotor and vasomotor responses). Quantitative and qualitative abnormalities in both the production and response to endogenous pyrogens, such as IL-1, IL-6, and TNF, are often noted in elderly.[4] Aging could also limit the ability of the hypothalamic circumventricular organs to allow endogenous pyrogens to cross the blood stream to exert their effect on the CNS.

Fever is not the first sign of infection in elderly. Moreover, the diagnosis of infection is often delayed due to the presence of atypical/non-specific complaints and lack of inflammatory response. Hence, the clinicians should have a higher clinical index of suspicion for infection in elderly. Most of the patients show cognitive impairment/change in mental status - frank delirium (50%), anorexia, functional decline, weight loss and failure to thrive. Cognitive impairment patients may not be able to express feelings of discomfort and their caregivers may have to rely on other changes to recognize symptoms suggestive of a possible infection.

Challenges in interpreting biomarkers of sepsis

Some of the commonly noted challenges in interpreting biomarkers of sepsis are discussed below:[10]

- Leukocytosis: May be absent in elderly. Serial increase in leucocyte count from baseline is more informative.
- Lactic acid: High levels indicate high mortality risk. But in elderly, dehydration and anemia can also result in high values.
- Collecting a urine sample that is not contaminated with skin bacteria can be challenging in a patient with cognitive impairment or incontinence.
- Physical disabilities (kyphosis/osteoporosis/immobility) make it difficult to obtain good diagnostic chest radiographs to assess for pulmonary infiltrates.

Infectious causes of fever

The various infectious causes of fever include lower respiratory tract infections (24 to 25%), urinary tract infections (14 to 15%; seen more in hospitalized patients [F>M]), skin and soft tissue infections (14 to15%), CNS infections (5 to 8%), surgical site infection (1-2%) and intra-abdominal infections (3-4%, highest mortality). Risk for such incidences is two-fold more in patients with underlying co-morbid conditions.

A study by Martin and colleagues reported that subjects >65 years were 1.31 times more prone to develop Gram-negative infection. Most common organism identified during urine culture in patients who developed sepsis from a urinary source was *Escherichia coli* (50%). *Proteus*, *Klebsiella*, and *Pseudomonas* were the other Gram-negative species detected during the study. *Staphylococcus aureus*, *Enterococci* and Streptococci species were the common Gram-positive organisms noted in elderly with bloodstream infections.[12]

Non-infectious causes of fever

The non-infectious causes of fever include rheumatological diseases (4-5%) like systemic vasculitis, temporal arteritis and adult Still's disease, solid tumors (3-5%) and hematological malignancies (5-7%). Non-infectious etiologies are more frequently identified in patients with known underlying disease. This is due to the relatively more severe immunocompromised state noted in such patients.[13]

Evaluation

Evaluation for fever is done by CBC with differential count, peripheral smear, ESR, CRP, renal function test including electrolytes, liver function test, urine routine and culture, blood culture, chest X-ray, CT abdomen and pelvis/chest.

Dengue panel, throat swab, sputum AFB/culture/Gene Xpert, HIV, Widal, malaria antigen, IgM ELISA: chikungunya/leptospirosis, HBV/HCV/HAV, serology for EBV/CMV, lumbar puncture, and TTE/TEE are generally carried out for infection diagnosis.

The hematologic malignancy diagnoses include serum protein electrophoresis, bone marrow biopsy, non-hematologic malignancies, mammogram, OGD/colonoscopy, PET/CT and biopsy.

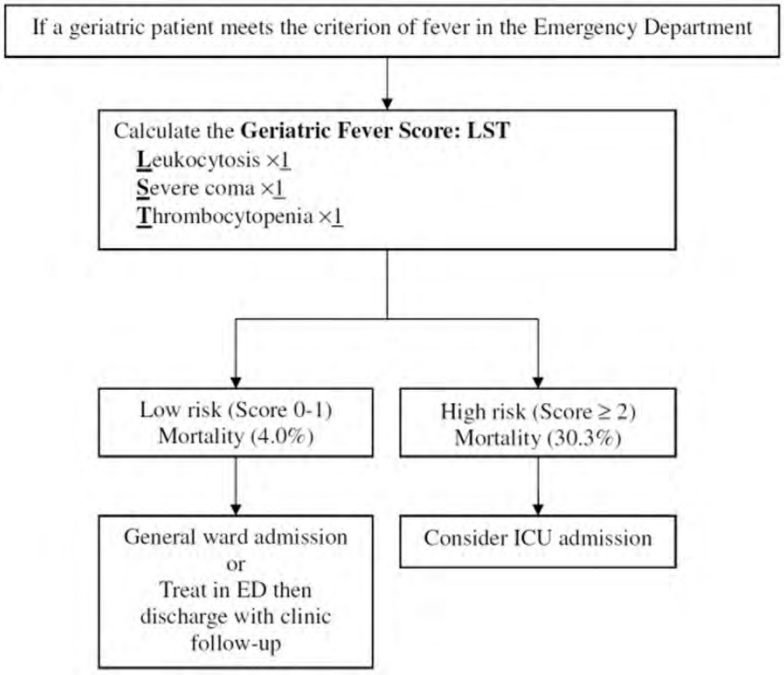
Rheumatological conditions are diagnosed by ANA, ANCA, RA factor, lymph node biopsy and temporal artery biopsy.

Outcomes

The advanced age is an independent risk factor for mortality in elderly. The rate of in-hospital mortalities in patients aged 65 -79 years is 30% - 60% and patients aged >80 years is 40-80%.[14] Patients with co-morbidities have higher mortality rate (26.4%) than those without co-morbidities (14%). Frailty is associated with an increased risk of mortality in critically ill patients of >80 years of age.[15]

A study performed by Chung et al. in Taiwan with a sample size of 330 patients developed the geriatric fever score for assessment. This is a simple and rapid rule for predicting 30-day mortality and for managing geriatric patients with fever in the emergency department (Fig. 3). In this scoring method, any patient fulfilling the criteria for fever would be scored based on leukocytosis (WBC count >12,000), severe coma (GCS scale <8) and thrombocytopenia (platelet count <1,50,000) (each will be given a score of 1). If the geriatric fever score is 0-1, the mortality risk is low (4.0%) and the patient needs admission in a general ward or ED followed by discharge with clinic follow-up. If the score is ≥2, the risk of mortality risk is high (30.3%) and the patient needs ICU admission.[16]

Fig. 3: Geriatric fever score



Limitations of this study are as follows:

- Data were collected from a retrospective chart review. The clinical presentations or records may not have been completely documented.
- It was a single-center study. Findings from database may not be generalizable to cohorts in other nations.
- Sample size might not be large enough (n=330) to make conclusions with good statistical power.
- External validation in other populations was not performed to confirm the usefulness of this score system.
- Known risk factors such as albumin, increase of leukocyte counts from baseline, lactate, and procalcitonin were not evaluated.

Conclusion

There is proportional increase in the number of geriatric patients and their mean age with increase in life expectancy. In elderly patients with no underlying predisposing factor, except for age, it is necessary to investigate the infectious etiology of fever. In subjects with underlying disease, it will be more rational to consider non-infectious etiologies as the cause of fever. The evaluation must be prompt, and the treatment should begin as early as possible to prevent mortality.

References

1. *WHO. Global Health and Aging. National Institute on Aging. National Institutes of Health. 2011. [Available from:* https://www.who.int/ageing/publications/global_health.pdf*]*
2. *Elderly in India. Central Statistics Office. Ministry of Statistics and Programme Implementation. Government ofIndia.2016.[* http://mospi.nic.in/sites/default/files/publication_reports/ElderlyinIndia_2016.pdf *]*
3. *McCabe JJ, Kennelly SP. Acute care of older patients in the emergency department: strategies to improve patient outcomes. Open Access Emerg Med. 2015 Sep 4;7:45–54.*
4. *Norman DC. Fever in the Elderly. Clin Infect Dis. 2000 Jul 1;31(1):148–51.*
5. *Jump RLP, Canaday DH. Infections in Older Adults, An Issue of Infectious Disease Clinics of North America, E-Book. Elsevier Health Sciences; 2017: 297 p.*
6. *Norman DC. Fever in the elderly. Clin Infect Dis. 2000 Jul;31(1):148–51.*
7. *High KP, Bradley SF, Gravenstein S, Mehr DR, Quagliarello VJ, Richards C, et al. Clinical Practice Guideline for the Evaluation of Fever and Infection in Older Adult Residents of Long-Term Care Facilities: 2008 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jan 15;48(2):149–71.*
8. *Mir T, Nabi Dhobi G, Nabi Koul A, Saleh T. Clinical profile of classical Fever of unknown origin (FUO). Caspian J Intern Med. 2014;5(1):35–9.*
9. *Ryan L, Hay M, Huentelman MJ, Duarte A, Rundek T, Levin B, et al. Precision Aging: Applying Precision Medicine to the Field of Cognitive Aging. Front Aging Neurosci. 2019;11:128.*
10. *Jump RLP, Canaday DH. Infections in Older Adults, An Issue of Infectious Disease Clinics of North America, E-Book. Elsevier Health Sciences; 2017 297 p.*
11. *Donna D. Ignatavicius, M. Linda Workman, Cherie Rebar. edical-Surgical Nursing - E-Book: Concepts for Interprofessional Collaborative Care. Elsevier Health Sciences2017. 41 p.*
12. *Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006 Jan;34(1):15–21.*
13. *Cagatay AA, Tufan F, Hindilerden F, Aydin S, Elcioglu OC, Karadeniz A, et al. The causes of acute Fever requiring hospitalization in geriatric patients: comparison of infectious and noninfectious etiology. J Aging Res. 2010 Aug 12;2010:380892.*
14. *Lagu T, Rothberg MB, Shieh M-S, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012 Mar;40(3):754–61.*
15. *Flaatten H, De Lange DW, Morandi A, Andersen FH, Artigas A, Bertolini G, et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). Intensive Care Med. 2017 Dec;43(12):1820–8.*
16. *Chung M-H, Huang C-C, Vong S-C, Yang T-M, Chen K-T, Lin H-J, et al. Geriatric Fever Score: A New Decision Rule for Geriatric Care. PLoS One [Internet]. 2014 Oct 23 [cited 2019 Dec 21];9(10). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207798/

Psychiatric aspects of fever

Dr. Lekhansh Shukla, MD, DM
Assistant Professor, Department of Psychiatry,
National Institute of Mental Health & Neurosciences (NIMHANS)

Fever and psychiatry: Historical perspectives

The earliest experiments with the use of biological treatments for psychiatric ailment was termed as 'fever therapy'. The basis of the therapy was relieving psychiatric symptoms by inducing fever. Malaria was chosen to induce fever by several research institutions, realising the fact that it can be treated with quinine and the infection was considered as an acceptable risk for patients.[1] A 2014 press release had noted that hundreds of individuals, including children, injected with the parasite causing malaria as part of research for a cure against syphilis, might had been infected with the disease.

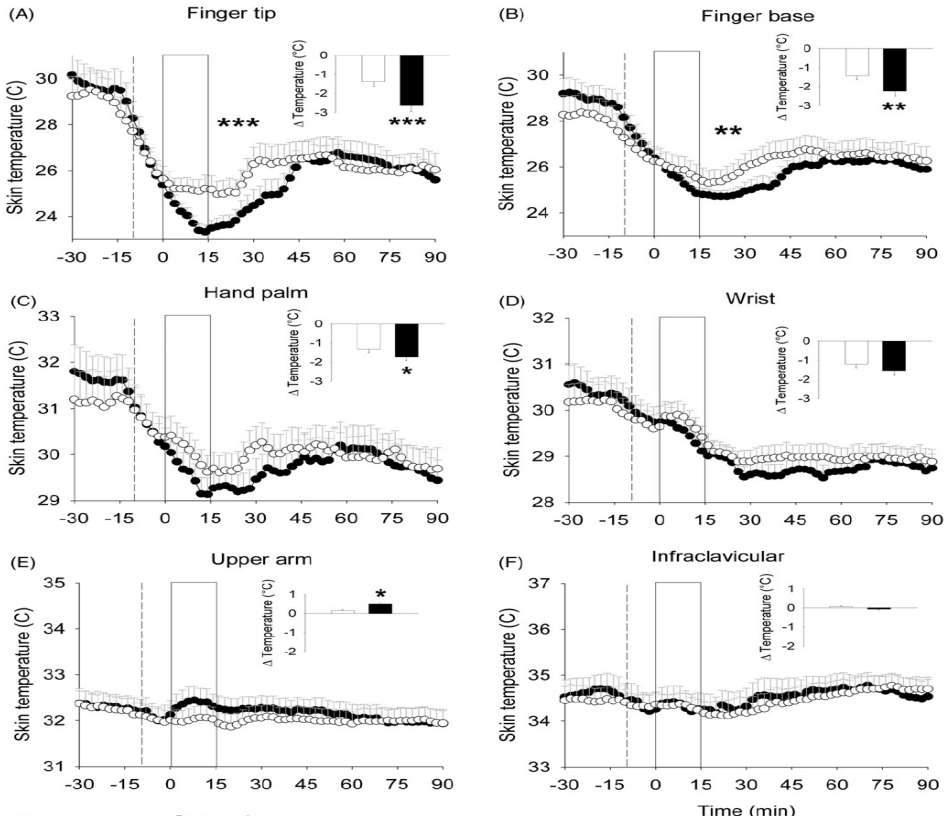
Fever as the sole manifestation of psychiatric Illness

A 2015 study by Oka et al. had evaluated how psychological stress affects body temperature in clinical population. The study has evaluated adolescent females who were in a stressful relationship. The study has noted an increase in core body temperature (up to 41°C) upon exposure to emotional events. The periodicity of the fever was acute or relapsing remitting and the treatment preferred was spiritual healing/ psychotherapy. Antipyretics were not found to be effective in treating psychogenic fever.[2] A literature search using the key word 'psychogenic fever' in PubMed had found 28 publications. Among these, 26 were from a single group in Japan. Most of the papers are theoretical in nature dealing with preclinical evidence, stress-induced fever, prudent models etc. A case study by Zhang et al. has described an exceptional case of psychogenic fever in a patient with small cell lung cancer. The study has concluded that patients with psychogenic fever needs to be differentiated from those

with infectious fever (including neutropenic fever), and tumor fever.[3] The concerns that preclude distinguishing psychogenic fever from other febrile episodes include improper diagnostic work-up, lack of reproducibility, long-term course and outcome data, and absence of reports from different parts of the world.

Another study published in the International Journal on the Biology of Stress has concluded that the amplitude and direction of stress-induced temperature are influenced by the site of temperature measurement in humans.[4] It also depends on the type of stress. Hence it is impossible to consider the evidence from preclinical and rodent models to correlate whether psychological stress may present as a syndrome of fever. Paradoxically, it has been noted that the exposure of healthy volunteers to stress contributes to the reduction of peripheral and core temperatures to certain period. The stress and peripheral temperatures noted at finger tip and base, hand palm, wrist, upper arm and infraclavicular region are depicted in fig.1.

Fig. 1: Stress and peripheral temperatures noted at fingertip and base, hand palm, wrist, upper arm and infraclavicular region



There is insufficient evidence to show that psychological stress can increase temperature to qualify for fever/hyperthermia. However, there is overwhelming evidence corroborating the role of psychological stress in altering inflammatory immune cascades, having secondary effects on fever pathologies such as infections, auto-immune/ auto-inflammatory causes and amyloidopathies.[5]

Factitious fever

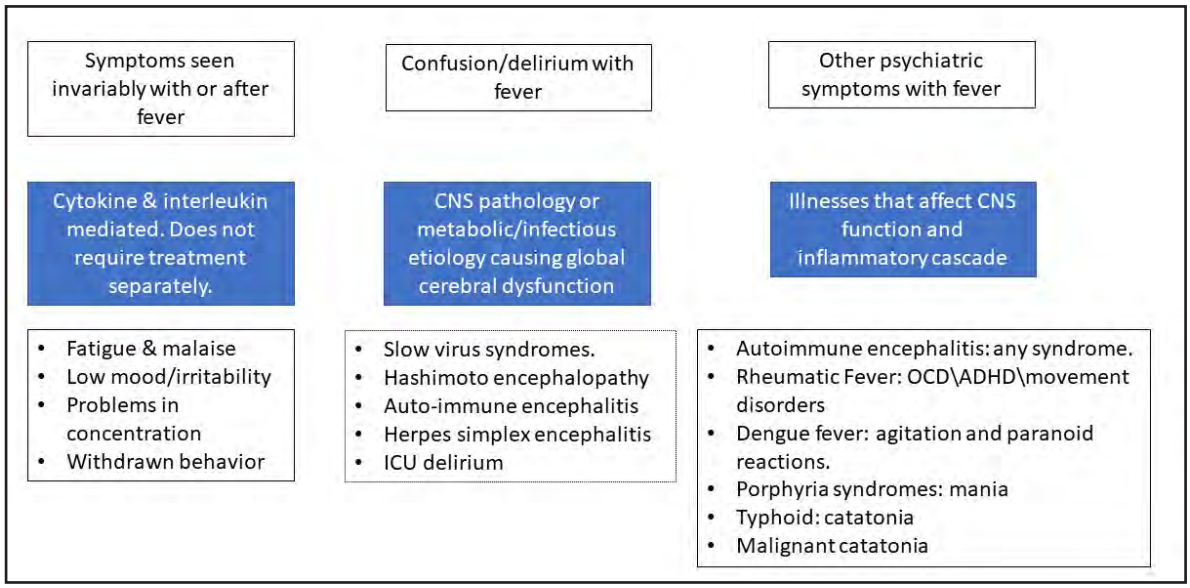
The incidence of factitious fever is rare following the introduction of electronic thermometers. Self-induced fever is reported in 2-3% of all PUO cohorts. It is mainly caused due to repeated sepsis, abuse of thermogenic drugs (anticholinergics, thyroxine etc.) and repeated infections due to foreign body insertion. The review of literature since 80s shows that the typical profile of a patient with factitious fever include young female with known history of psychiatric problems. The most common presentation of this fever is dermatitis artifecta.[6] However, there are scarce publications on factitious fever from India.

Other rare diagnoses, including habitual hyperthermia, should also be considered while doing the work-up. Certain cohort studies from Scandinavia has reported the incidence of 'habitual hyperthermia' in women, which shows a pattern of increase in diurnal temperature variation in the latter half of the menstrual cycle linked to the thermogenic effect of progesterone.[7]

Fever in 'mind-body' syndromes

Fever does not generally accompany chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. If fever occurs along with these diseases, prompt work-up should be carried out to investigate other causes of fatigue. The common psychiatric/psychosocial symptoms associated with fever are shown in fig.2.

Fig.2: Common psychiatric/psychosocial symptoms associated with fever



Research mainly from India has shown that agitation and paranoid reactions are noted in the late stages of dengue fever. Sometimes, the disease may be associated with delirium. The typical presentation of porphyria syndrome is development of fever along with psychiatric manifestations and their subsequent worsening. Typhoid may usually present as catatonia (if there are neuropsychiatric manifestations), which is a state of apparent unresponsiveness to external stimuli. Malignant

catatonia is a poorly understood condition and 5 cases have been reported from India. It is commonly seen in middle-aged males with no psychiatric history.[8] They typically show high fever and stupor, which is accompanied by increase in blood urea nitrogen before the onset of fever and its reduction during fever. Blood urea nitrogen and low serum iron are the specific markers of malignant catatonia.[9]

Psychiatric drugs associated with fever

Neuroleptic malignant syndrome is a rare, but life-threatening idiosyncratic or dose-related reaction to neuroleptic medications, which is marked by fever, muscular rigidity, autonomic dysfunction and altered mental status.[10] The use of antidepressants can cause serotonin syndrome and its incidence is rare in the absence of multiple serotonergic drugs. Stimulant overdose presents with various autonomic signs and increase in core body temperature at onset. Lithium can cause flu-like illness in the early part of treatment. The red flag signs for using clozapine are neutropenia and myocarditis. The abuse or overdose of anti-cholinergics can cause fever or worsening of existing fever.

The fever due to hallucinogen intoxication may be indistinguishable from malignant hyperthermia and rhabdomyolysis.[12] Phencyclidine overdose can cause vertical nystagmus, rigidity, rhabdomyolysis and death. Intoxication with synthetic cannabinoids can be fatal and are associated with seizure, rigidity and profound confusion.[13]

Cannabis and anticholinergics can cause increase in peripheral temperature due to peripheral vasodilation, but not associated with change in core temperature. Opioids may cause decrease in core body temperature, except meperidine, propoxyphene and loperamide.

Conclusion

The incidence of psychogenic / factitious fever is rare and should be considered only after ruling out other diagnoses. Fever due to common syndromes have many psychological symptoms and most of them do not require specific treatment. Fever with delirium or other psychiatric syndromes require a focussed work-up. Fever associated with substance abuse should be considered in young patients with sudden onset of high fever.

