Clinical Infectious Diseases Society

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From the Secretary's desk

This is the season for academic activities, and plenty of them are going around. Many of these are closely allied with our core interests and should represent future opportunities for collaboration.

The Hospital Infection Control Conference in Hyderabad was held in the first week of October. The effort of the organizing team headed by Dr Ranganathan Iyer deserves mention. The focus on problems specific to India, like control measures against multi drug resistant gram negative infections, are topics of interest to our members as well. This should be a focus area of development for the society, and the relevant subcommittee should explore ways to collaborate in such areas.

The other conference was the Indian Society of Organ Transplant, also in Hyderabad. Given the clash of dates with ID week, the effort was primarily with the use of our faculty available in India. Dr Suneetha Narreddy's efforts were appreciated immensely; the full hall and need for more chairs is reflection of the high quality of the program. The presence of nephrologists in the audience is an encouraging sign, and something the TID subcommittee plans to work on. This effort was ably supported by many of our members- Dr Rajiv Karthik, Dr Kirti Sabnis and Dr Vishnu Rao. As noted earlier, next year's program is expected to be at a much larger scale.

On the home front, there are continuous changes in the CIDS website, and the input of members is sought to improve it. The slides from our annual conference should make it to the website in time. The efforts of Dr Ram Gopalakrishnan and the team to improve content deserves our appreciation and support.

There have been enquiries about joining of subcommittees, and members are advised to contact the relevant Chair directly. Applications for other activities like city chapters will start soon, and members are requested to review the rules in this regard on the website.

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/M with diabetes, hypertension, hypothyroidism, coronary artery disease and left ventricular (LV) dysfunction underwent dual chamber pacemaker implantation in 2008. He underwent pacemaker re- implantation elsewhere in 2011. In August 2012, he developed gradual onset of fever not responding to antibiotics. During the workup for pyrexia of unknown origin, transthoracic echocardiography (TTE) revealed vegetations around the leads. Positive blood culture is shown in Figure 1.

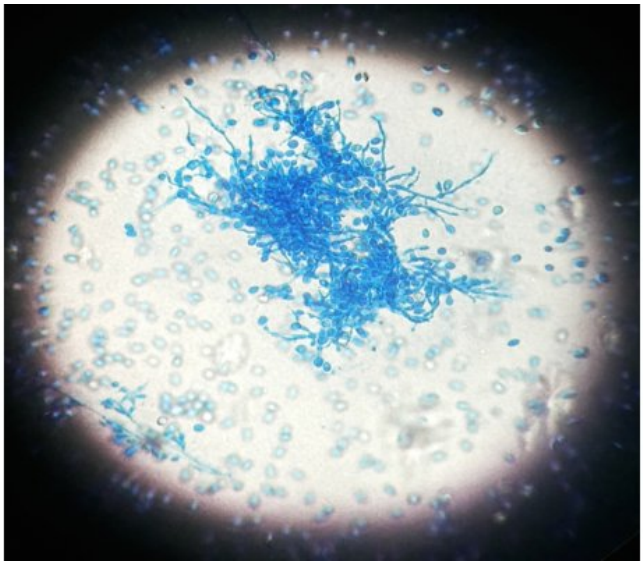


Figure 1: LPCB mount of the positive blood culture of the patient with infective endocarditis

What is your diagnosis?

ID NEWS

Health ministry confirms 22 Zika cases in Rajasthan on October 11, 2018

Contributed by Dr Ashwini Tayade, Dr Veeren Ganta

The Union Ministry of Health and Family Welfare confirmed 22 positive laboratory confirmed cases of Zika virus in Rajasthan's capital Jaipur. It was detected through Indian Council of Medical Research (ICMR) surveillance system and all suspected cases in the defined area and mosquito samples are being tested.

The Health Ministry has taken precautionary measures followed by daily monitoring. It has activated a control room at National Centre for Disease Control (NCDC) to undertake regular monitoring of the situation. Moreover a 7-member Central team also has been deputed to Jaipur following detection of the first case State government also has been supplied with IEC material prepared to create awareness about Zika virus disease and its prevention strategies. Besides extensive surveillance and vector control measures are also being undertaken in the area as per protocol by the state government.

The first outbreak of Zika Virus was reported in Ahmedabad, Gujarat in January/February 2017 and second outbreak in July 2017 from Krishnagiri District in Tamilnadu. Both these outbreaks were successfully contained through intensive surveillance and vector management. Even though Zika has been in Asia for several years, outbreaks here were small and saw no microcephaly.

