# Challenges in the management of Candida auris : cases and hospital outbreaks

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## Disclosure

Honorarium/speaker fees: Gilead, Basilea, Astellas, Pfizer Specialist advisor/consultancy: Pfizer, Astellas

#### **Candida auris**

#### ORIGINAL ARTICLE

#### *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital

Kazuo Satoh<sup>1,2</sup>, Koichi Makimura<sup>1,3</sup>, Yayoi Hasumi<sup>1</sup>, Yayoi Nishiyama<sup>1</sup>, Katsuhisa Uchida<sup>1</sup> and Hideyo Yamaguchi<sup>1</sup>

<sup>1</sup>Teikyo University Institute of Medical Mycology, 359 Otsuka, Hachioji, Tokyo 192-0395, <sup>2</sup>Japan Health Sciences Foundation, 13-4 Nihonbashi-Kodenmacho, Chuo-ku, Tokyo 103-0001 and <sup>3</sup>Genome Research Center, Graduate School of Medicine and Faculty of Medicine, Teikyo University, Otsuka 359, Hachioji, Tokyo 192-0395, Japan

- 1<sup>st</sup> case report, Japan 2009<sup>1</sup>
- 1<sup>st</sup> candidaemia cases, Korea 2011<sup>2</sup>
- Retrospective 1<sup>st</sup> isolate 1996<sup>2</sup>
- Multidrug-resistant (azoles, AmB, echino.)
- 28-70% mortality candidaemia

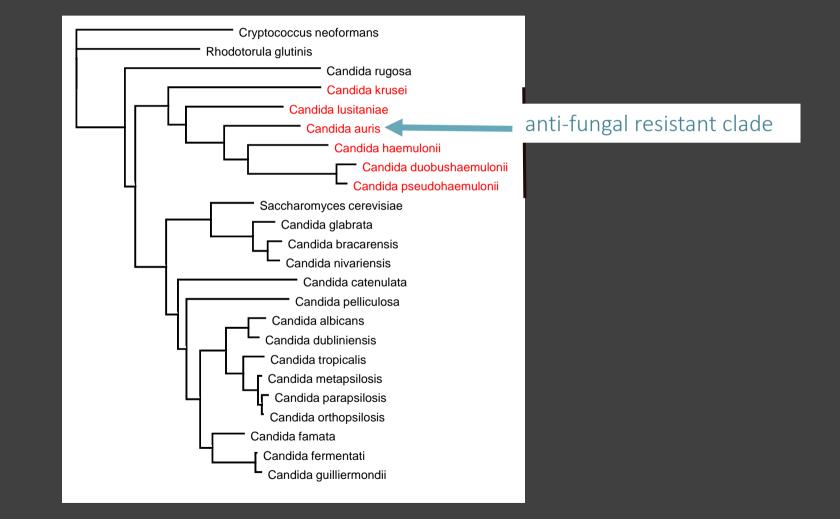
#### Often not 'speciated' or misidentified<sup>3</sup>

- Oval shape
- Growth at 37C and 42C
- No germtube/pseudo hyphae



CHROMagar (Mast)

#### Phylogenetic tree of *Candida* spp.



## Anti-fungal susceptibility: C. auris

Anti fungal drug	Resistanc	e Breakpoint MIC ug/mI
Fluconazole <sup>1,4</sup>	88-98%	≥32
Echinocandins <sup>1</sup>	7%	≥8
5-flucytosine <sup>2</sup>	5%	≥32
Amphotericin B <sup>1,4</sup>	10-35%	⁄o >2
Voriconazole <sup>1</sup>	54%	≥4
Posaconazole <sup>2</sup>	22%	≥8
Isavuconazole <sup>3</sup>	0%	>(0.03 - 0.25)
MDR isolates <sup>1</sup>		41%
Resistant to all 4 major antifungal classes <sup>1</sup>		4%

<sup>1</sup>Lockhart et al. CID 2017; 64,134, <sup>2</sup>Schelenz unpublished data, <sup>3</sup> Miranda-Cadena et al TIMM 2017 <sup>4</sup> Arendrup et al, AAC 2017;61;e00485 Clinical Infectious Diseases<sup>®</sup> 2017:64(2):134-40

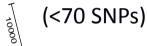
Simultaneous Emergence of Multidrug-Resistant Candida auris on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

Shawn R. Lockhart,<sup>1</sup> Kizee A. Etienne,<sup>1</sup> Snigdha Vallabhaneni,<sup>1</sup> Joveria Farooqi,<sup>4</sup> Anuradha Chowdhary,<sup>6</sup> Nelesh P. Govender,<sup>7</sup> Arnaldo Lopes Colombo,<sup>1</sup> Belinda Calvo,<sup>5</sup> Christina A. Cuomo,<sup>2</sup> Christopher A. Desiardins,<sup>2</sup> Elizabeth L. Berkow,<sup>1</sup> Mariana Castanheira,<sup>3</sup> Rindidzani E. Maqobo,<sup>7</sup> Kauser Jabeen,<sup>4</sup> Rana J. Asqhar,<sup>5</sup> Jacques F. Meis,<sup>10,11</sup> Brendan Jackson,<sup>1</sup> Tom Chiller,<sup>1</sup> and Anastasia P. Litvintseva<sup>1</sup>

