The HKSID Newsletter

October 2019

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Message from the President

It has been a while since the second HKSID newsletter was published. Your patience will be awarded by the interesting content of our present issue. First and foremost, there is an article on influenza related invasive aspergillosis. Bacterial superinfection is a well known phenomenon associated with influenza. However, invasive aspergillosis is much less well known but has been increasingly reported in literature among severe influenza patients without immunosuppression or underlying disease. All doctors caring for severely ill patients with influenza should be alert to this diagnostic possibility as specific diagnostic tests are needed to confirm the diagnosis. More, this issue also features a picture test of another uncommon but important fungal infection. Finally, we are glad to sponsor one of our members to the European Congress on Clinical Microbiology and Infectious Diseases 2019 and a report on the Congress was prepared for sharing. Last but not least, I wish to convey my sincere appreciation to the editorial board and contributors for their excellent work. I wish you enjoy reading our Newsletter and find it useful!

Dr Wong Tin Yau, Andrew

President, Hong Kong Society for Infectious Diseases

Society News and Announcement

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The Council of The HKSID 2018-2020

Back row left to right: Dr. Zee Sze-tsing Jonpaul, Dr. Wong Chun-kwan Bonnie, Dr. Wilson Lam, Dr. Wu Ka-lun Alan, Dr. Tso Yuk Keung Eugene, Dr. Tang Hing-cheung Tommy, Dr. Sin Wing-yin Winnie, Dr. Lung kwok-cheung

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Update your email address and personal particulars

HKSID regularly send out emails about important events and other useful information to our members. Having an updated member database will help us understand better your needs and plan our future direction.

Please update us your personal particulars by sending an email to secretary@hksid.org and provide the followings:

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Meeting highlights

The Hong Kong Society For Infectious Diseases 23rd Annual Scientific Meeting, co-organized by Hong Kong Society of Transplantation and HKSID was held at Hyatt Regency Hotel on 16th March 2019. There were over 180 participants with the majority being practicing doctors. Three lectures were delivered by local and overseas experts.

Prof. Monica Slavin, Department of Medicine, The University of Melbourne, Australia, presented a lecture entitled **"Update on Transplant Infection Management"** Recent advances in the management of CMV infection and invasive fungal infection were addressed. Newer agents for treating drug-resistant infection and the use of CMV quantiferon to guide prophylactic therapy were discussed. Apart from antimicrobial treatment, strong stewardship response as well as rapid diagnostic tests are needed to direct therapy in this group of patient. Manipulating microbiome and host immune response are the new frontiers for study in this vulnerable group to prevent and treat infection

Photo taken during Q&A of the final symposium
Left to right: Dr. William Lee, Dr. Bonnie Wong (chairperson of the session), Dr. Desmond Yap

Prof. Chin-hong Peter, Professor of Medicine and Director, Transplant and Immunocompromised Host Infectious Disease Program, University of California San Francisco, USA, delivered a lecture entitled **"Donor Derived Infections - What's the Risk and How to Prevent?** ". Prof. Chin-hong Peter shared with the audience his extensive experience in dealing with donor derived infection both in USA and South East Asia. The importance of environmental and hospital exposure, the type of prophylaxis and infective screen were illustrated with real outbreak cases. Creating policy that mandates a robust reporting system to communicate possible donor derived infection can decrease transmission risk in these vulnerable patients.

Dr. Wong tin-yau (right), president of the HKSID presenting a souvenir to Prof. Chin-hong Peter (left)

The final symposium **"Viral Hepatitis Infection in Kidney Transplant Recipients"** was delivered by Dr. Desmond Yap, Clinical Associate Professor, Department of Medicine, The University of Hong Kong. Advantage and disadvantage of different neucleotide/side analogues in management of chronic HBV in kidney transplant patient were discussed. The availability of direct acting agents has improved the outcome of HCV infection, however more data are required to demonstrate their effectiveness in kidney transplant patient. Recent local cases of chronic HEV infection in transplant patients were also addressed.

Three challenging ID cases were presented by Dr. Tracy Ho from Prince of Wales Hospital, Dr. Siu-tim Ng from Alice Ho Miu Ling Nethersole Hospital and Dr. Abram Chan from Pamela Youde Nethersole Eastern Hospital. The Panelist were Prof. Chin-hong Peter, Dr. Rocky Shum and Dr. Winnie Sin.

An HIV/AIDS symposium "**The New Horizons In HIV/AIDS Prevention and Care"** organized by C.H.O.I.C.E. and supported by HKSID was held on 9th Nov 2018 at YMCA Kowloon. Various aspect of HIV medicine were addressed by a number of local and overseas experts: from HIV vaccine, cure research, to mental health, chem fun and hepatitis co-infection.

