An Investigation of the Emerging Fungal "Superbug" Candida auris and its Potential Adverse Effects in Vulnerable Populations

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Abstract

Introduction

An aging woman in a nursing home struggles to survive. She relies on a breathing machine and feeding tubes for nutritional support. In addition to respiratory failure, kidney disease, high blood pressure, and irregular heartbeat, she has just received the diagnosis of a *Candida auris (C. auris)* infection that she likely received from her long term healthcare facility [1]. In May of 2018, an older gentleman was admitted to Mount Sinai Hospital for abdominal surgery. He underwent a blood test that revealed that he was infected with a newly discovered pathogen. The doctors proceeded to isolate him in the intensive care unit, where he eventually passed away. After the patient's death, *C. auris* was found to be everywhere - from the table where he kept his belongings to the sheets he laid on [2]. These are only a few of countless cases in which the mysterious emerging pathogen *C. auris* has infected vulnerable patients.

Known for its capability of causing severe illness in immunocompromised populations and its multidrug resistance, *C. auris* is a fungal pathogen that has become a serious global threat. Over the last five years, it has hit a neonatal unit in Venezuela; swept through a hospital in Spain; forced a prestigious British medical center to shut down its intensive care unit; and taken root in India, Pakistan, and South Africa [2]. Recently *C. auris* has reached New York, New Jersey, and Illinois, forcing the Centers for Disease Control and Prevention to add it to a list of pathogens deemed "urgent threats."

INTRODUCTION

An aging woman in a nursing home struggles to survive. She relies on a breathing machine and feeding tubes for nutritional support. In addition to respiratory failure, kidney disease, high blood pressure, and irregular heartbeat, she has just received the diagnosis of a *Candida auris (C. auris)* infection that she likely received from her long term healthcare facility [1]. In May of 2018, an older gentleman was admitted to Mount Sinai Hospital for abdominal surgery. He underwent a blood test that revealed that he was infected with a newly discovered pathogen. The doctors proceeded to isolate him in the intensive care unit, where he eventually passed away. After the patient's death, *C. auris* was found to be everywhere - from the table where he kept his belongings to the sheets he laid on [2]. These are only a few of countless cases in which the mysterious emerging pathogen *C. auris* has infected vulnerable patients.

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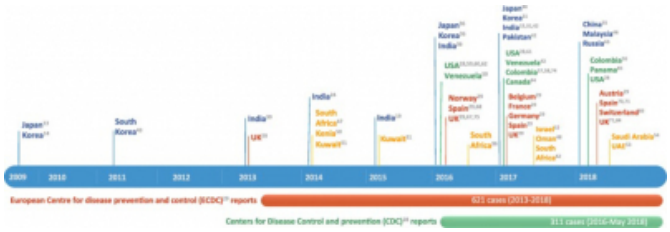
The *Candida* genus consists of various yeast species which can cause infections in humans by invading the bloodstream [2]. Due to its resistance against common forms of treatment, particularly antifungal drugs, *C. auris* is considered an emerging "superbug." In fact, out of the approximately 200 different species of *Candida*, only a

small number of species contained within the genus have the ability to infect humans [3]. *C. auris* and approximately 30 associated species have been identified as causes of human infection, and this list continues to expand [4].

Figure 1

Timeline chart of C. auris reported cases.



The reports from the European Centre for Diseases Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) are ongoing [8].

As of April 30, 2019, *C. auris* cases have been identified in 34 countries with 684 confirmed or probable clinical cases in the United States [5]. Because these pathogens are opportunistic and only over-colonize hosts that are immunocompromised, these factors contribute to an increased susceptibility to *C. auris* infections in hospital settings. A timeline of cases can be observed in Figure 1.

The first case in which *C. auris* was identified as an emerging pathogen dates back to 2009 when Satoh et al. first discovered the pathogen in the ear canal of a hospitalized patient in Japan [3]. As it was reported, a microorganism identified as a member of the *Candida* genus was found in discharge of the external ear canal of a 70-year-old at Tokyo Metropolitan Geriatric Hospital [6]. Subsequently, 15 patients in South Korea were found to have chronic otitis media with *C. auris* as the leading cause of infection in each patient [7]. Interestingly, the fungal species name auris translates to "ear" in Latin.

The number of *C. auris* cases has increased considerably over the past decade since the first reported infection in 2009. This steady growth has been associated with increased mortality rates in patients that are critically ill, have an immunocompromised status, have undergone invasive surgical procedures, or are taking broad spectrum antimicrobials [8]. *C. auris* has been found to be resistant to the three major classes of antifungal drugs, i.e. azoles, polyenes, and echinocandins [9]. The high rates of mortality associated with *C. auris* infections clearly demonstrate the dangers of this pathogen's developed resistance to commonly used antifungal agents. The fungus is also particularly dangerous due to the fact that *C. auris* remains unnoticed in routine microbiology laboratories, as 90% of the isolates characterized by commercial identification systems are misidentified as *Candida haemulonii* [10].

C. auris is a rapidly emerging pathogen that causes severe infections with high mortality rates. This paper aims to disseminate information on how to control further outbreaks, while exploring the medical, public health, and ethical issues pertaining to this "superbug" *C. auris*.

