The HKSID Newsletter

November 2018

INSIDE THIS ISSUE

Message from the President

It is with much pleasure to welcome all of you to the second edition of the HKSID Newsletter. Highlights in this issue include meeting summaries of local meeting organized by HKSID or overseas meetings attended by members with sponsorship from the Society. We hope that through such professional sharing, the salient practice points in infectious diseases can be communicated to our members and interested healthcare professionals.

In this issue, members have contributed 2 articles, one on liver abscess and one on influenza vaccination. The latter is indeed timely as the winter influenza season is coming. The vaccination uptake rate in Hong Kong is still far from satisfactory. We hope that, by dispelling the myths, healthcare workers can act as role models for our patients to promote vaccine uptake.

I wish you enjoy reading this issue. All members are encouraged to submit articles or photo quiz for the coming issues. Lastly, I wish to send my greatest appreciation to members of the editorial board and all contributors to make this Newsletter possible.

Dr Wong Tin Yau, Andrew

President, Hong Kong Society for Infectious Diseases

Society News and Announcement

Council of The HKSID 2018-2020

President Dr. Wong Tin-yau Andrew

Vice-president Dr. Choi Kin-wing

Honorary Secretary Dr. Lin Wai-chi Ada

Honorary Treasurer Dr. Chan Man-chun Jacky

Members

Dr. Chan Kai-ming
Prof. Hung Fan-ngai Ivan
Dr. Lam Wilson
Prof. Lui Chung-yan Grace
Dr. Tsang Kay-yan Joseph
Dr. Tsang Tak-yin Owen
Dr. Tso Yuk-keung Eugene
Dr. Wong Chun-kwan Bonnie
Dr. Wu Ka-lun Alan
Dr. Wu Tak-chiu
Dr. Zee Sze-tsing Jonpaul
Dr. Lung kwok-cheung (co-opted)
Dr. Sin Wing-yin Winnie (co-opted)

Immediate Past President

Dr So Man-kit Thomas (ex-officio)

Homepage

https://www.facebook.com/hongkongsid

http://www.hksid.org/

Newsletter committee

Chief Editor

Dr. Zee Sze-tsing Jonpaul

Editors

Dr. Chan Man-chun Jacky
Dr. Hui Wai-man Wyman
Dr. Lin Wai-chi Ada
Dr. Sin Wing-yin Winnie
Dr. Tang Hing-cheung Tommy
Dr. Wu Ka-lun Alan

Please email your comments to secretary@hksid.org

The new council 2018-2020 was elected during the 22nd AGM held on 17th March 2018 at Hyatt Regency Hotel

Back row left to right: Dr. Lung kwok-cheung, Dr. Wong Chun-kwan Bonnie, Dr. Lam Wilson, Dr. Chan Kai-ming, Dr. Tso Yuk Keung Eugene, Dr. Zee Sze-tsing Jonpaul, Dr. Lui Chung-yan Grace, Dr. Sin Wing-yin Winnie

Front row from left to right: Prof. Hung Fan-ngai Ivan, Dr. Tsang Tak-yin Owen, Dr. Chan Man-chun Jacky, Dr. Wong Tin-yau Andrew, Dr. Choi Kin-wing, Dr. Lin Wai-chi Ada, Dr. Wu Ka-lun Alan

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:

- Surname/ Given name(s)
- Title
- Correspondence address
- Home/ Office/ Mobile Tel. Nos.
- Qualification and Year Awarded
- Type of practice: Hospital Authority/ Department of Health/ University/ Private/ Retired/ Others (please specify)

Meeting highlights

The Hong Kong Society For Infectious Diseases 22nd Annual Scientific Meeting, co-organized by Hong Kong Society of Rheumatology and HKSID was held at Hyatt Regency Hotel on 17th Mar 2018. There were over 140 participants with the majority being practicing doctors. Three lectures were delivered by local and overseas experts.

Dr. Yoav Golan, Attending Physician, Division of Geographic Medicine and Infectious Diseases, Department of Medicine of Tufts Medical Center USA, presented a lecture entitled **"Fight against Deadliest Superbugs: a Race against Time!"** The problem of hospital acquired infection caused by multi-drug resistant organism (MDRO) in Asia and the need of early intervention with appropriate antibiotic to improve clinical outcome were addressed.

Dr Golan pointed out that risk stratification to identify patients at risk of MDRO infection as well as analysis of local hospital antibiogram are the two crucial components of successful antimicrobial stewardship.

Prof. Yoav Golan delivering the lecture

Photo taken during Q&A of the final symposium
Left to right: Dr. Priscilla Wong, Dr. Ronald Yip (Vice President, Hong Kong Society of Rheumatology), Dr. Choi Kin Wing

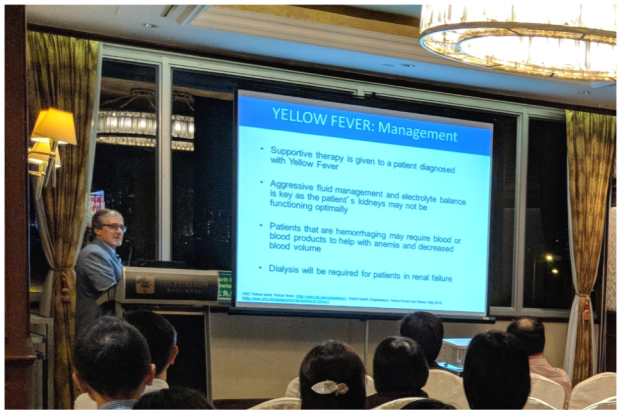
Dr. Alan Wu, Consultant Microbiologist of Pamela Youde Nethersole Eastern Hospital, Hong Kong, delivered a lecture entitled **"Hightlight of IMPACT Guidelines"**.