Round table discussion chaired by Dr Tsang Ho Fai Thomas (middle), vice president of Hong Kong College of Community Medicine. Dr Owen Tsang (left) and Dr Wilson Lam (right) shared their expert views.

An ID symposium co-organized by HKSID and Hong Kong Society of Community Medicine was held on 15 Nov 2018 at Princess Margaret Hospital. A lecture entitled "**Close encounters with Emerging Infectious Diseases - My Journey so far**" was delivered by Professor Daniel LUCEY, M.D., M.P.H. Adjunct Professor of Medicine - Infectious Diseases, Georgetown University Medical Center.

Professor Daniel LUCEY and colleagues of HKSID and HKSCM

Local and overseas ID conferences and short course

Annual scientific meeting on HIV medicine by C.H.O.I.C.E
Organized by **C.H.O.I.C.E** and supported by HKSID
Date: 25 Oct 2019
Venue: The Cityview, YMCA, 23 Waterloo Road, Kowloon

Evening symposium on HIV medicine
"An Epidemic in Evolution: The Need for HIV Care in the Chronic Disease Era" by Prof David Wohl, North Carolina Department of Corrections
Organized by HKSID
Date: 26 Nov 2019
Venue: Eaton Hong Kong, Jordan
https://hkomg.com/hiv/

The Hong Kong Society For Infectious Diseases 24th Annual Scientific Meeting
Organized by HKSID
Date: 14 Mar 2020
Venue: Hyatt Regency ballroom, Tsim Sha Tsui
http://www.hksid.org

Conference on Retroviruses and Opportunistic Infections (CROI) 2020
Date: 8-11 March 2020
Venue: Boston, Massachusetts
http://www.croiconference.org

European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) 2020
Date: 18-21 April 2020
Venue: Paris, France
http://www.eccmid.org

6th International Conference on Healthcare Associated Infections
Date: 26-30 March 2020
Venue: Atlanta, U.S.
https://decennial2020.org

Infectious Diseases in Adults 2020, Harvard Medical School
Date: 27 April - 1 May 2020
Venue: Boston, U.S.
https://id.hmscme.com

Picture Quiz

Dr. Jonpaul Zee
Associate Consultant
Microbiology, Department of Clinical Pathology, Tuen Mun Hospital

Case History

A 61-year-old gentleman with history of relapsed mixed phenotype acute leukemia was admitted for salvage chemotherapy. He was on prophylactic valacyclovir, trimethoprim-sulfamethoxazole and had a Hickman line. He was admitted for chemotherapy but complicated with multiple episodes of central line related bacteraemia due to ESBL-producing *E. coli, Enterococcus faecium* and *Corynebacterium resistens*. The Hickman line was removed.

Despite resolution of sepsis, there was no recovery of neutrophil count. 4 weeks later, the patient developed fever again and complained of multiple painful skin lesions. Both blood culture and pus swab from the skin lesions isolated the same organism. The neutrophil count was 0.0 x 10^9/L.