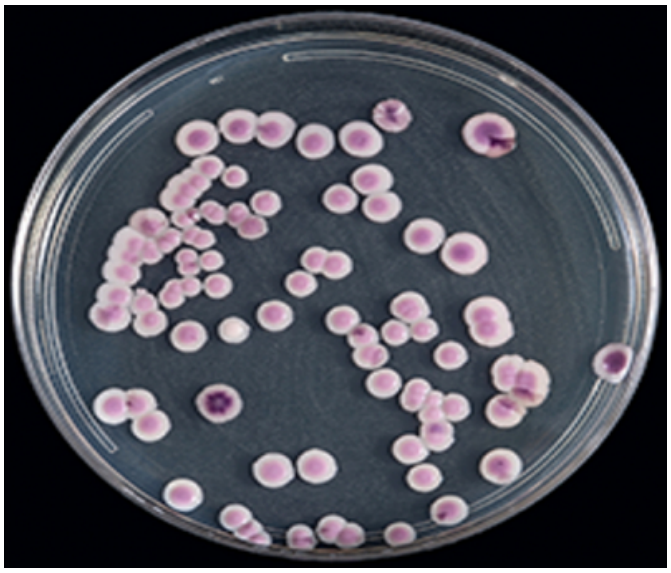
MEDICAL ISSUES

The "superbug" *C. auris* is an emerging pathogen that has caused invasive candidiasis in hospitals around the world, with mortality rates close to 60% [11]. As noted above, the fungal infection, related to the more commonly encountered fungus *Candida albicans*, was first isolated from a Japanese patient's ear canal in 2009 and was subsequently reported in South Korea as an infection of the bloodstream in 2011 [12]. The bloodstream, urinary tract, and respiratory tract have been cited as its most frequent sites of infection [11]. The high mortality rate associated with the pathogen is likely caused by multifactorial issues including its apparent resistance to conventional treatment and its resemblance to other fungal species, which makes it particularly difficult to accurately identify. According to the CDC, roughly 50% of patients who develop a *C. auris* infection die within 90 days [2].

Although a myriad of fungal species inhabit planet Earth, only a few hundred of them have thus far been reliably implicated in causing human disease [13]. By using whole genome sequencing, genetically different clades of the organism have been found in Southern Africa, South America, East Asia, South Asia, and Europe [10]. As shown in Figure 2, *C. auris* appears beige and pink on chromogenic agar. *C. auris* forms elongated oval cells rather than hyphae or pseudohyphae reminiscent of other species.

Figure 2

Candida auris on CHROMagar [3]



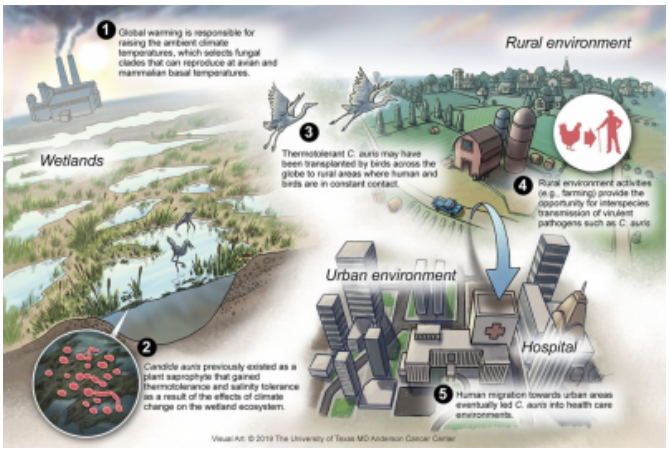
Although the exact reasons for the rise in *C. auris* infections are unclear, possible factors include specific characteristics of the fungal species, excessive use of antifungal drugs for prophylaxis or treatment, different methods of diagnosis, complexities in identifying species, and changes in healthcare environments [11]. The organism has demonstrated the ability to persist on medical devices and various objects in a hospital room including reusable equipment such as axillary temperature probes. A hospital in New York conducted tests on the room of a patient who died from the pathogen and revealed that the organism was found almost everywhere in the room, "the walls, the bed, the doors, the curtains, the phones, the sink, the whiteboard, the poles the pump... the mattress, the bed rails, the canister holes, the window shades, the ceiling…" [2]. The ability of the organism to survive on these various surfaces is a characteristic that further contributes to the proliferation of this fungal infection.

An additional factor which contributes to the persistence of *C. auris* is the fungal pathogen's ability to survive in a wide range of temperatures. In fact, a study published in the journal mBio theorized that the emergence of resistant organisms is related to the phenomenon of climate change [13]. Throughout history, natural fluctuations in climate have played a pivotal role in the shaping of many ecosystems. During the course of time that mammals have inhabited Earth, they evolved defences against fungal species. These include high body temperatures creating "thermal restriction zones" that serve to protect against invasive disease by these fungi [13]. Interestingly, climate change may lead to a decreased difference between ambient temperatures and mammalian temperatures that could result in the natural selection of fungal species which are able to grow at higher temperatures in general. Furthermore, when the thermal selectivity of *C. auris* was studied, research suggested that *C. auris* can tolerate a broader range of temperatures compared to other fungal species.

C. auris is not found in the gut where there are higher temperatures but is often observed on the skin where there are cooler temperatures [13]. These factors suggest that the organism originally colonized plant species and only later developed the ability to infect the mammalian species as well. This progression resembles the adaptive behavior of other environmental pathogens. It has been hypothesized that *C. auris* may have been a plant saprophyte which gained "thermotolerance and salinity tolerance as a result of effects on climate change on the wetland ecosystem" [13]. The transmission of *C. auris* with regard to its thermotolerance characteristics is illustrated in Figure 3.

