Clinical Infectious Diseases Society

Newsletter : February 2019

Website: www.cidsindia.org
Volume 6, Issue 2, February 2019
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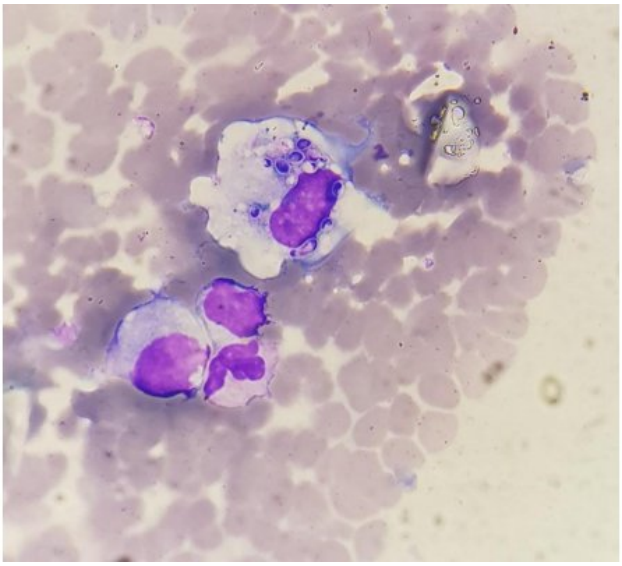
Photoquiz

A 53 year gentleman from Haryana with recently detected HIV 1 presented with complaints of weakness, weight loss and low grade fever for 10-15 days. Investigations revealed Hb 6 gm, WBC - 2800, platelets - 1,69,000, CD4 count- 59, HIV VL - 18,900 copies/ml. VDRL & TPHA was positive.

Contrast CT chest and abdomen did not reveal any significant lymphadenopathy or chest infiltrates.

Peripheral smear is shown:



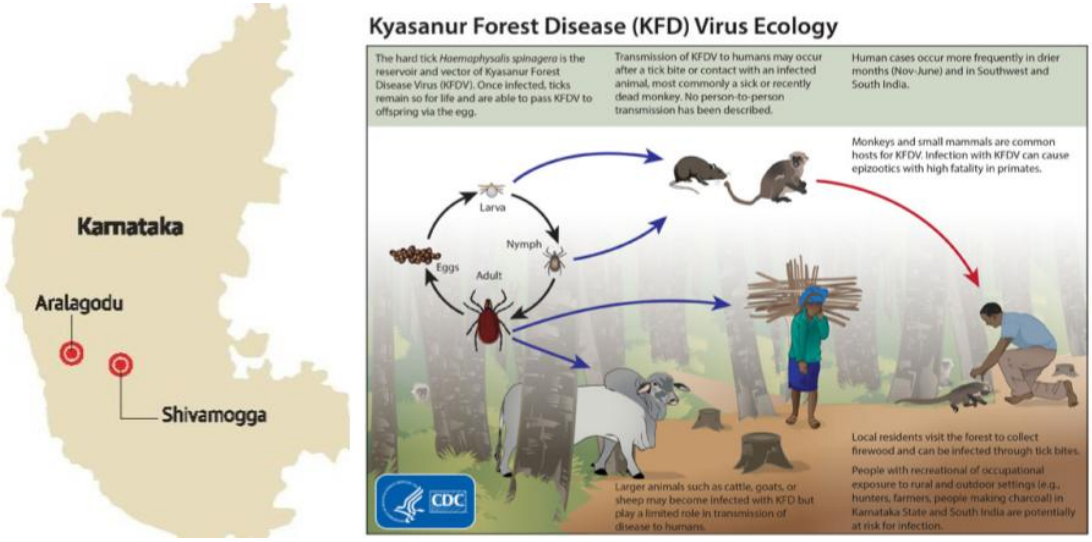
What is your diagnosis?

ID NEWS

Kyasanur Forest Disease: an old dog up to same old tricks?

Contributed by Dr R Surendran, Dr Ashwini Tayade

At least 65 people have tested positive in the ongoing outbreak of KFD in Karnataka, but the number of suspected cases —awaiting confirmation through blood tests — has touched 204. At least 38 monkeys have died in the plantations. Aralagodu is the epicentre of the outbreak, but infected areas are also being reported in villages across four districts of Karnataka (Shivamogga, Udupi, Dakshina Kannada, and Uttara Kannada) – and in Kerala (Wayanad) and Maharashtra (four cases).



