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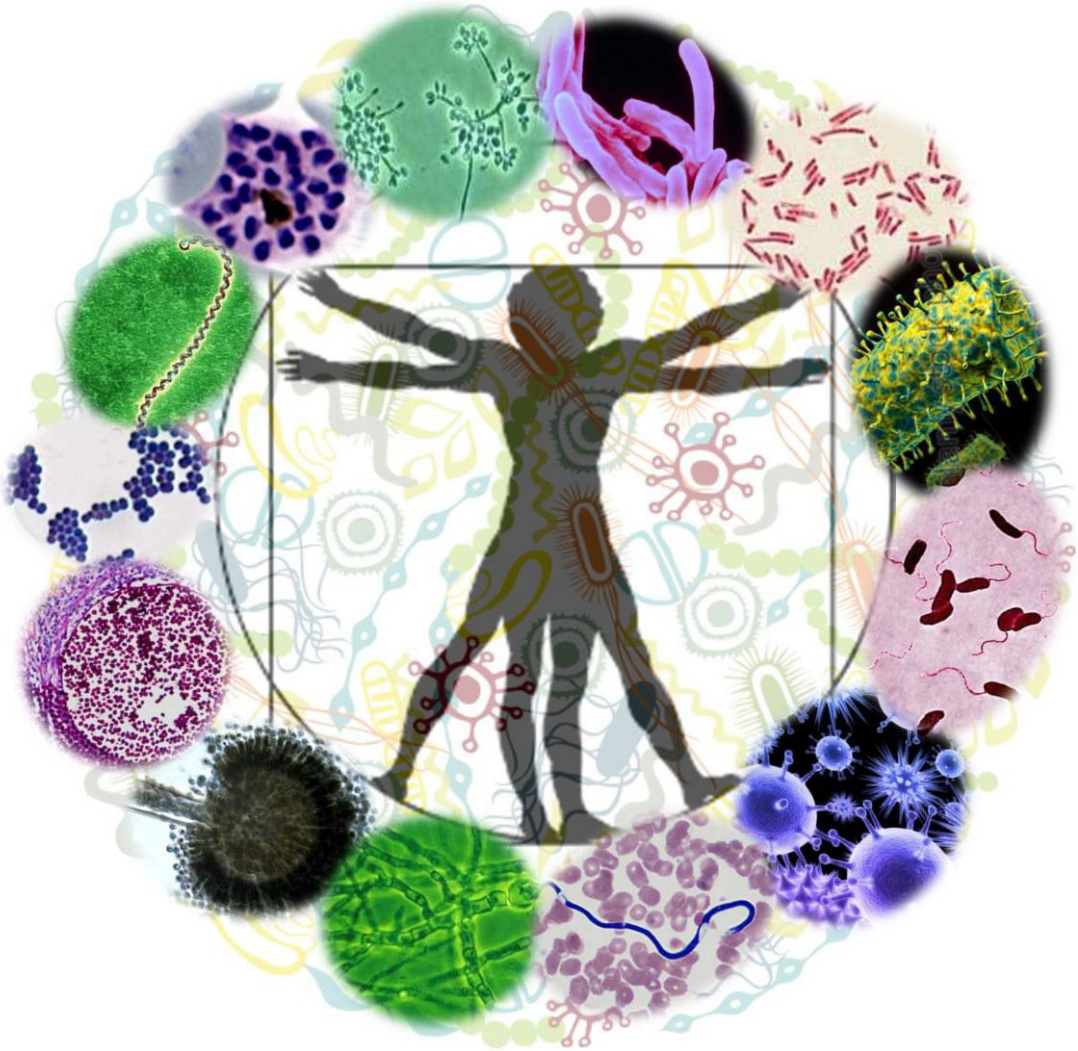

Editors

Poonam Loomba Sonal Saxena Jaswinder Oberoi Renu Gupta Manisha Jain

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Official publication of Indian Association of Medical Microbiologists-Delhi Chapter

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From the editor's desk

Greeting and welcome to the next edition of Jeevanu Times. The objective of Jeevanu Times is to publish up-to-date, high-quality and original research papers alongside relevant and insightful reviews and to encourage the young microbiologists to publish their articles. As such, the newsletter aspires to be vibrant, engaging and accessible, and at the same time informative and useful. This issue contains a review article on Clostridium difficile infection: a infection which is becoming increasingly prevalent with the misuse of antimicrobials. We also have a series of case reports on rare an unusual presentations of Aspergillosis, severe pneumococcal haemorrhagic pneumonia and misdiagnosis.

Any papers that you wish to submit, are much appreciated and will make a substantial contribution to the success of this newsletter. Best wishes and thank you in advance for your contribution to the Jeevanu Times

With best wishes

Dr Poonam Sood Loomba
Editor
Jeevanu times

Review article

Clostridium difficile infection: a review of literature

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Introduction

Clostridium difficile (*C. difficile*) is now widely recognized as the leading cause of nosocomial diarrhea worldwide with associated substantial morbidity and mortality [1,2]. Recent data suggest an increase in both the incidence and severity of *C. difficile* infection (CDI) [3]. Over 2,50,000 people need hospital care and at least 14,000 people die from CDI in the United States each year based on statistics from the Centers of Disease Control and Prevention [4]. Clostridium difficile (C. difficile) is a Gram-positive, strictly anaerobic, spore-forming bacterium that causes a spectrum of presentation ranging from mild, self-limiting diarrhea, to serious diarrhea, pseudomembranous colitis and life-threatening fulminant colitis, which may result in death [5]. It was first isolated in 1935 from feces and meconium of asymptomatic newborn infants, and was originally named Bacillus difficilis because of its morphology, and encountered the difficulties in cultivating it [6]. Since then, it was believed to be a commensal organism until the late 1970s, when it was recognized as the etiologic agent of pseudomembranous colitis [7].

