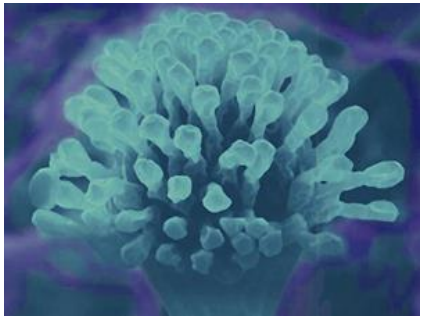
Clinical Mycology Update

National Infection Update 15th September 2017

Royal College of Pathologists

Elham Khatamzas



Disclosures

- None

Outline

- Epidemiology
- Diagnostics
- Drugs
- Stewardship

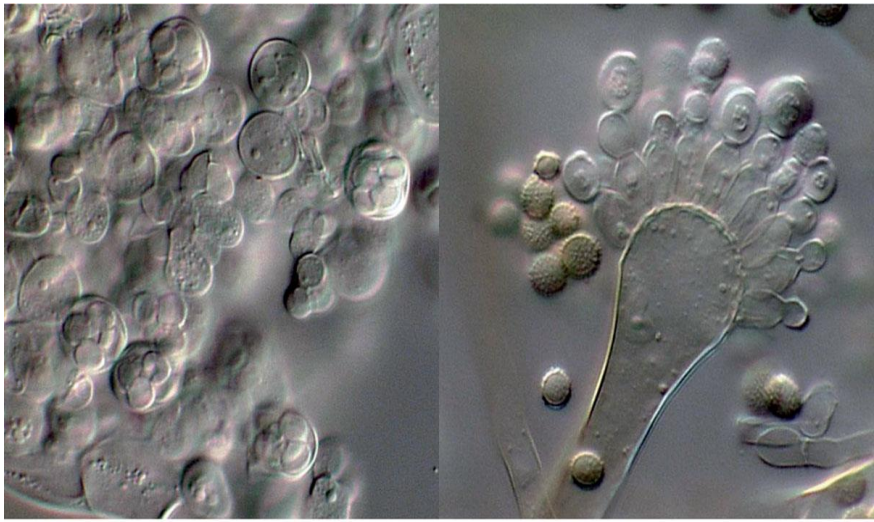
- EORTC criteria
- Guidelines
- Biofilm
- Stewardship
- Infection control
- Host immunity, mycobiome
- Combination Rx, immuntherapy
- *C. glabrata* breakpoints
- New *C. auris* guidance

but

- Fungal taxonomy
- Antifungal resistance: Aspergillus spp, Candida spp
- Cryptococcal meningitis
- PCP
- Stewardship
- Antifungal prophylaxis and ICU

Changes in fungal taxonomy – new age of enlightenment or more confusion?

- Impossible task: to discover and give names to all world's mushrooms, moulds and yeast.
- 'One fungus, one name' campaign
- Recently embraced modernization of nomenclature rules
  - discard Latin descriptions
  - endorse electronic publications
  - end dual system for nomenclature
  - develop standards for sequence-based classification
- BUT there will be many exceptions

