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CHAVE DE CORREÇÃO

PROVA ESCRITA PARA AFERIR CAPACIDADE DE LEITURA E COMPREENSÃO DE TRABALHO CIENTÍFICO ESCRITO EM INGLÊS, REALIZADA EM 03/10/2017

Com base no texto *"Clinical Alert: Candida Auris. A new pathogen is making its presence known",* disponível nas páginas 4 e 5, responda as questões de número 1 (um) a 5 (cinco).

CLINICAL ALERT: *CANDIDA AURIS*: A NEW PATHOGEN IS MAKING ITS PRESENCE KNOWN.

Emerging infections: April 2017 ▼ Vol. 117, Nº. 4, p. 53-54.

Reports of infections with multidrug-resistant Candida auris—a yeast that is difficult to identify, easily transmitted in the hospital set¬ting, and often deadly—are on the rise.1-3 Infection is also associated with prolonged hospital stays, es¬pecially on critical care units.4, 5 As with other inva¬sive fungal infections, diabetes, recent surgery, and multiple invasive procedures raise patients' risk of infection.

This novel Candida species was first identified in 2009, after it was isolated from the external ear of a hospital patient in Japan.6 Since then, there have been reports of C. auris infection in 10 other countries.3

In a June 2016 Clinical Alert, the Centers for Dis¬ease Control and Prevention (CDC) asked clinical lab¬oratories across the country to report any C. auris isolates that they may have previously identified.1 As of this writing, retrospective surveillance has identi¬fied 25 cases of C. auris infection in the United States since early 2013.3, 7

REASONS FOR CONCERN

Clinicians, researchers, and public health experts are worried about the recent increase in reported cases of C. auris for a number of reasons.

Multidrug resistance. According to the June 2016 clinical report from the CDC, of C. auris isolates from around the world that have been tested at the CDC, most were highly resistant to fluconazole, a typical first-line drug for the treatment of Candida infections; more than half were resistant to voriconazole; a third were resistant to amphotericin B; and “a few” were resistant to echinocandins, such as caspofungin or micafungin.1 In a multicenter, international analysis, more than 40% of isolates were resistant to drugs in two of the major antifungal classes, and two isolates were resistant to all three.4

Difficulties with identification. Blood, tissue, and fluid cultures for the detection of any Candida spe¬cies tend to grow slowly, and blood cultures may be falsely negative when candidemia occurs at low levels or is intermittent.8 Although these factors can delay the start of effective treatment for any invasive Can¬dida infection, identification of C. auris presents ad¬ditional challenges. Many clinical laboratories do not identify individual Candida species and report results only as “other Candida species.”1 Even in laboratories that do speciate (test for different species), C. auris is easily misidentified as C. haemulonii or other Candida species by commercially available biochemical testing methods.1

Molecular methods, such as DNA sequencing or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, are needed in order to differ¬entiate C. auris from other Candida species, but these technologies aren’t available in many clinical labo¬ratories.9 It’s likely, then, that there have been more C. auris infections in recent years than have been doc¬umented through laboratory testing.

Transmissibility. There is growing concern that C. auris may heavily contaminate the environment of infected or colonized patients, increasing the “res¬ervoir” of yeast available to infect others.10 Extensive culturing for C. auris in the rooms of patients infected or colonized with C. auris has shown a “persistent” presence of the yeast on many surfaces and even, on one occasion, in a sample taken from the air.11

High mortality. Invasive infections caused by any species of Candida are a major cause of hospital morbidity and mortality.8 Using 2012 surveillance data, the CDC puts the crude mortality rate from in-vasive Candida infections at 30%.12 A 2005 study by Morgan and colleagues that was limited to Candida bloodstream infections estimated rates between 19% and 24% once comorbidities were controlled for.13 The CDC describes invasive C. auris infections as being “associated with high mortality,”3 although it’s not clear whether people with invasive C. auris infections are more likely than people infected with other Candida species to die.14 An outbreak in 18 pa¬tients in a Venezuelan hospital had a 28% case fatality rate.15 A CDC investigation of 54 C. auris infections in five countries revealed a 59% mortality rate.

However, in a London outbreak involving 22 patients with inva¬sive C. auris infection, no deaths were attributed to the infections.11 This variation in mortality data is typical of emerging infections, in which the earliest cases iden¬tified are usually the most severe. Over time, if milder cases can be identified, the overall mortality rate may drop.