References

1. *Karamanou M, Liappas I, Antoniou C, Androutsos G, Lykouras E. Julius Wagner-Jauregg (1857-1940): Introducing fever therapy in the treatment of neurosyphilis. Psychiatriki. 2013 Sep;24(3):208–12.*
2. *Oka T. Psychogenic fever: how psychological stress affects body temperature in the clinical population. Temperature (Austin). 2015 Jun 3;2(3):368–78.*
3. *Psychogenic fever in a patient with small cell lung cancer: a case report [Internet]. [cited 2020 Feb 16]. Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4448880/
4. *Vinkers C, Penning R, Hellhammer J, Verster J, Klaessens JHGM, Olivier B, et al. The effect of stress on core and peripheral body temperature in humans. Stress (Amsterdam, Netherlands). 2013 Jun 24;16.*
5. *Seiler A, Fagundes CP, Christian LM. The Impact of Everyday Stressors on the Immune System and Health. In: Choukèr A, editor. Stress Challenges and Immunity in Space: From Mechanisms to Monitoring and Preventive Strategies [Internet]. Cham: Springer International Publishing; 2020 [cited 2020 Feb 16]. p. 71–92. Available from:* https://doi.org/10.1007/978-3-030-16996-1_6
6. *FACTITIOUS FEVER* | Annals of Internal Medicine | American College of Physicians [Internet]. [cited 2020 Feb 16]. Available from:* https://annals.org/aim/article-abstract/676529/factitious-fever
7. *Yang OO, Currier JS. Reimann's "Habitual Hyperthermia" Responding to Hormone Therapy. Open Forum Infect Dis [Internet]. 2016 Jul 26 [cited 2020 Feb 16];3(3). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5084720
8. *Park J, Tan J, Krzeminski S, Hazeghazam M, Bandlamuri M, Carlson RW. Malignant Catatonia Warrants Early Psychiatric-Critical Care Collaborative Management: Two Cases and Literature Review. Case Rep Crit Care [Internet]. 2017 [cited 2020 Feb 16];2017. Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5303832/
9. *Sienaert P, Dhossche DM, Vancampfort D, De Hert M, Gazdag G. A Clinical Review of the Treatment of Catatonia. Front Psychiatry [Internet]. 2014 Dec 9 [cited 2020 Feb 16];5. Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260674/
10. *Berman BD. Neuroleptic Malignant Syndrome. Neurohospitalist. 2011 Jan;1(1):41–7.*
11. *Physical Detoxification Services for Withdrawal From Specific Substances [Internet]. Substance Abuse and Mental Health Services Administration (US); 2006 [cited 2020 Feb 16]. Available from:* https://www.ncbi.nlm.nih.gov/books/NBK64116/
12. *Larbi E. Drug-Induced Rhabdomyolysis. Annals of Saudi medicine. 2004 Jan 1;18:525–30.*
13. *Keary CJ, Nejad SH, Rasimas JJ, Stern TA. Intoxications Associated With Agitation, Tachycardia, Hypertension, and Fever: Differential Diagnosis, Evaluation, and Management. Prim Care Companion CNS Disord [Internet]. 2013 [cited 2020 Feb 16];15(3). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3795575/

Drug-induced fever

Dr. Nirupam Prakash
Consultant Physician
CGHS, Lucknow

Case summary

In 2014, Schiller and co-workers published a rare case of drug fever. A 74-year-old woman admitted to the hospital after 8 hours of fever (maximum 38.9° C) and shivering following a 40 mg dose of pantoprazole. History revealed that she had similar symptoms with previous doses. She was in good health and had no recent changes in medications. Lab findings indicated WBC 20 x 10^9/L and absence of eosinophilia and CRP (9.8 mg/dL). Within 24 hours of treatment discontinuation, the patient had become afebrile and her laboratory tests were normal. She consented to a re-challenge and 15 hours after receiving a 40 mg pantoprazole dose, the patient developed headache and fever (38.8° C), along with a similar increase in WBC and CRP. She was later successfully treated with esomeprazole. Due to positive re-challenge and the lack of immune-mediated response, the authors categorized this case as an idiosyncratic reaction.[1]

Drug-induced syndromes

Drug-induced syndromes or iatrogenic (physician induced) syndromes are produced by drugs themselves and lead to certain pathological changes. There usually is a temporal relation with the administration of the drug and the symptoms and signs generally regress with treatment cessation.[2] Important risk factors for adverse drug reactions include drugs with narrow therapeutic range, polypharmacy, renal dependence for elimination of drugs, age >65 years and use of anticoagulants/ diuretics. The clinical implications of drug-induced fever are an increased treatment cost, unnecessary

work-up, misdiagnosis of the case as having refractory or resistant infection and prolonged hospital stay.[2] There is lack of incidence data due to the under-reporting of the condition and many cases are missed as refractory or resistant infections. It has been identified as the cause of fever in approximately 5% to 15% of hospitalized subjects. In elderly and females drug fever is mostly reported from use of antimicrobials other than antibiotics/ antiviral agents, subjects on polypharmacy, HIV infected patients, those on cardiovascular drugs while in young males it is due to antibiotic induced drug-induced fever.

Clinical presentation

Features of Drug fever are often not characteristic. Fever can be continuous, remittent or intermittent. High fever is noted in around 40% of individuals hospitalized for Drug fever. Drug fever is noted as the sole manifestation in 3-4% of the subjects. Onset of fever is generally noted within 7 to 10 days from the time of initiation of the culprit drug. However, it varies with drug class and the approximate time taken for fever onset is listed in table 1.[3]

Table 1: drug class and the approximate time taken for fever onset

Drug class	Median (days)	Mean (days)
Antineoplastics	0.5	6
Antimicrobials	6	7.8
CNS agents	16	18.5
Cardiovascular agents	10	44.7

Resolution of the fever within 3 days after discontinuation (max 4-7d) has been noted in most of the patients. Rechallenge of offending agent causes recurrence of symptoms in majority of the cases.[4] The affected individuals are mostly clinically well, and rashes may develop in 18-29%. A maculopapular rash may occur after discontinuation of the offending agent, which may have an urticarial component with or without petechiae. Relative bradycardia is noted in 10% of the patients and the common lab findings include thrombocytopenia, neutropenia, eosinophilia (20%), increased ESR/CRP, increased ALT/AST (9%), normal procalcitonin, deranged renal function, eosinophilic pyuria and interstitial nephritis.

Mechanism of drug-induced fever

Type 1 or type III immune reaction (directly antigenic or act as haptens) is the key mechanism underlying the drug-induced fever. Other drugs may influence the hypothalamic thermoregulatory setpoint or may impair the heat dissipation/conservation mechanism of the body to induce fever. In some cases, the drug itself can induce the production of interleukin or an inflammatory process.[5] The fever may also develop due to pharmacological response of the drug or as an idiosyncratic response in genetically predisposed subjects. The hypersensitivity reaction associated with drug fever may range from low-grade fever to severely intense allergic reaction accompanied by rash, urticaria, eosinophilia, serum sickness, drug-induced SLE, lymphadenopathy, arthritis, nephritis and/or edema.

Agents implicated in drug fever

The agents implicated are anti-microbials (penicillin, sulphonamides, nitrofurantoin, streptomycin, vancomycin, tetracycline, isoniazid), carbamazepine, heparin, phenytoin (pseudolymphoma, vasculitis, DIC delayed 2-6wks), methyldopa, and quinidine.[5] Such subjects may generally show a history of atopy, severe infections or SLE and rechallenge may cause an accelerated reaction. Most of these agents induce sepsis or serum sickness and may often be misdiagnosed as infection-related illness. It is important to consider drug-induce fever as a possibility in patients receiving anti-tubercular drugs, as they have been demonstrated to cause a late-onset drug fever. The drugs may influence the thermoregulatory pathway by central, peripheral or metabolic means. Anticholinergic agents, sympathomimetics, levothyroxine phenothiazines, tricyclic antidepressants, antihistamines and synthetic alkaloids impair hypothalamic function centrally and reduce sweating peripherally, leading to an anticholinergic toxidrome of diminished sweating, coma, hyperreflexia, tachycardia, psychosis, dilated pupils, urinary retention, flushing and pyrexia. Some of the descriptions of presentations of drug fever from commonly used drugs are provided below.

In patients receiving allopurinol, there is evidence of diffuse immune complex vasculitis in the form of immunoglobulin deposits in glomerular basement membranes and at the dermal-epidermal junctions of the skin. Renal insufficiency and concomitant administration of thiazide diuretics in such patients may induce hypersensitivity.

Similarly, contaminants or bacterial lysate present in certain drugs can also induce fever and this causes local inflammation or tissue damage. This is commonly noted after the administration of the following agents:

- IV injections or infusions of antibiotics (e.g. erythromycin, vancomycin, cephalothin or cephalosporins), cytotoxic drugs and other drugs, for example amiodarone, barbiturates, unemulsified diazepam)
- Hypertonic fluids and solutions given for parenteral nutrition
- Microorganism-produced exogenous pyrogens and injection-induced inflammation
- Components of certain drug products

Amphotericin B (50%) or bleomycin causes release of endogenous pyrogens from granulocyte, which gradually decreases with continued administration of amphotericin B so a gradual escalation of dose of these drugs is recommended.

Classical pharmacologic response to penicillins in subjects with syphilis also produces pyrogen release and Jarisch-Herxheimer reaction is a classic example for the same. The clinical features of the reaction include an abrupt onset of fever, myalgia, hyperventilation, and tachycardia about 6-8 hours after starting bactericidal therapy. It occurs in nearly 50% of the patients with early syphilis within a few hours of starting penicillin treatment.[6] Certain drugs may cause idiosyncratic response, mainly attributed to heritable biochemical defect in the individual as seen in malignant hyperthermia of anaesthesia on exposure to variety of inhaled gases.

Management approach to drug fever

The work-up for drug-induced fever should consider exclusion of the following causes:

- Malignancy
- Thromboembolic disease
- Cerebrovascular accidents
- Collagen vascular diseases
- Acute gout
- Surgery
- Trauma
- Serum sickness-like reactions, serotonin syndrome, neuroleptic malignant syndrome or malignant hyperthermia

It may also masquerade as PUO in individuals on polypharmacy, sepsis (INH, quinidine)/drug induced lupus, antimicrobial drug resistance/treatment failure, and relapsing fever. It is paramount to evaluate the temporal administration of medicines in the individual or recent change in medications and matching of the time of administration with onset of fever.

In subjects on multiple drug treatment, all nonessential drugs should be discontinued and the likely drugs should be noted. If the fever persists, essential drugs can be withdrawn, one at a time, every two to three days. The drug speculated as the most probable cause of fever should be withdrawn first or replaced with a chemically unrelated substitute.[7] If particular drug causing fever cannot be withdrawn, conjoined use of corticosteroids, but not antihistamines, should be considered. Treatment with drugs that are rarely or never been reported to cause drug fever should be instituted chloramphenicol, erythromycin, clindamycin and aminoglycosides. There is no role for antipyretics in the treatment of drug-induced hyperthermia due to alteration in thermoregulatory balance and hypermetabolism.

Prophylactic measures to be considered are as follows:

- Administering a test dose and avoiding the drug in febrile patients.
- Use of supportive treatment directed towards lowering the body temperature and maintaining the blood pressure.
- Parenteral administration of diphenhydramine and chlorpromazine.
- Addition of hydrocortisone to abolish or reduce chills.

References

1. *Buck - Pediatric Pharmacotherapy.pdf [Internet]. [cited 2020 Jan 31]. Available from: https://med.virginia.edu/pediatrics/wp-content/uploads/sites/237/2018/01/Jan18_Drug-Fever_PedPharmaco.pdf*
2. *Kumar BJM, Soumya M, Jyothi K, Jagadish BD. Drug Induced Syndromes: An Overview. Indian Journal of Pharmacy Practice. 2012;5(3):13–9.*
3. *Episode 64: How to identify drug fever - Pharmacy Joe - [Internet]. Pharmacy Joe. 2016 [cited 2020 Jan 31]. Available from: https://www.pharmacyjoe.com/how-to-identify-drug-fever/*
4. *Patel RA, Gallagher JC. Drug fever. Pharmacotherapy. 2010 Jan;30(1):57–69.*
5. *Tabor PA. Drug-induced fever. Drug Intell Clin Pharm. 1986 Jun;20(6):413–20.*
6. *Jarisch-Herxheimer reaction..pdf [Internet]. [cited 2020 Jan 31]. Available from: https://www.bmj.com/content/bmj/1/5537/384.full.pdf*
8. *Fang Y, Xiao H, Tang S, Liang L, Sha W, Fang Y. Clinical features and treatment of drug fever caused by anti-tuberculosis drugs. Clin Respir J. 2016 Jul;10(4):449–54.*

A challenging case of prolonged fever

Dr. Ghan Shyam Pangtey
Professor of medicine
LHMC and Associated Hospitals, New Delhi

History

A 16-year-old boy from Haryana presented with a 4-month history of high-grade fever and joint pain for 3 months. The patient had high TLC >16000/µL with neutrophilia. He was not responding to symptomatic treatment with NSAIDs, and antibiotic course of cefixime and azithromycin. He was referred to a super specialty center in Delhi for further evaluation of fever and arthritis. Re-evaluation showed that the intermittent high-grade fever, which persisted for 10-12 hours, used to relieve spontaneously or with NSAIDs. The erythematous rashes present over abdomen and upper chest also improved with fever resolution. There was no history of chills, rigors, bladder/ bowel complaints, weight loss, sweating, genital ulcers, conjunctivitis, gastroenteritis, photosensitivity, alopecia or oral ulcers.

The arthritis involved small joints of hands (MCP/PIP) wrists, elbows, and knees. There was no history of lower backache, alternating buttock pain, difficulty in turning in bed, papular raised lesions, nail changes, or enthesitis. Sudden onset of arthritis in the family or neighborhood was not reported.

Physical examination revealed that the patient was average built, febrile to touch, and had slight pallor with icterus and pedal edema. Multiple, small, firm and non-matted cervical lymph nodes (1 cm maximum) were observed (submental, sub-mandibular and upper cervical). His vitals were stable with pulse rate of 94/min, respiratory rate of 16/min and BP of 130/60 mmHg.

The abdominal examination revealed slight erythema of abdominal wall and hepatosplenomegaly. Other systemic examinations including chest, CVS and CNS were unremarkable.

Differential diagnoses considered were as follows:

1. Reticuloendothelial malignancy due to young age, fever of high grade, arthritis, lymphadenopathy, and hepatosplenomegaly
2. Infection (TB, sepsis, and endocarditis)
3. Miscellaneous (sarcoidosis, vasculitis, and systemic-onset juvenile idiopathic arthritis)

The clinical investigations revealed significant neutrophilia with TLC 17000/mm^3, platelets 3.05 lac/µl, ESR 40 mm/1sthr, normal bilirubin, ferritin 2015 µg/dl and serum ACE 48 IU/L. Rheumatoid factor, ANA and pANCA and cANCA were negative. USG findings indicated hepatosplenomegaly, sub-centimeter mesenteric lymph nodes, and absence of granulomas. X-ray of the joints revealed periarticular osteopenia without erosions. FNAC indicated reactive hyperplasia of lymph nodes and bone marrow examination suggested myeloid hyperplasia. CECT of chest showed presence of sub-centimeter lymph nodes. Based on the clinical and lab investigations conducted for pyrexia of unknown origin, reticuloendothelial malignancy and TB were ruled out. The provisional diagnoses considered were Still's disease and systemic juvenile idiopathic arthritis (JIA).

Criteria for diagnosing Still's disease

Although several diagnostic criteria have been proposed, Yamaguchi and Fautrel criteria are commonly employed for diagnosing Still's disease (Table 1). Yamaguchi criteria, developed in 1992, is the most widely used criteria. Yamaguchi requires exclusion of infections, malignancies and inflammatory diseases; whereas Fautrel considers glycosylated ferritin (GF) as a part of major criteria.[1]

Table 1: Comparison of Yamaguchi and Fautrel criteria

Criteria	*Yamaguchi* et al	*Fautrel* et al
Major criteria	1. Fever ≥39 °C lasting ≥1 week 2. Arthralgia lasting ≥ 2 weeks 3. Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes. 4. Leukocytosis ≥10,000/mm3 with neutrophilic leukocytosis (≥80%)	1. Spiking fever ≥39 °C 2. Arthralgia 3. Transient erythema 4. Pharyngitis 5. Neutrophilic leukocytosis (≥80%) 6. Glycosylated ferritin ≤20%
Minor criteria	1. Pharyngitis or sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver enzyme abnormalities (transaminitis) 4. RF (-ve) or ANA (-ve)	1. Typical rash 2. Leukocytosis ≥10,000/mm3
Exclusion criteria	1. Absence of infection, especially sepsis and Epstein–Barr viral infection 2. Absence of malignant diseases, especially lymphomas 3. Absence of inflammatory disease, especially polyarteritis nodosa (PAN)	None
Criteria requirement	At least 5 criteria including 2 major criteria and no exclusion criteria	4 major criteria or 3 major criteria and 2 minor criteria
Criteria performance	Sensitivity 96.3%, specificity 98.2%, PPV 94.6% and NPV 99.3%	Sensitivity 87%, Specificity 97.8%, PPV 88.7%, NPV 97.5%

Management

The patient was managed on oral prednisolone with a dosage of 1mg/per kg, which was gradually tapered over 6 weeks. Paracetamol and naproxen were used for relieving fever and pain. Methotrexate (10mg/wk) was also started for polyarthritis with folic acid. The patient showed good response in 6 months with significant improvement in fever and arthritis. He was advised to continue methotrexate and folic acid. The patient was receiving Prednisolone intermittently as SOS treatment. The patient did not turn up for further follow-up.

At the age of 24, he returned with a one-month history of high-grade fever, and increased pain and swelling of small and large joints. He had acute colicky abdominal pain, rectal bleeding and low Hb of 8 gm% due to upper GI bleed. He was stabilized with 2 units of packed RBC and referred to a super specialty center for further evaluation. Clinical examination revealed that the patient was severely pale with pulse 120/min, BP 142/96 mm Hg, and respiratory rate 20/min. He had synovitis of bilateral elbow, wrist, MCP, and PIP, and diffuse tenderness in the right hypochondrium and lower abdomen. Urgent endoscopy indicated massive pool of blood in the duodenum, but all the blood vessels were intact. He had normal bleeding and clotting time.

Further investigations revealed hemoglobin 10.1g/dl, TLC 9800 /µL (neutrophils 64%, lymphocytes 32%, with adequate platelets), ESR 44 mm/hr, urea 45 mg/dl, creatinine 0.5 mg/dl, cal/phos-9.4/3.2 mg/dl, Na/K-132/4.1 mg/dl, serum bilirubin, 1.1 mg/dl , AST/ALT 40/56 U/L, ALP 161 U/L, total protein 6.9 g/dl, serum albumin 3.6 g/dl and globulin 3.3g/dl. ANA, pANCA, c-ANCA, HIV, HbsA, and anti HCV were negative. The CECT of abdomen revealed large areas of hematomas (Fig. 1) in the liver, and digital subtraction angiography findings showed multiple pseudoaneurysm in splanchnic and renal vessels (Fig. 2). The patient was transfused with 2 unit of packed RBC during the procedure and sublingual nifedipine was also given for higher BP. A diagnosis of hepatic artery bleed into biliary radicles with hemobilia and hepatic hematoma was made, which would have occurred secondary to polyarteritis nodosa.

Fig. 1: CECT of abdomen showing large areas of hematomas

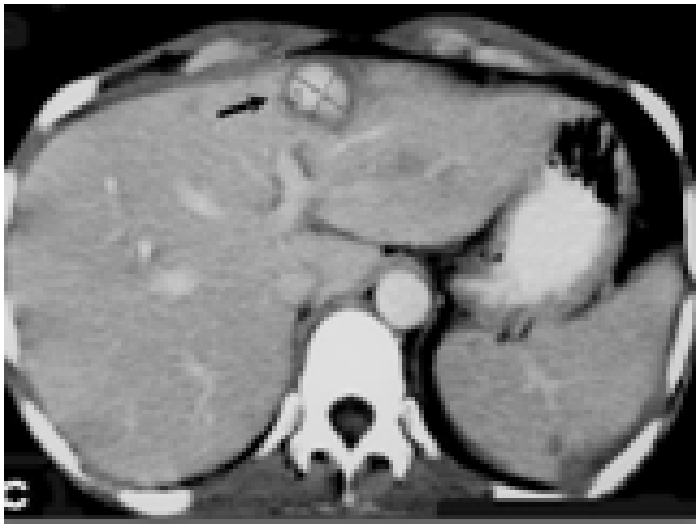
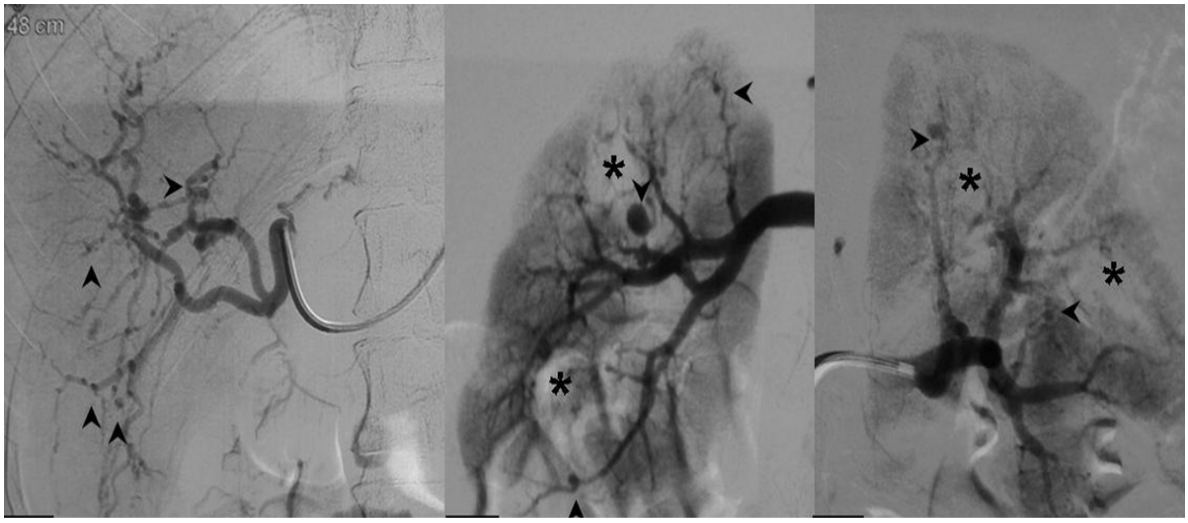
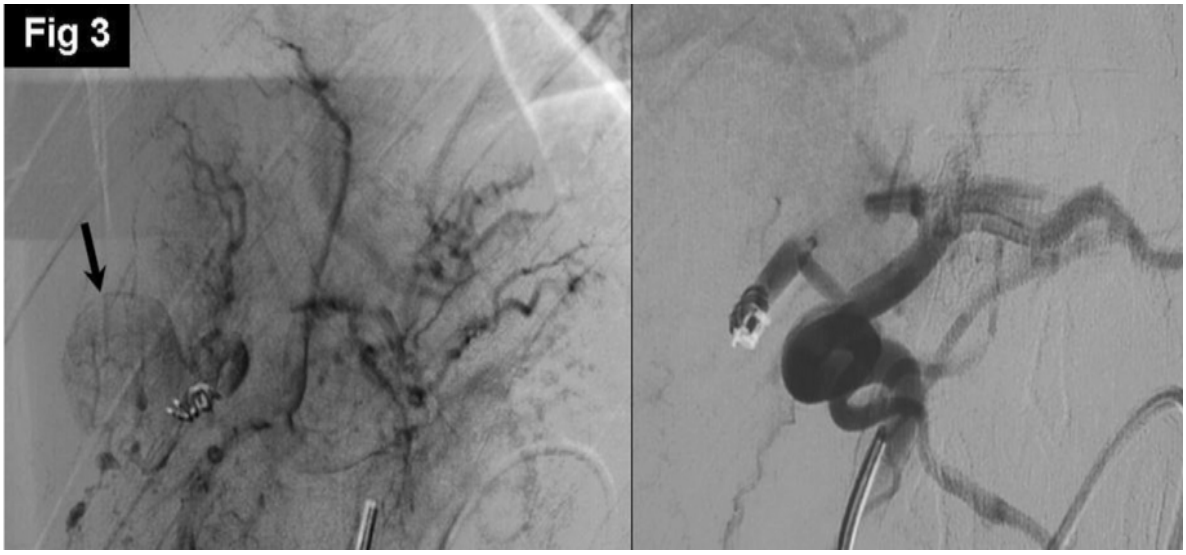


Fig. 2: Digital subtraction angiography showing areas of pseudo micro-aneurysm(arrow), and hemorrhage (star)



Post embolization CT angiography revealed thrombosed pseudoaneurysm of liver with no residual flow with resolving hemoperitoneum (Fig. 3). He was treated with injection of methyl prednisolone 1 gm daily for 5 days and intravenous cyclophosphamide (15 mg/kg). The patient was stabilized and he was discharged after 1 week. He was also advised to continue receiving IV cyclophosphamide once monthly for the next 5 months.