The Zika virus behind the ongoing outbreak in Rajasthan is closely related to the virus that caused the Brazilian outbreak, according to Balram Bhargava, Director General of the Indian Council of Medical Research (ICMR). Dr. Bhargava said that the National Institute of Virology (NIV) had fully sequenced the Rajasthan virus' genome, and this is the first time a Brazilian-like strain has been detected in India. Before this, a strain from a patient in Gujarat, sequenced partially by the NIV, was found to be close to a Malaysian Zika strain, isolated in 1966.

The Rajasthan outbreak is different from the Gujarat cases in several important ways.

Firstly, this is the largest in India, having affected more than 100 people at last count. Before this, only 4 Zika cases were detected by the NIV in 2016-17, despite widespread surveillance. These included 3 cases in Gujarat and 1 in Tamil Nadu. *Secondly*, in Gujarat and Tamil Nadu, the virus did not seem to be moving efficiently from person to person, via mosquitoes. Though researchers tested several people apart from the confirmed cases then, they were unable to find other infections, said Arunkumar Govindakarnavar, who heads Karnataka's Manipal Centre for Virus Research. One of the factors behind the improved transmission was a mutation called A188V in the viral genome, according to a 2017 Nature study. This mutation is not present in the Rajasthan strain. The NIV found another mutation called S139N in the Rajasthan strain, however. In a 2017 study published in Science, Chinese researchers linked this mutation to microcephaly. *Thirdly*, even though the ICMR has screened 50,000 mosquitoes at 8 sites across India since 2016, it did not detect the virus in mosquitoes until the Rajasthan outbreak, Dr. Bhargava said.

Patients status of current Zika outbreak : Though the virus is spreading quickly, most Zika cases have been mild, with 60 out of 72 patients healthy after treatment. There have been no deaths.

Mosquito bednets, window screens and permethrin repellent to skin have become suddenly more relevant to pregnant Indian women!

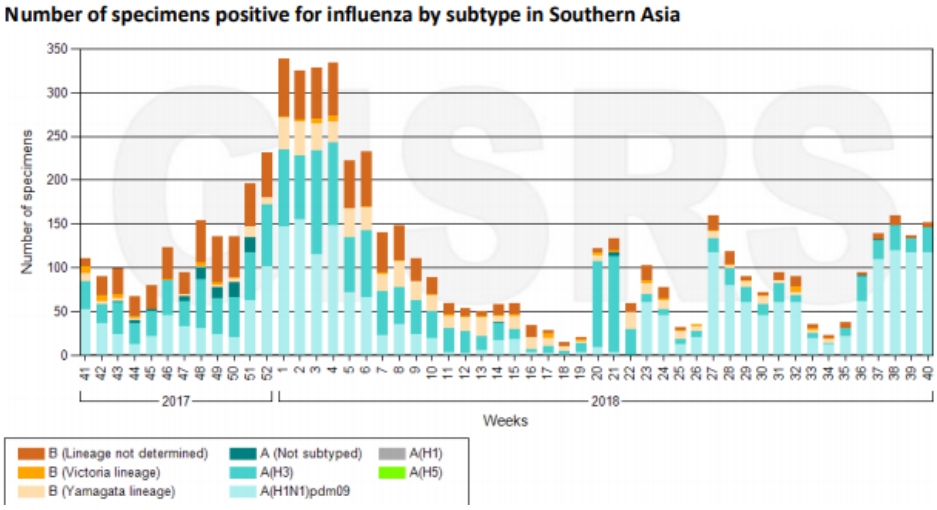
ID NEWS

H1N1 Update

As many as 95 cases of swine flu [Influenza A/H1N1] have been reported from Delhi. The figure accounts for cases reported until 30 Sep 2018, said the latest Integrated Disease Surveillance Programme (IDSP), a report by the Health Ministry. The report shows 2835 cases and 16 deaths due to H1N1 fever in 2017 in Delhi as compared to only 193 cases and 7 deaths in 2016.

In Rajasthan, till 18 Sep 2018, there were 148 deaths reported along with 1491 swine flu cases but, on 5 Oct 2018, the deaths increased to 180, and cases of swine flu further increased to 1776 cases [from 1 Jan 2018]. Other states wth similar outbreaks include Maharshtra, Gujarat, Madhya Pradesh.

In Southern Asia, influenza activity remained low across reporting countries with the exception of India where detections of influenza A(H1N1)pdm09 virus continued to increase.



Hope all CIDS members have taken their annual flu shots!