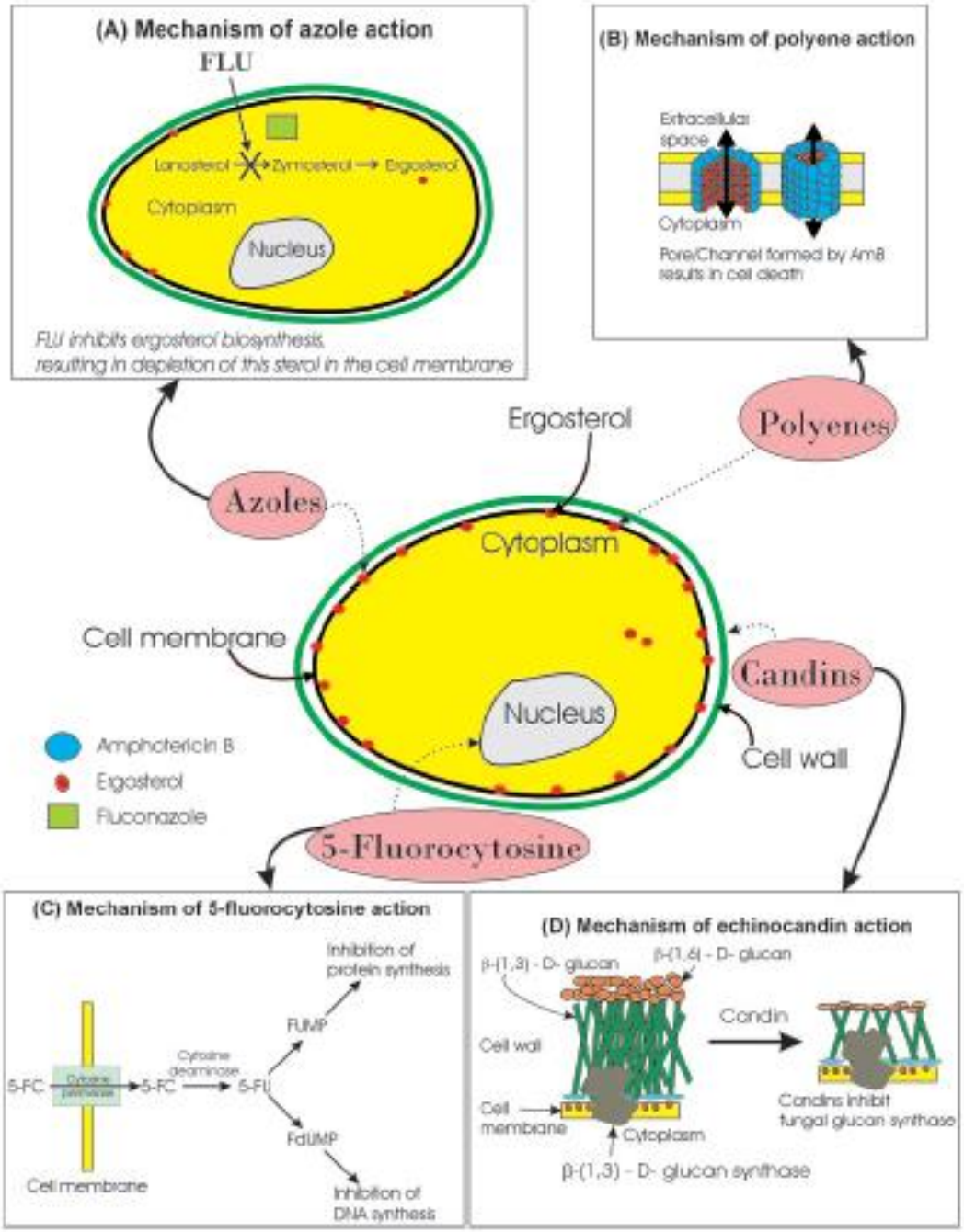


Nature Reviews | Microbiology

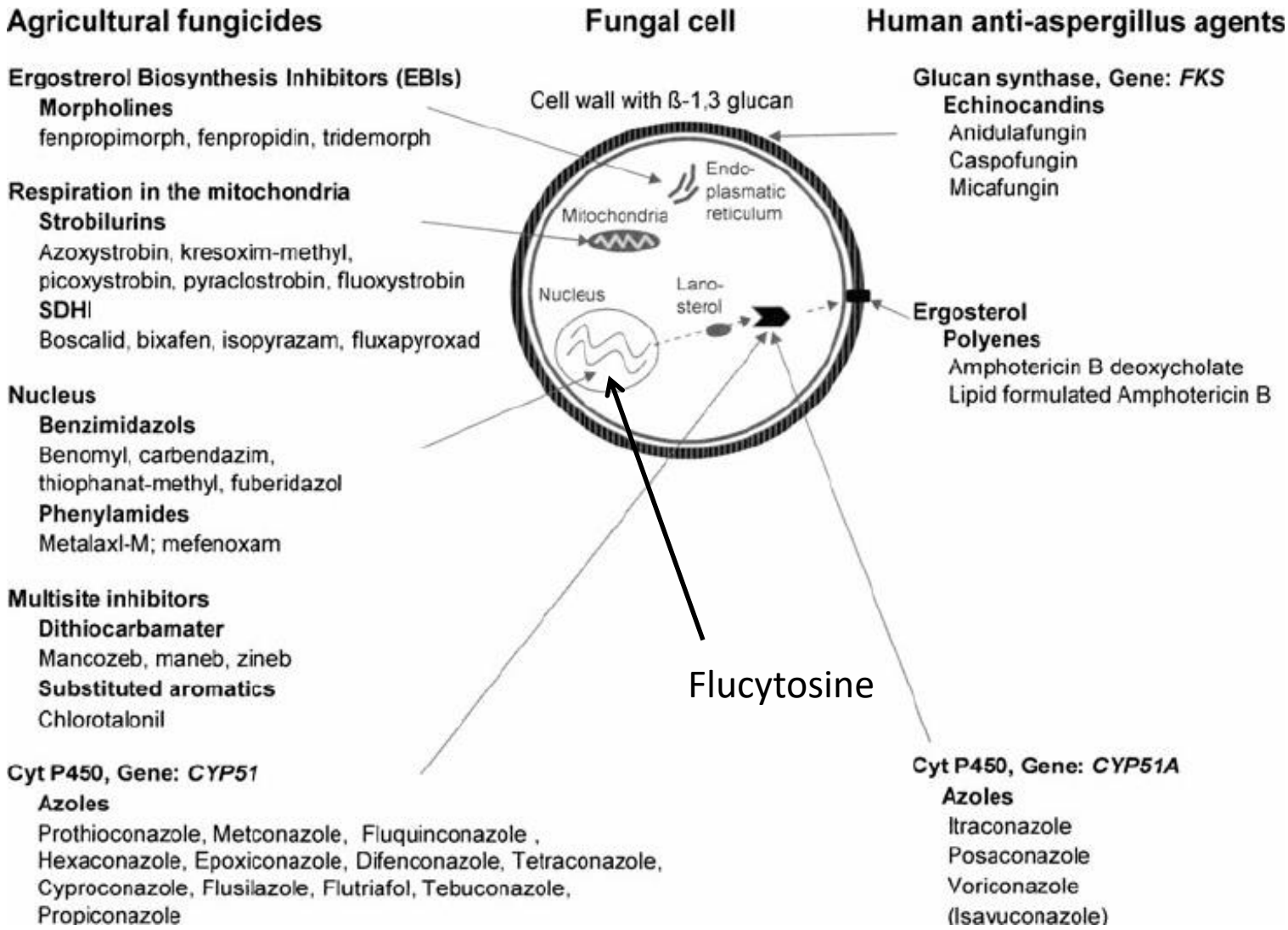
Eurotium herbariorum

Aspergillus glaucus

Hibbett and Taylor, Nat Rev Micro 2013


(A) Mechanism of azole action
FLU
Lanosterol
Zymosterol
Ergosterol
Cytoplasm
Nucleus
FLU inhibits ergosterol biosynthesis, resulting in depletion of this sterol in the cell membrane
(B) Mechanism of polyene action
Extracellular space
Cytoplasm
Pore/Channel formed by AmB results in cell death
Ergosterol
Polyenes
Azoles
Cytoplasm
Cell membrane
Candins
Nucleus
Cell wall
Amphotericin B
Ergosterol
Fluconazole
5-Fluorocytosine
(C) Mechanism of 5-fluorocytosine action
Inhibition of protein synthesis
FUMP
5-FC
Cytosine deaminase
5-FC
5-FU
FdUMP
Cell membrane
Inhibition of DNA synthesis
(D) Mechanism of echinocandin action
β-(1,3) - D- glucan
β-(1,6) - D- glucan
Cell wall
Cell membrane
Cytoplasm
β-(1,3) - D- glucan synthase
Candin
Candins inhibit fungal glucan synthase

Reminder targets of antifungal drugs



Increasing azole resistance in plant infecting fungi

- UK sprays ~250000 kg azoles per yr as crop protection
- Since 2000 6fold increase in application of azoles

Census-ward level estimates of the usage of fungicides for the year 2000 (UK Environment & Health Atlas)

Table 1. Overview of mutations identified in the CYP51 of field isolates

Organism	Crop affected	Alterations in the amino acid sequence	Reference
Zymoseptoria tritici	Wheat	L50S, D107V, D134G, V136A, V136C, V136G, Y137F, M145L, N178S, S188N, S208T, N284H, H303Y, A311G, G312A, A379G, I381V, A410T, G412A, Y459C, Y459D, Y459N, Y459P, Y459S, G460D, Y461D, Y461H, Y461S, ΔY459 or ΔG460, ΔY459/G460, V490L, G510C, N513K, S524T	12
Blumeria graminis f. sp. *tritici*	Wheat	Y136F	13
Blumeria graminis f. sp. *hordei*	Barley	Y136F, K147Q	14
Erysiphe necator	Grape	Y136F	15
Mycosphaerella fijiensis	Banana plants and plantain	Y136F, A313G, Y461D, Y463D, Y463H, Y463N	16
Venturia nasicola	Japanese pear	Y133	17
Pyrenopeziza brassicae	Oilseed rape	G460S, S508T	18
Puccinia triticina	Wheat	Y134F	19
Penicillum digitatum	Citrus fruit	V55A, Y136H, M144T, K253E, Q309H, E331A, T432, I440V, K449R, G459S, R462H, F506I, S507P, K508R, G511S	20
Oculimacula yallundae	Wheat	S35T, Q43H, D78Y, E106K, N244S, S505Q	21
Oculimacula acuformis	Wheat	A29P, V37A, Q167H, Y486H, S505Q	21

Piece et al Pest Manag Sci 2015;71

Azole resistance *A. fumigatus* – an impending disaster

- Prospective multi-centre international surveillance study of CYP51A resistance in *A. fumigatus* prevalance 3.9% including in UK isolates. van der Linden EID 2015
- First isolation of the pan-azole-resistant *A. fumigatus* cyp51A TR46/Y121F/T289A mutant in a UK patient. Moore et al Int J AntimicAg 2017
- High prevalence of azole resistance in *A. fumigatus* isolates from high risk patients. Fuhren et al. JAC 2015.

  2011-2013 Utrecht 105 isolates from ICU and Haematology

  All patients azole naïve

  Frequency of azole resistant isolates 16.2%

  Haematology 24.6%

  ICU 4.5%
- PHE data azole resistance 2013/4 2-3%→2015 5-6%→ 2016 7-8%

ECDC TECHNICAL REPORT

Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in *Aspergillus* species

Case 1

- 71y old male

24/01/15 admitted fever, vomiting, headache under medical team

- Background:
  - Previous Non-Hodgkins lymphoma 1990, relapse 2006
  - Previous transsphenoidal surgery for a pituitary adenoma in 2001
  - Previous frontal craniotomy 2009 for fibrodysplasia of the skull.
  - Ongoing communication between the frontal sinus and the nasal cavity
  - No drains/shunts in situ, no neurosurgery for at least the last 4 years.

- CT head: Stable large lobulated bony mass lesion in frontal region extending into anterior cranial fossa. No hydrocephalus. Unchanged appearances to Oct 2013.
- Radiology advise against LP because of fibrodysplasia related mass effect
- Treatment: Ceftriaxone + Metronidazole + Aciclovir


A
0cm
R
L
11cm
P

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26/01/15 EVD insertion

CSF WBC $300x10^6$/L (Polymorphs $298x10^6$/L, Lymphocytes $2x10^6$/L, RBC $2530x10^6$/L, Gram stain: No organisms seen. Cultures: No growth after 2 days.

Case 1 – further progress

19/02/15 CT head with contrast: Bilateral infected collection at both frontal lobes and ventriculitis.

- Treatment: Ceftazidime + Vancomycin + Metronidazole

23/02/15 Transnasal evacuation of pus frontal collection and insertion nasal pads

- Microbiology pus pus cells 1+, no organisms seen, no AFB seen, no growth
- Plan: For 6 weeks iv Ceftazidime and Vancomycin
- Remains with residual CSF leak

24/03/15 EVD drain dependent→VP shunt insertion

14/05/15 Drop in GCS with increased pneumocephalus on CT

- CSF WCC $84x10^6$/L, Polymorphs $26x10^6$/L, Lymphocytes $58x10^6$/L RBC 2790 x 10^6/L. No organisms seen. Cultures no growth after 2 days.

15/05/15 Endoscopic re-exploration and repair of skull bases defect with fascia lata

- Tissue culture: MSSA
- Treatment: Ceftazidime and Vancomycin

Case 1 – positive culture

24/05/15 CSF leak persists.

- Fluid pneumocephalus cavity: **Candida** (non albicans species), sent to PHE Mycology Reference Lab Bristol
- Imp: Complex intracranial infection.