Figure 3

Illustration of C. auris transmission mechanisms.



Global warming may have selectively chosen clades of fungi that could reproduce at mammalian basal temperatures. Climate change resulting in higher average global temperatures may lead to the selection of *C. auris* that could resist harsh environments and further the transmission of the fungal pathogen to urban environments [13].

In addition to thermoresistance capabilities, other characteristics of *C. auris* have been analyzed. The complete genome of *C. auris* has recently been investigated to develop a better understanding of the role of the different genes that influence its resistance mechanisms and virulence. When

comparing the *C. auris* genome to the related fungus *Candida lusitaniae*, which has shown resistance to powerful antifungals such as amphotericin B, research suggests that both species contain proteins involved in antifungal resistance [14]. When comparing *C. auris* and *Candida albicans*, many genes were identified that code for several resistance and worsening resilience factors such as biofilm formation, lipases, proteases [14].

C. auris is also resistant to commonly used antifungal treatments such as voriconazole, fluconazole, and posaconazole. Even more concerning, up to 18% of *C. auris* cases were resistant to a typically more efficacious and potentially toxic antifungal, amphotericin [11]. The organism has been able to spread rapidly amongst patients and can live on skin whereas other forms of candidiasis often arise from a patient's own gastrointestinal tract. This is primarily due to the poor growth of *C. auris* in anaerobic environments such as the gastrointestinal tract [12]. Over time, it would not be surprising if the organism were to develop new modes of growth which could potentially resist even harsher environmental conditions in the human body.

The high mortality rate of candidiasis may be due to the organism's ability to target patients whose immune systems are comprised. For example, patients with the condition neutropenia are vulnerable since they lack of neutrophils, a type of white blood cell which is the first line of defense against infection [12]. Research papers investigating the details of neutrophilic response to *C. auris* have demonstrated peculiarities in the formation of neutrophil extracellular trap formation, a mechanism by which neutrophils encapsulate and diminish the virulence of pathogens through phagocytosis and the binding of invaders to neutrophilic fibers [12]. It has been shown that these neutrophilic traps may not be effective in fighting *C. auris*. Whether this may be due to a morphological change caused by cytokine release from the pathogen or some other form of evasion is not yet completely understood.

Due to the organism's persistence, scientists have been studying different compounds which may prove to be effective against *C. auris* strains. As the organism exhibits multidrug resistance that has not been observed for other types of similar species, there has been renewed interest in utilizing other types of pharmacological agents apart from the normal major antifungal drug classes such as the -azoles, pyridine analogs, polyenes, and echinocandins. A study published in the journal Antimicrobial Agents and Chemotherapy produced interesting results regarding the efficacy of Histatin-5 (Hst 5), a compound known as an antimicrobial peptide (AMP), which normally plays a role in innate immunity [15]. In the study, which was conducted in vitro, the fungicidal activity of this antimicrobial peptide was studied against *C. auris* strains from different geographical sites. The study found morphological changes between different strains of *C. auris*. When grown on CHROME-agar, half of the fungal isolates formed light pink colonies while the other half grew dark pink colonies, suggesting that there are various subtypes of the organism which may respond differently to various types of medications. The study also found that fluconazole-resistant strains of *C. auris* have shown some susceptibility to Hst 5. At lower doses of Hst 5, only 38% of C. albicans isolates were killed whereas 58-98% of *C. auris* isolates were killed at those lower doses [15]. In addition, the "superbug" has shown higher tolerance to chemical and oxidative compounds that would normally be able to kill other pathogens. *C. auris* has even been found to be able to survive within neutrophils, which are the first line of defense of the immune system. Finding ways to combat this "superbug" will certainly require innovation and the utilization of certain peptides like histatin 5, which may provide alternate modes of infection control.

Despite the apparent lack of predictable patterns demonstrated by *C. auris*, the fungal pathogen has shown a predisposition for certain types of patients, such as those with a history of multiple surgical procedures, mechanical ventilation, gastrostomy tube placement, and vascular catheterization [12]. Given its predisposition for colonizing medical devices, the organism has the ability to create biofilms, films of organisms that have been shown to effectively evade host defenses. Several studies have been conducted in animal models which revealed varied virulence of *C. auris* compared to *C. albicans* species. Research using murine models involving immunocompetent and immunocompromised mice suggests that *C. auris* is more virulent in immunocompromised individuals. [12]. Ongoing research should focus on the role that the genetic and phenotypic diversity of *C. albicans* has in influencing virulence. Excessive antifungal usage will likely increase its resistance to treatment options.

PUBLIC HEALTH ISSUES

According to the Centers for Disease Control (CDC), public

health policy involves studying and implementing policies that encourage the prevention of disease and practices that protect and increase the well-being of the general public. *C. auris*, like other "superbugs," has proven to be a serious threat to global health for multiple reasons, including its persistence in the environment, resemblance to other fungal species, multidrug resistance capabilities, severe virulence profile, and associated high mortality rates.