Fig. 3: Post embolization CT angiography showing thrombosed pseudoaneurysm of liver



Systemic Juvenile idiopathic arthritis and adult-onset Still's disease (AOSD)

Juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis that begin before the age of 16 years. The disease persists for >6 weeks and the etiology is unknown. Systemic JIA is noted in

10–15% of children with JIA and is characterized by prominent systemic features such as high spiking fever, skin rash and serositis. Still's disease, a systemic autoinflammatory disorder first described by George Still in 1896, is characterized by presence of systemic features (quotidian fever), evanescent rash, and articular involvement.[2,3]

Considering the rarity of AOSD, the epidemiological data available on AOSD is limited. The corresponding estimated incidence rates noted in Japan, France and Norway were 0.22 (per 1,00,000 person), 0.16 and 0.4.[4] The Indian data pertaining to the disease incidence is lacking. The disease affects younger population with median age of onset 25 years and increased preponderance in women has been noted.[5]

Mechanisms underlying pathogenesis of AOSD are mostly hypothetical. Bacterial and viral infections may act as triggering factor of AOSD pathogenesis. The pathogens implicated include *Campylobacter jejuni*, *Chlaymdia trachomatis*, and measles, mumps, rubella, HIV and hepatitis A viruses.[6]

Cardinal Symptoms of AOSD

Fever (reaching 39°C): Fever persisting for 4 hours is noted in 60-100% of patients with AOSD. It is quotidian or double quotidian in nature. Fever may herald other manifestations such as sore throat, serositis, myalgias and arthralgias.

Arthritis: Arthritis associated with fever spikes is noted in more than two third of the patients. It may affect any joint, including SI and DIP. Arthritis can be erosive in certain cases and there is increased predilection for carpal bones, leading to isolated bilateral carpal ankylosis.

Skin rash: Salmon colored, macular or maculopapular transient rashes are generally noted in AOSD. It is typically seen in trunk and proximal extremities. Purpuric lesion may also occur and are suggestive of grave complications such as reactive hemophagocytic lymphohistiocytosis (RHL), disseminated intravascular coagulation (DIC) and thrombotic microangiopathy.

Leucocytosis and neutrophilia: Leucocytosis (>10000/mm^3) and neutrophilia are typically associated with AOSD. Counts >50000/mm^3 should raise the suspicion of leukemia and patients showing leukopenia should be investigated for RHL.[6]

Other manifestations

- Sore throat with fever is present in 70% of the patients.
- Diffuse and symmetric lymphadenopathy and hepatosplenomegaly generally occur in 40-50% of patients.
- Large and asymmetrical lymphadenopathy should raise the suspicion of hematological malignancy.
- Less frequent manifestations are myalgia, myositis, serositis, hepatitis, acute pancreatitis and lung infiltration.

It is important to rule out infections (virus, bacteria and parasites), malignancy (hematological malignancies and solid cancers), autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, myositis, vasculitis: PAN), autoinflammatory diseases (TNF receptor-associated periodic fever, neutrophilic dermatosis, Sweet syndrome) and drug-related hypersensitivity reactions.

Work-up

- Inflammatory markers: Increase in ESR and CRP is found in 90-100% patients with AOSD.

Leukocytosis with neutrophilia is generally found in 80% of cases. Anemia and thrombocytosis are also common. Decrease in leucocyte, platelets and ESR should raise the suspicion of RHL.

- Serum ferritin: The value >5 times the normal (i.e. 1000 ng/ml) is suggestive of AOSD. However, its specificity is low for diagnosing the disease, as it is a non-specific inflammatory marker. It is increased in other inflammatory conditions like neoplasms, infections and infiltrative disorders.
- Low GF in combination with high ferritin increases the specificity (92.9%) of diagnosing AOSD.
- Transaminitis
- Bone marrow examination may reveal granulocytic hyperplasia and hemophagocytosis may be suggestive of RHL. Bone marrow examination can be undertaken to rule out the possibility of RHL and lymphoma.
- Radiographs of wrist may show soft tissue swelling and mild juxta-articular osteoporosis. As the disease progresses, the patient may also develop joint erosions.
- Computed tomography may reveal hepatosplenomegaly and lymphadenopathy, and it is carried out to rule out neoplastic causes.[7]

The three different clinical patterns of AOSD are monocyclic, polycyclic and chronic articular disease. Monocyclic is self-limiting and enters drug free remission with time. This pattern generally occurs in 20-44% of the patients. Polycyclic is characterized by relapsing and remitting pattern and usually seen in 10-40% of affected patients. Both systemic and joint involvement occur in relapses. Chronic articular disease is marked by regular systemic flares with chronic erosive joint involvement. This is the common pattern seen in 35-67% of the patients.[8]

Treatment

NSAIDs are generally used as supportive treatment during diagnostic process. They should not be used as first line therapy, as retrospective studies have shown non-resolution of symptoms and increased side effects. Corticosteroids are effective in treating AOSD with systemic features. The initial dose ranges from 0.5 mg/kg to 1 mg/kg prednisolone. Tapering of dose is generally recommended after 4-6 weeks. High-dose steroids, i.e. intravenous methylprednisolone pulses, may be required if the patient develops organ-threatening complications such as RHL. Steroid dependence and associated side effects are noted in 42-45% of the patients.

Methotrexate is the most widely used drug for managing AOSD. Methotrexate can be considered as add-on therapy in patients demonstrating steroid dependence and decreased response to steroids. Cyclosporine is as effective as methotrexate and can be used in patients developing severe complications such as RHL. There are conflicting reports on the effectiveness of intravenous immunoglobulin (IVIg).[9] Patients with erosive arthritis, those not responding to methotrexate, and subjects having steroid dependency are treated with biologics like canakinumab, and TNF, IL-1, IL-6, and IL-18 inhibitors.[10-11]

Polyarteritis nodosa (PAN)

PAN can also have varied presentations. It is known to cause microaneurysms and the usual sites include gastrointestinal tract, liver, kidneys, spleen, and cerebral and coronary vasculature. Rupturing of aneurysms can be fatal. But the exact mortality and morbidity are unknown. In the current case, the massive pool of blood in the duodenum visualized in the upper GI endoscopy was due to the

rupture of hepatic artery aneurysm into the biliary tree, resulting in hemobilia, which seeped through the bile duct into the duodenum. A thorough search of current medical literature showed only ten such reported cases.[12]

Take home message

Still's disease developing into PAN with hemobilia is relatively uncommon. Pharyngitis, lymphadenopathy, hepatosplenomegaly, transaminitis, neutrophilic leukocytosis and hyperferritinemia are commonly seen in patients with AOSD. Despite the presence of all these classical features, the diagnosis of AOSD is made by exclusion of infections, malignancy and other known autoimmune and rheumatologic disorders (especially PAN). Extensive work-up is required in patients with persistent fever and /or arthritis, and they should be evaluated for autoimmune disorders and lymphoma. Undifferentiated autoimmune disease transforming into typical classical disease on follow-up is not uncommon in rheumatology.

References

1. *Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992 Mar;19(3):424–30.*
2. *Fautrel B, Zing E, Golmard J-L, Le Moel G, Bissery A, Rioux C, et al. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore). 2002 May;81(3):194–200.*
3. *Still GF. On a Form of Chronic Joint Disease in Children. Med Chir Trans. 1897;80:47-60.9.*
4. *Ali R. Adult Onset Stills Disease- "A Need for Early Diagnosis and Detection of Systemic Score." Indian Journal of Pharmacy Practice. 2020;13(1):83–94.*
5. *Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P, et al. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis. 1995 Jul;54(7):587–90.*
6. *Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol. 2008 Oct;22(5):773–92.*
7. *Fautrel B, Le Moël G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol. 2001 Feb;28(2):322–9.*
8. *Pouchot J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinsky-Sternbach M, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine (Baltimore). 1991 Mar;70(2):118–36.*
9. *Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010 Aug;62(8):2530–5.*
10. *Hong D, Yang Z, Han S, Liang X, Ma K, Zhang X. Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety. Drug Des Devel Ther. 2014 Nov 25;8:2345–57.*
11. *Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014 Jul;13(7):708–22.*
12. *Battula N, Tsapralis D, Morgan M, Mirza D. Spontaneous liver haemorrhage and haemobilia as initial presentation of undiagnosed polyarteritis nodosa. Ann R Coll Surg Engl. 2012 May;94(4):e163-165.*

ABC of CBC and some XYZ

Dr. Swati Pai MD DNB
Consultant Hematopathologist
Manipal Hospital, Bangalore

Introduction

Complete blood count (CBC) is a broad screening test and its use in conjunction with careful review is an effective diagnostic tool. The present paper focuses on some of the newer parameters that are not familiar to clinicians and can be considered as a part of CBC.[1]

Reported and research parameters

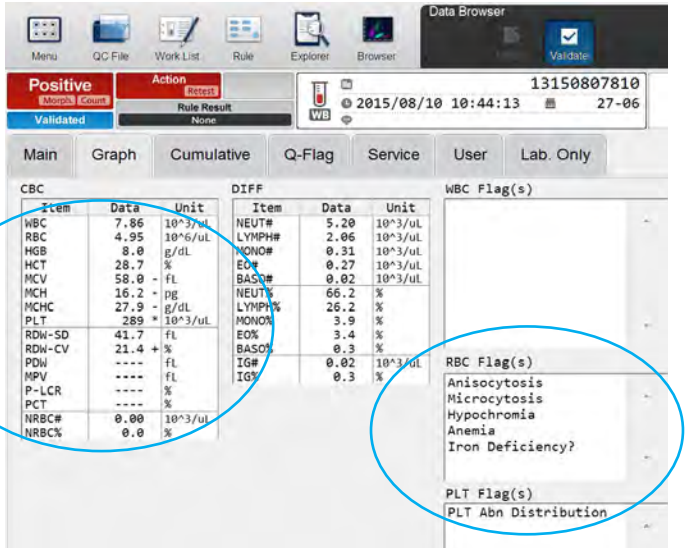
All machines used for hematology analyses have both reported and research parameters. Reported parameters are clinically proven and they can be used for clinical decision making in routine clinical practice. The current paper deals with some of the clinically useful research parameters and how they have gradually evolved into reported parameters.

Red cell indices

The mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW) are considered as red cell indices.[2] The fig.1 shows a hematology report indicating HGB: 8.0 g/dL, HCT: 28.7%, MCV: 58.0 fL, MCH: 16.2 pg, MCHC: 27.9 g/dL and platelet 289X 10^3 U/L. The asterisk on platelet count indicates an abnormal flag. The machine also suggests the possibility of anisocytosis, microcytosis, hypochromia, anemia or iron deficiency. In such cases, most of the clinicians do not perform a peripheral smear

test. The abnormal platelet distribution could be because the machine is counting both RBCs and platelets in the same channel. If the RBCs are smaller in size, there is more chance for the machine to show the same as falsely high platelets. So, it is important for the clinicians to note that the real platelet count may not be reflected by some machines, if the RBC size is relatively small.

Fig. 1: A hematology report with falsely high platelets



What is new in anemia diagnosis?

The use of MCV and RDW in differential diagnosis

MCV and RDW can be effectively used for the differential diagnosis of anemia. The use of RDW <15 with low, normal or high MCV may assist in differentiating thalassemia, iron deficiency anemia and aplastic anemia (Fig. 2).[3]

Fig.2: Differential diagnosis of anemia using MCV and RDW

	Low MCV	Normal MCV	High MCV
	Thalassemia trait	ACD	Aplastic anemia
RDW<15	Heterozygous HbE, HbC, etc.	Heterozygous HbS, HbCS, HbE, etc.	MDS Myeloma
	Anemia of chronic disease (ACD)	Hereditary spherocytosis	Liver disease hyperthyroidism
		Acute hemorrhage	

RDW>15	Iron deficiency anemia	Early or combined nutritional deficiency	B12 deficiency, folate deficiency
	Thalassemia intermedia	Myelodysplasia	AIHA
	Sideroblastic anemia		Drugs: HU, antiretroviral, AZA, etc.
	Severe ACD RBC fragmentation	Sickle cell anemia or Homozygous HbCS	

Macrocytic anemia

Hypersegmented polymorphs and ovalocytes are generally noted on examination of peripheral smear in megaloblastic anemia.[4] Their absence, and normal levels of folic acid and vitamin B12 may be suggestive of non-megaloblastic anemia, and a reticulocyte count can be recommended. It is a good clinical practice to conduct reticulocyte count in all cases of anemia. High reticulocyte counts are suggestive of macrocytosis due to hemolysis. If the count is low or normal, the probability of underlying oncologic reasons has to be considered. It is always recommended to perform a bone marrow test based on the reticulocyte count in macrocytic anemia.[4]

Reticulocyte Hemoglogin

A newer parameter called reticulocyte hemoglobin, measures the amount of hemoglobin in reticulocytes. This is a very good indicator of functional iron deficiency. This type of iron deficiency is caused due to insufficient iron incorporation into erythroid precursors with adequate iron stores.[5] Hepcidin plays a crucial role in the inhibition of iron absorption. Dysregulation of hepcidin due to inflammation, infection or malignancy can cause decreased gut iron absorption, thereby leading to functional iron deficiency.[6]

Manual counting of reticulocytes for diagnosing the iron deficiency is very cumbersome and observer dependent. Nowadays, automated reticulocyte counts are used, and they also measure reticulocyte hemoglobin equivalent (Ret-He). It reflects the hemoglobin content of the freshly produced reticulocytes and the actual iron supply for hemoglobin synthesis in the bone marrow.[7] Reference interval of RET-He followed in our laboratory is 28-35 pg and it correlates with the internationally recommended range. It is important for each lab to establish their own range for any newer research parameter.

RET-He has significant clinical relevance in detecting early stage iron deficiency. It helps in distinguishing classical and functional iron deficiency in anemia of chronic disease (ACD).[8] It can also be used for monitoring erythropoietin and iron treatment.[8] Some of the patient cases in which the RET-He value helped in concluding the diagnosis have been discussed below. In the case of a CKD patient on dialysis with a HB level of 9.2 g/dL, the RET-He value of 19.9 pg helped to rule out

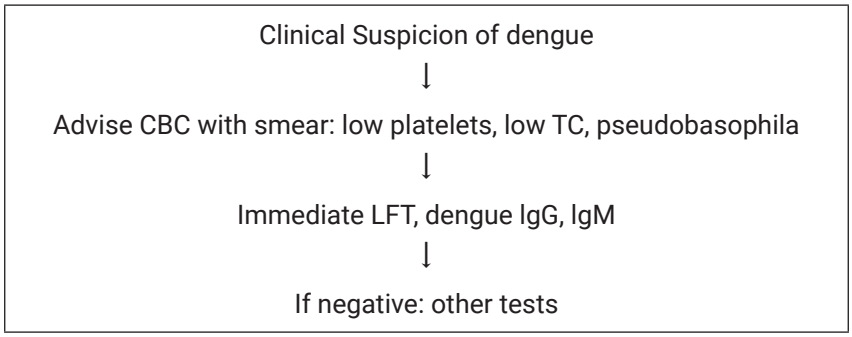
the possibility of having anemia due to CKD. The patient was diagnosed as having iron deficiency anemia based on the RET-He. In another patient with a RET-He value of 25.6, the HB level was 7.6 g/dL. The disease was concluded as iron-restricted erythropoiesis. In both the cases, the diagnosis was achieved without conducting extensive tests like TIBC, UIBC, transferrin etc.

Cell counters in febrile illnesses

Pseudobasophilia

Evaluation of the serological reports of certain dengue cases had demonstrated decreased platelets and increased hematocrit and basophil count. Further peripheral smear analysis demonstrated the presence of 'pseudobasophils', which may mimic a blast or a plasma cell. A study of dengue cases between 2009-2011 demonstrated that all the patients (n=477) demonstrated a clinical course of pseudobasophilia (flagging of atypical lymphocytes as pseudobasophil).[7] Based on this finding, an algorithm was made for screening dengue patients for immediate LFT and dengue IgG/IgM based on low platelets, low TC, and pseudobasophilia (Fig. 3). This algorithm has received a greater recognition, at the conference of the International Society for Laboratory Hematology (ISLH), as an effective screening tool for febrile illnesses.

Fig. 3: Algorithm for screening dengue patients



Pseudoeosinophilia

Certain malaria cases had demonstrated low platelet and high eosinophil counts, but the peripheral smear analyses showed the presence of plasmodium instead of eosinophils. Automated analyzers differentiate eosinophils from neutrophils based on side light-scattering differences. The incorrect flagging of malaria as eosinophilia (pseudoeosinophilia) is due to the incorrect classification of hemozoin-containing neutrophils in the parasite as eosinophils or two atypical eosinophil populations and two neutrophil populations.[9]

Reticulated or immature platelet

Reticulated platelets or immature platelets are newly released 1-2 days old platelets. They are larger than matured platelets in size and are analogous to the red blood reticulocytes. The immature platelet fraction (IPF) is a very good marker of thrombopoietic activity and platelet recovery, and a regulator of platelet transfusion.[10]

Two students residing in the same hostel were diagnosed with dengue. The first patient had a platelet count of 16X 10^3 U/L and IPF 6.8%. The corresponding values noted in the second patient were 24X 10^3 U/L and IPF 27.3%. Though the platelet counts were low in both the cases, the IPF helped in predicting the platelet recovery. Hence the former patient was admitted and the latter returned home. Monitoring the second patient demonstrated that his platelet level increased to 42X 10^3 U/L by next day.