TREATMENT

When invasive C. auris infection is suspected, empirical treatment should start with an echinocandin antifungal agent (capsofungin, micafungin, or anidulafungin) because the rate of resistance is, so far, low¬est in this class.9 Drug therapy should be revised if necessary after susceptibility information is available.

When urine, wounds, or respiratory cultures are positive for C. auris but the patient has no clinical signs of infection—that is, when the evidence suggests colonization rather than infection—antifungal treat¬ment is not recommended.9 Other than the choice of antifungal drug, the management of invasive C. auris infection is the same as that for any invasive candidiasis.8

INFECTION PREVENTION AND CONTROL

Infections can be treated and contained only when we know they’re there. The CDC therefore has asked cli¬nicians to be on the alert for C. auris infection and colonization. They should be vigilant in searching for C. auris in clinical specimens, especially those from critical care patients. Clinical laboratories should con¬sider updating their Candida testing methods and protocols, if they have not already done so. The CDC recommends the following9:

• A culture that grows bacteria identified as C. hae¬mulonii, C. famata, C. sake, Saccharomyces cere-visiae, or Rhodotorula glutinis may actually be C. auris that has been misidentified. Isolates so identified should undergo further testing.

• If an isolate has been identified only as “Candida species” and the patient is not responding to anti-fungal therapy, consider molecular testing. Any unspeciated isolates that are resistant to one or more classes of antifungal drugs should undergo further testing.

• If there is an increase in unspecified Candida iso¬lates (including in urine) from patients on an in-dividual unit, consider the possibility of C. auris infection.

Laboratories at the CDC as well as at some state and local health departments can assist with testing and should be contacted when C. auris is suspected.

In addition to closely examining clinical isolates, hospital and long-term care facilities can proactively perform a local “risk assessment” to determine the likelihood that their facility will encounter C. auris. Facilities should consider periodic screening

of critical care patients, some percentage of admissions, or trans¬fers from facilities with confirmed cases of C. auris infection or colonization. Certainly, facilities with on¬going outbreaks of C. auris will need to institute for¬mal patient-screening protocols.

Both confirmed and suspected cases of C. auris call for standard and contact precautions. Possible carriers, such as patients who have been exposed to a patient with C. auris (a roommate of a patient with a confirmed infection, for example), should also be iso¬lated and screened.

As with resistant bacteria, such as methicillin-resistant Staphylococcus aureus, colonization with C. auris can continue long after infection is resolved. The CDC recommends periodic axilla and groin swabs to check for C. auris colonization and advises that isolation be continued until at least two sets of swabs from specimens taken at least a week apart (and after the patient is no longer receiving antifun¬gal drugs) are negative.9 Individual patients may require samples from additional screening sites, such as urine, wounds, or drain fluid.

It’s not yet known whether chlorhexidine gluconate or alcohol can eliminate hand carriage of C. auris. Re¬searchers in Glasgow, Scotland, have demonstrated in in vitro studies that chlorhexidine is effective against C. auris, and they recommend that it be used for skin and wound cleansing,16 although current recommen¬dations have not yet changed. Public Health England, the public health wing of the United Kingdom’s De¬partment of Health, recommends that staff caring for people infected or colonized with C. auris perform soap-and-water handwashing followed by applica¬tion of an alcohol-based hand sanitizer.10

Careful daily and terminal cleaning and disinfec¬tion of the patient’s room are essential. A hospital-grade disinfectant registered with the Environmental Protection Agency should be used. (Check to be sure the product includes an antifungal claim; most do.) Public Health England and the Pan American Health Organization (an agency of the World Health Orga¬nization) suggest that chlorine-based disinfectants be used.5,▼

Responda as questões considerando o texto extraído do artigo científico acima:

QUESTÃO 1

Nos últimos anos, o aumento do número de casos de infecções por *Candida auris* tem despertado a atenção de profissionais e pesquisadores da área da saúde. Esses microrganismos apresentam um perfil de resistência a antifúngicos distinto das demais espécies do gênero *Candida*. Inserido neste contexto, descreva quais foram os resultados encontrados pelo CDC (*Centers for Disease Control and Prevention*) ao investigar a susceptibilidade a antifúngicos dos isolados de *C. auris* obtidos de várias partes do mundo.

