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CIDS Newsletter

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CLINICAL INFECTIOUS DISEASES SOCIETY

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Editor's note

Dear CIDS members

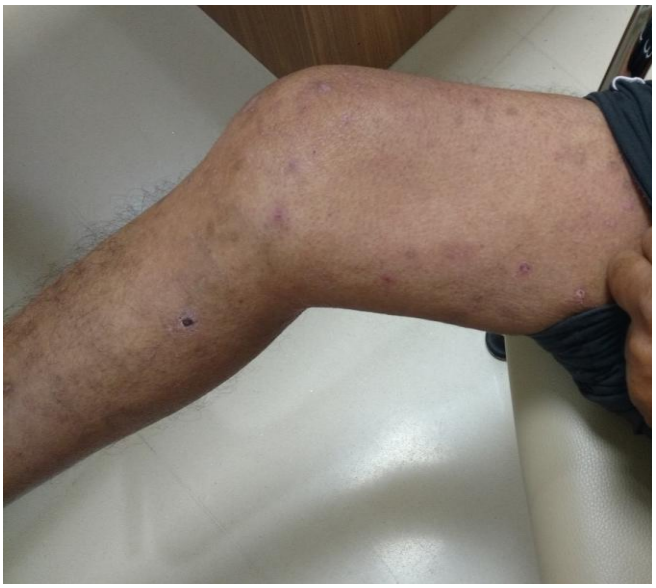
CIDSCON 2017 will be held at Nagpur on 18/19/20th August. Please mark your calendar.

Sincerely

Ram Gopalakrishnan

Photo quiz

63 year old male diagnosed with spinal TB was started on first line anti TB drugs. On initiation of drugs developed itching which was managed with antihistaminics. 6 weeks into treatment he developed erythematous itchy target like lesions all over hands and legs (Picture), followed by mouth ulcers and genital ulcers. Which drug is the likely culprit?



What is your diagnosis?

News from the ID world

Plasmid mediated colistin resistance reported in India too

Clin Infect Dis. (2016) 63 (9):1267-1268.

The authors report, for the first time, the co-emergence of *blaNDM-16*– and *mcr-1*–producing *E. coli* clinical isolates from India. *Escherichia coli* MK108 was isolated from a urine sample obtained from an inpatient at a university hospital in India in 2016. Bacterial identification was performed by standard biochemical analysis and confirmed by 16S ribosomal RNA sequencing. The isolate was resistant to carbapenems and colistin by micro-broth dilution testing. Polymerase chain reaction (PCR) screening of carbapenemase (NDM) and *mcr-1* was performed using the specific primers as described previously. Both genes were detected in *E. coli* MK108 and confirmed by sequencing.

TB epidemic in India larger than previously estimated: WHO

The tuberculosis epidemic in India is “larger” than what was previously estimated, the World Health Organization(WHO) on Friday said while assertinf that the country was one of six nations which accounted for 60% of the new cases in 2015. WHO said that the upward revisions to estimates of the burden of TB disease in India for the period 2000-2015 follow accumulating evidence that previous estimates were “too low” due to under-reporting by India.India has apparently reported only 56% of its TB burden in 2014 and 59% in 2015. The revised estimates put the incidence of TB in India at 217 per 100,000 population in 2015 as against the previous estimated 127 per 100,000.

Meanwhile the state government of Maharashtra is now drafting a bill that proposes to impose a fine to the tune of Rs. 10,000 to Rs, 50,000 on errant private practitioner who are failing to report cases to the government.

At UN, global leaders commit to act on antimicrobial resistance

(courtesy Dr Preeti Pillai)

On 21st September, world leaders signalled an unprecedented level of attention to curb the spread of infections that are resistant to antimicrobial medicines. For the first time, Heads of State committed to taking a broad, coordinated approach to address the root causes of AMR across multiple sectors, especially human health, animal health and agriculture. This is only the fourth time a health issue has been taken up by the UN General Assembly (the others were HIV, noncommunicable diseases and Ebola).

