Infectio®
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OBITUARY

Wife of **Prof. Ejaz Ahmed Vohra**, Chairman and Head of project Infectio® passed away on April 14th, 2017. **Madam Rafia Ejaz** dedicated her life as a social worker and house wife, her work for the education of girls in Pakistan is extraordinary. Her absence would definitely be missed by everyone who was associated with her. All the editorial board members, Management, Readers and SAMI Pharmaceuticals deeply condole her sad demise. May Allah Subhanaho Wa'Talla rest her soul in eternal peace and grant her Jannat-ul-Firdous (A'ameen).

Prof. Abdul Gaffar Billoo & Editorial Board

Infectio®
A quarterly Magazine

Editorial Correspondence

Dr. Muhammad Salman
Email: infectio@samikhi.com

Introduction

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Message of the Chairman Infectio®

This is a matter of immense satisfaction that Infectio® is on right track of disseminating updated quality knowledge across Pakistan. The mission of Infectio® team to keep maximum professionals across Pakistan abreast with latest information about infectious diseases is materializing.

With this mission in mind, the current issue is focused on the very common protozoal infections among the Asian and developing nations. With the outbreak of **Chikungunya fever**, it is essential to recognize the symptoms of this disease and manage it accordingly as well as understand the basics of Malaria. Another very frequently reported issue is of fungal infections, A study showed that out of 184,500,000 people in Pakistan, an estimated 3,280,549 (1.78%) are affected by serious fungal infections[1]. With the aim to make the prescribers aware of the therapies, an article on antifungal agents is added especially for the young professionals.

We are grateful to unconditional support of **SAMI Pharmaceuticals** for their continuous efforts to collaborate with the medical professionals for the benefit of medical community. I would also like to appreciate the efforts of the editorial board and the contributors of this edition of Infectio® magazine.

In the end, I would like to congratulate the winners of previous issue and acknowledge the determination of all quiz participants.

Thank you

Prof. Dr. Ejaz Ahmed Vohra
Chairman Editorial Board
Dean Post graduate clinical
Head, Department of Medicine
Dr. Ziauddin University Karachi

1-Jabeen, K., Farooqi, J., Mirza, S., Denning, D., & Zafar, A. (2017). Serious fungal infections in Pakistan. European Journal of Clinical Microbiology & Infectious Diseases, 1-8.

Malaria : New Challenges

Dr. Bushra Jamil Ali,
Professor and Section Head,
Adult Infectious Diseases &
Department of Medicine,
The Aga Khan University, Karachi

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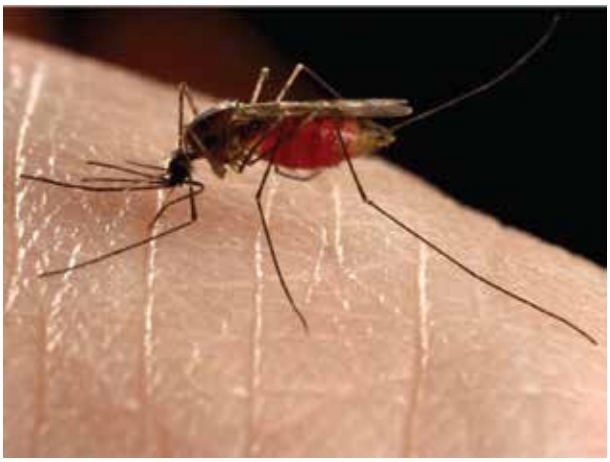

History of Malaria

Malaria is an ancient disease, known to mankind for more than 4000 years. There has always been some recognition of the association between swampy, marshy areas and the disease. We have inherited the word malaria from the Latin words malus aria, from Italian mal'aria through the contracted Italian mala aria which means "bad or evil air" because it was originally thought that this disease was caused by foul air, and particularly by vapors given off by swamps. It was also called "swamp fever", and it is one of the most ancient infections known to man. It is said that roman soldiers were wary of this association and would always camp away from the swamps to avoid the disease.

The earliest description of the disease is attributed to Hippocrates in the 5th century B.C. He classified the fever types as quotidian (daily), tertian (alternate days) and quartan (fever three days apart). He also noticed that those who drank the stagnant marsh water had large stiff spleens, a characteristic of the disease, and fatal dropsy was common among them.

Archaeological findings indicate that the Chinese were using wormwood to treat malaria more than 2,000 years ago. The weed—Artemisia annua or qing ho in Chinese—is even mentioned in the Recipes for 52 Kinds of Diseases, an early medical text found in a tomb dating from 168 BC. But its curative powers were not put to a rigorous test until 1967, when the government of the People's Republic of China began to examine systematically indigenous plants used in traditional remedies as potential sources of drugs. By 1972, the active ingredients were characterized and Artemsinin-based therapy has become the most potent treatment available for the treatment of malaria.

- Quinine, a derivative of Peruvian or Cinchona bark was also known for its medicinal properties, centuries before the malarial parasite was described by Charles Louis Alphonse Laveran in 1880. In 1897, Ronald Ross, a British officer in the Indian Medical Service, was the first to demonstrate that malaria parasites could be transmitted from infected patients to mosquitoes. Chloroquine was developed subsequently but was finally recognized and established as an effective and safe antimalarial in 1946. With the introduction of DDT for malaria control at the end of World War 2, WHO launched the ambitious plan of malaria eradication world-wide in 1955, which was eventually abandoned a few decades later.

  Pakistan joined the international partnership for Roll Back Malaria (RBM) established by WHO in collaboration with the World Bank, UNICEF and UNDP in 1999 and adopted the RBM strategies for the control of malaria in the country.