Dos isolados testados no CDC, verificou-se que:

1) a maior parte era altamente resistente ao fluconazol (uma droga de tratamento de primeira linha para infeccções por Candida;

2) mais de metade eram resistentes ao voriconazol;

3) um terço era resistente a anfotericina B;

4) apenas alguns eram resistentes a equinocandinas, tais como a caspofungina e a micofungina.

QUESTÃO 2

Há uma grande dificuldade em estabelecer a identificação correta da espécie *C. auris* baseando-se apenas em métodos bioquímicos. Dessa forma, *C. auris* pode ser facilmente confundida com outras espécies. Diante da afirmação, quais os métodos mais adequados para identificar corretamente essa espécie?

De acordo com o apresentado, a correta identificação de Candida auris só pode ser conseguida através da utilização de métodos moleculares, tais como o sequenciamento de DNA ou a Espectrometria de massa (tempo de vôo de desadsorção/ionização em matriz assistida por laser).

QUESTÃO 3

De acordo com o texto, como é realizado o manejo terapêutico do paciente com candidíase invasiva por *C. auris*? Essa informação é coerente com os resultados encontrados nos testes de susceptibilidade a antifúngicos realizados pelo CDC? Explique.

De acordo com o texto, na presença de suspeita de uma infecção invasiva por C. auris o tratamento orientado é a utilização da classe de agente antifúngico equinocandina (que engloba a capsofungina, a micafungina e a anidulafungina). Esta orientação terapêutica está de acordo com os resultados de resistência antifúngica divulgados pelo CDC, uma vez que apenas alguns dos isolados testados revelaram resistência às equinocandinas, contrariamente aos outros tratamentos antifúngicos disponíveis.

QUESTÃO 4

A colonização do paciente com *C. auris* pode permanecer mesmo após a melhora da infecção. Neste caso, quais são as recomendações do CDC para controle e prevenção da doença?

De acordo com o texto, as recomendações do CDC em situações de colonização por C. auris, após resolução da infecção, orientam para a realização de um esfregaço ("swab") das virilhas e das axilas, sendo que este isolamento deve ser realizado até que pelo menos duas análises consecutivas, com pelo menos 1 semana de intervalo, sejam negativas, num período em que o paciente já não apresenta sintomas da infecção. Para alguns pacientes, poderá ser necessária a coleta de amostras de outros locais ou fluidos, tais como urina, feridas ou líquido drenante (linfa).

QUESTÃO 5

De acordo com o texto, como os profissionais de saúde que cuidam de pacientes colonizados e/ou infectados com *C. auris* podem prevenir a disseminação do microrganismo? Neste mesmo contexto, como deve ser realizado o manejo do ambiente?

Existem ainda algumas dúvidas relativas aos melhores agentes para garantir uma eliminação eficiente de C. auris da pele e materiais contaminados.

A atual recomendação do Departamento de Saúde do Reino Unido é de que os profissionais de saúde que tratam indivíduos infectados ou colonizados com C. auris realizem a lavagem das mãos com agua e sabão, utilizando de seguida um definfectante de mãos com base alcoólica.

O manejo dos locais e ambientes em que estes pacientes se encontram deve ser efetuado por cuidadosa limpeza e desinfecção diária, utilizando sempre um desinfectante de grau hospitalar registrado na Agência de Proteção Ambiental ("Environmental Protection Agency")

Com base no artigo *"Unrecognized Emergence of Chikungunya Virus during a Zika Virus Outbreak in Salvador, Brazil"* cujos textos extraídos encontram-se abaixo, responda as questões de número 6 (seis) a 10 (dez).

UNRECOGNIZED EMERGENCE OF CHIKUNGUNYA VIRUS DURING A ZIKA VIRUS OUTBREAK IN SALVADOR, BRAZIL

Cardoso et al PLoS Negl Trop Dis. 2017 Jan 23;11(1):e0005334. doi:10.1371/journal.pntd.0005334

Abstract

Background

Chikungunya virus (CHIKV) entered Brazil in 2014, causing a large outbreak in Feira de Santana, state of Bahia. Although cases have been recorded in Salvador, the capital of Bahia, located ~100 km of Feira de Santana, CHIKV transmission has not been perceived to occur epidemically, largely contrasting with the Zika virus (ZIKV) outbreak and ensuing complications reaching the city in 2015.

