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CIDS Newsletter

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CLINICAL INFECTIOUS DISEASES SOCIETY

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Editor's note

Dear CIDS members

Our website has been updated, please check it out and encourage colleagues and postgraduates to do so. A complete revamping of the website is also being planned. You can access newsletter material directly from the website as open access material.

Please send me your feedback and material for website/newsletter is always welcome.

Sincerely

Ram Gopalakrishnan

Photo quiz

A 45-yr old gentleman presented with complaints of pain, floaters and blurring of vision in both the eyes since 10 days. Fundus examination revealed bilateral retinitis (Figure 1) with an initial suspicion of acute retinal necrosis (ARN) with positive Herpes Simplex Virus (HSV 1and 2) IgG. He was started on acyclovir. Subsequently, he was referred to Infectious Diseases (ID) opinion by the ophthalmologist for treatment. On enquiry, the patient also had maculo-papular, non pruritic rashes on the plantar surfaces of bilateral feet a month back.

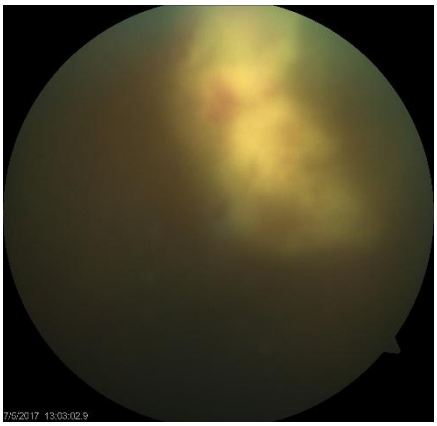

Figure 1: A "ground glass" retinitis, often associated with retinal vasculitis

What is your diagnosis?

News from the ID world

Meropenem-vaborbactam approved by US FDA

The U.S. Food and Drug Administration today approved meropenem-vaborbactam for adults with complicated urinary tract infections (cUTI). Meropenem-vaborbactam was designated as a qualified infectious disease product (QIDP). The safety and efficacy of meropenem-vaborbactam were evaluated in a clinical trial with 545 adults with cUTI, including those with pyelonephritis. At the end of intravenous treatment with meropenem-vaborbactam, approximately 98 percent of patients treated with meropenem-vaborbactam compared with approximately 94 percent of patients treated with piperacillin/tazobactam, another antibacterial drug, had cure/improvement in symptoms and a negative urine culture test. The most common adverse reactions in patients taking meropenem-vaborbactam were headache, infusion site reactions and diarrhea.The drug should be active against KPC-2 carbapenemases though it has not been studied or licensed for for this indication, but is unlikely to be active against NDM-1 type carbapenemases seen in India.

New drugs for HIV and HCV now available in India

The drug velpatasvir (100 mg) is now available in India, in combination with sofosbuvir (400 mg), as a once daily regimen. The combination is approved for the treatment of all genotypes of HCV as a 12 week course for those without decompensated cirrhosis, and in combination with ribavirin for those with decompensation. There are important drug interactions which need checking, including a recommendation not to use with efavirenz containing regimens.

Darunavir is now available as an 800 mg single tablet for once daily use in anti-retroviral naïve patients, in combination with ritonavir 100mg. The drug continues to be available as a 600 mg formulation for use in treatment experienced patients twice daily.

New members

CIDS welcomes the following new members:

S.No	Name	Place	Email
1	Dr. Kiran Kumar Vandna	Andhra Pradesh	vandaanakiran@gmail.com
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10	Dr. Kommineni Veerasankara Rao	Andhra Pradesh	

Snippets from the literature

Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults

Lancet ID 14th Sep 2017
http://dx.doi.org/10.1016/S1473-3099(17)30474-7

The authors prospectively obtained diagnostic cerebrospinal fluid (CSF) specimens during screening for a trial on the treatment of HIV-associated cryptococcal meningitis in Mbarara, Uganda. HIV-infected adults with suspected meningitis (eg, headache, nuchal rigidity, altered mental status) were screened consecutively at Mbarara Regional Referral Hospital. They centrifuged CSF, resuspended the pellet in 2 mL of CSF, and tested 0·5 mL with mycobacteria growth indicator tube culture, 1 mL with Xpert, and cryopreserved 0·5 mL, later tested with Xpert Ultra. They prospectively evaluated 129 HIV-infected adults with suspected meningitis for tuberculosis. 23 participants were classified as probable or definite tuberculous meningitis by uniform case definition, excluding Xpert Ultra results.