Pathogenesis

In order for *C. difficile* to cause disease, several important con-ditions must be met. A person must have contact with the spores of a toxin-producing strain of *C. difficile* in combination with alteration of the normal colonic microbiota, permitting coloniza-tion of the organism. CDI develops when a patient ingests the spores of a toxigenic strain of C. difficile via personal contact or environment. Among healthy people, C. difficile does not cause problems due to in part commensal bowel flora and antibody-mediated immunity; however, in the setting of an abnormal or disrupted colonic mucosa, these spores colonize the bowel and subsequently germinate, and vegetative bacteria start producing two large toxins, an enterotoxin, TcdA, and a cytotoxin, TcdB, which are encoded by tcdA and tcdB, respectively [8]. Toxin A, causes increased intestinal permeability and fluid secretion. Toxin B, leads to intense colonic inflammation. Toxins bound to receptors gain intracellular entry by modification of Rho proteins-small glutamyl transpeptidase-binding proteins. These proteins are involved in

actin polymerization, cytoskeletal architecture, and cell movement. The resultant effect is the loss of intercellular tight junctions leading to secretary diarrhea, and an inflammatory response with eventual cell death [9]. The fact that antibiotics alter the gut microbiota has been established since the 1940s, shortly after streptomycin became available and investigators noted the impact of oral administration of this agent on the bacteria present in the feces of mice[10]. Antibiotics are the major risk factor for the development of *C. difficile* disease because of the loss of endogenous microbiota that allows *C. difficile*, when present, to proliferate and invade. Several interesting studies of the gut microbiome using culture-independent methods have elucidated the significant alterations that fol-low antibiotic administration [11, 12]. Other important virulence factors that contribute to the pathogenesis of *C. difficile* include adhesins, fimbriae, flagella, a capsule, and a paracrystalline S-layer protein (important in cellular adhesion) [13-15].

Risk factors

The chief risk factor for the disease is prior to expose antimicrobials. In the hospital setting, the majority of CDI cases is associated with the use of antibiotics. However, up to 2/3 of cases of community-acquired CDI in a recent study did not have antibiotics in the 90 day prior to the development of symptoms suggesting a different pattern of disease between community-acquired and nosocomial cases [16]. The risk of developing disease after exposure to antimicrobials is highly variable and depends on host factors (age, diet, immune system function, etc.), the type and dose of antibiotic, and the duration of treatment. Although clindamycin usage was closely linked with the disease historically and still constitutes to be a major risk factor, more cases at the present are attributed to therapy with β-lactam agents because of their common use [17]. Other risk factors include advanced age (>65 years), recent surgery (transplant, gastrointestinal procedures), proton pump inhibitors, immunosuppressant, underlying debilitating conditions, inflammatory bowel disease, prolonged hospitalisation (>15 d), and nasogastric tube feeding [18,19].

Clinical features

The incubation period between spore ingestion and the onset of the disease has not been determined. However, most patients develop diarrhea during or shortly after taking antibiotics, or up to 8-10 weeks after its discontinuation [20,21]. CDI has a wide spectrum range of clinical presentations from mild, self-limiting diarrhea, to serious diarrhea, pseudomembranous colitis and life-threatening fulminant colitis, which may result in death. Watery diarrhea is the cardinal symptom of CDI[22]; it varies from mild, moderate to severe. Patients with colitis (with or without pseudomembranous colitis) usually present with wate-

ry diarrhea up to 10-15 times daily, abdominal cramping and pain, fever, anorexia and nausea [23]. The clinical presentation of CDI ranges from asymptomatic carriage, to mild or moderate diarrhea, to fulminant colitis [25,25]. Three or more watery, nonbloody stools per 24-h period is the hallmark of symptomatic illness [26]. Mild disease is characterized by diarrhea in the absence of signs and symptoms of colitis whereas moderate disease is characterized by moderate diarrhea with colitis manifested by fever, abdominal cramps and discomfort, usually in the lower quadrants [18]. Severe disease is characterized by white blood cell count of >15,000 cells/µL, serum albumin <3 g/dL, and/or a serum creatinine level ≥1.5 times the premorbid level [27].

The clinical features of CDI/fulminant colitis include fever, diarrhea leading to hypovolemia, severe lower quadrant or diffuse abdominal pain, abdominal distention, severe lactic acidosis, hypoalbuminemia, and significant leukocytosis (40,000 white blood cells/µL or higher) [28]. Fulminant colitis can lead to bowel perforation and toxic megacolon. Other complications of *C. difficile* include electrolyte imbalance, renal failure from severe dehydration, systemic inflammatory response syndromes and sepsis [29].

Laboratory methods for Clostridium difficile detection:

The diagnosis of CDI is based on the clinical features, confirmation of the presence of either toxin A alone or toxins A and B together in the stool, and sometimes endoscopy to verify pseudomembranous colitis. CDI should be suspected in any hospitalized patient who develops diarrhea or any person in the community who develops diarrhea after a course of antibiotics or in association with immunosuppressive therapy. CDI should only be investigated in patients with diarrhea. Diagnostic tests available include enzyme immunoassays (EIA) for toxins, EIA for *C. difficile* glutamate dehydrogenase (GDH) and nucleic acid amplification tests (NAATs, or Polymerase chain reaction (PCR) for *C. difficile* toxin genes. Other diagnostic tests include toxigenic cultures, or cell culture neutralization assays (CCNA) [30]. One strategy to improve sensitivity is through a two-step method that uses EIA detection of GDH as an initial screen. Antigen-positive specimens for GDH (and negative for toxin(s) if tested) are further assessed using a NAAT or CCNA. Toxigenic culture is considered the gold standard; however its use limited in the clinical setting given the duration of time for culture results to become available. NAATs (e.g. PCR) are highly specific (>95%), and highly sensitivity rapid tests for *C. difficile* detection. This diagnostic test affords a quick and efficient way of detecting CDI [31]

Management of CDI

Treatment of C. difficile infection involves stopping systemic antibiotics if possible provide appropriate supportive care with hydration and electrolyte replacement as needed. Studies have indicated higher cure rates and decreased relapse in patients in whom antibiotics were discontinued [32,33]. Metronidazole and vancomycin are the principal drugs used to treat C. difficile infection. Patients with mild or moderate diarrhea are generally treated with metronidazole 500 mg TID for 10 to 14 days, as studies have indicated similar cure rates with either metronidazole or vancomycin . Patients with severe diarrhea are treated with vancomycin 125 to 250 mg QID for 10-14 days, as patients with complicated C. difficile had a cure rate of 76% with metronidazole compared to 97% with vancomycin. Recurrence rates were also higher with metronidazole. Adjunct therapy is with vancomycin enema 500mg in 100 ml saline and /or intravenous metronidazole. Surgery with total colectomy is indicated in severe colitis with significant toxemic symptoms[34]. Other antibiotics that may be considered as alternative therapy for CDI in the unusual events (e.g. allergy or intolerance to both first- line agents) include fidaxomicin, bacitracin, teicoplanin, fusidic acid and nitazoxanide, rifaximin and rifampin. Most of the active comparator studies found no statistically significant difference in efficacy between vancomycin and these agents for initial therapy of CDI except teicoplanin and fidaxomicin. The recommended dose is 200mg every 12 hours for10 days. Teicoplanin appears to be better than vancomycin for bacteriologic cure and has borderline superior effectiveness in terms of symptomatic cure, while fidaxomicin appears superior to vancomycin in terms of lower recurrence rates and global clinical cure rates (i.e., clinical cure rates combined with recurrence rates). None antimicrobial therapies such as intravenous immunoglobulin, specific monoclonal antibodies therapy, toxin-binding agents (e.g., cholestyramine, tolevamer), probiotics [e.g., Saccharomyces boulardii (S. boulardii)] and faecal therapy have been studied for use as stand-alone treatments or in combination with standard therapy for CDI. Surgical intervention (colectomy) is indicated in patients with toxic megacolon who are not responding to medical treatment, in patients with ongoing severe sepsis despite antibiotic treatment, and/or when colonic perforation is clinically suspected [35,36].