Cell counters in sepsis

The WBC count of >12000 or <4000 plays a paramount role in the diagnosis of sepsis. Apart from WBCs, the counting of all types of immature granulocytes namely metamyelocytes, promyelocytes and myelocytes may serve as a diagnostic marker to discriminate between SIRS and sepsis.[11] It is a faster and cheaper marker for diagnosing neonatal sepsis, and >2% indicates acute infection. Both immature granulocyte count and nucleated red blood cell (NRBC) count are beneficial in monitoring sepsis in pediatric, neonatal and adult ICUs.[12]

References

1. *Sarma PR. Red Cell Indices. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations [Internet]. 3rd ed. Boston: Butterworths; 1990 [cited 2019 Dec 12]. Available from:* http://www.ncbi.nlm.nih.gov/books/NBK260/
2. *Yenilmez ED, Tuli A. Laboratory Approach to Anemia. Current Topics in Anemia [Internet]. 2017 Dec 20 [cited 2019 Dec 12]; Available from:* https://www.intechopen.com/books/current-topics-in-anemia/laboratory-approach-to-anemia
3. *Aslinia F, Mazza JJ, Yale SH. Megaloblastic Anemia and Other Causes of Macrocytosis. Clin Med Res. 2006 Sep;4(3):236–41.*
4. *Urrechaga E, Borque L, Escanero JF. Biomarkers of Hypochromia: The Contemporary Assessment of Iron Status and Erythropoiesis. Biomed Res Int. 2013; 2013: 603786.*
5. *Nemeth E, Ganz T. The Role of Hepcidin in Iron Metabolism. Acta Haematol. 2009 Nov;122(2–3):78–86.*
6. *Peerschke EIB, Pessin MS, Maslak P. Using the hemoglobin content of reticulocytes (RET-He) to evaluate anemia in patients with cancer. Am J Clin Pathol. 2014 Oct;142(4):506–12.*
7. *Gibbs G, Campbell G, Christie I. Pseudobasophilia and the Advia 120. Hematology. 2009 Jun;14(3):159–63.*
8. *Agarwal MB, Pai S. Reticulocyte Hemoglobin Content (CHr): The Gold Standard for Diagnosing Iron Deficiency. J Assoc Physicians India. 2017 Oct;65(12):11–2.*
9. *Huh J, Jung J, Yoon H, Chung W. Pseudoeosinophilia associated with malaria infection determined in the Sysmex XE-2100 hematology analyzer. Ann Hematol. 2005 Jun;84(6):400–2.*
10. *Grotto HZW, Grotto HZW. Platelet and reticulocyte new parameters: why and how to use them? Revista Brasileira de Hematologia e Hemoterapia. 2016 Dec;38(4):283–4.*
11. *Nierhaus A, Klatte S, Linssen J, Eismann NM, Wichmann D, Hedke J, et al. Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis–a prospective, observational study. BMC Immunol. 2013 Feb 12;14:8.*
12. *Nigro KG, O'Riordan M, Molloy EJ, Walsh MC, Sandhaus LM. Performance of an automated immature granulocyte count as a predictor of neonatal sepsis. Am J Clin Pathol. 2005 Apr;123(4):618–24.*

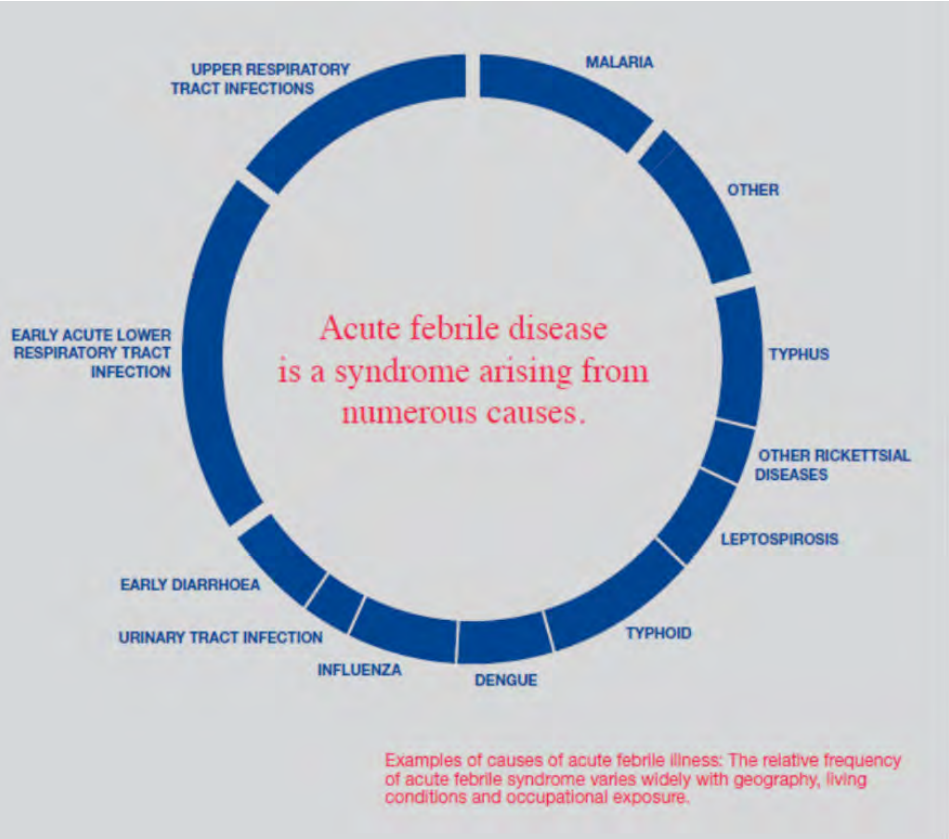
New Rapid Diagnostic Tests for Fever

Dr. Aruna Poojary
HOD, Dept. of Pathology & Microbiology
Breach Candy Hospital Trust &
Freelance Infection Control Advisor

Introduction

Fever is a very non-specific symptom associated with both infectious and non-infectious diseases. Fever due to infectious agents can be either community acquired or hospital acquired, and the key pathogens involved are bacteria, viruses, fungi and parasites. The key to the diagnosis of fever is history and thorough clinical examination. Laboratory assays for fever can be non-specific and specific. According to the WHO report, acute febrile disease syndrome can be due to various causes (Fig. 1) and it is more troublesome in certain risk groups such as returning travelers, and HIV-positive/ neutropenic patients.[1]

Fig. 1: Common causes of acute febrile illness



Fever syndromes are caused by a variety of pathogens and their accurate identification assists in the administration of targeted therapy, thereby to avoid anti-microbial resistance. Therefore, it is important to understand the epidemiology, prevalence and seasonal distribution of the pathogens. As per the WHO report, the case fatality rate for adults with febrile illness, who required hospital admission, ranges between 5% and 24%. Hence, early diagnosis is of paramount importance for the prevention of severe illness and mortality. Moreover, with newer technology for diagnosis; it is practical, affordable, accurate and accessible to everyone.

Laboratory diagnosis of infective fever syndromes

The routine diagnostic tests include CBC, ESR, and CRP. The specific conventional tests include microscopy, serology tests and culture. Molecular methods are the newer techniques for detecting pathogens. Microscopy involves both wet mounts and stained smears. But microscopy is insensitive when compared to other techniques and it is observer dependent.[2]

Different cultures can be performed using blood, sterile body fluids, pus/ abscesses (deep or superficial), tissue, CSF, stool, urine and respiratory secretions. Though culturing is considered as gold standard, there are certain disadvantages such as slow turnaround time (TAT), no growth in case of fastidious pathogens, non-cultivable pathogens like viruses and parasites, and effect of prior antimicrobial therapy.[2]

Serology-based tests are easily available diagnostic techniques for the detection of antigens and/or antibodies. Most of them are recommended by WHO as point-of-care techniques, which can be done at the physician office level or in a hospital setting. For example, Binax NOW is a urine antigen assay for Streptococcus pneumoniae and the test is very easy to perform, and no technical expertise is required. However, certain serology-based tests namely western blot, ELISA and fluorescent assays should be carried out in a lab setting. There are certain disadvantages such as late appearance of antibodies, low sensitivity of RDTs and false positives with Immunofluorescent methods.[3]

Diagnostic test: The need of the hour

The test should be sensitive, specific, objective and should allow direct specimen analysis. It should be able to identify different classes of pathogens, their drug resistance gene, and should have short TAT. Such a test helps in the administration of early appropriate therapy and implementing infection control measures, thereby to reduce the associated morbidity and mortality.

New molecular methods

Molecular methods assist in the pathogen detection using nucleic acids (DNA/RNA) of pathogens as targets. PCR, a highly sensitive molecular technique, can be used for performing either singleplex assays (detection of single pathogen at a time) or multiplex assays (multiple pathogens).

Singleplex PCR

GeneXpert is an easily available singleplex PCR, which is used for detection of TB with rifampicin resistance, C. difficile with hypervirulent gene, MRSA/SA, flu viruses, enterovirus (CSF), HIV, HCV and HBV.[4]

Hong et al. have concluded the superior diagnostic potential of GeneXpert over PCR for the detection of enteric RNA in the CSF of meningitis patients. The study found that 66 samples were positive by GeneXpert, while only 43 by RT-PCR.[5] Ben-Zvi et al. have evaluated the influence of GeneXpert test on the clinical outcomes of S. aureus bacteremia. The researchers found that the introduction of the test significantly improved the administration of appropriate antibiotic therapy and the reduction of vancomycin use.[6]

Multiplex assays

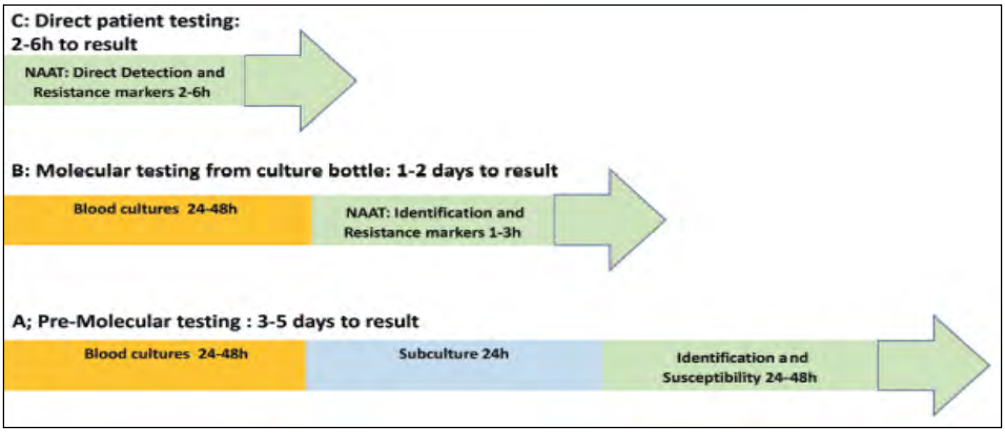
Multiplex assays have multiple targets. They are based on syndromic approach and can identify

pathogens causing syndrome complex. They also help in detecting drug resistance genes and have a rapid TAT of 3 to 24 hours. Direct samples can be used for the analysis and the samples that can be analyzed include blood, sterile body fluids, respiratory samples, stool and CSF.[7]

Direct blood-based tests

Blood culture is gold standard for the diagnosis of febrile illness (Fig 2). The volume of blood required plays a very crucial in the accuracy of blood assay and the minimum volume required is 20 ml. Contamination is a major problem in blood-based assays and skin antisepsis is very important to avoid contamination. After conducting blood-based assays, PCR-base testing can be carried to conclude the diagnosis. Researchers are currently working on tests that enable direct testing of the blood, without blood culturing.[8] The various assays available for the rapid diagnosis for blood cultures include PNA FISH, Verigene, GeneXpert, BioFire, Accelerate Pheno System and T2 Biosystem.[9] However, only GeneXpert and BioFire are currently available in India.

Fig 2: Progression in blood culture diagnostics with the development of molecular technologies over time



Pediatric cases for syndromic approach PCRs

Case 1

6yr male child presented with high grade fever and cough for the past 4 days. The child appeared comfortable but on auscultation had crackles. The child had been started on Amoxycillin /Clavulanic acid syrup for 3 days but the symptoms were not resolving. An X ray chest showed a patch in the left lower lobe suggestive of pneumonia. Based on these features , an atypical pneumonia was suspected. Apart from routine investigations like complete blood count, C reactive protein, IgM Mycoplasma , an upper respiratory PCR was also ordered. A nasopharyngeal swab was collected and the specimen was run using a syndromic approach PCR . The result was obtained in the next 2 hours which showed Mycoplasma pneumoniae. The IgM Mycoplasma came negative as it takes time for antibodies to appear and are seen only after 7 days of illness.

Implications of the respiratory PCR in this case :

- Accurate identification of the pathogen causing pneumonia within a few hours
- Initiation of appropriate antimicrobial agents e.g clarithromycin and stopping Amoxycillin / Clavulanic acid which does not act against Mycoplasma.
- Earlier indicator for an outbreak of pneumonia due to atypical pathogens in the community

Case 2

A 3 year old female child presented with high grade fever and drowsiness in the emergency unit. On examination, meningitis was suspected, for which the patient was admitted to the Pediatric ward for further management. The patient was immediately started on intravenous antimicrobial agents (Vancomycin and Meropenam) and a lumbar puncture was planned. The CSF routine examination showed 320 cells/mm3 with mild increase in proteins (54mg/dl) and normal glucose. A multiplex PCR panel was also requested for this CSF which flagged positive in two hours with Enterovirus. The CSF cultures remained negative.

Implications of the meningitis /encephalitis PCR in this case

- Accurate identification of the pathogen causing the CNS infection with a few hours
- De-escalation of antimicrobial agents as aseptic meningitis requires only supportive therapy
- This PCR cover all pathogens causing community acquired meningitis and encephalitis and requires about 100 microlitres of the samples making it a valuable test for all such suspected cases

Case 3

A 10 year old male child presented to the OPD with repeated loose motions for the past 1 month. The frequency was 4 to 5 episodes of large volume watery stool per day self limiting only to return back after a few days return back. There was no fever or abdominal pain. He had bee treated with multiple antibiotics in the past but the diarrhoea did not resolve. A stool routine did not show significant pus cells or red cells, but was watery with mucous present. The culture did not grow any significant bacterial pathogen after 48 hours. A gastrointestinal multiplex PCR was also requested since this was a non-resolving diarrhoea . The PCR detected Cryptosporidium species this changed his treatment. It was later found that the child was regularly swimming which could have been the source for the infection. Cryptosporidium can survive sodium hypochlorite which is the common disinfectant used for disinfection of swimming pools

Implication of the GI PCR in this case:

- Accurate identification of the pathogen causing the disease in a non-resolving diarrhoea
- Change in therapy as Cryptosporidium is not a common pathogen in immunocompetent individuals

References

1. *McGregor AC, Moore DA. Infectious causes of fever of unknown origin. Clin Med (Lond). 2015 Jun;15(3):285–7.*
2. *Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gilligan PH, et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiologya. Clinical Infectious Diseases. 2018 Aug 31;67(6):e1–94.*
3. *Caliendo AM, Gilbert DN, Ginocchio CC, Hanson KE, May L, Quinn TC, et al. Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. Clin Infect Dis. 2013 Dec 1;57(Suppl 3):S139–70.*
4. *Sah AK, Joshi B, Khadka DK, Gupta BP, Adhikari A, Singh SK, et al. Comparative Study of GeneXpert MTB/RIF Assay and Multiplex PCR Assay for Direct Detection of Mycobacterium tuberculosis in Suspected Pulmonary Tuberculosis Patients. Curr Microbiol. 2017 Sep;74(9):1026–32.*
5. *Hong J, Kim A, Hwang S, Cheon D-S, Kim J-H, Lee J-W, et al. Comparison of the genexpert enterovirus assay (GXEA) with real-time one step RT-PCR for the detection of enteroviral RNA in the cerebrospinal fluid of patients with meningitis. Virol J [Internet]. 2015 Feb 13 [cited 2019 Dec 11];12. Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4342037/
6. *Ben-Zvi H, Drozdinsky G, Kushnir S, Avni T, Scheuerman O, Bishara J, et al. Influence of GeneXpert MRSA/SA test implementation on clinical outcomes of Staphylococcus aureus bacteremia - a before-after retrospective study. Diagn Microbiol Infect Dis. 2019;93(2):120–4.*
7. *Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic Panel-Based Testing in Clinical Microbiology. Clin Microbiol Rev [Internet]. 2017 Nov 15 [cited 2019 Dec 12];31(1). Available from:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5740973/
8. *Samuel L. Direct Detection of Pathogens in Bloodstream During Sepsis: Are We There Yet? The Journal of Applied Laboratory Medicine. 2019 Jan 1;3(4):631–42.*
9. *Wolk DM, Johnson JK. Rapid Diagnostics for Blood Cultures: Supporting Decisions for Antimicrobial Therapy and Value-Based Care. The Journal of Applied Laboratory Medicine. 2019 Jan 1;3(4):686–97.*

Recent advances in management of dengue fever

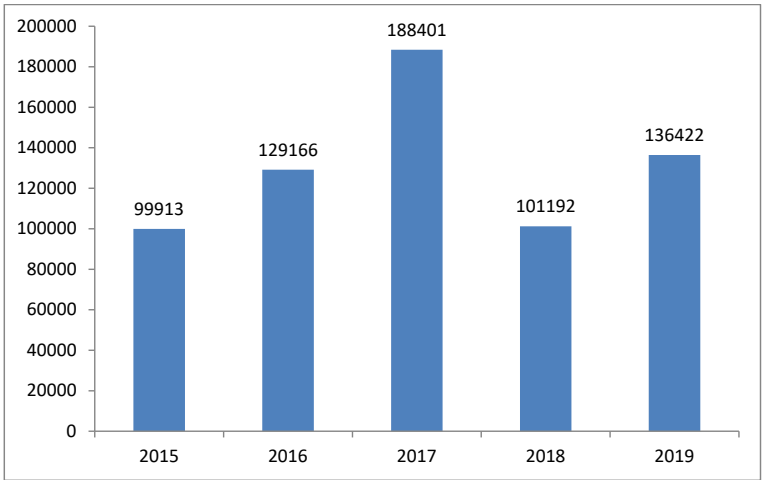
Prof. Channaraya V MD, DNB, FICP, FICC
Former HOD & Prof of medicine, KIMS
SENIOR PHYSICIAN, Sagar hospital, BSK, Bangalore

Introduction

Dengue is the cause for 390 million infections and 5,00,000 dengue hemorrhagic fever (DHF) annually. Though, the mortality associated with DHF is only 4%, there is a 4-fold increase in the number of cases in the last 20 years.[1] The disease may present with various range of clinical phenotypes. Severe end of the spectrum of the disease noted are capillary leak, coagulopathy, and organ impairment.

According to the data published by National Vector Borne Disease Control Programme (NVBDCP), the number of dengue cases in India as on November 2019 is 136422 (Fig. 1).[2] Recently, a case of sexual transmission of dengue has been reported from Spain.[3]

Fig.1: The incidence of dengue in India since 2015



Dengue cases reported at KIMS hospital

The analysis of 14-year data on dengue cases reported at KIMS hospital shows that the number of cases has increased to 1080 in 2017 when compared to 95 in 205. The dengue-associated mortality reported in these years were 11 and 3 respectively. The deaths reported were mainly due to multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), DHF, and dengue shock syndrome.

Table 1: Deaths reported due dengue at KIMS hospital, 2013-16

Causes	2013	2014	2015	2016
DSS	5	2	4	3
DSS with MODS	5	1	3	2
ARDS	1	2	1	2
SEVERE DENGUE	2	0	0	1
DHF	0	2	1	2
DHF with ENCEPHALOPATHY	0	0	0	0
DSS with T2DM	0	0	1	0
DSS with AKI	0	0	2	1
TOTAL	13	7	12	11

Cases reported at Sagar hospital

Data collected from 1st January to 28th September 2019 at Sagar hospital, BSK, included 437 dengue cases. The number of adult admissions reported was 364, and the male-to- female ratio was 189:175.

Age distribution of the subjects showed that highest number of cases was reported for the age group of 21-30 (106) followed by 31-40 (99), and the cases were more during the months of July and August (165 and 88). Among the admitted cases, only 27 patients needed platelet transfusion, and 25 of them showed bleeding manifestations before transfusion.

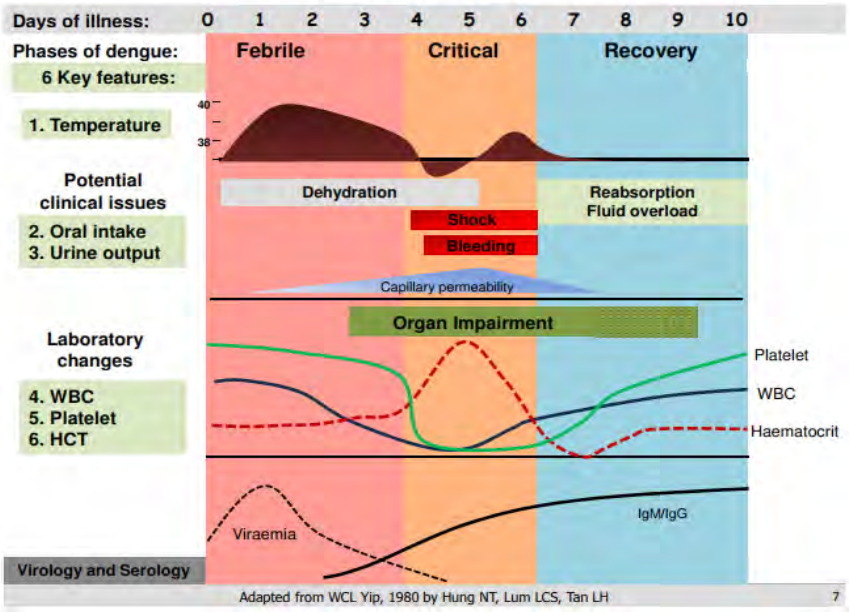
Complications encountered

Around 63 patients needed ICU admission and complications were reported by 172. The corresponding number of cases reported with hepatitis, severe hepatitis, dengue shock syndrome and multi-organ dysfunction were 151 (41.4 %), 11 (3%), 12 (3.1%) and 3 respectively. The longest duration of hospital stay noted was 31 days. The analysis also showed that 7 (1.92%) patients each had respiratory complications and acute kidney injury. In addition, one patient each was noted with acute coronary syndrome- inferior wall myocardial infarction and encephalopathy.