Countries reaffirmed their commitment to develop national action plans on AMR, based on the *"Global Action Plan on Antimicrobial Resistance"* — the blueprint for tackling AMR developed in 2015 by WHO in coordination with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). Leaders recognized the need for stronger systems to monitor drug-resistant infections and the volume of antimicrobials used in humans, animals, and crops, as well as increased international cooperation and funding. They pledged to strengthen regulation of antimicrobials, improve knowledge and awareness, and promote best practices — as well as to foster innovative approaches using alternatives to antimicrobials and new technologies for diagnosis and vaccines.

Kerala: Antibiotic awareness to be a part of MBBS curriculum

The Kerala University of Health Sciences has revised its curriculum. It has added an antibiotic chapter as a part of the MBBS study program for the current academic year. The policy on antibiotics under this program is supposed to be introduced to MBBS students on initiation of clinical interaction in the third year. The effort is to help house surgeons a-

-nd PG students to develop a better understanding of the policy. This is the first time that a health university is taking an initiative to teach antibiotic rationale policy to students in medical colleges. This is not needed as per Medical Council of India rules," said Dr K Mohanan, Member, KUHS Governing Council, who is accountable for curriculum revision at the university. KUHS officials are of the opinion that the policy needs to be introduced to doctors as a separate area of study, as he ever growing awareness need does not allow it to be curtailed to a chapter in a pharmacology or microbiology class. In accordance to the revised syllabus it is to be introduced to students right after their first year; and then gradually turned into an in depth analytical observation, during their clinical interactions in the third semester. Though a separate exam would not be conducted by colleges fot the subject, " Colleges on their own can conduct a test to review student understanding of the subject before and after class. Then we will know what needs to be done," added Dr Mohanan. " We hope this will be a beginning to ensure a rational antibiotiv prescription practice in future. This will be compulsorily taught in all colleges. At present, in introduction to pharmacology and microbiology, students are introduced to antibiotics in the second year," said MKC Nair, KUHS VC.

One hopes other staes will follow suit.

Snippets from the literature

Dolutegravir and low dose efavirenz based regimens are the way to go

Lancet HIV volume 3, No.11, e510-e520, November 2016

In this systematic review and network meta-analysis, the authors searched for randomised clinical trials published up to July 5, 2015, comparing recommended antiretroviral regimens in treatment-naive adults and adolescents. For viral suppression at 48 weeks, compared with efavirenz, the odds ratio (OR) for viral suppression was 1·87 (95% credible interval [CrI] 1·34–2·64) with dolutegravir and 1·40 (1·02–1·96) with raltegravir; with respect to viral suppression, low-dose efavirenz was similar to all other treatments. Both low-dose efavirenz and integrase strand transfer inhibitors tended to be protective of discontinuations due to adverse events relative to normal-dose efavirenz. The most protective effect relative to efavirenz in network meta-analyses was that of dolutegravir (OR 0·26, 95% CrI 0·14–0·47), followed by low-dose efavirenz (0·39, 0·16–0·92).

Standard dose efavirenz appears to cause discontinuations due to neuro-psychiatric side effects.

Travellers carry ESBL in their bowel

Lancet ID 2016
DOI: http://dx.doi.org/10.1016/S1473-3099(16)30319-X

In this prospective, multicentre COMBAT study, 2001 Dutch travellers and 215 non-travelling household members were enrolled. 633 (34·3%) of 1847 travellers who were ESBL negative before travel and had available samples after return had acquired ESBL-E during international travel (95% CI 32·1–36·5), with the highest number of acquisitions being among those who travelled to southern Asia in 136 of 181 (75·1%, 95% CI 68·4–80·9). Important predictors for acquisition of ESBL-E were antibiotic use during travel (adjusted odds ratio 2·69, 95% CI 1·79–4·05), traveller's diarrhoea that persisted after return (2·31, 1·42–3·76), and pre-existing chronic bowel disease (2·10, 1·13–3·90). The median duration of colonisation after travel was 30 days (95% CI 29–33). 65 (11·3%) of 577 remained colonised at 12 months. The probability of transmitting ESBL-E to another household member was 12%.