- Pakistan is among 107 countries with endemic malaria and among top 10 countries with highest estimated population at risk for vivax malaria. Malaria in Pakistan is epidemiologically unstable, which means that there is fluctuation in transmission from season to season with a propensity for epidemics; all ages are susceptible. Peak transmission occurs in the post-monsoon months of August to November and major vector species are *Anopheles culicifacies* and *Anopheles stephensi*. Prevalent causative parasites are *Plasmodium vivax* and *Plasmodium falciparum* and over 40% cases of falciparum are resistant to Chloroquine. In one study on *P. falciparum,* genes conferring resistance to Chloroquine were found in 93% isolates and those conferring decreased susceptibility to Sulphadoxine-Pyrimethamine were found in 92% isolates. However, true, high level resistance to Pyrimethamine-Sulfadoxine was uncommon in this study. On the other hand, efficacy studies conducted in Baluchistan (2001-2005) reported 56% treatment failure with Sulphadoxine-Pyrimethamine monotherapy

Current WHO guidelines for treatment of malaria (published 2010)

WHO guidelines address both diagnosis and management of malaria.

Diagnosis:

The introduction of Artemisinin based combination therapy (ACTs) has increased the urgency of improving the specificity of malaria diagnosis. The relatively high cost of these medicines and the propensity for increasing drug resistance makes unnecessary treatment of patients without parasitaemia unsustainable. Even Pakistan's national case management policy discourages treatment on the basis of clinical diagnosis alone.

- Uncomplicated malaria is symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction.
- Severe falciparum malaria is acute form of malaria, with signs of severity and/or evidence of vital organ dysfunction.
- **Cerebral malaria:** Severe *P. falciparum* malaria with cerebral manifestations, usually including coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 min after a seizure is considered to be cerebral malaria.

Recommendations:

- Use light microcopy where it is available.
- If microscopy is not available, use a falciparum detecting RDT (low cost).
- If the test result is negative but strong clinical evidence of malarial infection is present, make a clinical/presumptive diagnosis of vivax malaria and treat as such.
- Base treatment on clinical diagnosis only if both microscopy and RDTs are not available.

Advantages of parasitological diagnosis:

- Cost savings.
- Improved patient care in parasite-positive patients.
- Identification of parasite-negative patients in whom another diagnosis must be sought.
- Prevention of unnecessary exposure to antimalarials, thereby reducing side-effects, drug interactions and selection pressure.
- Improved health information.
- Confirmation of treatment failures.

Limitations of diagnostic tests

- DTs do not distinguish new infections from a recently and effectively treated past infection due to the persistence of target antigens (e.g. HRP2) in the blood for 1–3 weeks after effective treatment.
- Unpredictable sensitivity in the field: test performance is greatly affected by adverse environmental conditions such as high temperature and humidity.
- Microscopy requires training and is time consuming.
- There is a risk of misinterpreting a positive result as indicating malaria in semi-immune patients with concomitant illness.

Treatment

- The main objective of treatment is to prevent the patient from dying.
- Secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

The mortality of untreated severe malaria approaches 100%. With appropriate management the case fatality of severe malaria can be reduced below 10% overall. The risk of death is highest in the first 24 hours. It is important that health care providers at the first level of contact initiate appropriate treatment.

Plasmodium vivax

- For uncomplicated vivax malaria, Chloroquine remains the drug of choice.
- For Chloroquine-resistant vivax malaria, Amodiaquine, Mefloquine and Quinine are effective in the treatment.
- ACTs based on either Amodiaquine, Mefloquine or Piperaquine, rather than monotherapy, are the recommended treatment of choice.
- To achieve a radical cure, relapses must be prevented by giving Primaquine.
- At least a 14-day course of Primaquine is required for the radical treatment of P. vivax.

Severe or complicated vivax malaria is now becoming common. For treatment, it is recommended to follow the guidelines for treatment of severe falciparum malaria.

Plasmodium falciparum

- Artemesinin-based combination therapy (ACT) should only be given in confirmed falciparum cases.
- Artesunate is the preferred antimalarial for severe malaria because mortality is significantly lower when Artesunate is used than with quinine treatment in adults and children.
- The mortality rate among quinine treated patients was 22% and 10.9% in the SEAQUAMAT and AQUAMAT studies respectively; for Artesunate this was 15% and 8.5%, a significant reduction of 35% and 22.5% respectively.

New antimalarials

Piperaquine, synthesized in the 1960s, and is used extensively in China for prophylaxis and treatment of malaria. Its use declined in the 1980s as Piperaquine - resistant strains of *P. falciparum* arose and Artemisinin-based antimalarials became available. The fixed dose combination Dihydroartemesinin-Piperaquine is now available and has good efficacy. It is included as one of the first line agents for uncomplicated falciparum malaria and Chloroquine - resistant vivax malaria in WHO guidelines.

Treatment of P. falciparum malaria in special risk groups

Pregnancy

- Pregnant women with symptomatic acute malaria are a high-risk group. Maternal mortality is approximately 50% higher than in non-pregnant women.
- Fetal death and premature labor are common.
- Increased risk of severe malaria, complicated by pulmonary edema and hypoglycemia.
- There is insufficient information on the safety and efficacy of most antimalarials in pregnancy.
- The antimalarials considered safe in the first trimester of pregnancy are Quinine, Chloroquine, Proguanil and Sulfadoxine–Pyrimethamine.
- Of these, Quinine remains the most effective and can be used in all trimesters of pregnancy.

Treatment in the first trimester:

- Quinine plus Clindamycin to be given for 7 days (Artesunate plus Clindamycin for 7 days is indicated if this treatment fails).
- An ACT is indicated only if this is the only treatment immediately available, in case of treatment failure or uncertainty of compliance with a 7-day treatment.

Second and third trimesters:

- ACTs known to be effective in the country/region or Artesunate plus Clindamycin to be given for 7 days, or Quinine plus Clindamycin to be given for 7 days.

  Lactating women should receive standard antimalarial treatment (including ACTs) except for Dapsone, Primaquine and Tetracyclines.

Additional aspects of management of severe falciparum malaria

a. Exchange blood transfusion

There have been many anecdotal reports and several series claiming benefit for exchange blood transfusion (EBT) in severe malaria but no comparative trials, and there is no consensus on whether it reduces mortality or how it might work.

b. Treatments which are not recommended

- Heparin, Prostacyclin, Desferoxamine, Pentoxifylline, low molecular weight Dextran, Urea, High-dose Corticosteroids, Acetylsalicylic acid, Anti-Tumour Necrosis Factor Antibody, Cyclosporin, Dichloroacetate, Adrenaline and Hyperimmune serum.
- The use of corticosteroids increases the risk of gastrointestinal bleeding and seizures, and has been associated with prolonged coma resolution times when compared with placebos

Conclusions

Malaria remains prevalent and has become more severe in recent times. There is no justification for empiric treatment of malaria where RDT and peripheral smear examination are available. ACTs remain the therapy of choice and current evidence suggests superiority of IV Artesunate. Every effort should be made to procure it. Otherwise, use IV Quinine in severe malaria. For malaria control, role of Primaquine is gaining more attention. With these step, the duration of illness can be reduced and quality of life is increase significantly.

