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# Treatment of Candidemia / Invasive Candidiasis
## *Unmet Needs*

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# Disclosures

- Scientific advisor for Amplyx, Cidara, and Scynexis
- Participated in CME with support from Cidara and Pfizer.

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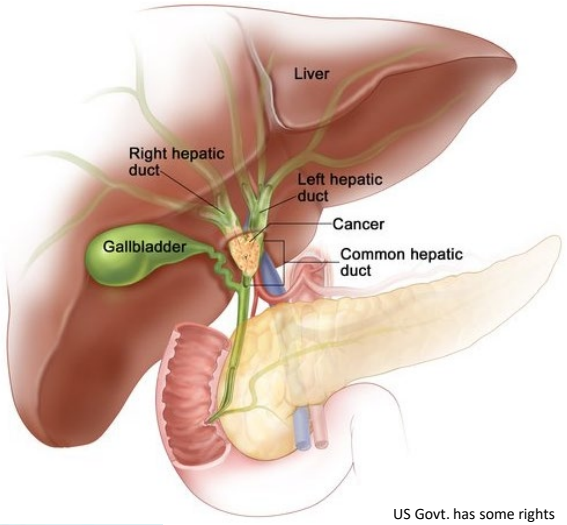
# Case Study

- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma

- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin

- Possible suture leak
- Abdominal CT inconclusive
- Blood cultures (still) negative

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Candida colonizing the gut

- What is the likelyhood of invasive candidasis?
- How can we diagnose invasive (abdominal) candidiasis?
- Should she have received antifungal prophylaxis?
- Should she receive empiric antifungal therapy?
- If so, aimed at which *Candida* species?

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# Unmet Needs

- ✓ Can we prevent invasive candidiasis in the ICU?

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# Antifungal prophylaxis in the ICU

- *Does it work?*
  - Yes, some reduction of incidence

- *Does it work well enough?*
  - No … Less than optimal results:

| Incidence | | | *P* | Reference | Year |
|---|---|---|---|---|---|
| ***Control*** | | ***Prophylaxis*** | | | |
| 17% | → | 10% | n.s. | Ostrosky-Zeichner | 2014 |
| 15% | → | 8.5% | 0.01 | Pelz | 2001 |
| 10% | → | 4% | 0.02 | Garbino | 2002 |
| 9% | → | 2% | n.s. | Eggimann | 1999 |

- *Has it been associated with reduced mortality?*
  - No … In none of the studies:

| Mortality | | | *P* | Reference | Year |
|---|---|---|---|---|---|
| ***Control*** | | ***Prophylaxis*** | | | |
| 14% | → | 17% | n.s. | Ostrosky-Zeichner | 2014 |
| 12% | → | 11% | n.s. | Pelz | 2001 |
| 41% | → | 39% | n.s. | Garbino | 2002 |
| 50% | → | 30% | n.s. | Eggimann | 1999 |

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# MSG-01: Echinocandin prophylaxis in high-risk ICU patients

## Randomised, double-blind, multicentre study of caspofungin vs. placebo

- Adult patients >48 h in ICU
- Mechanical ventilation
- Central venous catheter
- Broad-spectrum antibiotics
- ≥1 of: TPN, dialysis, major surgery, pancreatitis, steroids/immunosuppressants

| MITT[1], N=186 | Caspofungin[2] | Placebo | Difference *P* |
|---|---|---|---|
| Invasive candidiasis proven/probable[3], after baseline | 9.8% | 16.7% | P=0.14 |
| Proven invasive candidiasis | 1.0% | 4.8% | P=0.11 |
| Mortality | 16.7% | 14.3% | P=0.35 |
| Length of stay | | | n.s. |

Conclusions: 1. No support for antifungal prophylaxis among ICU patients
2. We are unable to identify the patient at risk for candidiasis

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[1] Modified intent-to-treat group: eligible patients without candidiasis at baseline, who received ≥1 dose of study drug
[2] Caspofungin has not been licenced for prophylactic use
[3] Probable candidiasis (EORTC/MSG): 2x ß-glucan>80 AND clinical signs

Ostrosky-Zeichner L, et al.
Clin Infect Dis 2014; 58(9):1219–26

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# Unmet Needs

- ✓ Can we treat invasive candidiasis in the ICU earlier?