If so common in travelers and spreads to household contacts, most Indian residents would almost certainly have ESBL gut carriage.

Antimalarial activity of KA 156 in falciparum and vivax malaria

(courtesy Dr Pratik Patil)
N Engl J Med 2016;375:1152-60

KAF156 belongs to a new class of antimalarial agents (imidazolo-piperazines), with activity against asexual and sexual blood stages and the preerythrocytic liver stages of malarial parasites. Assessment of parasite clearance rates in cohorts of patients with vivax or falciparum malaria who were treated with multiple doses (400 mg once daily for 3 days) was followed by assessment of the cure rate at 28 days in a separate cohort of patients with falciparum malaria who received a single dose (800 mg). Overall 28-day cure rate of 67% after a single dose of KAF156 suggested clinically significant in vivo potency. Parasite clearance times and rates were similar in infections with and those without molecular markers of artemisinin resistance. In comparison, cure rates after short courses of artemisinin derivatives (<5 days) are typically less than 80%.

This new drug may be useful in artemisinin resistant malaria and also has activity against the pre-erythrocytic phase.

Empiric TB Therapy Versus IPT in HIV-Infected Persons Initiating ART (ACTG A5274 48w)

Lancet 2016 Mar 19; 387:1141

The REMEMBER study was a multi-country randomized clinical trial comparing ART + four-drug empiric TB therapy vs. ART + isoniazid preventive therapy (IPT) in HIV-infected individuals with CD4 counts <50 cells/mm· Participants were screened for TB prior to entry using a symptom screen, locally available diagnostics, and GeneXpert when available· There was no demonstrable benefit of empiric TB therapy on mortality at 48 weeks. This study supports the implementation of enhanced screening with symptoms or tests for TB prior to ART initiation, rather than empiric ATT.

This study fails to answer the question of whether empiric therapy is valuable in patients with *suspected* TB who are initiating ART. Perhaps urine LAM is the best test to exclude disseminated TB in patients with CD4<50 prior to initiating ART.

Are we under dosing ATT drugs in Indian children, and is TDM needed?

(courtesy Dr Pratik Patil)
CID 2016;63(S3):S63-74

Plasma drug concentrations measured in Indian children with tuberculosis were modelled using compartmental pharmacokinetic analyses. Drug doses were based on body weight: 10 mg/kg for rifampin and isoniazid, 30–35 mg/kg for pyrazinamide, and 30 mg/kg for ethambutol. Entire therapy was intermittent (3/week) and targets for therapeutic drug monitoring were 2-hour post dose concentrations of 3 mg/L for isoniazid, 8 mg/L for rifampin, and 20 mg/L for pyrazinamide. The main predictors of therapy failure or death were a pyrazinamide peak concentration **<38.10 mg/L** and rifampin peak concentration **<3.01** mg/L. The relative risk of these poor outcomes below these peak concentration thresholds was **3.64.**

It appears that at least for intermittent regimens (which hopefully are being phased out) in Indian children, under dosing predicts a poor outcome. Daily regimens and high doses with TDM in selected cases is the way forward.

Adjunctive azithromycin prophylaxis for Caesarean section

(courtesy Dr Pratik Patil)
N Engl J Med 2016;375:1231-41.