Manifestations of dengue infections

Dengue fever is caused by four different serotypes. The infection with one type usually confers lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications. The major manifestations of dengue include undifferentiated fever, dengue fever with and without hemorrhage, and hemorrhagic fever with and without shock syndrome. Common bleeding complications noted are purpura, petechiae, hematemesis, gingival bleeding and nasal bleeding. The critical period in dengue occurs after subsiding the fever and it is marked by reduce platelet count/WBC, increased hematocrit, and increased risk for shock, bleeding, organ impairment, and increase in IgM/IgE antibodies (Fig.2).[4]

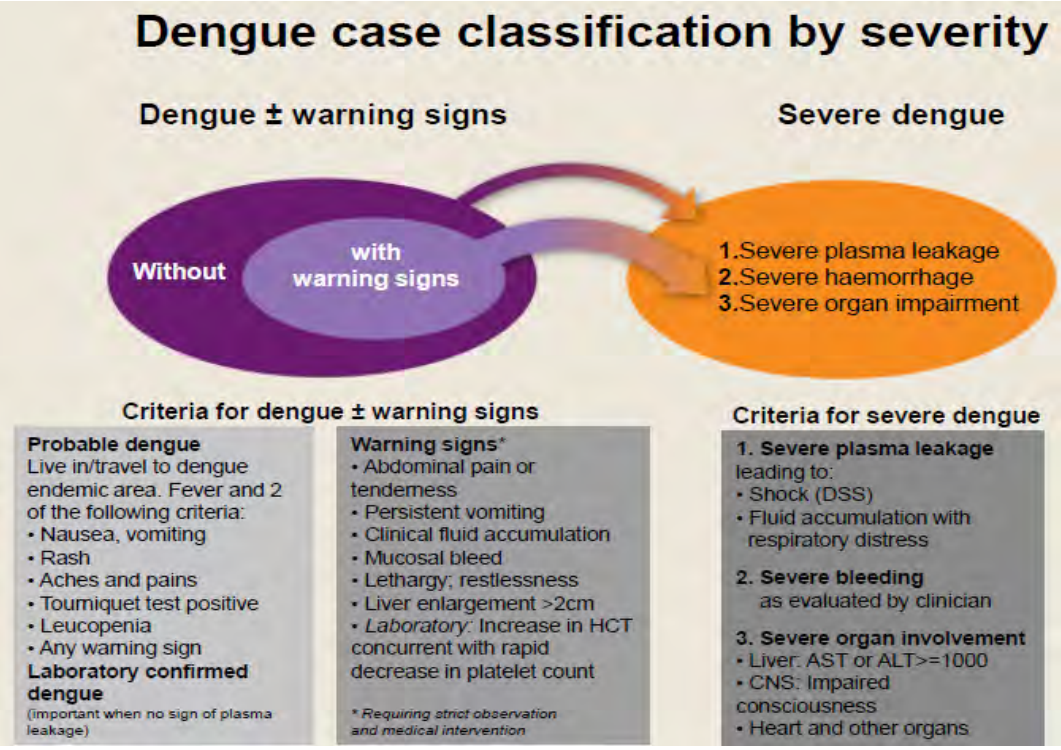
Fig.2: Phases of dengue fever



Classifying dengue cases

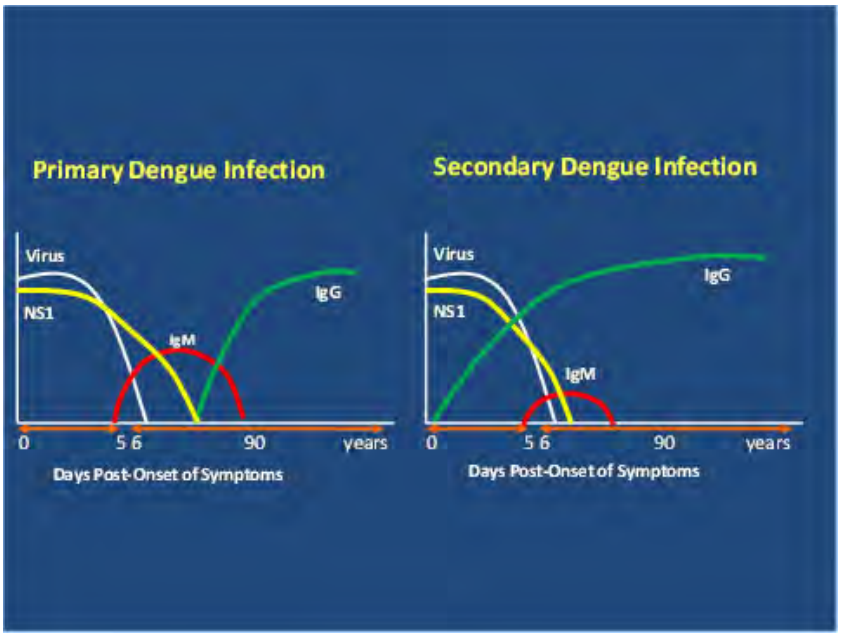
WHO has put forth the warning signs and criteria for classifying severe dengue. The warning signs are abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, liver enlargement>2 cm and increase in HCT concurrent with rapid decrease in platelet count. Severe plasma leakage, bleeding, and organ involvement are the criteria to be considered for classifying severe dengue (Fig. 3).[5]

Fig. 3: Classification criteria and warning signs put forth by WHO



In 2012, WHO has coined the term expanded dengue syndrome to describe cases that do not fall into either dengue shock syndrome or dengue hemorrhagic fever. The atypical manifestations noted in such patients include those with co-infections, end-organ damage and high-risk group subjects (infants, pregnant/geriatric subjects, subjects with hypertension, IHD and hemoglobinopathies and immunocompromised patients).[6]

Fig. 4: Course of antigen and antibody profile in patients with primary and secondary dengue infection



Lab diagnosis

Lab diagnosis is paramount in concluding the infection, because more than half are asymptomatic or have undifferentiated fevers. It is necessary to properly plan and conduct the investigations for accurate diagnosis. The recommended tests before 5 days post onset of fever are virus culture, viral RNA RT-PCR and NS1Ag. Mac ELISA IgM and Mac ELISA IgG are the preferred tests to be carried out after 5 days post onset of symptoms.[7] The following are some of the innovative and novel approaches for the laboratory diagnosis of dengue:

- POINT OF CARE-ASSURED (affordable, user friendly, rapid, and easy to handle and deliver)
- BIOSENSOR PLATFORM-NS1Ag (detection using screen printed carbon electrode)
- IGM Ab detection (based on optical biosensor/ nanoparticle on cellulose paper sheet)
- Genosensor (detection of dengue genome)
- RT-LAMP platform (PCR, microfluidic platform)

Case studies on dengue

Case 1: Dengue with MODS

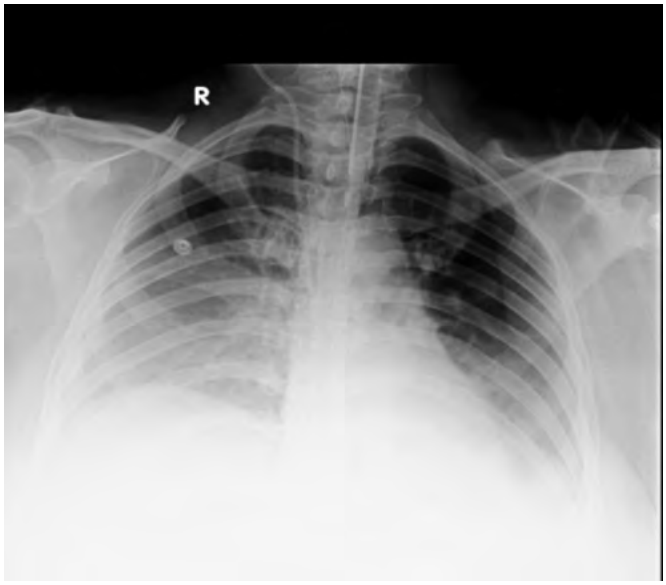
A 31-year-old female admitted to emergency department with complaints of fever, tiredness, myalgia and abdominal pain for 5 days and 1 episode of hematemesis. She had diabetes for last 6 months and physical examination revealed tenderness in abdomen.

The lab findings were as follows: Hb/PCV-14.5 g% /43.2%, TLC- 3420 /mm^3 platelet- 22,000 /mm^3,

bilirubin-2.53 g/dL (direct 2.11, indirect-0.42), albumin-2.6 g/dL, SGOT/PT-7660 /1840 U/L, ALP-550 U/L, GGT-691 U/L, creatinine-1.4 mg/dL, and Na/K-132 mmol/L./4.2 mmol/L. Ultrasound revealed mild hepatomegaly, moderate gall bladder wall edema and minimal ascites. The patient's condition deteriorated on the second day with increased severity of abdominal pain (HR- 126/min, BP: 100/70mm Hg, RR 40/min).

She had an episode of generalized tonic-clonic seizure. She was mechanically ventilated and started on inotrope support in view of severe respiratory distress with hemodynamic instability. Chest X-ray was suggestive of ARDS (Fig. 5). The patient had undergone hemodialysis due to the development of acute kidney injury. Multiple blood, FFP, and platelet transfusions were performed because of severe coagulopathy. She subsequently developed encephalopathy (non-recovering sensorium with normal CT brain). Hb and platelet count dropped to 7.6 g/dL and 18,000/mm^3 respectively. SGOT/PT raised to a maximum of 19280/3260 U/L. The organs involved were liver (hepatitis), kidney (AKI), lungs (ARDS), brain (seizures) blood (thrombocytopenia), and coagulation failure.

Fig. 5: Chest X-ray indicative of ARDS

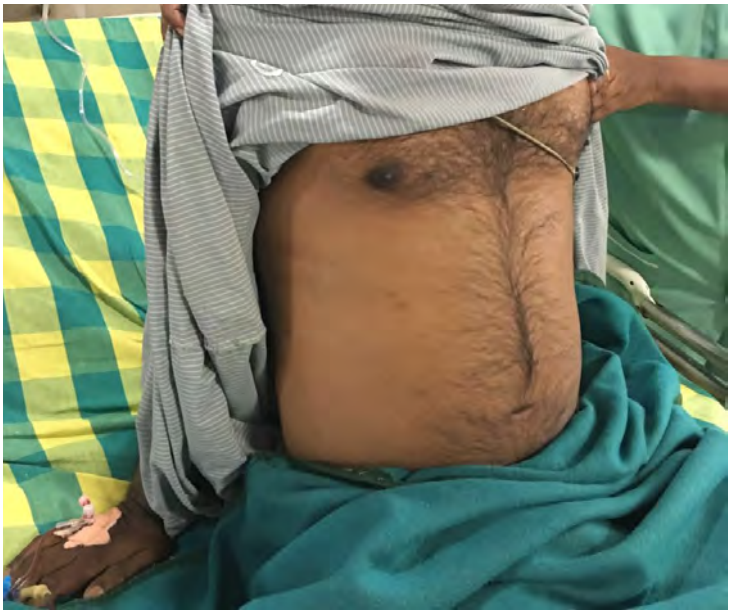


The patient's condition improved gradually. During the period of recovery, she developed upper GI bleed in the form of melena. Endoscopy and colonoscopy revealed diffuse mucosal bleed (secondary to coagulopathy). Urine output gradually improved and she was discharged on 31st day of admission after complete recovery.

Case 2: Dengue with unusual bleeding

A male patient was admitted with positive dengue and thrombocytopenia. His lab findings revealed Hb 16 g %, TC: 4000 cells/cumm, PCV 50.5%, platelet 0.86 lakhs/cumm, SGOT 73 IU/L, and SGPT 32 IU/L. Three days after admission, the patient developed severe pain and distention of abdomen. He was tachypneic and restless. He showed signs of abdominal distention and tenderness.

Fig.6: Signs of abdominal distention



Due to the development of hypoxia, he was shifted to ICU and further investigations revealed Hb: 4.1 g% platelet 0.99 lakhs/mm^3, PCV 20.4%, SGOT 944 IU/L and SGPT 434 IU/L. X- ray of abdomen indicated features of ascites (Fig. 7). Based on CT scan, the diagnosis was concluded as dengue hemorrhagic fever with hemoperitoneum (Fig. 8). Transfusion of the blood from peritoneum assisted in patient recovery.

Fig. 7: X- ray of abdomen revealing the features of ascites

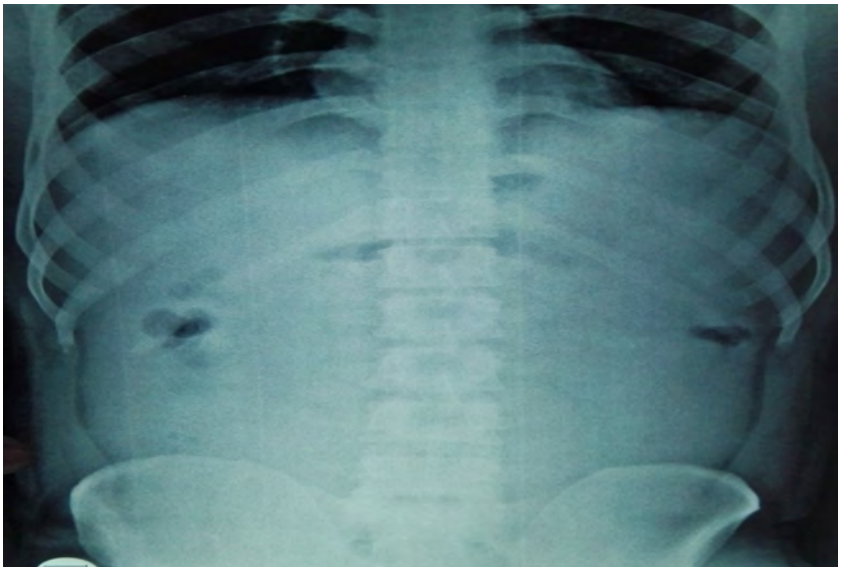
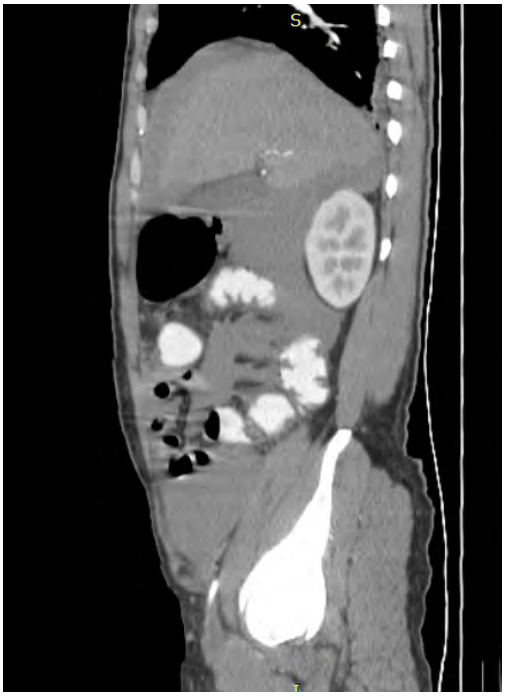


Fig. 8: CT scan revealing hemoperitoneum



Case 3: Dengue with rickettsial co-infection

A 26-year-old male presented with high-grade fever with chills, nausea, decreased appetite and headache, fever (102°F) for 4 days. There was no comorbid illness and history revealed a recent travel to Thirupathi. Lab findings revealed TC 5100 /mm^3, Hb 15.3 gm%, PCV 42%, Serum Creatinine 1.1 mg/dl, and random blood sugar 85 mg/dl. Dengue Elisa NS1Ag and IgM was positive. He was started on IV fluids and paracetamol as supportive treatment for dengue fever. However, the patient continued to have high-grade fever of around 102 to 103°F with rapid fall in platelet count on 5th day of fever i.e. 19,000 /mm^3. He was transfused with one unit of single donor platelet.

The patient was reexamined and revealed an eschar on leg. Weil-Felix was positive. (OX K was 1:160 and OX 2 was 1:160), indicative of rickettsial infection. He was started with doxycycline and became afebrile within 48 hours. He was discharged in hemodynamically stable condition.

Managing dengue

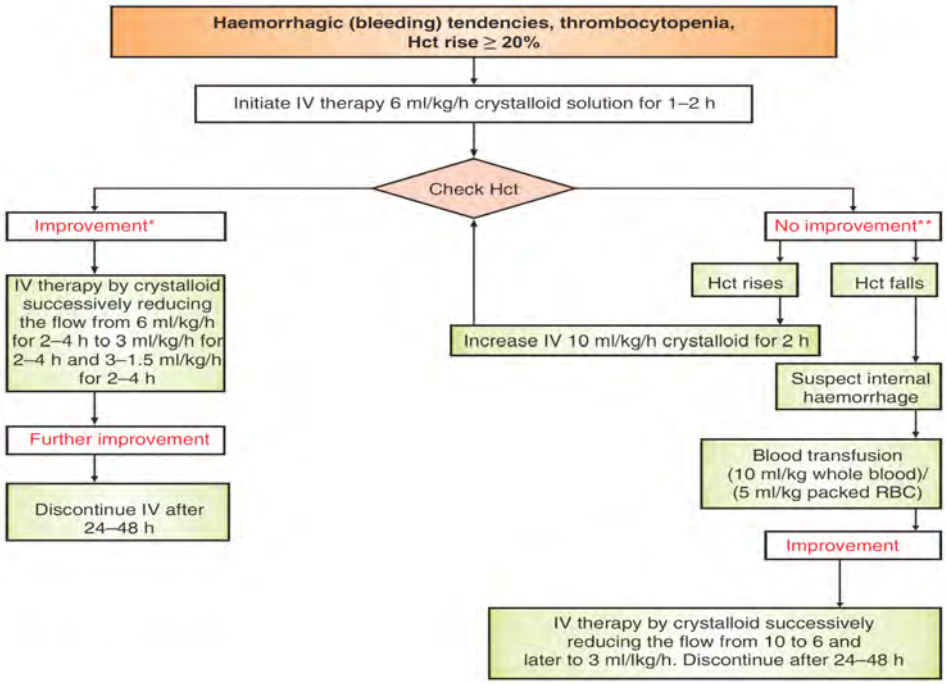
There is no specific treatment for dengue and the management should be focused on symptomatic and supportive care. Corticosteroids should not be used and platelet transfusion is recommended if platelet count <10,000 cu mm.[8] The potential of vaccines and thrombopoietin receptor agonists Like Eltrombopag are currently being evaluated in various clinical trials. The use of aspirins or NSAIDs for reducing fever is not recommended. Soft diet, and continuous rehydration with milk, fruit juice,

and oral rehydration solution (ORS) is necessary.[9] Early detection of pleural effusion and ascites as well as daily CBC follow-up assist in effective management and avoiding further complications. The ideal IV fluid management involves administration of isotonic salt solution in the critical period, 5% dextrose in normal saline solution, 5% Ringer acetate, and 5% Ringer-lactate.

In children, dose of paracetamol is calculated at 10 mg/Kg body weight per dose. It can be repeated every 6 hrs depending on fever and body ache.[10] Oral fluid and electrolyte therapy are recommended for patients with excessive sweating or vomiting. Patients should be monitored for 24 to 48 hours, after they become afebrile, for development of any complications.[10]

The management protocol to be followed for patients with bleeding tendencies, thrombocytopenia and hematocrit ≥20% is given in figure 8. Prothrombin time (PT) and aPTT should be evaluated in patients with massive hemorrhage to rule out coagulopathy. Patients with severe bleeding may have liver dysfunction. In rare circumstances, intracranial bleed may also occur.[11]

Fig. 8: Management protocol to be followed for patients with bleeding tendencies, thrombocytopenia and hematocrit ≥20%



Drugs indicated for managing dengue

An ideal drug for dengue should have good safety profile and can be taken orally (as majority of patients have mild symptoms). Drugs in development include those targeting host and viral factors. Based on mechanism of action, the anti-virals can be classified as protease inhibitors, translational inhibitors, capsid inhibitors, peptide inhibitors, RNA polymerase inhibitors, α glucosidase inhibitors

and host modulators. Some of the major drugs that are being investigated in clinical trials include balapiravir, celgosivir, sofosbuvir, statins, chloroquine and ivermectin.[12] A study by Garg et al. has reported that anti-dengue and anti-inflammatory activities of doxycycline are helpful in alleviating the severity of clinical symptoms such as dengue hemorrhagic fever, dengue shock syndrome and dengue fever.[13]

Monoclonal antibodies are emerging as promising therapeutics against dengue. These antibodies target either viral surface glycoproteins, thus preventing either viral attachment or fusion with host membrane, or viral NS1 (yet to be investigated in humans).

Other potential therapies

Randomized controlled trials carried out at 2 centres in Bengaluru concluded that Carica papaya leaf extract (CPLE) significantly increased platelet count in patients with thrombocytopenia associated with dengue with fewer side effects and good tolerability.[14]

There are no WHO guidelines recommending the use of corticosteroids in managing. Evidence is insufficient to evaluate the effects of corticosteroids in treating early stage dengue fever and dengue related shock. Corticosteroids may be effective in managing dengue, as immune pathology of dengue has many similarities to other autoimmune diseases.[15] Corticosteroids and intravenous immunoglobulin (IVIG) are found to be beneficial in atypical presentations of dengue, particularly prolonged thrombocytopenia, beyond the typical duration of 7-10 days.[16] Several clinical trials are investigating the effects of corticosteroids at different stages of dengue. Such studies have shown that corticosteroids do not have any effect on prolongation of viremia, reduction in incidence of shock or other complications, severe DSS, beneficial in host immune response, improvement in platelet counts and causing significant adverse effects.[17] However, the treatment is found to have significant mortality benefit and hemodynamic improvement. The treatment is beneficial in reducing the morbidity after recovery, as well as the incidence of bleeding, ascites and complications associated with dengue maculopathy.[18]

Dengue vaccines

No global vaccine is available for public health use against dengue. Major challenge for developing vaccine for dengue is the concern for antibody-dependent enhancement (ADE) with an unbalanced response to all 4 serotypes. First ever dengue vaccine named 'Dengvaxia' was licensed in Mexico, followed by Philippines in 2016. It is a tetravalent live attenuated vaccine licensed to market in >10 countries with high dengue case load (Mexico, Philippines, El Salvador, Paraguay, Thailand, Singapore, Brazil, Costa Rica, Guatemala, Peru and Indonesia).[19] The overall vaccine efficacy noted in Asian children was 56.5%. The results of first long-term follow-up (3 years post vaccination) has shown continued benefit of the vaccine in children aged 9-16 years.[20]

Subunit vaccines using DENV E protein as major immunogen have shown potential in preclinical trials. In addition, subunit vaccine (DEN-80E) developed by Merck has now progressed to clinical trials. Vaccines using epitope on E protein (EDE) (recently identified) are likely to develop in future.[21]

Conclusion

The response of patients to different therapeutic interventions is diverse, hence it is challenging to strictly follow the general guidelines. Newer technologies, such as biologic and genetic modification of mosquitoes, have shown promising results for future dengue control. Strategies need to be implemented at the community and state levels for the eradication of mosquito breeding sites. Early diagnosis and treatment are paramount in managing dengue.