In comparison to a composite gold standard, Xpert Ultra had 95% sensitivity (95% CI 77–99; 21 of 22 cases) for tuberculous meningitis, which was higher than either Xpert (45% [24–68]; 10/22; p=0·0010) or culture (45% [24–68]; 10/22; p=0·0034).
Xpert Ultra detected significantly more tuberculous meningitis than did either Xpert or culture. WHO now recommends the use of Xpert Ultra as the initial diagnostic test for suspected tuberculous meningitis.

A Randomized Controlled Trial Comparing 3 Single-Dose Antibiotic Regimens With Loperamide

Clinical Infectious Diseases 23 September 2017, cix693,
https://doi.org/10.1093/cid/cix693

A randomized, double-blind trial was conducted in 4 countries (Afghanistan, Djibouti, Kenya, and Hond--uras) between September 2012 and July 2015. US and UK service members with acute watery diarrhea were randomized and received single-dose azithromycin (500 mg; 106 persons), levofloxacin (500 mg; 111 persons), or rifaximin (1650 mg; 107 persons), in combination with loperamide (labeled dosing).

At 48 and 72 hours, efficacy among regimens was equivalent (approximately 91% at 48 and 96% at 72 hours). The median time to last unformed stool did not differ between treatment arms (azithromycin, 3.8 hours; levofloxacin, 6.4 hours; rifaximin, 5.6 hours).

Single-dose azithromycin, levofloxacin, and rifaximin with loperamide were comparable for treatment of acute watery diarrhea.

Candida auris candidemia in Indian ICUs: analysis of risk factors

(courtesy Dr Nitin Bansal)
J. Antimicrob. Chemother. 2017, 72, 1794–1801

- Previously reported clinical data from ICU-acquired candidaemia cases identified between April 2011 and September 2012 in 27 medical and surgical ICUs across India were retrieved.
- The identity of all C. auris isolates was confirmed by sequencing the internal transcribed spacer (ITS) region and the D1/D2 region of the large subunit (28S) of the ribosomal DNA. Antifungal susceptibility testing of C. auris isolates with amphotericin B, fluconazole, voriconazole, itraconazole, posaconazole, caspofungin, anidulafungin and micafungin was performed by broth microdilution using the CLSI M27-A3 guidelines
- Out of a total of 1400 patients, 5.3% (74 patients) were due to C. auris.

- C. auris candidaemia was identified in 19 of 27 ICUs across India, more frequently from ICUs in the north of the country (n=54, 73% and 10 of 11 ICUs) as compared with other regions (n=20, 27%; P,0.001). Isolation of C. auris was significantly higher in public-sector hospitals compared with private-sector hospitals

- The all-cause 30day crude and attributable mortality in C. auris candidaemia patients were 41.9%and 27%, respectively The sequencing of the ITS and D1/D2 regions of the 28S subunit of ribosome revealed 99%–100% homology with C. auris; .99% homology with an unrelated C. auris strain (HE797774.1) and an earlier reported isolate from New Delhi (KC692063.1), and 100% homology with Korean ear isolates.

- AFLP results showed that the majority of the C. auris isolates (45/51, 88.23%) had an identical (99%–100%) fingerprint, suggesting the clonal nature of the isolates. Six isolates (11.8%) clustered separately from the main clone and varied between 3% and 10.6%.

