Prevention of *Candida* transmission to neonates – a multifaceted issue

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Why are Candida species so dangerous for the new-borns and neonates ?

About the host

- All organ systems of the body undergo a dramatic transition at birth, from a sheltered intra-uterine existence to the radically distinct environment of the outside world
- This acute transition is then followed by a gradual, age-dependent maturation
- The newborns are NOT adult miniatures

About the host

The fetus and newborn face a complex set of immunological endeavors:

- **protection against infection**
- **avoidance of harmful inflammatory immune responses that can lead to pre-term delivery**
- **balancing the transition from a sterile intra-uterine environment to a world that is rich in foreign antigens (primary colonization of the skin and intestinal tract by microorganisms)**

Levy – Nat Rev Immunol 2007

About the host

Are them prepared for these challenges ?

Not really …

The newborns represent a vulnerable population susceptible to microbial infections.

About the host

Neonatal skin

- **Is fragile at birth and even small breaks in the integrity of the skin can serve as lead points for infection**
- **The vernix caseosa (a waxy coating on newborns) contains antimicrobial peptides and proteins (APPs) including lysozyme, α-defensins, ubiquitin and psoriasin, as well as antimicrobial free fatty acids that can act in synergy with APPs to kill microorganisms (including *Escherichia coli* and *Candida albicans*).**

Levy – Nat Rev Immunol 2007

About the host

Neonatal immune system

- In the very first period after birth, both innate and adaptive immune systems are deficient
- Neonates possess a developing immune system and have little immunological memory – vulnerability to infections
- Cellular immune system matures rapidly in the first three months of life – process influenced by multiple factors
- It is estimated that 40% of the annual 3 million worldwide neonatal deaths are the result from infections

Levy – Nat Rev Immunol 2007
Liu et al. – Lancet 2012
Basha et al. – Expert Rev Clin Immunol 2014

About the host

Neonatal neutrophils

- Major component of the innate immune system and are responsible for engulfing and killing pathogens during infection
- Characterized by quantitative and qualitative deficiencies; these defects in neutrophil amplification, mobilization and function make neonates particularly susceptible to sepsis
- Both neutrophil storage pools as well as production of neutrophil progenitor cells in neonates are less than those of adults leading to diminished neutrophil responses to infection.

Levy – Nat Rev Immunol 2007
Basha et al. – Expert Rev Clin Immunol 2014

About the host

Neonatal neutrophils

- **Show impairment of multiple functional aspects, including chemotaxis, rolling adhesion, transmigration and lamellipodia formation**
- **Have lower surface expression levels of TLR4 but similar levels of expression of TLR2 compared to adults**
- **Have reduced capacity to phagocytize pathogens and limited ability to degrade the ingested pathogens (reduced amounts of some APPs, including lactoferrin: 50% of adult levels)**
- **These neutrophil defects are even more pronounced with prematurity, but begin to correct within the first weeks of life**

Levy – Nat Rev Immunol 2007
Melvan et al. – Int Rev Immunol 2010
Basha et al. – Expert Rev Clin Immunol 2014

About the host

Other immune effectors

- **Antigen Presenting Cells (APCs) – monocytes and dentritic cells (DCs) are low in numbers and are found to express lower MHC-II (CD80 and CD86) compared to adult cells indicating their inability to fully activate antigen specific T and B cell responses**

- **Suboptimal Th1 responses (IL-1, TNF, IFN-gamma, IL-12, IL-18) and B-cell differentiation**

- **Plasma concentrations of complement components are diminished compared with those in adults (10–70% of adult levels) contributing to the impairment of neonatal adaptive responses**

Willems et al. – Eur J Immunol 2009
Basha et al. – Expert Rev Clin Immunol 2014

About the host

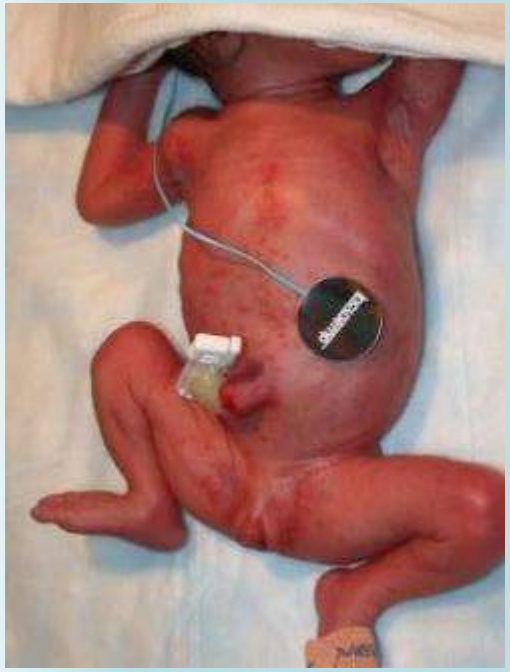
Other immune effectors

- Normally, this state of immune immaturity is a passing period that lasts few month after birth
- It can persist in a group of infants and young children (6–36 months) who display a Prolonged Neonatal-Like Immune Profile (PNIP)
- PNIP seems to be an important issue in toddlers (in the U.S. alone each year, there may be 1–1.2 million children with PNIP)