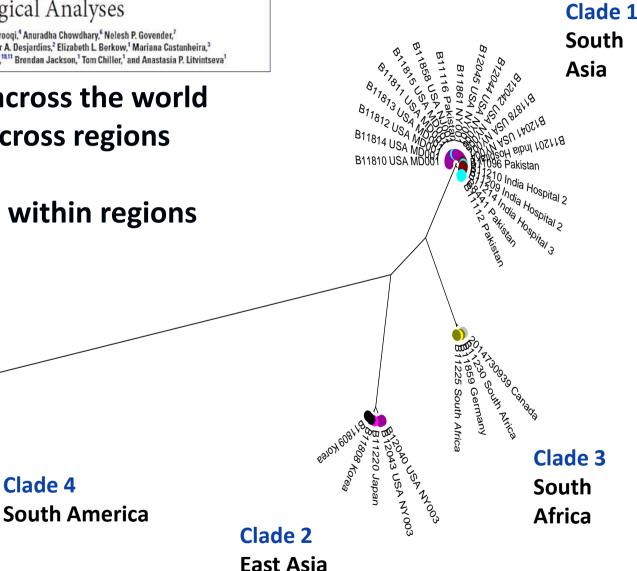
- 4 unique clads across the world
- Very different across regions

(>40K-400K SNPs)

Nearly identical within regions



B11895



B11245

Clade 4

B112

Lockhart et al, CID 2016

## **Diagnostic challenge**

Commercial assays for Candida ID	<i>C. auris</i> Identified as:	Correct <i>C. auris</i> ID
API 20C-AUX bioMerieux	C. sake, Rhodotorula glutinis, C. famata	No
Vitek 2 Yst (Ver <8) bioMerieux	C. haemulonii, C. famata, Rhodotorula glutinis, C lucitaniae	No
MicroScan (Beckman Coulter)	C tropicalis, C albicans, C. catenulate C guiliermondii, C lusitanae	No
BD Phoenix yeast ID	C catenulata, C. haemulonii,	No
AuxaColor 2 (BioRad)	Saccharomyces cerevisiae	
Chromogenic media	Beige, white, pink (no ID)	No
Vitek 2 YST card version 8.01 software	C. auris	yes
ITS sequencing and D1D2 region 28sDNA	C. auris	yes
MALDI Bruker version 3.1	C auris	yes
Vitek MS MALDI extended database	C. auris	yes
Whole genome sequencing	C. auris	yes

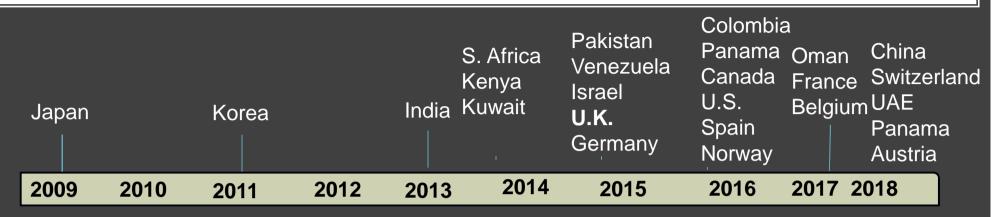
Modified: CMN Vol. 39, No. 13 July 1, 2017

National UK laboratory diagnostic survey 2017

Candida auris species	Laboratories that identify to		
identification	species level/respondents (%)		
Onsite			
MALDI			24/58 (41%)
VITEK			2/58 (3%)
API			0/58 (0%)
Chromogenic Agar			0/58 (0%)
PCR/Sequencing			0/58 (0%)

ESPAUR/UK CMN/ BSMM 2017

#### Rapid global emergence of C. auris



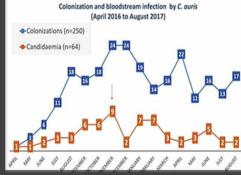


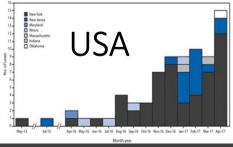
CDC October 2017

#### **Propensity to transmit and cause hospital outbreaks**

Country	year	Impact	Reference
India	2013	Mortality 44%, candidaemia ICU, NICU	Chowdhary A et al. 3013 Lockhart et al CID 2017
Pakistan	2013	Mortality 52%, candidaemia	Lockhart et al CID 2017, Mahmood TIMM 2017
Venezuela	2012	Mortality, candidaemia	Lockhart et al CID 2017, Calvo et al. 2016
Columbia	2015/16	candidaemia, high mortality, Hands HCW pos, environmental contamination	Escandón P eta I CID 2018
South Africa	2013/14	Mortality 46%	Lockhart et al CID 2017
UK	2015/16	environmental contamination, ICU	Schelenz et al. 2015
Spain	2015/16	38.7% mortality, breakthrough candidaemia, ICU	Ruiz-Gaitan et al 2017
USA	2016	Long term care facilities	Vallabhaneni S et al MMWR 2016
Canada	2016	ICU	Schwartz et al 2017
Israel	2017	Travel S Africa, ICU,	Belkin A et al. Em Inf Dis. 2018