ID NEWS

Leptospirosis outbreak Kerala post-flood

A total of 1711 cases with 70 deaths due to leptospirosis have been reported from Kerala. The DHS issued an alert on outbreak on August 28. “There is a sudden increase of Leptospirosis from Thrissur, Palakkad, Kozhikode, Malappuram and Kannur districts. All of them had indirect contact with flood water” the statement from the additional director for public health said. The highest number of cases were reported from Kozhikode district of Kerala, where the flood had hit badly.

Mass chemoprophylaxis after floods is not recommended by WHO. A Cochrane review published in 2009 examined the broader question of the use of prophylaxis and found inadequate evidence to support its use.

ID NEWS

Anthrax, Andhra Pradesh

A total of 7 villagers of Kodandarama Puram in Karveti Nagaram mandal, were diagnosed with having anthrax (Bacillus anthracis infection) at the government hospital at Puttur on Fri 26 Oct 2018. A 50-year-old person, who slipped into coma following infection of the digestive tract, was shifted to SVRR Hospital in Tirupati, where his condition is serious.

Personnel of the Animal Husbandry Department confirmed that 18 cows and buffaloes and 6 sheep had died during the last fortnight. It all started when a group of youth had skinned the carcass of 2 cows found dead in the fields in the village a fortnight ago and shared the meat among their families, the officials said. They further said that 18 head of cattle had died between [10 and 26 Oct 2018], and the villagers consumed the meat of the dead animals.

It's a good idea not to eat dead animal meat!

JOURNAL REVIEW

TB vaccines – light at the end of the tunnel?

N Engl J Med. 2018 Jul 12;379(2):138-149
Contributed by Dr Abi Manesh, Dr Rohan Vashisht

There is a need for better and effective TB vaccines –the effect of BCG vaccination especially among people who live in TB endemic areas is not clear! There are two studies in NEJM recently reported on this.

The first study tested a subunit vaccine H4:IC31 against repeat BCG vaccination or placebo among adolescents in South Africa. They did not include patients with latent TB infection or HIV infection. The authors assumed that sustained QFT conversion is associated with likely progression to symptomatic disease. Primary outcome was QFT positivity at day 84 along with the safety of the vaccine. The vaccines in the study arm (both the subunit and BCG vaccine did not have impressive effect in the outcome. BCG vaccine reduced the rate of sustained QFT conversion, with an efficacy of 45.4% (P=0.03); the efficacy of the H4:IC31 vaccine was 30.5% (P=0.16). There were no clinically significant between-group differences in the rates of serious adverse events, although mild-to-moderate injection-site reactions were more common with BCG re-vaccination.This study outcome is not optimal as sustained QFT positivity is not an equivalent of TB disease progression risk or active tuberculosis. In essence the study attempts to record the effect of the vaccine to protect against tuberculosis among people who are tested negative for latent TB infection.

Second Study: N Engl J Med. 2018 Oct 25;379(17):1621-1634

The other study is very interesting. It studied again patients from Africa and most of the patients had latent tuberculosis. The primary outcome was impressive - active confirmed pulmonary tuberculosis. The vaccine had mycobacterium antigens along with the AS01 adjuvant system used in the recoinant zoster and malaria vaccine trials before. A total of 10 cases of active pulmonary tuberculosis in the vaccine group and 22 cases in the placebo group met the primary case definition after a mean follow-up of 2.3±0.4 years. This vaccine has the potential as a true game changer in the control of tuberculosis if it works well in the real world scenario.

JOURNAL REVIEW

Does mopping up endotoxins result in better outcomes in patients with sepsis?

JAMA. 2018 Oct 9;320(14):1455-1463
Contributed by Dr Abi Manesh, Dr Veeren Ganta

The EUPHRATES Trial got published a few days ago.

Premise of the study:
Polymyxin B is a cationic polypeptide antibiotic which can bind to endotoxin. Parenteral administration of PMX, however, is associated with side-effects. Immobilizing polymyxin to polystyrene-derived fibers in a cartridge integrated in a hemoperfusion device therefore represents a method that permits adequate PMX therapy while avoiding systemic toxicity. It basically involves a dialyser like device which has microfibers with projections embedded with polymyxinB through which the blood is circulated. Patients include septic individuals on ionotropes with atleast one major organ dysfunction from 55 ICUs of USA and Canada + a documented endotoxin level of > 0.6.Patients were sort of equally divided between bacteremia, lung and abdominal source of infection and a significant majority had renal injury. This RCT included a sham treatment arm as well.