Dr. Liu Shao-haei (left), former Chief Manager, Infection, Emergency & Contingency, Hospital Authority presenting a souvenir to Dr. Alan Wu (right)

The final symposium **"Biologics and Infection – data from Biologics Registry of the Hong Kong Society of Rheumatology and the World National Registers"** was delivered by Dr. Priscilla Wong, Associate Consultant of Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong. Dr. Wong shared with audience the therapeutic application and mechanism of different types of biologics. The prevalence and characteristics of opportunistic infections associated with the use of these agents in Hong Kong and other countries were addressed.

Three challenging cases of infection in immunocompromised host were presented by Dr. Thomas Chik from Princess Margaret Hospital, Dr. Emily Lam from Queen Elizabeth Hospital and Dr. Anthony Tam from Queen Mary Hospital. The Panelist Dr. Jacky Chan, Prof. Ivan Hung and Dr. Bonnie Wong gave their expert opinions on management of these challenging conditions.

A travel symposium "**Prevention of vector-borne diseases for travellers"** was organized by HKSID on 11th Jun 2018 at The Excelsior Hong Kong. Professor Joseph Torresi, Faculty of Medicine, Denistry and Health Sciences of University of Melbourne was the speaker. The session was chaired by Dr. Bonnie Wong



Prof. Joseph Torresi delivering the lecture.

A symposium organized by the Hong Kong Society for HIV Medicine, co-organized by HKSID and HK College of Medical Nursing, was held on 11 April 2018 at Sheraton Hong Kong Hotel. A lecture entitled "**New Strategies for the Prevention of HIV**", was delivered by Professor F. Lisa Sterman, California Pacific Medical Center/University of California, San Francisco, U.S.. Dr Bonnie Wong served as the chairperson of the event.

Dr. Lee Man Po (left) presenting a souvenir to Professor F. Lisa Sterman (middle). The session was chaired by Dr. Bonnie Wong (right)

Local and overseas ID conferences and short course

The Hong Kong Society For Infectious Diseases 23rd Annual Scientific Meeting

Co-organised by HKSID and Hong Kong Society of Transplantation
Date: 16 Mar 2019
Venue: Hyatt Regency ballroom, Tsim Sha Tsui

http://www.hksid.org/

Conference on Retroviruses and Opportunistic Infections (CROI) 2019

Date: 4-7 March 2019

Venue: Seattle, Washington

http://www.croiconference.org/about

European congress of Clinical Microbiology & Infectious Diseases (ECCMID) 2019

Date: 13-16 April 2019

Venue: Amsterdam, Netherlands

http://www.eccmid.org/

The Society of Healthcare Epidemiology of America (SHEA) spring 2019 conference

Date: 24-26 April 2019

Venue: Boston, U.S.

http://sheaspring.org/

Infectious Diseases in Adults 2019, Harvard Medical School

Date: 23-27 April 2019

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 38-year-old Pakistani patient with DM on insulin, end stage renal failure (ESRF) on continuous ambulatory peritoneal dialysis (CAPD) since 2017 presented with few weeks' history of painful left face and eye, abdominal pain, turbid peritoneal dialysis (PD) fluid and partially blocked Tenckhoff catheter. He was having a trip to his home village in Pakistan during the onset of symptoms and received unknown antibiotic from a local hospital with poor clinical response.

After returning to Hong Kong, he was admitted to a regional tertiary hospital for further care. He had his Tenckhoff catheter removed and underwent multiple surgeries for control of infection

Fig. 1

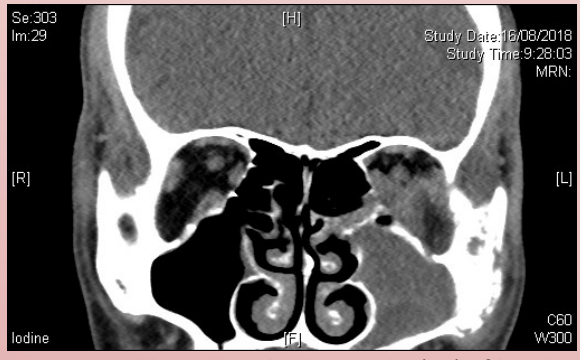


Fig. 2 Coronal computed tomography (CT) of head

Fig. 3 Blocked Tenckhoff catheter filled with dark purulent material

Fig. 4 Turbid PD fluid with black flakes

Questions

1. What are the clinical diagnoses ?
2. What is the likely group of pathogen ?
3. Name a few infection syndromes associated with this group of organism. What are the appropriate investigation and treatment options

(Answers on the page 11-12)

A "Forgotten" Cause of Liver Abscess in the Land of Plenty

Dr. Cheng Shui-kuen Lily
Resident, Department of Medicine and Geriatrics, United Christian Hospital

Hepatic abscesses are the most common type of intra-abdominal abscesses. It can be caused by bacterial, parasitic or fungal infections. In developed countries, approximately three-quarters of liver abscesses are pyogenic[1]. Here, two cases of liver abscesses caused by a relative uncommon cause in our locality are described.

