

## **Pathogenesis of Candida Auris: A Threat Emerging during Corona Pandemic**

### **Abstract:**

The genus *Candida* consists of several species including the *auris* species which is a pathogen which quickly colonizes and spreads on hospital surfaces causes invasive fungal infections even after regular disinfection. It is very potent as it is resistant to several antifungals like the Echinocandins and azoles, which are commonly used to treat invasive fungal infections. Due to this, there is a global threat to public health.

*C.auris* could also spread as a Nosocomial infection which could be through contaminated arm-pit thermometers which will increase spread and dissemination of *C. auris*, to seek protection against which, these multi use devices that are used on several patients should be cleaned carefully.

In patients hospitalized with COVID-19, systemic fungal co-infections have been very common which may increase severity of disease and be detrimental to the process of treatment and may also prove to be fatal.

COVID-19 infection suppresses immunity of the patients which can be explained by the attenuated CD80 upregulation of monocytes and abolished release of IL6, TNF, IL1a and IL1b against *Candida* species making the patient more susceptible to secondary co infections.

The similarity between Covid and Candidiasis is that, both emerge suddenly and spread astonishingly quick which cannot be easily comprehended by the traditional epidemiological analysis.

The dry biofilms formed in *C. auris* protects the microbe from complete removal due to robust cleaning. It was also found that *C. auris* particles were obtained from patients with chronic respiratory disease using genome sequencing and multilocus microsatellite genotyping.

In timeline of April to July 2020, two-thirds of the COVID cases affected by candidemia admitted in the Intensive Care Unit in New Delhi were due to *C. auris* and the mortality rate was around 60%.

**Key words:** fungal infections, candida auris, candidemia, immunocompromised, Corona

## **NARRATIVE REVIEW ARTICLE:**

### **Introduction :**

The first case of *Candida auris*, a new and opportunistic nosocomial fungal pathogen was initially found in Japan in year 2009. Since then, the cases have been found in hospitals across five different continents. As the trends depict, it has been observed that a particular rise in the incidence of occurrence of *Candida auris* has been seen during the COVID19 pandemic (1)

What generally makes treating *C. auris* difficult is that it is a multi-drug resistant fungus that can cause invasive infection.

**Objective :** The study of occurrence of novel *Candida auris* during covid pandemic and the risk factors, spread and prevention involved.

### **History and Attributes:**

First found in the year 2009, the retrospective analysis of the culture collections of *C. auris* led to the identification of some of its isolates which were often misidentified as *C. haemulonii*, including a bloodstream isolate obtained in 1996. This was basically because upon phylogenetic studies, *C. auris* was found to be closely related to *C. haemulonii* complex members. The criteria of identifying the clades of this complex are geographical origin and their different infective behaviour like some isolates causing infections that are invasive, while some cause frequent outbreaks. A possible explanation for these differences can be that *C. auris* initially emerged from a common ancestor and then migrated to different geographical locations, and diversified genetically partly steered by antifungal prescribing practices. (2)

Thermotolerance and salinity tolerance are two unique features of *C. auris* that distinguish it from its close relatives belonging to the *C. haemulonii* complex. Evolutionary stories explain this by suggesting that *C. auris* may have primitively existed as a plant saprophyte in specialized ecosystems and that climate change, specifically global warming, may have contributed to its ability to grow at higher temperatures leading to its evolution as a human pathogen proposing the aquatic environment as the natural habitat of *C. auris*. (2)

On further exploration, several; clades of *C. auris* were isolated from the untouched salt marsh area with absence of human activity and from a beach. The study therefore succeeded in isolating *C. auris* for the first time from the tropical coast, and not from the usual hospital environmental setup, suggesting its association with the marine ecosystem. Funnily, some of these were multidrug-susceptible while some were multidrug-resistant. These findings thus provided an environmental source for clinical isolates and that the common ancestor of *C. auris* has likely adapted to higher temperatures recently.

The virulence factors associated with *C. auris* infections are not completely understood yet Genome comparisons have shown that *C. auris* has the capacity to adapt to different environments and possesses many pathogenic mechanisms which are in common with other *Candida* species. For infection, *C. auris* has pathways for cell wall modelling and acquiring nutrients along with the production of hydrolytic enzymes such as phospholipases and proteinases likely involved in the adherence of the fungus and the invasion of host cells while infecting. Along with this, they were found to carry out, tissue invasion and immune destruction and multidrug efflux. *C. auris* genome also reads for several lytic enzymes like proteases, secreted lipases and phospholipases. It also reads for several *C. albicans* factors like the orthologs of agglutinin, that are needed for adhesion, biofilm formation and virulence. The ALS3 and ALS4 sequence of *C. albicans* are the adhesin genes identified in *C. auris*. ALS3 is needed for the fungal hyphae to attach to the epithelial cells, endothelial cells, and the extracellular matrix proteins and thus lead to the endocytosis of the host cell. (3)

*C. auris* can form dry biofilms on several surfaces thus making its own nosocomial transmission from several medical devices much easier. This is its survival mechanism in order to remain viable on such surfaces for months. This special ability to form biofilm, that belongs to *C. auris* has enhanced its role as a persistent colonizer and also increased its pathogenicity with an additional advantage of protecting it from antifungal drugs. Additionally, a number of genes, particularly those encoding efflux pumps such

as MDR and CDR homologs and enzymes that modify glucan with the key role in biofilm extracellular matrix formation were raised during biofilm formation, and their inhibition increased fluconazole - susceptibility of biofilms.