  Culture result in keeping with ongoing communication between anterior cranial fossa and nasal cavity/persistent CSF leak and use of broad-spectrum antibiotics.
- Plan: Add oral Voriconazole pending further neurosurgical plan

01/06/15 Clinical deterioration with GCS drop

Case 1 – *Candida auris* CNS infection

02/06/15 Revision of right frontal intracranial drain

- CT: Persistent intracranial collections
- CSF (EVD) WBC $36x10^6$/L (Polymorphs $6x10^6$/L, Lymphocytes $30x10^6$/L, RBC $51200x10^6$/L)

  Culture ***Candida auris***

  Sensitive to Amphotericine, Flucytosine, Posaconazole.

  Resistant to Fluconazole. Intermediate to Voriconazole
- Plan: Start liposomal Amphotericin and Flucytosine, change to Meropenem and Vancomycin

08/06/15 CSF Culture (shunt tap) ***Candida auris***

15/06/15 Definite procedure: Resection of bone flap and debris around anterior/frontal crania fossa with infill lat dorsi free flap seated within the frontal fossa and extruding through the cribiform plate into the ethmoidal cavity. Packs within nasal upper cavity

- Pus and tissue frontal cultures: ***Candida auris***

Case – *Candida auris* persists

18/6/15 CSF (EVD) ***Candida auris***

30/06/15 CSF (shunt) ***Candida auris.*** Now **resistant** to Flucytosine.

- Plan: Stop Flucytosine, add Micafungin

02/07/15 Shunt removal

- Shunt reservoir and CSF ***Candida auris*** 4/4 samples
- Further positive CSF cultures: 10/07/15, 20/07/15
- Discussions with family about ongoing therapy

20/07/15 VP shunt reinsertion

25/07/15 Cultures become negative

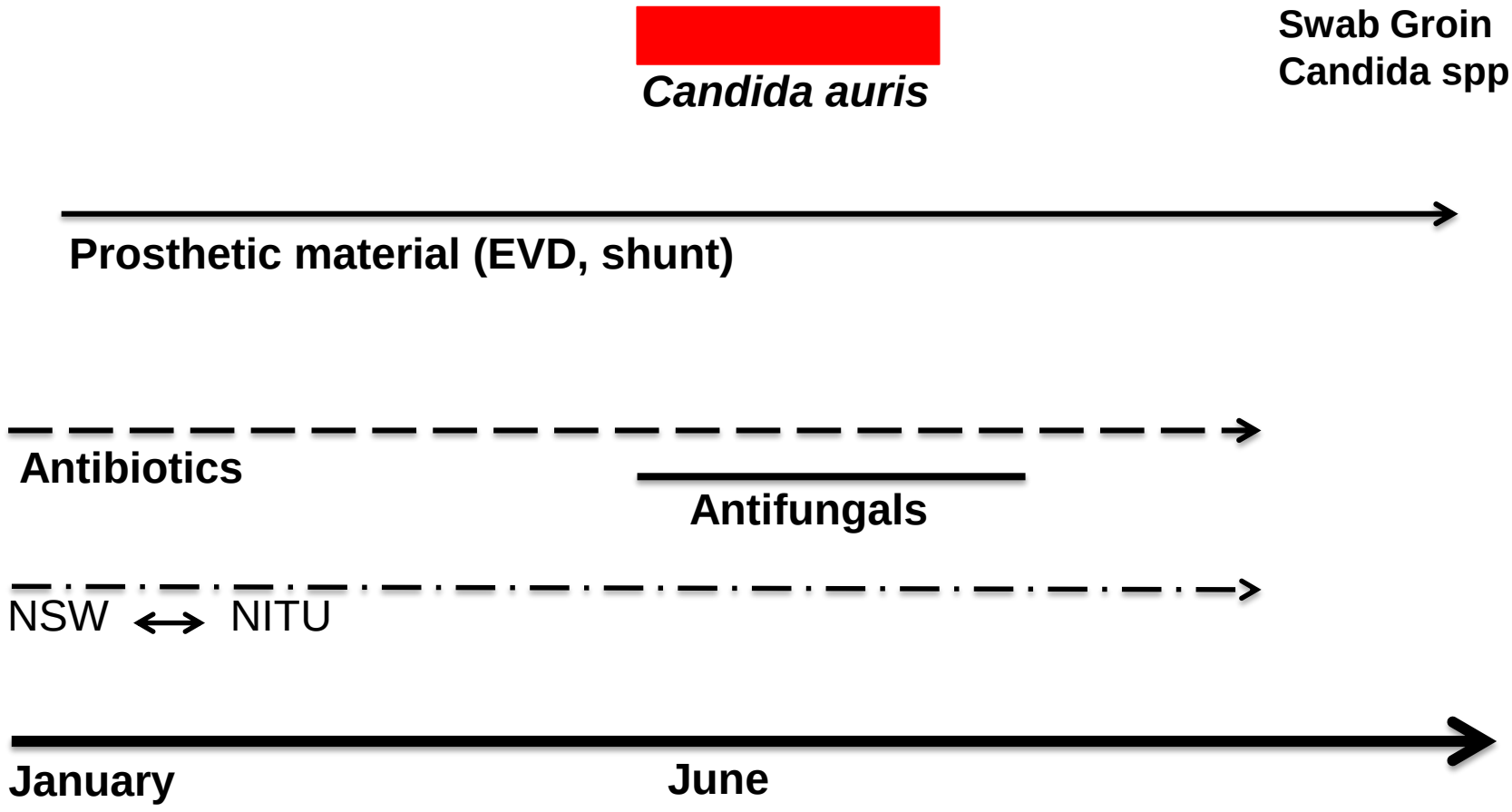
- Completes 2 weeks antifungals following new shunt insertion

Further progress:

19/10/15 Repatriated Buckinghamshire

16/02/16 Date of death

Case summary

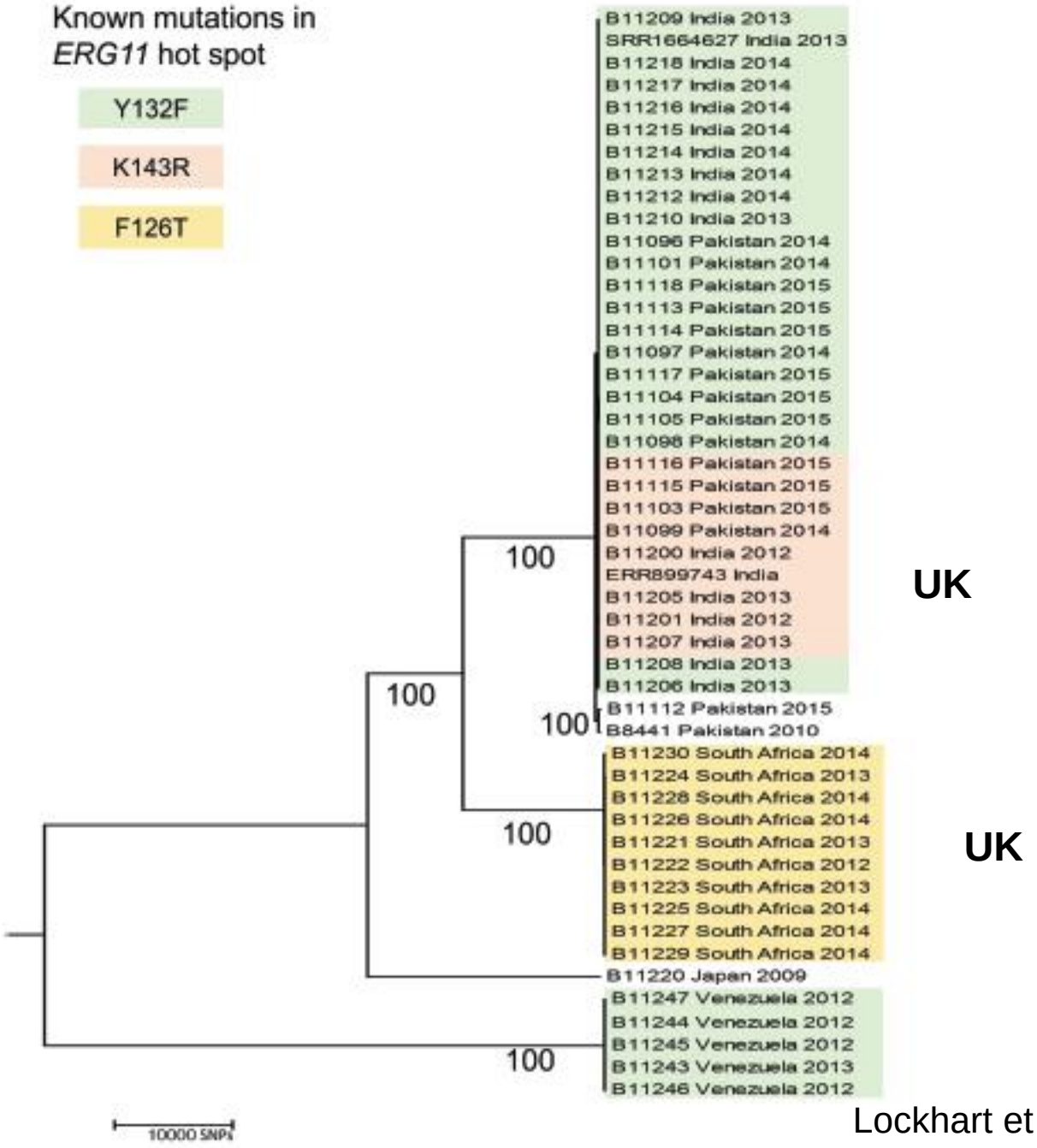


C auris in UK

Guidance for the laboratory investigation, management and infection prevention and control for cases of *Candida auris*