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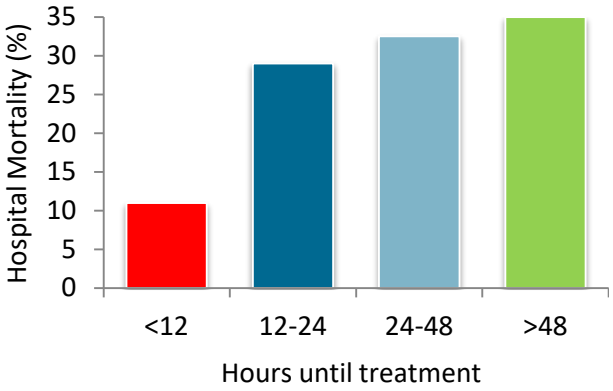
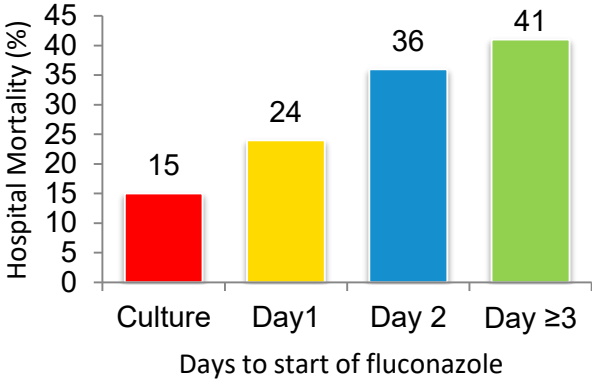
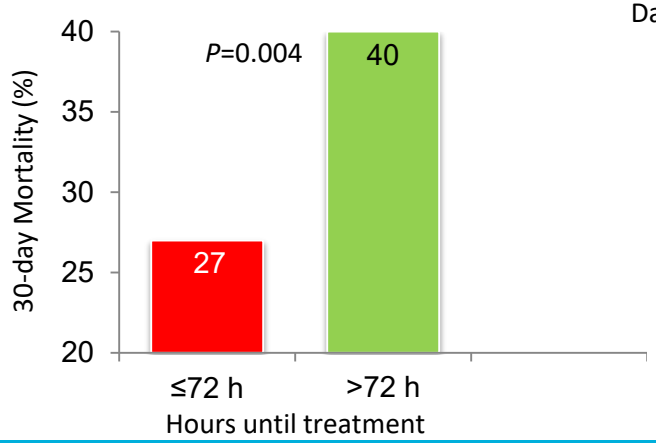
# Candidemia: Importance of early appropriate treatment




157 patients – 2001–2004
Initiation of antifungal therapy <12 to >48 h after culture sample
Morrell M, et al. *AAC* 2005




230 patients – 4 centres – 2002–2005
Initiation of fluconazole 0 to ≥3 days
Garey KW, et al. *Clin Infect Dis* 2006




446 patients – 2001–2009
Intent to treat: 31.6–36.3% - N.S.
Shown: when Rx for <24 h classified as inappropriate
Grim SA, et al. *J Antimicrob Chemother* 2012

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# Empirical micafungin in ICU patients with sepsis, organ failure and *Candida* colonization

Randomised, double-blind, multicenter study of micafungin vs. placebo

- Non-neutropenic adult patients in ICU
- Mechanical ventilation ≥5 days
- Broad-spectrum antibiotics ≥4 days
- ≥1 Site colonized with *Candida* species
- New ICU-acquired sepsis
- ≥1 Additonal organ dysfunction

| MITT[1], N=251 | Micafungin (14 days) | Placebo | Difference |
|---|---|---|---|
| 28-day Survival free of proven fungal infection | 68% | 60% | HR 1.35 (0.87-2.08) |
| Survival (d28) | 70% | 70% | HR 1.04 (0.64-1.67) |
| Invasive fungal infections | 9% | 12% | Δ 2.8% (-5.0, 10.8) |

Conclusions: 1. No support for empirical antifungals among ICU patients
2. We are unable to identify the patient at risk for candidiasis

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[1]Modified intent-to-treat group: patients who received ≥1 dose of study drug

Timsit JF, et al. JAMA 2016; 315(15):1555–64

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# Unmet Needs

- ✓ Are we able to identify the patient with invasive candidiasis?