The primary outcome was 15% reduction in 28 day mortality with 80% power – which the study failed to show(treatment group, 84 of 223 [37.7%] vs sham group 78 of 226 [34.5%]; risk difference [RD], 3.2%; 95% CI, −5.7% to 12.0%; relative risk [RR], 1.09; 95% CI, 0.85-1.39; P = .49) or in the population with a MODS of more than 9 (treatment group, 65 of 146 [44.5%] vs sham, 65 of 148 [43.9%]; RD, 0.6%; 95% CI, −10.8% to 11.9%; RR, 1.01; 95% CI, 0.78-1.31; P = .92). Overall, 264 serious adverse events were reported (65.1% treatment group vs 57.3% sham group).

One more RCT (EUPHAS trial) and some retrospective data had favoured the intervention strongly – the RCT had primary outcome of improved mean arterial pressures and other hemodynamic parameters, some flimsy and many not of clinical relevance. This highlights the misleading nature of retrospective and RCTs without strong clinically sound outcomes.

Once again this trial highlights the failure of therapies which target part of the sepsis puzzle. In a similar way, recombinant human activated protein C or dotrecogin alfa also failed.

JOURNAL REVIEW

Should you use Gentamicin impregnated beads – probably not!

J Antimicrob Chemother. 2018 Sep 5
Contributed by Dr Abi Manesh

Gentamicin or other antibiotic impregnated beads inside joint spaces is a commonly used practice in the management of prosthetic joint infections. While based on anecdotal evidence, it makes intuitive sense as it enables the antibiotic to achieve high concentrations at the target site. These Dutch investigators studied the efficacy of this practice in the setting of acute peri-prosthetic joint infection managed with Debridement, antibiotics and Implant retention (DAIR). This retrospective study evaluated whether deployment of Gentamicin beads during DAIR protected patients from prosthetic infection related death, implant removal, second DAIR or suppressive antibiotics for persistent implant infection. Interestingly the authors noted that the primary outcome was more in the group with gentamicin sponges (43% vs 24%, p = 0.001). The association lost statistical significance when a propensity matched scoring was performed – though the numbers were clearly higher in the gentamicin group. After propensity matching, early failure was 40.3% in the gentamicin group versus 26.0% in the control group (P - 0.06).The use of gentamicin beads again predicted the primary outcome in the multivariate analyses (OR 1.97, 95% CI1.12–3.48).

These results should question this practice as part of routine care.

JOURNAL REVIEW

Ceftazidime-Avibactam works well for OXA-48!

J Antimicrob Chemother. 2018 Nov 1;73(11):3170-3175
Contributed by Dr Abi Manesh

We know that different enzymes mediate carbapenem resistance among enterobacteriaceae in various regions of the world. In the US and some parts of Europe it is KPC for which CeftazAvi works well. If you consider India, OXA 48 and OXA with NDM are the most likely enzymes involved. Since NDMs do not inhibit monobactams, CeftazAvi+ Aztreonam could be good option in our setting. There is also clinical data to support the use of CeftazAvi for OXA 48 infections.

In this prospective study evaluating 57 patients with CRE infections mediated by OXA 48, Ceftazidime-avibactam was used as a monotherapy in most of the patients (81%). Almost half the patients had severe infection (defined as presence of sepsis or septic shock). The most frequent sources of infection were intra-abdominal (28%), followed by respiratory (26%) and urinary (25%). Mortality at 14 days was 14%. In multivariate analysis, the only mortality risk factor was INCREMENT-CPE score >7 (HR 11.7, 95% CI 4.2–20.6).

This real time data provides further confidence to use this agent in infections due to OXA 48 CRE.

JOURNAL REVIEW

The Significance of Prolonged and Saddleback Fever in Hospitalised Adult Dengue

PLoS One. 2016 Dec 9;11(12):e0167025
Contributed by Dr Kalpesh Sukhwani

Often we see that fever in dengue lasts more than the oft quoted 1 week. This is a retrospective cohort study from Singapore examining the prevalence of prolonged and saddle back fever in dengue as well as their associations with dengue severity.

A total of 2843 PCR confirmed dengue patients admitted from 2004 to 2008 were included in this study. Prolonged fever (fever >7 days duration) was present in 572 (20.1%) of patients. Dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and severe dengue (SD) were significantly (p-value-<0.01) more likely to occur in patients with prolonged fever. Saddle back fever was present in 165 (5.8%). Although DHF and SD were more likely to occur in patients in those with saddle back fever, DSS was not. Compared with prolonged fever, saddle back fever did not show many significant associations.