#### What makes *C. auris* transmissible in health care settings?

	Impact	Reference
Survival in desiccated state > 4 weeks	Prolonged persistence in environment and increased risk of exposure	Abdolrasouli, A et al Mycoses 2017
Reduced susceptibility to environmental disinfectants	quaternary ammonium	Cadnum JL et al ICHE 2017
Persistence on linen	In vitro (7 days)	Biswal et al 2017
Biofilm formation	In vitro	Larkin et al., 2017; Sherry et al., 2017
Ability to shed from skin into environment	Environmental contamination	Schelenz et al 2015
Lack of effective skin decontamination products	Chlorhexidine	Abdolrasouli, A et al Mycoses 2017 Moore, G et al J. Hosp. Infect 2017
Delayed detection	Lack of surveillance, lack of identification and early treatment	

# C. auris in the UK

- >2013: first 3 isolates from B/C from unrelated patients.
- >2014: 1 isolate, pleural fluid
- >2015: First outbreak (Royal Brompton H.)
- >June 2018, 227 cases in UK
  - (61 infections, 31 candidaemias, 160 colonisation,
  - 6 unknown)
- >Majority colonised, detected through enhanced surveillance.
- Large outbreaks in 3 hospital Trusts ICUs!
- Sequencing suggests 3 lineages (Indian, South African, Japan/Korea



Japanese fungus spreading in UK hospitals

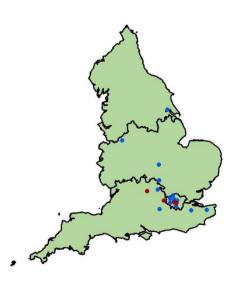
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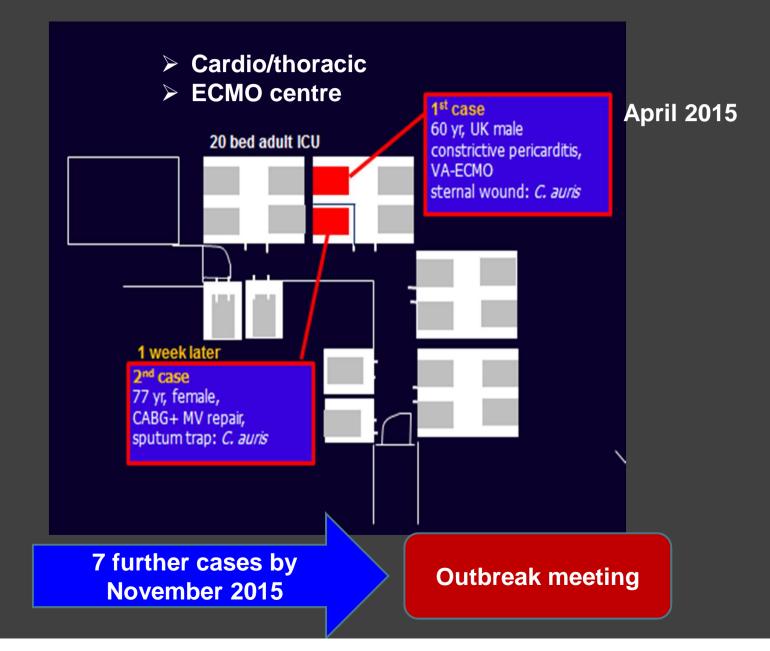
More than 200 patients in England have been infected or contaminated with a drug-ret

Hospitals help con

() 15 August 2017 Health



## Brompton experience 2015 C. auris outbreak



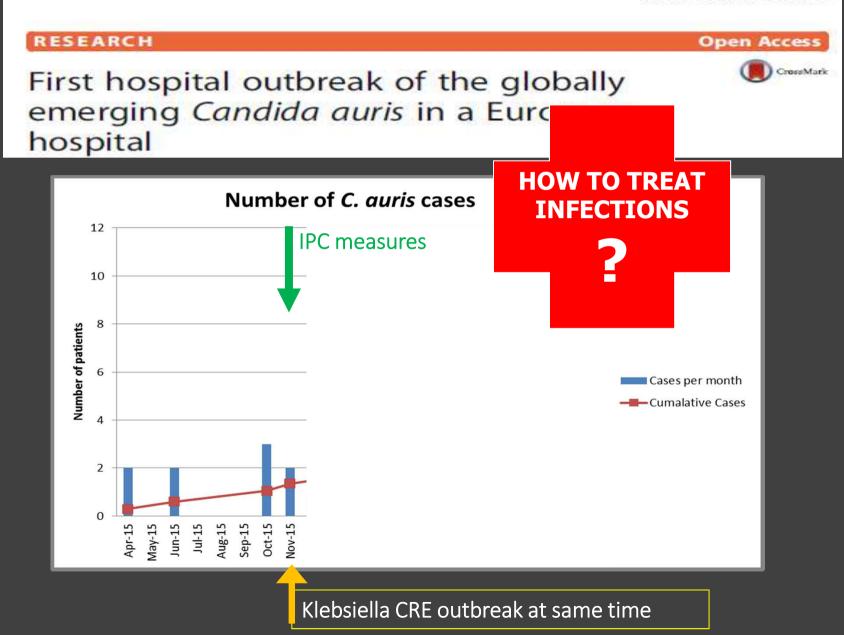
#### **Initial Infection Prevention Control measure 2015**



