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CIDS Newsletter

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CLINICAL INFECTIOUS DISEASES SOCIETY

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Editor's note

Dear CIDS members

We thank the organizing committee of CIDSCON 2017 for putting up an outstanding academic feast at Nagpur! The conference won all round praise from for academic standards, ambience, punctuality of sessions and overall smooth organization, and was attended by more than 500 delegates.

The general body meeting of the society was held on 19th August. Some of the salient decisions were: The 80G exemption for the society was acknowledged and the efforts to this end applauded. CIDSCON 2018 will be held in Vellore in the month of August. It was resolved that the newsletter will be made available to all, not just members, as well as linked with other societies in order to increase the visibility of our society and our specialty. A decision was taken to recruit part time secretarial help at the CIDS office, with appropriate support like computer, internet, phone and printer. It was decided to update the website on a regular basis with the help of CIDS members. The annual CMC winter PG course will be held in the first week of December. A group was formed to discuss the issues regarding the Transplant Infectious Diseases conference and to formulate an action plan for the future. CIDS plans to work with other societies, including at conferences, to strengthen our own society's position.

As usual we welcome contributions from members: important papers, interesting cases, ID news etc. Please send me the material by month end so as to get the newsletter out by the 1st week of the next month.
Our website is in the process of being upgraded and periodically updated, please check it out and encourage colleagues to do so. You can access newsletter material directly from the website as open access material.

Sincerely
Ram Gopalakrishnan

Photo quiz

A 57-year old gentleman with Budd-Chiari syndrome with decompensation underwent live –donor liver transplantation (LDLT) in 2015. He was subsequently on everolimus, mycophenolate mofetil (MMF) and prednisolone. Post LDLT, the patient had developed hypodense loculated collection inferomedial aspect of allograft liver with ? mild associated haematoma – Gram stain, KOH stain and cultures were negative. He received multiple antibiotics meropenem, colistin, linezolid & fluconazole (by the primary team). Patient later improved & discharged after 1 month hospital stay. He was on TMP/SMX and valganciclovir prophylaxis.

In June 2016, the patient presented with a midline swelling and LFT alteration. CT abdomen s/o soft tissue mass in the ant abdominal wall with multiple space occupying lesions (SOL) in transplant liver (Figure 1). The aerobic cultures of the aspirate grew carbapenem resistant *Klebsiella pneumonia*. Patient received colistin and tigecycline with no response.

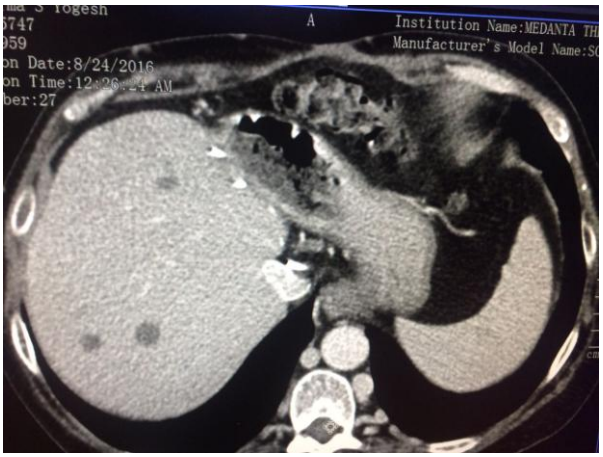


Figure 1: Multiple space occupying lesions in the transplant liver

What is your diagnosis?

News from the ID world

WHO downgrades oseltamivir

(Courtesy Dr Vasant Nagvekar)

Oseltamivir has been downgraded in the WHO's list of essential medicines from a "core" drug to one that is "complementary", a category encompassing drugs that are considered less cost effective. Oseltamivir reduces the duration of influenza by about a day but it does not reduce the number of patients admitted to hospital or complications of influenza. The WHO now advises that the use of oseltamivir be "restricted to severe illness with confirmed or suspected influenza virus infection in critically ill hospitalized patients".

It appears that we will need oseltamivir only to treat critically ill in-patients with influenza in the future.

New once-daily raltegravir formulation

(Courtesy Dr Laxman Jessani)

For patients with HIV infection, the most effective antiretroviral therapy regimens contain two different nucleoside reverse transcriptase inhibitors and an integrase strand transfer inhibitor (INSTI). Raltegravir, the first available INSTI, has traditionally required twice-daily dosing. In the United States, a new raltegravir formulation that allows once-daily dosing (two 600 mg tablets once daily) has recently been approved for treatment-naïve patients. This approval continues to expand the treatment options for patients with newly diagnosed HIV infection, particularly when drug interactions limit the use of other once-daily INSTIs.