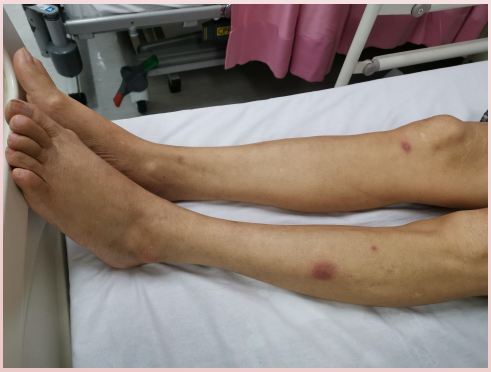


Fig. 1 Multiple painful skin lesions predominantly on extremities

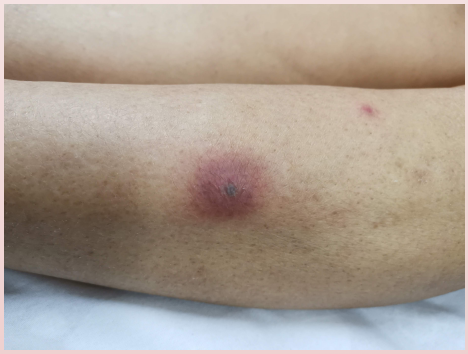


Fig. 2 Raised lesion with central pustule on leg

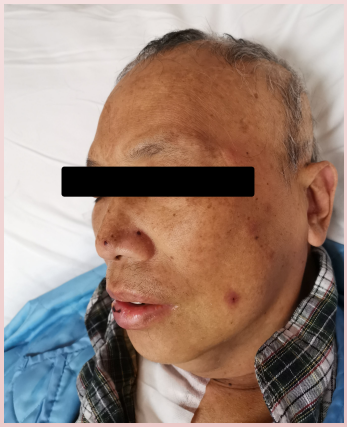


Fig. 3 Multiple painful skin lesions on face

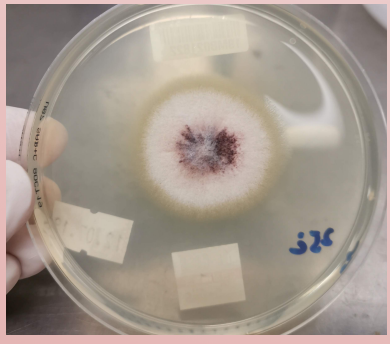


Fig. 4 Sabouraud dextrose agar (SDA) 25°C on day 5

SDA 37°C - no growth (not shown)
SDA with cycloheximide 25°C - no growth (not shown)

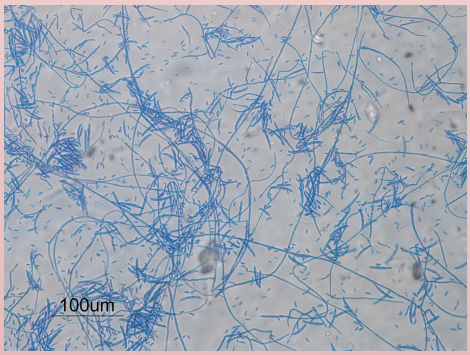


Fig. 5 Lactophenol cotton blue staining of the colony

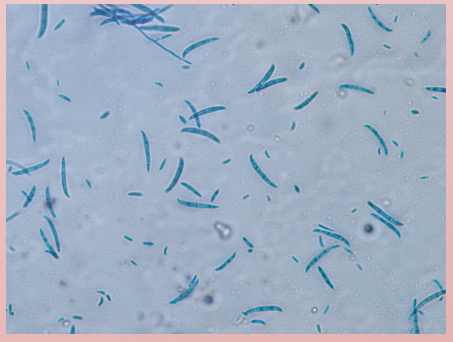


Fig. 6 Lactophenol cotton blue staining of the colony

Questions

1. What is the organism and how to confirm it?
2. What diseases does this organism cause?
3. What is/are the antimicrobial of choice?
4. What can be done to improve the survival besides antimicrobial?

(Answers on the page 11)

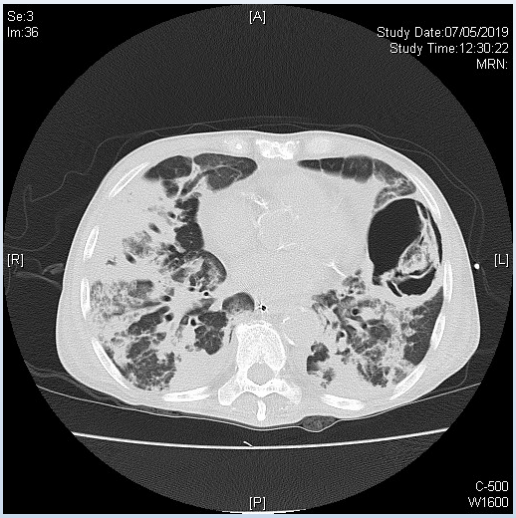
A fatal case of influenza A associated invasive pulmonary aspergillosis (IPA) in an immunocompetent patient

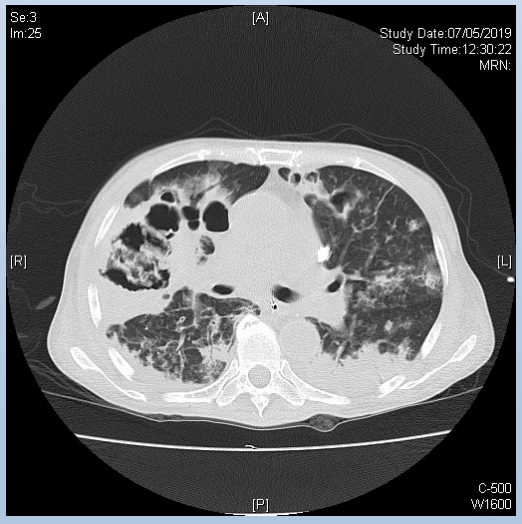
Dr. Ho Hoi-lung
Resident, Department of Medicine & ICU, Alice Ho Miu Ling Nethersole Hospital