CASE REPORTS

CASE 1

A 44-year-old lady presented to the emergency department with 3-day history of fever and vomiting. She denied diarrhoea nor urinary symptoms. Her medical history was unremarkable. She had no history of recent travel. She immigrated from Mainland China to Hong Kong over 15 years ago and was working as a hotel room attendant. Physical examination was unremarkable except for some tenderness over right posterior lower thoracic region. Blood tests on admission revealed a raised white cell count (19.6 $\times 10^9$/L), normal liver and renal function. Blood and urine cultures were all negative. The patient had persistent fever and back pain despite intravenous piperacillin-tazobactam. Computed tomography (CT) of abdomen showed a rim-enhancing collection in liver (Figure 1). Bowel loops are normal-looking. USG-guided drainage of liver abscess was performed on the day after CT imaging. The antibiotic was switched to intravenous ceftriaxone and oral metronidazole. About 100ml of pus was drained on post-drainage day 2. Pus aspirate smear did not reveal any organism. Fasting blood glucose and HIV serology were all normal. The patient demonstrated improvement at this point, becoming afebrile and was transferred to convalescence hospital for further care. Later serologic test for Entamoeba histolytica antibody came back to be positive. E. histolytica DNA was also detected in liver abscess pus specimen. Stool studies for ova and cysts were done twice but were negative.

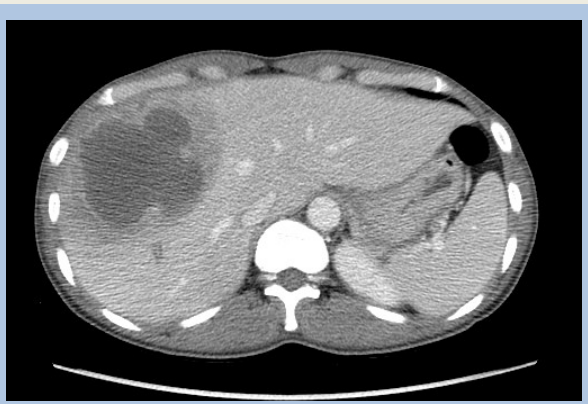


Figure 1. Transverse CT image of the abdomen showing liver abscess

CASE 2

A 47-year-old man who was a driver presented to the emergency department with 1-week of bloody diarrhoea accompanied with colicky abdominal pain. He has type 2 diabetes mellitus managed with diet control. He denied recent travel. On physical examination, he had evidence of peritonism. His white cell count was elevated (15.5 $\times 10^9$/L), liver and renal function test were normal. Urgent CT imaging of abdomen and pelvis showed a solitary liver abscess, and skipped circumferential mural thickening affecting descending colon down to rectum and another segment at ascending colon, caecum and appendix (Figure 2). Perforation near the tip of the appendix with abscess formation were also demonstrated. Open subtotal colectomy and end ileostomy were performed on the same day. The patient was transferred to intensive care unit for post-operative care. The liver abscess was drained on the next day. No organisms were seen on Gram stain of pus fluid. Fluid culture was negative. HIV serology was negative. Blood and stool microscopy repeated once were all negative. Peritoneal fluid grew *Escherichia coli, Streptococcus anginosus* and *Candida glabrata.* Later, pathology report revealed extensive ulceration with amoebae seen in the ulcer slough

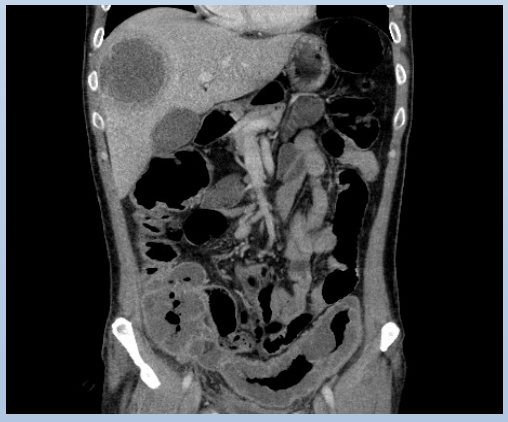


Figure 2. Coronal CT images of the abdomen and pelvis showing the liver abscesses, colonic mural thickening and appendiceal collection

A "Forgotten" Cause of Liver Abscess in the Land of Plenty

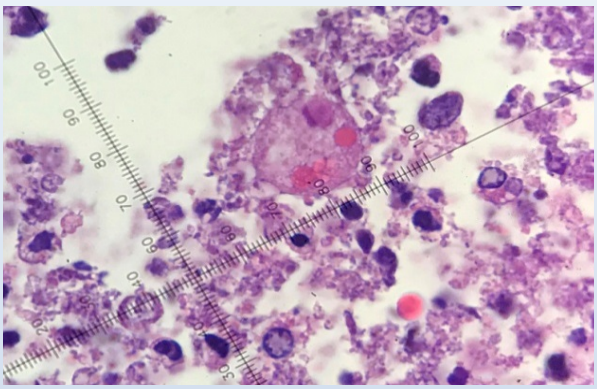


Figure 3. *Entamoeba histolytica* trophozoites in colonic ulcer containing engulfed red blood cells. H&E stain.

