Volume 3, Issue 5

CIDS Newsletter

May 2016

CLINICAL INFECTIOUS DISEASES SOCIETY

Editor's note

Dear CIDS members

It will be three years in June since our newsletter started, and while the associate editors have been of great help in the last year, it is probably time for new ideas and a change in editor!

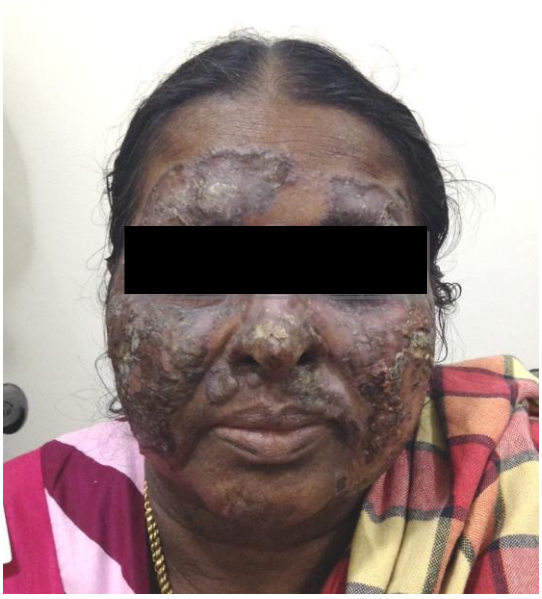
A good time for any members to express interest in taking over as newsletter editor would be at the annual general body meeting of the society on Aug 27th at CIDSCON. Of course, I will remain available for suggestions and guidance, and will continue to contribute to the newsletter in the future.

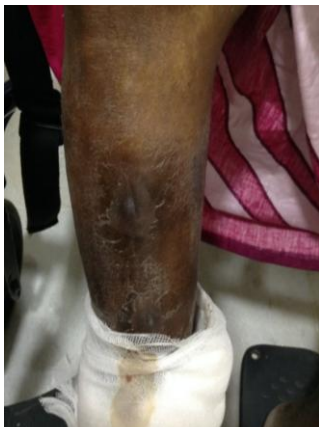
Sincerely

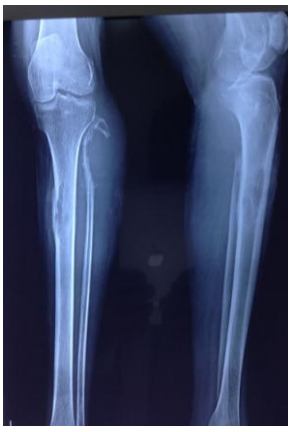
Ram Gopalakrishnan

Photo quiz

A 52/F from Tamil Nadu presented with lesions over the face for the last 5 years, and bilateral leg pain and swelling for the last 3 months (see photos). X ray showed evidence of osteomyelitis.







What is your diagnosis?

News from the ID world

US FDA advises restricting fluoroquinolone antibiotic use

http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system. As a result, the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs are required to be updated to reflect this new safety information.

Surely advisable for India to follow suit, especially given the widespread abuse of quinolones and consequent quinolone resistance in our country?

WHO approves SL-LPA and a shorter MDR-TB treatment

(courtesy Dr Surabhi Madan)

http://www.who.int/tb/Factsheet_SLLPAfinal.pdf
http://www.who.int/tb/Short_MDR_regimen_factsheet.pdf

Only Xpert MTB RIF and Hain first line LPA were approved by WHO for rapid diagnosis of MDR-TB. In May 2016, WHO issued new recommendations on the use of a rapid diagnostic test – a line probe assay to detect resistance to second-line anti-TB drugs (SL-LPA). The test identifies resistance to quinolones and injectable agents and WHO recommends this rapid diagnostic test for identifying those MDR- or rifampicin-resistant TB patients who can be placed on a new shorter MDR-TB regimen.

The test is approved for direct testing of sputum specimens as well as indirect testing on culture isolates from rifampicin-resistant or MDR-TB patients, including adults and children (irrespective of the smear status). For fluoroquinolones, resistance confirming mutations detected by SL-LPA are better correlated with culture-based phenotypic resistance to ofloxacin/levofloxacin in comparison to moxifloxacin; inclusion of moxifloxacin in a rifampicin-resistant or MDR-TB regimen is therefore best guided by phenotypic testing. These recommendations do not eliminate the need for phenotypic DST testing.

WHO RECOMMENDATIONS

ON THE USE OF THE SHORTER MDR-TB REGIMEI

In May 2016, WHO issued a conditional recommendation on the use of the shorter MDR-TB regimen. A flow chart outlining selection of patients on the shorter MDR-TB regimen is presented below.