Recurrent CDI

Between 20% and 35% of patients with CDI will fail initial antibiotic treatment and, of these, 40–60% will have a second recurrence. The majority of recurrences are due to relapses of CDI with the original strain rather than re-infection with a different strain . Resistance to vancomycin or metronidazole is not considered a factor in recurrent CDI, but such antibiotics may contribute to continued intestinal dysbiota. Recurrent infection is

continued intestinal dysbiota. Recurrent infection is more common in older patients (>65 years), females, Caucasian patients, those with current antibiotic use, concomitant use of proton pump inhibitors and more severe initial disease. The presence of comorbidities, anti-neoplastic chemotherapy, inadequate IgG antibody response to Toxin A after initial episode, inflammatory bowel disease, organ transplantation, chronic kidney disease, hypogammaglobulinaemia, immunodeficiency and exposure to an infant carrier or infected adult have also been recognized as risk factors . The contribution of proton pump inhibitors (PPIs) to CDI remains unclear. C. difficile spores are resistant to gastric acid, but vegetative forms are susceptible. In community-acquired CDI patients, PPI exposure was observed in 31% of patients with CDI, with no exposure to antibiotics . There have been reports of increased CDI risk with PPIs; however, other studies have reported no increase in risk following adjustment for co-existent conditions [37–41]. Probiotics may act through a number of mechanisms. These include temporary colonization, production of bactericidal acids and peptides, and competition with C. difficile for nutrients and epithelial adhesion. Lactobacilli have been shown to suppress growth of C. difficile in hamsters [42].

Prevention

Prevention of CDI is challenging health authorities. However, preventive measures are taken such as implementation of infection -control measures (contact isolation and following good hand - washing by everyone). In addition, the cornerstone to controlling this infection is the control of antimicrobial prescribing. A multidisciplinary antibiotic management program to restrict the inappropriate use of antibiotics can lead to a significant decrease in nosocomial infections caused by C. difficile[43]

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Our favourite bumper sticker:

"Support bacteria; it is the only culture we have left."

Did you hear about the famous microbiologist who visited 30 different countries and spoke 6 languages?

He was a man of many cultures

Case report

Severe haemorrhagic pneumococcal pneumonia in a child: A rare complication

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Introduction

Community acquired pneumonia (CAP) incidence is 4 million cases per year of which 20% cases require hospitalization. Mortality rate is between 1-5%, which may rise upto 25% in intensive care unit (ICU).[1] Haemorrhagic pneumonia (HP) is defined as pneumonia complicated by pulmonary haemorrhage which may further lead to haemorrhagic pleural effusion. Most common infectious causes of HP include Panton-Valentine Leukocidin producing *Staphylococcus aureus, Streptococcus pyogenes, Stenotrophomonas maltophilia, Chalamydia pneumoniae,* influenza viruses etc. Rare causes include pulmonary anthrax, pneumonic plague, allergic broncho-pulmonary aspergillosis (ABPA), *Pneumocystis jirovecii* pneumonia, leptospirosis, brucellosis, Varicella Zoster, and Parainfluenza viruses, etc.[2] Non-infectious causes includetrauma, haemorrhagic diathesis, pulmonary thromboembolic diseases, pleuropulmonary malignancy, splenic injury, etc.[3]

Streptococcus pneumoniae is a leading cause of CAP with associated parapneumonic effusions in more than 60% of cases. [4] Severity depends upon on age, associated co-morbidities, immune status etc. Here we discuss a rare case of haemorrhagic pneumococcal pneumonia with effusion in a 9-year-old child. On literature search through internet, we did not find a single case of haemorrhagic pleural effusion due to pneumococcus.

Case Report

A 9-year-old male child was admitted to paediatric emergency department with history of cough and fever for 4 days, fast breathing and decreased oral acceptance for 3 days. There was no history of previous hospitalization or immunization with pneumococcal vaccine. There was no other significant past history.

On general physical examination, patient was sick, nasal flaring was present, blood pressure 122/82 mmHg, heart rate 110beats/min, temperature 100°F, respiratory rate (RR) 76/min, oxygen saturation 92%. On chest examination,

there were decreased chest movements with stony dull note on percussion and absent breath sounds in right lung on auscultation. Rest of the systemic examination was normal. Total leucocyte count (TLC) was 9000/µl, platelet count 47000/µl, haemoglobin 10.1 g/dL. Initial bed side chest X-ray showed right sided pleural effusion. Pleural tap was done on same day of admission, which turned out to be haemorrhagic. Inter coastal chest tube (ICD) was inserted. As per the American thoracic society guidelines, since the patient showed three minor criteria for severe CAP (increased RR, thrombocytopenia, multi lobar infiltrates) patient was kept under intensive cardiorespiratory monitoring.[5]

Patient was immediately treated empirically with intravenous ceftriaxone (1g,12 hourly) and vancomycin (300mg,6 hourly). Pleural fluid was sent for gram stain and culture. A possibility of dengue haemorrhagic fever (DHF) was also considered and one unit of fresh frozen plasma was transfused. Ultrasonography of chest on day 3 of hospital stay showed right sided septal collection in lung and multiple air foci with basal consolidation. High resolution computed tomography features were consistent with ultrasonography suggestive of haemothorax. Patchy areas of consolidation were also seen in left upper and lower lobe, though left costophrenic angle was clear. Multiple enlarged prevascular group of lymph nodes were also seen.