(Figure 3). The liver pus aspirate was again examined using a trichrome stain. Protozoa trophozoites were identified (Figure 4). *E. histolytica* DNA was detected in liver abscess fluid. His antibiotics were tailored to intravenous metronidazole, ceftriaxone and micafungin, followed by oral diloxanide furoate. His symptoms improved gradually and was subsequently discharged. He was planned to have follow-up CT imaging and colonoscopy for review.

DISCUSSION

Two cases of amoebic liver abscesses were presented here, with the latter diagnosed to have severe colitis complicated by intestinal perforation. Despite being an important cause of space-occupying lesions worldwide, amoebic liver abscesses are rare in Hong Kong. In a local study of pyogenic liver abscess in a regional hospital over a 6-year period[2], *Klebsiella* spp. was the most commonly identified pathogen in cultures of blood and abscess aspirates. Among the 63 confirmed cases of amoebic dysentery reported to the Centre for Health Protection of the Department of Health from 2007 to 2017, only one patient developed liver abscess.[3]

Entamoeba histolytica is a protozoan parasite with human beings as the reservoir hosts. It exists in two stages, cyst and trophozoite. Cysts are the infective form that can survive long outside the host for weeks to months. Trophozoites are the short-lived invasive form. They are highly motile and can invade intestinal mucosa. People are infected through the faecal–oral route, either directly by person-to-person contact or indirectly by ingestion of faecally contaminated food or water. Ingestion of a single cyst is sufficient to cause infection. Incubation period ranges from a few days to several months, usually 2 to 4 weeks. Risk factors for acquiring infection include foreign birth in and travel to endemic areas, and living in institutions with poor sanity. Men having sex with men is also one of the groups at high risk.

The majority of amoebic infections are asymptomatic, and when symptomatic they usually present with self-limiting dysentery. Extra-intestinal amoebiasis is not common, reported in fewer than 1% of the individuals infected with *E. histolytica*.[4] Trophozoites penetrate the intestinal wall and spread haematogenously to extraintestinal sites. The most common manifestation is liver abscess, in which trophozoites reach the liver via the portal venous system. Other manifestations include pulmonary, cardiac, and brain involvement.

Amoebic liver abscesses are more common in adult men[5], with peak incidence rate in people aged 30-50 years[6]. They are also more frequently observed in people who are alcoholics and have altered cell-mediated immunity, such as HIV infection. Patients typically present with fever and right upper quadrant pain, usually of subacute onset. Diarrhoea was reported in less than one-third of patients, although some recalled a history of having dysentery within the past few months[7]. Rupture of liver abscess leading to peritonitis can occasionally occur in 2% to 7% of patients[8]. Laboratory results commonly reveal leukocytosis without eosinophilia. Elevated alkaline phosphatase levels are usually seen.

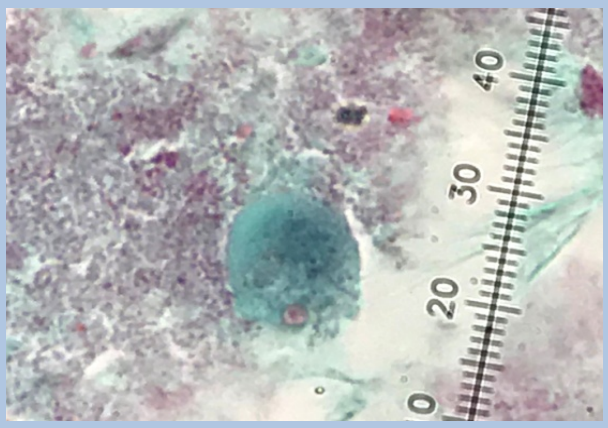


Figure 4. *Entamoeba histolytica* in liver abscess aspirate. Trichome stain.

On imaging, a cystic intrahepatic cavity is often demonstrated. Majority are usually solitary, although occasionally multiple lesions can be found. Radiographic findings are not specific and should be interpreted in light of other findings, such as serological or serum antigenic confirmation. Antibodies to *E. histolytica* are detectable in 92%-97% patients with amebic liver abscess at the time of presentation[9]. Positive anti-amoebic serologies may persist for years after successful treatment, so it should be interpreted with caution in patients from endemic areas. Of note, stool studies are often negative in patients with amoebic liver abscess, although a positive result can be helpful. Aspiration is not routinely required to establish the diagnosis. If aspirated, amebic liver abscesses contain acellular debris that forms a brown, thick fluid resembling anchovy paste. Trophozoites can only be seen on microscopy in fewer than 20% of aspirates and typically present only on the wall of the cyst sampled[10].

