# CIDS Newsletter (Volume 5, Issue 1, January 2018)

# www.cidsindia.org

## Editor's note

Dear CIDS members

**CIDSCON 2018 will be from August 16th to 18th 2018** (Thursday to Saturday). Please block your dates.

Our website has been updated, please check it out and encourage colleagues and postgraduates to do so. You can access newsletter material directly from the website as open access material.

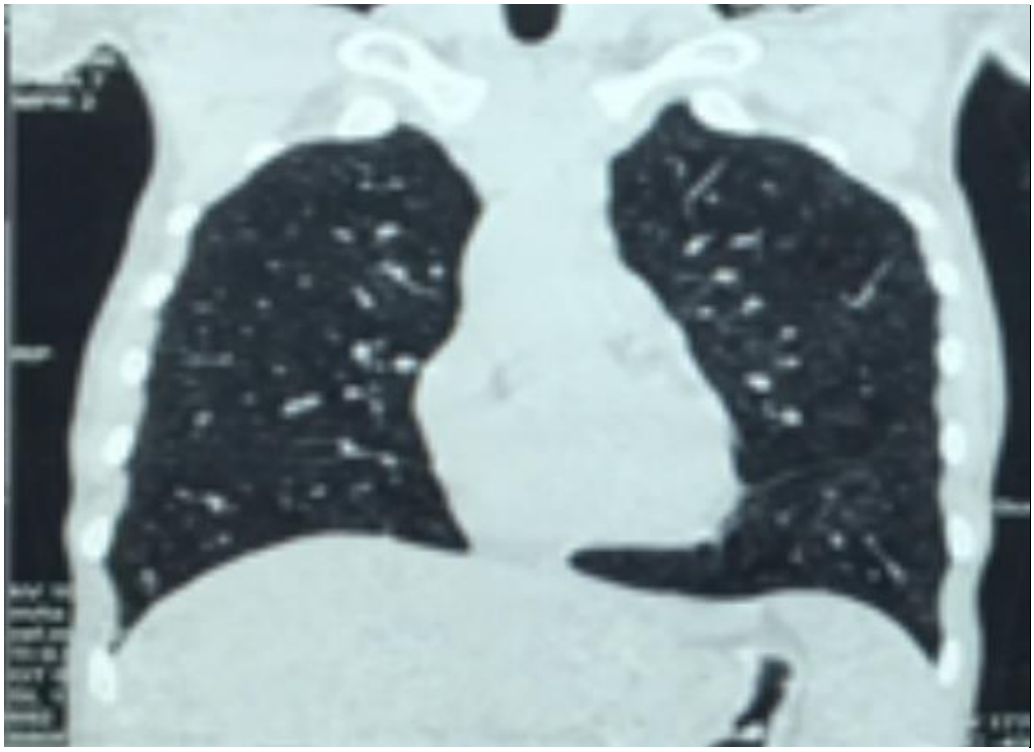
## Editorial Board

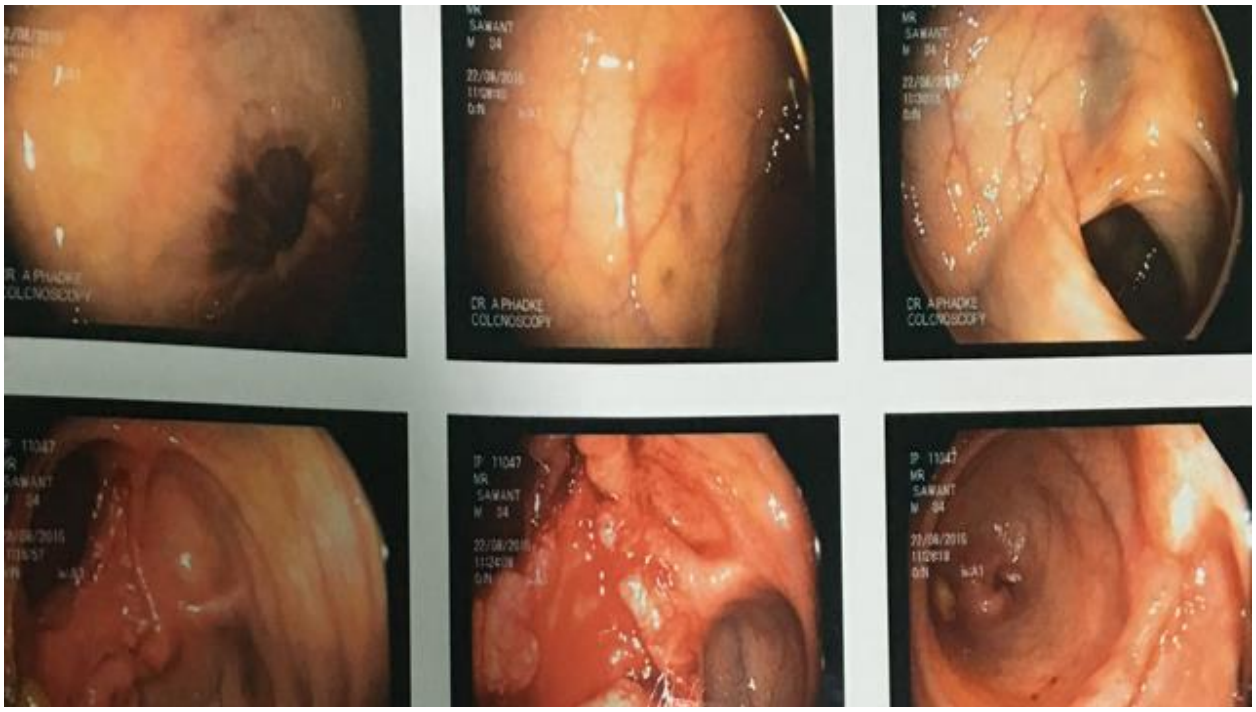


## Photo quiz

A 34 year HIV positive male with a CD4 count of 23 presented with abdominal pain, cough, loss of appetite and weight loss of 15 kg for one and half months. USG and CT SCAN of Abdomen and pelvis was suggestive of mild enhancing caecal wall thickening with few enhancing LN in mesentric region. Patient was diagnosed as ? abdominal TB and started on empirical ATT elsewhere, but had no clinical improvement.

HRCT CHEST (see fig) was done was showed multiple 1-2mm sized randomly distributed nodules in left lung field and right lower lobe along with the patchy ground glass opacities and multiple enlarged non necrotic mediastinal and axillary lymph nodes seen most likely s/o infective etiology. Retinal exam was suggestive of cotton wool spots. Colonoscopy was done due to bleeding per rectum and showed a large ulcer involving caecum, ileocaecal valve and terminal ileum (see fig). MRI Brain and CSF was normal.






What is your diagnosis?

## Snippets from the literature

## **Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study** (courtesy Dr Nitin Bansal)

Lancet Glob Health 2016; 4: e752–60

In this cohort study, teams prospectively followed up neonates born in one of three tertiary care centres in Delhi, India (Vardhaman Mahavir Medical College, Maulana Azad Medical College, and All India Institute of Medical Sciences [coordinating centre]) and subsequently admitted to the intensive care unit. Neonates were followed up daily until discharge or death. On clinical suspicion, neonates underwent sepsis work-up including blood cultures. The isolated organisms were identifi ed and tested for antimicrobial susceptibility. The authors defined Gram-negative isolates resistant to any three of fi ve antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam) as multidrug resistant.