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Supported by selected first-line TB drugs

FEATURES OF THE SHORTER MDR-TB REGIMEN

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months
- Indicated conditionally in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centred care and social support to enable adherence
- Programmatic use is feasible in most settings worldwide
- Lowered costs (<US$1,000 in drug costs/patient) and reduced patient loss expected
- Exclusion criteria: 2nd line drug resistance, extrapulmonary disease and pregnancy.

REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

Snippets from the literature

Short course therapy for gram negative bacteremia?

(courtesy Dr Ashwini Tayade)

Infectious Diseases in Clinical Practice May 2016
Vol. 24 - Issue 3: p 155–160

The authors reviewed medical records on patients with a documented Gram-negative bacteremia from August 2006 to November 2013. Patients meeting eligibility criteria were placed in the short-course, intermediate-course, and long-course treatment groups if their duration of antimicrobial therapy was less than or equal to 7 days, between 8 to 14 days, or greater than 14 days, respectively. Of 406 cases of Gram-negative bacteremia, 178 cases met eligibility criteria. Median age was 64 years with 67% females. Median SAPS II (Simplified Acute Physiology Score II) was 33 points. The most common infecting pathogen was *Escherichia coli* (46%), followed by *Klebsiella pneumoniae* (22%). The most common source of bacteremia was the urinary tract (53%), followed by indwelling catheters (14%). Clinical response rates at the end of therapy were 78.6%, 89.0%, and 80.6% for the short-course, intermediate-course, and long-course treatment groups, respectively ($P = 0.2$) and microbiological cure rates at the end of therapy were 83.3%, 89.0%, and 91.7% respectively.

The authors conclude that short-course therapy for Gram-negative bacteremia appears to achieve similar clinical response rates and microbiological cure rates compared with intermediate- and long-course therapy.

Cysticidal Efficacy of Combined Treatment With Praziquantel and Albendazole for Parenchymal Brain Cysticercosis

(courtesy Dr Surabhi Madan)

This was a randomized, double-blinded, placebo-controlled phase II evaluation of the pharmacokinetics of ABZ (15 mg/k/d, for 10 days) and PZQ (50 mg/k/d, for 10 days) in intraparenchymal brain cysticercosis. Thirty-two patients were included, 16 in each arm. All of them completed antiparasitic treatment and underwent follow-up brain MR imaging. Cysticidal efficacy was strikingly higher in the combined ABZ-plus-PZQ group than in the ABZ alone group (proportion of cysts resolved, 78 of 82 [95%] vs 23 of 77 [30%] [relative risk {RR}, 3.18; 95% confidence interval {CI}, 2.08–4.88; $P < .001$]; patients with complete cyst clearance, 12 of 16 [75%] vs 4 of 16 [25%] [RR, 3.00; 95% CI, 1.23–7.34; $P = .005$]).

The combination of ABZ plus PZQ seems more effective in destroying viable brain cysticercosis cysts than ABZ alone.

Staphylococcal bacteriuria in bacteremia: any prognostic relevance?

(courtesy Dr Ashwini Tayade)

Infectious Diseases in Clinical Practice May 2016
Vol. 24 - Issue 3: p 151–154

Staphylococcus aureus bacteriuria is reported in 15% to 27% of patients with *S. aureus* bacteremia. A retrospective study was performed on patients with staphylococcal bacteremia who had urine culture done. Demographics, clinical presentation, microbiology, clinical outcomes, complications, and mortality were collected for patients with and without staphylococcal bacteriuria. Of 274 patients with staphylococcal bacteremia, 179 had urine culture performed. Staphylococcal bacteriuria was found in 20%. Patients with bacteriuria did not have significantly longer median length of hospital stay (10.5 vs. 11.0 days, $P = 0.52$), intensive care unit stay (2.5 vs. 1.0 days, $P = 0.37$), other complications, or 30- and 90-day mortality. There was no significant statistical difference between *S. aureus* bacteriuria caused by methicillin-resistant *S-*

-*aureus* and methicillin-sensitive *S. aureus* for any of the factors studied. On univariate analysis, patients with staphylococcal bacteriuria were more likely to have a malignancy (33.3% vs. 16.9%, $P = 0.03$) and septic embolic events (22.2% vs. 7.7%, $P = 0.02$) and less likely to have renal disease (13.9% vs. 32.9%, $P = 0.04$) than those without bacteriuria.

The authors conclude that concomitant staphylococcal bacteremia and bacteriuria were not associated with increased mortality or worse clinical outcome

Polymyxin B: less nephrotoxic than colistin?

Antimicrob Agents Chemother. 2016; 60:2443--9.