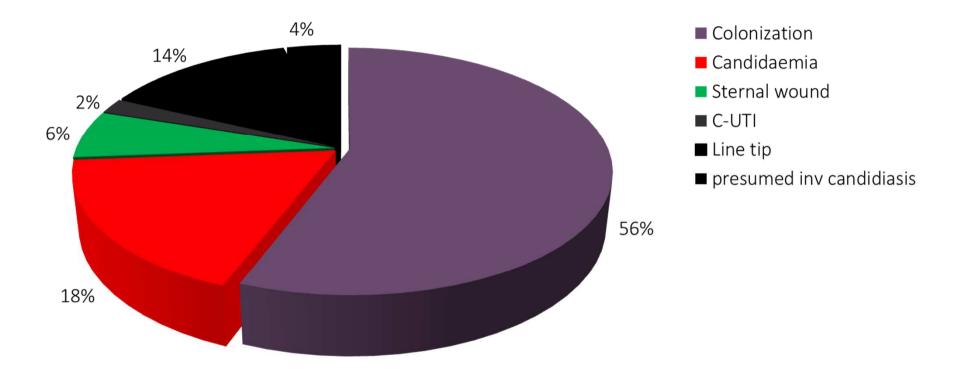
Positive *C. auris* patients Isolation/cohorting skin 'decolonization'-chlorhexidine Patient contacts of *C. auris* cases Isolation/cohorting Screening (N, A, G, T, urine, rectal) (3 x negative, de-isolate) Contacts & positive patients Gowns, aprons (as per CRE UK policy) Terminal clean with chlorine products

Schelenz et al. Antimicrobial Resistance and Infection Control (2016) 5:35 DOI 10.1186/s13756-016-0132-5

Antimicrobial Resistance and Infection Control



#### Clinical manifestations and management of *C. auris* patients (n=50)



External review of cases No direct attributable mortality

Antimicrob Res Infect Control (2016);5:35

## Management of *C. auris* infection at RBH

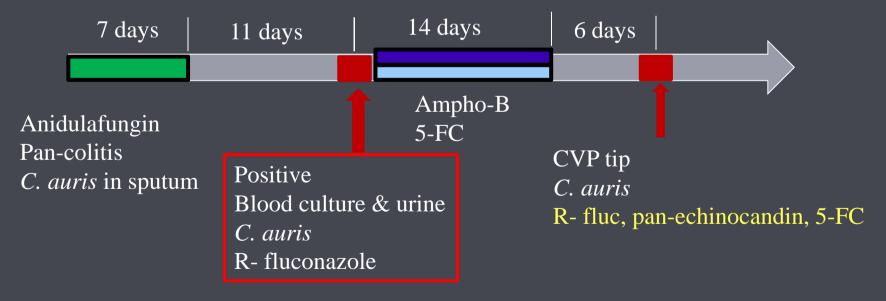
Candidaemia/deep seated infection 1<sup>st</sup> line echinocandin (break through infections?) 2<sup>nd</sup> line Amphotericin,+/- 5FC (reserve 3<sup>rd</sup> generation triazole)

Urinary tract infection, CNS infection 1<sup>st</sup> line Amphotericin plus 5FC (reserve 3rd generation triazole)

Monitor serum B-D Glucan in at risk patients

# Development of MDR *C. auris* case during treatment at RBH

50yr, male Admitted with SOB, HAP Placed on ECMO *C. auris* sputum 26 d after admission to ICU



Rhodes J et al 2018

## C. auris Anti-fungal resistance mechanism

**Flucytosine R** Echinocandin R **F211I FUR1** S652Y FKS 1 phenylalanine serine for for isoleucine tyrosine Polyenes Azoles Echinocandins 5-Fluorocytosine 5) Mutation in FKS1/2 ß-1,3-glucan FKS1/2 β-(1,3)-Glucan synthase Squalene ERGI 3) Point mutation or e (FURI Cytosine overexpression in ERG11 FRGt permease deaminase FUMP ERG2\* 5FUTP ERG3\* 5FdUMP 0 Ergosterol DNA synthesis RNA synthesis **TROS** DNA 02 Damag H2O2 6) Loss of cytosine permease. 2) Effux pump deaminase activity overexpression and/or FUR1 mutation Mitochondria Pore formation damage 1) Decrease in ergosterol in membrane Reales-Calderon 2016 ERG2 and ERG3 mutants

Fluconazole R 100% isolates **Y132F ERG11** tyrosine for phenylalanine

(same India, Pakistan, Venezuela)

Rhodes J et al 2018

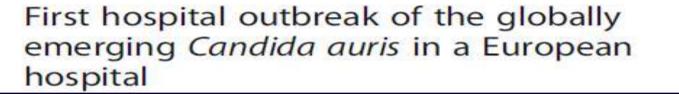
Schelenz et al. Antimicrobial Resistance and Infection Control (2016) 5:35 DOI 10.1186/s13756-016-0132-5