References

1. *WHO | Dengue and severe dengue [Internet]. WHO. [cited 2020 Feb 8]. Available from:* http://www.who.int/mediacentre/factsheets/fs117/en/
2. *Hariharan D, Das MK, Shepard DS, Arora NK. Economic burden of dengue illness in India from 2013 to 2016: A systematic analysis. International Journal of Infectious Diseases. 2019 Jul 1;84:S68–73.*
3. *RRA-sexual-transmission-dengue-in-Spain.pdf [Internet]. [cited 2020 Feb 8]. Available from:* https://www.ecdc.europa.eu/sites/default/files/documents/RRA-sexual-transmission-dengue-in-Spain.pdf
4. *Heilman JM, De Wolff J, Beards GM, Basden BJ. Dengue fever: a Wikipedia clinical review. Open Med. 2014;8(4):e105–e115.*
5. *Dengue — With or Without Warning Signs [Internet]. [cited 2020 Feb 8]. Available from:* https://www.cdc.gov/dengue/training/cme/ccm/page47831.html
6. *Kadam DB, Salvi S, Chandanwale A. Expanded Dengue. J Assoc Physicians India. 2016;64(7):59–63.*
7. *Serologic Tests for Dengue Virus | Dengue | CDC [Internet]. 2019 [cited 2020 Feb 8]. Available from: https://www.cdc.gov/dengue/healthcare-providers/testing/serologic-tests.html*
8. *Dengue-National-Guidelines-2014 Compressed.pdf [Internet]. [cited 2020 Feb 8]. Available from:* http://pbhealth.gov.in/Dengue-National-Guidelines-2014%20Compressed.pdf
9. *Clinical Practice Guidelines ofDengue/Dengue HemorrhagicFever Management for AsianEconomic Community[Internet]. [cited 2020 Feb 8]. Available from:* http://www.pgh.gov.ph/static/media/uploads/documents/clinicaldepartments/pediatrics/denguelecture/6clinical.pdf
10. *Indian National Guidelines for Clinical Management of Dengue Fever, 2015.Available at* https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
11. *Sam JE, Gee TS, Nasser AW. Deadly intracranial bleed in patients with dengue fever: A series of nine patients and review of literature. J Neurosci Rural Pract. 2016;7(3):423–34.*
12. *Boldescu V, Behnam MAM, Vasilakis N, Klein CD. Broad-spectrum agents for flaviviral infections: Dengue, Zika and beyond. Nat Rev Drug Discov. 2017 Aug;16(8):565–86.*
13. *Garg P. Role of Doxycycline in the Management of Dengue Fever. Indian Journal of Clinical Practice. 2018;(29)2:132-35.*
14. *Effect of Carica papaya Leaf Extract Capsule on Platelet Count in Patients of Dengue Fever with Thrombocytopenia. - PubMed - NCBI [Internet]. [cited 2020 Feb 8]. Available from:* https://www.ncbi.nlm.nih.gov/pubmed/27739263
15. *Zhang F, Kramer CV. Corticosteroids for dengue infection. Cochrane Database Syst Rev. 2014 Jul 1;(7):CD003488.*
16. *Rajapakse S. Intravenous immunoglobulins in the treatment of dengue illness. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009 Mar 1;103:867–70*
17. *Bandara SMR, Herath HMMTB. Effectiveness of corticosteroid in the treatment of dengue – A systemic review. Heliyon [Internet]. 2018 Sep 22 [cited 2020 Feb 8];4(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6151849/*
18. *Rajapakse S, Rodrigo C, Maduranga S, Rajapakse AC. Corticosteroids in the treatment of dengue shock syndrome. Infect Drug Resist. 2014 May 22;7:137–43.*
19. *Aguiar M, Stollenwerk N, Halstead S. The Impact of the Newly Licensed Dengue Vaccine in Endemic Countries. PLoS Neglected Tropical Diseases. 2016 Dec 21;10*
20. *Thomas SJ, Yoon I-K. A review of Dengvaxia®: development to deployment. Hum Vaccin Immunother. 2019 Oct 7;15(10):2295–314.*
21. *Torresi J, Ebert G, Pellegrini M. Vaccines licensed and in clinical trials for the prevention of dengue. Hum Vaccin Immunother. 2017 Feb 14;13(5):1059–72.*

Recent advances in the diagnosis and management of typhoid fever

Prof. Dr. Ketan K. Mehta MD (Med.), FCPS, FICP, FISE
Asian Heart Institute
Suchak Hospital
Namaha Hospital
Lifeline Medicare Hospitals

Enteric fever is caused by *Salmonella enterica serovar* Typhi (*S. Typhi*) *and Salmonella enterica serovar Paratyphi* A *(S. Paratyphi A*), *B and C***.** It is a multi-system disease characterized by prolonged fever, sustained blood stream infection, activation of the endothelial system, metastatic infections and immunologic complications due to immune complex deposition leading to multi-organ dysfunction.[1] The routes of disease transmission are mainly through feco-oral route, close contact with patients or carriers, contaminated water & food, flies and cockroaches.

Case definitions

The 2015 Journal of the Association of Physicians in India has published the following definitions for classifying the typhoid fever.[2]

- **Confirmed enteric fever***:* Fever ≥38°C for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. Typhi.*
- **Probable enteric fever:** Fever ≥38°C for at least three days, with a positive serodiagnosis or antigen detection test but without *S. Typhi* isolation.
- **Chronic carrier state***:* Excretion of *S. typhi* in stools or urine (or repeated positive bile or duodenal string cultures) for longer than one year after the onset of acute enteric fever; sometimes, *S. typhi* may be excreted without any history of enteric fever.

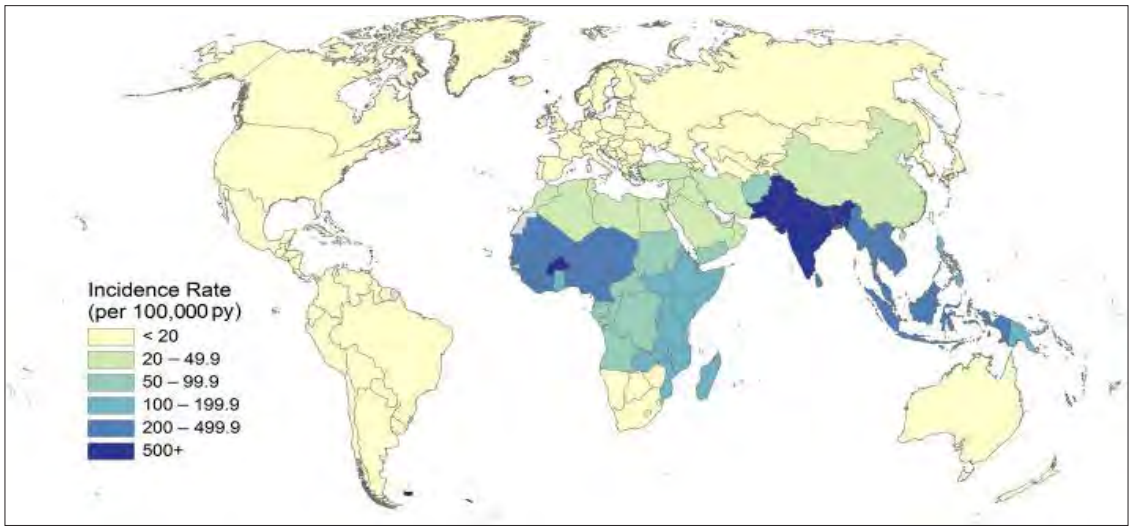
Typhoid fever: History milestones

- Thomas Willis provided the first description of typhoid fever in 1659.
- French physician Pierre Charles Alexandre Louis first proposed the name 'typhoid fever'.
- William Wood Gerhard for the first time differentiated between typhus fever and typhoid in 1837.
- Carl Joseph Eberth discovered the typhoid bacillus in 1880.

Epidemiology

Annually around 22 million new typhoid cases occur globally, and the worst sufferers are young children in poor and resource limited areas. The South-east Asian countries bear the brunt of the disease, particularly children and young adults. Both typhoid and paratyphoid fevers may be fatal, if left untreated. The estimated global mortality rate was 178,000 deaths in 2015 worldwide. The estimated incidence of typhoid and paratyphoid fevers by country per 100,000 population in 2015 is given in figure 1. The incidence data shows that the burden of the disease in India is substantial.[3]

Fig. 1: The estimated incidence of typhoid and paratyphoid fevers by country in 2015



Clinical features of typhoid fever

The prominent clinical features noted at each stage of typhoid fever are listed below:[2]

Stage 1

The first week is marked by gradual increase in temperature for 4-5 days, abdominal pain, myalgia, malaise, headache and constipation. Rose spots on the upper abdomen and on the back, cough, splenomegaly may appear by the end of first week.

Stage 2

Second week is marked by progression of the signs and symptoms. Delirium and development of other complications, coma and death (if untreated).

Stage 3

The patient will be generally febrile, toxic and anorexic. Significant weight loss, confusion, psychosis and high risk (5-10%) of hemorrhage and perforation leading to death are noted in stage 3.

Stage 4

If the individual survives to the 4th week; the fever, mental state, and abdominal distension slowly improve over a few days. Intestinal and neurologic complications may still occur in surviving untreated individuals.

Extraintestinal complications of enteric fever

Extraintestinal complications of the fever can affect any of the organ systems. The major complications and the organ systems affected are listed in table 1.[2]

Table 1: Extraintestinal complications of the fever

Organ system	Prevalence	Complications
CNS	3-35%	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia seizures, Guillain–Barré syndrome, psychosis
Cardiovascular	1-5%	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary	1-6%	Pneumonia, empyema, bronchopleural fistula
Bone and joint	< 1%	Osteomyelitis, septic arthritis
Hepatobiliary	1-26%	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary	< 1%	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue	17 reported*	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematological	5 reported*	Hemophagocytosis syndrome

Lab diagnosis

Bacteriological diagnosis of enteric fever consists of isolation of bacilli, demonstration of antibodies/ circulating antigen and other laboratory tests. The routine serological tests may be suggestive of mild anemia, low to normal total leucocyte/ platelet count, eosinopenia, and 2 to 3 times increase in serum transaminase levels. Significant hepatic dysfunction is rare.

Isolation of bacilli

Blood, urine, feces and aspirated duodenal fluid are the commonly used specimens for the isolation of bacilli. Other specimens include bone marrow, bile, rose spots discharge, pus and suppurative lesions, CSF and sputum. Blood culture is the standard diagnostic method and the commonly used modality for isolation of bacilli. The results can be positive in 60-80% of patients, provided that a large volume of blood (typically 15 ml for adults) is cultured. The probabilities of getting a positive culture result in 1st, 2nd 3rd weeks and till the subsidence of pyrexia are 90%, 75%, 60%, and 25% respectively.[4]

Diagnostic tests available in India

Widal test remains the most widely available and frequently used test in the community for diagnosis of enteric fever. Blood cultures are still not performed in many of the healthcare facilities in India. Moreover, the test is relatively expensive for patients with average income. It costs around 5-6 times the average daily wage rate (INR 272). Typhidot and TubexM are the serological tests used in some laboratories in India for detecting antibodies against 50kD outer membrane protein and LPS respectively. They have comparable sensitivity and specificity as that of Widal test. Though molecular techniques hold greater promise, the small number of bacteria in clinical samples may result in low sensitivity. Some researchers have overcome this limitation using techniques such as pre-incubation of blood cultures followed by PCR.[5]

Disadvantages of serological diagnostic methods

Salmonella has three major antigens: H or flagellar antigen, O or somatic antigen, and Vi or capsular antigen. The O antibodies usually appear on days 6-8 and H antibodies on days 10-12 after the onset of the disease. The role of the classic Widal test is controversial in diagnosing Salmonella, with divergent views on the test's utility in various areas of endemicity. One of the studies from southeast Asia has noted that some cultures for patients who tested positive for the Widal agglutination test, with titers ranging from 1:80 to 1:320, were negative for Salmonella. The results suggest that serological investigations alone may not be a reliable index for the diagnosis of Salmonella infections. Malaria can interfere with serological diagnosis of typhoid and hence can lead to over diagnosis of typhoid.

Recent advances in diagnosis

There are studies validating the use of PCR for diagnosis of typhoid fever by gene amplification in clinical samples; but it may not be cost-effective. Salivary IgM test has also been used, though not yet available. Recent advances in molecular immunology have led to the identification of sensitive and specific markers. Currently, alternative methods for biological molecular analysis are enzyme immunoassay, surface plasmon resonance, and electrochemical immunoassay.1 Feasible diagnostic tests according to the days of presentation are listed in table 2.[2]

Table 2: Feasible diagnostic tests according to the days of presentation

Week of illness	Feasible tests	Non-feasible tests
1st week	Hematological tests - Eosinopenia Blood culture Typhidot/Typhidot-M Widal (basal)	Bone marrow culture PCR Duodenal aspirate culture Dipstick
2nd week	Hematological tests - Leukocytosis Blood culture Stool culture Typhidot/Typhidot-M Widal (basal or repeat - to see rising titer)	Bone marrow culture Rose spot culture PCR Tubex Duodenal aspirate culture Dipstick
3rd week	Hematological tests USG abdomen (hepatosplenomegaly) Blood culture Stool culture Widal (very high titer) Typhidot/Typhidot-M	Bone marrow culture PCR Tubex Duodenal aspirate culture Dipstick
4th week	Hematological tests USG abdomen Blood culture Stool culture Widal (very high titer) Typhidot/Typhidot-M	Bone marrow culture PCR Tubex Duodenal aspirate culture Dipstick

Managing enteric fever

The management should be aimed at adopting a holistic approach comprising of self-care, treatment, surgery and vaccination. The measures used to control typhoid fever include case detection and treatment, isolation, disinfection stool and urine, water and food sanitation, excreta disposal, fly control, immunoprophylaxis, and health education.

Self-care

The following are the WHO recommended self-care measures for controlling enteric fever.[6]

- Practice hand washing with soap and running water before food preparation and eating, after using the toilet, handling soiled diapers, bed linen, etc., and maintain a high standard of personal hygiene in general.

- Maintain rigorous standards of cleanliness in food preparation and handling of food, especially salads and other cold-serve foods.
- Make sure to properly refrigerate food where possible.
- Eat foods that have been thoroughly cooked and that are still hot and steaming.
- Ensure that cooked food is covered to protect it from flies.

Treatment

Supportive measures are vital for managing enteric fever such as oral or intravenous hydration, tepid bath and sponging and appropriate nutrition. More than 90% of patients can be managed at home with oral antibiotics, a reliable caretaker, and close medical follow-up for complications or failure to respond to therapy. More than 99% of the people with typhoid fever are cured with prompt antibiotic therapy, although convalescence may last for several months.[7]

Efficacy, availability and cost are important criteria for the selection of first-line antibiotics to be used in developing countries. Due to the increased resistance to the antibiotic chloramphenicol, other antibiotics were used worldwide for treatment. However, it has shown a comeback in developing countries, as the reduced use of the drug has increased its sensitivity. The recommended dosage is 50 - 75 mg per kg per day for 14 days divided into 4 doses per day, or for at least five to seven days after defervescence.[7] Fluoroquinolones are widely regarded as optimal for the treatment of typhoid fever in adults. They are relatively inexpensive, well tolerated, more rapid in action and reliably effective than the former first-line drugs, viz. chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole.[8]

Azithromycin should be reserved for quinolone-resistant cases. The drug is capable of attaining intracellular concentrations 50-100 times greater than serum levels, and this explains its efficacy against Salmonella species. It has excellent intracellular penetration and a long half-life allowing once-daily oral administration, although the cost is higher than its alternatives. It has been found to be superior in treating uncomplicated enteric fever and has been demonstrated to show comparable efficacy as that of ceftriaxone. Recently, azithromycin resistance and treatment failure in patient with *S. paratyphi* A infection have been reported.[9]

Current approaches in the treatment of enteric fever in India

The API recommendations put forth for managing uncomplicated and complicated fever are listed in table 3 and 4. Combination therapy may be considered in patients not responding to monotherapy. Fluoroquinolone is the first drug of choice and if the response is inadequate; oral cephalosporin or cefixime is added. Former drug is replaced with azithromycin, if improvement is still not satisfactory.[2]

Table 3: Treatment recommendations for managing uncomplicated enteric fever

Susceptibility	Patient	Antibiotic	Dosage
Uncomplicated enteric fever			
Quinolone sensitivity areas	Adult	**Responders:** Fluoroquinolones, namely Ciprofloxacin or Ofloxacin	15 mg/kg body weight/day × 10 days
		OR 3rd Generation Cephalosporin like Cefixime	15-20 mg/kg body weight/day × 10 days
		Nonresponders: Chloramphenicol OR	50-75 mg/kg body weight/day × 14 days
		Amoxicillin	75-100 mg/kg body weight/day × 14 days
	Child	**Responders:** 3rd Generation Cephalosporin like Cefixime	15-20 mg/kg body weight/day × 10 days
		Nonresponders: Chloramphenicol OR	50-75 mg/kg body weight × 14-21 days
		Amoxicillin	75-100 mg/kg body weight × 14 days
Quinolone resistance areas	Adult	**Responders:** Cefixime	20 mg/kg body weight/day × 14 days
		Nonresponders: Azithromycin	10-20 mg/kg body weight/day × 7 days
	Child	**Responders:** Azithromycin	10-20 mg/kg body weight/day × 7 days
		Nonresponders: Cefixime	15-20 mg/kg body weight/day × 14 days

Table 4: Treatment recommendations for managing complicated enteric fever

Complicated enteric fever			
Quinolone sensitivity areas	Adult	**Responders:** 3rd and 4th Generation Cephalosporins like	
		Ceftriaxone	60 mg/kg body weight/day IV × 14 days
		Cefotaxime	80 mg/kg body weight/day IV × 14 days
		OR Fluoroquinolone like Ciprofloxacin or Ofloxacin	15 mg/kg body weight/day IV × 14 days
		Nonresponders: Chloramphenicol	100 mg/kg body weight/day IV × 14-21 days
		Ampicillin	100 mg/kg body weight/day IV × 14 days
	Child	**Responders:** Ceftriaxone or Cefotaxime	50-75 mg/kg body weight/day IV × 14 days
		Nonresponders: Chloramphenicol	100 mg/kg body weight/day IV × 14-21 days
		Amoxicillin	100 mg/kg body weight/day IV × 14 days
Quinolone resistance areas	Adult	**Responders:** Ceftriaxone or	60 mg/kg body weight/day IV × 14 days
		Cefotaxime	80 mg/kg body weight/day IV × 14 days
		Nonresponders: Fluoroquinolone	20 mg/kg body weight/day IV × 14 days
	Child	Ceftriaxone or Cefotaxime	50-75 mg/kg body weight/day IV × 14 days

Multidrug-resistant typhoid fever

Multidrug-resistant typhoid fever (MDRTF) is defined as typhoid fever caused by *Salmonella enterica serovar* Typhi strains (*S. Typhi*), which are resistant to the first-line recommended drugs for treatment such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. The first Indian outbreak of MDR *Salmonella enterica serovar Typhi* was reported from Calicut in 1960. The first reported epidemic of quinolones-resistant typhoid fever was from Tajikistan in 1996. Studies conducted in India has demonstrated increase in incidence of antimicrobial resistance. A study has found that 57% of isolates were resistant to nalidixic acid, 1.6% to ciprofloxacin, and 7% were multidrug-resistant (resistant to chloramphenicol, ampicillin and cotrimoxazole).[10]

Surgery

Typhoid ulcer in the bowel may require one of the three common methods of surgery, i.e. Wedge excision, anastomosis or segmental resection and simple closure. Wedge resection is found to be associated with increased risk for re-perforation and mortality rate when compared to segmental resection and anastomosis. Segmental resection/ anastomosis seems to be the best treatment for typhoid perforation.[11]

Vaccination

The use of affordable vaccines seems to be the most lucrative prophylactic intervention. It is recommended for individuals travelling to areas of the world where typhoid is endemic, people who are in close contact with a chronic carrier of typhoid, and laboratory staff that handle samples containing *S. typhi* bacteria. Two types of typhoid vaccines are available in the Indian market for clinical use, namely the Vi polysaccharide (Vi-PS) vaccine and the Ty21a oral vaccine.[6]

The Coalition against Typhoid (CaT) is a global forum of immunization experts, which is aimed at reducing the suffering by accelerating the delivery of typhoid vaccines to needy populations. Since May 2011, CaT has featured monthly articles in the WHO's Global Immunization Newsletters (GIN). The articles, written by CaT members from around the world, highlight important work being done to accelerate adoption of typhoid vaccines.[12]

Conclusion

The absence of a reliable rapid diagnostic test poses a challenge in managing typhoid fever. Disease can be very effectively treated with appropriate use of drugs such as fluoroquinolones, cephalosporins, and azithromycin. However, indiscriminate use of antibiotics has led to increase in incidence of drug-resistant enteric fever. Strategies to reduce disease burden include supply of purified water, effective disposal of sewage and other wastes, practicing hygienic food habits, identification and treatment of chronic carriers of enteric fever, and vaccination of susceptible hosts.

References

1. *Teh CSJ, Chua KH, Thong KL. Paratyphoid Fever: Splicing the Global Analyses. Int J Med Sci. 2014 May 14;11(7):732–41.*
2. *Upadhyay R, Nadkar MY, Muruganathan A, Tiwaskar M, Amarapurkar D, Banka N, et al. API Recommendations for the Management of Typhoid Fever.J Assoc Physicians India.2015 Nov; 63 (11), 77-96.*
3. *Radhakrishnan A, Als D, Mintz ED, Crump JA, Stanaway J, Breiman RF, et al. Introductory Article on Global Burden and Epidemiology of Typhoid Fever. Am J Trop Med Hyg. 2018;99(3_Suppl):4–9.*
4. *Basnyat B, Maskey AP, Zimmerman MD, Murdoch DR. Enteric (typhoid) fever in travelers. Clin Infect Dis. 2005 Nov 15;41(10):1467–72.*
5. *Divyashree S, Nabarro LEB, Veeraraghavan B, Rupali P. Enteric fever in India: current scenario and future directions. Trop Med Int Health. 2016 Oct;21(10):1255–62.*
6. *Typhoid [Internet]. [cited 2020 Feb 12]. Available from:* https://www.who.int/news-room/fact-sheets/detail/typhoid
7. *Kalra S, Naithani N, Mehta S, Swamy A. Current Trends in the Management of Typhoid Fever. Med J Armed Forces India. 2003 Apr;59(2):130–5.*
8. *Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, et al. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004530*
9. *Molloy A, Nair S, Cooke FJ, Wain J, Farrington M, Lehner PJ, et al. First Report of Salmonella enterica Serotype Paratyphi A Azithromycin Resistance Leading to Treatment Failure. J Clin Microbiol. 2010 Dec;48(12):4655–7.*
10. *Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries. 2011 May 28;5(5):324–37.*
11. *Caronna R, Boukari AK, Zaongo D, et al. Comparative analysis of primary repair vs resection and anastomosis, with laparostomy, in management of typhoid intestinal perforation: results of a rural hospital in northwestern Benin. BMC Gastroenterol. 2013;13:102.*
12. *Lindsay S, Gellin B, Lee A, Garrett D. The Coalition Against Typhoid: Mobilizing a Community for a Global Fight. Clin Infect Dis. 2019 Mar 15;68(Suppl 2):S161–4.*

Approach to Antibiotic Selection

Dr. D. Suresh Kumar MD, FNB (Inf Dis)
American Certified Tropical Medicine, Fellowship in HIV/ AIDS Medicine,
Adjunct Associate Professor, AHERF, NABH Assessor, Co- Founder Best of IDs –
(Dr's Dr.- Facilitator) Sr. Consultant Infectious Diseases, Apollo Hospitals, Chennai

Introduction

Indiscriminate use of antibiotics has led to the development of several multi-drug resistant pathogens. The physician poll conducted during the FeFcon 2019 conference indicated that 20-30% of the patients consulted in the out-patient department are prescribed with antibiotics. In addition, 64% of the clinicians participated in the conference voted amoxicillin/clavulanate potassium as their preferred antibiotic in daily clinical practice.

