# Clinical Infectious Diseases Society

## Newsletter : October 2018

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Editor: **Dr Ram Gopalakrishnan**
Associate Editors: Dr Neha Gupta, Dr Ashwini Tayade, Dr Abi Manesh

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### From the Secretary's desk

The first message seems to have gone down well- I have taken it upon myself to see if this can be kept up. There has been a lot of feedback on our conferences. A lot of constructive ideas- we shall build upon them next year. With respect to the TID, the timing of the conference has come in for considerable debate. Going forward, we will ensure that there will not be an issue of having to choose between our annual events. The next year's TID will be held in conjunction with the Congress of the Asian Society of Transplantation at Delhi between September 29th and October 2nd. This year the academics came in for a lot of appreciation, and the highlight was the pro-con debate between two of our stalwarts- the Rams from Chennai.

CIDSCON had a galaxy of international and domestic stars. The sessions were well thought out and were delivered by excellent orators who had a good grasp of the subject. The highlights included the talk on Sepsis 3 guidelines by Dr Sriram Sampath- he communicated his ideas with amazing simplicity, which was indeed the theme of the effort by many of the speakers. Next year's conference will be at Kochi, on August 23-25, 2019. More details to follow from Dr Anup Warrier, who will be the organizing secretary.

The PG course at Hinduja Hospital was conducted over the 2nd week of September, and many CIDS faculty were involved in the same. I am hearing a lot of positive feedback on that initiative as well. I have had the opportunity to attend the MYCOCON conducted by the FISF this year at Delhi. Dr Prakash Shastri and his team should be congratulated for the effort- it was quite an effort. The audience response was heartening; all sessions saw good questions and debate from the audience. The plenary sessions were incredible, as was the effort by Dr Subhash Todi to discuss the current guidelines. Who knew that discussing guidelines could be this interesting!

On the administrative front, we have now decided on the launch of subcommittees; Dr Rajeev Soman will head the HIV subcommittee and we anticipate some more news in this regard soon. Dr V Ramasubramanian will take charge of the Adult Vaccination and Travel Medicine group, Dr Anup Warrier will be tasked with Infection Control and Dr George M Varghese, the Tropical Medicine effort. I will chair the Transplant ID group, with the guidance of some of our senior colleagues. The chairs will be making decisions on the conduct of these committees soon, and will be adding members to the respective groups: this will be an exciting opportunity for our junior members to volunteer and contribute to the society.

I would like to congratulate Dr Ram Gopalakrishnan for making the linkage with IAMM possible, enabled by input from Dr Arunaloke Chakrabarti. This should give opportunities for interaction with a closely related society and hopefully result in mutual growth.

Many of the policies and decisions of CIDS have now been updated on the website, and this is becoming more interactive. Members are encouraged to visit the site and check out the details- the endorsement policy for CMEs, the visiting Professorship program, the regional chapters, and the subcommittees, among others. Updates on other areas, including EC membership is being worked on. Ideas and inputs in this regard may be sent to the secretary's email.
There are many more upcoming academic programs this year, and we encourage members to identify ideas that we could use to improve the content and conduct of next year's programs.

*Dr Subramanian Swaminathan*

## Editor's note

Dear CIDS members,

Please encourage colleagues and postgraduates to visit our updated website; check out the literature review and a fresh set of challenging cases presented at this year's CIDSCON!

## Photoquiz

A 50 year old male presented with fever, non productive cough of 2 weeks duration along with 6 kg weight loss in the last 1 month. CXR was s/o right sided moderate pleural effusion and diagnostic aspiration (20ml) showed amber coloured fluid (WBC 220, N20/L80, protein-3gm/dl, sugar -30gm/dl), which was negative for AFB and gram stain, along with negative Xpert M TB. HIV ELISA was positive. He was started on empiric ATT along with deflazacort and referred in view of persistent symptoms despite 3 weeks of ATT.

Examination revealed oral candidiasis. CXR showed a right sided moderate pleural effusion (fig.1) CD4 count was 40 (6%), HIV-1 VL was 20,00,000 and serum cryptococcal antigen was negative, Hb- 10, Wbc 3600, plt 140,000. USG thorax showed loculated pleural fluid with multiple septae ( fig2 ). Sspiration showed amber colored fluid (wbc 150 - N8/L92, sugar 18.4mg/dl, protein -2.3gm/dl). Gram, AFB and fungal stain of the fluid was negative and cytology showed no malignant cells.