Malaria: Kenya, Ghana and Malawi get first vaccine

Contributed by;
Prof. Ejaz Ahmed Vohra

Infectio®

The world's first vaccine against malaria will be introduced in three countries - Ghana, Kenya and Malawi - starting in 2018

The RTS,S vaccine trains the immune system to attack the malaria parasite, which is spread by mosquito bites.

The World Health Organization (WHO) said the jab had the potential to save tens of thousands of lives.

But it is not yet clear if it will be feasible to use in the poorest parts of the world.

The vaccine needs to be given four times - once a month for three months and then a fourth dose 18 months later.

This has been achieved in tightly controlled and well-funded clinical trials, but it is not yet clear if it can be done in the "real-world" where access to health care is limited.

It is why the WHO is running pilots in three countries to see if a full malaria vaccine programme could be started. It will also continue to assess the safety and effectiveness of the vaccination.

Dr Matshidiso Moeti, the WHO regional director for Africa, said: "The prospect of a malaria vaccine is great news.

"Information gathered in the pilot programme will help us make decisions on the wider use of this vaccine.

"Combined with existing malaria interventions, such a vaccine would have the potential to save tens of thousands of lives in Africa."

The pilot will involve more than 750,000 children aged between five and 17 months. Around half will get the vaccine in order to compare the jab's real-world effectiveness.

In this age group, the four doses have been shown to prevent nearly four in ten cases of malaria.

This is much lower than approved vaccines for other conditions.

Malaria vaccine: How good is good enough?

It also cuts the most severe cases by a third and reduces the number of children needing hospital treatment or blood transfusions.

But the benefits fall off significantly without the crucial fourth dose.

Ghana, Kenya and Malawi were chosen because they already run large programmes to tackle malaria, including the use of bed nets, yet still have high numbers of cases.

Each country will decide how to run the vaccination pilots, but high-risk areas are likely to be prioritized.

Despite huge progress, there are still 212 million new cases of malaria each year and 429,000 deaths.

Africa is the hardest hit and most of the deaths are in children.

The pilots are being funded by: Gavi, the Vaccine Alliance, the Global Fund to Fight Aids, Tuberculosis and Malaria, Unitaid, the WHO and GSK.

Dr Seth Berkley, the chief executive of Gavi, said: "The world's first malaria vaccine is a real achievement that has been 30 years in the making.

"Today's announcement marks an important step towards potentially making it available on a global scale.

"Malaria places a terrible burden on many of the world's poorest countries, claiming thousands of lives and holding back economies.

"These pilots are crucial to determining the impact this vaccine could have on reducing this toll."

Reference:

Health and science reporter, BBC News website 24 April 2017

ARCEVA™

Artemether + Lumefantrine

Differentiating Malaria from Dengue & Chikungunya

	P. falciparum	P. vivax	Dengue	Chikungunya
Vector	**Anopheles**	**Anopheles**	**Aedes aegypti**	**Aedes aegypti**
Organism	**Protozoa**	**Protozoa**	**RNA virus** (Flavivirus)	**RNA virus** (Togavirus)
Clinical Features				
Fever (≥ 38°C)*	+++	+++	+++	+++
Myalgia	+	+	+++	+++
Headache	++	++	+++	+++
Rash	+/-	+/-	++	++
Jaundice	+	+/-	+/-	+/-
Vomiting	++	+	+	+
Abdominal pain	+/-	+	+/-	+
Hepatomegaly	+	+	+/-	+/-
Splenomegaly	+	+	+/-	+/-
Leukopenia	+/-	+/-	+++	++
Anaemia	++	++	+	+
Thrombocytopenia	++	++	+++	+++
Pharyngitis	-	-	-	++
Conjunctivitis	-	-	-	++
Photophobia	-	-	-	+
Migratory arthralgia	-	-	-	++

* +++ = 70%–100% of patients; ++ = 40%–69%; + = 10%–39%; +/–= <10%; –= 0%.

Adapted: who.int/emerging _ diseases/documents/DC.Module5.pd

Sources: Nimmannitya S et al. Am J Trop Med Hyg, 1969; 18:954–971. Halstead SB et al. Am J Trop Med Hyg, 1969; 18:972–983. Beg et al. Int J Inf Dis, 2008; 12:37–42.Robinson et al. J Travel Med, 2001; 8(2):76–81. Luxemburger et al. Tran R Soc Trop Med Hyg, 1998; 92:42-49, aide memoire of pan American health organization and WHO, January 2014 Chikungunya, Chikungunya - Chapter 3 - 2016 Yellow Book | Travelers' Health | CDC, Clinical Profile of Chikungunya Fever

Chikungunya

Professor Dr. Dilshad Qureshi
Head Of Pediatrics Medicine Unit-IV,
Sandeman Provincial Hospital Quetta.
Dr.Aimal Khan
Medical Officer/Post Graduate Trainee
FCPS-II,Pediatric Medicine Unit-IV,
Sandeman Provincial Hospital Quetta

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Key facts

- Chikungunya is a viral disease transmitted to humans by infected mosquitoes. It causes fever and severe joint pain. Other symptoms include muscle pain, headache, nausea, fatigue and rash.
- Joint pain is often debilitating and can vary in duration.
- The disease shares some clinical signs with dengue, and can be misdiagnosed in areas where dengue is common.
- There is no cure for the disease. Treatment is focused on relieving the symptoms.
- The proximity of mosquito breeding sites to human habitation is a significant risk factor for chikungunya.
- The disease occurs in Africa, Asia and the Indian subcontinent. In recent decades mosquito vectors of chikungunya have spread to Europe and the Americas. In 2007, disease transmission was reported for the first time in a localized outbreak in north-eastern Italy. Outbreaks have since been recorded in France and Croatia.