Findings 13 530 neonates of 88 636 livebirths were enrolled between July 18, 2011, and Feb 28, 2014. The incidence of total sepsis was 14·3% (95% CI 13·8–14·9) and of culture-positive sepsis was 6·2% (5·8–6·6). Nearly two-thirds of total episodes occurred at or before 72 h of life (defined as early onset; 1351 [83%] of 1980). Two-thirds (645 [64%]) of 1005 isolates were Gram-negative including, Acinetobacter spp (22%), Klebsiella spp (17%), and Escherichia coli (14%). The pathogen mix in early-onset sepsis did not differ from that of late-onset sepsis (ie, after 72 h). High rates of multidrug resistance were observed in Acinetobacter spp (181/222, 82%), Klebsiella spp (91/169, 54%), and Escherichia coli (52/137, 38%) isolates. Methicillin resistance prevailed in 61% (85/140) of coagulase-negative staphylococci and 38% (43/114) of Staphylococcus aureus isolates. Nearly a quarter of the deaths were attributable to sepsis. The population attributable risks of mortality were 8·6% in culture-negative sepsis, 15·7% in culture-positive sepsis by multidrug resistant organisms, and 12·0% in culture-positive sepsis by non-multidrug-resistant organisms.

Alarming numbers: >75% were ESBL producers, carbapenem resistance was reported in Acinetobacter spp (0–30%) and E coli (0–15%). NDM-1 has been documented in nearly a quarter of Acinetobacter spp and three-quarters of Klebsiella spp among the pool of carbapenem-resistant strains

## **Determinants of treatment-related paradoxical reactions during anti-tuberculosis therapy: a case control study** (courtesy Dr Nitin Bansal)

*BMC Infectious Diseases* 2016;**16**:479

https://doi.org/10.1186/s12879-016-1816-4

Prospective and retrospective clinical and laboratory data were collected on TB patients seen between January 1999–December 2008 at four UK centres selected to represent a wide ethnic and socio-economic mix of TB patients. Data on ethnicity and HIV status were obtained for all individuals. The associations between other potential risk factors and PR were assessed in a nested case-control study. All PR cases were matched two-to-one to controls by calendar time and centre.

Of 1817 TB patients, 82 (4.5 %, 95 % CI 3.6–5.5 %) were identified as having a PR event. The frequency of PR was 14.4 % (18/125; 95 % CI 8.2–20.6 %) and 3.8 % (64/1692; 2.9–4.7) for HIV-positive and HIV-negative individuals respectively. There were no differences observed in PR frequency according to ethnicity, although the site was more likely to be pulmonary in those of black and white ethnicity, and lymph node disease in those of Asian ethnicity. In multivariate analysis of the case-control cohort, HIV-positive patients had five times the odds of developing PR (aOR = 5.05; 95 % CI 1.28–19.85, $p = 0.028$), whilst other immunosuppression e.g. diabetes, significantly reduced the odds of PR (aOR = 0.01; 0.00–0.27, $p = 0.002$). Patients with positive TB culture had higher odds of developing PR (aOR = 6.87; 1.31–36.04, $p = 0.045$) compared to those with a negative culture or those in whom no material was sent for culture. Peripheral lymph node disease increased the odds of a PR over 60-fold (9.60–431.25, $p < 0.001$).

HIV was strongly associated with PR. The increased potential for PR in people with culture positive TB suggests that host mycobacterial burden might be relevant. The increased risk with TB lymphadenitis may in part arise from the visibility of clinical signs at this site. Non-HIV immunosuppression may have a protective effect.

## Want to reduce antibiotic use? Test for dengue and malaria

*Clinical Infectious Diseases*, 04 December 2017

cix1059, https://doi.org/10.1093/cid/cix1059

Febrile adults and children admitted to a public tertiary care hospital in Pune, India were enrolled. Antibiotic usage and clinical history were recorded. Immunoassays for mosquito-borne disease and bacterial cultures were performed by protocol and clinician directed testing. Clinical factors were assessed for association with empiric antibiotic initiation and discontinuation by day 5 using multivariable logistic regression and propensity score matched Cox proportional hazard models.