August 2017 v2.0

- First isolate submitted to PHE 2013
- July 2017: >200 patients in 20 trusts
  >35 trusts have received colonized patients
- ~One quarter clinical infections, including 27 candidaemias
- 3 ICU outbreaks, South England
- Misidentified by API AUX 20C, VITEK-2 YST, BD Phoenix and MicroScan
- All UK isolates reduced susceptibility to fluconazole, often cross-resistant to other azoles, variable resistance to polyenes (~20% amphotericin B) and echinocandins (~10%)
- Resistance can develop rapidly
- First line therapy echinocandins, combination therapy for complex (CNS, urinary) cases



Lockhart et al CID 2017

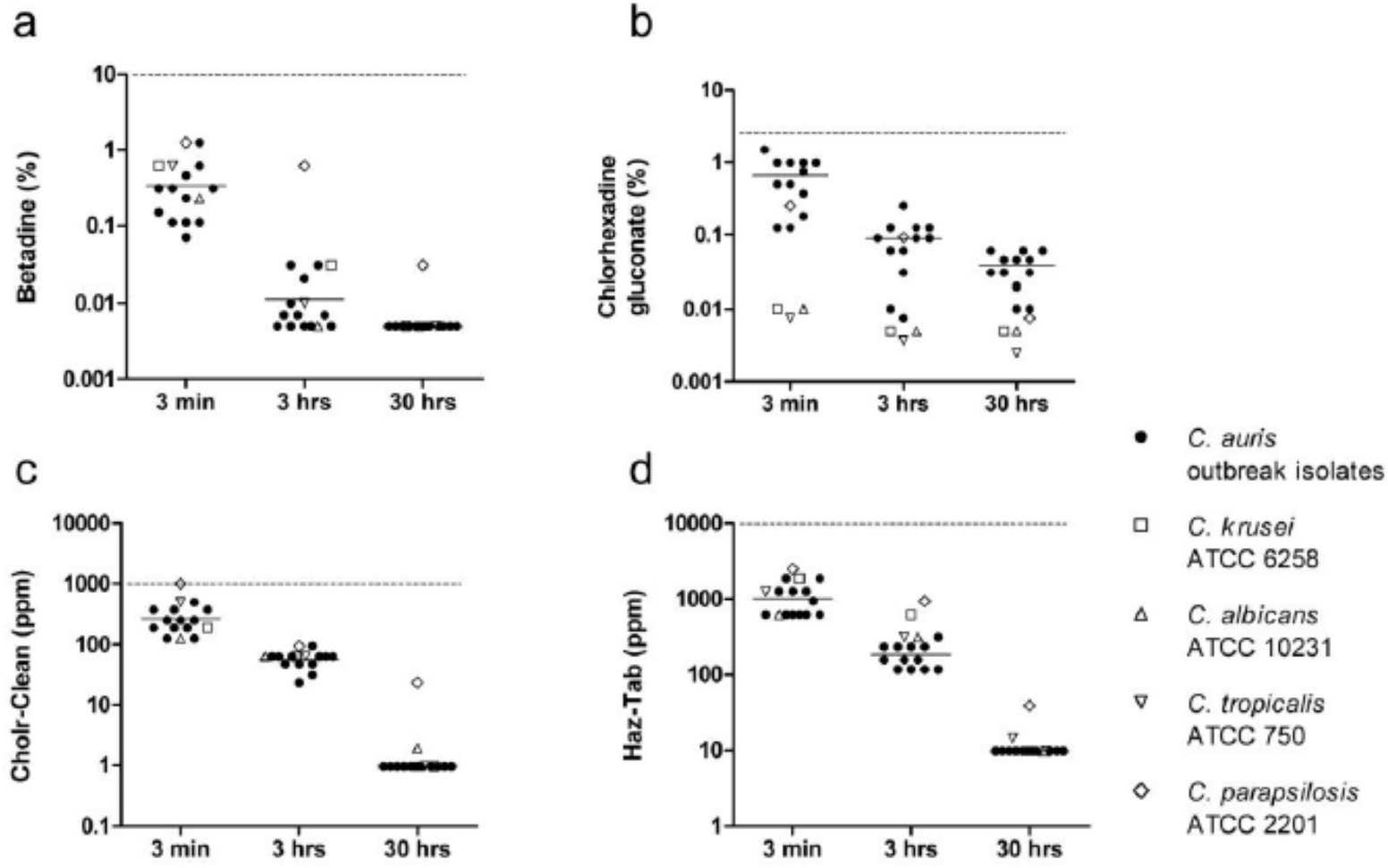
C auris and screening

Guidance for the laboratory investigation, management and infection prevention and control for cases of *Candida auris*

August 2017 v2.0

- Local risk assessment
- Precise mode of transmission not known
- Time from initial exposure to colonisation as low as four hours reported
- Screening all patients who have been transferred from an affected UK hospital or a hospital abroad
- Screening sites: axilla, groin, urine, nose and throat, perineal, stool, clinical sites.

C auris and disinfectants



Abdelrasouli et al 2017

Candida auris – successful control

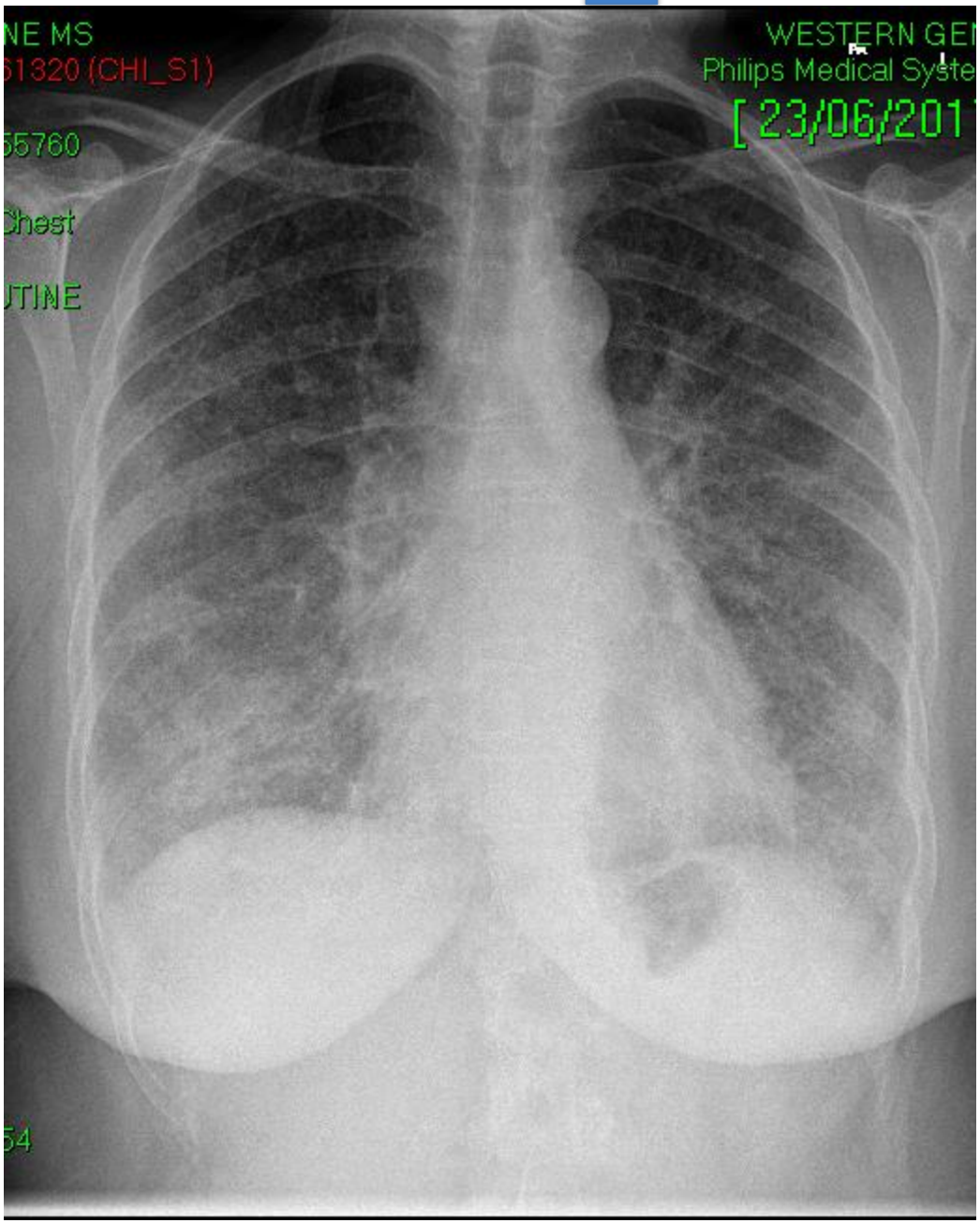
- Comprehensive screening policy
- Strict isolation
- PPE
- Strict adherence to bundles and aseptic technique
- Room/equipment cleaning three times per day with 1000ppm chlorine based reagents
- Terminal deep clean (10000ppm chlorine based) followed by hydrogen peroxide vaporization
- Chlorhexidine washes