Ref: Istentress prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022145s036,203045s013,205786s004lbl.pdf

Snippets from the literature

One week amphotericin plus flucytosine best for cryptococcal meningitis?

(IAS meeting, Paris 2017)

The ACTA (Advancing Cryptococcal Meningitis Treatment for Africa) trial recruited 721 participants with first-episode cryptococcal meningitis in Malawi, Zambia, Cameroon, and Tanzania. Study results showed that one week of amphotericin plus flucytosine and two weeks of the oral combination of fluconazole plus flucytosine both provided safe, effective, and sustainable induction therapy. The two-week treatment with amphotericin B and flucytosine had a 79% greater risk of all-cause mortality compared with the one-week regimen with amphotericin B plus flucytosine. Two weeks of amphotericin B plus fluconazole had a 97% increased risk of mortality compared to the one-week of amphotericin B plus flucytosine. One-week of amphotericin B plus fluconazole put patients at a 154% greater risk of mortality compared to short-course treatment with amphotericin and flucytosine.
In the amphotericin B arms, researchers compared fluconazole and flucytosine as adjunctive treatments and found that flucytosine was superior. It appears that one week of amphotericin plus flucytosine followed by fluconazole is the best option to maximize efficacy and minimize toxicity.

Empiric Therapy With Carbapenem-Sparing Regimens for Bloodstream Infections due to ESBL Producing Enterobacteriaceae

(Courtesy Dr Vasant Nagvekar)

Clinical Infectious Diseases 19 August 2017, cix606, https://doi.org/10.1093/cid/cix606

A multinational retrospective cohort study of patients with BSI due to ESBL-E who received empiric treatment with OADs (other active drugs) or carbapenems was performed. Overall, 335 patients were included; 249 received empiric carbapenems and 86 OADs. The most frequent OADs were aminoglycosides (43 patients) and fluoroquinolones (20 patients). Empiric therapy with OADs was not associated with mortality (hazard ratio [HR], 0.75; 95% confidence interval [CI], .38–1.48) in the Cox regression analysis. Propensity score–matched pairs, subgroups, and sensitivity analyses did not show different trends; specifically, the adjusted HR for aminoglycosides was 1.05 (95% CI, .51–2.16). OADs were neither associated with 14-day clinical failure (adjusted odds ratio, 0.62; 95% CI, .29–1.36) nor length of hospital stay.
The authors were unable to show that empiric treatment with OAD was associated with a worse outcome compared with carbapenems. However in India, most ESBLs are resistant to quinolones and aminoglycosides have limited utility in infections outside the urinary tract.

Dependency of dengue vaccine Efficacy on Pre-Exposure and Age: useful for the second infection only?

Clinical Infectious Diseases 24 August 2017, cix766, https://doi.org/10.1093/cid/cix766

A recombinant, live-attenuated, tetravalent dengue vaccine (CYD-TDV) was licensed for children of 9 years old or older in a few countries. Combining the two phase III trials, CYD14 and CYD15, the authors estimated the vaccine efficacy. Baseline seropositive subjects showed high efficacy for all serotypes, 70.2% (95% confidence interval [CI]: 57.4, 80.1) for dengue 1 (DENV-1), 67.9% (95% CI: 49.9, 82.0) for DENV-2, 77.5% (95% CI: 64.3, 90.2) for DENV-3, 89.9% (95% CI: 79.8, 99.9) for DENV-4, and 75.4% (95% CI: 68.3, 81.6) overall. In contrast, baseline seronegative subjects showed moderate efficacy against DENV-4, 51.2% [95% CI: 20.0, 72.8] but no significant efficacy against other serotypes. Among seropositive children, the overall efficacy tended to increase with age, 35.9% (95% CI: -7.6, 69.3) for children ≤5 years old, 65.6% (95% CI: 40.3, 84.2) for 6 – 8 years old, 73.4% (95% CI: 62.6, 82.1) for 9 – 11 years old, and 80.6% (95% CI: 72.9, 87.3) for 12 years or older.
The CYD-TDV vaccine was highly efficacious for all dengue serotypes among children older than 5 years who have acquired baseline immunity from previous exposure. So is testing for immunity prior to vaccination, either on an individual or population level, indicated?

Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial

Lancet ID Volume 17, No. 9, p981–989, September 2017

In this phase 4, randomised, placebo-controlled trial, the authors enrolled two consecutive sequential annual cohorts of pregnant women from the Sarlahi district in southern Nepal. We randomised mothers 1:1 to receive seasonally recommended trivalent inactivated influenza vaccine or saline placebo, stratified by gestational age at enrolment (17–25 weeks *vs* 26–34 weeks). In the 26-34 week cohort, immunisation reduced maternal febrile influenza-like illness with an overall efficacy of 36%. In infants aged 0–6 months, immunisation had an efficacy of 60% in preventing laboratory-confirmed influenza infections. Maternal immunisation reduced the rates of low birthweight by 15% (95% CI 3–25) in both cohorts combined.

It is time for administration of influenza vaccine to all women in the third trimester of pregnancy, and incorporation into national vaccine programs.

Meta-analysis of antimicrobial stewardship

Lancet ID Volume 17, No. 9, p990–1001, September 2017

The authors included 32 studies in the meta-analysis, comprising 9 056 241 patient-days and 159 estimates of IRs. Antibiotic stewardship programmes reduced the incidence of infections and colonisation with multidrug-resistant Gram-negative bacteria (51% reduction; IR 0·49, 95% CI 0·35–0·68; p<0·0001), extended-spectrum β-lactamase-producing Gram-negative bacteria (48%; 0·52, 0·27–0·98; p=0·0428), and meticillin-resistant *Staphylococcus aureus* (37%; 0·63, 0·45–0·88; p=0·0065), as well as the incidence of *C difficile* infections (32%; 0·68, 0·53–0·88; p=0·0029). Antibiotic stewardship programmes were more effective when implemented with infection control measures (IR 0·69, 0·54–0·88; p=0·0030), especially hand-hygiene interventions (0·34, 0·21–0·54; p<0·0001), than when implemented alone.

Stewarship significantly reduced the incidence of infections and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients. When starting a program, infection control measures and hand hygiene, should be optimized first.

Time to start vitamin D with TDF?

Clinical Infectious Diseases 21st August 2017, cix753, https://doi.org/10.1093/cid/cix753

This was a randomized double-blind placebo-controlled trial of directly observed VITD3 vs. placebo every 4 weeks for 48 weeks in youth ages 16-24 years with HIV, viral load <200 copies/mL, taking TDF-containing combination antiretroviral therapy (TDF-cART) for ≥180 days. Participants (N=214) received a daily multivitamin containing VITD3 400 IU and calcium 162 mg, plus monthly randomized VITD3 50,000 IU (N=109) or placebo (N=105). Outcome was change from baseline to week 48 in lumbar spine BMD (LSBMD). At baseline 62% had 25-hydroxy vitamin D [25-OHD] <20 ng/mL.

From baseline to week 48, LSBMD increased by 1.15 (-0.75, 2.74)% in the VITD3 group (N=99; P<0.001) and 0.09 (-1.49, 2.61)% in the placebo group (N=89; P=0.25), without between-group difference (P=0.12). VITD3 group changes occurred with baseline 25-OHD <20 ng/mL (1.17 (-0.82, 2.90)%; P=0.004) and ≥20 ng/mL (0.93 (-0.26, 2.15)%; P=0.033).

For youth taking TDF-cART, LSBMD increased significantly through 48 weeks with VITD3 independent of baseline vitamin D status. Perhaps we should routinely consider this practice.

Antibiotic therapy for skin abscess

(courtesy Dr Laxman Jessani)
N Engl J Med. 2017;376(26):2545.

Management of skin abscess consists of incision and drainage; the role of antibiotic therapy depends on individual clinical circumstances, including abscess size. Uncomplicated skin abscesses are common, yet the appropriate management of the condition in the -

era of community-associated methicillin-resistant Staphylococcus aureus (MRSA) is unclear. In a randomized trial including more than 780 patients with skin abscess ≤5 cm (most were larger than 2 cm) who underwent incision and drainage, higher cure rates were observed among those who received antibiotic therapy with methicillin-resistant *Staphylococcus aureus* (MRSA) coverage (trimethoprim-sulfamethoxazole or clindamycin) than those who received placebo (82 or 83 percent versus 69 percent); MRSA was isolated in 49 percent of cases .