Plasticity of both morphologic and metabolic types, increase virulence in pathogens of both bacterial and fungal origin, this versatility allows the pathogenic organisms to adapt quickly to different environmental conditions.

### **Epidemiology in Relation with COVID-19:**

The initial patient with respiratory colonization by *C. auris* died within 8 days in the intensive care unit even before the results of the culture could be obtained. The patients admitted next were diagnosed with *C. auris* almost a month post being admit for COVID. This, then brought forth the need for screening of patients admitted to the ICU for *C. auris*. As a result, all patients except the first one infected with *C. auris* received prophylaxis of long-term broad-spectrum antibiotics for bacterial infections, before *C. auris* colonization could be diagnosed. (2)

In COVID patients diagnosed with *C. auris* candidemia almost 50% people were diagnosed for covid after the start of colonization. Except the first patient, all the patients infected with *C. auris* were simultaneously infected with other diseases.

Multiple strains of *C. auris* were found to be resistant to azoles and some also to amphotericin B, but some were susceptible to echinocandins. In candidemia patients, a mortality rate of 50% was reported in a month after isolation of *C. auris*. The sequencing of the entire genome of the isolated strains showed a proximal genetic relationship of the strains. (3)

The *auris* species can be transmitted very easily in healthcare setups, similar to the transmission of pathogens that are resistant to multiple drugs, such as the members of Enterobacteriaceae family resistant to carbapenem and those like *Staphylococcus aureus* resistant to methicillin. (4)

Although the equipment used by healthcare professionals for protection significantly reduces the transmission of pathogens by medical personnel, despite of even the best infection control measures, a significant increase in the rate of staph infection has been recorded in patients with SARS during the outbreak. (5)

The COVID19 pandemic will likely affect underserved public health systems in developing countries that are not adequately prepared for this worst pandemic. ICU teams must confront the challenge of bed overcrowding and vulnerable infection prevention practices to prevent spread of *C. auris* under such conditions (6)

### **Risk factors:**

The factors that increase the risk for raised incidence of candidiasis in patients with COVID19 involve procedures that are invasive such as intubation, which would predispose the lung tissue to the formation and proliferation of fungal colonies especially in patients with a history of chronic lung disease. Other risk factors include prolonged corticosteroid therapy, the patient's improper immune disposition, and antimicrobial therapy.

When considering risk factors, in a study that compared coinfections in terminal patients with and without COVID19, the need for invasive ventilation was shown to be the most relevant factor in the development of coinfections with pathogens resistant to antifungals, in severe cases of COVID19.

Risk factors for COVID19-related candidiasis includes prolonged hospitalizations, mechanical ventilators, venous catheterization, surgery, and the use of broad-spectrum antibiotics.(7)

Similarly, COVID19 patients with candidemia are mostly found in the ICU and receiving immunosuppressants. For identifying risk factors, other studies demonstrated raised incidence of secondary candida infections that are resistant to echinocandins in an elderly patient hospitalized with COVID19, the antifungal treatment administered was ineffective and likely worsened the disease. The need for strict monitoring of resistance to antifungals was also observed to regulate the dynamic use of effective antifungal agents while managing the patients in the intensive care unit.(8)

### **Pathogenesis of Candidiasis in relation with COVID19:**

Due to the coronavirus, the symptoms that are indicative of the infection include difficulties in breathing.

In severe cases some typical symptoms are noted, on occurrence of which, immediate intervention in hospitals, which will include, oxygenation and mechanical ventilation is of utmost importance. In such cases, a variety of other complications have been seen, which

includes secondary infections acquired through hospital infections with pathogens that are highly opportunistic in nature, including yeast and fungal infections. Fungal co-infections have increased in COVID-19 patients in intensive care units (ICU) affected by the current pandemic due to.(9)

Case incidence of the patients of COVID-19 that are critically ill being affected by aspergillosis and yeast infections has been found to be 14.1% and 12.6%, respectively. This has been reported amongst several medical centres across Wales.(10)

One of the greatest concerns worldwide before the COVID pandemic hit us was how the microbes posed a threat to mankind as the bacteria and fungi developed antimicrobial resistance. To minimize the impact of this antimicrobial resistance, it has been advised to have adequate proper execution of measures to control infection. (11)

In patients with COVID, maximizing the prescription of antimicrobials is a difficult process, especially in critical cases, as the characteristics of the images and parameters followed in the laboratories due to which there is confusion thus distinguishing between bacterial coinfection and effects of SARS-CoV-2 becomes difficult. The proper execution of measures to limit the spread of pathogens that are resistant in facilities such as, COVID-19 intensive care units could be particularly difficult.