Pichichero et al. – Pediatr Infect Dis J 2013

About the host

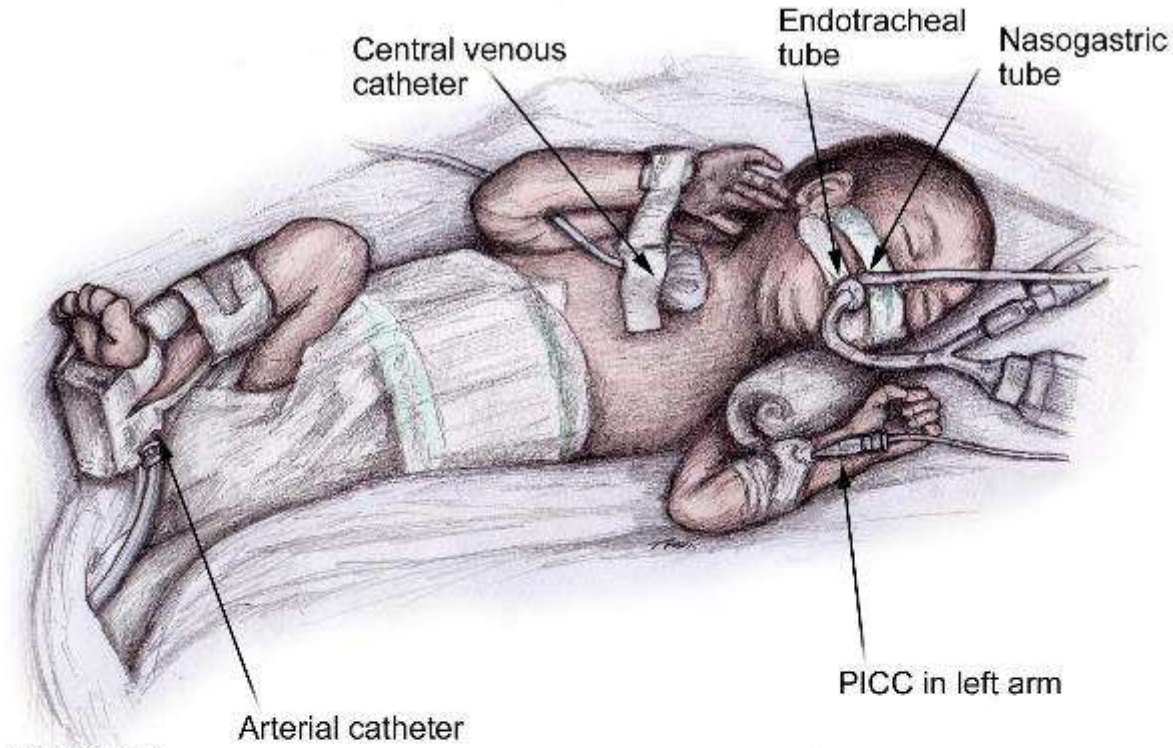
Risk factors for *Candida* infection



The major risk factor – preterm birth

- The younger gestational age and lower birth weight, the higher risk to develop invasive fungal infections
- The incidence increases in an inverse linear pattern (3% at 28 weeks' gestation to 24% at 23 weeks' gestation)
- Incidence of candidemia is reported as 2-6.8% among VLBW infants (<1500 g) and higher in ELBW infants (<1000 g), ranging from 4-16%

Makhoul et al. – Pediatrics 2001
Johnsson and Ewald – Acta Paediatr 2004
Benjamin et al. – Pediatrics 2010



Risk Factors

Invasive therapies
Central vascular catheters
Endotracheal tube

Patient factors
Immature skin
Dermatitis
Colonization
Necrotizing enterocolitis
Focal bowel perforation
Cholestasis

Infusates
Parenteral nutrition
Lipid emulsions

Medications
Postnatal steroids
Broad-spectrum antibiotics
H2 antagonists

Fungal Infection
Sepsis
Urinary tract infection
Meningitis

End-Organ Dissemination
Endocarditis
Abscess formation
(kidneys, liver, brain, skin)
Endophthalmitis
Bone and joints

Kaufman 2014
(http://emedicine.medscape.com/article/980487)

- **Other "added" risk factors (mainly iatrogenic)**
- **Immunocompromised infants usually require invasive therapies, broad spectrum antibiotics and parenteral nutrition**
- **High risk for invasive fungal infections**