These findings support our approach to management of patients with skin abscess, in which we suggest antibiotic therapy in addition to incision and drainage for patients with skin abscess ≥2 cm.

Cefiderocol: the next blockbuster?

Eur J Clin Microbiol Infect Dis 2017 Jul 26.

The siderophore cephalosporin cefiderocol has high stability against most β-lactamases, including serine- and metallo-carbapenemases. In this study, salient features were:

- High activity with low MIC_{50} and MIC_{90} values against Enterobacteriaceae strains producing either one or the other, or both, of extended spectrum ß-lactamases and KPC-, OXA-48-, NDM-, VIM-, and IMP-carbapenemases
- Only 24 of the 753 multiresistant isolates (3%) showed a cefiderocol MIC ≥8 μg/mL.
- Carbapenemase-producing *Pseudomonas aeruginosa* were susceptible to cefiderocol and colistin only.
- Similarly, for carbapenemase producing-*Acinetobacter baumannii*, only cefiderocol, colistin, and tigecycline retained activity.

Is this the next savior for our problems in India with MDR-GNB? Time will tell, but the bugs are usually smarter.

Indirect Protection Afforded by Vaccinating Children Against Seasonal Influenza

(courtesy Dr Ashwini Chowdhary)
Clinical Infectious Diseases, Volume 65, Issue 5, 1 September 2017, Pages 719–728,https://doi.org/10.1093/cid/cix420

The authors systematically the literature on "herd"/indirect protection protection effectiveness (IPE) from vaccinating children aged 6 months to 17 years against influenza. In meta-analyses of 6 cRCTs with full randomization (rated as moderate quality overall), significant IPE was found in 1 cRCT in closely connected communities where school-aged children were vaccinated: 60% (95% confidence interval [CI], 41%–72%; $I2$ = 0%; N = 2326) against laboratory-confirmed influenza, and 3 household cRCTs in which preschool-aged children were vaccinated: 22% (95% CI, 1%–38%; $I2$ = 0%; N = 1903) against acute respiratory infections or influenza-like illness. Significant IPE was also reported in a large-scale cRCT (N = 8510) that was not fully randomized, and 3 ecological studies (N > 10000) of moderate quality including 36% reduction in influenza-related mortality among the elderly in a Japanese school-based program.
The available evidence suggests that influenza vaccination of children confers indirect protection in some but not all settings.

How to deal with organ recipients from donors with carbapenem resistant gram negative infections?