KFD virus was first reported in Kyasanur village of Shivamogga district, way back in 1957. The virus belongs to the family Flaviviridae, whose other members are responsible for causing Yellow Fever, Zika and Dengue. Multiple species of ticks of the genus Haemaphysalis are the principal vectors. Infections peak between November and March, which coincides with the larvae-nymph cycles of ticks. Since 1957, it has flared up in sporadic outbreaks. Post-2013, it has even expanded its range, with fatal consequences in Maharashtra, Kerala and Goa. According to State data, in the past 15 years, KFD has infected 2,067 people and killed 42. The demographic group most vulnerable to KFD are people more than 40 years old.

Nearly every study on the disease so far has highlighted the role of forest degradation in the spread of KFD. SK Kiran, who has helmed multiple research papers on KFD, says that villagers living near highly-fragmented forests are more susceptible to the disease. He says, “Tick densities remain high in these forests, and with the presence of monkeys, peacocks, rodents and other reservoirs, there is always a chance of the disease spilling over to the village. This risk factor is not given its due in the health response to KFD [The Hindu - 26 Jan 2019].

Vaccination with formalin-inactivated tissue-culture vaccine has been the primary strategy for controlling KFD. The strategy involves mass vaccination in areas reporting KFD activity (i.e., laboratory evidence of KFD virus [KFDV] in monkeys, humans, or ticks) and in villages within a 5-km radius of such areas. Two vaccine doses are administered at least 1 month apart to persons 7–65 years of age. Vaccine-induced immunity is short-lived, so the first booster dose of vaccine is recommended within 6–9 months after primary vaccination; thereafter, annual booster doses are recommended for 5 years after the last confirmed case in the area. Though a vaccination programme began on November 30, it was too late for Aralagodu. The first dose hardly provides protection, while the efficiency of the second dose (administered after a month) is only of 63% efficacy. Of the seven dead, two persons had received their first dose, while one had been administered the second dose. A study done by S.K.Kiran et al, investigating and outbreak of KFD in 2013-2014 reveals - low vaccine coverage, low vaccine effectiveness, and spread of disease to areas beyond those selected for vaccination and to age groups not targeted for vaccination. To control disease, vaccination strategies need to be reviewed [Emerg Infect Dis. 2015 Jan; 21(1): 146–149]

ID NEWS

Malaria in Maharashtra: decreasing incidence

Contributed by Dr Ashwini Tayade

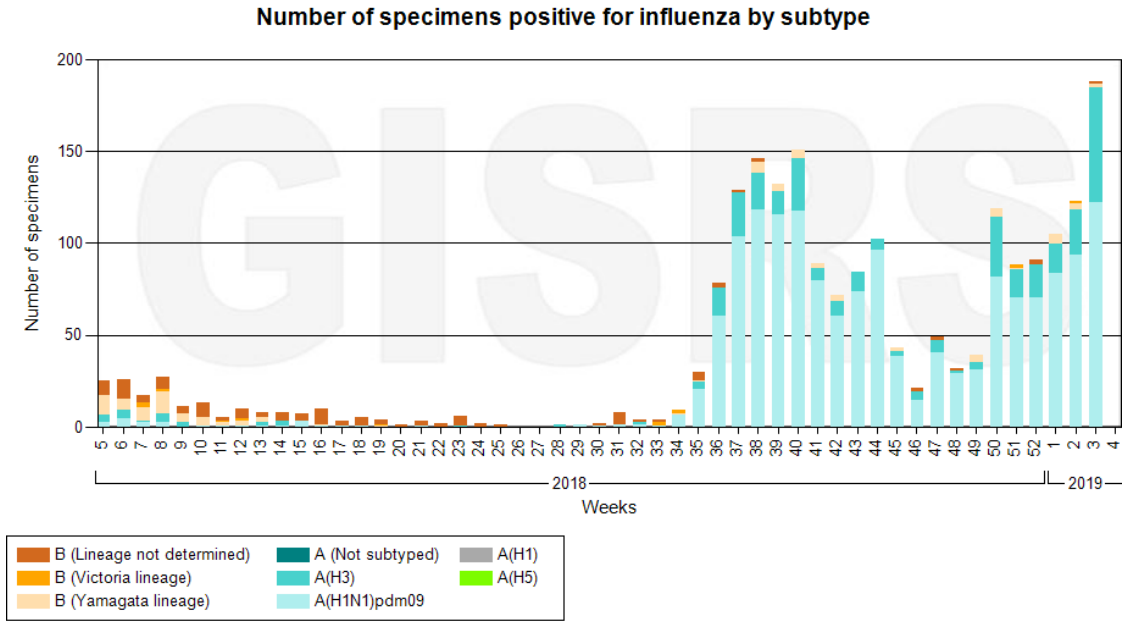
Cases of malaria and related deaths in the state have been decreasing over the last 3 years, reveals government data. While the state recorded 23 983 cases in 2016, the cases have decreased to 17 710 cases in 2017 and 9322 in 2018 respectively. Interestingly, according to state surveillance officer and entomologist, the number of cases in rural Maharashtra have gone down, while they have seen a rise in city areas like Mumbai and Thane. Entomologist Mahendra Jagtap said, "In the malaria-problem areas, especially Gadchiroli, we have distributed around 6.5 lakh [650 000] long-lasting insecticidal nets (LLINs) which are promoted by WHO as a sustainable method for protection against malaria.