Cases of *C. auris* have been documented in countries including Austria, Australia, Bangladesh, Belgium, Canada, China, Colombia, France, Germany, India, Iran, Israel, Kenya, Kuwait, Malaysia, Netherlands, Norway, Oman, Pakistan, Panama, Russia, Saudia Arabia, Singapore, South Africa, South Korea, Spain, Thailand, United Arab Emirates, United Kingdom, United States, and Venezuela [18]. *C. auris* outbreaks have been reported in numerous countries including Colombia, India, Pakistan, Panama, Spain, the United Kingdom, the United States, and Venezuela [19]. The widespread impact of *C. auris* is a cause for concern and necessitates the establishment of standardized guidelines for prevention and control of such infections.

Currently, there are no established hospital protocols for dealing with *C. auris*; however, the CDC has provided some guidelines in treating this "superbug." According to the CDC, the mainstay of infection control measures for *C. auris* in acute care hospitals and high acuity post-acute care settings is as follows:

- Place the patient with *C. auris* in a single-patient room and use Standard and Contact Precautions. These precautions include the usage of hand hygiene, gloves, gowns, and proper eyewear [3].

- Emphasize adherence to hand hygiene following any patient contact. Clean and disinfect the patient care environment and reusable equipment (daily and terminal cleaning) with recommended products [3].

- Maintain inter-facility communication about patient's *C. auris* status at transfer to another healthcare facility. When patients are transferred to other healthcare facilities, receiving facilities should receive notification of the patient's *C. auris* infection or colonization recommended infection control precautions [3].

- Screen contacts of newly identified case patients to identify *C. auris* colonization.

A study by Arastefar et al. developed a tetraplex Polymerase Chain Reaction (PCR) method that would allow for a more accurate low cost screening of *C. auris* [20]. PCR involves amplifying DNA fragments and subsequent sequencing enables the identification of fungal and bacterial pathogens when used in a clinical diagnostic setting. Misidentifying *C. auris* can lead to futile courses of action that do not stop the infection. Even if there is difficulty with directly identifying the presence of *C. auris*, research suggests that isolating non-*Candida albicans* samples with fluconazole resistance would also be an indicator of a potential problem involving *C. auris* [21]. This information regarding *C. auris* identification would be useful for informing physicians and other healthcare providers involved in the potential diagnosis and treatment of the infection. Treating the wrong infection is dangerous not only because it fails to address the root cause of the ailment but could also further contribute to drug resistance.

- Conduct surveillance for new cases to detect ongoing transmission. The CDC recommends that all yeast isolates obtained from a normally sterile site such as from the bloodstream, cerebrospinal fluid, etc. should be identified to the species level so that appropriate initial treatment can be administered based on the typical, species-specific susceptibility patterns. *C. auris* has been identified from several different body sites including the urine, bloodstream, respiratory tract, biliary fluid, wounds, and external ear canal. Approximately half of clinical cases in the United States have been in the bloodstream and the remainder have been found in non-invasive body sites. Many clinical laboratories do not typically determine the species of isolates from non-sterile sites since presence of C. in these sites may represent colonization rather than infection and would not require treatment. However, it is important to note, that *C. auris* should be identified even from a non-sterile body site because its presence in any body site can represent wider colonization, posing a risk for transmission and requiring implementation of infection control precautions [3].

Similar to bacterial "superbugs" that are resistant to various antibiotic treatment, *C. auris* is classified a "superbug" due to its resistance to many common classes of antifungal drugs. In some cases, *C. auris* can be eliminated with the use of an antifungal drug class known as echinocandins, which target cell wall synthesis. Echinocandins have been shown to eliminate fungal pathogens from the same *Candida* genus, including *Candida albicans*, *Candida parapsilosis*, and

Candida guilliermondii [22]. The specific mechanism of action involves echinocandins allosterically inhibiting - (1, 3) - D-glucan synthase responsible for fungal cell wall formation [22]. The loss of a functional cell wall leads to the inability to regulate osmotic pressure and eventually causes cell death. However, *C. auris* is becoming increasingly resistant to echinocandin treatment and other antifungal drug classes including azoles and polyenes [23]. Azoles and polyene drugs work by interfering with the structure and function of fungal cell membranes. While azoles inhibit C14-demethylase to prevent ergosterol biosynthesis, polyenes form channels that cause the leakage of molecules from fungal cells by interacting with sterols present in the membrane [24].

The increased usage of antifungal treatments such as those from the previously discussed drug classes may allow *C. auris* to become more drug resistant due to natural genetic variation. Such antifungals eliminate sensitive strains of *C. auris* but allow the more resistant strains that possess different versions of genes for encoding protein kinases or efflux pump transporter proteins to proliferate [17]. Due to the pathogen's increased resistance to antifungal treatments, extra care should be taken regarding the administration of such drugs to patients. Furthermore, individuals must not attempt to treat their own infections by taking such medications to prevent further development of drug-resistant strains.

While multiple studies concerning alternative antifungal treatments for *C. auris* have been published, more research is needed before the drugs can be incorporated into established treatment protocols and guidelines. Some compounds that have been shown to significantly inhibit *C. auris* include suloctidil, ebselen, pyrvinium pamoate and dimethisoquin hydrochloride, suloctidil and ebselen [23,25]. Although these compounds have been shown to treat *C. auris*, it is important that these drugs are not used excessively to reduce the chance of developing more "superbugs."