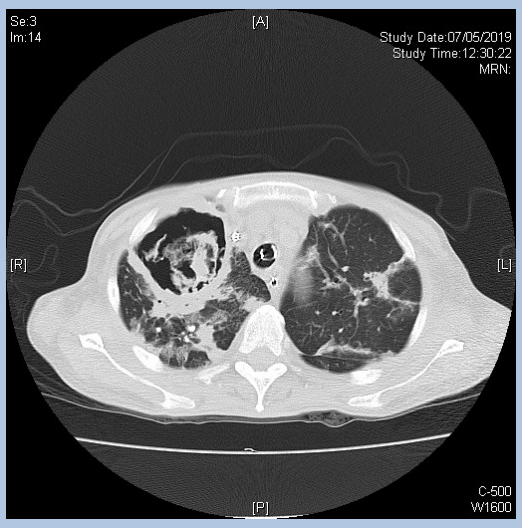
CASE REPORTS

We report a fatal case of probable influenza A associated invasive pulmonary aspergillosis (IPA) in a critically ill but previously immunocompetent patient. The patient was a 65-year-old woman with history of familial hyperlipidemia, iron deficiency anemia and extrapulmonary tuberculosis treated many years ago. She presented to Alice Ho Miu Ling Nethersole Hospital (AHNH) Accident and Emergency Department (AED) in late March 2019 with one week of cough, one day of increased dyspnea and decreased general condition. Her temperature was 36.6°C, blood pressure was 140/50mmHg, pulse rate 80 bpm, respiratory rate 16/min and SpO2 98% on room air. Initial chest x-ray (CXR) showed right lower zone and left upper zone haziness. Computed tomography (CT) brain was unremarkable. She was found to have acute kidney injury (AKI) with hyperkalemia and hyponatremia. Her sodium, potassium and creatinine, were 120 mmol/L, 7.7 mmol/L and 699 umol/L respectively. She deteriorated quickly after admission to medical ward. Arterial blood gas (ABG) showed type I respiratory failure, and severe metabolic acidosis. The pH, pCO2, pO2 and HCO3 of ABG were 7.08, 2.9 kPa, 7.7 kPa and 6.2mmol/L respectively. Her complete blood count showed leucocytosis with white cell count 19.9 x10^9/L while platelet count was normal. Her hemoglobin dropped from baseline 8.4 g/dL to 6.9 g/dL. She was subsequently admitted to Intensive care unit (ICU) on hospital day (HD) 1 for further management. She was put on non-invasive ventilation (NIV) via high-flow nasal cannula (HFNC) and continuous veno-venous hemofiltration (CVVH). Oseltamivir, doxycycline and meropenem were given empirically. She could not expectorate any sputum for culture. Nasopharyngeal aspirate multiplex PCR was positive for influenza A (subtype H1N1). Her urine *Legionella pneumophila* antigen and *Streptococcus pneumoniae* antigen were both negative. Urgent contrast-enhanced computed tomography of abdomen revealed bilateral swollen kidneys with grossly impaired bilateral renal function. Her blood and urine culture subsequently were positive for *Escherichia coli* which was susceptible to cefuroxime and ciprofloxacin. The diagnoses were severe influenza A pneumonitis and *E. coli* pyelonephritis with bacteremia. Antibiotic was streamlined to ceftriaxone. She was transferred back to general ward after stabilization on HD 4. Serial CXRs in general ward showed persistent lung infiltrates. She later developed fever and desaturation again on HD 11. Antibiotic was then escalated to piperacillin-tazobactam and later to meropenem to cover for nosocomial pneumonia. Sputum culture was positive for *Stenotrophomonas maltophilia*. Meropenem was therefore discontinued and changed to ceftazidime plus levofloxacin according to susceptibility test. Bronchoscopy was performed on HD 20, which showed right upper lobe whitish necrotic tissue. CT thorax with contrast was performed on HD 23, revealing multifocal consolidation in both lungs with upper zone predominance which showed progression and multiple cavitary lesions. Bronchoalveolar lavage (BAL) for *mycobacterium tuberculosis* (MTB) DNA PCR was positive and acid-fast bacilli (AFB) culture was also positive for MTB later. She was given anti-TB treatment since HD 23 based on MTB DNA PCR result. However, her BAL culture was also positive for *Aspergillus fumigatus* and *Aspergillus niger* on HD 24. No transbronchial biopsy was performed as patient was not stable at that juncture. She deteriorated and was readmitted to ICU on HD 32 requiring intubation and mechanical ventilation. CVVH was also resumed for AKI. Intravenous (IV) liposomal amphotericin B was given and IV anidulafungin was added as dual therapy after ICU admission. Serum 1,3 beta-D-glucan was positive at 233.8 pg/ml. Repeated bronchoscopy in ICU on HD 38 showed widespread whitish pseudomembranous lesions compatible with pseudomembranous aspergillus tracheobronchitis (ATB). Her condition continued to deteriorate despite antifungal treatment. Blood for galactomannan (aspergillus antigen) collected on HD 23 eventually turned out to be positive. Repeated CT thorax on HD 42 revealed progression of consolidations and enlarging cavitations with suspected mycetoma within. Patient eventually succumbed on HD 45. The BAL AFB culture from the second bronchoscopy was negative for MTB. Postmortem examination was not performed.