Gram stain of pleural aspirate revealed many pus cells and gram positive diplococci, suggestive of pneumococcal infection. Ziehl Neelsen stain for acid fast bacilli was negative. Culture grew *S. pneumoniae.* Antibiotic susceptibility testing (AST) by Kirby Bauer method showed sensitivity to penicillin (oxacillin), amoxycillin-clavulanic acid, chloramphenicol, ciprofloxacin, ceftriaxone, levofloxacin, linezolid and piperacil-

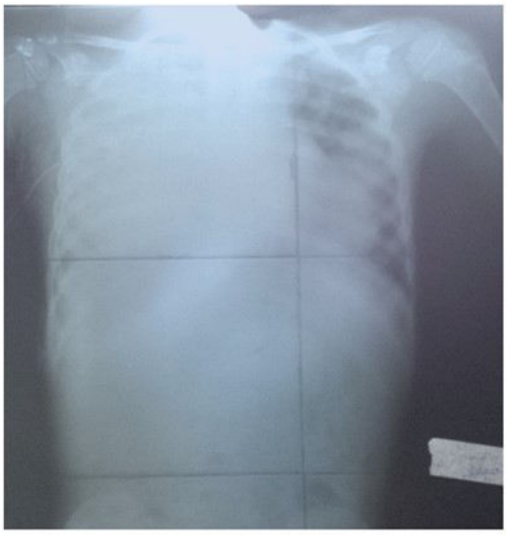

Figure 1: Chest X-ray findings (Day 1)

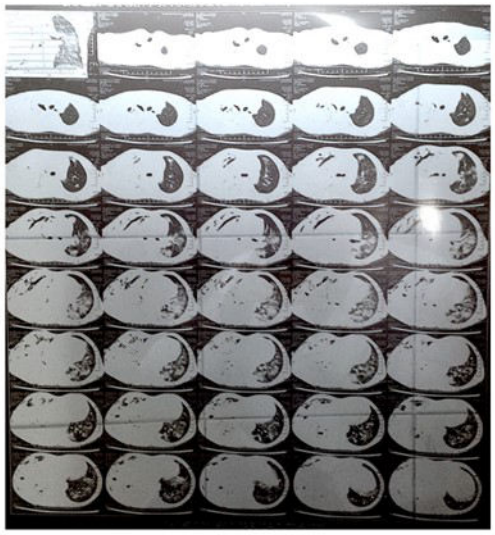

Figure 2: CT Chest findings of patient (Day 3)

Isolate was resistant to clindamycin, co-trimoxazole and erythromycin. Following the AST report, levofloxacin (8mg/kg/day) was added to the initial regimen on day three. Dengue serology, blood culture were negative, & sputum culture was unremarkable.

Clinical course during hospital stay

During first six days of stay, TLC and temperature increased to 14100/µL and 103°F respectively, returning to normal by day eight. Platelet count and RR became normal by the sixth day. Haemorrhagic fluid kept on decreasing over 5 days and ICD was removed on day 6 of admission. Patient's distress also kept on decreasing over time, with O_2 saturation maintained at 99-100%. He started accepting oral feeds, was discharged on day 9 after giving first dose of pneumococcal vaccine and was advised to follow up. Follow up visit at one month showed resolution with complete recovery.

Discussion

This case highlights the rare presentation of most common bacteria associated with CAP. The presentation was consistent with severe pneumonia but haemorrhagic tap pointed towards differential diagnosis of DHF in view of current dengue outbreak, haemorrhagic pleural effusion, fever and thrombocytopenia. Once gram positive diplococci were seen on gram stain and further *S. pneumoniae* grew on pleural fluid culture, antibiotics were further rationalized. This isolate showed resistance to macrolides and lincosamides but susceptibility to β lactams and fluroquoinoles (FQ). Hence a combination of a β lactam and FQ was given as per ATS guidelines for inpatient, ICU treatment. [5]

Invasive pneumococcal disease is defined as an infection confirmed by *S. pneumoniae* isolation from sterile sites e.g. cerebrospinal fluid, pleural fluid and blood.[6] Mortality rate varies from 15-20% in invasive disease but can go upto 50% in severe cases.[7] In invasive disease, secondary complications such as arthritis, meningitis, endocarditis and myocarditis may occur. Treating physician should have high diagnostic suspicion of them. [8,9] Our patient was brought in a very sick condition with haemorrhagic pneumococcal pneumonia and had associated many poor prognostic factors like young age, ICU admission and high RR. Timely medical and surgical interventions in the paediatric emergency department itself followed by definite microbiological diagnosis helped the patient survive.

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Answers to Microbiology quiz published in Jeevanu Times January

Across

2. Inventor of Hot air oven: **Koch**

5. JC Polyoma virus causes: **PML**

8. Rapid method for TB diagnosis: **CBNAAT**

10. Cell wall deficient form: **Protoplast**

13. Cervical cancer cell line: **HeLa**

14. Spore staining method: **Fulton**

15. Disease caused by Ureaplasma: **NGU**

17. Medium for Campylobacter: **Skirrow**

18. Zoonotic disease with hepatorenal involvement: Weil

19. Cells seen in vaginosis**: Clue**

20. West African hemorrhagic fever: **lassa**

Down

1. Vector borne agent associated with Microcephaly: **Zika**

3. Pigment seen in Prevotella: **hemin**

4. Beta Lactam active against MRSA: **ceftbiprole**

6. Test for pneumococcus: **Optochin**

7. Reaction on staining Anthrax bacilli from blood films:**McFaydean**

9. Adolescent vaccination indicated for: **HPV**

11. Risus Sardonicus is seen in: **Tetanus**

12. Lytic area on bacterial culture by phage:**Plaque**

16. Treponema carateum is etiological

Case report

Aspergillosis in a patient on extracorporeal membrane oxygenation support

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Introduction

Extracorporeal membrane oxygenation (ECMO) for intensive care patients with severe cardiac or reversible pulmonary failure has become more common over the last few years[1].Complications resulting from ECMO further increase the mortality in this group of patients, which is already high due to severity of underlying illness [2]. Patients on ECMO are often receiving broad-spectrum antibiotics; they have multiple entry points for pathogens and their immune system is impaired by blood circuit interaction. These factors are thought to predispose them to fungal infections specially *Candida spp.* and *Aspergillus spp* [3]. We here describe a case where ECMO was used as a part of the management of a patient of ILD with ARDS (Acute respiratory distress syndrome) and the patient developed invasive pulmonary aspergillosis.