Chikungunya is a mosquito-borne viral disease first described during an outbreak in southern Tanzania in 1952. It is an RNA virus that belongs to the alphavirus genus of the family Togaviridae. The name "chikungunya" derives from a word in the Kimakonde language, meaning "to become contorted", and describes the stooped appearance of sufferers with joint pain (arthralgia).

Signs and symptoms

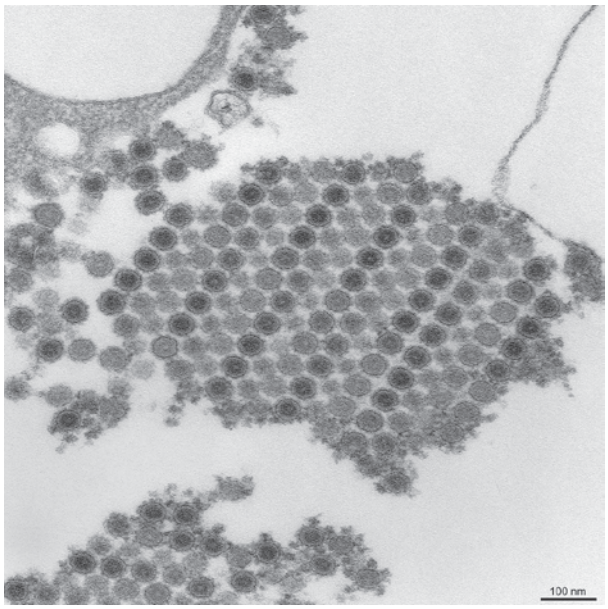
Chikungunya is characterized by an abrupt onset of fever frequently accompanied by joint pain. Other common signs and symptoms include muscle pain, headache, nausea, fatigue and rash. The joint pain is often very debilitating, but usually lasts for a few days or may be prolonged to weeks. Hence the virus can cause acute, subacute or chronic disease. Most patients recover fully, but in some cases joint pain may persist for several months, or even years. Occasional cases of eye, neurological and heart complications have been reported, as well as gastrointestinal complaints. Serious complications are not common, but in older people, the disease can contribute to the cause of death. Often symptoms in infected individuals are mild and the infection may go unrecognized, or be misdiagnosed in areas where dengue occurs.

Transmission

Chikungunya has been identified in over 60 countries in Asia, Africa, Europe and the Americas.
The virus is transmitted from human to human by the bites of infected female mosquitoes. Most commonly, the mosquitoes involved are *Aedes aegypti* and *Aedes albopictus,* two species which can also transmit other mosquito-borne viruses, including dengue. These mosquitoes can be found biting throughout daylight hours, though there may be peaks of activity in the early morning and late afternoon. Both species are found biting outdoors, but Ae. aegypti will also readily feed indoors.
After the bite of an infected mosquito, onset of illness occurs usually between 4 and 8 days but can range from 2 to 12 days.

Diagnosis

Several methods can be used for diagnosis. Serological tests, such as enzyme-linked immunosorbent assays (ELISA), may confirm the presence of IgM and IgG anti-chikungunya antibodies. IgM antibody levels are highest 3 to 5 weeks after the onset of illness and persist for about 2 months. Samples collected during the first week after the onset of symptoms should be tested by both serological and virological methods (RT-PCR).



The virus may be isolated from the blood during the first few days of infection. Various reverse transcriptase–polymerase chain reaction (RT–PCR) methods are available but are of variable sensitivity. Some are suited to clinical diagnosis. RT–PCR products from clinical samples may also be used for genotyping of the virus, allowing comparisons with virus samples from various geographical sources.

Treatment

There is no specific antiviral drug treatment for chikungunya. Treatment is directed primarily at relieving the symptoms, including the joint pain using anti-pyretics, optimal analgesics and fluids. There is no commercial chikungunya vaccine.

Prevention and control

The proximity of mosquito vector breeding sites to human habitation is a significant risk factor for chikungunya as well as for other diseases that these species transmit. Prevention and control relies heavily on reducing the number of natural and artificial water-filled container habitats that support breeding of the mosquitoes. This requires mobilization of affected communities. During outbreaks, insecticides may be sprayed to kill flying mosquitoes, applied to surfaces in and around containers where the mosquitoes land, and used to treat water in containers to kill the immature larvae.

For protection during outbreaks of chikungunya, clothing which minimizes skin exposure to the day-biting vectors is advised. Repellents can be applied to exposed skin or to clothing in strict accordance with product label instructions.

Repellents should contain DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). For those who sleep during the daytime, particularly young children, or sick or older people, insecticide-treated mosquito nets afford good protection. Mosquito coils or other insecticide vaporizers may also reduce indoor biting.

Basic precautions should be taken by people travelling to risk areas and these include use of repellents, wearing long sleeves and pants and ensuring rooms are fitted with screens to prevent mosquitoes from entering.

Disease outbreaks

Lasbela/Pakistan: Suspected Cases of Chikungunya were reported in March 2017 that are being investigated and their reports are still awaited to be positive.

Karachi/Pakistan: Out of the five cases sent to the National Institute of Health (NIH), Islamabad, for diagnosis, three have tested positive for Chikungunya, it emerged on Thursday.

The samples were taken from Saudabad Hospital in Malir and sent to NIH. These three were the first confirmed cases of patients suffering from Chikungunya – a viral disease transmitted to humans by infected mosquito bites – in Pakistan.

The disease has emerged after some patients suffering from high grade fever and joint pain were taken to Saudabad Hospital in Malir on November 19

According to the findings of the reports, the blood specimen sent by Saudabad Hospital, Karachi, of Zohaib, 9, Umer, 11, and Ikhlaque, 45, have been declared positive for Chikungunya. The reports pouring in suggested that more than 3,000 people have suffered from this virus, which first spread in Tanzania in 1952, after which it was identified in over 60 countries in Asia, Africa, Europe and America.