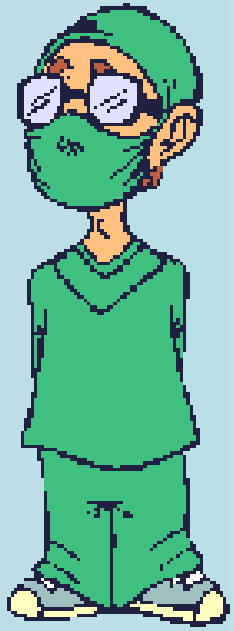
About the microorganisms

The main players

Candida parapsilosis

Candida auris

Other species



Pfaller et al. – J Clin Microbiol 2002
Armstrong et al. – CDC EIS Conference 2017

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About the microorganisms

Emerging pathogen *Candida auris*

Clinical Infectious Diseases
EDITORIAL COMMENTARY

IDSA hivma

Emergence of *Candida auris*: An International Call to Arms

Cornelius J. Clancy[1,2] and M. Hong

Journal of Hospital Infection

Available online at www.sciencedirect.com

ELSEVIER

journal homepage: www.elsevierhealth.com/journals/jhin

Review

Multidrug-resistant *Candida auris*: 'new kid block' in hospital-associated infections?

A. Chowdhary[a,*], A. Voss[b,c], J.F. Meis[b,c]

Antimicrobial Resistance and Infection Control

RESEARCH Open Access

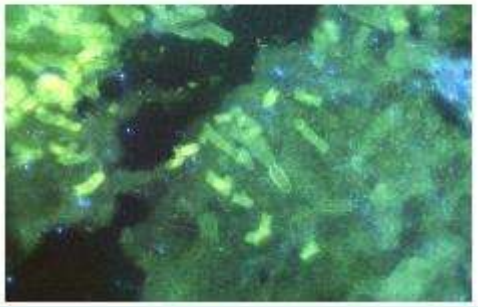
First hospital outbreak of the globally emerging *Candida auris* in a European hospital

PLOS PATHOGENS

The Emerging Pathogen *Candida auris*: Growth Phenotype, Virulence Factors, Activity of Antifungals, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation

Emily Larkin,[a] Christopher Hager,[a] Jyotsna Chandra,[a] Pranab K. Mukherjee,[a] Mauricio Retuerto,[a] Iman Salem,[a] Lisa Long,[a] Nancy Isham,[a] Laura Kovanda,[b] Katyna Borroto-Esoda,[c] Steve Wring,[c] David Angulo,[c] Mahmoud Ghannoum[a]

Deadly strain of yeast infection pops up in hospitals around the world



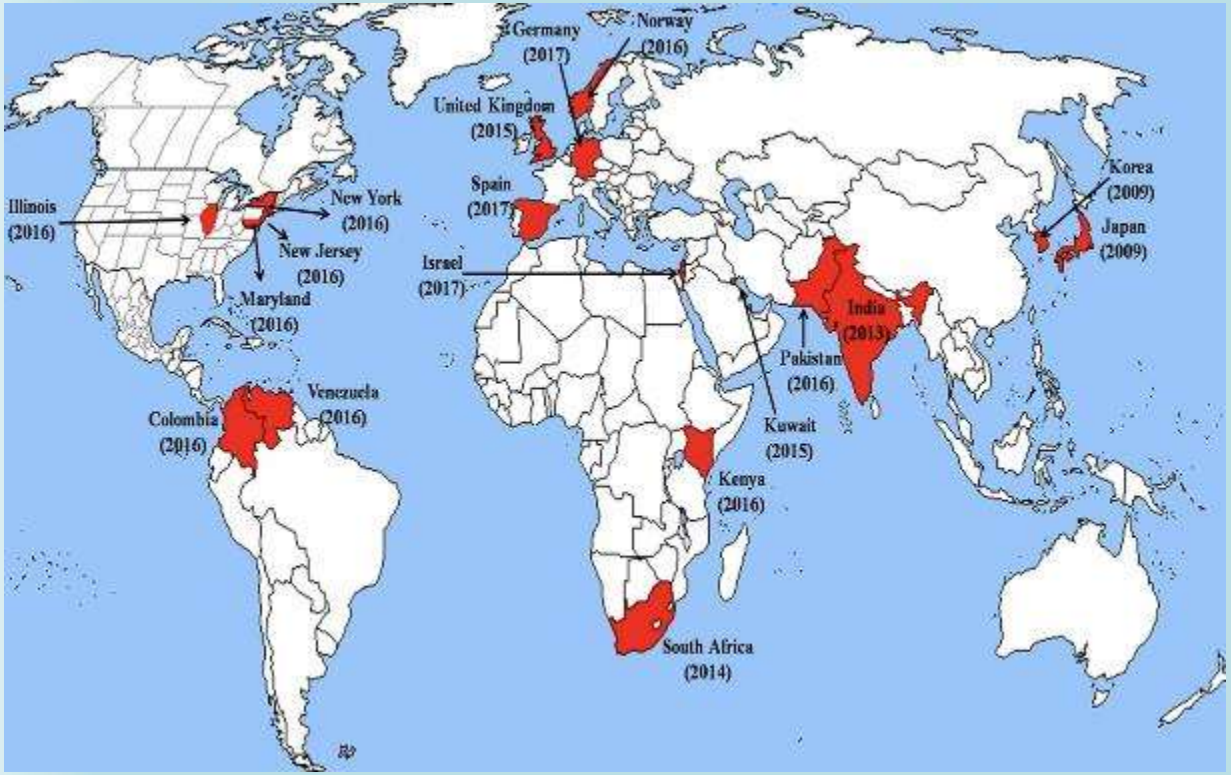
PEARLS

Candida auris: A rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally

Anuradha Chowdhary[1,*], Cheshta Sharma[1], Jacques F. Meis[2,3]