- Antifungal resistance was notedto amphotericin B (n=10, 13.5%), fluconazole (n=43, 58.1%), voriconazole (n=2, 2.7%), itraconazole (n=3, 4.3%) and caspofungin (n=7, 9.5%).

- Multidrug resistance was noted in 12 (16.2%) isolates, of which 11 (91.7%) showed resistance across two antifungal classes and one isolate showed resistance across three antifungal classes

- The incidence of C. auris candidaemia was significantly higher in patients who had previous exposure to fluconazole.

Invasive intervention in ICUs may lead to nosocomial acquisition of C. auris infection. Automated identification systems misidentify this agent as Candida haemulonii/Candida famata/Candida sake or Rhodotorula glutinis. The emergence of a few isolates with high MICs of caspofungin (9.5%) is a major concern, as an echinocandin is the first line of choice to treat candidaemia in the ICU.

Evaluation of a Rapid Molecular Drug Susceptibility Test for Tuberculosis

(courtesy Dr Rajalakshmi A and Dr Nitin Bansal)
N Engl J Med 2017;377:1043-54.
DOI: 10.1056/NEJMoa1614915

The authors conducted a prospective diagnostic accuracy study to compare the investigational assay against phenotypic drug-susceptibility testing and DNA sequencing among adults in China and South Korea who had symptoms of tuberculosis. The Xpert MTB/ RIF assay and sputum culture were performed. M. tuberculosis isolates underwent phenotypic drug-susceptibility testing and DNA sequencing of the genes katG, gyrA, gyrB, and rrs and of the eis and inhA promoter regions.

When DNA sequencing was used as the reference standard, the sensitivities of the investigational assay for detecting mutations associated with resistance were 98.1% for isoniazid (95% CI, 94.4 to 99.6), 95.8% for fluoroquinolones (95% CI, 89.6 to 98.8), 92.7% for kanamycin (95% CI, 80.1 to 98.5), and 96.8% for amikacin (95% CI, 83.3 to 99.9), and the specificity for all drugs was 99.6% (95% CI, 97.9 to 100) or greater.

This investigational assay accurately detected M. tuberculosis mutations associated with resistance to isoniazid, fluoroquinolones, and aminoglycosides and holds promise as a rapid point-of-care test to guide therapeutic decisions for patients with tuberculosis, especially when short course WHO approved regimens are planned.

Increasing Incidence of Penicillin- and Cefotaxime-resistant Streptococcus pneumoniae Causing Meningitis in India

(courtesy Dr R Surendran)
Indian J Med Microbiol 2017;35:228-36

The authors present the antibiotic susceptibility profile of pneumococcal meningeal isolates from January 2008 to August 2016 to elucidate treatment guidelines for pneumococcal meningitis. Invasive pneumococcal isolates from all age groups, were included in this study. Minimum inhibitory concentr-

-ations for the isolates were identified by agar dilution technique and VITEK System 2. Serotyping of isolates was done by co-agglutination technique.

Out of 830 invasive pneumococcal isolates, 167 (20.1%) isolates were from meningeal infections. Cumulative penicillin resistance in pneumococcal meningitis was 43.7% and cefotaxime non-susceptibility was 14.9%. Penicillin resistance amongst meningeal isolates in those younger than 5 years, 5–16 years of age and those aged 16 years and older was 59.7%, 50% and 27.3%, respectively, with non-susceptibility to cefotaxime in the same age groups being 18%, 22.2% and 10.4%. Penicillin resistance amongst pneumococcal meningeal isolates increased from 9.5% in 2008 to 42.8% in 2016, whereas cefotaxime non-susceptibility increased from 4.7% in 2008 to 28.5% in 2016. Serotypes 14, 19F, 6B, 6A, 23F, 9V and 5 were the most common serotypes causing meningitis, with the first five accounting for over 75% of resistant isolates.