*C. auris* can also form colonies on the skin of patients that remain for a long time and contaminate the surrounding area, causing outbreaks in hospitals.(12)

### **Diagnosis and Identification:**

The screening programme for Carbapenemase Producing Organisms (CRO) identified a person recently hospitalized abroad who was housed in a single room under preventive contact arrangements tested positive for colonization of CRO. The authorities of healthcare department demanded the patient to undergo tests for colonization by *C. auris*. In anticipation of the results of the tests, the laboratory under microbiology department of the hospital identified specimen of *C. auris* in the isolate obtained from patient. The case of *C. auris* led to the implementation of an extensive prevention plan for the infection in collaboration with the healthcare unit which included isolation, cleaning and disinfection of surroundings, education, hygienic precautions.

Reducing traffic in the operating room would be safer for the patients admitted in the hospital. The project included the need for properly assessing, making observations directly

during cases, proper presentation of data analysis, proper literature research, and training for leadership.

### **Treatment and difficulties:**

Immunosuppressants inhibit all sorts of immune responses of the individual through appropriate mechanisms of immune mismanagement, thus increasing the susceptibility of patients to invasive fungal diseases. The ways of treatment used currently for those affected by severe COVID19 are immunomodulatory. These immunomodulators are anti-inflammatory and thus important to counteract the increased and unregulated release of cytokines that are pro-inflammatory in action. During the SARSCoV2 infection, these cause a cytokine storm, primarily in the lungs. Therefore, immunosuppressants are used for treatment of severe cases of COVID19 in the intensive care unit. (13) The medications hence usually used are, dexamethasone, methylprednisolone, hydrocortisone etc.

In particular, corticosteroids have a qualitative immunosuppressant effect on the immunity through the impairment of various effector immune cells, such as the monocytes, polymorphonuclear leukocytes, T lymphocytes, and macrophages, and are an important immune risk factor acquired for pulmonary aspergillosis. (14)

Therefore, the use of corticosteroids to treat end-stage COVID patients have contraindications like promoting secondary microbial infections in patients.

In the current COVID pandemic, the possible link between the use of corticosteroids based immunosuppressants and the prevalence of fungal infections in patients with end-stage COVID19 has been discussed. A study conducted in multiple COVID19 ICUs in Wales found that when corticosteroids are used in high dosages, they significantly raise the likelihood of COVID19 patients developing aspergillosis.

Even in Brazil, in a Chicago study of 111 COVID19 patients who received tocilizumab, scientists found a severe increase in candidemia in many seriously ill COVID19 patients who received high-dose corticosteroids. Also, the risk of fungal pneumonia in such cases can be identified by presence of the antibody that inhibits the binding of IL6 to the membrane and soluble receptors. (15)

Contradicting, it was also observed, in a study report of 4,313 COVID19 patients in New York, corticosteroids usage did not seem to have a link with an increase in bacteraemia or fungal disease compared to those who did not use corticosteroids when given in the first

week of ingestion. This report, thus advocates the administration of low doses of corticosteroids early itself. However, several other reports, also seem to have explained the high incidence of systemic fungal infections by administration of high doses of corticosteroids over a long period of time thus negating the benefits of these drugs. (16)

### **Conclusion:**

Multiple types of hospital infections with poor scope of treatment due to *C. auris* have been identified. Thus, there is an immediate need of effective treatment guidelines and to definitively identify *C. auris* infection in patients. Best disinfection and safety protocols are needed to prevent colonies of this opportunistic pathogen from forming in intensive care units and hospital wards. (17)

Increasing incidence of *C. auris* outbreaks in many countries on all inhabited continents makes *C. auris* the leading cause of invasive fungal infections in recent years. The outbreaks of this pathogenic fungus primarily in facilities that deal with care for elderly patients with debilitating comorbidities leading to high mortality rates making it a threat for healthcare. Incorrect detection through routine diagnostics along with rapid transmission and resistance to elimination by disinfection procedures carried out in surroundings. (18) The potential of *C. auris* to develop resistance to multiple classes of antifungal medications and their ability to survive in the healthcare sector escaping elimination makes *C. auris* the leading cause for invasive fungal infections in many healthcare facilities today.

Rapid and reliable identification methods and careful infection control measures can help contain the spread of *C. auris* and prevent and control outbreaks. Coinfection is possible in patients with COVID19 and while diagnosing it, clinicians cannot rule out co-infection with other respiratory pathogens, nor can they exclude COVID19 by detecting non-SARSCoV2 respiratory pathogens. (19)

Prevalence of coinfection by COVID19, risk of coinfection, distribution and influence of coinfection on the health of patients with COVID19. After receiving data on SARSCoV2 coinfection, antimicrobial agents may be recommended in suspected. The rapid transmission of *C. auris* in medical care despite rigorous infection control measures leads to outbreaks occurring amidst the COVID19 pandemic. Thus, rapid case detection and reporting is essential. The need for national and regional surveillance programmes is necessary to better understand the extent of *C. auris* infection and assess the clades, thus guiding the implementation of rigorous strategies in order to contain the spread of this pathogen. (20-28)

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