Standard treatment of amoebic liver abscess consists of a tissue agent followed by a luminal agent. Metronidazole for 7 to 10 days is often the tissue therapy used, of which the cure rate is over 90%.[11] Treatment with a luminal agent, either iodoquinol or diloxanide furoate, is warranted to clear intestinal cysts, even if stool microscopy is negative. A Cochrane review suggests that current evidence is not sufficient to support or refute that therapeutic aspiration in addition to metronidazole hasten clinical or radiologic resolution of uncomplicated amoebic liver abscesses. However it can be considered if there is high risk of rupture, no response to appropriate therapy, or if exclusion of alternative diagnoses is needed.

Microscopy images courtesy of Dr Sandy Chau, Department of Pathology, United Christian Hospital

REFERENCES

1. Krige JE, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system. BMJ. 2001 Mar 3;322(7285):537-40.
2. Lok KH, Li KF, Li KK, Szeto ML. Pyogenic liver abscess: clinical profile, microbiological characteristics, and management in a Hong Kong hospital. J Microbiol Immunol Infect. 2008 Dec;41(6):483-90.
3. Choi D. Update on amoebic dysentery in Hong Kong, 2007-2017. Communicable Diseases Watch Volume 14, Number 17; 67
4. Choudhuri G, Rangan M. Amebic infection in humans. Indian J Gastroenterol 2012;31:153-62.
5. Acuna-Soto R, Maguire JH, Wirth DF. Gender distribution in asymptomatic and invasive amebiasis. Am J Gastroenterol 2000;95:1277-83.
6. Blessmann J, Van Linh P, Nu PA, et al. Epidemiology of amebiasis in a region of high incidence of amebic liver abscess in central Vietnam. Am J Trop Med Hyg 2002;66:578-83.
7. Maltz G, Knauer CM. Amebic liver abscess: a 15-year experience. Am J Gastroenterol 1991;86:704-710.
8. Ravdin JI. Amoebiasis. Clinical Infectious Diseases 1995;20:1453-66.
9. Anesi JA. Gluckman S. Amebic liver abscess. Clinical Liver Disease 6(2):41-43
10. Othman N, Mohamed Z, Verweij JJ, Huat LB, Olivos-Garcia A, Yeng C, et al. Application of real-time polymerase chain reaction in detection of Entamoeba histolytica in pus aspirates of liver abscess patients. Foodborne Pathog Dis 2010;7:637-641
11. Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr. Amebiasis. N Engl J Med 2003;348:1565-1573.
12. Chavez-Tapia NC, Hernandez-Calleros J, Tellez-Avila FI, Torre A, Uribe M. Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD004886.

An update on influenza vaccination

Dr. To Ki-wai Heather
Specialist in Infectious Disease

An update on Influenza vaccination

Influenza is a common disease that brings along with it major healthcare burdens. There are 3 subtypes of influenza viruses that cause human disease; namely Influenza A, B and C. H1N1 and H3N2 are the 2 main subtypes of Influenza A viruses that are currently circulating within humans. In Hong Kong, flu seasons lies between January to March, July to August. During the last flu peak in early January to late March 2018, there was a major outbreak mostly caused by Influenza B, leading to around 590 cases of severe influenza illness requiring ICU admission or death, mostly affecting elderly aged 65 or above[1].

Influenza vaccine plays an important role in prevention of clinical influenza with its high effectiveness of approximately 70-90%. In Hong Kong, pregnant women, elderly living in residential care homes, long-stay residents of institutions for people with disabilities, persons aged 50 years or above, persons with chronic medical illnesses, healthcare workers, children aged 6 months to 11 years, poultry workers and pig farmers or pig-slaughtering industry personnel are regarded as high risk population and hence should receive the vaccine with priority[2].

There are two main types of influenza vaccines, the inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV). IIV stimulates the humoral immune response resulting in the production of serum antibody against hemagglutinin.

The antibodies generated are not only effective against the specific strains covered in the vaccine, they are also able to reduce risks of severe influenza or complications caused by strains that are antigenically similar. Besides, "back-boost" effect has been observed in adults, in which after vaccination the antibody titers against Influenza A viruses, mainly H3N2, previously encountered via vaccination or natural infection may increase. However, the degree of back-boost effect may significantly vary among individuals[3].

Increasing evidences have demonstrated that single injection of standard dose IIV has lower efficacy in elderly and immunocompromised hosts. In one meta-analysis looking into the effectiveness of influenza vaccination in community-dwelling elderly people, it is found that the adjusted vaccine effectiveness for elderly aged 75 or above was only 16.29% compared to 32.76% in individuals of less than 75 years old, although the difference was not statistically significant[4]. This dampened response can be due to immune dysregulation associated with aging and therefore a reduced response to standard dose influenza vaccines. In view of this, different strategies have been proposed to increase the vaccine efficacy in immunocompromised host who has the highest risk of developing complications associated with influenza illnesses.