Methodology/Principal Findings

This study aimed to determine the intensity of CHIKV transmission in Salvador between November 2014 and April 2016. Results of all the CHIKV laboratory tests performed in the public sector were obtained and the frequency of positivity was analyzed by epidemiological week. Of the 2,736 tests analyzed, 456 (16.7%) were positive. An increasing in the positivity rate was observed, starting in January/2015, and peaking at 68% in August, shortly after the exanthematous illness outbreak attributed to ZIKV.

Conclusions/Significance

Public health authorities and health professionals did not immediately detect the increase in CHIKV cases, likely because all the attention was directed to the ZIKV outbreak and ensuing complications. It is important that regions in the world that harbor arbovirus vectors and did not experience intense ZIKV and CHIKV transmission be prepared for the potential co-emergence of these two viruses.

INTRODUCTION

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Brazil has been in the spotlight for arbovirus transmission, especially since epidemics of Zika virus (ZIKV) in early 2015 [4–6] were followed by outbreaks of GBS in adults and microcephaly in newborns [7,8]. During January-September 2016 (up to

epidemiological week 37), Brazil recorded 200,465 ZIKV cases, 236,287 CHIKV cases and 1,438,624 DENV cases [9]. Oropouche and Mayaro virus infections have been identified sporadically in the country, restricted so far to the North and Midwest region [10–14], whereas Yellow Fever occurs endemically in the Amazon region with occasional transmission in the Midwest, South and Southeast regions, with 322 reported cases from July 2014 to June 2015 in Brazil [15]. Salvador, the largest city in the northeastern region of Brazil, and the capital of Bahia State, was one of the cities most affected by ZIKV. While there was widespread occurrence of ZIKV cases in Salvador, transmission of CHIKV appeared to have been much less intense, to the extent that an outbreak was not detected by local health authorities, as during the period an outbreak of acute exantematous illness (AEI) attributed to ZIKV occurred over 14,000 AEI cases were reported in contrast to 58 CHIKV cases reported in Salvador [6]. This is intriguing, since CHIKV has caused large outbreaks in most places where it is introduced [16–19], and CHIKV cases were first detected in Brazil in May 2014, in Feira de Santana, a city located approximately 100 km north of Salvador [20]. In Feira de Santana, CHIKV reached outbreak levels, with 4,088 reported cases in 2015 (an incidence of 668.0 cases/100,000 inhabitants) [21]. In contrast, in Salvador, 1,240 CHIKV cases were reported in 2015 (an incidence of 42.7 cases/100,000 inhabitants, more than an order of magnitude lower) [21].

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DISCUSSION

The increase in the frequency of CHIKV positive laboratory results among Salvador patients during 2015 suggest that the intensity of CHIKV transmission in the city followed the same temporal pattern observed for the laboratory exams, with CHIKV transmission likely peaking in August, shortly after the exanthematous illness outbreak attributed by excess to ZIKV only [6]. Although Salvador established a surveillance for CHIKV detection following Feira de Santana's outbreak in 2014 [26], the virus' introduction and subsequent spread in the city was not promptly noticed by the health authorities, because their main focus was on the AEI outbreak attributed to ZIKV, which affected about 14,000 people over a two month period [7]. Additionally, due to the overwhelming demand, especially during the AEI outbreak, laboratory testing was not performed in a timely manner. Therefore, the health authorities were only informed of the increase of CHIKV cases retrospectively.

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This finding also suggests that the CHIKV transmission in Salvador was less explosive than the 2015 ZIKV outbreak (over 17,000 reported cases in nearly 10 weeks) (7), but, in contrast, was of longer duration and may have resulted in established endemic transmission, given that the percentage of CHIKV positive

samples from Salvador remained at levels of ~10–20% through the rest of 2015 and the first weeks of 2016. It is also possible that the CHIKV outbreak reported here is under-estimated, while the ZIKV outbreak is over-estimated (i.e., all severe manifestations observed in Salvador were attributed almost entirely to ZIKV circulation). Even though the number of people infected by both viruses was certainly under-estimated given how surveillance of cases was assembled, health-seeking behavior and the general perception that AEI was a self-limited mild disease.