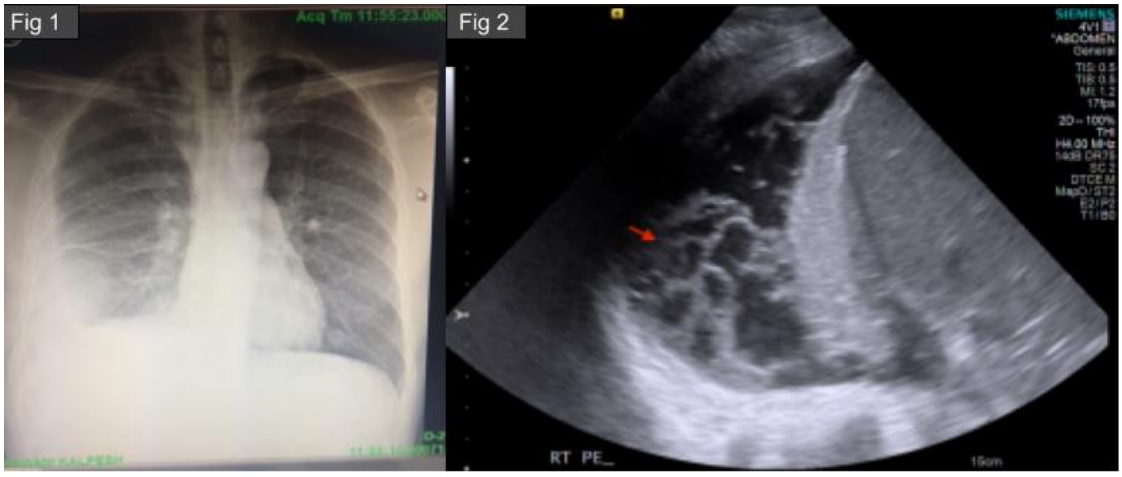



*Figure 1*: CXR (PA) s/o right sided Pleural effusion *Figure 2*. USG right thorax s/o multiloculated effusion (red arrow-septa, yellow arrow-collapsed lung)

What is your diagnosis?

ID NEWS

## List Of Banned Antibiotic FDCs

Contributed by Dr R Surendran

The Govt. of India has banned 328 Fixed Drug Combinations in a recent notification which prohibits the manufacture for sale or distribution for human use with immediate effect, based on DTAB's (Drugs Technical Advisory Board) recommendation that there is no therapeutic justification for the ingredients. The list includes syrups, suspensions, tablets, creams, ointments etc. The full list can be accessed online here.

Following antibiotic tablet FDC formulations are banned

Serial Number - FDC Name (Notification Number)

1. Amoxicillin + Cefixime + Potassium Clavulanic acid *(757)*
2. Amoxicillin + Dicloxacillin *(753)*
3. Amoxicillin 250 mg + Potassium Clavulanate diluted 62.5 *(754)*
4. Amoxicillin + Dicloxacillin + Serratiopeptidase *(771)*
5. Amoxycillin + Tinidazole *(764)*
6. Azithromycin + Cefixime *(752)*
7. Azithromycin + Cefpodoxime *(772)*
8. Azithromycin + Levofloxacin *(755)*
9. Azithromycin + Ofloxacin *(763)*
10. Cefixime + Levofloxacin *(766)*
11. Cefixime + Linezolid *(756)*
12. Cefpodoxime Proxetil + Levofloxacin *(759)*
13. Cefuroxime + Linezolid *(774)*
14. Clindamycin + Clotrimazole + Lactic acid bacillus *(854)*
15. Clindamycin + Telmisartan *(786)*
16. Combikit of Azithromycin + Secnidazole + Fluconazole *(760)*
17. Combikit of Azithromycin + Fluconazole + Ornidazole *(769)*
18. Diethyl Carbamazine + Chlorpheneramine + Guaifenesin *(938)*
19. Diethyl Carbamazine Citrate + Cetrizine + Guaifenesin *(892)*
20. Diethyl Carbamazine + Cetrizine + Ambroxol *(923)*
21. Diphenoxylate + Atropine + Furazolidone *(768)*
22. Doxycycline + Serratiopeptidase *(765)*
23. Furazolidone + Metronidazole + Loperamide *(844)*
24. Levofloxacin + Ornidazole + Alpha Tocopherol Acetate *(761)*
25. Metronidazole + Norfloxacin *(776)*
26. Metronidazole + Tetracycline *(779)*
27. Nimorazole + Ofloxacin *(762)*
28. Norfloxacin + Metronidazole + Zinc Acetate *(847)*
29. Ofloxacin + Metronidazole + Zinc Acetate *(767)*
30. Ofloxacin + Nitazoxanide *(758)*
31. Ofloxacin + Ornidazole + Zinc Bisglycinate *(775)*