Among 1486 participants, 683 (82%) adults and 614 (94%) children received empiric antibiotics. Participants suspected of having mosquito-borne disease were less likely to receive empiric antibiotics, adjusted odds ratio (AOR) 0.5, 95% confidence interval (CI) 0.4-0.8. Empiric antibiotics were discontinued in 450 (35%) participants by day 5. Dengue or malaria testing performed before day 4 was positive in 162 (12%) participants, and was associated with antibiotic discontinuation (AOR 1.7, 95% CI [1.2 – 2.4]). In a propensity score matched model accounting for admission suspicion of mosquito borne disease, positive dengue or malaria tests increased hazard of antibiotic discontinuation (hazard ratio 1.6, 95% CI 1.2-2.0).

Most patients with acute febrile illness in an Indian public hospital setting receive empiric antibiotics. Mosquito-borne disease identification is associated with reduced empiric antibiotic use and faster antibiotic discontinuation.

## Chikungunya arthritis persists but virus undetectable

*Arthritis Rheum* *2017; doi:10.1002/art.40384.*

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One-quarter of Latin American patients who were infected with chikungunya virus had persistent arthritis almost 2 years later, despite the finding that there was no detectable virus in the synovial fluid.In a follow-up study of a prospectively enrolled cohort of 485 patients with chikungunya during an epidemic in Colombia in 2014-2015, 123 (25%) had ongoing joint pain after a mean of 20 months, which was less than the 48% that had been predicted. On a multivariate analysis, these factors were associated with persistent joint pain:

- College education, OR 5.53 (95% CI 1.13 to 27.17, *P*=0.0353)
- Headache, OR 2.17 (95% CI 1.16 to 4.07, *P*=0.0157)
- Knee pain, OR 4.69 (95% CI 1.91 to 11.51, *P*=0.0007)
- Missed work, OR 5.23 (95% CI 2.87 to 9.52, *P*<0.0001)
- Normal activities disrupted, OR 8.80 (95% CI 3.89 to 19.89, *P*<0.0001)

- Initial symptoms persisting for 4 days or more, OR 2.69 (95% CI 1.57 to 4.60, $P$=0.0003)
- Initial joint pain persisting for 4 weeks or more, OR 2.39 (95% CI 1.40 to 4.08, $P$=0.0014)

In extensive synovial fluid analyses of 38 of the patients, there was no detectable virus on PCR, culture, or mass spectrometry. For this analysis, patients were a median of 22 months post-infection, and had an average of 5.5 and 3 tender and swollen joints, respectively. Global disease activity on a 100-point scale was 93, and the Disease Activity Score in 28 joints was 4.52. The researchers performed various tests on a subset of their cohort with serologically confirmed viral infection, seeking evidence of the virus itself in cultures of synovial fluid, as well as viral RNA using PCR, and viral proteins with mass spectrometry. All were negative. With no evidence of viral persistence, potential mechanisms for arthritis included epigenetic changes to host DNA, as has been observed with Epstein Barr virus infection, modification of macrophages, and molecular mimicry, according to the authors.

This finding suggests that chikungunya virus may cause arthritis through induction of potential host autoimmunity, suggesting a role for immunomodulating medications in the treatment of chikungunya virus arthritis. Various immunosuppressants such as methotrexate and hydroxychloroquine and biologics such as adalimumab and etanercept have been tried.

**Seasonality in risk of pandemic influenza emergence** (courtesy Dr Ashwini Tayade)

PLoS Comput Biol 13(10): e1005749.

https://doi.org/10.1371/journal.pcbi.1005749

Influenza pandemics emerge via genomic reassortment between circulating human and animal strains. The risk of pandemic emergence should therefore be high during the flu season, when viruses are abundant and conditions favor transmission. However, the six pandemics on record since 1889 all emerged in the Northern Hemisphere following the flu season, suggesting that other forces may predictably constrain pandemic risk. The authors find that seasonal influenza epidemics leave a wake of

immunity that impedes pandemic emergence. This transient refractory period is consistent with the spring-summer emergence, multiple wave dynamics of recent pandemics, and may cause initial underestimation of the viral transmission rate. These findings may improve pre-pandemic risk assessments and real-time situational awareness, particularly as we gain greater insight into the extent of immunity.