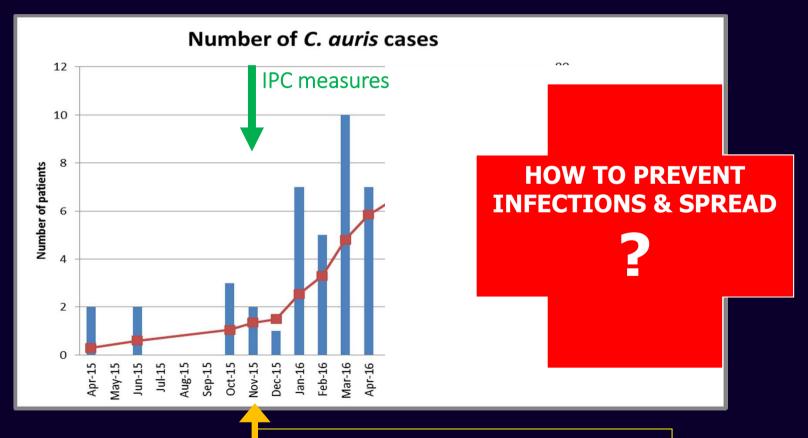
Antimicrobial Resistance and Infection Control

#### RESEARCH

**Open Access** 

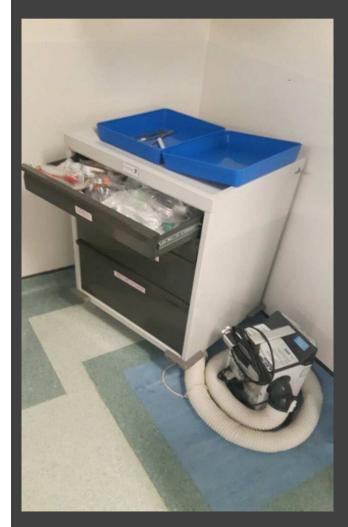
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Klebsiella CRE outbreak at same time





# More Infection Prevention Control measures implemented...

- Route course analysis/each patient
- Screening of all patient on effected wards (2 x week)
- > AICU ward closure/refurbishment
- Opening HDU as AICU on different floor, restricted access
- Disposing medicines/items on discharge
- Single use items: bronchoscope,pillows...
- >Enhanced cleaning (3xday) & audit
- >Enhance hygiene awareness, audits
- >2 x week formal outbreak meetings

# How to implement IC measures when there was no published evidence or guidance in 2015?

C. auris : Key questions 2015	Answers?
Clonal strains? What is reliable typing method?	No typing service in UK
Cause/route of transmission?	<ul><li>Unknown, possible patient to patient via</li><li>HCW?</li><li>Equipment, environment?</li></ul>
Effective agents for skin/gut decolonization?	Unknown
How to screen 'contacts' and new admissions?	Best body sites ? unknown Best lab methods? unknown
How to decontaminate equipment and environment?	Best products? unknown
Lack of published evidence based guidance	Hospital management questioning validity and justified expense

# High impact ICP interventions

Back to BASICS

#### Prevention of ventilator associated pneumonia

Prevention of infections associated with peripheral vascular access devices Prevention of infections associated with central intravascular access devices Prevention of surgical site infection Prevention of infections in chronic wounds Prevention of urinary catheter associated infections Promotion of stewardship in antimicrobial prescribing

## Aseptic Non Touch -Technique

Implementation of chlorhexidine 'biopatch' line exit site

 Training, implementation, recording and checking (monitoring compliance!)

# **High impact ICP interventions**

Back to BASICS

Prevention of ventilator associated pneumonia Prevention of infections associated with peripheral vascular access devices Prevention of infections associated with central intravascular access devices Prevention of surgical site infection Prevention of infections in chronic wounds Prevention of urinary catheter associated infections

Promotion of stewardship in antimicrobial prescribing

Not open wound dressings unless necessary
 Not to include dressed wounds in routine weekly *C. auris* screening

3EPIC, Journal of Hospital Infection 86S1 (2014) S1–S70

# High impact ICP interventions

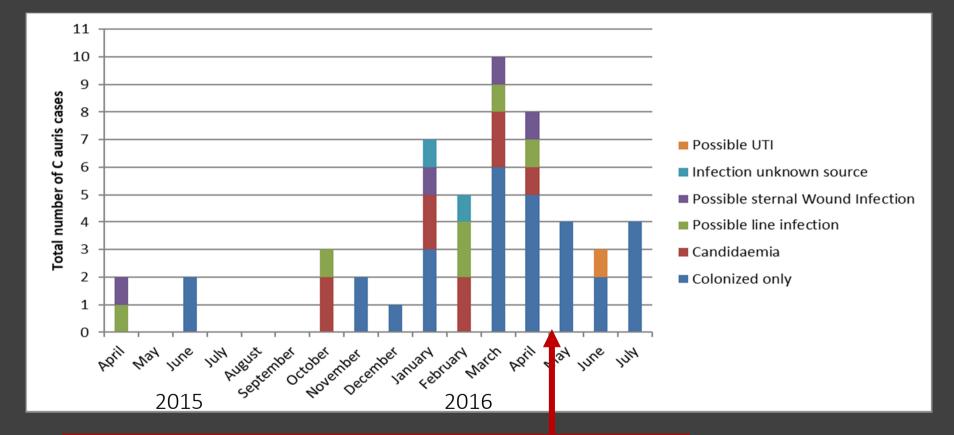
Back to BASICS

Prevention of ventilator associated pneumonia Prevention of infections associated with peripheral vascular access devices Prevention of infections associated with central intravascular access devices Prevention of surgical site infection Prevention of infections in chronic wounds Prevention of urinary catheter associated infections Promotion of stewardship in antimicrobial prescribing