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# Abdominal candidiasis – The missing 50%

2-year retrospective cohort, U Pittsburg Medical Center

| Patients | N |
|---|---|
| Candidemia<br>Intraabdominal candidiasis | 161<br>163 |
| | |
| | |
| Intraabdominal candidiasis<br>▪ GI tract source<br>▪ Secondary peritonitis/abscess (post GI leak, surgery) | 163<br><br>103 |
| ▪ Hepatobiliary/pancreatic source<br>▪ Secondary peritonitis/abscess, panceatits/cholangitis<br>▪ Primary peritonitis | <br>52<br>8 |
| Mortality (100 days) | 28% |
| Bacterial co-infection | 67% |
| Candidemia | 6% |



Vergidis P, Clancy CJ et al, PLoS ONE 2016:11(4);e015247

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# Unmet Needs

- ✓ Can we detect invasive candidiasis in the ICU earlier?

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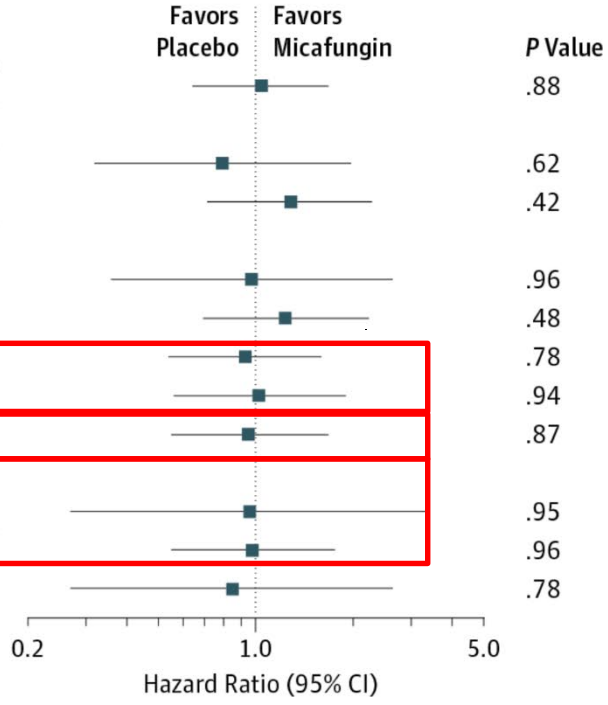
# Determinants for success of Micafungin in ICU patients with Sepsis, Organ failure, and Candida colonization

28-Days' Survival

| | Micafungin | | Placebo | | | |
|---|---|---|---|---|---|---|
| | Survived at Day 28, No. | Total No. | Survived at Day 28, No. | Total No. | Hazard Ratio (95% CI) | *P* Value |
| All patients | 90 | 128 | 86 | 123 | 1.04 (0.64-1.67) | .88 |
| SOFA score | | | | | | |
| ≤8 | 53 | 66 | 58 | 68 | 0.79 (0.32-1.96) | .62 |
| >8 | 37 | 62 | 28 | 55 | 1.28 (0.71-2.27) | .42 |
| Admission category | | | | | | |
| Surgical | 23 | 34 | 23 | 31 | 0.97 (0.36-2.63) | .96 |
| Medical | 67 | 94 | 63 | 92 | 1.23 (0.69-2.22) | .48 |
| Colonization index ≥0.5[a] | 70 | 101 | 70 | 99 | 0.93 (0.54-1.59) | .78 |
| Corrected colonization index ≥0.4[b] | 54 | 76 | 56 | 80 | 1.02 (0.56-1.89) | .94 |
| Candida score ≥3 | 66 | 96 | 58 | 85 | 0.95 (0.55-1.67) | .87 |
| (1-3)-ß-D-glucan, pg/mL[c] | | | | | | |
| >250 | 14 | 21 | 17 | 25 | 0.96 (0.27-3.33) | .95 |
| >80 | 61 | 91 | 58 | 84 | 0.98 (0.55-1.75) | .96 |
| ≤80 | 29 | 37 | 28 | 39 | 0.85 (0.27-2.63) | .78 |

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Timsit JF, et al. *JAMA* 2016; 315(15):1555–64

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# T2 *Candida* in ICU patients at high risk of candidemia / invasive candidiasis in Europe

- Adult patients in ICU (N=126)
- Initiation of antifungal treatment (prophylactic/empiric)
  OR
- T>38°C despite 3 days of Broad-spectrum Abx
  AND ≥2 risk factors:
  - Abdominal surgery
  - Secondary peritonitis
  - Central venous catheter
  - TPN
  - Hemodialysis
  - Steroids/immunosuppressants
  - Liver transplant

| Candidiasis* | N | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Proven | 11 (9%) | | | | |
| - BC | 5/11 | 45% | 100% | 100% | 95% |
| - T2 | 6/11 | 55% | 93% | 50% | 96% |
| - Mannan Ag | 4/11 | 36% | 94% | 36% | 94% |
| Likely | 6 (5%) | | | | |
| Proven + Likely | 17 (14%) | | | | |
| - BC | 5/17 | 29% | 100% | 100% | 90% |
| - T2 | 10/17 | 59% | 96% | 83% | 94% |
| - Mannan Ag | 7/17 | 41% | 96% | 64% | 91% |
| Possible | 11 (9%) | | | | |
| Prov+Poss+Likely | 28 (22%) | | | | |
| - BC | 5/28 | 18% | 100% | 100% | 81% |
| - T2 | 11/28 | 39% | 97% | 92% | 85% |