Doctors confirm that 86 suspected cases of Chikungunya have surfaced but the number of cases is declining with each passing day. "Lots of people visit hospitals with fever but we have only 86 suspected in Saudabad and Al Mustafa Welfare Hospital in Malir district," said Karachi health director Dr Waheed Panhwar. "We have now started proper [treatment with] medicines of suspected patients suffering from this disease." Panhwar feared that the disease, which is only confined to Malir for now, can spread to other areas, too.

"Though it is rarely a fatal disease but there is a dire need of precautionary measures," he said. "Negligence can take lives. There is no specific medicine for it. Doctors are [advised to] only prescribe Paracetamol to reduce the fever and pain, which takes a week to recover. There is no commercial vaccine for it. We also suggest patients to drink plenty of water."

According to the World Health Organization (WHO) advisory, the name, Chikungunya, originates from a verb in Kimakonde language, meaning 'to become contorted', which refers to the 'stopped' appearance of those suffering from joint pain.

"Aedes aegypti mosquito is the primary transmission agent of Chikungunya virus," says the WHO advisory, adding that these mosquitoes breed and live around stagnant water and later infect humans with the virus. "Chikungunya does

not spread through person-to-person interaction. However, a mosquito that bites an infected person will transmit the virus to an uninfected person when it bites them." Referring to the advisory, doctors said that apart from high grade fever and joint pain, headache, muscle pain, joint swelling or widespread red rash, nausea and vomiting are also among the symptoms of this disease.

"The virus remains in the human system for five to seven days and mosquitoes feeding on an infected person during this period can also become infected. Recovery from an infection will confer life-long immunity," said Dr Zakir Hussain Qaimkhani, a medical consultant who deals with infectious diseases.

Regarding precautionary measures, doctors advise that people should be extra cautious from dawn to dusk, maintain good hygiene, wear proper clothing and reduce mosquito habitat and breeding places such as stagnant water, sewers and garbage landfills, which is the main source of it. "High risk group for more severe disease includes newborns, older adults and persons with chronic medical conditions," said doctors.

There were reports that some cases with these symptoms have also emerged in Korangi, Orangi and Ibrahim Hyderi, but no officials confirmed them. After the cases with these symptoms, 72 samples have been taken by Dow University of Health Sciences for investigation while Aga Khan University Hospital has also sent multiple samples for verification to a US laboratory.

Health Minister Dr Sikandar Mandhro said that they will soon launch a campaign educating people about the disease. "For the first time, scientifically, this viral disease has surfaced," he said. "In [such] cases, precision [is the] best strategy." He added that every person suffering from fever with joint pain cannot be a case of this disease and patients need to be properly checked for diagnosis and treated accordingly

Chikungunya occurs in Africa, Asia and the Indian subcontinent. Human infections in Africa have been at relatively low levels for a number of years, but in 1999–2000 there was a large outbreak in the Democratic Republic of the Congo, and in 2007 there was an outbreak in Gabon.

Starting in February 2005, a major outbreak of Chikungunya occurred in islands of the Indian Ocean. A large number of imported cases in Europe were associated with this outbreak, mostly in 2006 when the Indian Ocean epidemic was at its peak. A large outbreak of Chikungunya in India occurred in 2006 and 2007. Several other countries in South-East Asia were also affected. Since 2005, India, Indonesia, Maldives, Myanmar and Thailand have reported over 1.9 million cases. In 2007 transmission was reported for the first time in Europe, in a localized outbreak in north-eastern Italy. There were 197 cases recorded during this outbreak and it confirmed that mosquito-borne outbreaks by *Ae. Albopictus* are plausible in Europe.

In December 2013, France reported 2 laboratory-confirmed autochthonous cases in the French part of the Caribbean island of St Martin. Since then, local transmission has been confirmed in over 43 countries and territories in the WHO Region of the Americas. This is the first documented outbreak of Chikungunya with autochthonous transmission in the Americas. As of April 2015, over 1 379 788 suspected cases of Chikungunya have been recorded in the Caribbean islands, Latin American countries, and the United States of America. 191 deaths have also been attributed to this disease during the same period. Canada, Mexico and USA have also recorded imported cases.

On 21 October 2014, France confirmed 4 cases of locally-acquired Chikungunya infection in Montpellier, France. In late 2014, outbreaks were reported in the Pacific islands. Currently Chikungunya outbreak is ongoing in Cook Islands and Marshall Islands, while the number of cases in American Samoa, French Polynesia, Kiribati and Samoa has reduced. WHO responded to small outbreaks of chikungunya in late 2015 in the city of Dakar, Senegal, and the state of Punjab, India.

In the Americas in 2015, 693, 489 suspected cases and 37480 confirmed cases of Chikungunya were reported to the Pan American Health Organization (PAHO) regional office, of which Colombia bore the biggest burden with 356, 079 suspected cases. This was less than in 2014 when more than 1 million suspected cases were reported in the same region.

The decreasing trend continues in 2016, with about 31,000 cases reported to PAHO as of 18 March 2016, representing a 5-fold decrease compared to the same period in 2015. Despite this trend, Chikungunya remains a threat for the region with Argentina recently reporting its first Chikungunya outbreak.

More about disease vectors

Both *Ae. aegypti* and *Ae. albopictus* have been implicated in large outbreaks of Chikungunya. Whereas *Ae. aegypti* is confined within the tropics and sub-tropics, *Ae. albopictus* also occurs in temperate and even cold temperate regions. In recent decades Ae. albopictus has spread from Asia to become established in areas of Africa, Europe and the Americas.

The species *Ae. albopictus* thrives in a wider range of water-filled breeding sites than *Ae. aegypti,* including coconut husks, cocoa pods, bamboo stumps, tree holes and rock pools, in addition to artificial containers such as vehicle tyres and saucers beneath plant pots. This diversity of habitats explains the abundance of *Ae. albopictus* in rural as well as peri-urban areas and shady city parks.

Ae. aegypti is more closely associated with human habitation and uses indoor breeding sites, including flower vases, water storage vessels and concrete water tanks in bathrooms, as well as the same artificial outdoor habitats as *Ae. albopictus.*

In Africa several other mosquito vectors have been implicated in disease transmission, including species of the *A. furcifer-taylori* group and *A. luteocephalus.* There is evidence that some animals, including non-primates, rodents, birds and small mammals, may act as reservoirs.