High dose influenza vaccines (HD-IIV) were shown to have a higher vaccine efficacy than standard dose influenza vaccines (SD-IIV) in selected high risk populations. HD-IIV contains typically 60μg of hemagglutinin per strain compared to 15μg in the SD-IIV. This induces a stronger immune response and hence translates into a higher antibody titer and vaccine effectiveness. In one earlier study looking into the effect of HD-IIV in elderly, it was found that the relative efficacy of HD-IIV was 24% when compared with SD-IIV[5]. The hemagglutinin inhibition assay (HAI) antibody geometric mean titers and seroprotection rate 28 days after vaccination were significantly higher after vaccination with HD-IIV when compared with SD-IIV. In another study involving residents of a nursing home who are aged 65 or above, it was found that although the crude number of deaths recorded in both HD-IIV and SD-IIV vaccination groups were similar, there was a reduction in hospital admission rate related to respiratory conditions in HD-IIV group [6].

Similar findings have been demonstrated in solid organ transplant recipients (SOTR). Seroconversion rates to A/H1N1, A/H3N2 and B strains were found to be significantly higher in recipients of HD vaccine when compared with those received SD vaccine (40.5% vs 20.8% for A/H1N1; 57.1 vs 32.5% for A/H3N2 and 58.3% vs 41.6% for B strains)[7]. The geometric mean fold rise of antibody titer after vaccination was also significantly greater in the HD vaccine group for A/H1N1, A/H3N2 and B/Brisbane strains. On the other hand, receiving mycophenolate mofetil of more than 2g/day was found to be independently associated with poorer seroconversion after vaccination. Other factors that may affect vaccine effectiveness in SOTR include lung transplantation and recent transplantation done within 6 months[8]. The vaccine effectiveness for A/H1N1 and B strains were also better with HD vaccines among HIV infected patients when compared with SD vaccines as demonstrated by a more favorable seroconversion rate or seroprotection outcome[9]. The immunogenic response of HD vaccine was also shown to be better in children or young adults with leukemia[10]. However, the clinical implications of such findings e.g. effect on frequency and severity of influenza attacks and risk of associated pneumonia or deaths, were not studied. Overall, HD influenza vaccines were well tolerated among different populations and were not associated with more adverse effects.

Another approach for improving the vaccine efficacy is to consider same-season booster shortly after initial dosing. In a trial comparing the vaccine effectiveness of SOTRs given either a single dose of standard dosing nonadjuvanted trivalent influenza vaccine or with a booster dose of the same vaccine given 5-weeks apart, it was found that the seroprotection rate at 10 weeks was higher in the booster group: 54% vs 43.2% for A/H1N1 (P=0.026), 56.9% vs 45.5% for A/H3N2 (P=0.020) and 83.4% vs 71.8% for influenza B (P=0.004)[11]. The number needed to seroprotect 1 patient was <10. The vaccination safety was comparable between both groups. However, such approach may be difficult to implement in clinical practice due to the low update rate of multi-dosing vaccination. The vaccine efficacy of same-season booster in other high-risk groups, long-term effect on immunogenicity due to more frequent dosing of vaccines, timing and dosing of booster vaccine require further investigations.

Adjuvantation is a well-established method used to enhance vaccine efficacy. MF59, a squalene-based-oil-in-water emulsion, is used as adjuvant in trivalent influenza vaccines. MF59 acts by facilitating the recruitment of antigen-presenting cells to the administration site and increasing the binding strength of the antibody to the influenza virus, resulting in a more efficient antigen update and immunological response[12]. The adjuvanted trivalent influenza vaccine (aTIV) was found to elicit a significantly higher antibody response in elderly above 65 years old, especially against A/H3N2. It was generally well tolerated. The most common adverse reaction was injection site pain and tenderness which were mild to moderate and transient. This improved immunogenicity was also found to be associated with better clinical outcomes in terms of reducing hospitalization and influenza-associated complications[13].

Differing from the conventional inactivated influenza vaccine, the hemagglutinin antigen (HA) proteins in recombinant influenza vaccine (RIV) are produced via the introduction of genetic sequence for HA protein into an insect cell line via a *Baculovirus* viral vector. Neither live influenza viruses nor eggs are involved in the production process. This technique allows vaccine to be produced within 6-8 weeks instead of 6 months with the egg-grown process[14]. RIV was shown to be non-inferior to inactivated influenza vaccines. The probability of influenza-like illness was 30% lower with RIV4, a quadrivalent form of recombinant vaccine, when compared with IIV4, an inactivated quadrivalent vaccine. The safety profile of both vaccines were comparable.

Influenza and its associated complications are preventable with effective vaccination. With all the advances in vaccine development and strategies, it is possible to further improve the vaccine effectiveness especially in high risk populations. Meanwhile, annual influenza vaccination should continue to be recommended.

Reference:

1.Respiratory Disease Office, Centre for Health Protection, Department of Health, *Flu Express.* Volume 15 Number 13 (Published on April 6 2018).

2.Scientific Committee on Vaccine Preventable Diseases, *Recommendations on Seasonal Influenza Vaccination for the 2017/18 Season.* June 2017.

3.Kim, J.H., et al., *Prior infection with influenza virus but not vaccination leaves a long-term immunological imprint that intensifies the protective efficacy of antigenically drifted vaccine strains.* Vaccine, 2016. **34**(4): p. 495-502.