Amazing how these irrational preparations were permitted for decades, very good news for the ID community indeed! Hopefully the ban will help reduce skyrocketing antimicrobial resistance in the country.

ID NEWS

## US FDA Approves Two New HIV Medications

The US FDA has approved two new HIV oral drugs to treat adults, doravirine and the combination tablet (doravirine/lamivudine/tenofovir disoproxil fumarate). The latter was approved with a boxed warning to "flag risk of worsening hepatitis B infection."

JOURNAL REVIEW

# Should we re-learn how to treat MDR TB?

Lancet. 2018 Sep 8;392(10150):821-834
Contributed by Dr Abi Manesh

This seminal paper summarises the clinical outcomes of individual from 50 studies across 25 countries. This individual patient data meta-analysis included potentially eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016.

Of 12 030 patients from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died.

Compared with failure or relapse, treatment success was positively associated with the use of:

1. linezolid (adjusted risk difference 0·15, 95% CI 0·11 to 0·18)
2. levofloxacin (0·15, 0·13 to 0·18), moxifloxacin (0·11, 0·08 to 0·14),
3. carbapenems (0·14, 0·06 to 0·21)
4. bedaquiline (0·10, 0·05 to 0·14)
5. clofazimine (0·06, 0·01 to 0·10)

There was a significant association between reduced mortality and use of

1. linezolid (−0·20, −0·23 to −0·16)
2. levofloxacin (−0·06, −0·09 to −0·04), moxifloxacin (−0·07, −0·10 to −0·04)
3. bedaquiline (−0·14, −0·19 to −0·10)

For the drugs that are commonly used in the Indian scenario:

1. Amikacin in people with susceptible strains was associated with greater success (adjusted risk difference 0·06, 95% CI 0·04 to 0·08) but no difference in death
2. Kanamycin was associated with significantly lower success (−0·07, −0·08 to −0·05) but no difference in death (0·01, −0·01 to 0·02)
3. Capreomycin use with lower success (−0·03, −0·06 to 0·00) and more deaths (0·04, 0·01 to 0·07).
4. Use of ethambutol, ethionamide and protionamide, or para-aminosalicylic acid were associated with no benefit in patients with susceptible isolates, and worse outcomes in patients with resistant isolates
5. Use of pyrazinamide was associated with lower mortality (adjusted risk difference −0·03, 95% CI −0·05 to −0·01) if isolates were susceptible, but significantly less success (−0·05, −0·08 to −0·03) and higher mortality (0·05, 0·02 to 0·07) if isolates were resistant.
6. Use of cycloserine was beneficial in patients with susceptible isolates contributing to treatment success and protection from death

This study is the basis of the recent WHO MDR-TB update. While this is the largest summary of clinical data we have, the following points merit special attention.

- The high baseline FQ resistance in many parts of India should be borne in mind.
- Bedaquiline availability is an issue in India
- The paper did not look at toxicity data – prolonged use of linezolid requires close monitoring for bone marrow toxicity and neuropathy
- Probably, amikacin should be our aminoglycoside of choice for MDR TB

JOURNAL REVIEW

## Drug MICs and relapse risk in TB – is there a correlation?

N Engl J Med. 2018 Aug 30;379(9):823-833
Contributed by Dr Abi Manesh

While we are aware that a small percentage of patients (5%) with drug-susceptible tuberculosis have a relapse after 6 months of therapy, the underlying reasons are not clear. The authors evaluated whether any correlations between the minimum inhibitory concentration (MIC) of a drug below the standard resistance breakpoint could predict the relapse risk after treatment.