(courtesy Dr Balavinoth R)
Am J Transplantation 2015;15:2674-2682

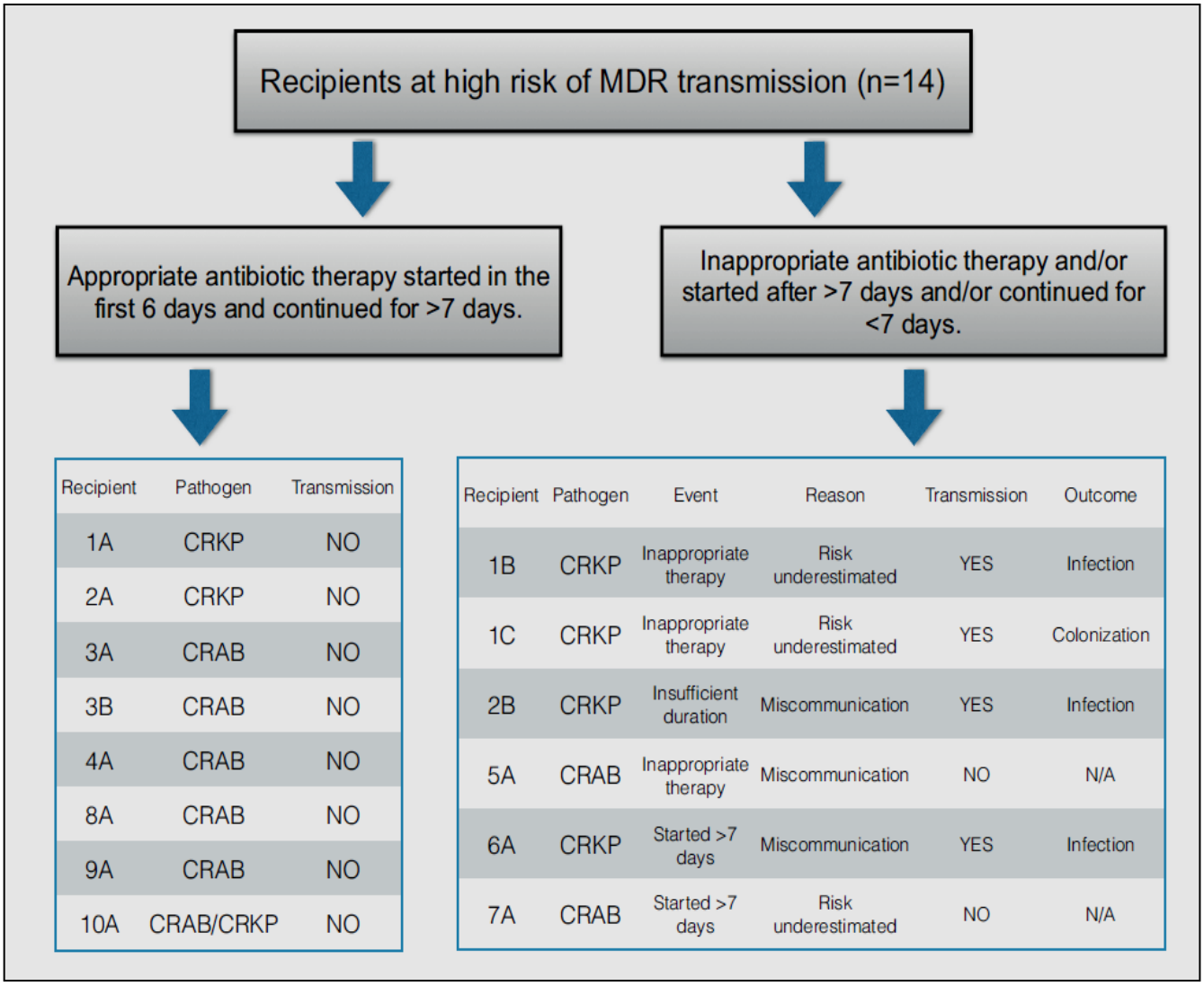
This study from Italy classified transplants from donors with carbapenem resistant gram negative infections into two categories:

- **High risk of donor-derived infection transmission**:

Organs from donors with blood stream infection (BSI) or with an infection of the same transplanted organ, e.g., urinary tract infection (UTI) in cases of kidney transplants or lower respiratory tract infection (LRTI) in cases of lung transplants

- **Low risk of donor-derived infection transmission**:

Received an organ from donors with infection/ colonization of a nontransplanted organ and without bacteremia



Recipient	Pathogen	Transmission
1A	CRKP	NO
2A	CRKP	NO
3A	CRAB	NO
3B	CRAB	NO
4A	CRAB	NO
8A	CRAB	NO
9A	CRAB	NO
10A	CRAB/CRKP	NO

Recipient	Pathogen	Event	Reason	Transmission	Outcome
1B	CRKP	Inappropriate therapy	Risk underestimated	YES	Infection
1C	CRKP	Inappropriate therapy	Risk underestimated	YES	Colonization
2B	CRKP	Insufficient duration	Miscommunication	YES	Infection
5A	CRAB	Inappropriate therapy	Miscommunication	NO	N/A
6A	CRKP	Started >7 days	Miscommunication	YES	Infection
7A	CRAB	Started >7 days	Risk underestimated	NO	N/A

- Unexpected transmission occurred in 4 of the 30 recipients, who received a late or short antibiotic course.
- Transmission did not occur in high-risk recipients who received a prompt and appropriate antibiotic therapy for at least 7 days
- The majority of recipients at low risk of infection did not undergo any donor-targeted MDR antibiotic treatment in the early posttransplant course, and no cases of proven transmission were recorded
- It is not necessary to treat the recipient of an allograft from a deceased donor with nonbacteremic, localized infection not involving the transplanted organ
- If the donor is bacteremic at the time of procurement, antibiotic treatment should be administered to each recipient for at least 14 days in case of infection with CRGN bacilli.
- A shorter course, of at least 7 days, should be provided to recipients in good clinical condition and with posttransplant negative cultures
- Kidney transplantation from a donor with an MDR UTI infection, and lung transplantation from a donor with MDR pneumonia or LRTI, carry a high risk of nontreatable graft infection.

Transplantation of an organ from a donor infected or colonized with a carbapenem resistant gram negative organism is a scenario often encountered in India, and this study helps devise a management strategy for the recipient.