Reduce use of broad spectrum antibiotics
 Reduce use of antifungals (azoles)
 Monitor B D-glucan

3EPIC, Journal of Hospital Infection 86S1 (2014) S1–S70

## We managed to stop infections but ongoing transmission of *C. auris*



Implementation of High Impact prevention measures

#### How to prevent transmission of *C. auris*?

Isolation/co-horting C.auris positive patients crucial (Spain, Pakistan, India)

- Need for patient decolonization to reduce 'shedding'
- Cohort contacts until screen negative
- Control & prevent contamination of equipment and environment
- Increase and monitor hand hygiene
- Enhanced drastic IPC measures have impact on:
- >day to day running of clinical services
  - (bed closure, cancelled admissions and surgery)
- High cost (single use items, more cleaning staff, etc)
- Pressure on communication, commitment from senior management, HCW, doctors, cleaners etc.

# Management of *C. auris* Patient colonization - reduce infection



- reduce shedding in environment/transmission

Product	concentration	Site/application
Chlorhexidine	2%	Wash cloth
Aqueous Chlorhexidine	4%	Body wash
Chlorhexidine	nk	Impregnated exit line patch
Chlorhexidine	0.2%	Mouth wash
Nystatin	1ml qds	Mouth
Chlorhexidine dental gel	1%	Trachy site

- Echinocandins had no effect on skin carriage
- Patient presumed long term carrier
- Persistent colonization on chlorhexidine

# Skin decontamination for *C. auris*

Skin decontamination	Strength/concentration	Proven Efficacy	Reference
Videne alcoholic tincture: w/w povidone-iodine	10% + 30% IMS		Moore <i>et al.</i> 2017
Iodinated povidone Videne antiseptic solution	10% w/w cutaneous solution		Abdolrasouli <i>et al.</i> 2017, Moore <i>et al.</i> 2017
Chlorhexidine gluconate HiBiScrub antimicrobial hand and body wash	2-4% w/v		Abdolrasouli <i>et al.</i> 2017, Moore <i>et al.</i> 2017
Chlorhexidine gluconate Clinell wash cloths/Sage pads	2% (20 mg/mL solution)		Abdolrasouli et al. 2017,
Terbinafine	Topical versus systemic	little data	

# **Standard Principles of ICP**

**Back to BASICS** 



Available online at www.sciencedirect.com

Journal of Hospital Infection

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



H.P. Loveday<sup>a\*</sup>, J.A. Wilson<sup>a</sup>, R.J. Pratt<sup>a</sup>, M. Golsorkhi<sup>a</sup>, A. Tingle<sup>a</sup>, A. Bak<sup>a</sup>, J. Browne<sup>a</sup>, J. Prieto<sup>b</sup>, M. Wilcox<sup>c</sup>

- IV catheter and urinary catheter care
- Hand hygiene
- The use of personal protective equipment
- Hospital environmental hygiene







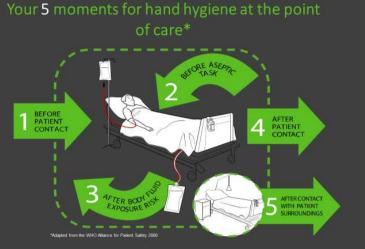


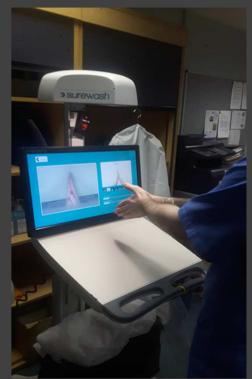
### C. auris carriage by Health care workers

Site positive for C. auris	Place	Reference
Nose of nurse	London	Schelenz et al.
Sole healthcare worker's shoe	Columbia	Escandón P eta I CID 2018
Hands HCW (doctors, nurses)	Columbia, India	Escandón P eta I CID 2018 Biswal et al 2017
Groin HCW	Columbia	Escandón P eta I CID 2018

# Standard Principles: Hand hygiene

 Improve Hand hygiene
 Mandatory training (Surewash)
 Monitored compliance (audit 3 x wk)
 Feed back: outbreak meeting
 Email from medical director to all doctors
 <u>Staff screening</u>







# Standard Principles: Personal & Protective Equipment



#### **Gloves**

protect hands and patients
 training
 Long sleeved gowns
 protect skin and/or clothing
 Aprons
 to be used in isolation bays when dealing with patient