Resistance to various forms of treatment makes *C. auris* difficult to eliminate, allowing this fungus to cause a high morbidity and mortality. According to current literature reviews on *C. auris*, mortality is estimated to be between thirty to seventy-two percent [26]. *C. auris* poses a particular threat to severely ill and/or immunocompromised patients [8]. Furthermore, mortality is more frequent in older populations [27], particularly among hospital patients and nursing home residents. For these reasons, special attention and stricter protocols are necessary in these healthcare facilities.

Studies have shown that similar to other members of the *Candida* genus, *C. auris* possesses the ability to form biofilms which allow the fungal pathogen to persist in the environment and further contribute to its virulence and drug resistance [28]. The virulence factor capability of the biofilms further contributes to patient morbidity and mortality since the pathogen can better adhere to surfaces such as the skin of the patient or a medical device or hospital equipment [29]. A biofilm is composed of a community of microbes and extracellular polymeric substances that facilitates microbial communication within its cellular members and acts as a protective mechanism [30]. *C. auris* biofilms are primarily made up of budding yeasts and at times, pseudohyphae [29]. As such, extensive disinfection protocols should be established.

In addition to biofilms, *C. auris* possess other virulence capabilities that enable the fungal pathogen to cause disease. Some of these virulence factors include adhesions, transporters, and enzymes that break down specific macromolecules including proteins, lipids, and phospholipids [29]. Such virulence factors allow the fungal pathogen to possess resistance capabilities to antifungal treatments including azoles. In fact, azoles are only effective for about 50% of *C. auris* isolates [26]. *C. auris* has been found to be resistant to the azole, fluconazole, about 90% of the time [26].

Furthermore, *C. auris* may be difficult to identify using common laboratory methods, often leading to an inaccurate diagnosis. In addition to having a low accuracy rate, these tests are relatively costly [20]. *C. auris* has been misidentified as different fungal pathogens including *Candida haemulonii*, *Candida albicans*, *Candida famata*, *Candida sake, Rhodotorula glutinis, Rhodotorula mucilaginosa, Saccharomyces, Candida catenulata, Candida lusitaniae, Candida guilliermondii*, and *Candida parapsilosis* [8]. This misidentification often arises due to the genetic similarity of *Candida auris* and other fungal pathogens, specifically those of the *Candida* genus. In particular, *C. auris* is most commonly misidentified as *Candida haemulonii* [31]. Furthermore, due to phenotypic similarity, *Candida haemulonii, Candida famata, Candida sake, Saccharomyces cerevisiae*, and *Rhodotorula glutinis* have also been misidentified as *C. auris* [18].

From a microbiology standpoint, *C. auris* has an oval shape when viewed with a microscope, though its morphology may vary depending on environmental conditions. Typical morphologies that have been reported include round, elongated and pseudohyphal-like [8]. When cultured on Sabouraud's agar, *C. auris* appears as smooth and white cream-colored colonies, while on CHROMagar *Candida* medium, *C. auris* colonies may appear pale to dark pink and occasionally beige [8].

It is noted that *C. auris* has the ability to survive at 42 °C, while *Candida haemulonii* does not [8]. It has been theorized that the ability to withstand higher temperature stresses can be attributed the ability of *C. auris* to secrete increased levels of aspartyl proteinase relative to *Candida albicans* when isolates are grown in the same temperature conditions [32]. This difference allows for a more accurate identification of *Candida haemulonii*.

Regarding the transmission of *C. auris* within hospital settings, it has been hypothesized that the presence of *C. auris* on the surface of the skin is spread through patients' natural skin shedding process, although the exact mechanism of transmission is not entirely known [34]. In addition to colonization of the skin, *C. auris* may also infect other parts of the body. This makes it more difficult to treat and contain infections, especially in Intensive Care Units [19].

Furthermore, it was reported that while some patients may be asymptomatic, *C. auris* has been isolated from their urine samples [27]. The issue with individuals who do not experience symptoms of a *C. auris* infection is that these patients may be carriers of the fungal pathogen and unknowingly contribute to disease transmission. Preventative measures are necessary to protect immunocompromised patients who are at the most risk of becoming infected.

Additionally, another challenge to effective treatment of *C. auris* includes the issue of coinfections. For patients who are the most at risk for *C. auris* infections, the chance of developing a concurrent or additional infection most likely increases. Based on a retrospective study conducted in Pakistan, approximately 31.5% of patients with *C. auris* also had coinfections. Some of these include urinary tract infections and coinfections with multidrug-resistant bacteria [27].

Part of the issue involving the spread of this fungal pathogen involves the fact that *C. auris* can persist on plastics for fourteen days outside of the host environment [35]. The fungus has been isolated from numerous sources including medical equipment, furniture, and sinks that have come into contact with infected patients [21]. This means that extensive cleaning and careful precautions must be implemented in nursing homes and hospital settings. Some studies suggest that products including Quaternary Ammonium Compounds (QACs) and cationic surfactants are not effective, however, products containing chlorine appear to effectively decontaminate surfaces infected with *C. auris* [33]. Research suggests that the use of one percent chlorine, as sodium hypochlorite, is effective for disinfecting all species of *Candida* [33]. Another study has shown that using a high level of chlorine several times a day during the length of a hospital stay followed by final cleaning with chlorine followed with hydrogen peroxide can decontaminate the environment [21]. Research that examined the effectiveness of sodium hypochlorite on different surfaces including stainless steel, ceramic, plastic, and glass confirmed that the compound can completely kill *C. auris* [33].