4.Darvishian, M., et al., *Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies.* The Lancet Respiratory Medicine, 2017. **5**(3): p. 200-211.

5.DiazGranados, C.A., et al., *Efficacy of high-dose versus standard-dose influenza vaccine in older adults.* N Engl J Med, 2014. **371**(7): p. 635-45.

6.Gravenstein, S., et al., *Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial.* The Lancet Respiratory Medicine, 2017. **5**(9): p. 738-746.

7.Natori, Y., et al., *A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients.* Clin Infect Dis, 2018. **66**(11): p. 1698-1704.

8.Chong, P.P., L. Handler, and D.J. Weber, *A Systematic Review of Safety and Immunogenicity of Influenza Vaccination Strategies in Solid Organ Transplant Recipients.* Clin Infect Dis, 2018. **66**(11): p. 1802-1811.

9.Zhang, W., et al., *Influenza vaccination for HIV-positive people: Systematic review and network meta-analysis.* Vaccine, 2018. **36**(28): p. 4077-4086.

10.Hakim, H., et al., *Immunogenicity and safety of high-dose trivalent inactivated influenza vaccine compared to standard-dose vaccine in children and young adults with cancer or HIV infection.* Vaccine, 2016. **34**(27): p. 3141-3148.

11.Cordero, E., et al., *Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1-2, a Randomized Controlled Clinical Trial.* Clin Infect Dis, 2017. **64**(7): p. 829-838.

12.Frey, S.E., et al., *Comparison of the safety and immunogenicity of an MF59(R)-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects.* Vaccine, 2014. **32**(39): p. 5027-34.

13.Domnich, A., et al., *Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis.* Vaccine, 2017. **35**(4): p. 513-520.

14.Dunkle, L.M., et al., *Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older.* N Engl J Med, 2017. **376**(25): p. 2427-2436.

Answers to Picture Quiz

Q1 What are the clinical diagnoses?

The left facial painful swelling with periorbital swelling and proptosis are suggestive of sinusitis with orbital extension of infection. Periobital cellultitis, orbital cellulitis and subperiosteal abscess are all severe complications of sinusitis and can be progress to meningitis and sinus bone osteomyelitis. The CT image shows fluid level in left maxillary sinus, inferior orbital soft tissue swelling and swollen rectus muscles. The abdominal pain and turbid PD fluid are suggestive of CAPD peritonitis.

Q2 What is the likely group of pathogen ?

Acute sinusitis is commonly caused by viruses and bacteria; however, in patient with impaired immunity, many environmental fungi can cause locally invasive infection which can be the tell-tale sign of systemic or disseminated infection. The subacute presentation of abdominal pain, turbid PD fluid which did not respond to empirical antibiotic are suggestive of CAPD peritonitis caused by an etiology other than bacteria. Both fungal and mycobacterial peritonitis are important etiologies considering his ethnicity and the recent travel to rural area of Pakistan with possible soil exposure. The presence of black flakes and purulent material in the PD fluid and catheter are suggestive of infection caused by a dematiaceous (dark) mold.

PD fluid fungal culture was requested. A pure growth of a black mold was noted after 5 days of incubation in sabouraud dextrose agar (fig. 5) at both 25℃ and 37℃. On microscopy, the fungus has branching septate hyphae and thicked-walled 4-celled conidia. Further molecular identification was performed (ITS sequencing) and the fungus confirmed to be *Curvularia hawaiiensis* (formerly *Bipolaris hawaiiensis*) - a dematiaceous (dark) mold. The patient was put on IV amphotericin B and underwent endoscopic sinus surgery and debridement of periorbital abscess. Unfortunately, orbital exenteration was eventually required to control the infection. The same fungi could not be isolated from the sinus and orbital specimen probably due to treatment with effective antifungal therapy.

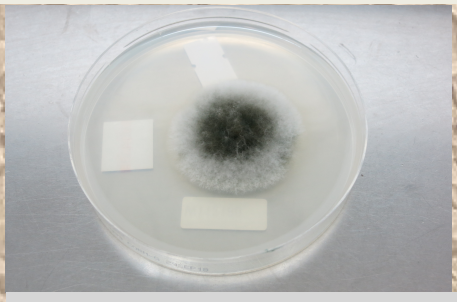


Fig. 5 Sabouraud dextrose agar (25℃/37℃) on day 5
SAB with cycloheximide : no growth

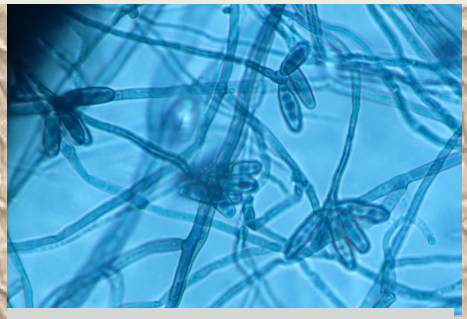


Fig. 6 Lactophenol cotton blue stain

Dematiaceous mold (also known as “melanized” “dark” “phaeoid” mold) are ubiquitous saprobes inhabiting living and dead plant and soil, distributed worldwide and frequently regarded as contaminants in clinical specimen. The dark appearance is a result of profuse melanin production which is important in protection against solar irradiation when growing on exposed surface and may confer protection against phagocytosis. Clinically significant dematiaceous fungi span several ascomycetous orders in the kingdom Fungi. There are over 100 species and 60 genera implicated in human disease. [1,2] Traumatic inoculation and inhalation are the main routes of exposure. Dematiaceous mold has a complicated taxonomy and many species are being re-named and re-categorized according to new molecular phylogenetic findings. The sexual and asexual stage of the same fungus often have completely different name.