ID NEWS

Influenza Update

Contributed by Dr Ashwini Tayade

National Influenza Centres (NICs) and other national influenza laboratories from 104 countries, areas or territories reported data to FluNet for the time period from 24 December 2018 to 06 January 2019 a(data as of 2019-01-18 04:01:21 UTC). The WHO GISRS laboratories tested more than 191778 specimens during that time period. 39161 were positive for influenza viruses, of which 38493 (98.3%) were typed as influenza A and 668 (1.7%) as influenza B. Of the sub-typed influenza A viruses, 13313 (79.4%) were influenza A(H1N1)pdm09 and 3446 (20.6%) were influenza A(H3N2). Of the characterized B viruses, 45 (38.1%) belonged to the B-Yamagata lineage and 73 (61.9%) to the B-Victoria lineage.



JOURNAL REVIEW

Linezolid for drug-sensitive tuberculosis

Lancet Infect Dis. 2019 Jan;19(1):46-55
Contributed by Dr Kiran Kumar, Dr Abi Manesh

The long duration of treatment for tuberculosis is cumbersome and translates to poor compliance. Multiple attempts in the past to shorten treatment using fluoroquinolones (RIFAQUIN, OFLOTUB, and REMoxTB trials) have been disappointing. Importantly fluoroquinolones have better culture conversions at 8 weeks but later relapses were the predominant problem. Drugs with better sterilization capacity could potentially help in this regard. Linezolid, an oxazolidinone, substantially improves treatment outcomes of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. The authors looked at whether, if linezolid substituted ethambutol, the rate of sputum culture conversion at 8 weeks of treatment in patients with drug-susceptible tuberculosis would improve.

The authors performed a phase 2, multicentre, randomised, open-label trial for patients with pulmonary tuberculosis at three centers in South Korea. Adult patients with a positive sputum test for pulmonary tuberculosis, but without resistance to rifampicin by Gene Xpert, were randomly assigned at a 1:1:1 ratio into three groups. The control group received ethambutol (2 months) with isoniazid, rifampicin, and pyrazinamide. The second group used linezolid (600 mg/day) for 2 weeks and the third group for 4 weeks, instead of ethambutol for 2 months. In the modified intention-to-treat analyses, negative cultures in liquid media at 8 weeks of treatment were observed in 103 (76·9%) of 134 control patients, 111 (82·2%) of 135 in the linezolid 2 weeks group, and 100 (75·8%) of 132 in the linezolid 4 weeks groups. The difference from the control group was 5.4% (95% CI -4·3 to 15·0, p=0·28) for the linezolid 2 weeks group and -1·1% (-11·3 to 9·1, p=0·83) for the linezolid 4 weeks group.