References

1. Mayo Clinic, What is chikungunya fever, and should I be worried?, accessed 19 February 2016.
2. Characterization of reemerging chikungunya virus, Marion Sourisseau et al., PLOS Pathogens, doi: 10.1371/journal.ppat.0030089, published online 29 June 2007.
3. World Health Organization (WHO) , Chikungunya, accessed 19 February 2016.
4. Centers for Disease Control and Prevention (CDC), Modes of transmission, accessed 19 February 2016.
5. Chikungunya at the door — déjà vu all over again?, David M. Morens et al., The New England Journal of Medicine, doi: 10.1056/ NEJMp1408509,published 4 September 2014
6. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study, Clémentine Schilte et al., PLOS Neglected Tropical Diseases, doi: 10.1371/journal.pntd.0002137, published 21 March 2013.

Antifungal Agents

Prepared by: Prof. Col. Nasarullah Malik
Professor of Microbiology
CMH Peshawar

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Objectives:

1. To learn the general classes of fungal infections
2. To learn the subclassification of antifungal drugs
3. To know the mechanism of action and basic uses for antifungal drugs

Fungus is among us

Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nonetheless been increasing in incidence in the human population over the last 15 years or so, largely as a consequence of increased numbers of cancer and immunocompromised patients, who are at greater risk owing to weakened immune systems and the chronic nature of the diseases. In addition, a number of fungal infections can be difficult to treat (oft referred to as 'stubborn'), even when the offending organism is identified and appropriate therapy is applied. On the other hand, like bacteria, fungi have unique characteristics, distinct from their mammalian hosts, allowing for selective targeting of therapeutic drugs. Fungi are, however, much more complex organisms in comparison to bacteria, are in fact eukaryotic and often grow fairly slowly. Consequently, only a few drugs are aimed at interfering with cell division and have limited use. Most antifungal drugs are targeted to the cell membrane.

Major fungal infections

The number of different kinds of fungi out there is vast, and, of course, some of them are pleasant to eat. Only a small subset is capable of infecting humans. The following is a very general breakdown of types of fungal infections that occur based on site of infection:

Cutaneous	**Most Common**	Example: 'Athlete's foot', Ringworm, and Tinea cruris
Mucocutaneous	**Common**	Example: GI, perianal and vulvovaginal areas eg. Candida albicans
Pulmonary/Systemic	**Less**	Example: Invasive Aspergillus, cryptococcal meningitis, pulmonary histoplasmosis; also, systemic candidiasis

Systemic fungal infections are more serious as they are usually more difficult to diagnose, are chronic in nature, and, in some cases, can become life-threatening. They occur more frequently in individuals with compromised immune systems (AIDS patients; transplant patients; cancer patients). Prophylactic treatment is sometimes indicated in AIDS patients and bone marrow transplant patients, but risk of developing resistance is high. Life-threatening infections require the use of more potent but much more toxic antifungals.

Superficial fungal infections are almost always caused by dermatophytes or yeasts. In some instances, they can be rather tenacious, requiring very long treatments, sometimes with both oral and topical drugs.

Drug Classes

Note that the antifungals are classified by structure or mechanism, not by site of action, as some of them may be used, for example, either topically or systemically depending on the infection

1. **(Macrolides)**
   Amphotericin B
   Mechanism of action: binds to sterols present in the plasma membrane more selective for ergosterol = major fungal sterol forms cytotoxic pores
   broadest spectrum of any antifungal

   Absorption: very poor
   given slowly IV as liposome suspension, or used topically given orally for GI fungi, but as such is really acting 'topically'

   Uses:
   initial **drug of choice** for **life-threatening systemic infections**

Invasive Aspergillus (30% survival); used with itraconazole Cryptococcal meningitis; used with flucytosine (alternative: fluconazole)
Rapidly developing Histoplasmosis
some limited use for cutaneous (dermatophytic) infections or mucocutaneous infections

Adverse effects: fairly toxic [some binding to mammalian membranes; effects reduced via use of liposome delivery]

fever and chills; vomiting; muscle spasms; modest hypotension (nearly 100% but treatable; small test dose usually given to assess reactions)

- **renal impairment** (near 80%)
- hypokalemia (= reduced serum K)

Nystatin
Mechanism of action: same as for Amphotericin B
Absorption: extremely poor
Uses: much too toxic for systemic (parental) use

used only **topically**
local (dermal), oropharyngeal, GI and vaginal candidiasis only [other than its nasty, bitter taste, adverse effects are uncommon]

2. **(Antimetabolite)**
Flucytosine
Mechanism of action: selectively converted by fungi to active metabolites inhibits fungal RNA and DNA synthesis

Absorption: well absorbed; used orally (only)

Uses: only in combination with
amphotericin B for cryptococcal meningitis
itraconazole for blastomycoses
[high incidence of resistance as well as toxicity reduced via use in drug combinations]

Adverse effects: (narrow therapeutic window)

- results from fluorouracil = major metabolite
- inflamed bowel (enterocolitis)
- **bone marrow toxicity**
- possible liver toxicity

3. **(Cytoskeleton Agent)**
Griseofulvin
Mechanism of action: proposed to inhibit microtubules blocks fungal mitosis, therefore is fungistatic
also binds keratin

Absorption: poor - very insoluble
orally administered in a microcrystalline form (improved when taken with fatty foods)

Uses:
systemic uses for dermatophytosis (eg. skin and, esp. nail infections, though for the latter terbinafine is preferred),
requiring extended treatments [after or sometimes with treatment with triazoles] [also highly effective against Athlete's foot and ringworm]

Adverse effects: (low incidence)

- allergic syndrome (like serum sickness: fatigue.. - rare)
- hepatitis
- drug interaction with warfarin or phenobarbital

4. **(Imidazoles)**
Mechanism of action: inhibit fungal ergosterol biosynthesis selectively inhibit fungal cytochrome P_{450} enzymes

Ketoconazole
(original oral 'azole', not as selective as newer azoles, ie. significant inhibition of mammalian P_{450} enzymes)

Absorption: low - improved with food and low gastric pH
used orally, but has very slow onset; poor CSF and urinary tract penetration