Table 3. Outcomes and complications occurring in hospitalized adult dengue patients.

	Control (n = 2106)	Prolonged fever (n = 572)	p-value[#]	Saddleback fever (n = 165)	p-value[#]
Dengue with warning signs (2009)	1314(62.4)	433(75.7)	<0.01	117(70.9)	0.03
Dengue hemorrhagic fever	385(18.3)	147(25.7)	<0.01	44(26.7)	0.01
Dengue shock syndrome	65(3.1)	31(5.4)	<0.01	9(5.5)	0.1
Severe dengue	219(10.4)	104(18.2)	<0.01	29(17.6)	<0.01
Severe plasma leakage	63(3)	29(5.1)	0.020	15(9.1)	<0.01
Severe bleeding	130(6.2)	53(9.3)	0.010	13(7.9)	0.4
Severe organ involvement	49(2.3)	38(6.6)	<0.01	5(3)	0.6
Nosocomial infections	(0)				
Urinary tract infection	2(0.1)	7(1.2)	<0.01	2(1.2)	0.04
Pneumonia	7(0.3)	8(1.4)	0.01	1(0.6)	0.49
Clostridium difficile	0(0)	0(0)	NA	0(0)	NA
Bacteremia	1(0)	6(1)	<0.01	0(0)	NA
Intensive care unit admission	9(0.4)	2(0.3)	0.570	2(1.2)	0.19
Length of stay (days)	5(3–7)	6(4–9)	<0.01	6(4–8)	<0.01
Death	1(0)	0(0)	NA	1(0.6)	NA

This study demonstrates that prolonged fever may be associated with various warning signs and more severe forms of dengue (SD, DSS, DHF) and should therefore prompt detailed evaluation for complications of dengue.

JOURNAL REVIEW

Sustained undetectable equals untransmissable!

AIDS. 2018 Sep 24;32(15):2151-2159
Contributed by Dr Abi Manesh

One of the important advancements in HIV care is the prominent role of ART in reducing disease transmission. If the viral load is less than 200 copies/ml, then the transmissibility of the infection is zero. This data is from at least four large trials, thousands of patients and thousands of acts of sex without condoms or PrEP. However, most bodies would suggest that this statement would hold true where the viral load has remained suppressed for at least six months. Why should we wait for six months? Is it because the virus particles have a slower disappearance from various tissues compared to the blood?

This longitudinal study of twelve patients started on DTG based ART with serial monitoring of viral loads and DTG levels in the blood and rectal tissue. All attained plasma virologic suppression by week 6. 11 of 12 (91.7%) had detectable rectal tissue HIV RNA at baseline, and only three of 11 (27.3%) achieved rectal tissue virologic suppression at any time-point.

Hence a sustained blood viral load suppression is needed to ensure clearance at the various mucosal surfaces as well. The six month rule remains valid.

Chandra's Corner

Dr P H Chandrasekhar

"Youth is wasted on the young"
- Bernard Shaw

A landmark: fifty years since I joined the Christian Medical College, Vellore. To celebrate, reunite, reminisce, grateful to be alive and intact, I returned home to Vellore in August. The thought of encountering my "old" classmates, after forty plus years, ignited joy mixed with anxiety and trepidation. I was not sure what to expect. Happily, the entire event was memorable; everyone had a friendly smile, caught up on stories, but just not enough time. It was striking to realize people were just the same-growing old simply does not alter people. Almost everyone's behavior was the way I remembered and was quite predictable; that was somewhat disappointing. Our batch had chosen an apt song for the entertainment portion of the evening. I liked it, so would like to share a part of the lyrics. This should strike a chord in at least a few of you as it surely did in me.

Enjoy yourself, it's later than you think
Enjoy yourself, while you're still in the pink
The years go by, as quickly as a wink
Enjoy yourself, enjoy yourself, it's later than you think
You're gonna take that ocean trip, no matter, come what may
You've got your reservations made, but you just can't get away
Next year for sure, you'll see the world, you'll really get around
But how far can you travel when you're six feet underground?
You work and work for years and years, you're always on the go
You never take a minute off, too busy makin' dough
Someday, you say, you'll have your fun, when you're a millionaire
Imagine all the fun you'll have in your old rockin' chair
Enjoy yourself, it's later than you think
Enjoy yourself, while you're still in the pink
The years go by, as quickly as a wink
Enjoy yourself, enjoy yourself, it's later than you think