A fatal case of influenza A associated invasive pulmonary aspergillosis (IPA) in an immunocompetent patient







Selected CT images showing suspected mycetoma within lung cavities and multifocal consolidations

Discussion

Diagnostic difficulty was encountered in this case. Firstly, the patient was not severely immunocompromised and secondly, she was diagnosed to have concurrent pulmonary tuberculosis which is a common cause of cavitary lesions in lung. Therefore, the isolation of *Aspergillus* species may have been regarded as colonization. The diagnosis of IPA was supported by the subsequent bronchoscopic finding of suspected pseudomembranous ATB, CT findings of mycetoma-like lesions within cavities and a positive galactomannan. The fact that the second BAL AFB culture was converted to negative also suggests that subsequent deterioration was due to IPA rather than uncontrolled TB infection. This case fulfilled both the clinical criteria and mycological criteria but not host factor criteria (immunosuppression) according to the EORTC/MSG classification [1]. The diagnosis of IPA was therefore only probable without histopathological proof.

Ideally voriconazole should be the first-line treatment for IPA as recommended by IDSA [2]. Intravenous use is contraindicated in patients with creatinine clearance <50 ml/minute because of the accumulation of the toxic vehicle sulfobutylether-beta-cyclodextrin sodium (SBECD).

To our best knowledge, there was only one pharmacokinetic study suggesting that IV voriconazole could be safely used in continuous renal replacement therapy (CRRT) without dose reduction as CVVH could effectively remove SBECD but not voriconazole [3]. However, it also received comment that it might only be valid if CVVH with dose of 35 ml/kg/hour and regional citrate anticoagulation were used [4]. Paralytic ileus and gastrointestinal tract malfunction in critically ill patient also limited the use of voriconazole via the oral route. Due to the lack of clinical experience, liposomal amphotericin B was chosen as alternative and anidulafungin was co-administered as salvage therapy.

Invasive aspergillosis typically occurs in severely immunocompromised patient such as those with hematologic malignancies, neutropenia, and transplant recipients. However, invasive pulmonary aspergillosis associated with severe influenza infection has been gaining recognition in recent years. A report of two cases and systematic review of the literature by Khaled Alshabani et al. found there were at least 68 reported

cases by 2015 [5]. Another literature review by Melisa M. Shah et al. identified 36 immunocompetent patients who had IPA and influenza co-infection from 1952 to 2017. Twenty-six (72%) of them died, of which 21 (81%) received antifungal therapy [6].

A retrospective multicentre cohort study involving ICUs across Belgium and the Netherlands showed that influenza was an independent risk factor for IPA and that co-infection was associated with high mortality [7]. For patients with influenza who were immunocompromised, incidence of IPA was 32% (38 of 117 patients), whereas in the non-immunocompromised influenza case group, incidence was 14% (45 of 315 patients). Conversely, only 16 (5%) of 315 patients in the control group developed IPA. Influenza was found to be independently associated with IPA (adjusted odds ratio 5·19; 95% CI 2·63-10·26; p<0·0001). The 90-day mortality was 51% in patients in the influenza cohort with IPA and 28% in the influenza cohort without IPA (p=0·0001).

In short, IPA is potentially a complication following Influenza even in immunocompetent patients. The isolation of *Aspergillus* species from respiratory tract samples should not be presumed to be contamination or colonization in critically ill patient. Empirical antifungal treatment should be considered while waiting for further investigation results to confirm the diagnosis.

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Take a glance at ECCMID 2019

Dr Shuk-ying CHAN
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Over 13500 of infectious disease physicians, microbiologists, researchers, laboratory technicians, pharmaceutical and diagnostic manufacturers from 130 countries gathered at RAI Amsterdam on 13 April 2019, to celebrate the opening of the 29th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID).

The scientific programme provides various education platforms within the 4-day congress, including keynote lectures, scientific symposia, "meet-the-expert" sessions, interactive education workshops, oral poster, paper poster and e-poster presentations. Attendees can gain insights in managing challenging clinical scenarios from renowned clinicians, present their own research findings and grasp the latest diagnostic and therapeutic developments.