Uses:
mucocutaneous candidiasis coccidioidomycosis (non-meningeal) in shampoos for seborrheic dermatitis (largely supplanted by more expensive itraconazole or fluconazole)

Adverse effects: (narrow therapeutic window)
highly dose-dependent

- nausea and vomiting

- endocrine: interferes with adrenal and gonadal steroid synthesis*
- hepatotoxicity (rare but can prove fatal)
- drug interactions

→ *action on human cytochrome P450 (eg. ↑warfarin; ↑ cyclosporine; and vice versa)

→ decreased absorption of ketoconazole when administered with rifampin, H2 antagonists or antacids

Miconazole and Clotrimazole
Absorption: extremely poor - both used topically: creams and, in the case of clotrimazole, oral troches (=lozenges)

Uses: wide-spread, over-the-counter use as **topical**
antifungals vulvovaginal candidiasis
dermatophytic infections (eg. tineas corporis)
oropharyngeal thrush (candidiasis; alternatives to nystatin)

5. **(Triazoles)**
Mechanism of action: inhibit fungal ergosterol biosynthesis
Itraconazole ***
Absorption: OK, low bioavailability (no CSF penetration)
- improved with food and low gastric pH

Uses:
most potent of the azoles for systemic infections drug of choice for persistent dermatophytic infections effective against all types of Aspergillus infection preferred agent for endemic mycoses (eg. Histoplasma)

Adverse effects:
- drug interactions (esp. non-sedating antihistamines) (no effect on steroid biosynthesis; variable effect on mammalian P_{450} system, less than with ketoconazole but still of potential concern)

Fluconazole
Absorption: good; used orally and IV (excellent **CSF penetration)**

Uses:
agent of choice for cryptococcal meningitis (unless life-threatening: use AmpB) mucocutaneous candidiasis prophylactically for bone marrow transplants and AIDS patients

Adverse effects: (widest therapeutic window) few and mild
concern for all azoles: newly observed emergence of resistant strains in AIDS [resistance to azoles is otherwise fairly rare]

Voriconazole (most recently approved (2002) azole, derived from fluconazole)
Absorption: good; used orally and IV (good CSF penetration, however*)

Uses:
agent of choice for invasive Aspergillus
active against Candida (even those resistant to fluconazole), Cryptococcus and endemic mycoses, but ineffective against mucormycosis (soil saprophytes)

Adverse effects: sporadic visual disturbances* (~30%); hepatotoxicity (2-3%)

6. **(Allylamines)**
Naftifine and Terbinafine
Mechanism of action: inhibits fungal squalene metabolism
increased levels of squalene are toxic to fungi; also reduces ergosterol

Uses: effective for most cutaneous mycoses either topically (eg. tinea corporis and tinea cruris) or, in the case of terbinafine, orally for **nail infections** (90% cure rate, without side effects)
[not effective against Candida]

7. **(Echinocandin)**
Caspofungin (most recently approved antifungal – Jan 2001) Mechanism of action: inhibits beta (1,3)-D-glucan synthesis, blocking cell wall synthesis

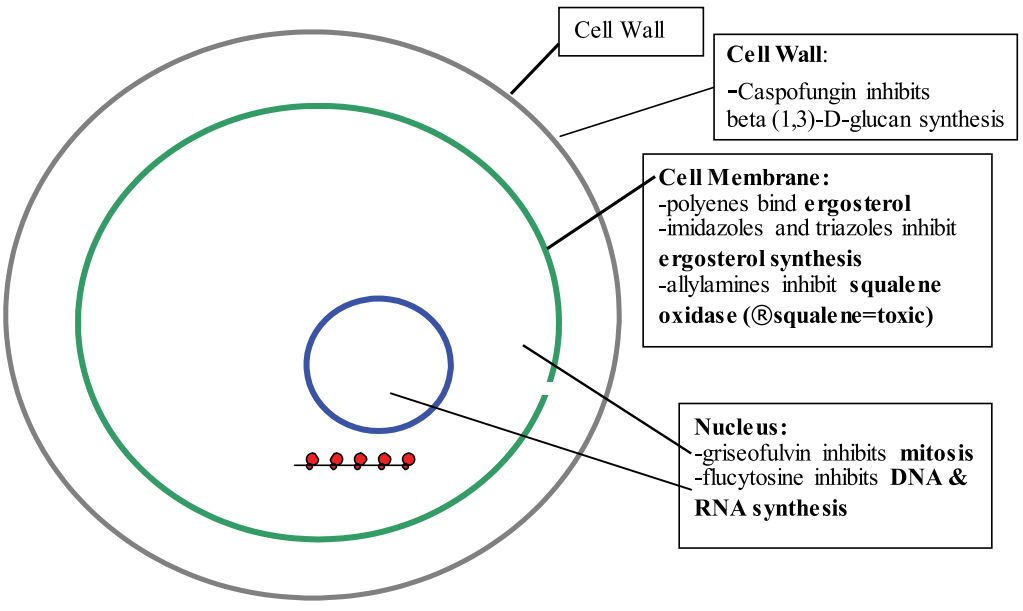
Absorption: poor; highly protein; administered IV

Uses: active against a number of fungi, but particularly effective against **invasive candidiasis** and **aspergillosis** (promising new alternative to amphotericin) via once daily IV administration; no activity against cryptococcus

Adverse effects:
fever, nausea, vomiting, flushing; some irritation at inj site; small elevation of liver enzymes

Quicklist of key drugs:

Drugs Name	Action	Use
Amphotericin B	Cytolytic via ergosterol binding: Forms pores in membrane	Broad spectrum: mainly for life-threatening infections; given IV via liposome suspension oral: not absorbed - topical
Nystatin	Cytolytic via ergosterol (as for Amp B)	Topical only (too toxic for systemic use); for Candida
Flucytosine	Antimetabolite (toxic to bone marrow)	in combination only for meningitis & blastomycoses
Griseofulvin	Antimitotic via microtubule Inhibition	Oral for dermatophytosis
Ketaconazole	Blocks ergosterol synthesis via P_{450} inhibition (not selective)	Oral for mucocutaneous candidiasis; coccidoidal mycoses
Miconazole Clotrimazole	Blocks ergosterol synthesis	Topical for Candida; dermatophytes oropharyngeal infection
Intraconazole	Selective block of ergosterol	Oral (no CSF penetration) for Dermatophytoses; Aspergillus; Endemic mycoses
Fluconazole	Selective block of ergosterol	Oral (good CSF penetration) for Meningitis; Candida; prophylactic for marrow transplants & AIDS
Voriconazole	Selective block of ergosterol	Latest triazole; oral and IV (good CSF penetration) for Aspergillus; Meningitis; Candida
Terbinafine Naftifine	inhibits squalene metabolism - squalene is toxic; also blocks Ergosterol	Cutaneous mycoses
Caspofungin	Blocks cell wall synthesis via IV: & inhibition of beta (1,3)-D- Glucan synthesis	invasive candidiasis aspergillus



Face to Face with Dr. Kauser Rehman

MBBS, FCPS General Surgery, MRCS
Honorary fellow, Royal Marsden Hospital, London
Consultant Breast Oncoplastic Surgeon, South City Hospital
Interviewed by: Dr. Fawad Yousuf

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General surgery is a large and varied surgical speciality. It encompasses not only gastrointestinal surgery (oesophagogastric, hepatopancreaticobiliary and colorectal) but also breast, vascular, transplant and endocrine surgery. A surgeon sees variety of elective and critically ill patients, and it is this variety which appeals to many aspiring surgeons, especially when it comes to formulating a diagnosis from a huge array of surgical and medical conditions. Other people are drawn to the challenges and rewards of the operating theatre, where increasing technological advances demand less invasive procedures with improved outcomes. Surgery is a constantly evolving specialty, which increases the scope for continuous learning and academia.

Dr. Kauser Rehman, is one of the emerging general surgeon in Pakistan, her area of interest is breast oncoplastic surgeries she started her career from Quetta and soon after training she moved to Karachi. She is known for her hard work and fine surgeries. During interview she shared her experiences and highlight different aspects of General and Breast surgeries.

Q# 1. What was it that led you to become a General/Breast Surgeon? Tell us about your education and work experience?

A: General surgery has always been my inspiration since medical school. I found it thrilling & interesting saving lives and achieving results in days, be it stab wound, gunshot or simple appendicitis. I selected breast cancer surgery in order to do something different and provide better service in a specialized field. I searched, checked different cultures worldwide; all have the same issue i.e. lack of awareness in this area which leads to loss of lives. Breast oncoplastic surgery training was something new and unique, that is believed to bring change in timeworn practices of mammary infections in our country

Q# 2. What is the happiest moment being a doctor in your life?

A: Every other day; when you cure disease, give hope and help find a better way of living to patients, it gives a sense of fulfillment in life

Q# 3. What is the most interesting part of your job?

A: Surgery-Surgery-Surgery, I find it very interesting to perform difficult and complicated surgery in my usual practice. Every case of surgery is different that makes my job interesting, and keep me updated of new complications and developments in this field

Q# 4. Could you name the most challenging aspects of your role?

A: As breast cancer specialist- breaking bad news to patients is the most challenging part of my job but then showing them ways of treatment & giving hope makes it interesting and satisfying

Q# 5. Who is your inspiration/role model?

A: Without any doubt Prof. Mumtaz Meher, who is role model for number of Surgeons practicing in Pakistan. His work in the field of laparoscopic surgery, advanced procedures for the treatment of hernias, colorectal diseases and obesity as well as conducting various workshops in which international surgeons have been invited to share their experiences. His passion towards education and development is commendable, and motivates his followers to do their best

Q# 6. How do you keep balance in your professional & personal commitments?

A: Training as a surgeon is not a story of days or months. It is learning experience, based on years and you acquire time management skills by doing the right things at the right time

Q# 7. What is the most important piece of advice you can give to other doctors and medical students?

A: Sincerity to profession, Commitment, Never give up.

Q# 8. Any message for betterment of magazine or this initiative?

A: I am very delighted to see this academic initiative from SAMI. This magazine has established itself as the informative and up-to-date in terms of its contents. The names associated with the magazine are leading the developments in their respective fields. I would suggest to keep this magazine updated, and stick to your commitment of spreading knowledge among all the healthcare community in Pakistan

Choose the correct answer

Chikungunya has spread widely from Asia and Africa into the Caribbean in recent years. This has been mainly facilitated by:

a) Mutation in the virus allowing replication in the mosquito Aedes albopictus

b) Air Travel

c) Climate change

d) Poor mosquito control and the absence of DTT

Winners of Lucky Draw

The editorial board of Infectio® magazine is pleased to announce the names of winners for quiz from the 6th edition. The lucky draw was held in a meeting at Dr. Ziauddin University hospital, Karachi on **25th May 2017**. Following are the names of lucky draw winners drawn at randomly by Prof. Ejaz Ahmed Vohra and his team.

We congratulate the winners and once again thank all contestants for their participation in quiz

1. **Prof. Dr. Muhammad Shahid Hussain, Darul Sehat Hospital, Karachi**
2. **Dr. Abdul Majeed Memon, Red Crescent Hospital, Sukkur**
3. **Dr. Mahmud Sultan Paracha, Paracha Nursing Home, Peshawar**
4. **Dr. Asma Kanwal, Get-well Medical Centre, Islamabad**
5. **Dr. Afshan Akram, Shalamar Hospital, Lahore**
6. **Dr. Hina Pervaiz, DHQ Hospital, Jhang**
7. **Prof. Mukhtar Ahmed, AMC, Abbottabad**
8. **Dr. Salman Akhtar, Bethania Hospital, Sialkot**
9. **Dr. Muhammad Azam Khan, NMC, Multan**
10. **Dr. Mazhar Hussain Raja, Shifa International, Islamabad**

ANTIBIOTICS ARE LOSING THEIR POWER

BECAUSE OF MISUSE

BE PART OF THE SOLUTION

- ☑ Always take the full prescription, even if you feel better
- ☑ Never share or use leftover antibiotics
- ☑ Never buy antibiotics without a prescription

World Health Organization
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