*T2*

- False positives?
  3 putative FP in this study
- Sensitivity better than BC but underwhelming (with current gold standard)

Proven: +ve BC or normally sterile site
Likely: Colonization ≥2 sites AND either SIRS or Mannan Ag>250
Possible: Colonization ≥2 sites +MAg>125 OR Mag≥250 OR Colonized + SIRS despite ABx

Arendrup et al, Open Forum Infect Dis 2019

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# Fungal Immunogenetics for Personalized Therapy

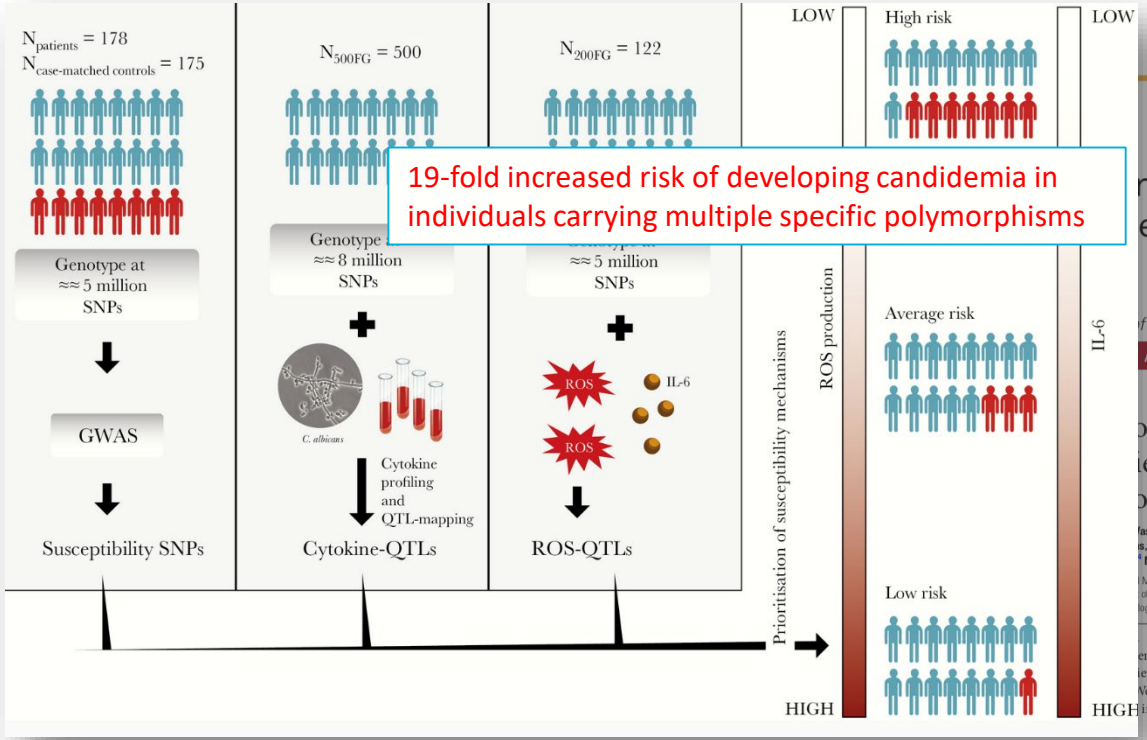
nature COMMUNICATIONS

Host susceptibility to candidiasis in an ICU cohort

ARTICLE

Received 7 Jan 2014 | Accepted 11 Jul 2014 | Published 8 Sep 2014 DOI: 10.1038/ncomms5675

## Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia




19-fold increased risk of developing candidemia in individuals carrying multiple specific polymorphisms

roach identifies
e candidaemia

f Infectious Diseases

ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

ome-Wide Functional Genomics Approach
es Susceptibility Pathways to Fungal Bloodstream
on in Humans

asiliki Matzaraki,[1,2,a] Raúl Aguirre-Gamboa,[2,a] Mark S. Gresnigt,[1] Xiaojing Chu,[2] Melissa D. Johnson,[3] Marije Oosting,[1] s,[1] Sebo Withoff,[2] Iris Jonkers,[2] John R. Perfect,[3] Frank L. van de Veerdonk,[1] Bart-Jan Kullberg,[1] Leo A. B. Joosten,[1] Yang Li,[2] Mihai G. Netea,[1,5] and Vinod Kumar[1,2]

Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands; [2] University of Groningen, University Medical Center of Genetics, the Netherlands; [3]Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; [4] K.G. Jebsen Coeliac Disease Research Centre, gy, University of Oslo, Norway; [5] Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

Candidemia, one of the most common causes of fungal bloodstream infection, leads to mortality rates up to 40% ents. Understanding genetic mechanisms for differential susceptibility to candidemia may aid in designing host- ies.

Ve performed the first genome-wide association study on candidemia, and we integrated these data with variants that in different cellular systems stimulated with *Candida albicans*.

Kumar et al, Nat Commm 2014; Matzaraki et al, PLoS One 2017; Jaeger et al. J Infect Dis 2019

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# Unmet Needs

- ✓ Can we cover the emerging spectrum of *Candida* species?

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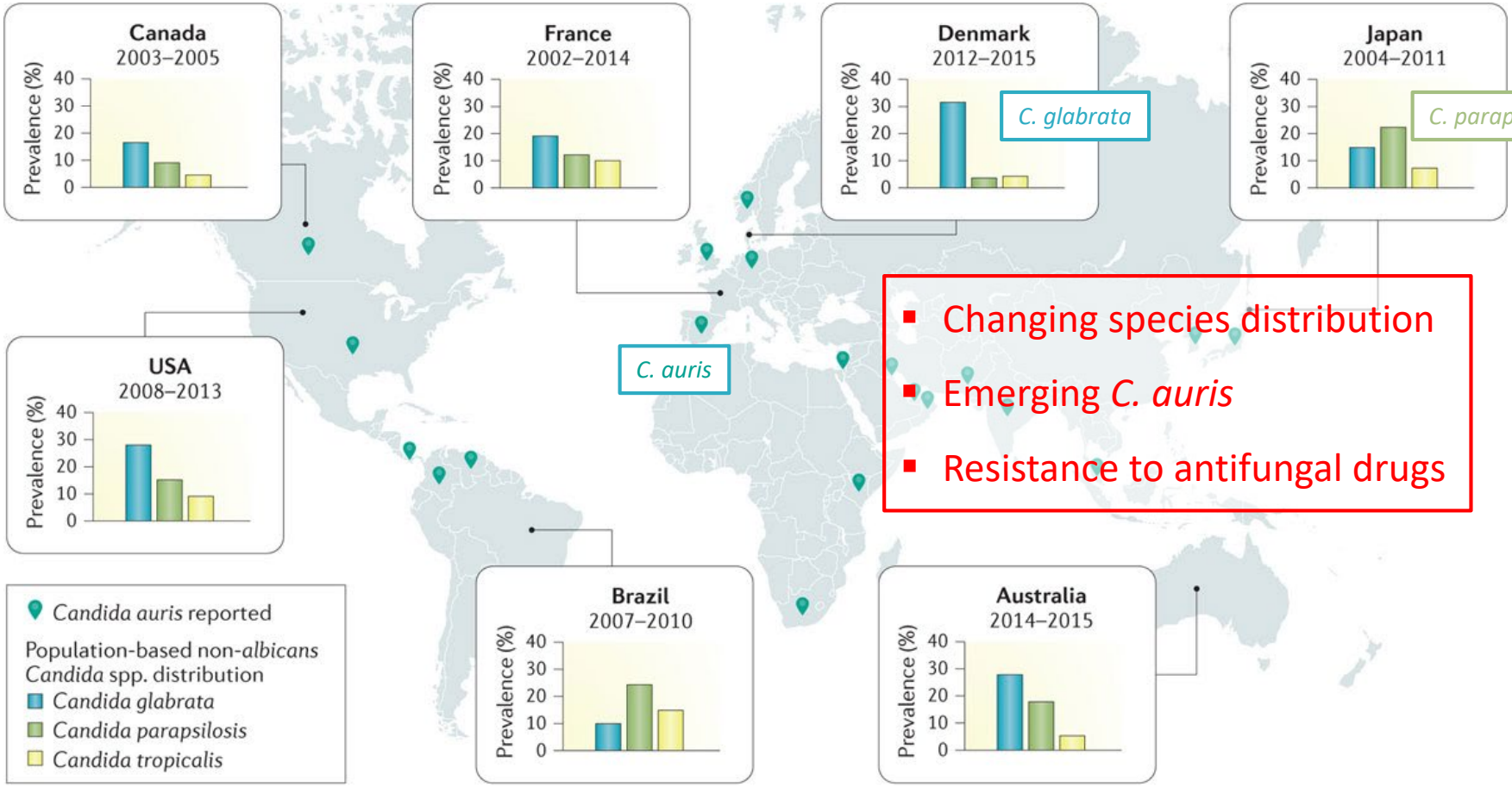
# Changing epidemiology of invasive candidiasis






Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ
Invasive candidiasis. Nat Rev Dis Primers 2018: 4; 18026

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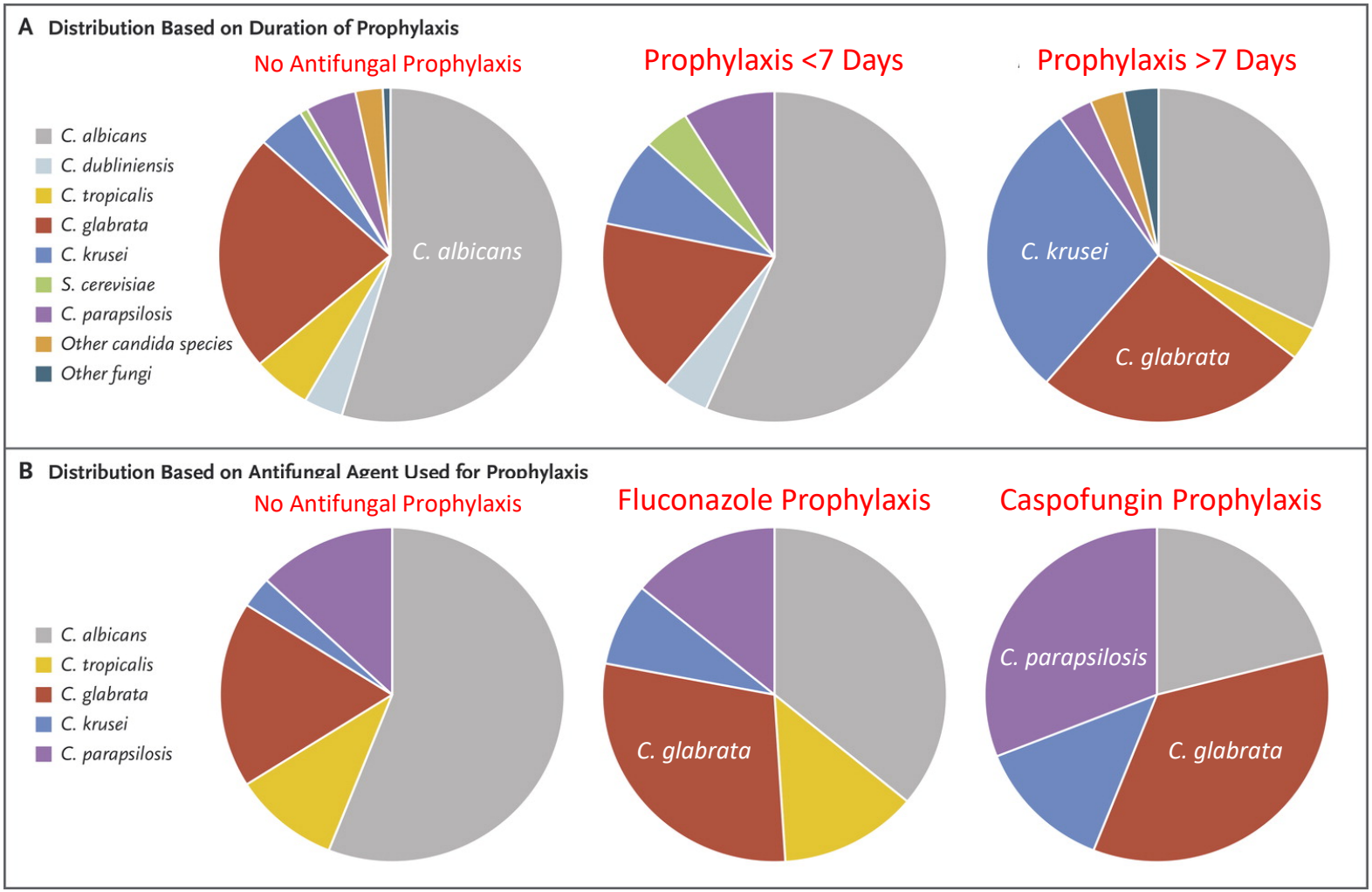
# Distribution of *Candida* species according to prophylaxis used

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Kullberg BJ, Arendrup MC. N Engl J Med 2015;373:1445-1456

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# Unmet Needs

- ✓ Can we select the most effective initial antifungal drug?