Current UK problem fungi

- Aspergillus fumigatus – environmentally acquired azole resistance
- *C auris*
- *Fusarium spp* – increase in cases keratitis
- *Lomentospora prolificans* (previous *scedosporidum prolificans*) – pan R
- Mucoromycotina – remain susceptible to amphotericin, often posaconazole/isovuconazole susceptible

Case 2

- 60F
- Background: Rheumatoid arthritis, on long term methotrexate
- 23rd June shortness of breath, type 1 respiratory failure
- ITU intubation and ventilation
- Treatment: Co-trimoxazole, co-amoxiclav, prednisolone


NE MS
51320 (CHI_S1)
55760
Chest
UTINE
54
WESTERN GE
Philips Medical Syste
[23/06/201

Respiratory PCR results

Bronchoalveolar lavage 25/06/2017

Bronchoalveolar lavage
M. pneumoniae
Ct: ^0.00
Mycoplasma pneumoniae
PCR: Negative
Metapneumovirus
Ct: ^0.00
Metapneumovirus
PCR: Negative
Rhinovirus
Ct: ^0.00
Rhinovirus PCR: Negative

P jirovecii
Ct: ^38.14
Pneumocystis jirovecii PCR: POSITIVE

Legionella pneumophila
CT: ^0.00

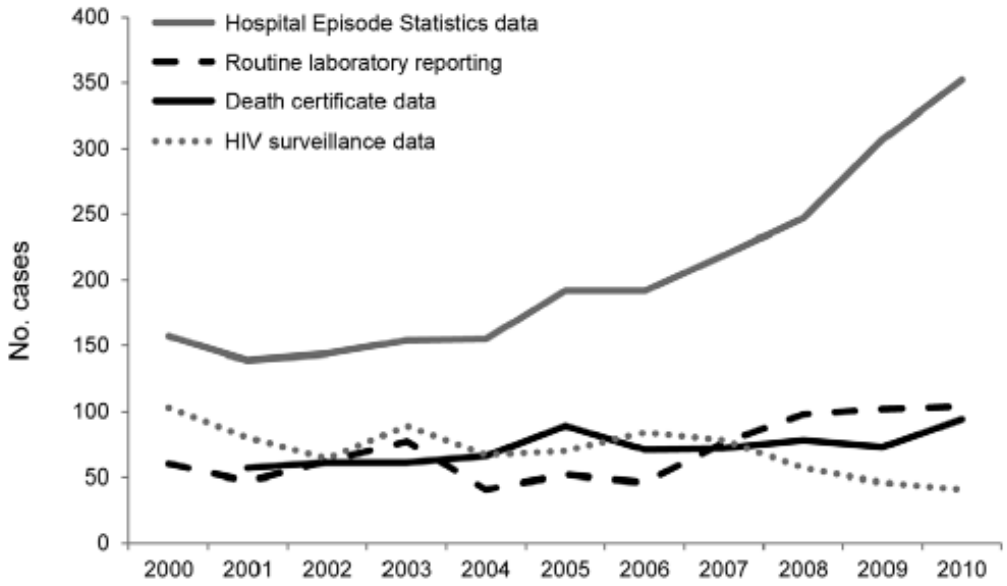
BAL for virology 25/06/2017

Metapneumovirus
PCR: Negative
Rhinovirus
Ct: ^0.00
Rhinovirus PCR: Negative

P jirovecii
Ct: ^0.00
Pneumocystis jirovecii PCR: Negative

Legionella pneumophila
CT: ^0.00
Legionella pneumophila
PCR: Negative
Legionella Spp
CT: ^0.00
Legionella Spp
PCR: Negative

Epidemiology of *Pneumocystis jirovecii* pneumonia – is there a shift?



Maini et al EID 2013

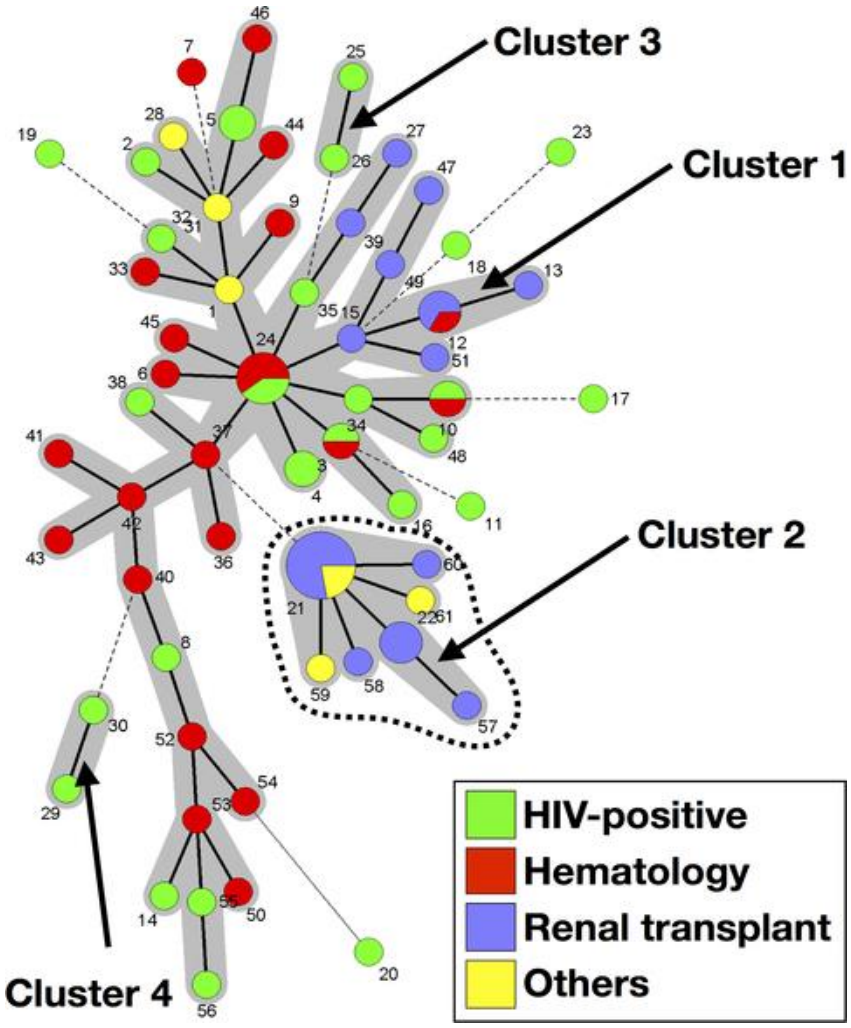
Thirty outbreaks worldwide

- 70% in Europe
- 25/30 in solid organ transplant units (renal)
- Median number of patients 12.5
- median outbreak duration 9 months

Shared nosocomial facilities, out- and inpatient

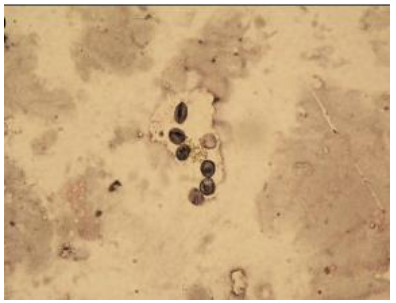
Yiannnakis, Boswell. J H Inf 2016

Fig 2. Minimum spanning tree analysis of 61 genotypes from 55 samples harboring a unique genotype (one allele per marker) or multiple genotypes (multiple alleles in one marker).