Using available trial data samples they evaluated MIC values of isoniazid and rifampin that were below the standard resistance breakpoint (0.1 µg per milliliter for isoniazid and 1.0 µg per milliliter for rifampin) using methods which are not available in regular clinical practice.

In the development cohort, the mean (±SD) MIC of isoniazid below the breakpoint was 0.0334±0.0085 µg per milliliter in the relapse group and 0.0286±0.0092 µg per milliliter in the cure group, which represented a higher value in the relapse group by a factor of 1.17 (P=0.02). The corresponding MIC values of rifampin were 0.0695±0.0276 and 0.0453±0.0223 µg per milliliter, respectively, which represented a higher value in the relapse group by a factor of 1.53 (P<0.001). In the validation cohort, the MIC values either alone or combined with other patient characteristics were also predictive of relapse, with AUC values of 0.964 and 0.929, respectively.

The most important message of this trial is that it highlights the short comings of the artificial black and white separation of “susceptible” or “resistant,” isolates made for clinical use. Few things unexplained are in the INH cohort the risk did not show a steady increase with increasing MICs – actually there is a dip in the relapse risk in Fig 1A. While it improves our understanding of tuberculosis, it may not change existing clinical practice.

JOURNAL REVIEW

## Should we use combination therapy for typhoid?

PLoS Negl Trop Dis 12(4): e0006380
Contributed by Dr Sowmya Sridharan

Typhoid fever remains an important cause of AFI in many part of India. An open-label, comparative trial was conducted Nepal to evaluate the role of combination therapy in culture-confirmed TF cases. Patients were allocated to one of four study arms:

1. hospitalized patients received either intravenous ceftriaxone or a combination of ceftriaxone and oral azithromycin
2. outpatients received either oral azithromycin or a combination of oral azithromycin and cefixime.

The primary outcome evaluated was fever clearance time (FCT) and the secondary outcomes included duration of bacteremia.

Among the 105 blood culture-confirmed patients included in the trial, FCT was significantly shorter for the combination therapy group (95 versus 88 hours, respectively, p = 0·004), and this effect was exhibited in both the hospitalized and the outpatient sub-groups. Repeat blood cultures, drawn on day 3, were positive for 8/47 (17%) patients after monotherapy, versus 2/51 (4%) after combination therapy (p = 0·045). No severe complications or fatalities occurred in any of the groups.

The advantage of this trial is that it includes patients with multidrug resistant typhoid similar to our setting. The trial is not randomized, the doses of azithromycin used were low and after 48 hours of therapy the inpatient group was discharged on oral antibiotics, the details of which are not provided.

JOURNAL REVIEW

## Acute Encephalitis Syndrome in Gorakhpur, Uttar Pradesh, 2016: Clinical and Laboratory Findings

Pediatr Infect Dis J. 2018 May 9
Contributed by Dr R Surendran

This is an etiological study of 407 cases of Acute Encephalitis Syndrome (AES) admitted during August – October 2016 in BRD Medical College (BRDMC) – a tertiary care hospital in Gorakhpur, Uttar Pradesh.

Inclusion: AES + CSF pleocytosis (>5cells/ccm) were included. Out of 1037 patients who had AES with CSF pleocytosis, 407 cases were selected randomly and their blood and CSF samples were subjected for etiological analysis. Sera were tested for presence of Scrub typhus IgM antibodies (ST), Japanese Encephalitis Virus (JEV) and dengue. CSF was tested for presence of IgM antibodies against JE and OT. Genomic DNA from whole blood and CSF are extracted and PCR for ST and SFGR (Spotted Fever Group of Rickettsia) were done.

Of the 407 AES patients, 266 (65.4%), 42 (10.3%) and 29 (7.5%) were diagnosed to have ST, JEV and dengue respectively. Four patients were diagnosed to have SFGR infection. A significantly higher proportion of scrub typhus patients with AES had hepatomegaly, splenomegaly, and facial edema. The common hematological and biochemical abnormalities among ST positive patients include thrombocytopenia raised liver enzymes and bilirubin levels.