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# Treatment for candidemia

## IDSA 2016

| Compound | Recommendation | Evidence |
|---|---|---|
| *Initial therapy* | | |
| Anidulafungin 200→100 mg | Strong | High |
| Caspofungin 70→50 mg | Strong | High |
| Micafungin 100 mg | Strong | High |

## ESCMID 2012

| Compound | Recommendation | Evidence |
|---|---|---|
| Anidulafungin 200→100 mg | A I | I |
| Caspofungin 70→50 mg | A I | I |
| Micafungin 100 mg | A I | I |
| L-Amphotericin B 3 mg/kg | B I | I |
| Voriconazole 6→3 mg/kg bid | B I | I |
| Fluconazole 400→800 mg | C I | I |



Pappas PG et al. Clin Infect Dis 2016;62(4):409–17
Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37

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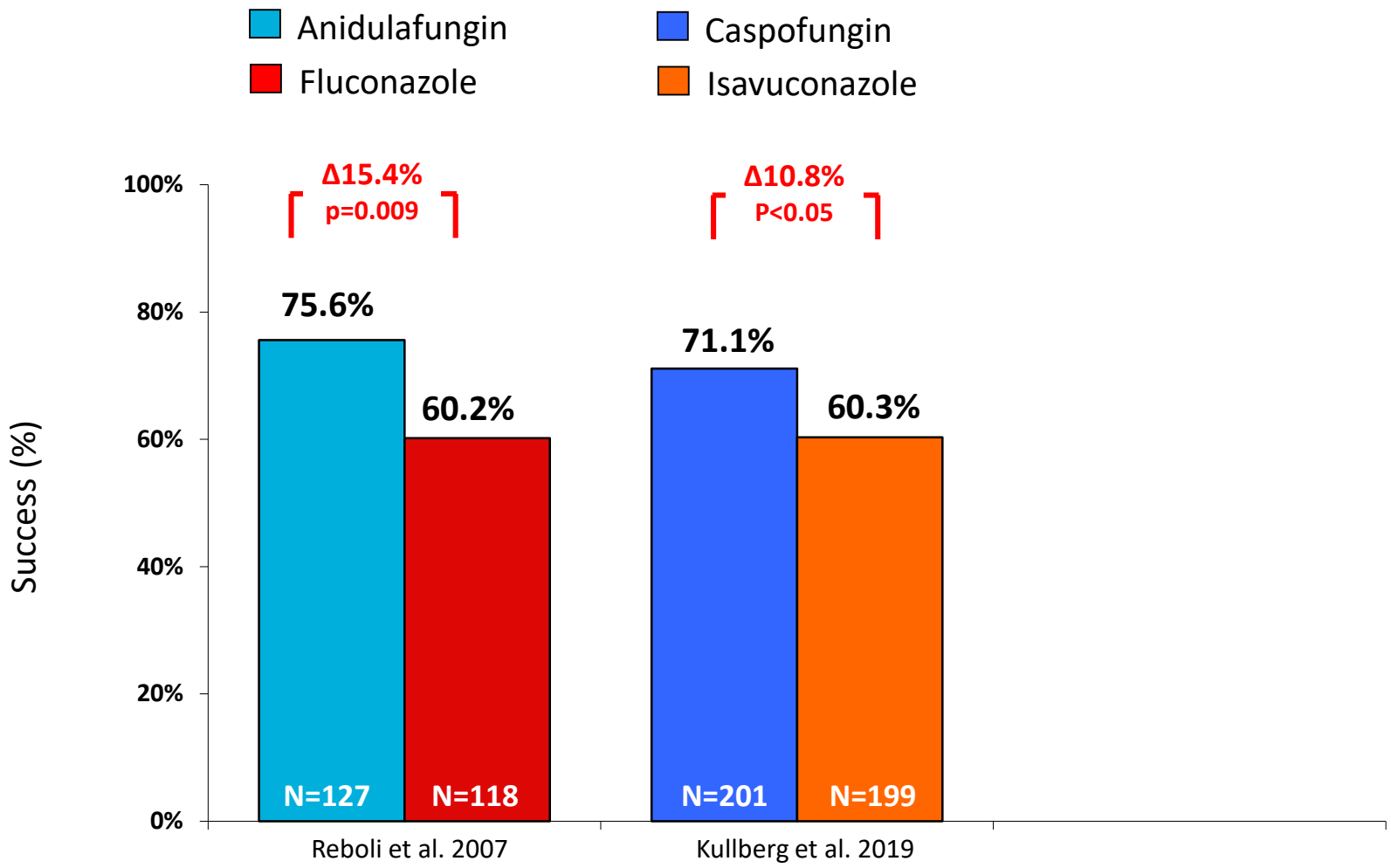
# Echinocandin superior to azole for candidemia