The authors evaluated the benefits and safety of azithromycin-based extended-spectrum prophylaxis in women undergoing non-elective cesarean section. Excluded were women undergoing a scheduled cesarean section and those with intrapartum chorioamnionitis. 2013 women who had a singleton pregnancy with a gestation of 24 weeks or more and

who were undergoing cesarean delivery during labor or after membrane rupture. They randomly assigned 1019 to receive 500 mg of intravenous azithromycin and 994 to receive placebo. All the women were also scheduled to receive standard antibiotic prophylaxis (cefazolin). The primary outcome was a composite of endometritis, wound infection, or other infection occurring within 6 weeks. There were significant differences between the azithromycin group and the placebo group in rates of endometritis (3.8% vs. 6.1%, P = 0.02), wound infection (2.4% vs. 6.6%, P<0.001), and serious maternal adverse events (1.5% vs. 2.9%, P = 0.03).

Azithromycin covers ureaplasma organisms, which are more commonly associated with infections after cesarean section. It is unclear whether the prevalence of ureaplasma organisms in Indian women warrants recommendation of azithromycin in the Indian setting.

Back to antibiotics rather than adjunctive therapies for severe sepsis

JAMA 2016 Oct 3; [e-pub].
N Engl J Med 2016 Oct 5; [e-pub]

Two recent randomized trials in severe sepsis led to disappointing results in the intervention being studied. The first involved the use of hydrocortisone (50-mg bolus, 200 mg daily as a continuous infusion for the first 5 days, and tapered over 11 days). Incidences of septic shock and mortality and hospital and intensive care unit lengths of stay were the same in both groups, with more hyperglycemia in hydrocortisone patients. The second study was on levosimendan, a calcium-sensitizing medication that has both inotropic and vasodilatory properties. Organ dysfunction and mortality occurred with equal frequency in both groups. Patients who received levosimendan experienced more adverse events (32 vs. 23), required more norepinephrine, had more arrhythmias, and were slower to be liberated from ventilators.

Early appropriate antibiotics remain the cornerstone for septic shock. We ID physicians will still remain in business!

Secondary Hemophagocytic Lymphohistiocytosis, a Sepsis Mimic

Crit Care Med 2016 Nov 44:e1045

To identify diagnostic and prognostic factors in secondary HLH, researchers retrospectively assessed data on 11,004 adult patients admitted to one ICU between January 2000 and August 2012. Of these patients, 252 received a bone marrow aspiration for investigation of thrombocytopenia not related to malignancy or chemotherapy. HLH was diagnosed in 106 (42%). Bacterial infections were the precipitating factor for HLH in 76%, with a predominance of Gram-negative pathogens. Underlying malignant and autoimmune disorders were present in about 9% and 6%, respectively. The mortality rate was 43%. On multivariate analysis, only hyperferritinemia (ferritin levels >4780 µg/L) was significantly associated with ICU mortality.

Postinfectious HLH is likely underdiagnosed in critically ill patients. Persistent, otherwise-unexplained thrombocytopenia in apparently "septic" patients who do not improve with standard treatment should alert the clinician to test ferritin levels, which are both a diagnostic and prognostic marker in such patients. Tuberculosis is an important additional cause of HLH in India.

Can we discontinue therapy for chronic eAg negative hepatitis B?

Hepatology 2016 Jan 11;

In a systematic review, investigators evaluated factors associated with long-term viral remission (VR) in patients with HBV infection (HBeAg-positive and HBeAg-negative) in whom oral antiviral therapy was discontinued. Duration of therapy was >12 months and post-therapy follow-up was ≥12 months. Taking therapy duration into account, pooled VR rates were 68%, 51%, 39%, and 38% at 6, 12, 24, and 36 months, respectively, after treatment discontinuation. Among eAg negative patients, on-therapy VR duration ≤24 months were less likely to achieve VR at 12 months

after discontinuation than those with on-therapy VR duration >24 months (36% vs.75%;*P*=0.005).
Current guidelines for eAg positive hepatitis B recommend discontinuation of treatment after consolidation therapy for at least 12 months with persistently normal ALT levels and undetectable serum HBV DNA levels. This study suggests that this approach can be considered for eAg negative patients after 24 months of consolidation, but the viral remission rate drops into the 30% range at 3 years. This means close long-term monitoring is needed to identify virologic relapse.