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Some limitations need to be acknowledged. First, the majority of the samples were tested only using IgM-based serology, and thus cross-reaction to other alphavirus has to be considered. However, although the occurrence of other alphavirus such as Mayaro have been described in the North and Midwest regions of Brazil [10,12], there is no evidence for their circulation in Salvador. Second, our epidemiological curve is based on the time when a sample was taken from the patient, which might not necessarily represent the time of infection, especially as CHIKV infections may result in chronic clinical manifestations and serum samples may have been collected for diagnosis a long time after disease onset. In this case, IgM antibodies would no longer be present and IgG-ELISA would be more appropriate. Also, although RT-PCR for acute-phase samples and IgM detection in paired samples would provide a more accurate diagnosis [31], a different algorithm for CHIKV testing was adopted due to limited resources. Third, this study included only cases that sought healthcare and whose attending physician requested laboratory testing for either CHIKV or differential diagnosis of an AEI, thus underestimating CHIKV cases. Additionally, with syndromic surveillance it is not possible to define accurately the etiology of cases, therefore laboratory testing is essential. In this study, we tried to address this limitation by analyzing the available laboratory results for all patients tested for CHIKV in Salvador, and our results are supported by previously published data showing that the AEI outbreak in Salvador that peaked in May was mainly due to ZIKV [6]. Yet, community-based studies using serological tests are needed to help better ascertain the intensity of CHIKV transmission, and there is an urgent need for ZIKV serological tests to accurately assess the intensity of ZIKV transmission. Fourth, CHIKV outbreaks in Feira de Santana appear to have occurred in two waves, the first in June-December 2014 and the second starting at January-2015 [32]. Since the first patients from Salvador to be tested for CHIKV infection were not tested until November 2014, we might have missed any earlier CHIKV transmission in Salvador during the first wave of transmission in Feira de Santana. Lastly, both viral isolation and genome sequencing are not routinely performed by LACEN-BA; thus, detailed information on strains responsible for this outbreak was not available. However, other studies have identified CHIKV infections in Bahia associated with the East-Central-South African (ECSA) strain [32,33].

Responda às questões considerando os textos anteriores:

QUESTÃO 6

Qual o motivo principal para a realização da investigação descrita neste artigo?

Embora casos de CHIKV, iniciados em Feira de Santana, tenham sido registados em Salvador, a transmissão de CHIKV não foi percebida como ocorrendo epidemicamente. Este padrão foi diferente do que aconteceu com o ZIKV, o que originou complicações em 2015.

QUESTÃO 7

Qual o número de casos registados e a incidência de casos registados, de infecção por vírus chikungunya, em Salvador e Feira de Santana, em 2015?

Em Feira de Santana 4088 casos, incidência de 668,0 casos/100000 habitantes.

Em Salvador, 1240 casos, incidência de 42,7 casos/100000 habitantes

QUESTÃO 8

Na seção da discussão: refira a razão principal para que as autoridades de saúde não tenham notado rapidamente o impacto das infecções por vírus chikungunya, em termos de número de casos.

A atenção dada ao surto de AEI, atribuído ao ZIKV, e o uso total dos recursos laboratoriais para lidar com este surto, desviaram a atenção e os recursos laboratoriais necessários para a detecção eficiente de CHIKV. Desta forma, as autoridades de saúde só tiveram as informações sobre o surto de CHIKV retrospectivamente.

QUESTÃO 9

Na seção da discussão: porque os autores referem que a transmissão de vírus chikungunya pode ter atingido a condição de endêmica?

Os resultados sugerem que a transmissão de CHIKV tenha sido de longa duração (maior duração do que a de ZIKV), já que a porcentagem de amostras positivas, em Salvador, se mantiveram em 10-20% ao longo de 2015 e nas primeiras semanas de 2016.

QUESTÃO 10

Na seção da discussão, os autores referem as limitações deste estudo. Especificamente, sobre a limitação onde escrevem que este estudo inclui apenas casos que procuraram cuidados de saúde, explique o que os autores fizeram para atenuar esta limitação e a outra forma que sugerem poder atenuar este viés nas futuras investigações.

Eles analisaram os resultados laboratoriais disponíveis para todos os pacientes testados para CHIKV, em Salvador, no período referido. Em futuras investigações, será necessário o uso de testes serológicos aplicados na comunidade, de forma a conseguir uma melhor estimativa do número de casos de ZIKV na população (atenuando o viés de seleção), levando a melhores análises da transmissão de ZIKV.