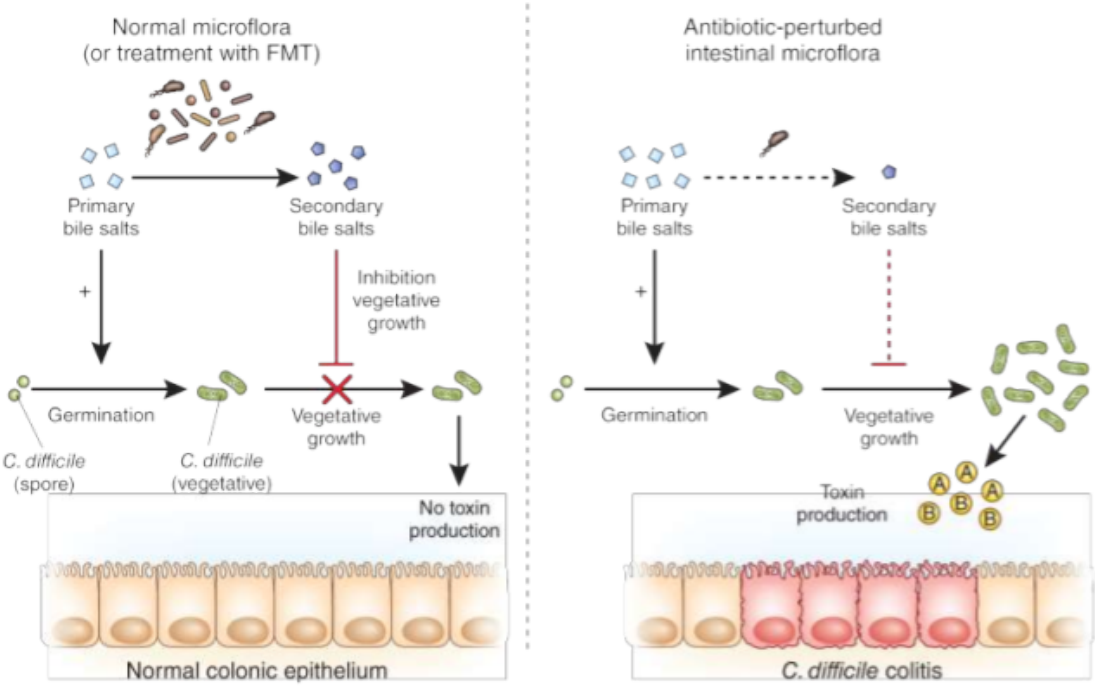
The authors concluded that linezolid substitution did not result in better culture conversions at 8 weeks. One reason may be reduced linezolid levels after the first two weeks due to hepatic enzyme induction by rirampicin. The treatment of drug sensitive TB remains the same for the last almost 5 decades despite many trials, millions of dollars and enthusiastic efforts.

JOURNAL REVIEW

UDCA for recurrent C.difficile!

Clin Infect Dis. 2019 Jan 18;68(3):498-500
Contributed by Dr Abi Manesh

Image source: *Nature Med. 2014 Mar;20(3):246-7*



It is always interesting when the pathophysiological basis of diseases form the basis for their treatments. Clostridium difficile associated pseudomembranous colitis is a serious disease especially among hospitalized immunocompromised individuals receiving broad-spectrum antibiotics. C.difficile, a spore former is rare in a healthy gut except among infants. Primary bile salts produced from the liver induce germination of these spores resulting in vegetative forms – the first step in the pathogenesis. However, secondary bile salts, the deoxycholated primary bile salts inhibit the growth of these vegetative forms – thereby protecting the body from developing C.difficile disease. For formation of secondary bile salts we need the normal microbiota. When you have a patient on broad spectrum antibiotics this second step is lost resulting the continued proliferation of the C.difficile vegetative forms resulting in clinical disease.

Addition of ursodeoxycholic acid (UDCA), a pharmaceutical secondary bile acid should then reverse the second step. In this study, the authors describe the off-label use of UDCA as salvage therapy to prevent CDI recurrence in 16 patients with contraindications for fecal microbiota transplant. All but one patient had multiple prior CDI episodes (median 3.5; IQI, 2.3–5). UDCA was prescribed as adjunctive therapy following a CDI episode in 11 patients (68.8%) and as prophylaxis in the setting of ongoing need for systemic antibiotics in 5 patients (31.2%). Fifteen patients (93.8%) ultimately received systemic antibiotics while on UDCA. In sum, 14 of the 16 (87.5%) patients remained free of recurrent CDI at a median follow-up of 264 days (IQI, 152–406) from UDCA prescription.