About the microorganisms

Emerging pathogen *Candida auris*



First described in Japan in 2009 (ear swab) and reported as cause of BSI in 2011 (South Korea)

Isolated from deep-seated infections in countries from five continents

Chowdhary et al. – J Hosp Infect 2016
Chowdhary et al. – PLOS Pathogens 2017

About the microorganisms

Emerging pathogen *Candida auris*

- **Outbreaks in several neonatal ICUs in Colombia (USA) in 2016 (four hospitals in three different cities)**
- **40 cases with 56% in-hospital mortality (all patients with central venous catheter)**
- **Two nurses' hands yielded *C. auris*, suggesting the route of transmission was transient colonization from other patients or equipment and environmental surfaces (reservoirs within the healthcare setting)**

Clancy and Nguyen – Clin Infect Dis 2017
Armstrong et al. – CDC EIS Conference 2017

What makes *C. auris* a redoubtable pathogen?

- **It causes serious infections – bloodstream infections with high mortality (more than 1 in 3 patients with *C. auris* invasive infection die)**
- **It's becoming more common – since its discovery in 2009, it has spreading in more than 15 countries (Oman reported in 2017)**
- **It's difficult to identify – phenotypically misidentified as *Candida haemulonii, C. famata, C. lusitaniae, C. sake, S. cerevisiae*, and *R. glutinis* by commercial ID systems**
- **The correct identification requires molecular sequencing (ITS or LSU region) or MALDI-TOF MS**

Chowdhary et al. – J Hosp Infect 2016
Mohsin et al. – Mycoses 2017
Chowdhary et al. – PLOS Pathogens 2017

What makes *C. auris* a redoubtable pathogen?

- **It's often resistant to antifungals** (highly resistant to FLC (MIC_{90}>64 mg/L)
- 50% of isolates exhibit high MICs to VOR (>2 mg/L) and 15-30% to AMB (>2 mg/L)
- Few isolates proved to be resistant to all classes of antifungals (4%)
- **Multidrug-resistant organism - It's acting like a super bug!**

Kathuria et al. – J Clin Microbiol 2015
Chowdhary et al. – J Hosp Infect 2016
Chowdhary et al. – PLOS Pathogens 2017

What makes *C. auris* a redoubtable pathogen?

- ATP Binding Cassette (ABC)-type efflux activity by Rhodamine 6G transport was significantly greater among *C. auris* than *C. glabrata* isolates, suggesting the intrinsic resistance of *C. auris* to azoles
- Whole genome sequencing (WGS) data shows *C. auris* to be a close phylogenetic relative of *C. lusitaniae*, a species recognized for intrinsic antifungal resistance
- Able to produce biofilms (CAS predominantly inactive against *C. auris* biofilms)

Chowdhary et al. – J Hosp Infect 2016
Ben-Ami et al. – Emerg Infect Dis 2017
Sharma et al. – New Microbes New Infect 2016

What makes *C. auris* a redoubtable pathogen?

- **It can spread in hospitals and nursing homes**
- **Prolonged persistent patient colonization at multiple anatomic sites (especially axilla and groin)**
- ***C. auris* can live on inanimate surfaces several weeks**

Satoh et al. – Microbiol Immunol 2009
Chowdhary et al. – J Hosp Infect 2016

Candida contamination of new-borns and neonates

- Many sources / many ways
- Vaginal delivery (maternal fungal colonization)
- Patient to patient transmission
- Health care workers colonization
- Indoor environment contamination
- Contaminated infusates