Furthermore, some studies suggest that many patients who become infected with "superbugs" such as the fungal pathogen *C. auris* or bacterial pathogens reside in long term care facilities [36]. Such patients in these healthcare facilities are often older and immunocompromised, making them more susceptible to "superbug" infections. In a study published in Clinical Infectious Diseases, published by the Infectious Disease Society of American (IDSA), a random sample of residents of long term care facilities and nursing homes were tested for multidrug-resistant organisms (MDROs). These organisms included carbapenem-resistant *Enterobacteriaceae* (CRE), extended spectrum beta-lactamase producing organisms (ESBL), vancomycin-resistant Enterococcus (VRE), along with methicillin-resistant *Staphylococcus aureus* (MRSA) [37]. The presence of these organisms was tested using swabs of the nares, peri-rectal area, axilla, and groin areas of 50 randomly selected adults. Surprisingly, the prevalence of these multidrug resistant organisms was found to be 80% in the long-term acute care facilities and 65% in the nursing homes [37]. Another study published in the Journal of Antimicrobial Chemotherapy, showed that elderly residents in these long-term care facilities also had more than four times the rate of *E. coli* and *Klebsiella UTI* caused by antibiotic resistant bacteria compared with individuals age seventy or above living outside of hospitals and long-term care facilities [37]. These statistics are troubling and emphasize the need to

control the spread of MDROs such as *C. auris* in healthcare settings. The research also highlights the need for judicious medication use and infection control strategies. Possible factors for the observed increase in *C. auris* infections in these healthcare facilities may include a low provider-to-patient ratio, the need for increased education on "superbug" prevention and control, and the lack of specific protocols which are put into place to control the spread of fungal infections [36].

Strategies that may help to prevent and limit the further spread of *C. auris* infections can be implemented. From both a health-status and cost point of view, it is generally accepted that prevention is the most effective strategy for the containment of infections. In the health-care setting, the CDC guidelines suggest using single or a combination of disinfectants including alcohols, chlorine and chlorine compounds, formaldehyde, glutaraldehyde, ortho-phthalaldehyde, peracetic acid hydrogen peroxide, iodophors, phenolics, and quaternary ammonium compounds. At the present, there do not appear to be any specific guidelines for addressing *C. auris*. However, based on research, hospitals should be encouraged to utilize sodium hypochlorite over other less effective disinfectants such as quaternary ammonium compounds, phenolics, peracetic acid, and hydrogen peroxide. Studies have suggested that the frequency of cleaning as well as the cleaning method may also prevent infections from spreading [21]. Since a potential source of *C. auris* transmission may be through skin shedding, it may be beneficial to disinfect surfaces in a patient's room multiple times a day as well as frequently changing the patient's hospital gowns and bedding.

Additionally, increasing the medical staff to patient ratio may also contribute positively to infection prevention [36]. Some hospitals have adopted a screening program which involves analyzing swabs taken from the nose, axilla, groin, and throat of healthcare professionals who have been in contact with patients [21]. Healthcare staff members that have positive samples for the fungal pathogen can be treated with chlorhexidine to prevent infection. Furthermore, other precautions would include having the medical staff wear cuffed long-sleeved disposable gowns, gloves, and aprons when contacting *C. auris* patients [21]. These practices could also be extended to the cleaning staff and visitors to enhance preventative measures.

Furthermore, developing a better understanding of the fungal pathogen as well as other "superbugs" from the perspective of each individual involved in patient care would assist in the effective prevention and control of infections. This would allow for more specific protocols to be developed and would likely increase the chances of adherence to such guidelines. For instance, it may be particularly helpful if guidelines were in place for the separation of patients who are older and/or possess a weakened immune system. For facilities that may not be able to accommodate the isolation of at-risk vulnerable patients, a larger focus on disinfection measures is suggested.

Additionally, while medication is an important part of treatment, the excessive use of prescription drugs, especially the use of a drug that does not treat the infection source further contributes to drug resistance and may even lead to the development of new "superbugs." This is especially the case with antibiotics, which only treat bacterial infections. Antibiotics are often viewed as medications that will cure all kinds of illnesses. These drugs may be even more dangerous when taken as a treatment for an infection that does not involve bacteria but may instead involve a viral or fungal pathogen. Antibiotics may decimate beneficial bacteria, allowing for a fungal pathogen to further proliferate and worsen a fungal infection. While it may be logical to take medications for symptoms of infection, the characteristics of *C. auris* make the pathogen difficult to properly identify and treat, even for trained healthcare providers. Therefore, when dealing with this pathogen, extreme caution needs to be exercised to maintain the safety of both infected individuals and that of other patients who are vulnerable to infection.

Overall, more education concerning the development and transmission of *C. auris* and other "superbugs," proper diagnosis of *C. auris*, effective disinfection techniques, and standardized protocols for *C. auris* treatment can greatly reduce its threat to vulnerable patient populations in healthcare settings such as hospitals and nursing homes. Since *C. auris* is a relatively new "superbug" that has emerged in the last few years and is still not fully understood, the many uncertainties and complexities involved makes it particularly challenging to obtain an accurate diagnosis and formulate appropriate treatment plans. By gaining a deeper understanding of *C. auris*, the infections caused by this fungal pathogen can be effectively managed and contained.