Gits-Muselli M, Peraldi MN, de Castro N, Delcey V, Menotti J, et al. (2015) New Short Tandem Repeat-Based Molecular Typing Method for Pneumocystis jirovecii Reveals Intrahospital Transmission between Patients from Different Wards. PLOS ONE 10(5): e0125763. https://doi.org/10.1371/journal.pone.0125763
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0125763

PCP
control measures



Investigation of outbreaks of *Pneumocystis jirovecii* pneumonia in two Scottish renal units

T. Inkster [a,d,*], S. Dodd [a], R. Gunson [b], L. Imrie [a,c], E. Spalding [d], S. Packer [a], C. Deighan [a], C. Daly [a], J. Coia [a], T. Imtiaz [d], C. McGuffie [d], R. Wilson [d], A.M. Bal [d]

- Via external sources rather than re-activation
- Found in air samples collected within 1 m infected patients
- Risk factor: rejection
- Measures

  Re-institution of prophylaxis for 6 months in high risk patients

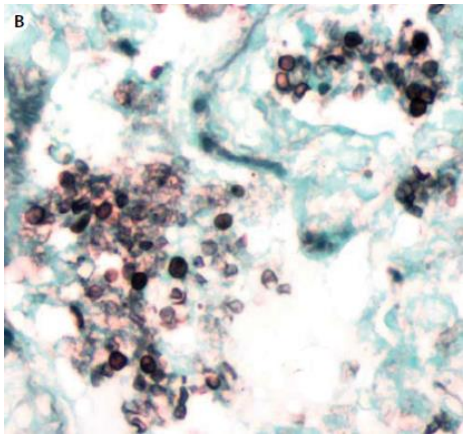
  Single room isolation

  Assess ventilation standards, e.g. clinic room 6 changes per hr

  Alert organism

Pneumocyctis jirovecii - diagnostics

- Wright-Giemsa, methenamine silver and other stains
- Single copy PCR (infection) vs nested PCR (colonization/infection)
- Antigen detection systems in development
- Serum Beta-D-glucan>100 pg/ml highly supportive of diagnosis



Case 3

- 17/6/17 59M Headache, nausea and vomiting
- Fever whilst waiting in ED
- Management: BC, BBV screen, CT, LP

Progress

- HIV Ab positive (negative test Dec 2015), CD4 count 51/ul, VL 236000 copies/ml
- 18th June Blood culture and CSF: *Cryptococcus neoformans*. Sensitive to fluconazole, itraconazole, voriconazole. Resistant to caspofungin.
- Treatment?
- Treatment in times of flucytosine shortage?

Progress

- HIV Ab positive (negative test Dec 2015), CD4 count 51/ul, VL 236000 copies/ml
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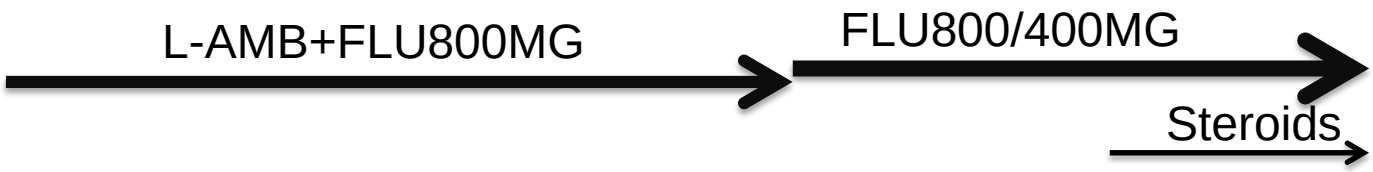
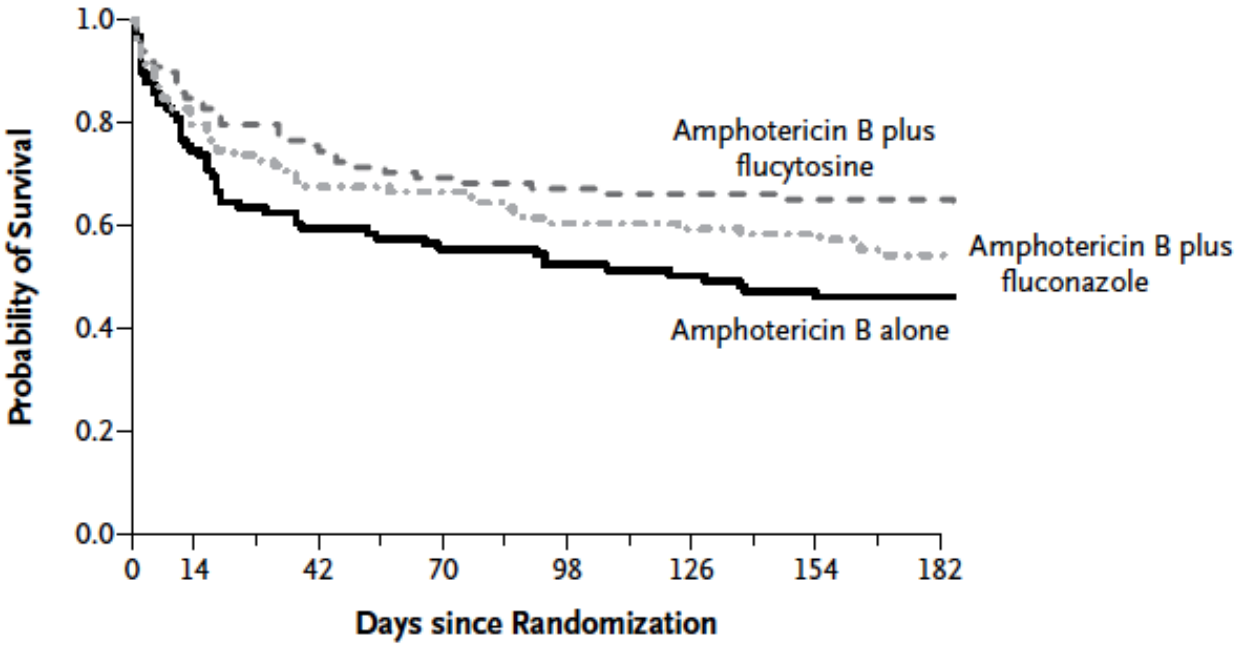
- Treatment?

	21/6	**23/6**	**4/7**	**14/7**	**22/8**
CSF CRAG	512	1024	128	256	256
Serum CRAG				512	256
CSF culture	*C. neoformans* +++	*C. neoformans* +	*C. neoformans* +	NG	NG