Acknowledging the limitations like small sample size and absence of control group, these results represent proof of concept that UDCA may be effective in preventing CDI in patients with high probability of recurrence and merit further evaluation to determine if they are reproducible.

JOURNAL REVIEW

Tafenoquine for radical cure of P vivax

N Engl J Med. 2019 Jan 17;380(3):215-228
Contributed by Dr Abi Manesh

Hypnozoites, the dormant liver malarial parasites are important causes of recurrent Plasmodium vivax infections. Primaquine, an 8-aminoquinoline given at 15 mg base per day for 14 days has been the standard of care to eliminate hypnozoites, to produce 'radical cure'. Primaquine treatment is complicated by poor adherence and hemolysis among patients with G6PD deficiency. Tafenoquine, a recently FDA approved 8-aminoquinoline is characterized by a longer half-life (15 days vs 5 hours) and shares the ability to produce hemolysis among G6PD deficient. G6PD deficiency is X linked - male hemizygotes and female homozygotes remain clinically deficient while the female heterozygotes are genetic mosaics with varying degree of deficiency. Approximately, 10% of malaria endemic population in the world has G6PD deficiency. Qualitative testing for G6PD may miss some of the female heterozygotes – thereby putting them at risk of life-threatening hemolysis with long-acting tafenoquine. Hence, quantitative tests ensuring G6PD activity is more than 70% is required before tafenoquine is administered. Such rapid tests are not commonly available in field settings.

The investigators studied the role of tafenoquine to ensure 'radical cure' in an RCT involving 522 patients from Ethiopia, Peru, Brazil, Cambodia, Thailand, and the Philippines. All patients received a 3-day course of chloroquine (total dose of 1500 mg). In addition, patients were assigned to receive a single 300-mg dose of tafenoquine on day 1 or 2 (260 patients), placebo (133 patients), or a 15-mg dose of primaquine once daily for 14 days (129 patients). The primary outcome was the Kaplan–Meier estimated percentage of patients who were free from recurrence at 6 months, defined as P. vivax clearance without recurrent parasitemia.

The percentage of patients free from recurrence at 6 months was 62.4% in the tafenoquine group (95% confidence interval [CI], 54.9 to 69.0), 27.7% in the placebo group (95% CI, 19.6 to 36.6), and 69.6% in the primaquine group (95% CI, 60.2 to 77.1). The hazard ratio for the risk of recurrence was 0.30 (95% CI, 0.22 to 0.40) with tafenoquine as compared with placebo (P<0.001) and 0.26 (95% CI, 0.18 to 0.39) with primaquine as compared with placebo (P<0.001).

In summary, provided optimal G6PD testing strategies are available, tafenoquine is a more convenient alternative for primaquine to ensure radical cure in P. vivax malaria.