From Vellore, after a brief stop in Chennai, I went to Hyderabad to attend the Annual Transplant Infectious Diseases Meeting. The audience size was modest, the content however was good. One of the case management sessions left a 'teaching message' in me. A renal transplant recipient with fever, acute breathlessness and pulmonary infiltrates was admitted to the intensive care unit. During the management discussion, a discussant (a non-ID physician) proceeded to give rationale for combined empiric therapy against tuberculosis, MDR Gram-negative pneumonia and pneumocystosis, totaling about ten drugs including corticosteroids. Not surprisingly, "just in case" was the argument presented for the steroid-inflated regimen. It is true that empiric therapy often is lifesaving, particularly in the intensive care unit, but the pragmatic ID physician, in such cases, prioritizes, uses clinical judgment, provides careful stewardship and prescribes drugs with sound rationale. This ingredient of clinical judgment is that which distinguishes the ID specialist from others. The discussion we had around the case highlighted the desperate need for good, clinical ID physicians in India. Appropriate use of antibiotics is crucial such that their precious lifespan may be prolonged. This point came across loud and clear during the case discussion, leaving me somewhat relieved with a broad smile on my face.

A few weeks ago, I saw a HIV-infected, non-adherent patient with swelling and a deep tender ulcer of his lower lip, along with impressive, painful enlargement of lymph nodes ('bubo") over his left neck. HSV was ruled out; persistent exam/testing ultimately confirmed a diagnosis of Lymphogranuloma venereum (LGV). PCR from the lip ulcer was positive for LGV, and his throat swab revealed for chlamydia. Therapy with doxycycline led to dramatic improvement. LGV orolabialis with cervical lymphadenitis was a new one for me; literature search revealed nothing. As sexual mores change, newer/unusual clinical presentations become the norm. Keep up with the times, lest you'll be left behind, as text books are re-written!

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

Infectious Diseases CME for Postgraduates (20 – 22 December, 2018) at Wheeler Hall, CMC Vellore. Last date to apply – 15th December 2018

Answer to the photoquiz

The patient underwent emergency surgery with removal of pacemaker and the leads. Microbiological cultures of the vegetation grew Scedosporium prolificans.

He was treated with L-AmB and voriconazole by the CTVS team and discharged in stable condition. Two months later, in November 2012, he presented with complaints of syncope. Investigation revealed a vegetation on the tricuspid leaflet. He underwent excision of the vegetation and tricuspid valve replacement (TVR). Blood cultures and valve cultures grew S.prolificans. Post surgery, he was continued on voriconazole and terbinafine. In May 2013, he underwent a repeat PPI and in October 2013 (one year post first TVR), again presented with complaints of syncope while still on voriconazole and terbinafine. TTE revealed TV IE. A redo TVR with removal of 2 out of 3 leads of the pacemaker was done. Blood cultures grew S. prolificans and DST revealed an AmB resistant and voriconazole sensitive isolate. He was initiated on caspofungin, voriconazole and terbinafine. In March 2014, he presented with a 4th episode of S. prolificans IE of TV and underwent 3rd TVR along with voriconazole, caspofungin and terbinafine. However, a month later, there was recurrence of the vegetation on the TV along with pulmonary embolic episode. Surgical intervention was not possible this time and despite aggressive antifungal therapy, the patient eventually succumbed to the fungal sepsis.

- The most common presentations of Scedosporium infections are pulmonary and bone and soft tissue infections in immunocompetent hosts.
- Disseminated infections are more common and often more complicated in immunocompromised patients with hematological malignancies or those on immunosuppressive treatment regimens.
- S. prolificans endocarditis is rare with high mortality. Risk factors for endocarditis including IV drug use, pacemaker implantation and porcine bio- prosthetic valves.
- Diagnosis is established by microbiological cultures (Blood cultures and vegetation/valve cultures)
- No standard therapy for S. prolificans based on clinical evidence has been established.
- Combination of surgery with medical management appears to have best chances of cure.
- Combination antifungal drug therapy has been successful in several cases. In vitro, the combinations of itraconazole + terbinafine, voriconazole + terbinafine, ravuconazole + caspofungin and voriconazole + miltefosine have synergic effects.
- Effective infection control measures during interventional cardiac procedures is most imperative for prevention of such life threatening infections.

Final diagnosis: Scedosporium prolificans pacemaker infection with tricuspid valve endocarditis

Case provided by: Dr Prerna Khurana (ID Fellow), Dr Smita Sarma, Dr Prasad Rao Voleti, Dr Anil Bhan, Dr Usha Baveja, ***Dr Neha Gupta***