Case: A 62 year old male known case of hypertension, Diabetes mellitus type II, hypothyroidism and interstitial lung disease was admitted in some other hospital on 03/09/13 with complaints of fever and breathlessness. Further investigation confirmed ILD with superadded respiratory infection. Patient was not on any treatment for ILD in spite of being; it was diagnosed in July 2013. He was given antibiotics, steroids and other supportive management. In between patient was little improved however again developed breathlessness, shifted to ICU, put on BIPAP support and IV antibiotics. In spite of all the efforts the breathlessness was persistent and patient was shifted to our hospital on 05/10/13.

After admission to our hospital the lab parameters were as follows Hemoglobin- 7.8 gm./dl, Platelet count was 1.35 lakhs/ µl, total leucocyte count was 17,800/µl , serum Creatinine 3.9 mg/dl , INR 1.13. Serum Creatinine was increasing and urine output was decreasing gradually, Patient was in persistent hypoxia even on 100% FiO_2 and was going into metabolic and respirato-

-tory acidosis so he was put on ECMO support. Because of poor clinical progression and persistent respiratory insufficiency BAL samples were sent for microbiological investigations. Both BAL and serum sample were sent for galactomannan (GM) assay. In fungal microscopy (KOH mount) septate fungal hyphae with acute angle branching were seen. *Aspergillus flavus* was also isolated from BAL culture later on.

Chest X ray showed bilateral opacities , both serum and BAL galactomannan was positive so voriconazole 400 mg BD IV and Caspofungin 70 mg IV was started along with other supportive management. From 5th day of admission bilirubin started to rise rapidly .Ultrasound imaging of upper abdomen revealed mild to moderate ascites and intrahepatic cholestasis secondary to systemic illness. There was persistent rise of bilirubin so voriconazole was stopped and liposomal amphotericin B 3mg/kg along with anidulafungin 200mg IV were started. In spite of that general condition of patient remained critical, he was in respiratory failure, distributive shock with hyperbilirubinemia.

Total serum bilirubin was still 11.9 mg/dl on 9th day of admission other parameters were also continuing to be deranged and worsened further. Blood culture was found to be positive for *Enterobacter cloacae* , antibiotic colistin 2MU IV was added to treatment. Now the patient was a case of Invasive Aspergillosis, *Enterobacter* blood stream infection, respiratory failure on ECMO, distributive shock, metabolic acidosis, abdominal distension, hyperbilirubinemia. Patient ultimately succumbed to death on 12th day of admission.

Discussion:

Aspergillus is a ubiquitous environmental hyaline mould. Typically, invasive aspergillosis(IA) affects patients with inherited immune deficiencies, advanced HIV infection, prolonged neutropenia and allogeneic hematopoietic stem cell transplantation (HSCT) [2]. Aspergillosis is also an emerging opportunistic infection in critically ill patients in the ICU, particularly in patients with COPD or severe liver disease [4]. From the last few decades the use of ECMO for the management of life threatening pulmonary or cardiac failure has increased. Prolonged ECMO use has been identified as a risk factor for ECMO-related nosocomial infection [5,6]. Patients are at risk of nosocomial infection whilst on ECMO as they have multiple portals of entry [5,7].

We here reported a case of invasive aspergillosis in a patient following ECMO treatment. There are three major types of bronchopulmonary Aspergillus infections: invasive aspergillosis, chronic aspergillosis, and allergic aspergillosis. Aspergillosis infection can also manifest as sinus disease in immunocompromised hosts. If left untreated, invasive aspergillosis can have mortality approaching 100%. In cases of suspected invasive aspergillosis, an extensive diagnostic workup is

is necessary, but treatment should be initiated as early as possible to reduce morbidity and mortality. Despite antifungal therapy also mortality ranges from 30-70 % in few cases [8,9].

In an otherwise immunocompetent person, *Aspergillus* conidia are inhaled and taken up by phagocytes in the lungs. The conidia germinate into hyphae at body temperature. In immunocompetent hosts, phagocytes secrete mediators which activate neutrophils. Neutrophils kill the invasive hyphae, and the *Aspergillus* infection is kept at bay. If any of these mechanisms are impaired in an immunocompromised patient, the infection may be allowed to spread.

A strong clinical suspicion to identify patients at risk for invasive aspergillosis is the first step in evaluating for aspergillosis. The fungal microscopy of the sputum should be done first to identify a patient with invasive aspergillosis (shows angular dichotomously branching septate hyphae in IA). In normal hosts the mere presence of *Aspergillus* does not necessarily indicate acute infection, however, in the immunocompromised host, finding the fungus should prompt the clinician to treat as an acute infection. The culture of the *Aspergillus* species in the sputum or by bronchoalveolar lavage with the identification of hyphae, which is the gold standard, will confirm that the infection is from *Aspergillus* and not another mould or fungus. Tissue biopsy of an aspergilloma may be helpful to confirm the diagnosis and exclude other conditions that may cause lung masses.

Serum biomarkers such as galactomannan assays are helpful; it can also be measured in sample from a bronchoalveolar lavage. Test should be used as a screening tool for the early detection of IA. Single or consecutive positive assays (serum) with high OD index can serve as a microbiological criterion for probable IA. Galactomannan from BAL fluid - demonstrated excellent sensitivity in haematology and non-haematology patients ,solid organ transplant recipients, intensive care unit patients, patients with auto-immune disorders, AIDS patients, used as a confirmatory (diagnostic) assay in patients with unexplained radiological features. It's not suitable for the early detection of IA however BAL GM assays yet be recommended to assess the outcome of antifungal therapies.

Chest radiographs may show parenchymal opacities of pulmonary aspergilloma (fungus ball). CT imaging of the lungs will show characteristic nodules with surrounding attenuation ("halo sign"), aspergilloma (fungal ball in a pre-existing lung cavity), cavitations, or fibrosis. Blood cultures in such cases are of limited value, often not positive even in disseminated infection. The presence of (1,3)-beta D-glucans in serum signifies the presence of fungal invasion but is not specific for Aspergillus species. PCR-based diagnosis have not been standardized and remain investigational.