The authors carried out a retrospective analysis of their use at 6 Brazilian hospitals—3 that used CMS and 3 PB. Each hospital had standard dosing protocols; loading doses were recommended for CMS but not PB. The primary outcome for the analysis was the development of renal failure by the RIFLE criteria. Renal failure occurred in 38.3% of CMS recipients and only 12.7% of those given PB (relative risk, 4.27 [95% confidence interval, 2.5–7.3]; $P < .001$).

CMS is a prodrug whose conversion in plasma, in contrast to other antibacterial prodrugs, is extraordinarily slow, requiring hours. In patients with severe sepsis or septic shock, in whom the rapid initiation of effective antibacterial therapy is critical, this slow appearance of active drug within the bloodstream may have detrimental consequences. In addition, the resultant prolonged residence may potentially lead to accumulation in renal tubular cells and resultant injury. Little PB appears in the urine, and this has at least 2 consequences: dose adjustment for altered renal function is not necessary, simplifying its use, and it is not a good choice for the treatment of urinary tract infections (UTIs). In contrast, CMS does achieve significant concentrations in urine, where it is slowly converted to the active parent moiety. As a consequence, dose adjustments are necessary in the presence of reduced renal function; in addition, CMS can be effective in the treatment of UTIs.

An RCT is needed to help us decide which polymyxin preparation is more efficacious and less nephrotoxic.

Upcoming meetings

Apollo Infectious Diseases Course (CIDS endorsed CME)
Chennai, June 10-12.

For details contact umashankar-r@apollohospitals.com or 7299060535.

Chandra's Corner

Notes from the United States

I was on the Immunocompromised Host-Infectious Diseases service for the past few weeks. Cases are frightfully fascinating; in particular, two case histories are worthy of report for their teaching value.

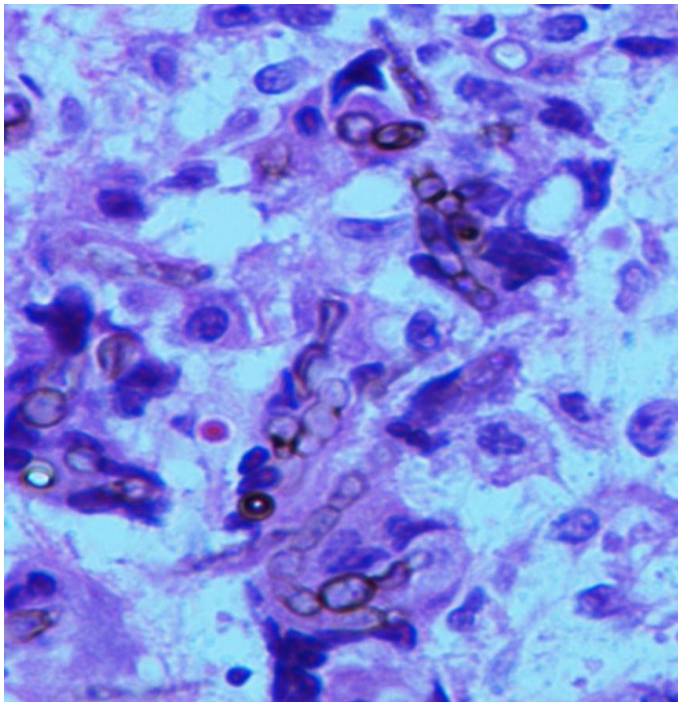
First is an HIV-negative, renal transplant recipient from Nigeria, who noted an enlarging inguinal mass; CT pelvis showed regional pelvic adenopathy. Biopsy of mass revealed Kaposi Sarcoma (KS). KS appears to be a common post-transplant neoplasm in the Mediterranean/African region. Post-transplant malignancies, which occur either de novo or as cancer recurrences, are due to chronic exposure to immunosuppressive drugs, particularly calcineurin inhibitors. Mammalian target of rapamycin (mTOR) inhibitors have antitumor and immunosuppressive effects. This dual effect may provide adequate immunosuppression to prevent organ rejection while simultaneously reducing the risk of post-transplant malignancy. Therapy of KS in our patient consisted of switching from tacrolimus (a calcineurin inhibitor) to mTOR inhibitor, everolimus. Data show control of KS with the use of mTOR inhibitors. Appropriate therapy of KS in this setting was a valuable learning point for me.