ETHICAL ANALYSIS

In April 2019, the United Nations Ad Hoc Interagency

Coordinating Group on Antimicrobial Resistance "warned that if no action is taken, drug resistant diseases could cause 10 million deaths each year by 2050 and damage to the economy as catastrophic as during the 2008-2009 global financial crisis" [38]. *C. auris* is one of those pathogens that is preying on the most vulnerable people in the world. It is spreading around the globe and has been identified in 34 countries with 684 confirmed cases in the United States [5]. Public health officials worldwide have sounded the alarm regarding the widespread overuse of pharmaceutical medications that has reduced the effectiveness of the drugs that once cured fatal microbial infections. These new "superbugs" are targeting the most vulnerable members of society who have compromised or immature immune systems. "Scientists say that unless more effective new medicines are developed and unnecessary use of antimicrobial drugs is sharply curbed, risk will spread to healthier populations" [2]. A multidimensional approach must be initiated to combat this stealth enemy. This should include new financial incentives for pharmaceutical companies to develop new antimicrobial compounds, new laws to limit the sale of antibiotics, more effective protocols in hospitals and nursing facilities to prevent the spread of these deadly pathogens, and the development of a fast-screening test that can quickly analyze a skin swab in a matter of hours. Ethically, all health care and public health professionals have a responsibility to address this issue. Unless major changes are made on many different levels, millions of vulnerable people will continue to die from these dangerous pathogens. The issue of *C. auris* as a growing public health treat will be evaluated by using basic ethical principles of respect for persons, beneficence, nonmaleficence, and justice.

Respect for persons incorporates two ethical convictions: first, individuals should be treated as autonomous agents, and second, persons with diminished autonomy are entitled to protection. The principle of respect for persons divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy [39]. The patient-physician relationship is a covenant based on mutual respect and trust. A fiduciary relationship is based on honesty. Ethicist Edmund Pellegrino argues the patient-physician relationship is composed of three elements: the patient who is ill and seeking assistance with a need, the physician who will take responsibility for assisting with the needs, and the act of medicine [40]. In this relationship the patient is vulnerable requires the assistance of the physician to help make appropriate medical decisions. "The decision-making process initiates the relationship between the two and will result in a chosen form of treatment" [40]. Physicians must be sensitive to the patient's vulnerability and respect patient autonomy unless it violates the conscience of the physician. The next phase is medical intervention. The physician employs his or her skills to help restore the patient to health or alleviate as much pain and suffering as possible. The patient and physician are in a relationship that hopefully results in a particular medical treatment. Ethicists Pellegrino and Thomasma argue among obligations that arise from the patient-physician relationship is technical competence: the act of the medical professional is inauthentic and a lie unless it fulfills the expectation of technical competence [41]. Regarding *C. auris*, this means that patients can expect their physicians to be aware of *C. auris*, requirements of mandatory pre-admission screening for those most vulnerable are implemented, and that at-risk patients are placed in isolation. Patients can also expect their physicians to be aware that drug-resistant pathogens thrive among immunocompromised and ventilated patients in long-term, acute care hospitals so basic protocols and strategies must be initiated to contain these infections. The final phase of the relationship is outcome. The effect of the caring activity is assessed according to the physical well-being of the patient. Reciprocity of the relationship completes the patient-physician relationship and upholds respect and dignity of the patient. Physicians must not only be aware of *C. auris*, but they have the medical and ethical responsibility to treat the patient holistically. If vulnerable patients have *C. auris*, then they must be placed in isolation, be treated with the appropriate protocols for the containment of the infection and must be followed. If patients are vulnerable to *C. auris* because they are immune compromised due to severe illness or ventilation dependence, physicians must make sure the hospital and long-term care facility utilize sodium hypochlorite to disinfect all equipment and consistently utilize disposable gowns and latex gloves. Failure to care for the patient holistically clearly violates the ethical principle of respect for persons. If physicians are committed to treating every person with dignity and respect, then the barriers to containment of infections and treatment must be lifted to ensure this commitment, and emphasis must be placed on patient dignity and respect. Recognizing the impact of *C. auris* and advocating for new regulations will help to achieve this goal.