The case fatality ratio was significantly higher among ST negative AES patients (36.2% vs 15.2%, $p<0.05$). Azithromycin was given to 96% of patients.

About two thirds of patients presented more like an AFI later complicated with AES – they had longer history of illness, rash, thrombocytopenia and elevated liver enzymes; their scrub tyhus serology was positive and PCR was positive in a minority of people. They also had a better prognosis. Brain biopsy and serology also showed evidence of Rickettsial spotted fevers being present as well.

A significant minority of patients had more than one etiological diagnosis and no patient had an eschar, which suggests overdiagnosis of scrub typhus. Still, empiric therapy for scrub typhus in patients with encephalitis appears reasonable till the diagnosis is excluded.

JOURNAL REVIEW

## Effects of Rifampin and Doxycycline Treatments in Patients with Uncomplicated Scrub Typhus: An Open-Label, Randomized, Controlled Trial

Clin Infect Dis. 2018 Aug 1;67(4):600-605
Contributed by Dr R Surendran

While doxycycline is the drug of choice in the treatment of scrub typhus, research for effective alternative agents are required. In this open-label randomised control trial, the authors compared doxycycline 100 mg twice daily for 5 days (121 cases) and rifampin 600 mg once daily for 5 days (119 cases) for scrub typhus patients (total 240 cases) admitted to Hospitals in the Republic of Korea between 2007 and 2009. Confirmed scrub typhus was defined as Scrub typhus IgM positivity or PCR positivity from the buffy coat or eschar. Severe scrub typhus was not included in the study. Only two third of the patients included had lab confirmed scrub typhus. The primary outcome – fever defervescence was same in both the groups. There was no significant difference in the occurrence of side effects following drug administration between groups.

This trial suggests that rifampin could be used as an alternative agent in the treatment of non severe scrub typhus, especially among children, pregnant women and those with contra-indications to doxycycline.

JOURNAL REVIEW

# MERINO trial – Piperacillin-tazobactam vs meropenem for ceftriaxone resistant GNB bacteremia

JAMA. 2018 Sep 11;320(10):984-994
Contributed by Dr Abi Manesh, Dr Sowmya Sridharan

The much awaited MERINO trial is finally published.

This is a pragmatic RCT which studied whether piperacillin-tazobactam was non inferior to meropenem as definitive therapy among patients with ceftriaxone resistant (and mostly pip-taz susceptible) Ecoli or Klebsiella bacteremia. The primary outcome was 30 day mortality.

This study was conducted in 9 centres (mainly Singapore and Australia, no Indian centres were included) Patients were randomised at 72 hrs when the susceptibilities were available from the microbiology lab. The non inferiority margin used was 5% Patients received the therapy between 4 and 14 days - the treating physician decided the duration of therapy.

Points to note:

- Piptaz group had more immune compromised patients (27.1 vs 20.9%).
- At resolution almost 40% of patients in both arms had no fever, elevated TC or positive blood cultures.
- The trial was terminated early as per DSMB's suggestion (391 recruited, sample size calculated was 454).
- Since the trial evaluated the role of piptaz as definitive therapy,
- all patients received varied therapies before randomisation.

A total of 23 of 187 patients (12.3%) randomized to piperacillin-tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6%). The number needed to harm was 11.6. The effect was consistent across subgroup analyses.

Now, why did pip-taz fail? Likely the reason is due to complex resistance mechanisms exhibited by the isolates. On WGS, 67.6 % showed OXA 1 narrow spectrum oxacillinases in addition to ESBLs and ampCs. These are of course are not inactivated by tazobactam. The duration of infusion could be another reason but the investigators used a high dose. Inoculum effect is unlikely to be operational here as most of the patients were not septic at recruitment and had already received appropriate therapy.

Overall, piperacillin-tazobactam did not meet non inferiority to meropenem in patients with ESBL gram negative bacteremia and hence should be avoided in this setting!

JOURNAL REVIEW

# Improvement of Mycobacterium tuberculosis detection by X pert MTB/RIF Ultra: A head-to head comparison on X pert-negative samples

PLoS One. 2018 Aug 13;13(8):e0201934
Contributed by Dr Kalpesh Sukhwani

This is a retrospective single center study (Italy) where authors DE-identified frozen samples collected over a 4-year period, which had previously resulted smear-negative, Xpert-negative but MTB culture-positive and analyzed with X pert Ultra to assess increase in sensitivity of MTB detection.