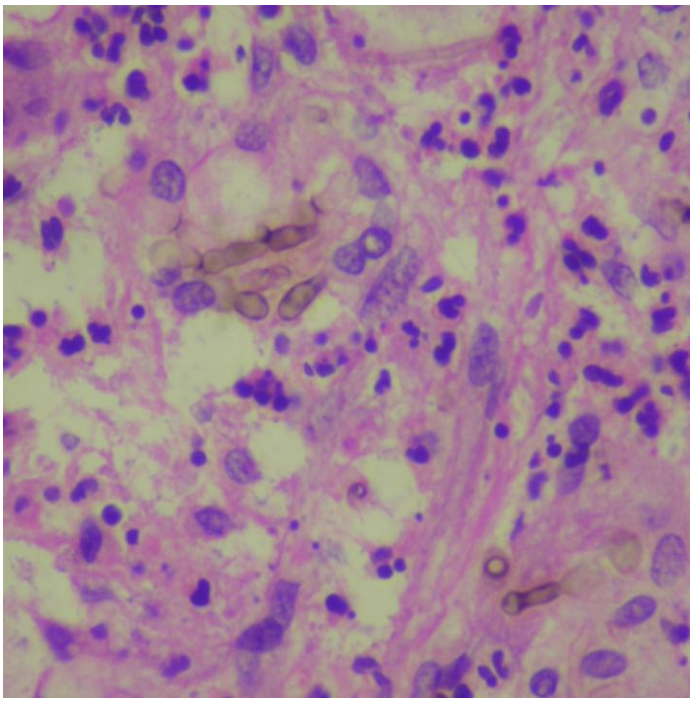
The second patient, also a renal transplant recipient, was non-adherent with medications. Five years after transplant he presented with "hypertensive encephalopathy". Correct diagnosis of cryptococcal meningitis was significantly delayed until several days after admission when cerebrospinal fluid exam revealed cryptococci. Unique points of interest included: a) encephalopathy was mistakenly attributed to poorly controlled hypertension, delaying the diagnosis, b) difficulty with controlling elevated intracranial pressure despite repeat lumbar punctures, eventually requiring lumbar drains, and c) development of cryptococcal endophthalmitis with quantitative cryptococcal antigen in the high range in the vitreous fluid. Literature review revealed limited information on cryptococcal endophthalmitis in the presence of meningitis. The patient survived but unfortunately lost his renal graft. He continues to have visual and hearing problems. The learning points for me were: 1) in transplant recipients with altered mentation, always consider opportunistic infections first, 2) altered vision in cryptococcal meningitis may not always be due to elevated pressure but infection itself, sometimes requiring intravitreal antimicrobial therapy and vitrectomy as in our patient.

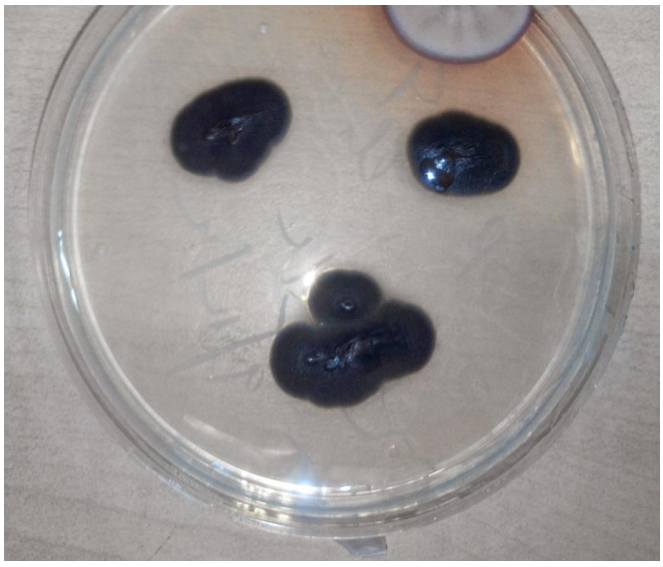
On another note, in the March issue of Science there was an interesting paper on colistin resistance among Gram-negative bacteria. This is a deeply troubling phenomenon particularly for India. Colistin resistance may arise through at least two mechanisms, one attributable to chromosomal mutation and another via a horizontally transferred plasmid-mediated polymyxin-resistant gene. The relevant references are: Giani T et al, J Clin Microbiol 53:3341, 2015 and Liu YY, Lancet Inf Dis, 16:161, 2016. Such infections, as you may have guessed, may become untreatable. The exact relationship between colistin use and the resistant bacteria found in animals, meat and humans is unclear. Both papers are of importance to the CIDS readers who regularly deal with antimicrobial resistance and prescribe a good amount of colistin.

Answer to photo quiz

Histopathology on skin and bone specimens showed pigmented septate hyphae, and culture grew Exophiala spinifera, a dematiaceous fungus. The patient improved after debridement of the bone lesion, and a prolonged course of itraconazole and terbinafine







Diagnosis: Disseminated phaeohyphomycosis caused by Exophiala spinifera (case provided by Dr Laxman G. Jessani).


CIDS
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6th Annual Conference of
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