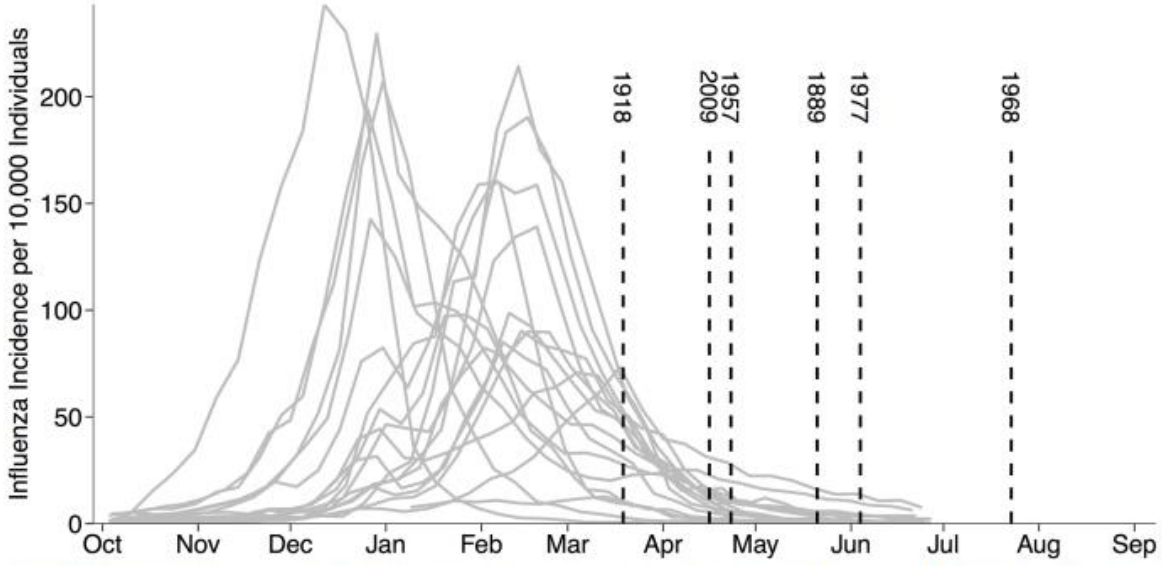



**Fig 1. Historical pandemics emerged at the tail-end of flu seasons.** Gray curves show the 1997-2015 flu seasons in the US, excluding the 2009 H1N1 pandemic, as estimated by the CDC's ILINet surveillance system [29]. Vertical dashed lines indicate emergence week of historical pandemics in their source populations, defined as the first reported outbreak of severe influenza preceding the initial pandemic wave. These estimates were obtained from: 1889 [17], 1918 [18, 19], 1957 [20, 21], 1968 [22, 23], and 1977 [24]. To be consistent, we date the emergence of the 2009 pandemic according to the first significant outbreak preceding the initial wave, rather than the earlier outbreaks in rural Mexico that were identified only in retrospect [30].

https://doi.org/10.1371/journal.pcbi.1005749.g001

## **CNS infections in the absence of CSF pleocytosis** (courtesy Dr Balavinoth)

Int J Inf Dis 2017; 65:107-109

- CSF pleocytosis is important in establishing the diagnosis of central nervous system (CNS) infections such as meningitis, encephalitis, and meningoencephalitis.
- The absence of pleocytosis represents a diagnostic challenge to clinicians when suspecting a CNS infection
- **The Infectious Diseases International Research Initiative (IDIRI) study group** analysed ID-IRI studies to identify patients without CSF pleocytosis (WBC count of <=5 x $10^6$ cells/l).
- Clinical presentations, laboratory findings, and outcomes were assessed to provide an insight into this particular condition for the treating clinician.