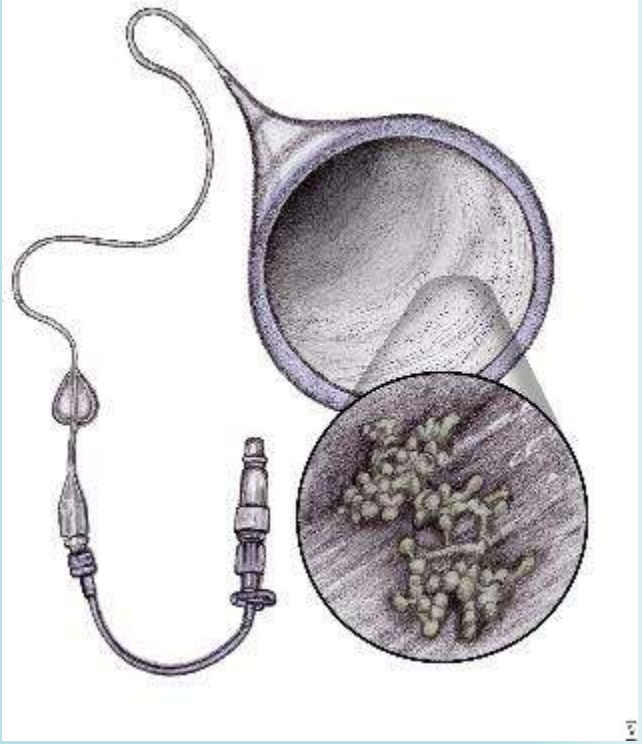
Kaufman and Fairchild – Clin Microbiol Rev 2004
Armstrong et al. – CDC EIS Conference 2017

About the microorganisms

Transmission

- In preterm infants, vertical and horizontal transmission leads to colonization of the skin, mucosal membranes (GI and respiratory tracts), and central vascular catheters (biofilms)

- Broad-spectrum antibiotics (3rd generation cephalosporins), postnatal steroids (dexamethasone), histamine type-2 antagonists, parenteral nutrition contribute to an extensive colonization and dissemination



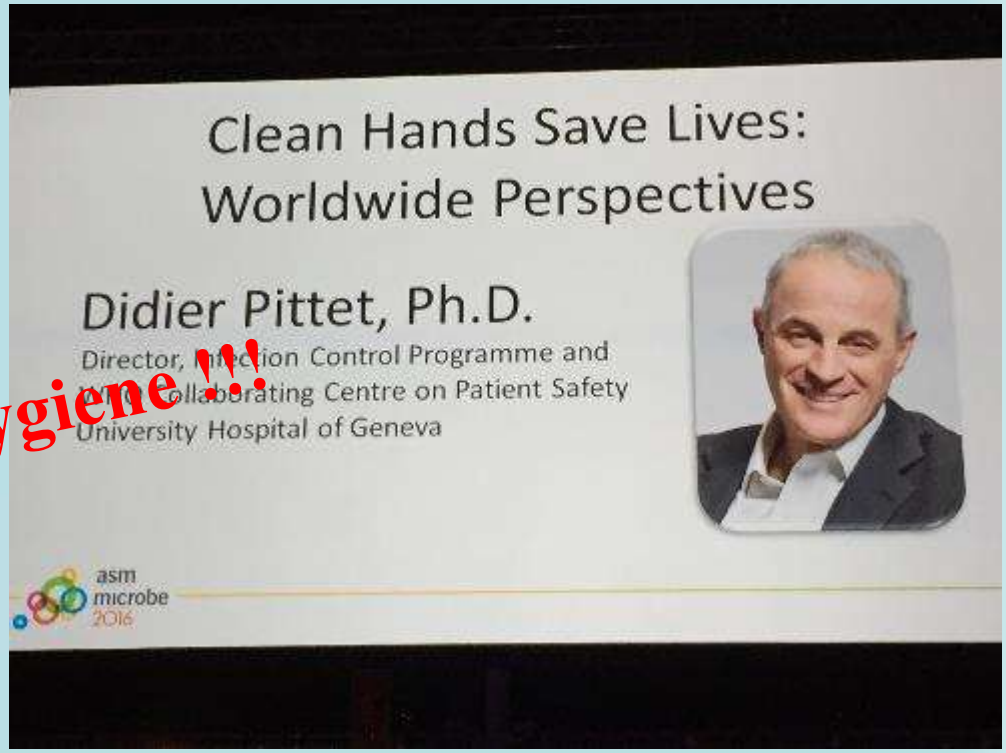
Kaufman 2014
(http://emedicine.medscape.com/article/980487)

How we can prevent *Candida* transmission in new-borns and neonates ?