Our patient was in respiratory distress & on ECMO. Chest x ray was showing bilateral opacities in both lower lobes, both serum and BAL galactomannan were positive, fungus microscopy (KOH) was positive for acute angle branched fungal hyphae. According to EORTC/MSG (European organization for research and treatment of cancer/Mycosis study group); it was fulfilling the criteria of Probable Invasive Aspergillosis so voriconazole was started immediately for the patient. Voriconazole is formulated as sulfobutyl-ether cyclodextrin solution for IV administration and cyclodextrin molecule is renally cleared so accumulation of the vehicle occurs in individuals with renal insufficiency[10]. This drug is hepatically metabolized, with only 5% of the drug appearing unchanged in the urine. Since in our patient both serum creatinine and serum bilirubin started to rise, moreover clinical progression was very poor so voriconazole was kept on hold, amphotericin B along with anidulafungin was started. Unfortunately patient also developed gram negative sepsis, was on intravenous colistin for the same but expired on 12th day of admission. Cause of death was attributed to invasive aspergillosis, ARDS , gram negative sepsis or ILD with multi organ failure.

Conclusion: Patients undergoing ECMO are at increased risk of infections compared to other patients in ICU. Clinicians should consider infection with fungus in patient not responding to antibiotics. ECMO patients with IPA did not always have classic underlying risk factors[2]. Diagnosing IPA in ICU patients can be difficult but a clinical algorithm to diagnose IPA in such patients can be useful thoughts should not be given for using combination antifungal therapy. Clinicians should also monitor voriconazole level in the serum to guide dosing and to avoid antifungal interaction and side effects.

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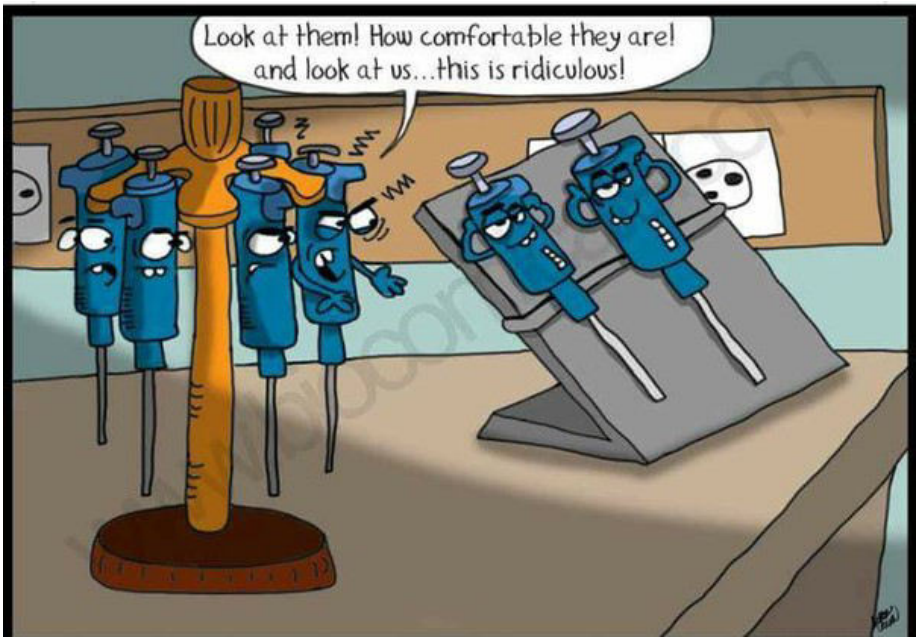

Case report

A case report of misdiagnosed breast abscess

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Introduction

Breast inflammation in women of reproductive age group is seen more commonly in lactating as compared to non-lactating women. Acute inflammation of breast can be attributed to the increased activity of the breast tissue in response to female hormones. Infective causes of breast abscess include *Staphylococcus aureus* with the predominant pathogen implicated in both the groups. Whilst, *Klebsiella pneumoniae, Peptostreptococcus magnus, Streptococcus group B, Enterobacter cloacae, Methicillin resistant staphylococcus aureus (MRSA)* and *Mycobacterium tuberculosis* were responsible for breast abscesses only in non lactating women.[1]

Breast abscess due to Salmonella infection is rare, though few cases have been reported from India.[2-4] Salmonella infections are a major public health problem in India and are transmitted orally by contaminated food and water. Intracellular survival strategies after phagocytosis help these bacteria to disseminate throughout the body and localize in the reticulo-endothelial system.[5] Salmonellosis may clinically manifest as enteric fever, food poisoning septicaemia with or without local suppurative lesion. It has been implicated in endocarditis, osteomyelitis,[5] miscarriage,[6,7]meningitis,[8] abscess formation in liver,[5] pancreas,[9] gall bladder and spleen.[10]

Here we present a case of breast abscess due to Salmonella without any known predisposing factors.

Case Report

A 32 years old young lady presented with a painful lump in right breast. She had fever on and off for 15-20 days with 2 episodes of diarrhoea around the same time which was self resolving. This patient was a known case of hypothyroidism with a past history of two first trimester abortions. She had a 2 years old male child who was not breast-fed. Her last pregnancy was une-

ful except for the history of gestational diabetes. She also denied any history of gall stones.

The patient had taken medical opinion from a local practitioner and was put on anti-inflammatory medication along with amoxicillin-clavulanic acid as an empirical antibiotic. Thereafter an ultrasound was performed that revealed a well defined oval hypo echoic lesion of 19.1 mm in upper inner quadrant. A mildly enlarged node with thickened cortex was seen in the right axilla. Cytology of the breast lesion revealed granulomatous mastitis. Based on the findings of imaging results she was empirically started on antitubercular therapy (ATT).

Now, the patient presented seeking a second opinion to us. On local examination, the area was warm with mild tenderness in the upper inner quadrant of right breast. A small mobile lump could be elicited non adherent to the skin. The patient was afebrile with a pulse rate of 86 per minute. No other abnormality was detected on systemic examination.

The abscess was drained by ultrasound guided aspiration and sample was obtained for microbiological evaluation to rule out any infective pathology. Staining for acid fast bacilli, Genexpert and Mycobacterium culture were negative. Direct Gram's stain showed plenty of leucocytes but no bacteria were seen. Blood, urine and stool cultures were non contributory and Widal test was non reactive.

Aerobic culture of the abscess grew *Salmonella Paratyphi A* which was resistant to Nalidixic acid with intermediate susceptibility to ciprofloxacin. It was susceptible to Ampicillin, azithromycin, cefixime, ceftriaxone, chloramphenicol and co-trimoxazole. The patient was put on intravenous ceftriaxone 1 gram 12 hourly for 7 days. Thereafter, she was put on oral cefixime 200 mg twice daily for another 8 days. There was a significant response to treatment. The lump subsided and patient recovered completely.