- 32 of 141 patients (18%) with neurosyphilis, 39 of 496 patients (7.9%) with herpetic meningoencephalitis, 19 of 507 patients (3%) with tuberculous meningitis, five of 294 patients (1.7%) with Brucella meningitis, and one of 306 patients (0.2%) with pneumococcal meningitis did not present with CSF pleocytosis

**Table 1**
Characteristics of patients with a CNS infection with no CSF pleocytosis.[a]

| | Pneumococcal meningitis | Tuberculous meningitis | Brucella meningitis | Neurosyphilis | HSV meningoencephalitis |
|---|---|---|---|---|---|
| ID-IRI study | Erdem et al. (2014b) | Erdem et al. (2015a) | Erdem et al. (2015b) | Ozturk-Engin et al. (2016) | Erdem et al. (2015c) |
| Number | 306 | 507 | 294 | 141 | 496 |
| CSF analysis | | | | | |
| Pleocytosis absent, *n* | 1 | 19 | 5 | 32 | 39 |
| Pleocytosis absent, % | 0.2% | 3% | 1.7% | 22% | 7.9% |
| Protein (mg/dl), mean ± SD | 1446 | 305.5 ± 457.63[b] | 89.2 ± 363.43 | 74.9 ± 114.7 | 77 ± 48.89 |
| CSF/blood glucose, mean ± SD | 0.1 | 0.45 ± 0.16[c] | 0.51 ± 0.89 | 0.63 ± 0.13 | 0.68 ± 0.57 |
| Demographic and clinical parameters | | | | | |
| Age (years), mean ± SD | 68 | 49.15 ± 17.03 | 55.4 ± 20.27 | 52.15 ± 14.09 | 57 ± 20.99 |
| Sex, male, *n* (%) | 1 | 9 (47%) | 2 (40%) | 26 (81%) | 17 (44%) |
| Fever >38 °C, *n* (%) | 38.2 °C | 13 (68%) | 3 (60%) | 4 (12%) | 19 (49%) |
| Neck stiffness, *n* (%) | (−) | 12 (63%) | 1 (20%) | 6 (18%) | 6 (15%) |
| Headache, *n* (%) | (+) | 6 (31%) | 4 (80%) | 13 (40%) | 22 (56%) |
| Mental changes | (+) | 13 (68%) | 1 (20%) | 13 (40%) | 33 (85%) |
| Classic triad[d] | (−) | 1 (5%) | 1 (20%) | 1 (3%) | 4 (10%) |
| GCS | 5 | 10.13 ± 3.99 | 15 ± 2.38 | 14.26 ± 1.45 | 11 ± 3.92 |
| Potential immunosuppressive conditions | | | | | |
| HIV-positive | (−) | 2 | (−) | 7[e] | (−) |
| Diabetes mellitus | (−) | (−) | (−) | 3 | (−) |
| Immunosuppressive drugs | (−) | 1 | (−) | (−) | 4[f] |
| Solid tumor | (−) | (−) | (−) | (−) | 1 |
| Drug addiction | (−) | (−) | (−) | 3 | (−) |
| Number (%) | 0 (0) | 3 (15.8%) | 0 (0) | 12 (37%) | 5 (12.8%) |
| Outcome | | | | | |
| Sequelae, *n* (%)[g] | (−) | 6 (31%) | 1 (20%) | 12 (37%) | 15 (39%) |
| Death, *n* (%) | Died | 5 (26%) | (−) | 3 (9%) | 8 (21%) |

The authors concluded that the absence of pleocytosis was relatively infrequent but not rare in these CNS infections; such patients have a high rate of unfavorable outcomes, including sequelae and death. The examining clinician should not underestimate the presence of a CNS infection despite the lack of CSF pleocytosis for a patient with a suspicion of meningitis or encephalitis. The mean values of protein and CSF/blood glucose suggested the probable presence of a CNS infection in these patients and stresses the importance of considering the total CSF profile when ruling out a CNS infection.