Answer to the photo quiz

Biopsy of hepatic SOLs showed mixed septate with partially septate hyphae suggestive of primary invasive fungal infection (Post LDLT) (Figure 2).
Source control was advised but was not feasible. Immunosuppression was reduced. The patient was initiated on L-AMB along with deferasirox (iron-chealtor) & later, posaconazole. Antifungal agents were discontinued after 5 months.
Clinical and radiological stability was acheived. However, patient relapsed 1 month after stopping the antifungals and subsequently, succumbed.

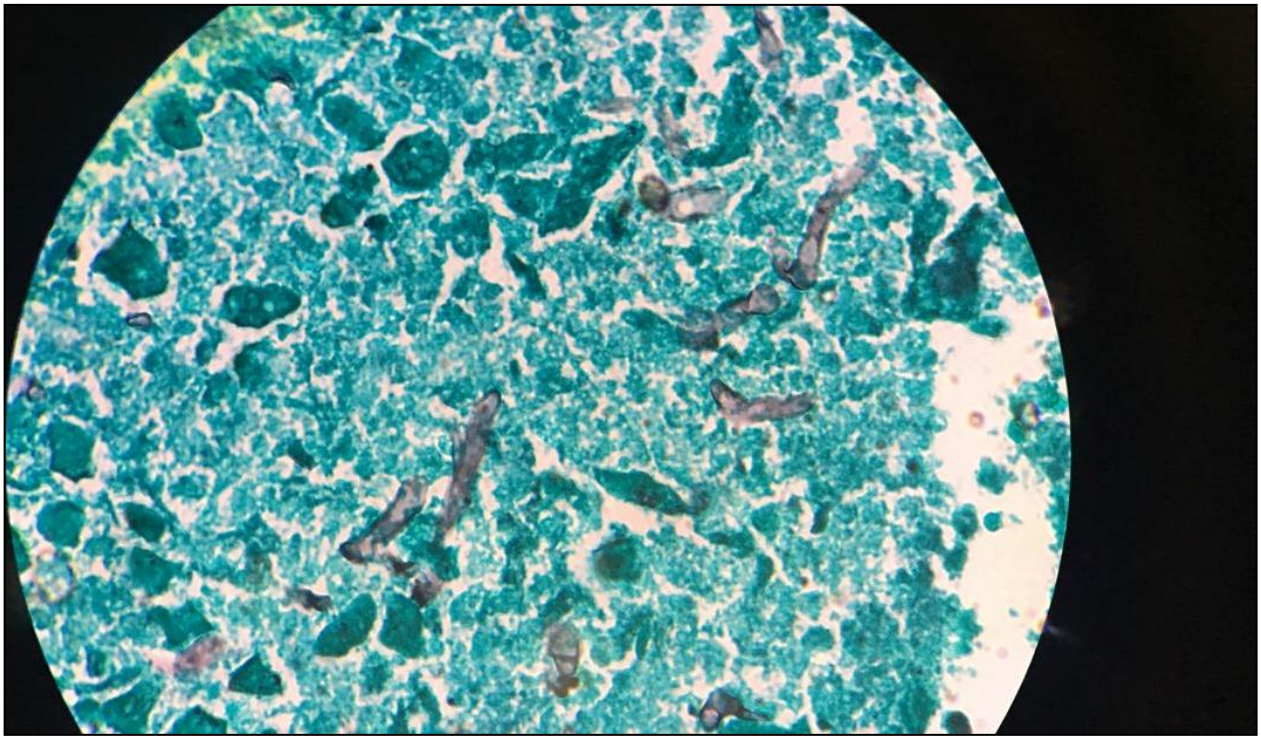


Figure 2: Mixed septate with partially septate fungal hyphae

Invasive mucormycosis is an emerging fungal infection complicating solid organ transplantation (SOT) with a cumulative incidence of around 2% during the first year after SOT.
Renal failure (OR 3.17), DM (OR, 8.11), and prior voriconazole &/or caspofungin use (OR) a/w with a higher risk of mucormycosis. Tacrolimus (OR, 0.23) associated with a lower risk of mucormycosis
The associated mortality rate is high, and surgical debridement is frequently required as part of the management.

Final diagnosis: Invasive fungal infection, possibly mucormycosis

(Case provided by Dr Neha Gupta (ID), Dr Neeraj Saraf (Hepatologist) and Dr Dheeraj [Histopathologist])