Q3 Name a few infection syndromes associated with this group of pathogen. What are the appropriate investigation and treatment options ?

The clinical syndromes caused by dematiaceous mold include chromoblastomycosis, eumycetoma, phaeohyphomycosis and allergic disease. Chromoblastomycosis is a chronic infection of skin and subcutaneous tissue of predominantly lower limbs resulting in suppurative and granulomatous response. The condition is mainly seen in tropic and subtropics (Madagascar, Brazil, Mexico, Dominican Republic, Venezuela, India and Southern China contribute the majority of cases). [3] Eumycetoma is a chronic deep tissue infection that spread along fascia and is characterised by sinuses draining mycotic granules. Most cases have lower limbs involvement as a result of repeated traumatic inoculation.[4] Eumycetoma tend to progress less rapidly, with delayed bone involvement but a more proliferative morphology when compared with their bacterial counterpart, acintomycetoma.[5] Phaeohyphomycosis

Answers to Picture Quiz

is a catch-all term generally reserved for the remainder of clinical syndromes which include systemic (e.g. pneumonia, central nervous system infection) and disseminated disease. The associated clinical conditions of the relatively more common species are shown in table 1.

Several *Curvularia* species have been reported to cause peritonitis in patient on CAPD. In a review of six cases of *Curvularia* CAPD peritonitis, two patients had Tenckhoff catheter obstruction and five cases had black fungal material grossly visible in the catheters. All of the cases required removal of Tenckhoff catheter to control infection. Duration of antifungal treatment is highly variable and both amphotericin B as well as voriconazole were used with success.[7] Rare cases of invasive fungal rhinosinusitis caused by *Curvularia* and other dark mold have also been reported. [8,9]

Diagnosis of infection can be made by culture of infected tissue. Routine fungal media (e.g. SDA, cornmeal dextrose agar) will support the growth of dematiaceous mold, however phenotypical tests are generally not useful for speciation. Sequencing of ribosomal and other genes (e.g. ITS as in this case) will give a more accurate microbiological diagnosis. Histology may demonstrate mixed granulomatous and pyogenic inflammation; sclerotic body is a specific finding in chromoblastomycosis and Fontana-Masson stain will demonstrate melanin production.

Regarding antifungal chemotherapy, itraconazole, voriconazole and amphotericin B generally have good in vitro activity against dematiaceous mold while fluconazole has negligible activity. There are only limited data supporting the use of posaconzole, echinocandin and flucytosine. Despite little in vitro data, terbinafine has been used extensively for treatment of chromoblastomycosis. [1,2] For cutaneous infection, physical methods including surgery, cryotherapy and photodynamic therapy can be used in combination with systemic antifungal treatment.[3]

Table 1	Risk factor	Implicated organisms
Chromoblastomycosis	Traumatic inoculation, exposure of wound to contaminated soil	Fonsecaea pedrosoi is the most common cause Others: *Cladophialophora*, other *Fonsecaea* species, *Phialophora*, and *Rhinocladiella* species
Eumycetoma		*Madurella, Phaeoacremonium, Exophilia* and *Phialophora* species
Phaeohyphomycosis		
Pneumonia	Immunocompromised	
Brain abscess	Immunocompromised Probably acquired by inhalation, then hematogenous dissemination Complicate chronic fungal sinusitis	The most common neurotropic fungi: *Rhinocladiella mackenziei,* *Cladophialophora bantiana,* *Exophiala dermatitidis,* *F. monophora*
Disseminated infection	Immunocompromised 50% blood culture positive ~ 10% eosinophilia	*L. Prolificans* accounts for > 1/3 of cases *Bipolaris, Curvularia* and *Exophiala* species

Reference

1. *Sanjay G. Revankar et al. Clinical Microbiology rReview, Oct. 2010, p. 884–928*
2. *Sanjay G. Revankar. Mycoses (2007), 50, 91-101*
3. *Flavio Queiroz-tells. Rev Inst Med Trop Sao Paulo. 2015 Sep; 57(Suppl 19): 46–50.*
4. *Carmelia Matos Santiago Reis. An Bras Dermatol. 2018;93(1):08-18.*
5. *Emmanuel et al. Ann Clin Microbiol Antimicrob (2018) 17:35*
6. *Anuradha Chowdhary et al. Cold Spring Harb Perspect Med 2015;5:a0195705*
7. *Jason D. Pimentel et al. Journal of Clinical Microbiology, Aug. 2005, p. 4288–4292*
8. *John R. Ebright Et al. Clinical infectious disease 1999; 28 (march)*
9. *Kishore Shetty et al. Spec Car Dentist 26(4) 2006*