## Chandra's Corner

Dr PH Chandrasekar

A few months ago, I shared a wrenching story with you about Radhika, an Indian-American physician who underwent an allogenic stem cell transplant for acute myelogenous leukemia. Here is the update –

as it happens all too often, most unfortunately, I do not have good news. Radhika underwent a second stem cell transplant for relapsed leukemia; within a period of three months, she succumbed to severe ravaging, bloody colitis due to human cytomegalovirus infection. CMV wreaked havoc despite aggressive combination therapy with toxic chemical compounds, ganciclovir and foscarnet. Finally, after weeks of hospitalization, as her body was assaulted with numerous chemicals, her young 36-year-old heart gave out. But the physicians were not ready to give up. All the thumping and pumping failed – her heart knew better, refused to budge, relieving Radhika from anymore suffering. How many Radhikas do we have to lose to cytomegalovirus around the world?

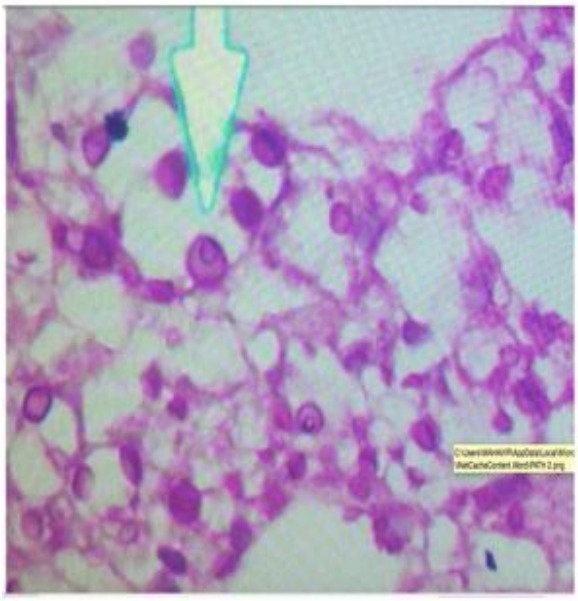
In the late 90s and early 2000s, aspergillus was a commonly fatal fungal infection in transplant recipients. After candida was conquered with fluconazole, then came voriconazole, the first anti-aspergillus, non polyene drug. Voriconazole, then posaconazole and now isavuconazole, together have helped change the landscape of managing invasive mold infections. While aspergillus is no longer a common player on the transplant field, CMV continues to reign supreme, causing fatal gastroenteritis/colitis and less commonly pneumonitis. CMV dominates with or without concomitant graft versus host disease. Establishing diagnosis of invasive disease remains elusive, particularly in the presence of graft-host-disease. Limited weapons we have include IV ganciclovir (oral valganciclovir) and IV foscarnet, both of which are toxic and antiviral resistance is becoming frequent. Where do we go from here? How much longer do we watch lives lost to this herpes virus, with our arms folded?

Suddenly, there is promise. What has been plain noise has now become worthy of attention. A new drug has just been FDA approved for CMV prophylaxis in stem cell recipients. Letermovir (marketed by Merck) compared to placebo reduced all cause mortality (9.8% vs. 15.9%) and CMV infection (38% vs. 51%) at 24 weeks among CMV seropositive transplant recipients. Importantly, the drug was well tolerated with little myelo or nephrotoxicity. Letermovir is a non-nucleoside drug with a site of action

that targets the viral terminase complex. Hence, it may be particularly useful in CMV infection resistant to available drugs. Brincidofovir, a drug that was eagerly anticipated, failed to meet the primary endpoint, so the drug will no longer be pursued for CMV prophylaxis, but it shows promise against adenovirus. Maribavir has been shown to have clinical activity in drug-resistant CMV infection. Most promisingly, restoring cellular immunity via adoptive T-cell transfer is no longer a pie-in-the sky. Donor-derived CMV specific cytotoxic T-cells have been shown to prevent and treat CMV infections in patients failing other conventional therapies. Small studies have demonstrated feasibility, challenges include cost and manufacturing logistics. Two different CMV vaccines are in phase 2 trials. What about hormonal immunity against CMV? Of course. A phase 2 trial utilizing a combination of 2 monoclonal antibodies that bind to glycoprotein complexes on the surface of CMV to inhibit entry into host cells has shown good results. All in all, there is a lot to look forward to combat CMV infection/disease.