During the study period 382 MTB culture-positive samples were archived: 314 resulted X pert-positive and 68 X pert-negative. Thirty-one of the 68 X pert-negative samples resulted positive with Ultra, with an overall improvement in MTB detection of 45.6%.

Out of 36 X pert negative respiratory samples, 18 resulted Ultra-positive with the following semi-quantitative loads: “low”(n = 1), “very low”(n = 11), “trace”(n = 6), with an improvement in MTB detection of 50%. The best performance was achieved on BAL specimens (53.8%).

Out of 32 X pert-negative non-respiratory samples, 13 resulted Ultra-positive with the following semi-quantitative loads: “very low”(n = 7), “trace”(n = 6), with an improvement in MTB detection of 40.6%. The best performance was achieved on biopsies (55.6%) and lymph nodes (50%). Category “trace” detected 12 out of the 31 Ultra-positive MTB samples; in the remaining 19 samples RIF susceptibility was determined with 100% concordance with the phenotypic susceptibility test.

This study further confirms the better performance of Ultra compared to the previous version in both respiratory and non-respiratory smear-negative samples, with an overall improvement of 45.6%

**Table 1. Mean “time to positivity” and Ultra results of 68 Xpert-negative culture-positive samples according to type of specimen and semi-quantitative load.**

| Mean TTP[#] days ±sd | Ultra results | TOTAL n = 68 | RESPIRATORY n = 36 | | NON-RESPIRATORY n = 32 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | BAL[*] n = 26 | Sputum n = 10 | Lymphnode n = 10 | Biopsy n = 9 | Cavitary fluid n = 8 | Gastric aspirate n = 2 | Urine n = 3 |
| **16.4 ± 3.4** | **Positive** | **31** | **14** | **4** | **5** | **5** | **2** | **1** | **0** |
| 17.5 | Low | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 15.8 ± 3.2 | Very low | 18 | 10 | 1 | 3 | 2 | 1 | 1 | 0 |
| 17.0 ± 3.7 | Trace | 12 | 4 | 2 | 2 | 3 | 1 | 0 | 0 |
| **24.1 ± 9.1** | **Negative** | **37** | **12** | **6** | **5** | **4** | **6** | **1** | **3** |

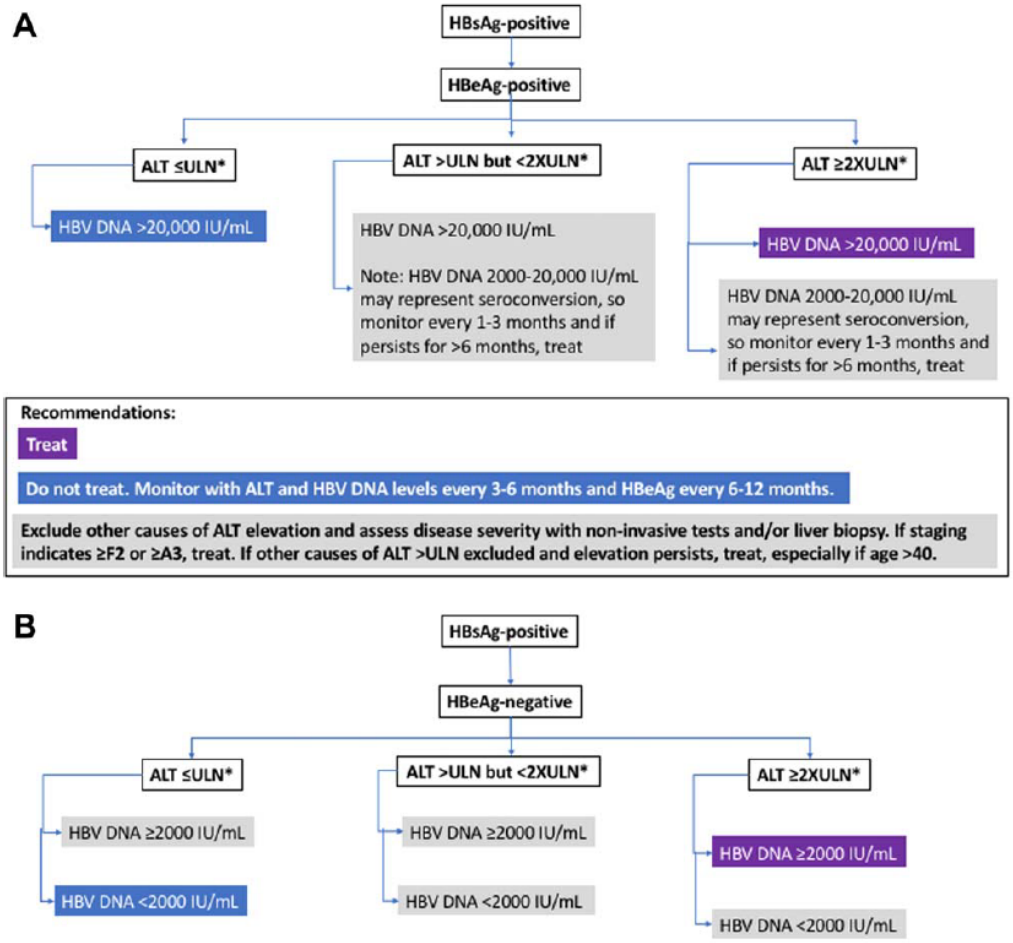
[#]Time to positivity: number of days from time of MGIT inoculation to the positive culture result