# AICU Environmental C. auris contamination



Impact of Environmental Decontamination in a *Candida auris* Outbreak. Abstract: 5172; FIS/HIS 2016



### **Contaminated environment: global experience**

Site positive for <i>C. auris</i>	Place	Reference
Patient floor surface	London, Columbia	Schelenz et al. 2015, Escandón P eta I CID 2018
Air positive around bed spaces	Oxford	K Jeffrey https://doi.org/10.1101/149054
Bedrails, chairs, closet cabinets	Columbia	Escandón P eta I CID 2018
door handles,	Columbia	Escandón P eta I CID 2018
sink basins	Columbia	Escandón P eta I CID 2018

#### **Assure clean environment**

Engage with cleaning manager
Training cleaners, share problems
Right technique
Right cleaning products
Audit cleaning of

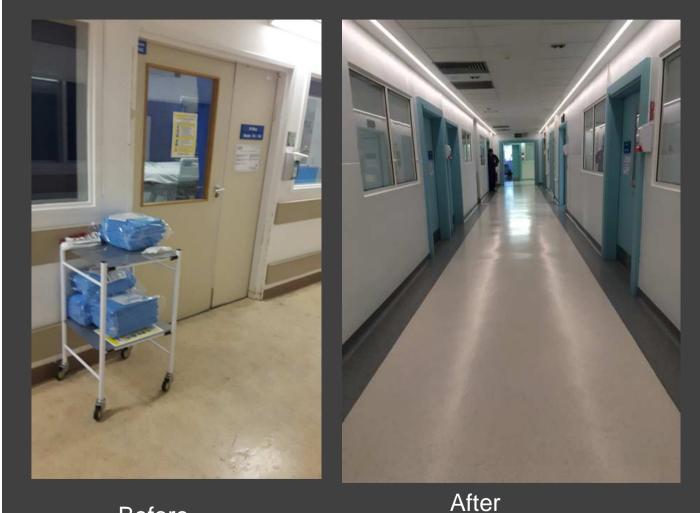
Equipment, floor, beds...

Use fluorescent marker
Use of 'I am cleaned stickers'
With date, time, signature



This equipment was cleaned on by I am clean	Vernacare	@Velles

#### Intensive care Unit refurbishment of environment



- ➢ More side rooms
- Removed wooded furnishing
- Smooth surfaces
- > New floor
- > Declutter
- Minimal equipment in corridor

Before

## **Contaminated Equipment: global experience**

Equipment positive for <i>C. auris</i>	Place	Reference
Reusable temperature probes	Oxford	K Jeffrey https://doi.org/10.1101/149054
Pulse oximeter	Oxford	K Jeffrey https://doi.org/10.1101/149054
Blood culture cuffs	Valencia	A. Ruiz-Gaitan TIMM 2017
Dialysis syphon ICU	Valencia	A. Ruiz-Gaitan TIMM 2017
Infusion pump	Valencia	A. Ruiz-Gaitan TIMM 2017, Biswas et al 2017
non-disposable mop	Columbia	Escandón P eta I CID 2018
cellular phone	Columbia	Escandón P eta I CID 2018
alcohol gel dispensers	Columbia	Escandón P eta I CID 2018
bedpans, and mop buckets	Columbia	
Ventilator attachment	India	Biswal et al 2017







## Standard Principles: Decontamination & Re-processing of Equipment











**Back to BASICS** 

#### Equipment and devices: improve decontamination

Assess risk of transmission through multiuse equipment
Introduce single use devices such as bronchoscopes (expensive)
Dispose of all materials in *C. auris* isolation room (empty trollies)
Dispose all medicines that were in *C. auris* patient room
Assess decontamination of medical devices
Train cleaners, audit cleaning
Exposure to Hydrogen peroxide vaporisation





#### **Focus on Environmental decontamination**

Enhanced cleaning
 3x day 1,000 ppm (Chlor-clean)
 Equipment cleaning, assurance

3x day 1,000 ppm or chlorine dioxide wipes

Terminal cleaning 10,000ppm Chlorine based (Haztab) Followed by H<sub>2</sub>O<sub>2</sub> vaporization



#### Revised Healthcare Cleaning Manual

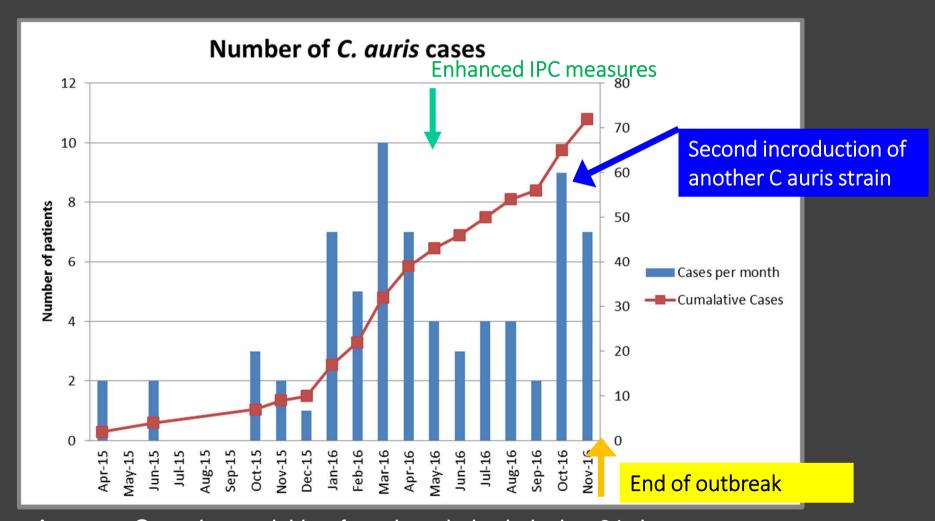
Published in June 2009, the Revised Healthcare Cleaning Manual is designed to be used across different healthcare settings, including acute care, mental health care, primary care and the ambulance service.