Management of infections due to multiple-drug resistant gram-negative bacteria (MDR-GNB) is one of the challenges infectious diseases physicians and clinical microbiologists facing nowadays. In recent years, novel agents (new beta-lactams and beta-lactamases combinations) seem to give us hope in treating MDR-GNB infections, especially in critically ill patients. Professor Marin Kollef announced their prospective, double-blind, multi-center phase 3 clinical trial of ceftolozane/tazobactam for treatment of ventilated nosocomial pneumonia in adult patients (P1917). The trial included 726 adult patients (44% were ≥65 years old and 72% had ventilator-associated bacterial pneumonia), who were randomly assigned to receive 3g ceftolozane/tazobactam or 1g meropenem, both by IV infusion over 1 hour every 8 hours for 8-14 days. Primary endpoint was 28-day all-cause mortality. Baseline characteristics were balanced between treatment arms, causative GNB were mainly Enterobacteriaceae (74%) and *Pseudomonas aeruginosa* (25%). Ceftolozane/tazobactam was non-inferior to meropenem for the primary endpoint, 24.0% (87/362) and 25.3% (92/364) in the intention-to-treat population. Adverse events were similar between groups (11% of ceftolozane/tazobactam and 8% of meropenem).

Cefiderocol, a novel parenterally administered siderophore cephalosporin antibiotic, was showed to be non-inferior to imipenem/cilastatin for complicated urinary tract infection (cUTI) due to MDR-GNB in a multinational, multicenter, double-blind trial (APEKS-cUTI) involving 452 adult patients [1]. In the latest in vitro susceptibility evaluation study (P1853), cefiderocol was tested against 1873 clinical isolates of GNB collected from 213 medical centers in 51 countries worldwide. The investigators used Clinical & Laboratory Standards Institute (CLSI) guidelines and broth microdilution to determine minimum inhibitory concentrations (MICs) for cefiderocol, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin, and meropenem. Cefiderocol MIC90 of 570 KPC-producing Enterobacteriaceae, 345 metallo-β-lactamase (MBLs) producers (200 VIM, 130 NDM, and 15 IMP), and 480 OXA producers (136 OXA-48, 232 OXA-23, 109 OXA-24/40, and 8 OXA-58) was 4, 4, and 2 mg/L, respectively. The authors concluded cefiderocol demonstrated potent in vitro activity against carbapenem non-susceptible isolates of Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* collected worldwide and can be a potential treatment option for infections caused by these pathogens. Two Phase III studies on cefiderocol are ongoing in patients with nosocomial pneumonia (APEKS-NP) and with severe infection due to carbapenem-resistant GNB (CREDIBLE-CR).

Combining vancomycin with anti-staphylococcal beta-lactams for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia has demonstrated synergistic effect in vitro studies. Recent Phase II study (CAMERA1, 60 patients were enrolled) also revealed a shortening of duration of MRSA bacteremia when intravenous vancomycin 1.5g given every 12 hours was combined with intravenous flucloxacillin 2g given every 6 hours [2]. As latebreaker session, Dr Steven Tong showcased the results of Phase III, randomized, multicenter study comparing standard therapy (vancomycin or daptomycin) versus addition of anti-staphylococcal beta-lactams (flucloxacillin, cloxacillin or cefazolin) on top of standard therapy in adults with MRSA bacteremia (CAMERA2, L0014). The study terminated prematurely before completion of enrollment (352 participants instead of planned 440 subjects) due to a higher incidence of acute kidney injury in the combination arm than standard

therapy, 30% and 9%, respectively. Patients in the combination arm cleared the bacteremia significantly faster (measured at day 5) than patients who received standard therapy but there was no difference in composite primary endpoint (90-day all cause mortality, persistent bacteremia at day 5 or beyond, microbiological failure and relapse) between both arms. In a post-hoc analysis, 7 patients in the combination arm (versus 2 patients in the standard therapy arm) needed renal replacement therapy and acute kidney injury was more common with flucloxacillin/vancomycin than with cefazolin/vancomycin. The results warrant further evaluation of the effectiveness and safety of using combination therapy to treat MRSA bacteremia, especially the use of duration of bacteremia as a surrogate endpoint in clinical studies.

Apart from the MDR pathogens, managing infections in immunocompromised hosts is also not an easy task for many infectious physicians and clinical microbiologists. The intrinsic immune defects due to the malignancy or rheumatological diseases increase the risk of infection, while the use of chemotherapy and biologics further reduce the host's immune response to infections. Therefore, a high index of suspicion and prompt investigations and treatment even before the signs and symptoms develop are pivotal to manage infections in these groups of patients. The advancement in cancer therapy gives hope to patients, but also poses newer infectious risks to them. ECCMID provided the audience with latest updates on managing infections in patients with cancer and after transplantation. SY052 brought together specialists in mycology in order to discuss hot issues in fungal infections. Dr Kieran Marr illustrated the advances in technologies and approach to diagnose aspergillosis, while Dr Dionysios Neofytos highlighted the fungal infection related to new immunotherapies and biologicals, especially on novel agents for chronic lymphocytic leukemia (CLL), e.g. ibrutinib, and venetoclax. In the symposium "Possible impact of new immunomodulators on infection and infection management (SY073), Prof Olivier Lambotte gave an overview on immune checkpoint inhibitors, particularly on the toxicity related to these agents. He commented that immune checkpoint inhibitors have no intrinsic infectious risk [3] but the use of corticosteroid given for the immune related adverse events (irAEs) may contribute a substantial risk of infective complications. When to stop antibiotics in patients with febrile neutropenia is always a question for debate among infectious diseases physicians, oncologists, transplant specialists and hematologists. 3 distinguished speakers (Monica Slavin, Genovefa Papanicolaou, Inge C. Gyssens) shared their ways to handle patients with neutropenic fever with evidence from latest studies in an education workshop (EW214) on the last day of ECCMID.