Approach to antibiotics: Red flag signs

The following red flag signs need to be considered prior to the prescription of antibiotics:

- Prostration: Unable to stand, sit or walk without support
- Temperature: Hyperpyrexia >41.5°C or hypothermia <36°C or rigors
- Neurological: Altered mental status (Glasgow coma scale <13), convulsions, positive meningeal signs (such as neck stiffness and Kernig's sign)
- Respiration: Shortness of breath, respiratory rate >22 breaths/minute, SpO2 < 92% in room air
- Circulation: Blood pressure <100 mmHg systolic, cold clammy extremities, capillary refill >3 seconds
- Abdominal pain: Severe or persistent vomiting
- Severe conjunctival or palmar pallor, jaundice on examination of sclera, petechial or purpuric rash or cyanosis

- Bleeding from nose, gums, or venipuncture sites, hematemesis or melena

The sequential organ failure assessment score (qSOFA score) assists in identifying patients with suspected infection and his/her stability status. The score, which ranges from 0-3 points, uses three criteria, assigning one point for high respiratory rate (≥22 breaths per min), low blood pressure (SBP≤100 mmHg) or altered mental status (Glasgow coma scale<15).[1] The presence of ≥2 qSOFA points near the onset of infection suggests a greater risk for mortality or prolonged ICU stay.

The 5 moments of hand hygiene recommended by WHO for healthcare workers are:[2]

1. Before touching a patient
2. Before clean/aseptic procedures
3. After body fluid exposure/risk
4. After touching a patient
5. After touching patient surroundings

Similarly, The Journal of American Medical Association (JAMA) has specified the hypothetical scenarios incorporating the 4 moments of antibiotic decision making into daily clinical practice.[3]

Fig. 1: Hypothetical scenario incorporating the 4 moments of antibiotic decision making into daily clinical practice

Table. Hypothetical Scenario Incorporating the 4 Moments of Antibiotic Decision Making Into Daily Practice

Moment	Scenario	Patient and Symptom Description	Decision
1	Does this patient have an infection that requires antibiotics?	Patient is a 34-year-old previously healthy woman with dysuria, fever, hypotension, and flank pain	Patient has signs and symptoms concerning for pyelonephritis
2	Have I ordered appropriate cultures before starting antibiotics? What empirical antibiotic therapy should I initiate?	Urine dipstick indicates pyuria and bacteriuria	• Urine and blood cultures are obtained prior to administering antibiotic therapy • Ceftriaxone is prescribed as empirical therapy for pyelonephritis • Broader therapy is not indicated because the patient has no risk factors for pseudomonal or antibiotic-resistant infection • Vancomycin is not administered because methicillin-resistant *Staphylococcus aureus* is not a common cause of pyelonephritis
3	A day or more has passed. Can I stop antibiotics? Can I narrow therapy? Can I change from intravenous to oral therapy?	• Patient has an appropriate response to therapy • Urine cultures grow *Escherichia coli* resistant to trimethoprim and sulfamethoxazole but susceptible to ciprofloxacin	• Because *E coli* recovered in the urine has oral treatment options available, ceftriaxone is stopped and ciprofloxacin is initiated • The patient is able to tolerate oral therapy and shows clinical improvement; thus, patient is switched from intravenous to oral therapy
4	What duration of antibiotic therapy is needed for this patient's diagnosis?	Patient is on day 3 of therapy and is ready to be discharged home	• Treatment with ciprofloxacin for 7 d has been shown to be effective for pyelonephritis • The patient is discharged home to complete additional 4 d of antibiotic therapy

Source: Tamma PD, Miller MA, Cosgrove SE. Rethinking How Antibiotics Are Prescribed: Incorporating the 4 Moments of Antibiotic Decision Making Into Clinical Practice. JAMA. 2019 Jan 15;321(2):139-140.

Identification of the right syndrome

The signs and symptoms provided in table 1 may assist in identification of syndromes. The syndrome identification may ease a clinician job of prescribing the appropriate antibiotic. Proper history collection and examination are vital for identifying the syndrome. Appropriate lab testing is always recommended for early diagnosis and prevention of antibiotic abuse.

Table 1: Signs and symptoms indicated for the identification of syndromes

Signs and symptoms	Syndrome
Fever, headache, seizures, LOC, weakness	Meningitis/ meningoencephalitis
Fever, running nose, sneeze, headache, facial swelling, throat pain	Rhinitis/ Rhino Sinusitis/ Pharyngitis
Fever, ear pain, ear discharge, headache	Otitis media, Otitis externa
Fever, cough, chest pain, shortness of breath	Pneumonia
Fever, abdominal pain, abdominal distension, bowel disturbances	Intra-abdominal infections: peritonitis, cholangitis, pancreatitis
Fever, diarrhea, dysentery, vomiting	Acute gastroenteritis
Frequency, urgency, dysuria, hematuria, lower abdominal pain	Lower UTI/ cystitis
Fever, dysuria, Lower abdominal pain, loin pain, vomiting, constipation	Upper UTI/ pyelonephritis/ prostatitis
Fever, redness, pain, swelling of skin	SSTI: cellulitis

Appropriate lab diagnosis

A variety of clinical decision rules and algorithms have been developed to enhance the clinical diagnosis. For example, Centor criteria is used for the differentiation of group A beta-hemolytic streptococcal pharyngitis from a viral infection. The bacterial infection is more likely (1 point for each) if the following criteria are satisfied: tonsillar exudate, tender anterior cervical left mentoanterior, history of fever and absence of a cough.[4]

Appropriate lab testing is integral prior to the prescription of antibiotics. For example, culturing is always recommended in an Indian setting, prior to the prescription of antibiotics, in patients presenting with symptoms of UTI. There are increased chances of resistance and the prevalence of extended-spectrum beta-lactamase (ESBL) producing bacteria at the community level is around 70%.[5] The preferred lab tests for various infectious diseases are listed in table 2.

Table 2: Preferred lab tests for various infectious diseases in resource rich and poor countries

Diseases	Resource rich countries	Resource poor countries	Ideal approach	Problematic approach
Malaria	PS, MP QBC	Rapid card test	Repeat the test	Clinical malaria
Typhoid	Blood culture	CBC, LFT	History, physical examination, and antibiotics	Widal test
Scrub typhus	PCR, raising titer	Scrub IgM ELISA	History, examination and antibiotics	Weil-Felix test
Leptospirosis	Culture, PCR	Lepto IgM ELISA	History, physical examination and antibiotics	DFM
Influenza	RT- PCR	Empirical treatment	Test and treat, stop if it is negative	Rapid tests
Dengue	PCR, NS-1, seroconversion	Symptomatic treatment with HB, platelet transfusion	Symptomatic treatment	Card test
TB	Xpert MTB/RIF, AFB smear, AFB culture	Xpert MTB/RIF, HPE	Xpert MTB/RIF, AFB culture	Trial ATT
HIV	4th gen ELISA, ID NAT	2-3 types of card test	ELISA/ CLIA, VL and CD4 counts	Western blot
UTI	Symptoms + urine R/e, urine C & S	Symptoms + urine R/e, urine C & S	Symptoms + urine R/e, urine C & S	Urine C & S
AGE	PCR, stool R/e and C & S	Stool R/e	Syndrome-based management	Stool ova and cyst alone

The test accuracy may also depend on the right volume of sample used. For blood culturing, 15-20 ml is the minimum volume of blood required and for Xpert MTB/RIF, the CSF sample should be around 6 ml.

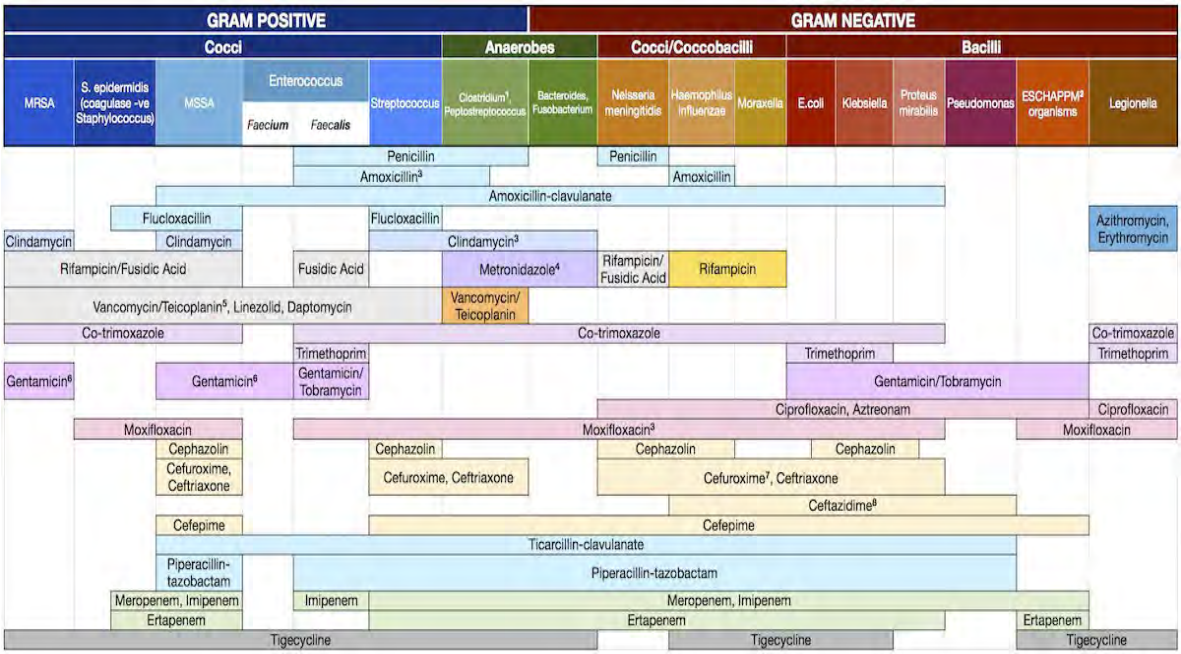
Recommended tests based on fever duration

It is preferred to watch and wait for 3 days for short fever without localization. For fever ranging between 3-5 days, CBC and quantitative buffy coat for malarial parasite are advocated. Blood culturing is needed for fever between 7-14 days. Some of the diagnostic tests that are not preferred include Widal, Mantoux, microscopic agglutination test (MAT) for leptospirosis, 1 bottle blood culture, and urine culture without routine test in the absence of symptoms.

The spectrum of antibiotics

The simple rule of thumb for deciding antibiotics is that for any infection above diaphragm, Gram-positive cover is needed; whereas for treating infections below diaphragm, Gram-negative cover should be considered. A broad-spectrum antibiotic is that acts against both Gram-positive and Gram-negative anaerobes (Eg: amox-clav). It is important to know the spectrum of coverage of each antibiotic for prescribing the drug in routine practice (Fig. 2).

Fig. 2: Spectrum of activity of different antibiotics



Irrational use of antibiotics

Inappropriate/ excessive use of antibiotics is one of the major causes for emergence of bacterial resistance. Calculating the appropriate dosage of the medication, according to the patient body weight, is very important to curb the irrational use.

Table 4: The recommended adult and pediatric doses for various antibiotics and commonly noted side effects

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

Inappropriate use of these drugs can cause major side effects. Linezolid treatment can cause serious side effects including lack of taste, tongue discoloration, and peripheral/optic neuropathy. Similarly, treatment with fluroquinolones can lead to enthesopathy. It is important to consider the pharmacokinetics and tissue penetration profile while prescribing the antibiotics. For example, nitrofurantoin is not indicated for treating upper UTI and bacterial pyelonephritis, as it does not reach therapeutic concentrations in the upper urinary tract.[6] With regard to the duration of antibiotic therapy, recent clinical evidence has proven that shorter is better to achieve the optimal cure rates. Several randomized controlled trials have demonstrated that both short-course and traditional longer courses have comparable efficacy for treating community-acquired/ nosocomial pneumonia, chronic bronchitis and sinusitis, complicated urinary and intra-abdominal infections, Gram-negative bacteremia, acute bacterial skin infections, and neutropenic fever.[7]

Majority of the antibiotic abuse occur in the OPD settings. Antibiotic abuse has been classified as a global crisis by UN, recognizing its threat to humanity, on par with Ebola and HIV.[8] It is important to increase awareness about antibiotic resistance by shifting the focus from hospital to community level by engaging public and healthcare professionals. In order to encourage best practices among healthcare workers, policy workers and public, World Antibiotic Awareness Week was celebrated between November 18-24, 2019.

References

1. *qSOFA : What is qSOFA? [Internet]. [cited 2019 Dec 17]. Available from:* https://qsofa.org/what.php
2. *WHO | About SAVE LIVES: Clean Your Hands [Internet]. [cited 2019 Dec 17]. Available from:* https://www.who.int/gpsc/5may/background/5moments/en/
3. *Tamma PD, Miller MA, Cosgrove SE. Rethinking How Antibiotics Are Prescribed: Incorporating the 4 Moments of Antibiotic Decision Making Into Clinical Practice. JAMA. 2019 Jan 15;321(2):139-140.*
4. *Pharyngitis - StatPearls - NCBI Bookshelf [Internet]. [cited 2019 Dec 17]. Available from:* https://www.ncbi.nlm.nih.gov/books/NBK519550/
5. *Kuralayanapalya SP, Patil SS, Hamsapriya S, Shinduja R, Roy P, Amachawadi RG. Prevalence of extended-spectrum beta-lactamase producing bacteria from animal origin: A systematic review and meta-analysis report from India. PLoS One. 2019; 14(9): e0221771.*
6. *Squadrito FJ, del Portal D. Nitrofurantoin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Dec 17]. Available from:* http://www.ncbi.nlm.nih.gov/books/NBK470526/
7. *Spellberg B, Rice LB. Duration of Antibiotic Therapy: Shorter Is Better. Ann Intern Med. 2019 Aug 6;171(3):210.*
8. *Antibiotic resistance is 'crisis we cannot ignore,' UN warns, calling for responsible use of these medicines | UN News [Internet]. [cited 2019 Dec 17]. Available from:* https://news.un.org/en/story/2017/11/635832-antibiotic-resistance-crisis-we-cannot-ignore-un-warns-calling-responsible-use

Adult vaccinations

DR. A. Muruganathan., MD,
FICP, FRCP (Glasg, London, Ire), FACP (USA), FPCP (Philippines), FICP.,
Emeritus Professor – The Tamil Nadu Dr. M.G.R Medical University
Governor – American College of Physicians India Chapter

When meditating over a disease,
I never think of finding a remedy for it,
but, instead, a means of preventing it.
Louis Pasteur
(1822-1895)

Introduction

Considering the non-availability of potable water in several parts of developing countries, WHO has recommended vaccines as the most effective intervention in reducing and preventing infectious diseases.[1] It is imperative to increase the awareness regarding the consequences of antibiotic abuse and the significance of adult vaccination. Vaccinating adults has emerged as a national health priority owing to the change in demographics of the growing elderly population and significant increase in the life expectancy. Immunization is a time-tested approach to reduce the morbidity and mortality due to infections. However, the potential of adult immunization remains untapped in India. Moreover, there is insufficient evidence on the incidence of several diseases and data on vaccine use in India.

The need of vaccinating adults

Vaccination is also recommended for adults from the age of 19 years. Many adults may no longer be protected by vaccines received in childhood or they may not have been fully immunized as a child.[2] Vaccines play a vital role in maintaining a healthy immune system. The adult immunization also assists in protecting other vulnerable individuals in the community including non-vaccinated

infants, elderly relatives/ other family members and co-workers. it is beneficial for adults who deter seeking medical consultation owing to their busy schedules. In addition, it helps in protecting highly vulnerable populations (pregnant women, those with asthma, heart/lung disease or diabetes, and patients with HIV/weakened immune system or liver disease) from contracting vaccine-preventable diseases. The healthcare expenditure associated with the management of vaccine-preventable disease is substantial. Contacting flue can cause an adult to miss an average of six working days and one month for those infected with hepatitis. Older adults are at higher risk for contracting and developing serious complications due to influenza, invasive pneumococcal disease, and shingles.[3] There is a 200-fold increased risks for morality in adults as opposed to children.[4]

The Centre for disease control and prevention (CDC) recommends a single dose of Tdap for adults ≥19 years who have not previously received the vaccine, and a tetanus and diphtheria booster (called Td) every 10 years. It is also advocated in every trimester of gestation in pregnant women. Shingles (Zoster), a painful disease with possible life-long after-effects, can be prevented by vaccination. Human papillomavirus (HPV) vaccine (depending on type) prevents cervical cancer in young women and genital warts/anal cancer in both the sexes. The recommended adult immunization schedule by age group and by medical indications are given in table 1 and 2 respectively.[5] The recommended vaccine for healthcare workers and travelers are depicted in table 3 and 4 respectively.

Table 1: Recommended adult immunization schedule by age group

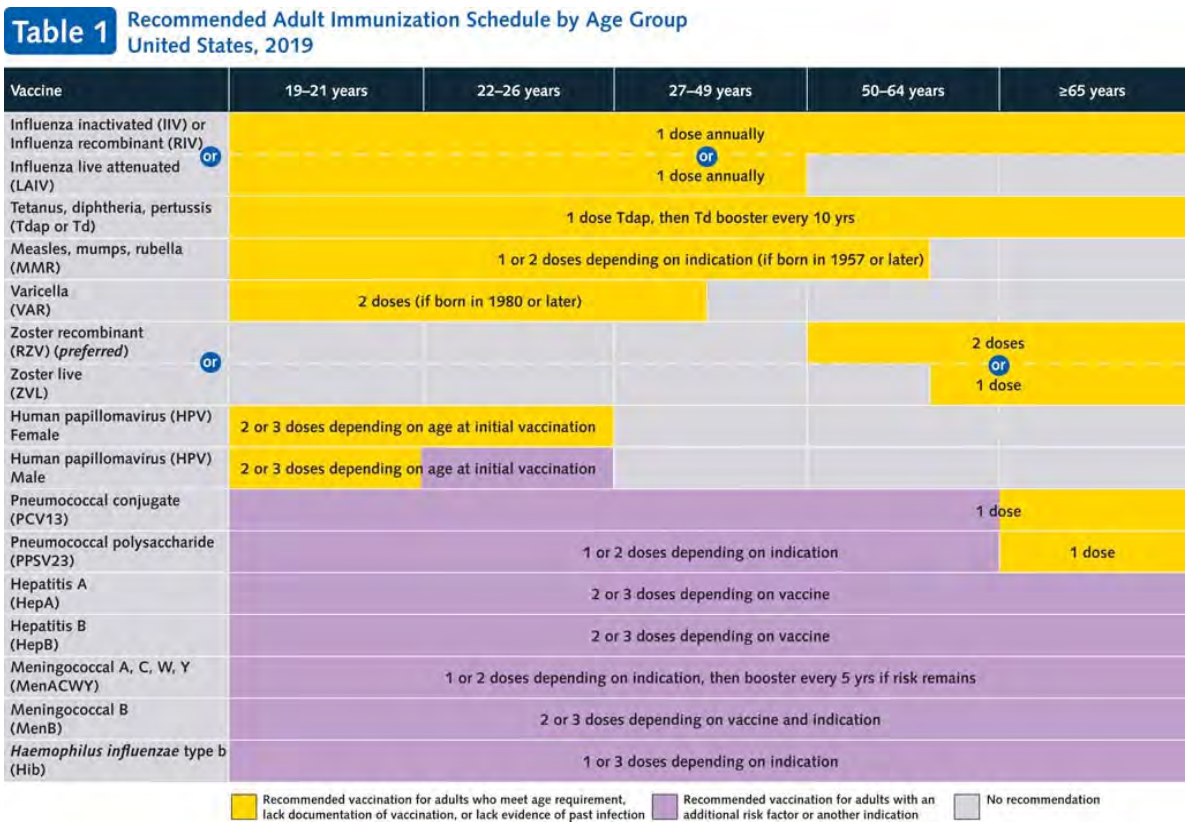


Table 2: Recommended adult immunization schedule by medical conditions and other indications