Discussion

Salmonella Typhi and *Paratyphi A* are responsible for morbidity and mortality especially in developing countries. The clinical spectrum of salmonellosis is varied and may present in the form of gastro-intestinal infection, bacteraemia, focal disease or may lead to a carrier state.[5] Extra-intestinal focal manifestations are varied and depend on factors like extremes of age, immune-suppression, intra-venous drug abuse, previous trauma etc.

Breast abscess as a manifestation of Salmonella infection is a rare condition. Reports of Salmonella Paratyphi A chronic breast abscess in India have been reported from Mysore[3] and Pune.[4] In the absence of any significant past history of

fever, gastro-intestinal infection (other than two self limiting episodes of diarrhoea) or trauma, the source of infection in the present case still remains doubtful. Although blood, stool and urine samples obtained from the patient did not yield Salmonella, the probability of the patient being a carrier cannot be ruled out. In a non lactating female, seeding of Salmonella in the breast tissue through a carrier state, although unlikely, is the only probability considered by the authors.

To summarize, this case highlights the fact that Salmonella can present with atypical clinical pictures and must be considered as a differential diagnosis in such situations.

The use of ATT is rampant in our country. As seen in this case, without any conclusive evidence, the patient was started on ATT. Thus it is imperative to state that clinical judgement along with a robust microbiological support is helpful to clinch the diagnosis and institute appropriate treatment.

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Microbiology Updates from around the world….

Microbiology Update 1:

WHO recommends typhoid conjugate vaccine in endemic settings

- The World Health Organization (WHO) recommends implementation of national typhoid vaccination programs as part of broader control efforts in settings where typhoid is endemic. In March 2018, the WHO indicated a preference for typhoid conjugate vaccine (TCV) over other typhoid vaccines and recommended TCV administration for children six months or older, with catch-up vaccination campaigns for children up to 15 years old.

- Compared with other typhoid vaccines, TCV has greater and longer lasting immunogenicity and has established safety in infants and young children. A TCV licensed in India and Nepal is undergoing licensure in other endemic countries; TCV is not available in the United States or Europe.

Reference:

World Health Organization. Typhoid vaccines: WHO position paper. March 2018. http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf

Microbiology Update 2:

Large outbreak of listeriosis in South Africa

- Listeriosis is a foodborne bacterial illness that causes invasive infections, primarily in individuals with a predisposing factor, such as pregnancy or immunosuppression. The largest listeriosis outbreak detected to date began in South Africa in January 2017, with more than 975 laboratory-confirmed cases reported as of mid-March 2018.

- The likely source of the outbreak, a ready-to-eat processed meat product called polony, was identified through whole genome sequencing. Recalls were subsequently issued in South Africa and 15 other African countries to which the product was distributed

Reference:

Listeriosis – South Africa Available at http://www.who.int/csr/don/28-march-2018-listeriosis-south-africa/en/

Microbiology Update 3:

Oral fecalmicrobiota transplantation for recurrent C. difficile infection

- Fecalmicrobiota transplantation (FMT) delivered via colonoscopy is resource-intensive and invasive. In a noninferiority trial, 116 patients with recurrent Clostridium difficile infection (CDI) were randomly assigned to FMT administered via oral capsules or colonoscopy. At 12 weeks, 96 percent in both groups were free of CDI recurrence.
- Fecal microbial diversity rates increased and were maintained for up to 12 weeks following FMT in both groups. While oral capsules appear to be a viable delivery method for FMT, their clinical availability is limited, and their cost-effectiveness is still to be determined.

Reference: Kao D, Roach B, Silva M, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered FecalMicrobiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2017; 318:1985

Microbiology Updates from around the world….

Microbiology Update 4:

ART initiation on day of HIV diagnosis in resource-limited settings

- The World Health Organization (WHO) recommends initiation of antiretroviral therapy (ART) within the first seven days of an HIV diagnosis. Initiation of antiretroviral therapy (ART) early in the course of HIV infection rather than waiting for CD4 cell decline reduces severe AIDS and non-AIDS illnesses.

- Several trials in resource-limited settings have demonstrated the benefit of ART at progressively higher CD4 cell counts.[1,2,3] Nevertheless, the optimal strategy for implementation remains uncertain.

- In a trial in Lesotho, ART initiation at home on the day of diagnosis improved subsequent linkage to care (69 versus 43 percent) and virologic suppression (50 versus 34 percent) compared with routine health facility referral for ART initiation.[4]
- However, those rates were still unacceptably low, and many trial patients experienced treatment interruption, putting them at risk for drug-resistant HIV.
- Further study is warranted to identify successful approaches, which may differ by location, patient population, and ART regimen utilized.

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Microbiology Update 5:

Nipah virus outbreak in India

- In May 2018, an outbreak of Nipah virus was reported in India's Kerala state, and at least 16 people died. Most cases occurred in family members or health care workers caring for infected patients, who had high fever, vomiting, and breathing difficulties. Transmission can be bat-to-human (through direct contact or an intermediate animal host) or human-to-human. There is no established treatment for Nipah virus; thus, education and appropriate infection control precautions remain key to preventing spread of infection

Reference: Chatterjee P. Nipah virus outbreak in India. Lancet 2018; 391:2200.

Microbiology Updates from around the world….

Microbiology Update 6:

Meropenem-vaborbactam in complicated urinary tract infection

- Meropenem-vaborbactam is a novel antibiotic combination of a carbapenem with a broad-spectrum beta-lactamase inhibitor that potently inhibits certain carbapenemases.
- Vaborbactam is a novel broad-spectrum beta-lactamase inhibitor that potently inhibits class Acarbapenemases (including K. pneumoniae-carbapenemases [KPC]). It is not active against class B or D carbapenemases (ie, metallo-beta-lactamases and OXA-type enzymes).
- The addition of vaborbactam to meropenem reduces the MICs to meropenem among class Acarbapenemase-producing Enterobacteriaceae to wild-type MIC levels.
- Meropenem-vaborbactam was comparable to piperacillin-tazobactam in a trial of patients with complicated urinary tract infection and it is being evaluated in patients with bacteremia, hospital-acquired pneumonia, and complicated intraabdominal infections. The main role of this agent is for treatment of KPC-producing Enterobaceriaceae but it does not enhance the clinical activity of meropenem against carbapenem-resistant P. aeruginosa or Acinetobacter spp. Data evaluating outcomes with such organisms are limited but emerging.