Treating Blood Before Transfusion Reduces Malaria Incidence

Lancet 2016 Apr 23; 387:1701

The Mirasol pathogen-reduction system (Terumo BCT) uses ultraviolet light and riboflavin to reduce pathogen load, including *Plasmodium falciparum* parasites, in vitro. In an industry-supported, randomized, double-blind trial at a teaching hospital in Ghana, a total of 223 hospitalized adults requiring up to 2 whole blood units received either treated (pathogen-reduced) or untreated blood and were followed for 28 days.
Post-transfusion malaria was significantly lower in those receiving treated blood (4% vs. 22%).
Apparently the system can also inactivate a broad range of pathogens, including well-established viruses such as hepatitis B and C as well as emerging ones such as Zika. Further studies and commercial availability are awaited, especially in areas where resources to test donated blood are unavailable.

Candida auris emerges worldwide

Clinical Infectious Diseases 2016 published 20 October 2016, 10.1093/cid/ciw696

- emerged recently, independently and almost simultaneously on three continents, rather than as a result of worldwide dissemination of a dominant clone
- evidence for hospital outbreaks and clonal spread, different from invasive candidiasis due to most other Candida species
- C. auris requires specialized methods for identification and it could therefore be misidenti-fied as another yeast when using traditional biochemical methods.

- Nearly all C. auris isolates have had high minimum inhibitory concentrations (MICs) for fluconazole, suggesting that they are fluconazole-resistant.
- More than half of isolates have had high MICs for voriconazole, and a lower proportion for amphotericin B and echinocandins.
- Some isolates have had elevated MICs for all three major antifungal classes (azoles, polyenes, echinocandins)
- Mortality rates are high, approaching 70% during candidemia.
- Particularly close phylogenetic relative of C. krusei and C. lusitaniae, species notable for intrinsic or inducible antifungal resistance
- C. auris also demonstrates hardy phenotypes such as salt-tolerance and cell aggregation into large, difficult-to-disperse clusters, which may promote survival in hospital environments.
- Moreover, isolates exhibit the thermotolerance necessary to infect humans, growing optimally at 37°C and maintaining viability at up to 42°C
- In troubling publications from India, C. auris already accounted for >5% of candidemia in a national survey of ICUs, and as much as 30% of candidemia at individual hospitals.
- Other properties of C. auris may contribute to this perfect storm, including difficulties in timely and definitive identification by commonly-used commercial methods, intrinsic virulence that may be similar to C. albicans rather than attenuated like most non-C. albicans species, ability to cause lengthy outbreaks and possibly persist within hospital environments, and occupancy of as-yet unidentified ecological niches.

If events come together, we could witness the fungal counterpart to the worldwide expansion of carbapenem-resistant Enterobacteriaceae.

Chikungunya Virus: In Vitro Response to Combination Therapy With Ribavirin and Interferon Alfa 2a

(courtesy Dr. Amarjit Singh Vij)
J Infect Dis. (2016) 214 (8): 1192-1197.

The authors evaluated the antiviral activities of riba-

-virin (RBV) and interferon (IFN) alfa as monotherapy and combination therapy against chikungunya virus (CHIKV). Vero cells were infected with CHIKV in the presence of RBV and/or IFN alfa, and viral production was quantified by plaque assay. RBV and IFN alfa were effective against CHIKV as monotherapy at supraphysiological concentrations. However, RBV and IFN alfa were highly synergistic for antiviral effect when administered as combination therapy. Simulations with our mathematical model predicted that a standard clinical regimen of RBV plus IFN alfa would inhibit CHIKV burden by 2.5 $\log_{10}$ following 24 hours of treatment. In the HFIM system, RBV plus IFN alfa at clinical exposures resulted in a 2.1-$\log_{10}$ decrease in the CHIKV burden following 24 hours of therapy.