[*] Bronchoalveolar lavage

## Guideline watch

### Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance

*Courtesy: Dr R Surendran*




# Upcoming conferences

42nd Annual Conference for Indian Association of Medical Microbiologists (28 Nov – 2 Dec 2018) at NIMHANS Convention Centre, Bengaluru. Details at www.microcon2018.com

## Answer to the photoquiz

Pleural fluid gram stain showed Gpc in pairs. It was inoculated directly into a blood culture bottle which flagged positive on day 2 and culture grew Strep pneumoniae (Figure 3). AFB culture showed no growth at 2 weeks.

Fig 3

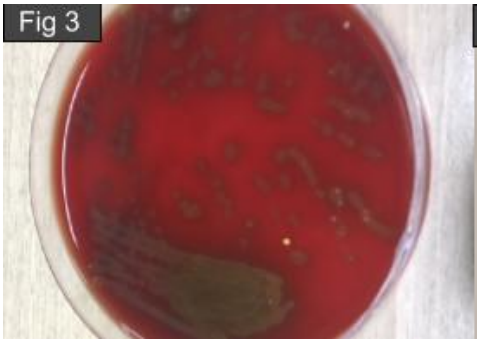


Fig 4

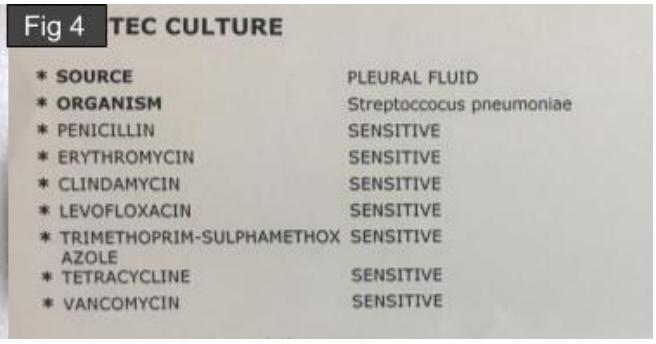



*Figure 3* Small grey moist colonies with alpha hemolysis on blood agar (courtesy Dr Rupali Suryawanshi and Dr Nita Munshi ) *Figure 4* Antibiotic susceptibility testing

His ATT was discontinued and ceftriaxone 2 g iv OD added along with TDF/FTC/EFV. He required right thoracotomy and drainage in view of multiple septations and multiloculated empyema but in view of cost constraints, this was not done. At 2 weeks follow up patient was clinically better with good weight gain, no fever.

The prevalence of invasive pneumococcal disease is very high in patients with HIV, and pneumococcal infection should be considered and covered for in the appropriate clinical scenario. HIV patients should be routinely offered influenza and pneumococcal vaccination.

**Final diagnosis**: Pneumococcal empyema in a newly diagnosed PLHIV

*Case provided by: Dr Kalpesh Sukhwani*