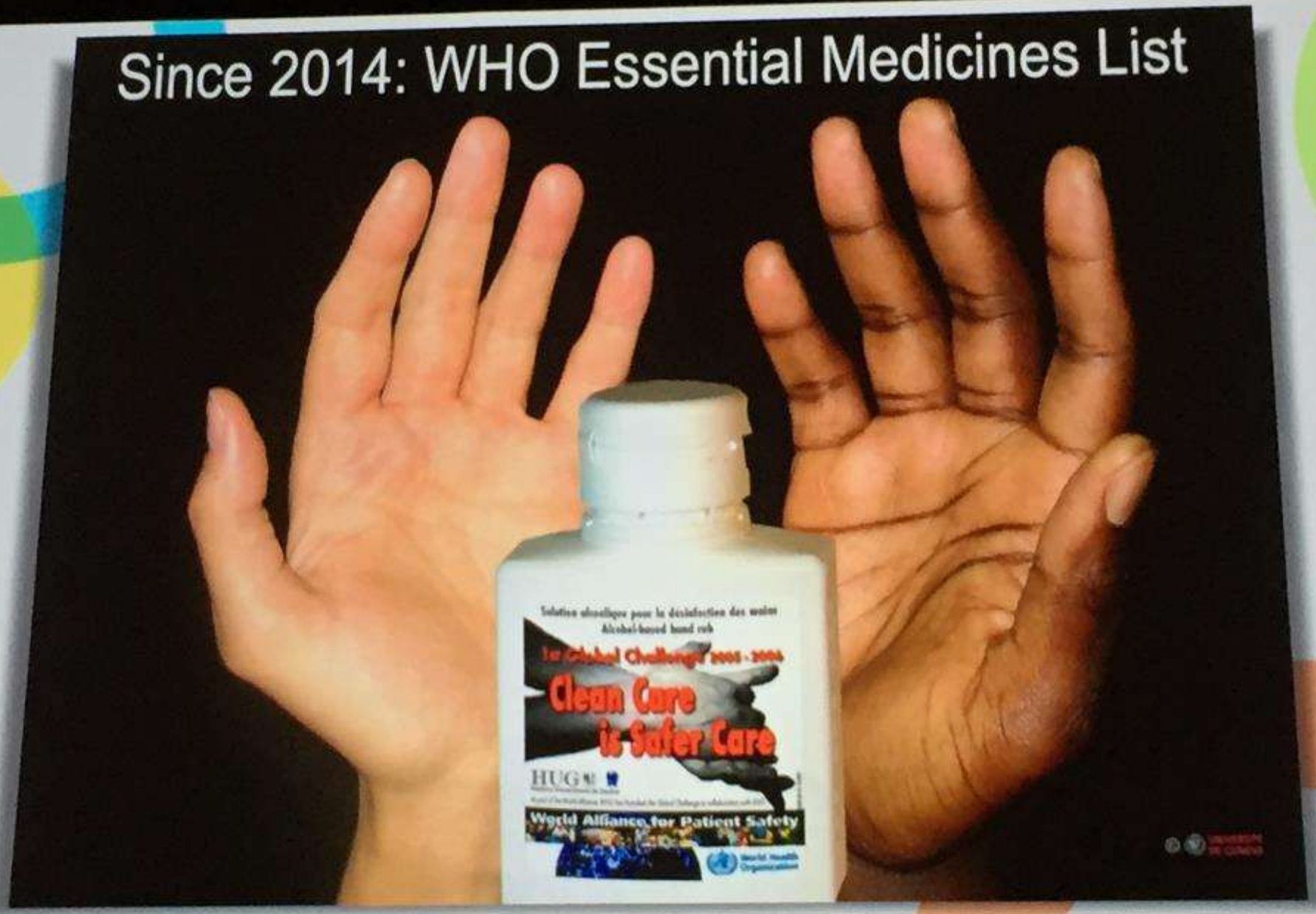
- Strict adherence of healthcare workers to hand hygiene !!!
- Clean indoor environment in hospitals
- Decolonization of patients

How we can prevent *Candida* transmission in new-borns and neonates ?

Hands hygiene !!!



Since 2014: WHO Essential Medicines List



How we can prevent *Candida* transmission in new-borns and neonates ?

Clean indoor environment in hospitals

- Daily cleaning and disinfection of patient rooms are recommended, as well as terminal cleaning and disinfection between patients
- *C. auris* can persist weeks on surfaces in healthcare environments
- Quaternary ammonia products routinely used for disinfection may not be effective

How we can prevent *Candida* transmission in new-borns and neonates ?

Clean indoor environment in hospitals

- Exposure to H_2O_2 vapors as per routine bio-decontamination technology in healthcare settings is 96.6-100% effective in killing *C. auris* and 100% for other clinically important *Candida* species
- Chlorine releasing agents at 1000 ppm for routine cleaning around patient bed areas and 10000 ppm for terminal environmental cleaning are active against *C. auris* and other *Candida* spp. (C. parapsilosis seems to need higher conc.)
- A disinfectant effective against *Clostridium difficile* spores is recommended (CDC) - List K of US Environmental Protection Agency

How we can prevent *Candida* transmission in new-borns and neonates ?

Decolonization should be considered...

- Mothers with vaginal candidiasis or a high load of vaginal yeasts (before the delivery) – topical antifungals
- Colonized patients
- Chlorhexidine gluconate and iodinated povidone are effective in killing *C. auris* and other *Candida spp*. at concentrations used in clinical practice
- Useful for decolonization of patients skin and decontamination of health care workers (Iodinated PVP > chlorhexidine gluconate)