The Association of Healthcare Cleaning Professionals (AHCP) worked jointly with the

## Effective surface decontamination: *C. auris*

Surface decontamination	Strength/concentration	Proven Efficacy	Reference
Sodium hypochloride (Clorox, Chlor-clean, HazTab®)	≥ 1000 ppm 0.39-0.65%, 10%		Cadnum <i>et al.</i> 2017 Abdolrasouli <i>et al.</i> 2017, Moore <i>et al.</i> 2017
Quaternary ammonium (Lysol all, Virex II 256)			Cadnum <i>et al.</i> 2017
Peracetic acid hydrogen peroxide <1%, acetic acid (OxyCide)	1200ppm,		Cadnum et al. 2017
Ethyl alcohol 29.4% (Purell disinfectant)	29.4%		Cadnum <i>et al.</i> 2017
Acetic acid (White distilled vinegar)	>5% (pH 2.0)		Cadnum <i>et al.</i> 2017
Carbolic acid (phenol)	5%	?	?
Hydrogen peroxide (Oxivir Tb, Clorox)	0.5%, 1.4%		Cadnum et al. 2017
Vaporized hydrogen peroxide (BioQuell)	8g/peroxide/m <sup>3</sup>		Abdolrasouli <i>et al.</i> 2017
Ultra violet light	(D90 value of 515 J/m2)		Schelenz <i>et al.</i> unpublished

#### Brompton: 72 cases over 20 months period 2015-16



Average *C. auris* acquisition from hospital admission 21 days Average *C. auris* acquisition from admission to affected ward 17 days

# Post outbreak IC practice

Continue 'high level' cleaning, hand hygiene
 Routine speciation of *Candida* from clinical sites
 *C. auris* admission screening (pooled N,A,G,T)
 Hospital transfers from an HDU, ICU to our HDU/ICU
 Known positive *C. auris* patient
 Patients from another unit known to have

- Patients from another unit known to nave C.auris cases
- UK national prevalence low

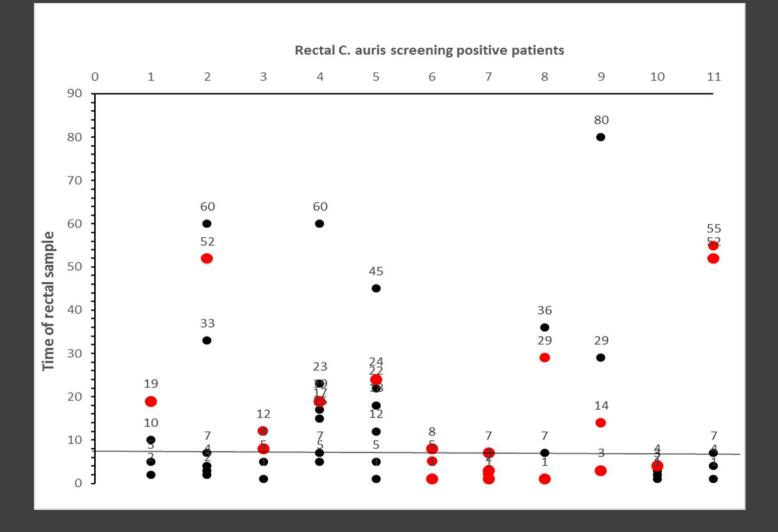
#### **Conclusion:** C. auris Infection control

- Transmissible within care setting
- Early detection/speciation of C. auris crucial
- Environment easily contaminated-poses major risk of transmission
- Isolation and screening
- Enhanced IPC measures & high impact interventions and cleaning is vital
- Outbreak: very costly, resource intensive
- Need for good communication and resource allocation during outbreaks

#### ACKNOWLEDGEMENT

IC nurses: Jo Shackleton, Lisa Ryan, Rosie Cervera-Jackson (RBHT) Anne Hall (microbiologist, RBHT)) AICU team (nurses, doctors) **RBH** microbiology laboratory staff Jacques Meis, Ferry Hagen (Canisius Wilhelmina Hospital, Nijmegen, NL) Matthew Fisher, Jo Rhodes, Ali Abdolrasouli, D Armstrong-James (Imperial College) PHE staff And many, many, more people...

#### Intermittent rectal carriage



8% (4/50) patients screened positive on their 1st rectal screen swab 55% of patients never tested rectum positive over time