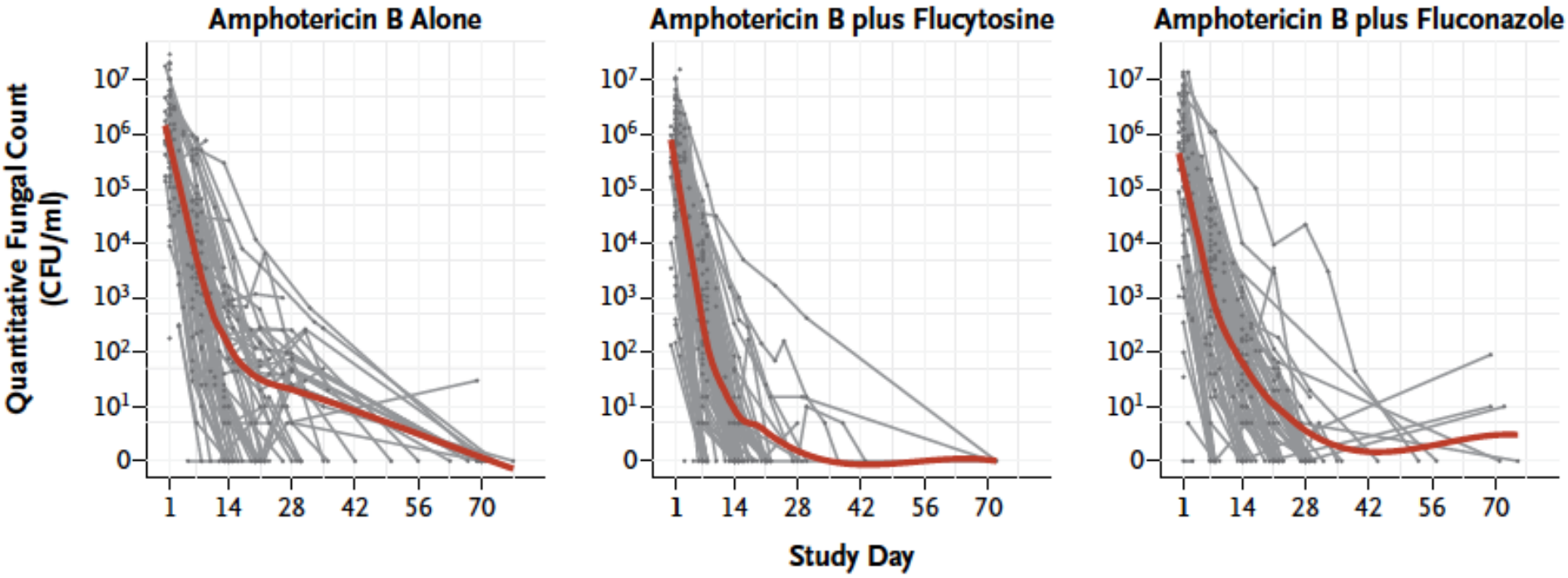


Cryptococcal meningitis treatment – in the era of flucytosine shortage



JN Day et al NEJM 2013;368:1291-302

Cryptococcal meningitis treatment – in the era of flucytosine shortage



JN Day et al NEJM 2013;368:1291-302

ACTA trial – Advancing Cryptococcal Treatment for Africa

- **Oral**: fluconazole (1200mg/day) plus flucytosine (100mg/kg/day) for 2 weeks.
- **1-week**: Amphotericin B (1mg/kg/d), plus fluconazole (1200mg/day), or flucytosine (100mg/kg/day) (ratio 1:1), for 7 days. Days 8-14, fluconazole 1200mg/day.
- **2-weeks**: Amphotericin B (1mg/kg/d) plus fluconazole (1200mg/day), or flucytosine (100mg/kg/day) (ratio 1:1), for 14 days.

Flucytosine

Summary of regulatory status of the medicine

Flucytosine (5FC) was developed in 1957 and has been a generic medication for decades. The originator manufacturer is Meda Pharmaceuticals (France). 5FC is registered in Europe and North America; however, there is only one FDA- approved manufacturer (Sigmapharm (US)). 5-FC is currently unavailable in most countries. 5FC availability in Africa is zero.

Application for WHO List of Essential Medicines

Antifungal Stewardship - Challenges

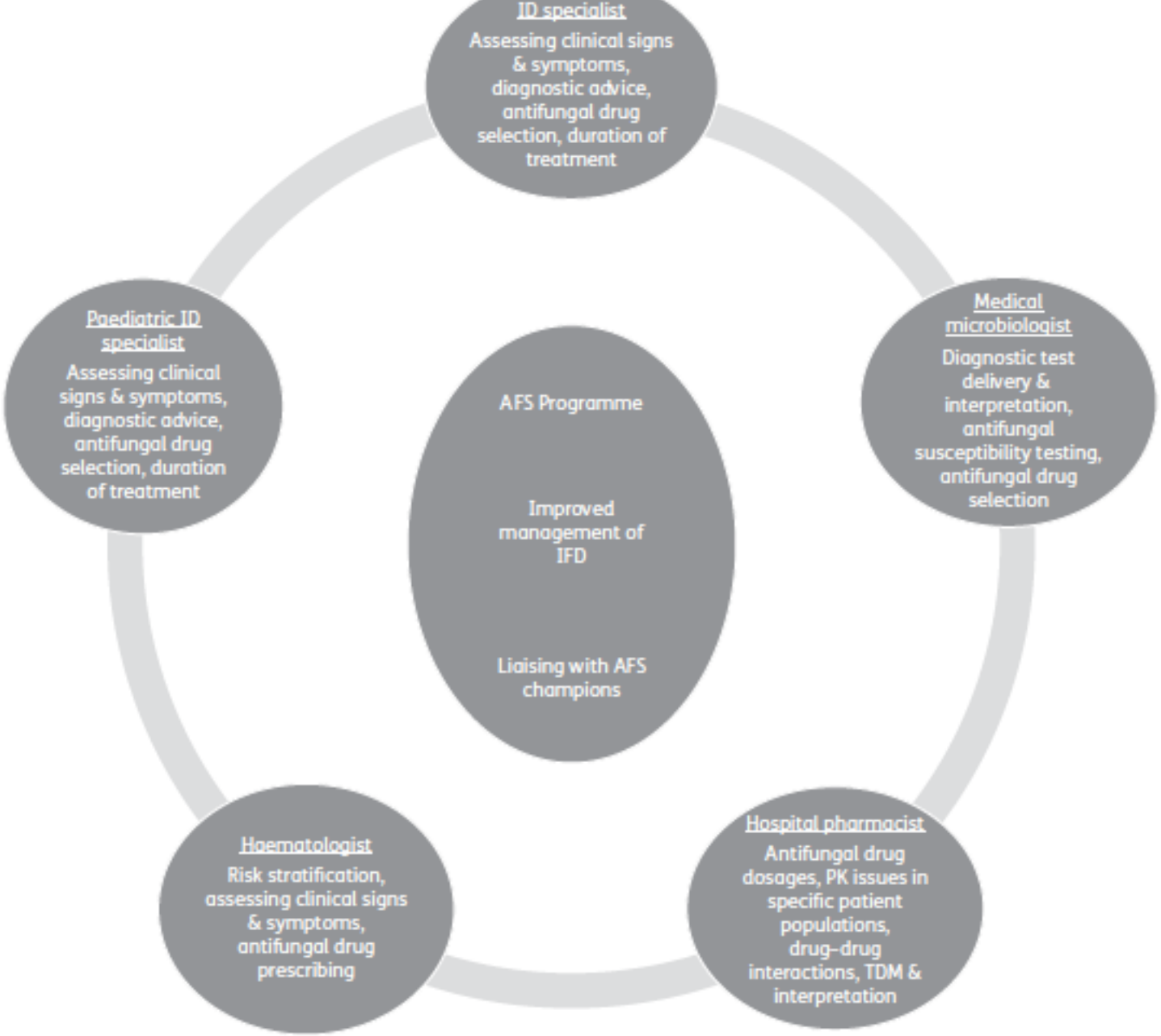
- High case fatality rates
- High drug costs
- Risk of antifungal resistance
- Drug toxicities and interactions
- Complexity of patients
- Complexity of epidemiology and risk factors

Requires different approach than most antibiotic stewardship programmes

Members of antifungal stewardship team

- Should have specialist experience in clinical management of relevant patient populations, epidemiology, susceptibility patterns, laboratory diagnostics, pharmacokinetics and drug interactions.

1. Clinical pharmacist
2. Microbiologist
3. Paediatric ID specialist
4. Adult ID specialist
5. Haematologists
6. Others: ICU, respiratory, surgeons



Aggrawal et al, JAC 2016;71 Suppl 2:ii37-ii42

ESPAUR 2016

- National data required
- Antifungal consumption, resistance
- Antifungal stewardship and laboratory survey

Table 6.6: Extent of AFS Programmes in acute trusts

	Percentage (n = 47)
Yes - we have a dedicated antifungal stewardship programme	11
Sort of - we include antifungal stewardship as part of our antimicrobial stewardship programme	43
Not really, but we do monitor antifungal usage	26
No	19