Abdolrasouli et al. – Mycoses 2017

My group experience

Carbohydrate Polymers 152 (2016) 306–316

Contents lists available at ScienceDirect

Carbohydrate Polymers

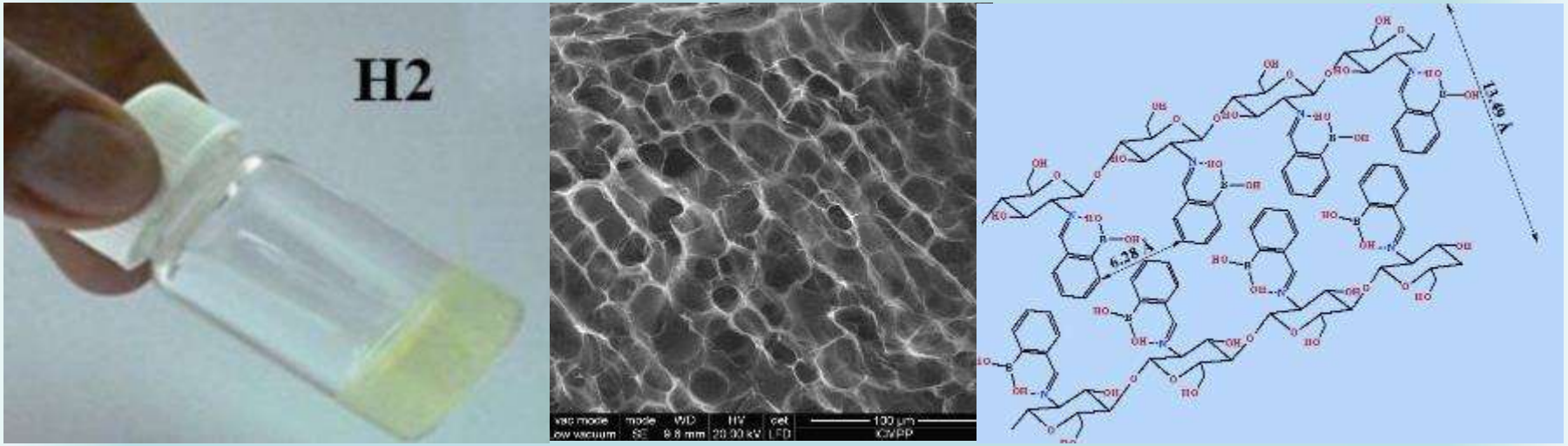
journal homepage: www.elsevier.com/locate/carbpol

Dual crosslinked iminoboronate-chitosan hydrogels with strong antifungal activity against *Candida* planktonic yeasts and biofilms

Daniela Ailincai[a], Luminita Marin[a,*], Simona Morariu[a], Mihai Mares[b], Andra-Cristina Bostanaru[b], Mariana Pinteala[a], Bogdan C. Simionescu[a,c], Mihai Barboiu[a,d]

- **Supramolecular self-assembling hydrogel based on chitosan and 2-formylphenylboronic acid**
- **Designed for the treatment of vulvovaginal candidiasis and vaginal Candida decolonization**

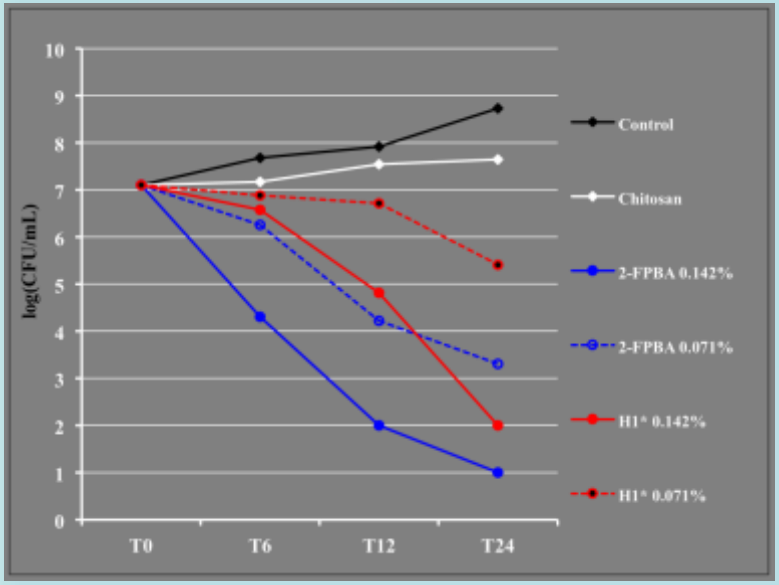
- **Screening for boron derivatives with antifungal activity and ability to build supramolecular structures with natural polysaccharides (2-formylphenylboronic acid)**