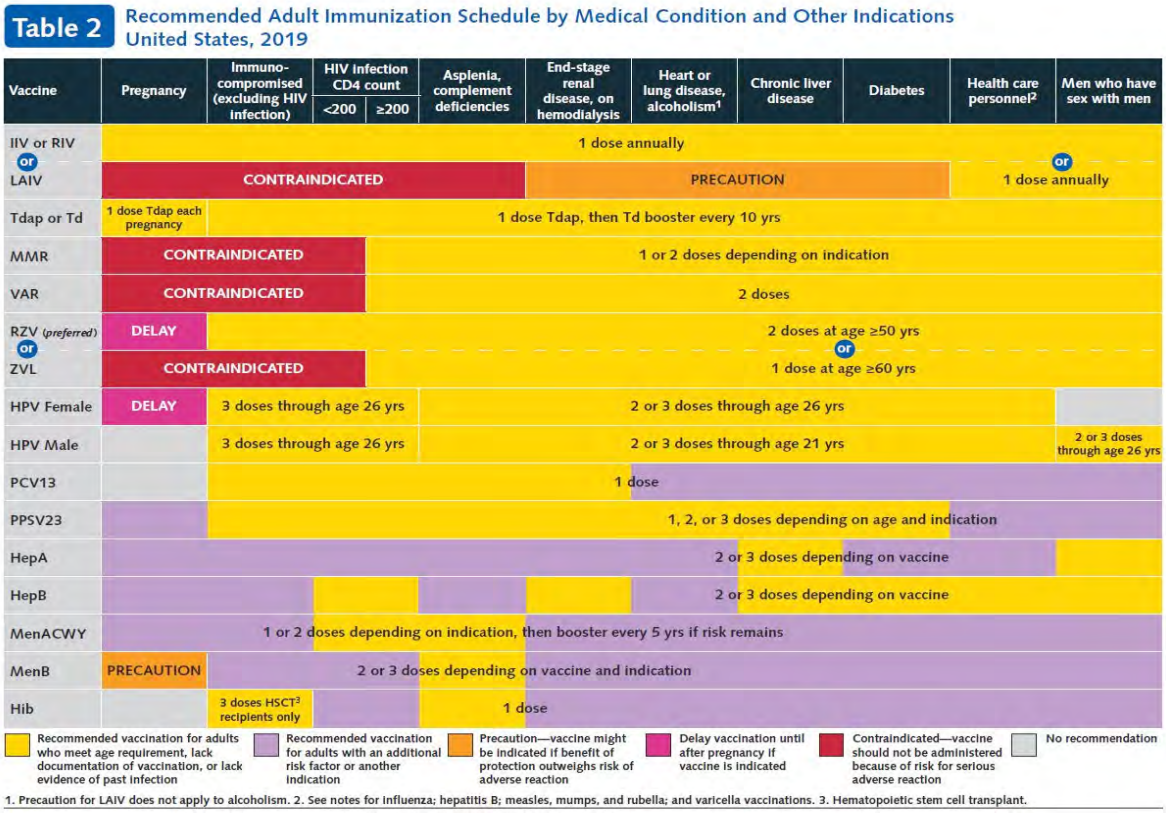


Table 3: Vaccines indicated for healthcare workers

Vaccination for healthcare workers	
Influenza	One dose annually
T dap	Similar to healthy adults
Hepatitis B	3 doses if no immunity followed by booster dose once in 5 years
Varicella	Two doses (unless had documented disease or proof of immunity)
MMR	One dose at the time of joining health care job
Typhoid	For food handlers in the hospital kitchen and microbiology laboratory personnel once in 3 years

Table 5: Vaccines indicated for travelers

Travel vaccination			
	Visitors travelling India	*Indians travelling to USA*	*Travel vaccines*
Typhoid	2 weeks before the travel	—	
Hepatitis A	2 weeks before the travel		
Hepatitis B	2 months before travel	Similar to healthy adults	
Rabies	3 doses (0, 7, 21) 1 month before travel	—	
Japanese B encephalitis	2 doses at 4 week interval, 1 month before travel	—	
Influenza	1 dose annually	1 dose annually	
Tdap		Students and visitors above the age of 65 years going to handle children	
MMR		One or two doses for students going for higher studies	
Polio			Travelers to Afghanistan, Cameroon, Equatorial Guinea, Ethiopia, Iraq, Israel, Nigeria, Pakistan, Somalia, and Syria
Meningococcal vaccine		One or two doses for students going for higher studies	To persons going for Haj pilgrimage
Yellow fever			**Africa:** Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d' Ivoire, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, South Sudan,Togo, Uganda. **South America:** Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guyana, Guyana, Suriname, Trinidad (Trinidad only), Venezuela, Panama, Paraguay, Peru.

Influenza vaccination

As per the estimates of WHO, 5–15 % of the population are affected with influenza every year. Influenza leads to 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths.[6] Clinical evidence shows that influenza can trigger coronary complications, and the risk for CVD in this sub group is around 2-4 fold.[7] Influenza vaccination helps in secondary prevention of cardiac abnormalities. Two types of vaccines recommended for the prevention of influenza are nasal live attenuated influenza vaccine (LAIV) and unadjuvanted injectable trivalent inactivated vaccines (TIV). Both LAIV and TIV contain strains of influenza viruses that were antigenically equivalent to the annually recommended strains, i.e. one strain each from influenza A (H3N2) virus, influenza A (H1N1) virus and influenza B virus. A quadrivalent influenza vaccine contains one influenza A (H3N2), one influenza A (H1N1) and two influenza B vaccine strains, one from each lineage of circulating influenza B viruses.[8]

Ideal time for vaccination in India

Monsoon is considered as peak influenza season in India. Hence, it is ideal to administer the vaccine

during pre-monsoon season (April/May). The second peak occurs during winter (Nov-Feb) in Northern states of J&K, Himachal, and Delhi. Tamil Nadu also shows peak season during November-February due to north-east monsoon. It is ideal to conduct semiannual influenza vaccination in elderly residents (>65 years) of tropical countries to improve serological measures of protection against infection.[9] It is preferred over annual vaccination for preventing influenza-like illness.

Pneumococcal vaccination

Diabetes subjects are more prone to develop pneumonia due to hyperglycemia, poor long-term diabetes control, longer duration of diabetes, decreased immunity, impaired lung function, pulmonary micro angiopathy, increased risk of aspiration and coexisting morbidity. Longer duration of diabetes and impaired glycemic control are associated with 25–75% increase in the relative risk of pneumonia-related hospitalizations in diabetes.[10] There are currently 2 types of pneumococcal vaccines.[11]

- Pneumococcal polysaccharide vaccine 23 (PPV 23): It comprises of 25 µg each of purified capsular polysaccharide from 23 serotypes of *S. pneumoniae* antigens.
- Pneumococcal conjugate vaccine 13 (PCV 13): It comprises of 2.2 µg of polysaccharide of 12 serotypes and 4.4 ug of polysaccharide from 6B serotype conjugated with nontoxic diphtheria protein adsorbed on aluminium salt.

It is recommended to administer a single standard dose (0.5 ml) via intramuscular or subcutaneous route. PPV 23 vaccination can be offered to diabetes patients aged 19 to 64 years. In patients >65 years of age, a one-time revaccination is recommended. For diabetes subjects of >65 years or those having immunocompromising condition (e.g., end stage renal failure), PCV 13 vaccine should be administered first, followed by PPV 23 vaccine after 8 weeks. In subjects who have already received PPV 23, a minimum of one-year interval is required before the administration of PCV 13.[11]

Hepatitis B vaccination

Hepatitis B vaccine is a recombinant subunit vaccine (inactivated vaccine), available either alone or in combination with hepatitis A vaccine. The current standard vaccination schedule followed is 3 doses (20µg/mL) at 0-, 1-, and 6-months. Booster dose is not routinely required for immunocompetent persons. Four doses of 40 µg each (0, 1, 2 and 12 months) is recommended for patients with chronic kidney disease and those undergoing dialysis.[12] The list of high-risk groups of adults requiring vaccine protection are listed in table 6.

Table 6: High-risk groups of adults requiring vaccine protection

Box 1: Adults recommended receiving hepatitis B vaccination
• Person at risk for infection by sexual exposure ■ Sex partners of HBsAg-positive persons ■ Sexually active persons, who are not in a long-term, mutually monogamous relationship (e.g. persons with more than one sex partner during the previous 6 months) ■ Persons seeking evaluation or treatment for a sexually transmitted disease ■ Men who have sex with men • Persons at risk for infection by percutaneous or mucosal exposure to blood ■ Current or recent injection-drug users ■ Household contacts of HBsAg-positive persons ■ Residents and staff of facilities for developmentally disabled persons ■ Healthcare and public safety workers with reasonably anticipated risk for exposure to blood or blood contaminated body fluid ■ Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients ■ Diagnosis of a disease, requiring blood products or multiple blood transfusions is made, e.g. hemophilla, aplastic anemia, leukemia, hemoglobinopathies and patients awaiting major surgeries • Others ■ Persons with chronic liver disease ■ Persons with HIV infection ■ All other persons seeking protection from HBV infection

Tdap vaccination

Considering the resurgence of pertussis in various part of India, Tdap (tetanus, diphtheria, and pertussis), vaccination is advocated in adults. T dap vaccine contains acellular pertussis combined with tetanus toxoid and reduced diphtheria toxoid. It is recommended to any adult who is not sure if he/ she has had the vaccine. Tdap vaccination should be followed by administration of a tetanus and diphtheria booster every 10 years.[13] The amount of diphtheria and pertussis antigen in T dap is lower when compared to DTP.

Herpes zoster vaccination

The CDC recommends administering herpes zoster vaccination to people ages ≥50 years. Herpes zoster vaccination should be used within 30 minutes after reconstitution.[14] The vaccination schedule comprises of 0.65 ml single dose subcutaneously in the upper arm and each 0.65 ml dose contains a minimum of 19,400 plaque-forming units. However, currently the vaccine is not available in India.

Hepatitis A vaccination

Hepatitis A vaccine (HAV) is an inactivated vaccine, currently available as both single-antigen vaccine and a combination vaccine containing both HAV and hepatitis B virus (HBV) antigens. All susceptible persons living, traveling or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated (Central or South America, the Caribbean, and Mexico). Persons who have had a serious adverse reaction to a previous dose of the vaccine or its ingredients should not receive another dose.

Contraindications to vaccination

The vaccination is contraindicated in the following scenarios:[15]

- Hypersensitivity to the active substances or to any of the excipients of the vaccine.
- History of chicken egg allergy particularly when considering flu shot.
- Recent history of Guillain–Barre syndrome within 6 weeks of a previous influenza vaccination in the case of flu shot.

In addition, immunization should be postponed in patients with febrile illness or acute infection.

Conclusion

Higher costs, poor public health and private infrastructure, lack of knowledge among both patients and providers, and inadequate funding and public programs are the major challenges in wider adoption of adult immunization. In Indian settings, the diabetologist, dietitian, diabetes educator, pharmacist, psychologist, and other members of the diabetes care team can take up the responsibility of counseling the patients on the availability and requirement of routine vaccinations. Use of educational material in local language, discussion on vaccination during diabetes education and the use of vaccination cards help in boosting the confidence among the patients.

References

1. *Seven Key Reasons Why immunization must remain a priority in the WHO European Region. [Internet]. 2019 [cited 2020 Jan 16]. Available from:* http://www.euro.who.int/__data/assets/pdf_file/0017/84302/Seven_Key_Reasons.pdf
2. *10 Reasons To Get Vaccinated [Internet]. National Foundation for Infectious Diseases. 2019 [cited 2020 Jan 16]. Available from:* https://www.nfid.org/immunization/10-reasons-to-get-vaccinated/
3. *Smetana J, Chlibek R, Shaw J, Splino M, Prymula R. Influenza vaccination in the elderly. Hum Vaccin Immunother. 2017 Aug 4;14(3):540–9.*
4. *Guyer B, Smith DR, Chalk R. Calling the shots: immunization finance policies and practices. Executive summary of the report of the Institute of Medicine. Am J Prev Med. 2000 Oct;19(3 Suppl):4–12.*
5. *Adult Immunization Schedule by Vaccine and Age Group | CDC [Internet]. 2019 [cited 2020 Jan 16]. Available from:* https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
6. *Influenza (Seasonal) [Internet]. [cited 2020 Jan 16]. Available from:* https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)
7. *Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. Lancet Infect Dis. 2009 Oct;9(10):601–10.*
8. *Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012 Jan 1;8(1):81–8.*
9. *Young B, Sadarangani S, Haur SY, Yung CF, Barr I, Connolly J, et al. Semiannual Versus Annual Influenza Vaccination in Older Adults in the Tropics: An Observer-blind, Active-comparator-controlled, Randomized Superiority Trial. Clin Infect Dis. 2019 Jun 18;69(1):121–9.*
10. *Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schønheyder HC, Sørensen HT. Diabetes, Glycemic Control, and Risk of Hospitalization With Pneumonia. Diabetes Care. 2008 Aug;31(8):1541–5*
11. *About Pneumococcal Vaccine | For Providers | CDC [Internet]. 2019 [cited 2020 Jan 16]. Available from:* https://www.cdc.gov/vaccines/vpd/pneumo/hcp/about-vaccine.html
12. *Hepatitis B and the Need for a Booster Dose | Clinical Infectious Diseases | Oxford Academic [Internet]. [cited 2020 Jan 16]. Available from:* https://academic.oup.com/cid/article/53/1/68/492859
13. *Diphtheria, Tetanus, and Whooping Cough Vaccination | What You Should Know | CDC [Internet]. 2019 [cited 2020 Jan 16]. Available from:* https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/public/index.html
14. *zostavax_pi2.pdf [Internet]. [cited 2020 Jan 16]. Available from:* https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf
15. *McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018 Feb;141(2):463–72.*

Fever Apps & Technology: What's up?

Dr. Suresh Kumar D MD, FNB (Inf Dis)
American Certified Tropical Medicine, Fellowship in HIV/AIDS Medicine,
Adjunct Associate Professor- AHERF, NABH Assessor, Doctorpraneur,
Co- founder Best of IDs (Doctor's Doctor)
Senior Consultant, Infectious Diseases
Apollo Hospitals, Chennai

Labelling the generations

Based on the general characteristics and behavior, the generations can be classified as: builders (age 71+), baby boomers (age 52-70), generation X (age 37-51), generation Y (age 22-36), generation Z (age 7-21) and generation alpha (age <7).

Statistical estimate shows that the number of individuals belonging to generation Z (people born between 1995 and 2005) will be more by 2020 when compared to 2013 and the millennials will constitute 50%. The corresponding percentages of generations in 2013 and the newer estimates for 2020 are listed in table [1].

Table 1: Percentages of generations in 2013 and 2020

Generations	2013 (%)	2020 (%)
Traditionalists	5	4
Baby Boomers	39	16
Gen X	32	20
Millennials	24	50
Gen Z	-	10

Characteristics of gen Z

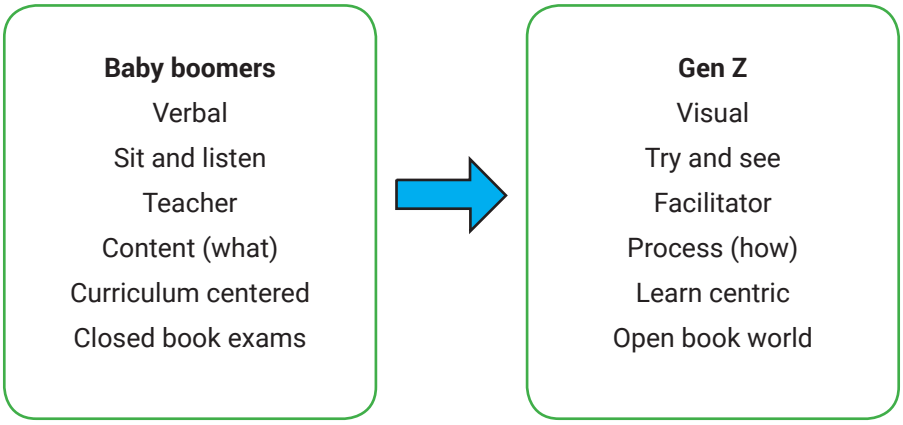
The millennials have a characteristic of searching and collecting information from internet, whereas generation Z needs the information instantaneously. The key characteristics of generation Z are given in table [2].

Table 2: Characteristics of gen Z

- Global population to reach 2.56 billion by 2020.
- 96% own a smartphone and 85% uses social media.
- 50% will be online up to 10 hours and 33% watches 1 hour of online video per day.
- 63% prefer to see real people in ads and they will make up 40% of all consumers.
- 50% to be a part of minority or ethnic group.
- They have an attention span of 8 seconds.

The Indian population of Gen Z in projected to outnumber the total number of individuals in the US and China by 2020. The figure 1 provides a comparison of preferences of baby boomers and gen Z.

Fig.1: A comparison of preferences of baby boomers and gen Z



Apps and technologies revolutionizing healthcare

The world is presently undergoing the 4th revolution and it is witnessing the emergence of artificial intelligence, machine learning, digital integration and cloud computing.[1] The near future will witness the use of chatbots and virtual assistance by gen Z doctors for online consultation, fixing appointments and communicating with the patients. Nowadays, the advent of several online app-based consultation services has made the healthcare facilities more accessible to the people, without physically visiting the hospital. The technology has facilitated the monitoring of 24-hr temperature, blood pressure, heart rate and other vital parameters through several wearable devices, smartwatches and mobile apps. Evolution of wearable devices including spectacles, headsets, clothing, shoes, arm band etc. has introduced the concept of real-time disease monitoring for personalized care.[2]

The use of oral thermometers in the earlier days was associated with increased risk for cross infections due to sharing. The availability of patch-based temperature monitoring facility has helped to avoid such drawbacks and predict the pattern based on 24-hr monitoring. A study by the University Hospitals Seidman Cancer Center in Cleveland has reported that the use of digital wearable thermometer is more effective than the current standard-of-care (SOC) method in detecting increase in body temperature up to 180 minutes.[3] Through big data, machines can analyze and interpret lakhs of data together.

There are apps to predict the possibility of vector-born and other diseases and to understand the most vulnerable areas based on the google search analytics.[4] The implementation of Mo-Buzz in Sri Lanka helped in direct improvement of dengue surveillance and effective communication with the people in vulnerable areas.[5] The technology called eDOT has been found to be beneficial in remotely monitoring TB patients.[6]

Through technology, it is now possible to non-invasively detect anemia using smartphone apps.[7] Researchers are currently investigating converting a smartphone into microbiology lab for clinical diagnosis. Several implantable and ingestible devices are on the way to monitor cardiovascular signals, saliva/sweat and intestinal fluid. Online pharmacy/medical stores are revolutionizing the pharma industry throughout the world. It is even possible to get the medications without prescription by availing online consultation through app-based services. Smart pills embedded with absorbable sensors and pill counters are beneficial in improving the adherence to treatment in HIV, TB etc. Cancer-fighting nanobot to destroy tumors by cutting off the blood supply is another promising tool in the field of oncology.[8]

In future, chatbots, robots and artificial intelligence will play a crucial role in medical education. The advances in technology and adoption of AI machines are projected to replace the jobs of telemarketers (99%), cashiers (97%), accountants/auditors (94%), and waiters/waitresses (94%).[9] In addition, AI may replace the jobs of dermatologists, radiologists, occupational health and safety specialists, microbiologist and general practitioners in future.

Despite the greater potential of AI in healthcare, implementation of such newer technologies raises serious ethical concerns, threats of privacy issue and medical errors. A 2019 report published by UK Academy of Medical Royal Colleges titled 'Artificial Intelligence in Healthcare' has attempted to address the concerns of medical professionals. As per the report, AI is not likely to replace the jobs of the clinicians, but training the doctors in data science will definitely change their way of working and providing patient care.[10]

The academy has also put forth the following key recommendations with regard to the adoption of AI in healthcare:[10]

- To ensure patient safety, AI must be developed in a regulated manner by considering the perspectives of both clinician and computer experts.
- AI should be implemented to reduce the health inequality (socially geographically and economically) and not to increase it.
- There should be clear guidance on the responsibility accountability and the legal implications of AI implementation in healthcare.

References

1. *The Fourth Industrial Revolution. [Internet]. [cited 2019 Dec 15]. Available from:* https://luminariaz.files.wordpress.com/2017/11/the-fourth-industrial-revolution-2016-21.pdf
2. *Appelboom G, Camacho E, Abraham ME, Bruce SS, Dumont EL, Zacharia BE, et al. Smart wearable body sensors for patient self-assessment and monitoring. Arch Public Health. 2014 Aug 22;72(1):28.*
3. *Wearable Digital Thermometer Detects Fever Quicker than Current SOC method [Internet]. Wearable Technologies. 2018 [cited 2019 Dec 15]. Available from:* https://www.wearable-technologies.com/2018/05/wearable-digital-thermometer-detects-fever-quicker-than-current-soc-method/
4. *Babu AN, Niehaus E, Shah S, Unnithan C, Ramkumar PS, Shah J, et al. Smartphone geospatial apps for dengue control, prevention, prediction, and education: MOSapp, DISapp, and the mosquito perception index (MPI). Environ Monit Assess. 2019 Jun 28;191(Suppl 2):393.*
5. *Lwin MO, Jayasundar K, Sheldenkar A, Wijayamuni R, Wimalaratne P, Ernst KC, et al. Lessons From the Implementation of Mo-Buzz, a Mobile Pandemic Surveillance System for Dengue. JMIR Public Health Surveill. 2017 Oct-Dec; 3(4): e65.*
6. *Implementing an Electronic Directly Observed Therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs [Internet]. [cited 2019 Dec 15]. Available from:* https://www.cdc.gov/tb/publications/pdf/TBeDOTToolkit.pdf
7. *Mannino RG, Myers DR, Tyburski EA, Caruso C, Boudreaux J, Leong T, et al. Smartphone app for non-invasive detection of anemia using only patient-sourced photos. Nat Commun. 2018 Dec 4;9(1):1–10.*
8. *Ma W, Zhan Y, Zhang Y, Shao X, Xie X, Mao C, et al. An Intelligent DNA Nanorobot with in Vitro Enhanced Protein Lysosomal Degradation of HER2. Nano Lett. 2019 Jul 10;19(7):4505–17.*
9. *Amplifying human potential [Internet]. [cited 2019 Dec 15]. Available from:* https://www.infosys.com/aimaturity/Documents/amplifying-human-potential-CIO-report.pdf
10. *Artificial Intelligence in Healthcare. [Internet]. [cited 2019 Dec 15]. Available from:* https://www.aomrc.org.uk/wp-content/uploads/2019/01/Artificial_intelligence_in_healthcare_0119.pdf