Appropriate for this holiday season, these data should lift our spirit. Plenty to look forward to in the field of antiviral therapeutics. Antivirals (non-HIV, non-Hepatitis C), in the near future, may enjoy the same reputation achieved by antibacterials decades ago. These are major in-roads in advancing the management of key pathogens among transplant recipients. Soon, within the realm of reality, one hopes we can save many Radhikas who may watch their children grow and enjoy their families. Is there a better purpose?

## Answer to photo quiz:



Rectal biopsy showed cryptosporidium (Fig 1)

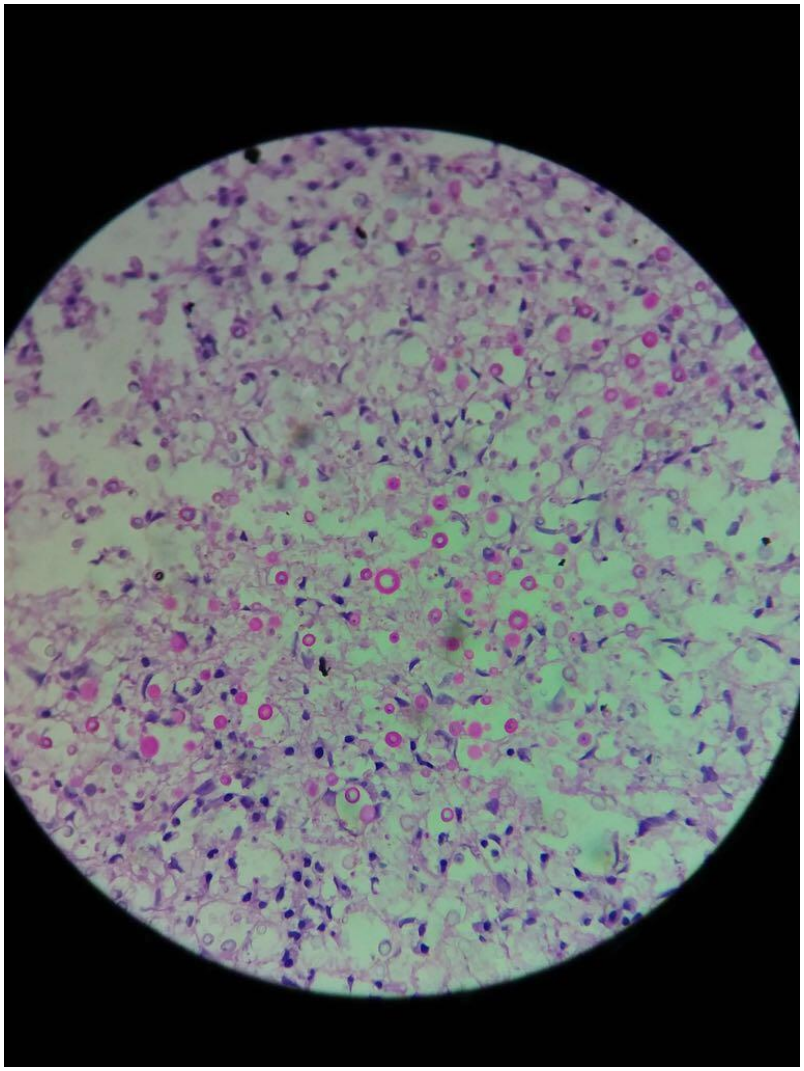


Fig 2: Lymph node biopsy showing Cryptococcus

Rectal biopsy showed cryptosporidium (fig 1).
His blood cultures sent grew yeast, identified as cryptococcus.
USG guided axillary lymph node biopsy showed Cryptococcus like yeast (Fig 2) and lymph node and BAL grew cryptococcus.
He was started on Conventional Amphotericin B and 5 Flucytosine. He did well and was discharged.

Final diagnosis:

Disseminated Cryptococcosis with rectal ulcer due to cryptosporidiosis, in setting of HIV/AIDS.

[Case provided by Dr Vasant Nagvekar]