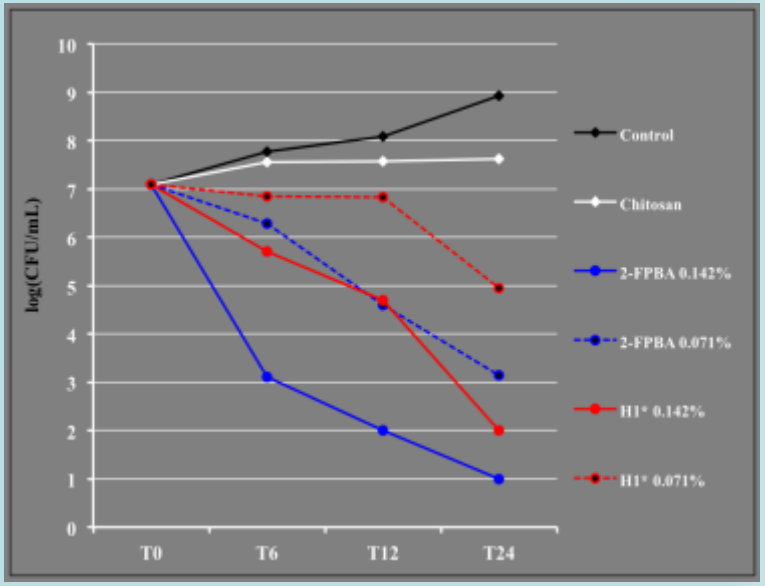
Ailincai et al. – Carbohyd Polym 2016

- **Antimicrobial evaluation of the complex compound in biomimetic conditions (synthetic vaginal simulative medium pH 4.2) and in a model of VVC in Balb/C mice**
- **Planktonic and biofilms of *C. albicans* and *C. glabrata (in vitro)***
- ***C. albicans (in vivo)***

Ailincai et al. – Carbohyd Polym 2016



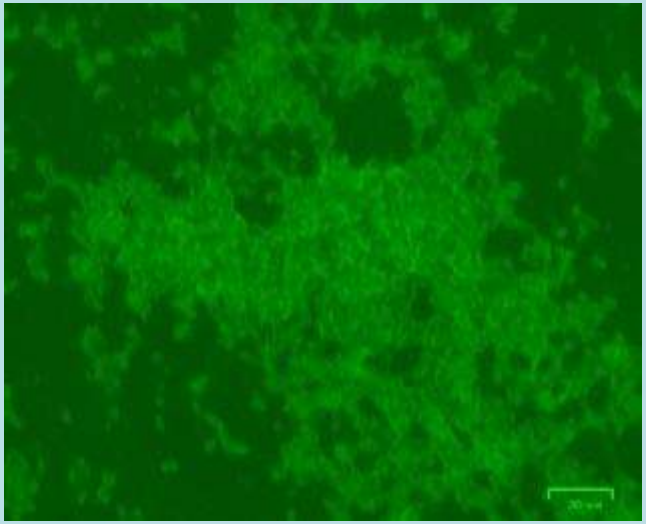
Candida albicans



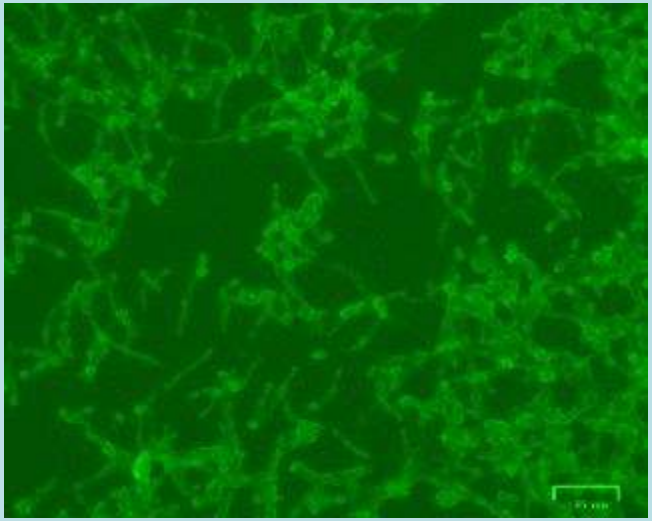
Candida glabrata

Table 3. XTT assay – Decreasing of biofilm metabolic activity

Tested strains	Control	0.142% **2-FPBA** in **H1***		0.284% **2-FPBA** in **H1***	
	Abs ($\bar{x}$)	Abs ($\bar{x}$)	% reduction	Abs ($\bar{x}$)	% reduction
C. albicans 1112	0.758	0.002	99.74	0.001	99.87
C. glabrata 1532	1.020	0.007	99.31	0.003	99.71



Mature biofilm in a drug-free control well after 48 h: abundant matrix embedding the filaments and sessile yeast cells



Biofilm after the treatment with 0.284% 2-FPBA hydrogel, for 24 h: visible filaments and sessile yeast cells, matrix in trace amounts

- **Murine model of VVC – C. albicans wild type SC5314** Yano and Fidel – J Vis Exp 2011
- **Balb/C mice**
- **3 log reduction (single dose) and > 5 log reduction (3 doses)**

Take-home messages

- Multiple sources and transmission ways
- Preterm birth (low weight) is the major risk factor
- Central vascular catheters are colonized (biofilms)
- C. albicans and C. parapsilosis more frequent, C. auris emergent threat
- Strict adherence to hand hygiene and hospital environment decontamination are extremely important for infection control
- Decolonization of skin/vagina should be considered

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