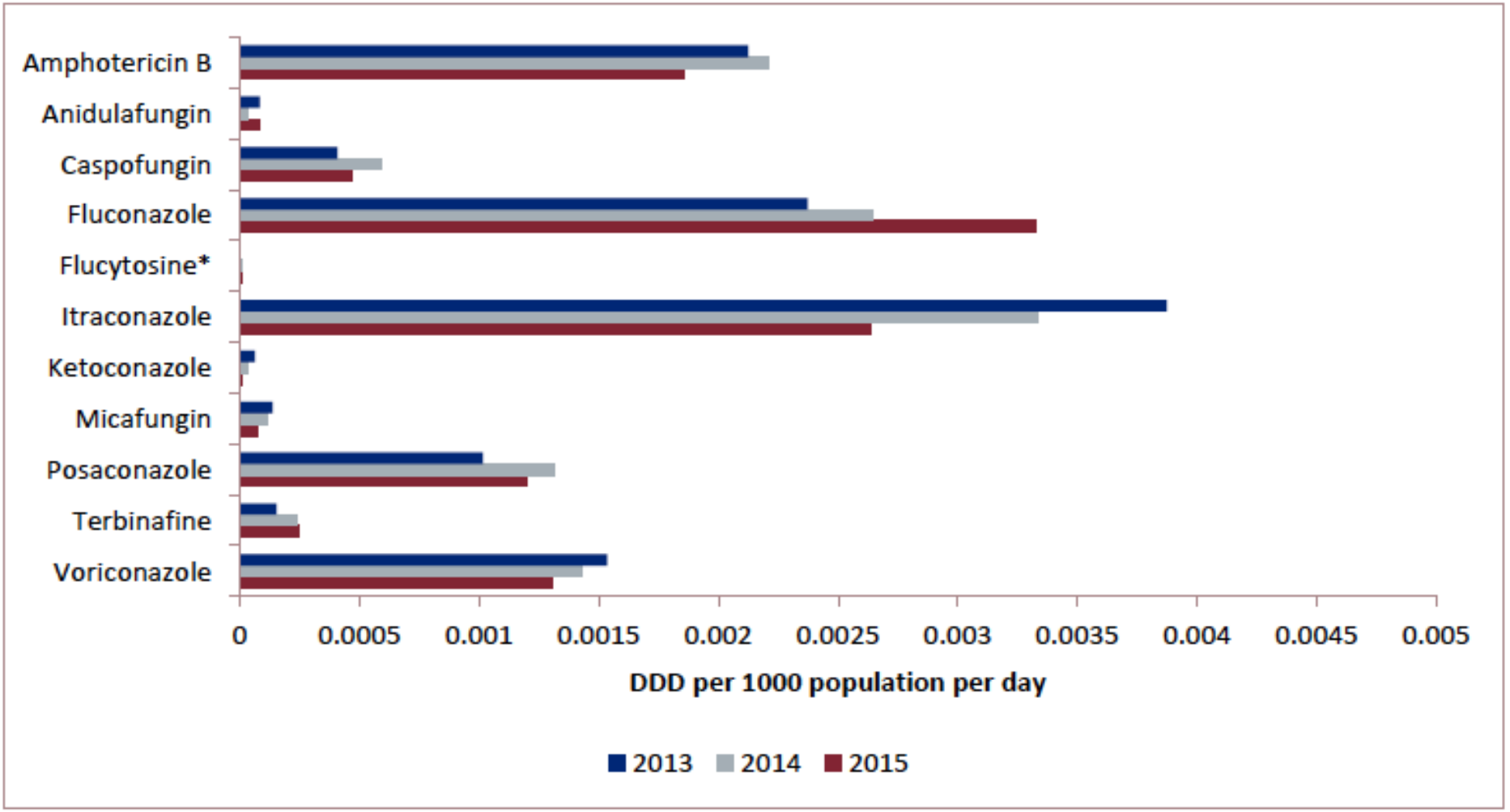


Figure 6.8 Antifungal prescribing in NHS hospitals by antifungal group, expressed as DDD per 1000 inhabitants per day, England, 2013-2015

Focus of stewardship

- Haematology?
- Respiratory?
- **ICU?**

Score	Patient Population	Model Risk factors	Value	Sens/Spec PPV/NPV
Candida Score (2006)	Medical/Surgical ICUs for ≥7days	Severe Sepsis (2), major surgery (1), TPN (1), multifocal candida colonization (1)	Score ≥3	81/74 16/98
Ostrosky Rule (2007,11)	Medical/Surgical ICUs for ≥4days	Major: antibiotics d1-3, CVL Minor: surgery, immunosuppressants, TPN, pancreatitis, dialysis	2 major 2 major + at least 1 minor	89/38 (4/99) 66/69 (6/98)
Nebraska Medical Center Rule (2011)	Medical/Surgical ICUs for ≥4days	Antibiotics (1.5), CVL (0.9), TPN (0.9), steroids(0.4), abdominal surgery (0.9), pre-ICU length of stay x0.039	Score>2.45	84.1/60.2 4.7/99.4

Cochrane Analysis 2016

CLINICAL QUESTION:

- Are antifungal agents associated with **lower rates of mortality and invasive fungal infections** when administered **before** definitive diagnosis of an invasive fungal infection in **critically ill patients** without neutropenia?

BOTTOM LINE:

- Antifungal treatment administered prior to diagnosis of an invasive fungal infection is **not associated with either higher or lower rates of all-cause mortality**. Antifungal treatment in this setting is associated with **lower rates of invasive fungal infection**s compared with placebo or no intervention in critically ill patients without neutropenia, but the **quality of the evidence is low**.

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 17 ISSUE 3 FEBRUARY 2013
ISSN 1366-5278

Development and validation of a risk model for identification of non-neutropenic, critically ill adult patients at high risk of invasive *Candida* infection: the Fungal Infection Risk Evaluation (FIRE) Study

HTA Antifungal prophylaxis in ICU

Objectives:

To develop and validate risk models to identify non-neutropenic, critically ill adult patients at high risk of invasive Candida infection, who would **benefit** from antifungal prophylaxis, and to assess the **cost-effectiveness** of targeting antifungal prophylaxis to high-risk patients based on these models.

Design:

Systematic review, prospective data collection, statistical modelling, economic decision modelling and value of information analysis.

Setting: Ninety-six UK adult general critical care units.

Participants: Consecutive admissions to participating critical care units.

Interventions: None.

Main outcome measures: Invasive fungal disease, defined as a blood culture or sample from a normally sterile site showing yeast/mould cells in a microbiological or histopathological report. For statistical and economic modelling, the primary outcome was invasive Candida infection, defined as IFD-positive for Candida species.

HTA Antifungal prophylaxis in ICU

- Results:

  60778 admissions between 2009-11

  only 0.6% developed IFD

  IFD associated with higher mortality, more support, longer ICU stay

  risk models at day 0, day 1 and day 3

  most cost effective treatment strategy is risk stratification and prophylaxis (fluconazole 400mg) at day 3

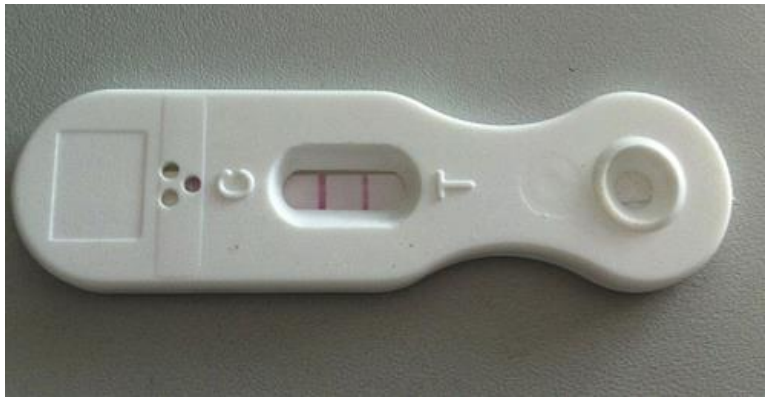
Summary

- Emerging resistant fungi
- Infection prevention and control
- Stewardship still low on the agenda

- EORTC/MSF revision of definition of invasive fungal infections due end 2017
- Aspergillus Lateral Flow Device CE marketing early 2018

Aspergillus lateral flow kit device

- “Novel” point of care test. Developed by University of Exeter
- Based on detection of aspergillus antigen by monoclonal Ab to JF5 Specific to Aspergillus spp
- Immunochromatography, i.e. qualitative data
- Time to result ~15 min
- Cheap, easy to offer locally once CE marked
- Latest estimate commercial release Jan 2018, new format comparable to old prototype in BAL, serum results outstanding.



Aspergillus lateral flow kit device

- A number of single center studies all showing reasonable correlation with culture and excellent NPVs
- One small multicentre study among SOT recipients in Austria,
  - Among 47 pts, 10 with probable IPA and one case proven IPA
  - sensitivity for probable IPA 91%,
  - for possible 83%. PPV 63%, NPV 97%
- Kits optimised for serum or BAL
- If performed in BAL not influenced by antifungal Rx or prophylaxis
- 100% NPV quoted on BAL samples
- Some cross reactivity with certain penicillium spp especially if in high titre