Though the development of new antimicrobials lags behind the evolution of superbugs, we still have some good news on this aspect. Upcoming therapeutic pipelines, which were presented in plentiful posters and in the Pipeline Corner during the congress, showed promising results in the pre-clinical and early clinical stages, which include Murepavadin, which targets *P. aeruginosa*; the new beta-lactam/beta-lactamase combinations targeting Enterobacteiaceae and *A. baumannii* infections (meropenem/nacubactam, enmatazobactam, cefepime/WCK522, cefepime/VNRX-5133, ceftibuten/VNRX-7145, cefpodoxim/ETX1317, sulbactam/ETX2514, cefpodoxim/ETX0282). Glucan synthase inhibitor (GSI), Rezafungin, is a structural analog of anidulafungin with enhanced stability, which has an extremely long half-life to allow less frequent dosing. Ibrexafungerp (formerly SCY-078) an orally available structurally distinct GSI subclass (triterpenoids), was shown to be effective active against which *Candida* species (even *Candida auris*), *Aspergillus* species and pneumocystis [4]. The preliminary results of a Phase 3, open-label, single arm study involved 20 adult patients who had difficult-to-treat infections (e.g. endocarditis, intra-abdominal abscesses) demonstrated favourable effects against different *Candida* species (L0010). The congress also illustrated the possibility of using non-traditional options such as bacteriophage therapy, antibody to neutralize virulent effectors and immunotherapy to treat infections.

Reference:

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[2] Davis JS, Sud A, O'Sullivan MVN, et al. Clin Infect Dis. 2016 Jan 15;62(2):173-180. Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial

[3] Redelman-Sidi G, Michielin O, Cervera C, et al. Clin Microbiol Infect 2018 Jun;24 Suppl 2:S95-S107. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors).

[4] Van Daele R, Spriet I, Wauters J, et al. Med Mycol 2019 Jun 1;57(Supplement_3):S328-S343. Antifungal drugs: What brings the future?

Answers to Picture Quiz

Q1 What is the organism and how to confirm it?

The cottony growth on SAB is suggestive of a mold. The lactophenol cotton blue stain shows septate hyphae, numerous canoe-shaped macroconidia and microconidia suggestive of *Fusarium* species.

Matrix-assisted laser desorption/ionization (MALDI) Biotyper (ver 4.1.8) identified the organism as *fusarium petroliphilum* (a species belongs to *Fusarium solani complex*), molecular test (sequencing using D2 large ribosomal subunit rDNA) identified the organism as *F. solani complex*.

Majority of the *Fusarium* species are plant pathogens, they are commonly found in soil, organic debris. Among the numerous Fusarium species, 7 species complexes are involved in human infection: *F. solani species complex (SC), F. oxysporum SC, F. fujikuroi SC, F. dimerum SC, F. incarnatum-equiseti SC, F. tricinctum SC, F. sambucinum SC*, in the order of decreasing incidence. [1] They are not difficult to culture, and will grow on standard mycology media without cycloheximide, mature in 4 days, giving a white cottony growth with rose-red, lavender pigment. [2] In the past, speciation relying on microscopy morphology can be very difficult and impractical as specialized agar and prolonged culture is needed to induce the formation of distinguishing features. Molecular identification by sequencing different regions of the genes e.g. translation elongation factor 1α (EF-1α), RNA polymerase (RPB1 / RPB2) is currently the method of choice. [3] Serum 1,3 B-D glucan is a nonspecific fungal marker and is usually positive in invasive fusariosis. Serum galactomannan was reported to be positive in some cases only. [4]

Q2 What disease does this organism cause?

Fusarium causes superficial infection including keratitis, onychomycosis, locally invasive infection. Disseminated infection occurs mainly in severely immunocompromised individuals with prolonged neutropenia. Metastatic skin lesions in the form of painful papules, nodules with erythema and necrosis occurs in 72%; lung involvement with alveolar, interstitial infiltrate, nodules and cavities occurs in 39%. Other common presentations includes invasive sinusitis with necrotic mucosa, paranasal cellulitis and endophthalmitis. Fungaemia is a common finding. [5,6]

Q3 What is/are the antimicrobial of choice?

