黴菌感染之診斷與治療

臺中榮總　感染科

林詩萍　醫師

Distribution of patients with IA:

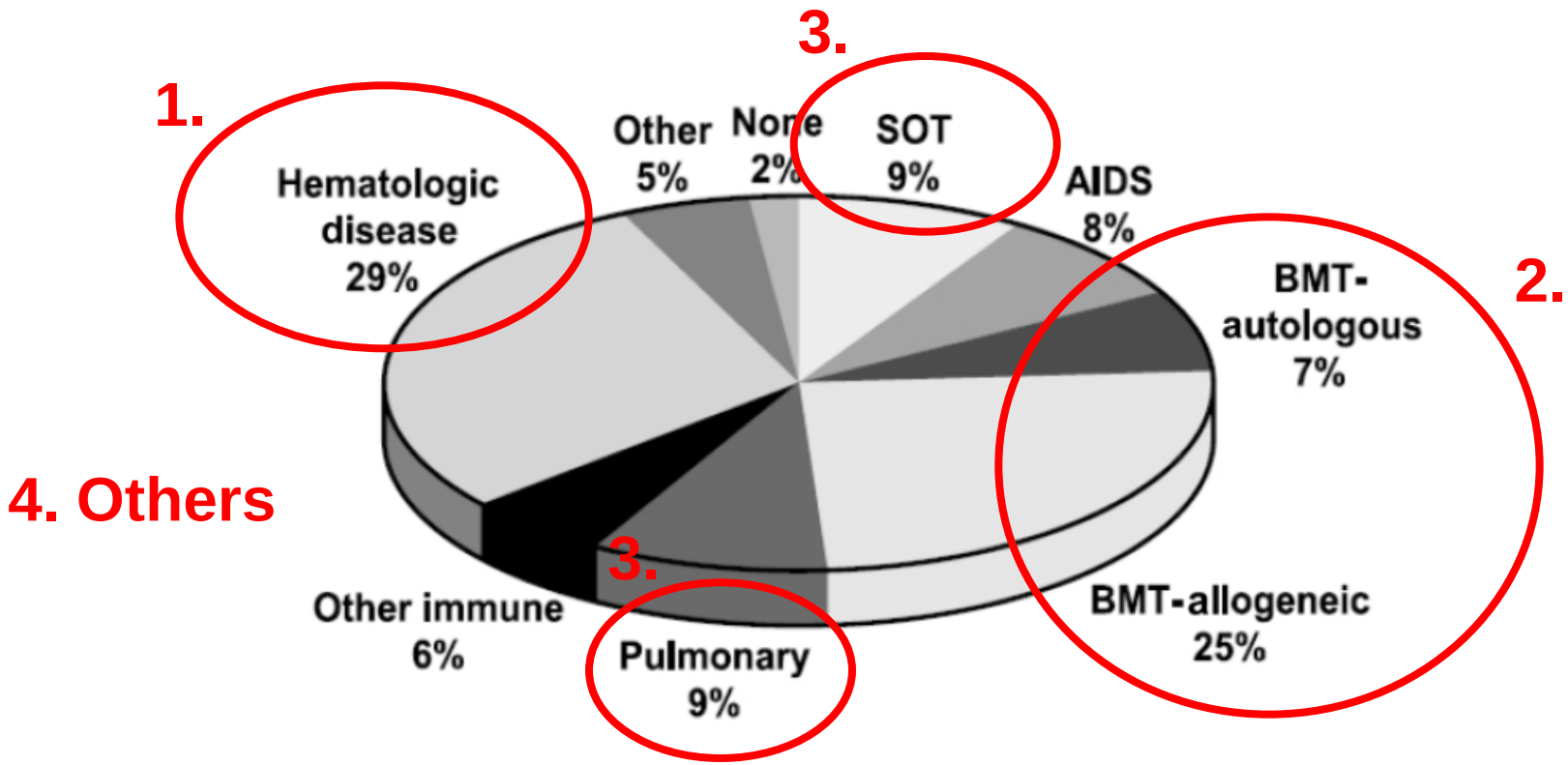


Figure 3. Underlying disease in 595 patients with invasive aspergillosis [19]. BMT, bone marrow transplant; SOT, solid-organ transplant.