These studies illustrate the promise of RBV plus IFN alfa as a potential therapeutic strategy for the treatment of CHIKV infections.

Guideline watch

There is a surge of Chikungunya virus infection in the country with many cases reported from New Delhi. As of 11th September 2016, 14656 clinically suspected cases reported, prompting updated guidelines on management of chikungunya.
National guideline for clinical management if chikungunya 2016. Released by National Vector borne Diseases Control Programme,DGHS,Ministry of Health and Family welfare,Government of India.

http://www.nvbdcp.gov.in/Doc/National-Guidelines-Clinical-Management-Chikungunya-2016.pdf
(courtesy Dr Preeti Pillai)

Miscellaneous

International consortium publishes the first Primer on Tuberculosis in Nature Reviews Disease Primers

At the start of the 47th Union World Conference on Lung Health in Liverpool, UK, an international group of top TB experts from several leading institutions published a primer on tuberculosis (TB) in the journal *Nature Reviews Disease Primers* (http://www.nature.com/nrdp). The 23-page primer, part of a series featuring the latest state-of-the-art advances in various health fields, can be freely downloaded at http://www.nature.com/articles/nrdp201676 for a 1-month period only.

This Primer comes close on the heels of the newly released World Health Organization (WHO) Global TB Report 2016. The report shows that TB continues to be a major cause of morbidity and mortality worldwide, with an estimated 10.4 million new cases in 2015, and 1.8 million deaths, including 0.4 million among people with HIV. TB is now the leading infectious killer and among the top 10 biggest causes of deaths worldwide, responsible for more deaths than HIV and malaria.

Opportunity for fellows

At the next ECCMID in Vienna at the educational session “Clinical Grand Rounds”, fellows in training will for 15 minutes discuss a case from their own institutions with a panel of experts. Ideally, the presented case

should depict a realistic and representative scenario on a hospital ward round. It should be clinically challenging with demanding therapeutic decisions to make and also contain elements of microbiology/virology/mycology/parasitology, good pathology and other investigations such as imaging. Size is one A4 page only. Based on power-point presentations of the shortlisted abstracts the session organizers will select the six best cases for presentation. ECCMID will cover the registration fee and the travel costs according to the attached ECCMID rules and regulations for speakers and chairs.
For the presenting fellows the speaker rules apply.

Fellows in training are encouraged to submit their case abstract by 1 November 2016 to the ECCMID Scientific Secretariat (eccmid@escmid.org). Fellows may also contact Dr Camilla Rodrigues at dr_crodrigues@hindujahospital.com

Upcoming meetings and conferences

MYCOCON 2016

Nov 11-13, Mumbai

Contact mycocon2016@gmail.com or Dr Rajeev Soman (rajeev.soman@yahoo.com)

NATCON 2016

16th to 18th December, PGI, Chandigarh

71st National Conference on Tuberculosis and Chest Diseases (NATCON 2016), under the joint auspices of the Tuberculosis Association of India and the Tuberculosis Association of U.T. Chandigarh along with the Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research (PGI, Chandigarh) and the Academy of Pulmonary Sciences (APS)

http://www.natcon2016.in/

Answer to photo quiz

The skin lesion morphology was typical of erythema multiforme, likely drug induced.

All drugs were stopped till all the lesions healed. After one week, two drugs to which the patient had not been exposed, levofloxacin and streptomycin, were started along with gradual introduction of first line drugs one by one, in smaller doses and with a gradual increase in dose. Ethambutol and pyrazinamide have been reported to be associated with erythema multiformae and so were the last to be started. On challenging with ethambutol, the patient developed itching. Ethambutol was withheld and other first line drugs along with a quinolone were continued.

Final diagnosis: Erythema multiforme/ Steven-Johnson's syndrome caused by ethambutol

(case provided by Dr Preeti Pillai)