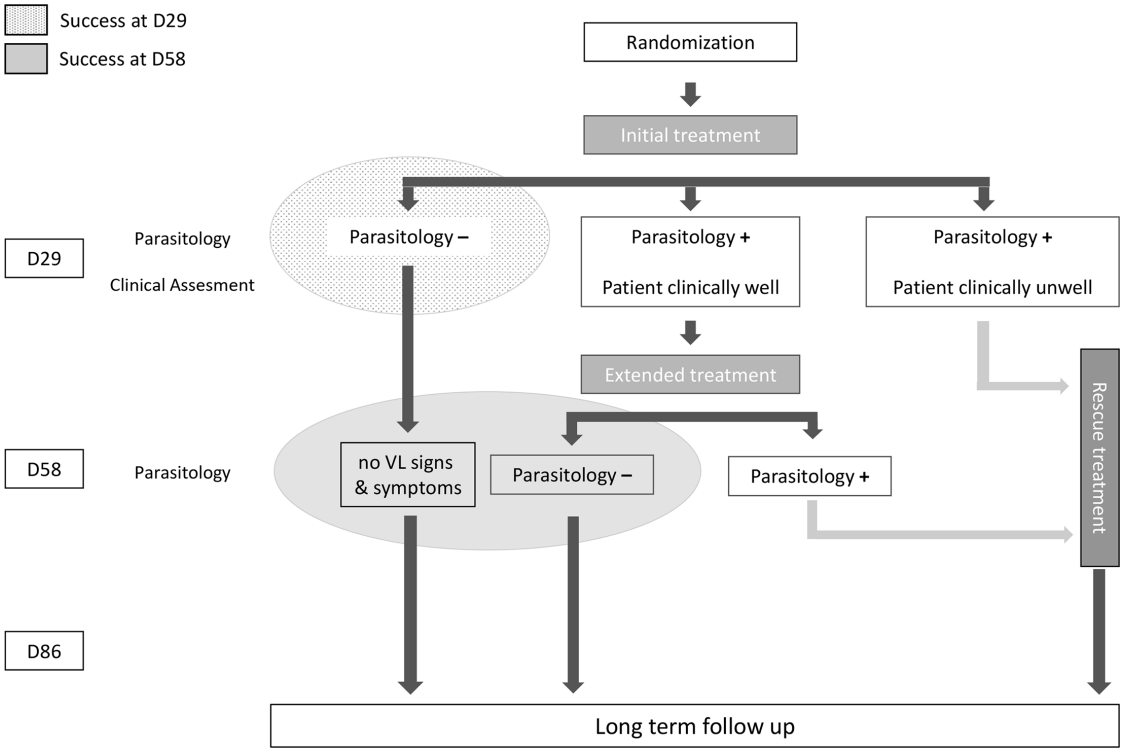
JOURNAL REVIEW

Combination therapy for Visceral Leishmaniasis in HIV infected hosts

PLoS Negl Trop Dis. 2019 Jan 17;13(1):e0006988
Contributed by Dr Abi Manesh

HIV co-infection is an important factor that impedes the elimination of visceral leishmaniasis. Uncontrolled HIV infection will unmask many asymptomatically infected individuals to develop VL and they also contribute to ongoing disease transmission. Higher doses of LipoAmpho B are typically required for the treatment of VL and HIV co-infection (30-40 mg/kg cumulative dose) and addition of miltefosine has some benefits based on two large retrospective data (CID. 2015;61(8):1255, PLoSNegl Trop Dis. 2014;8(6):e2869.). WHO recommends high dose (40 mg/kg) liposomal amphotericin as the first line of therapy. This RCT compared AmBisome (30 mg/kg) with miltefosine (100 mg/day for 28 days), and AmBisome monotherapy (40 mg/kg) among Ethiopian VL patients co-infected with HIV. It used a complicated sequential design which basically had flexible sample size which was titrated to the evolving data from the trial probably secondary to low number of patients with HIV VL coinfection. The primary outcome was parasite clearance at day 29, after the first round of treatment. Patients with clinical improvement but without parasite clearance at day 29 received a second round of the allocated treatment. Efficacy was evaluated again at day 58, after completion of treatment.

Recruitment was stopped after inclusion of 19 and 39 patients in monotherapy and combination arms respectively. At D29, intention-to-treat efficacy in the AmBisome arm was 70% (95% CI 45–87%) in the unadjusted analysis, and 50% (95% CI 27–73%) in the adjusted analysis, while in the combination arm, it was 81% (95% CI 67–90%) and 67% (95% CI 48–82%) respectively. At D58, the adjusted efficacy was 55% (95% CI 32–78%) in the monotherapy arm, and 88% (95% CI 79–98%) in the combination arm. The rescue treatment in patients who did not respond was sodium stibogluconate and paromomycin combinationation therapy. The following schematic representation may explain the trial flow.



In short, most of the patients required an extended treatment with the trial drugs. The combination arm with Ambisome (30mg/kg) with miltefosine performed better overall. This trial has potential treatment implications – however the relative poor performance of high dose Ambisome is surprising. A similar trial is underway in the Indian setting as well.