Antifungal susceptibility testing is not commonly performed as it is technically difficult and there is no reference to guide the interpretation. *Fusarium* species in general have high MIC towards most of the classes of antifungals. [1] In one study, a large number of *Fusarium* isolates from different countries were tested against different antifungal agents in an attempt to determine their (epidemiological cutoff value) ECV. ECV of amphotericin B (AMB) were found to be 4-8 ug/ml, voriconazole (VOR) 4-32 ug/ml, posaconazole (POS) 2-32 ug/ml. [7] Take the reference from invasive aspergillosis, favorable clinical response is associated with AMB MIC <2 ug/ml, VOR MIC </=1, POS MIC </=0.5ug/ml). [8] Despite their poor in vitro activity, VOR has been associated with 45-47% of complete or partial response. [1] For AMB, lipid formulation was associated with a higher response rate when compared with AMB deoxycholate, 46% vs 32%. [9] In another study, it was found that VOR was associated with better survival than AMB deoxycholate used in historical control (90-day probabilities of survival 43% vs 22% p <0.001). There is little clinical experience with POS but it has been used as a salvage therapy. [1] The optimal treatment and usefulness of combination therapy remain unresolved due to lack of randomized control trial and rarity of the infection.

Q4 What can be done to improve the survival besides antimicrobial?

Reversal of underlying immunocompromised state is the most important in improving the survival. Persistent neutropenia and use of corticosteroid were associated with hazard ratio of 5.43 and 2.18 in a cohort of hematological patients whose 90-day survival was 21% after the diagnosis of fusariosis. [10] Other adjuvant therapies including G-CSG, infusion of granulocyte can be tried but their efficacy is unknown. Source control including surgical debridement of infected tissue, removal of infected central venous catheter may also be helpful.

[1] J. Guarro. Fusariosis. A complex infection caused by a high diversity of fungal species refractory to treatment. Eur J Clin Microbiol Infect Dis (2013) 32:1491–1500

[2] Medically Important Fungi: A Guide to Identification 5th edition

[3] Anne D. van Diepeningen et al. Diagnosis of Fusarium Infections: Approaches to Identification by the Clinical Mycology Laboratory. Curr Fungal Infect Rep (2015) 9:135–143

[4] A. M. Tortorano et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clinical Microbiology and Infection, Volume 20 Supplement 3, April 2014

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[8] M38 Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. CLSI.

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Membership application form

THE HONG KONG SOCIETY FOR INFECTIOUS DISEASES

APPLICATION FOR MEMBERSHIP

This form should be completed and returned to:

Dr. Ada LIN, Hon. Secretary
c/o 9/F Kowloon Bay Health Centre,
9 Kai Yan Road
Kowloon Bay, KLN
HONG KONG

SECTION A TO BE COMPLETED BY THE APPLICANT

Type of membership applied for: ☐ ORDINARY MEMBER ☐ ASSOCIATE MEMBER

Surname		Given Name(s)			
Name in Chinese		Title		Sex	
Date of Birth		Place of Birth			
Nationality		HKID Card/Passport No.			
Home Address					
E-mail		Tel. No.		E-mail	
Office Address					
		Tel. No.		Fax No.	

Academic and professional qualifications:

Qualification	Awarding Institute	Year Awarded

Membership of professional and scientific societies:

Name of Society	Category of Membership

Publications: Please use separate sheets if necessary

Note: All personal data collected is held on the Society's Membership Database. It is used in the business of the Society and members' names and addresses will only be supplied to reputable professional bodies when the Council believes that the disclosure will genuinely be of interest to the majority of members.

The information provided by me in support of this application is accurate and complete.

Date _____ Signature _____

SECTION B TO BE COMPLETED BY THE PROPOSER

I hereby propose _____
for admission as an Ordinary/Associate Member of the Hong Kong Society for Infectious Diseases.

I am an Ordinary Member of the Society.

Date _____ Signature _____

Name (in full) _____

SECTION C TO BE COMPLETED BY THE SECONDER

I hereby second the proposal that _____
be admitted as an Ordinary/Associate Member of the Hong Kong Society for Infectious Diseases.

I am an Ordinary Member of the Society.

Date _____ Signature _____

Name (in full) _____

SECTION D FOR OFFICE USE ONLY

Application _____ accepted _____ rejected

at the Council Meeting held on _____

NB For sections B & C, usually application requires a proposer and seconder who are members of the Society. However, if an applicant does not personally know two members of the Society, then one may forward the form to the Society which will seek to obtain signatures on the applicant's behalf.