This study reports increasing penicillin resistance and cefotaxime non-susceptibility to pneumococcal meningitis in our setting. This highlights the need for empiric therapy with third-generation cephalosporins and vancomycin for all patients with meningitis while awaiting results of culture and susceptibility testing, especially if <5 years old. The commonest five serotypes are covered by the conjugated 13 valent pneumococcal vaccine, highlighting the importance of universal childhood vaccination.

Food significantly reduces plasma concentrations of first-line anti-tuberculosis drugs

(courtesy Dr Ashwini Tayade)

Indian J Med Res [serial online] 2017 [cited 2017 Sep 14];145:530-5

Newly diagnosed adult TB patients were recruited from the Revised National Tuberculosis Control Programme (RNTCP) treatment centres in Chennai Corporation, Chennai, India. Two-hour post-dosing plasma concentrations were determined in 25 patients, and a semi-intensive pharmacokinetic study was undertaken in six patients. RMP, INH and PZA concentrations were determined by high- performan-ce liquid chromatography. The geometric mean two-hour concentrations with food and under fasting conditions were 2.2 and 5.5 μg/ml for RMP (P<0.001), 3.9 and 11.3 μg/ml for INH (P<0.001), and 18.0 and 28.2 μg/ml for PZA (P<0.001), respectively. Drug administration with food caused the plasma concentration to decrease by 50, 45 and 34 per cent for RMP, INH and PZA, respectively. Significant decreases in peak concentrations and exposures of drugs and delay in time to attain peak concentrations of drugs when taken with food were also observed.

Food lowered anti-TB drug concentrations significantly and delayed absorption. Patients may be explained the beneficial effects of taking anti-TB drugs in a fasting state and advised to do so.

Point-of-Care C-Reactive Protein Testing to Facilitate Implementation of Isoniazid Preventive Therapy for People Living with HIV

(courtesy Dr Veeren Ganta)

J Acquir Immune Defic Syndr. 2014 April 15; 65(5): 551–556. doi:10.1097/QAI.0000000000000085.

The authors measured CRP levels (normal < 10mg/L) using a point-of-care (POC) assay on stored serum samples from HIV-infected Ugandan adults initiating antiretroviral therapy. They assessed diagnostic accuracy in reference to baseline tuberculosis status adjudicated by an expert committee and calculated net reclassification improvement (NRI) to quantify the incremental discriminatory benefit of POC-CRP in determining IPT-eligibility compared to the WHO symptom screen.

Of 201 patients (median CD4 cell-count 137 cells/μL, IQR 83-206), five (2.5%) had tuberculosis. Compared to the WHO symptom screen, POC-CRP had similar sensitivity (100% vs. 80%, p=0.30) but greater specificity (21% vs. 87%, p<0.0001) for tuberculosis. If based on the WHO symptom screen, no patients with tuberculosis but only 42/196 patients without tuberculosis would have been considered IPT-eligible. If POC-CRP were used instead, one patient with tuberculosis (reclassification of cases -20%, p=0.32) and 129 patients without tuberculosis (reclassification of non-cases +66%, p<0.001) would have been reclassified as IPT-eligible, an NRI of -

-46% (p=0.03). In addition, POC-CRP testing would have reduced the proportion of patients without active tuberculosis requiring confirmatory tuberculosis testing (87% vs. 21%, p<0.0001).

A common condundrum is how to exclude active TB before offering IPT to HIV infected patients. POC-CRP testing increased more than four-fold the proportion of HIV-infected adults immediately identified as IPT-eligible and decreased the proportion of patients requiring referral for further tuberculosis diagnostic testing. POC-CRP testing could substantially improve implementation of tuberculosis screening guidelines.

Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data meta-analysis

(courtesy Dr Ashwini Tayade)
Clin Inf Diseases 11th Sep 2017

The authors systematically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and trial registers (all until July 2017) for eligible trials. Data from 1,506 individual patients in six trials were analyzed using uniform outcome definitions. They investigated pre-specified effect modifiers using multivariable hierarchical regression adjusting for pneumonia severity, age, and clustering effects. Within 30 days of randomization, 37 of 748 patients (5.0%) assigned to corticosteroids and 45 of 758 patients (5.9%) assigned to placebo died (adjusted odds ratio [aOR], 0.75; 95% confidence interval [CI], 0.46-1.21, p=0.24). Time to clinical stability and length of hospital stay were reduced by approximately one day with corticosteroids (-1.03 days; 95% CI, -1.62-(-0.43), p=0.001; and -1.15 days; 95% CI, -1.75-(-0.55), p

Adjunct corticosteroids for patients hospitalized with community-acquired pneumonia (CAP) reduce time to clinical stability and length of hospital stay by approximately one day without a significant effect on overall mortality but with an increased risk for CAP-related rehospitalisation and hyperglycaemia.

Use of a Dual-Antigen Rapid Diagnostic Test to Screen Children for Severe Plasmodium falciparum Malaria

(courtesy Dr Ashwini Tayade)
Clinical Infectious Diseases 24th August 2017, cix592, https://doi.org/10.1093/cid/cix592

In this prospective, observational cohort study, the authors assessed the accuracy of a dual-band (histidine-rich protein-2/*pan*-lactate dehydrogenase [HRP2/pLDH]) rapid diagnostic test (RDT) to differentiate uncomplicated from severe malaria. They included children aged <12 years who presented to a rural clinic in western Uganda with a positive HRP2 or HRP2/pLDH RDT. They estimated the test characteristics of a dual-antigen (HRP2+/pLDH+) band positive RDT compared to World Health Organization–defined clinical and laboratory criteria to detect severe malaria.

A total of 2678 children underwent testing for malaria with an RDT, and 83 (9.0%) satisfied criteria for severe malaria. The sensitivity and specificity of a HRP2+/pLDH+ result for severe malaria was 97.6% (95% confidence interval [CI], 90.8%–99.6%) and 75.6% (95% CI, 73.8%–77.4%), respectively. An HRP2+/pLDH+ result was significantly more sensitive (97.6% vs 68.7%, $P < .001$) for the detection of severe malaria compared to algorithms that incorporate screening for danger signs.

This test may prove useful in identifying and rapidly referring patients with severe malaria in remote malaria endemic regions.

Follow-up blood cultures in Gram-negative bacteremia: are they needed?

(courtesy Dr R Surendran)
Clin Infectious Diseases Sep 2017

To investigate the value of repeat blood cultures, the authors analyzed 500 episodes of bacteremia to determine frequency of FUBC and identify risk factors for persistent bacteremia. Of 500 episodes of bacteremia. 383 (77%) of 500 had at least 1 FUBC.

Antibiotic use did not affect the rate of positivity of FUBC, unless bacteria were not sensitive to empiric antibiotic. Fever on the day of FUBC was associated with higher rates of positive FUBC for Gram-positive cocci (GPC) but not GNB. Mortality and care in the intensive care unit were not associated with positive FUBC. Seventeen FUBC and 5 FUBC were drawn for GNB and GPC to yield one positive result.

Table 2. Differences between patients whose FUBC were positive or negative

	positive (n=55)		negative (n=328)		*P*
On antibiotics when cultures drawn	54	98%	312	95%	0.49
Medical disease (vs. surgical)	49	89%	265	81%	0.18
Fever when cultures drawn	27	49%	100	30%	**0.008**
Presence of a urinary catheter	11	20%	82	25%	0.50
Presence of an IV central catheter	34	62%	121	37%	**<0.001**
Neutropenia (ANC<1000/ml)	4	7%	29	9%	1.00
Diabetes mellitus	31	56%	121	37%	0.19
HIV positive	3	5%	20	6%	1.00
End stage renal disease on hemodialysis	24	44%	65	20%	**<0.001**
Liver cirrhosis	5	9%	33	10%	1.00
ICU care required	18	33%	119	36%	0.65
Death	3	5%	35	11%	0.33

FUBC added little value in the management of GNB bacteremia. Exceptions may include persistent fever, retention of a central line and CKD patients on HD. However studies on MDR-GNB, such as we see in India, are needed before final conclusions.