Reference:

1. Lomovskaya O, Sun D, Rubio-Aparicio D, et al. Vaborbactam: Spectrum of Beta-Lactamase Inhibition and Impact of Resistance Mechanisms on Activity in Enterobacteriaceae. Antimicrob Agents Chemother 2017; 61.
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Microbiology Update 7:

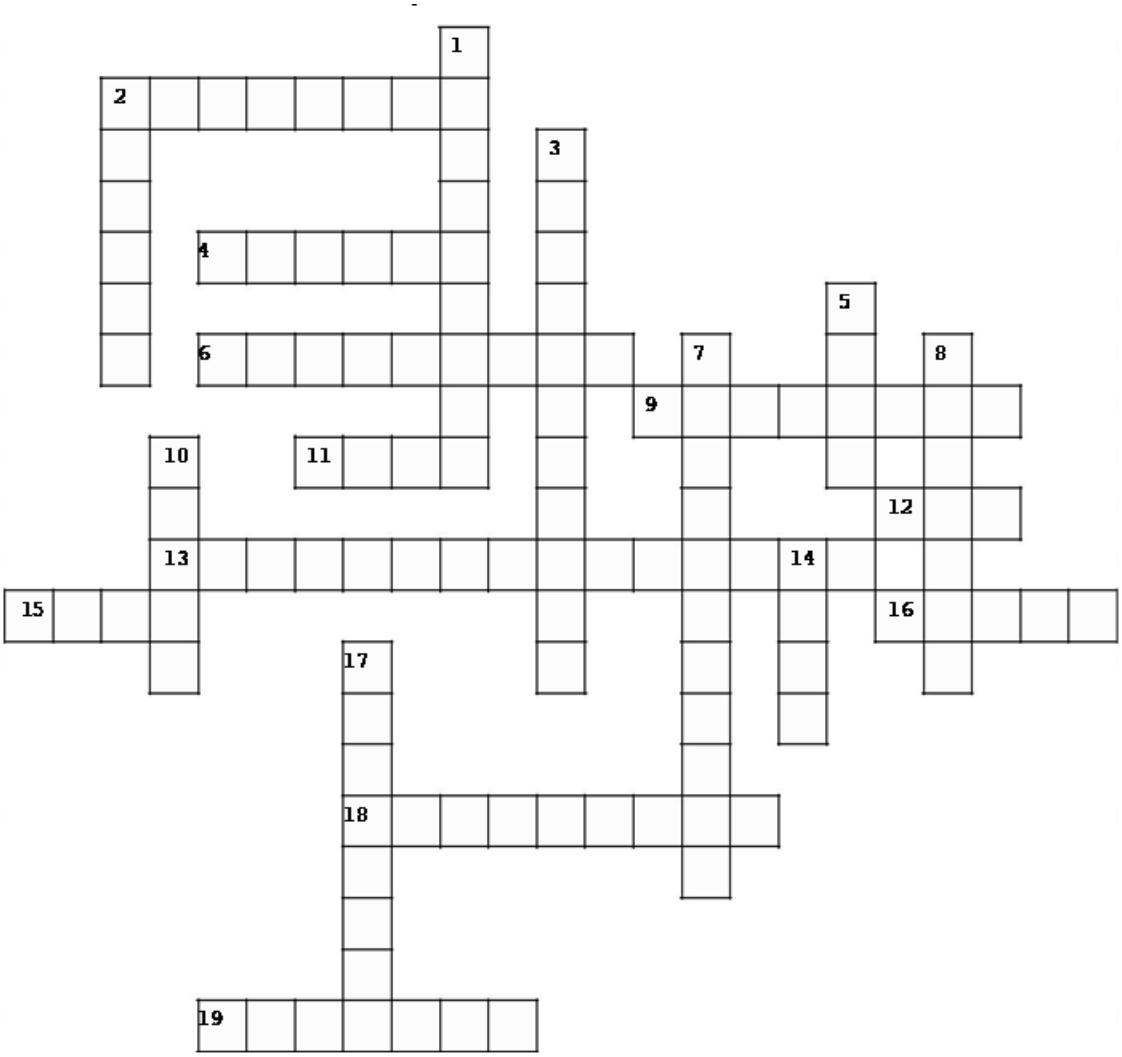
More evidence for controversial theory that Herpesviruses play role in Alzheimer's disease

- The quest to understand what causes Alzheimer's disease -- and to treat it -- is complicated by the disease's long, slow progression and the difficulty of collecting brain tissue samples. But in a large-scale analysis published June 21, 2018 in the journal Neuron, researchers at the Icahn School of Medicine at Mount Sinai use data from three different brain banks to suggest that human herpesviruses are more abundant in the brains of Alzheimer's patients and may play a role in regulatory genetic networks that are believed to lead to the disease.
- Also, researchers at the Institute of Human Behaviour and Allied Sciences identified eight candidate genes related to oxidative stress/ inflammation as potential AD risk markers with potential involvement in viral pathogenesis. These works supports the controversial hypothesis that viruses are involved in Alzheimer's disease and offers potential new paths for treatment.

Reference:

- Ben Readhead, Jean-VianneyHaure-Mirande, et al. Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus. Neuron, 2018; DOI: 10.1016/j.neuron.2018.05.023
- Talwar Puneet, Gupta Renu, etal. Elucidating role of oxidative stress and inflammatory markers in Alzheimer's disease using systems biology approach. Doi:10.2174/1570159X16666180419124508

Microbiology Crossword 02



Clues

Horizontal

2. Species of Bacillus used as control for ETO
4. travellers diarrhea caused by this strain
6. most potent toxin for bioterrorism
9. Shows tumbling motility at 25 degree celcius C
11. transport medium for streptococcus pyogenes
12. Danish 1331 strain used for this vaccine
13. Mickey mouse appearance of yeast
15. Mosquito transmitted virus causing congenital infection
16. strain responsible for Coagglutination
18. species of Koch-Weeks bacillus
19. shows maltese cross forms in blood smear

Vertical

1. CCFA used as selective medium for this species
2. Belongs to genus Nairovirus
3. horizontal transfer of 'R' factor
5. Gel precipitation test for diphtheria
7. Dermatophyte not affecting nail
8. Cells seen in leprosy
10. Fruit bat transmitted fatal encephalitis
14. travellers diarrhea caused by this strain
17. Antigen binding site on antibody

Answers: Next Jeevanu times

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