Guideline watch

- New DHHS Perinatal HIV Guidelines
    - For couples in which one partner has HIV and the other does not, sexual intercourse without a condom limited to 2–3 days before and the day of ovulation is a way to conceive that carries "effectively no risk" of HIV transmission as long as the person with HIV is on ART and has achieved sustained virologic suppression.
    - Regardless of CD4 cell count, ART should be started as early as possible during pregnancy or, even better, before conception.
    - Dolutegravir is not recommended during the first trimester or in women who are trying to conceive.
    - Dolutegravir is a preferred medication in the second and third trimesters.
    - Preferred regimens: TDF/ABC + 3TC/FTC + RAL/DTG/DRV-rtv/ATV-rtv
- WHO MDR-TB guideline update (*courtesy Dr Sowmya Sridharan*) Linezolid, bedaquiline, cycloserine and clofazimine get upgraded while injectables and ethionamide get downgraded.

- IDSA influenza practice guidelines (*courtesy Dr Sowmya Sridharan*), [Link]

Chandra's corner

Dr PH Chandrasekar

Wish each of you a warm, happy and productive 2019. My best wishes and hopes for 2019 and beyond for ID in India – a) less antimicrobial resistance via improved hygiene/sanitation, better stewardship and due recognition of ID specialists in all sectors of public health, b) better judgment among physicians, notably ID clinicians to avoid "antibiotic-cocktails" for 'just in case' infections and c) increased ID research and academic productivity in all medical institutions.

During rounds, I came across a hand transplant recipient. Life's lessons for ID specialists are frequently through cases, provided we have our senses open and are willing to receive. This man had lost his right hand in an industrial accident, with subsequent successful hand transplant. Tacrolimus was used to prevent graft rejection; unfortunately after some years, he developed metastatic squamous cell carcinoma of skin, a dreaded not-so-uncommon complication of tacrolimus. I was consulted for management of his pneumonia in the intensive care unit. As usual, he was on multiple antibiotics. Pneumonia, of course, was from metastatic cancer and against the objections of the ICU physicians, after many discussions, antibiotics were discontinued (stewardship!). In order to use an experimental immunotherapy protocol for management of metastatic skin cancer, administration of tacrolimus had to be stopped. Prior to discontinuation of tacrolimus, he was advised to have the transplanted hand removed. Hard to believe, the semi-functioning transplant hand, at the request of the patient was amputated, so the patient can stop taking tacrolimus and receive cancer immunotherapy. I was astonished. I had to sit down during rounds to digest this information. Life indeed is precious, and the extent we go to extend our lives! Who am I to judge?

Keeping with my interest in transplant, I wish to mention an article from Kolkata, India in the New York Times (Dec 16, 2018) titled, "Organ Donation's Burden in Women". Data presented were eye-opening. About 90% of organ transplants in India are living donor transplants while in the US, nearly 60% of organs transplanted are of cadaveric origin. As per the author, Sohini Chattopadhyay, cadaveric donation rate in India is abysmally low because of cultural misgivings, mistrust in health care system arising from reports about organ trafficking and absence of state initiatives and infrastructure to facilitate it. Nearly 75% of kidney donors and well more than 50% of liver donors in India are women. Likewise in the US, 62% kidney donors and 53% liver donors during 2008to 2017 were women. While women are dominant donors, as recipients however, they are in the minority. In India, only 19% women are kidney recipients, and 24% women are liver recipients. Indian women give more and receive far less. Why? The author proposed economics as part of the explanation. Donor surgery requires considerable time to recover, which means taking time off from work. Women who do work are paid >30% less than male workers. So, by that calculation, Indian women are cost effective donors (as they earn less) and considered poor returns on investments as recipients. The author, Sohini Chattopadhyay, "chickened" out from being a liver donor for her dad and ultimately, the author's mother stepped in to save her husband's life. And the mother wears her surgical scar with ease and pride.
This disparity with gender-biased healthcare in India is stunning. Present time with #MeTooMovement, is the perfect time to raise this issue. Is anyone prepared to hear?.

Answer to the photoquiz

Budding intra-cellular yeasts consistent with Histoplasma capsulatum are seen.

Histoplasmosis is being increasingly reported from different parts of India, even outside the Ganga-Brahmaputra basin (see CIDS newsletter Dec 2018). Disseminated disease in immune compromised hosts carries a high mortality.

Final diagnosis: (Presumed) Progressive disseminated histoplasmosis in setting of AIDS

Case provided by: Dr Ritu Chadha (Haematopathologist), Dr Ranjit Sah (Infectiou Diseases Fellow), ***Dr Neha Gupta (ID)***