Systemic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam

(courtesy Dr Mohan Gurjar)
Clinical Infectious Diseases 2017;64(5):666-74

This meta-analysis (PROSPERO: CRD42016041646) includes 14 studies (11 adult studies and 3 children studies; total 3549 patients), and showed that there was significant increase in incidence of acute kidney injury (AKI) if vancomycin was used with piperacillin/tazobactam [unadjusted OR 3.12; 95% CI, 2.04 - 4.78; and adjusted OR 3.11; 95% CI 1.77 – 5.47]. Possible mechanism for increased incidence is additive effect from acute interstitial nephritis and direct cellular necrosis. When they analyzed studies where >50% patients received care in intensive care units (ICU), increase in AKI incidence was not found significant [aOR, 2.83; 95% CI, 0.74-10.85].

This meta-analysis suggests that concomitant use of vancomycin and piperacillin/tazobactam increases nephrotoxicity among non-ICU patients and clinicians should monitor renal function.

Guillain-Barre syndrome complicating chikungunya virus infection

(courtesy Dr Amarjit Singh Vij)
J Neurovirol. 2017; 23(3):504-507

While outbreaks have been earlier reported from India and other parts of the world, the recent outbreak in India witnessed more than 1000 cases. Various systemic and rarely neurological complications have been reported with CHIKV. The authors report two cases of Guillain-Barré syndrome (GBS) with CHIKV. GBS is a rare neurological complication which may occur after subsidence of fever and constitutional symptoms by several neurotropic viruses. The two cases of severe GBS presented with rapidly progressive flaccid quadriparesis progressing to difficulty in swallowing and breathing. Both required mechanical ventilation and improved partly with plasmapheresis. The cases emphasize that (1) description of this rare complication in a setting of outbreak with CHIKV (2) acute axonal as well as demyelinating neuropathy may occur with CHIKV (3) accurate identification of this entity during outbreaks with dengue, both of which are vector borne and may present with similar complications.

Answer to photo quiz:

The patient had a reactive VDRL (1:64) test and positive TPHA. Anti-HIV antibody test was non-reactive. He had history of unprotected exposure 10 months earlier. Further work up revealed a normal magnetic resonance imaging (MRI) brain with contrast with no leptomeningeal enhancement. Patient was started on Inj. Ceftriaxone 2 gm q12h along with oral steroids. Acyclovir was discontinued. He responded well to treatment with 6/6 vision of follow up.

Neuroretinitis is an infectious or immune-mediated process. The common etiologies include tuberculosis, sarcoidosis, brucella, syphilis, CMV, HSV, VZV, toxoplasmosis. Others include Lyme's disease, leptospirosis, mumps, salmonella, histoplasmosis, and cat-scratch disease.

Syphilitic retinitis (SR) is painless progressive unlike ARN which is painful and may be associated with an antecedent viral syndrome. Manifestations of syphilitic retinitis include multifocal inflammatory accumulations, ground glass retinitis, and granulomatous features. An interesting fact here was that although neurological involvement is otherwise a manifestation of tertiary syphilis, our patient presented with retinitis during secondary stage (presence of skin lesions on soles).

CDC recommends a CSF analysis in all cases of ocular syphilis, especially because the neurological involvement which is associated with greater morbidity and mortality may be late in manifestation and missed clinically. Although penicillin is the drug of choice, in cases of penicillin allergy or unavailability, ceftriaxone, tetracyclines, or macrolides may be alternatives.

Final diagnosis: Syphilitic retinitis during secondary syphilis

Case provided by: Dr Neha Gupta, Dr Ashima Jain Vidyarthi (Medanta ID Fellow), Dr Varun Gogia (Opthalmologist), Dr Mayank Bansal (Opthalmologist)