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Reboli AC, et al. N Engl J Med 2007; 356(24):2472–82
Kullberg BJ, et al. Clin Infect Dis 2019;68(12):1981–9

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# Case Study (2)

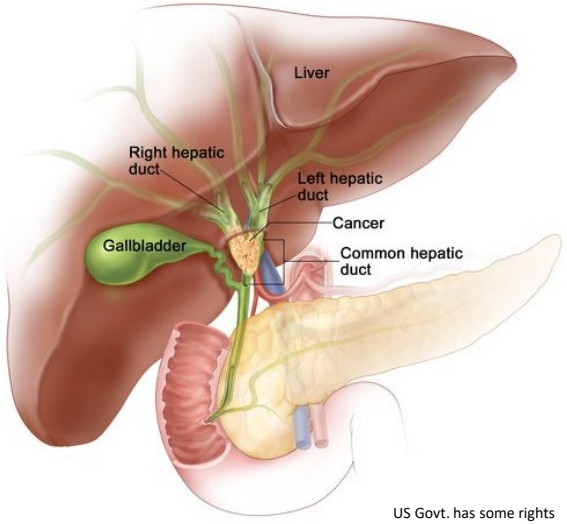
- A 62 year-old woman underwent abdominal surgery for a cholangiocarcinoma

- Post-operative ICU stay, fever 39.6°C
- Piperacillin-tazobactam and vancomycin

- Rule out suture leak

- Repeat abdominal CT negative
- Blood cultures negative
- T2 *Candida* positive: *C. krusei/glabrata*
- Started on caspofungin

- Afebrile, clinically stable
- Ready for discharge – which antifungal – if any?

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# Unmet Needs

- ✓ Do we know the optimal duration of treatment?

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# Early echinocandin to azole stepdown in candidemia patients

| All pts started on iv anidulafungin | All patients | Early (≥ Day 5) switch population |
|---|---|---|
| | % (N) [95% CI] | % (N) [95% CI] |
| MITT population (N) | 250 | 102 |
| Global success at EOT | 68% (170/250) [62.2–73.8] | 79% (81/102) [71.6–87.3] |
| | | |
| Mortality (ITT population) | 23% (65/282) | 14% (14/102) |
| | | |
| Success at end of iv therapy | 83% (208/250) [78.6–87.8] | 95% (97/102) [90.3–99.3] |

Current practice:

- ✓ Start all patients on echinocandin
- ✓ Continue echinocandin until stabilization
- ✓ DO switch early after stabilization and negative follow-up blood culture, if azole-susceptible

Unknowns:

- ✓ What if ready for early discharge / azole-resistant / azole drug-drug interactions?

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EOT, end of therapy; MITT analysis: missing/unknown values set as failures

Vazquez J, et al. *BMC Infect Dis* 2014:14;97

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# Summary thoughts – Unmet needs

- Changing epidemiology / species distribution / resistance / emerging species at least partly under pressure of prophylactic/empiric antifungal use
- Non-culture *Candida* detection and biomarker studies mostly underwhelming but nevertheless the way to go
- Need to better identify patients at risk for candidemia/invasive candidiasis (with conventional methods or immunogenetics)
- Supporting data on superiority of echinocandins for candidemia/invasive candidiasis
- Rapid step down to azoles in stabilized patients is feasible, but limited by susceptibility and drug-drug interactions
- Need for additional iv/oral antifungal classes with broad spectrum, deep tissue penetration for in/outpatient use

Reviewed in: Kullberg & Arendrup. N Engl J Med 2015;373:1445-1456 *and*
Pappas, Lionakis, Arendrup, Ostrosky-Zeichner, & Kullberg. Invasive candidiasis. Nat Rev Dis Primers 2018: 4; 18026

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# Thank you

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