Beneficence involves the obligation to prevent and remove harms and to promote the good of the person by minimizing possible harms and maximizing possible benefits. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim Primum non nocere: Above all do no harm. A number of initiatives can be instituted by physicians, and state and federal regulatory departments to help maximize benefits and minimize harms. First, physicians need to become better educated on *C. auris* and how this infection is spread. Second, physicians must become better educated about the use of infection control protocols and procedures in order to protect their patients. A study published in June in the Journal of Clinical Infectious Diseases found that patients and residents in long-term care settings have alarmingly high rates of drug-resistant colonization, which means they carry the germs on their skin or in their bodies, usually without knowing it, and can transmit them to staff members, relatives or other patients. Elderly or severely ill people with weakened immune systems who carry the germ are at high risk of becoming infected [1]. Hospitals and physicians should require mandatory pre-admission screening of all patients believed to be at risk and isolate these patients. Third, as stated above, the CDC guidelines suggest using single or a combination of disinfectants including alcohols, chlorine and chlorine compounds, formaldehyde, glutaraldehyde, ortho-phthalaldehyde, peracetic acid hydrogen peroxide, iodophors, phenolics, and quaternary ammonium compounds. At the present, there do not appear to be any specific guidelines for addressing *C. auris*. However, based on research, hospitals should be encouraged to utilize sodium hypochlorite over other less effective disinfectants such as quaternary ammonium compounds, phenolics, peracetic acid, and hydrogen peroxide. Studies have suggested that the frequency of cleaning as well as the cleaning method may also prevent infections from spreading [21]. This is in addition to making sure basic infection control measures are being used such as latex gloves, disposable gowns, hand sanitizers, etc. Hospitals and physicians must make sure these infection control protocols are being utilized to protect their patients and all who come in contact with them. Fourth, Departments of Health must make controlling the spread of *C. auris* a public health priority by requiring extensive training and education on infection control strategies and monitoring closely that these strategies are being followed. Fifth, physicians should become advocates to reduce the unnecessary use of antimicrobials and to create regulatory systems for the responsible use of antimicrobials by professionals in humans, animals and plants. This will entail educating their patients about the overuse of antibiotics and their potential dangers. To combat *C. auris* and other potential "superbugs" state and federal regulations must be implemented and monitored carefully. Unless acute care hospitals and long-term nursing facilities are protected from these infections, the lives of our most vulnerable citizens will be placed in jeopardy. The principle of beneficence demands that we promote the good of the person by minimizing potential harms and maximizing potential benefits. Failure to address these issues will cause direct harm to patients. There is no doubt that there will be push-back from many areas, including the pharmaceutical industry, however, profit can never stand in the way of patient safety. Unless we immediately initiate these actions we will never satisfy the tests of both beneficence and nonmaleficence.

Finally, the principle of justice recognizes that each person should be treated fairly, equitably, and given his or her due. Justice pertains to distributive justice, which concerns the fair and equitable allocation of resources, benefits and burdens, according to a just standard. Some in the public health arena have referred to the "superbug" problem as a "modern day tsunami." To fight these drug-resistant microbes will take a coordinated, multidisciplinary effort. One area that must be at the forefront of this fight must be the development of new drug therapies. The problem is that many of the pharmaceutical companies developing new versions of drugs are hemorrhaging money and closing their doors. Even large pharmaceutical companies have abandoned research and development in this area. "Experts say the grim financial outlook for the few companies still committed to antibiotic research is driving away investors and threatening to strangle the development of new lifesaving drugs at a time they are urgently needed" [42]. The problem is that these pharmaceutical companies have not realized sustainable profits in this area. Physicians becoming better educated regarding the usage of pharmaceutical drugs are now less likely to prescribe the newest medications, thus limiting the ability of the pharmaceutical companies to recoup their investment in research and development. In addition, many hospital pharmacies will dispense cheaper generic drugs even when the new drugs have been shown to be more effective. The cost of these new drugs can range from $1000 to $2000 to

fight these multi-drug resistant infections. The generic versions are much cheaper but less effective. In addition, "coming up with new compounds is no easy feat. Only two new classes of antibiotics have been introduced in the last 20 years-most new drugs are variations on existing ones-and the diminishing financial returns have driven most companies from the market. In the 1980s, there were 18 major pharmaceutical companies developing new antibiotics; today there are three" [42]. Justice demands that all people should be treated fairly and equitably. If this is true, then the federal government needs to create financial incentives to help with the research and development of these new antibiotics. "Among the ideas that have wide backing are increased reimbursements for new antibiotics, federal funding to stockpile drugs effective against resistant germs and financial incentives that would offer much needed aid to start-ups and lure back the pharmaceutical giants" [42]. The reallocation of resources to fight these "superbugs" is necessary to treat all people fairly and justly. Federal legislation must be enacted to protect the common good against this inevitable tsunami of destruction. Unless all people are given the drugs necessary to fight these "superbugs," human life as we know it will be in jeopardy. This is a serious issue and one that all people must recognize and be educated about before it is too late. Justice dictates we address this urgent problem. Failure to create new financial initiatives to encourage pharmaceutical companies to increase research and development in this area is ethically irresponsible and morally objectionable.

RECOMMENDATIONS AND CONCLUSION

Although more research on *C. auris* needs to be performed, based on the current knowledge of this fungal pathogen, it is recommended that the following guidelines are followed to prevent and control infection. These recommendations may be useful for other multidrug resistant organisms as well.

1. *Candida auris* is a nationally notifiable condition and is reportable in many states. Laboratories that identify cases of *C. auris* should report all cases to the state or local health department and to the CDC at candiddaauris@cdc.gov as soon as possible.
2. Pre-admission screening of patients who are at risk of acquiring *C. auris*. Also, screening and precautionary measures for healthcare professionals who come in contact with *C. auris* patients are necessary.
3. The CDC suggests that "those infected or even just colonized with the fungus -- meaning they carry the disease without being infected-- should be isolated in individual rooms."
4. Encourage extensive cleaning and disinfection with chlorine-based compounds, particularly sodium hypochlorite, in health care facilities.
5. Develop standard protocols in ICUs, NICUs, hospitals, and nursing homes for preventing, limiting the spread, and optimally treating *C. auris*.
6. Conduct research on multidrug-resistant microbes and early indicators of *C. auris*
7. Globally ban the use of medically important drugs for promoting growth in farm animals because these drugs may contribute to new multidrug resistant pathogens.
8. Create financial incentives for drug companies to develop new antimicrobial compounds. These may include government financing for research or regulatory changes that would increase reimbursements for newly approved pharmaceutical drugs considered medically important.
9. Place rules to limit the sale of medication in countries where drugs can often be bought without a prescription.

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