Pfaller et al. CID. 2006;43:S3-14

一半以上的IA發生在非血液腫瘤科病人入住ICU

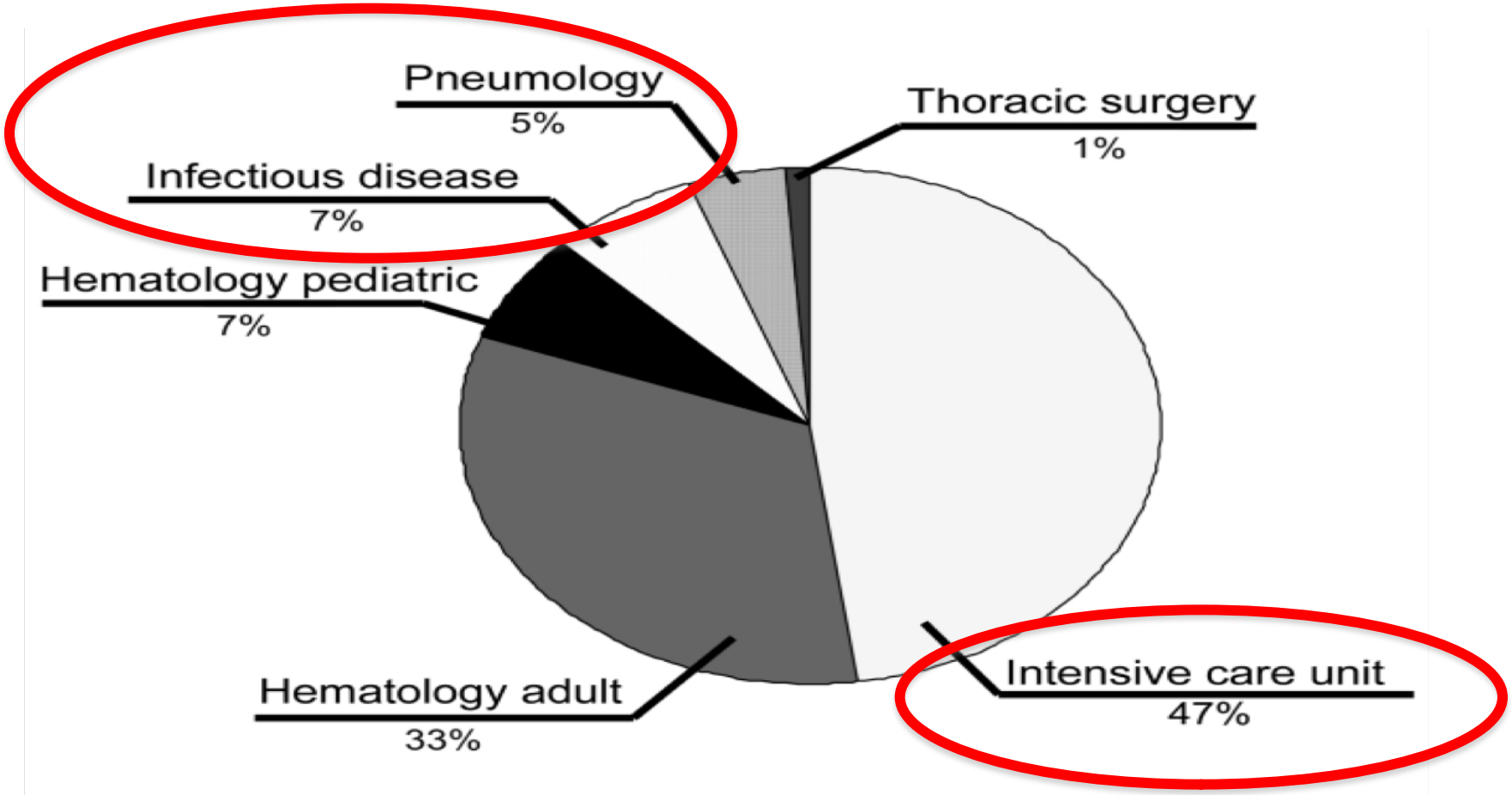


Figure 1. Distribution of invasive aspergillosis cases, by hospital ward.

Clinical Infectious Diseases 2006;43:577–84

Invasive fungal diseases (IFDs) in ICU

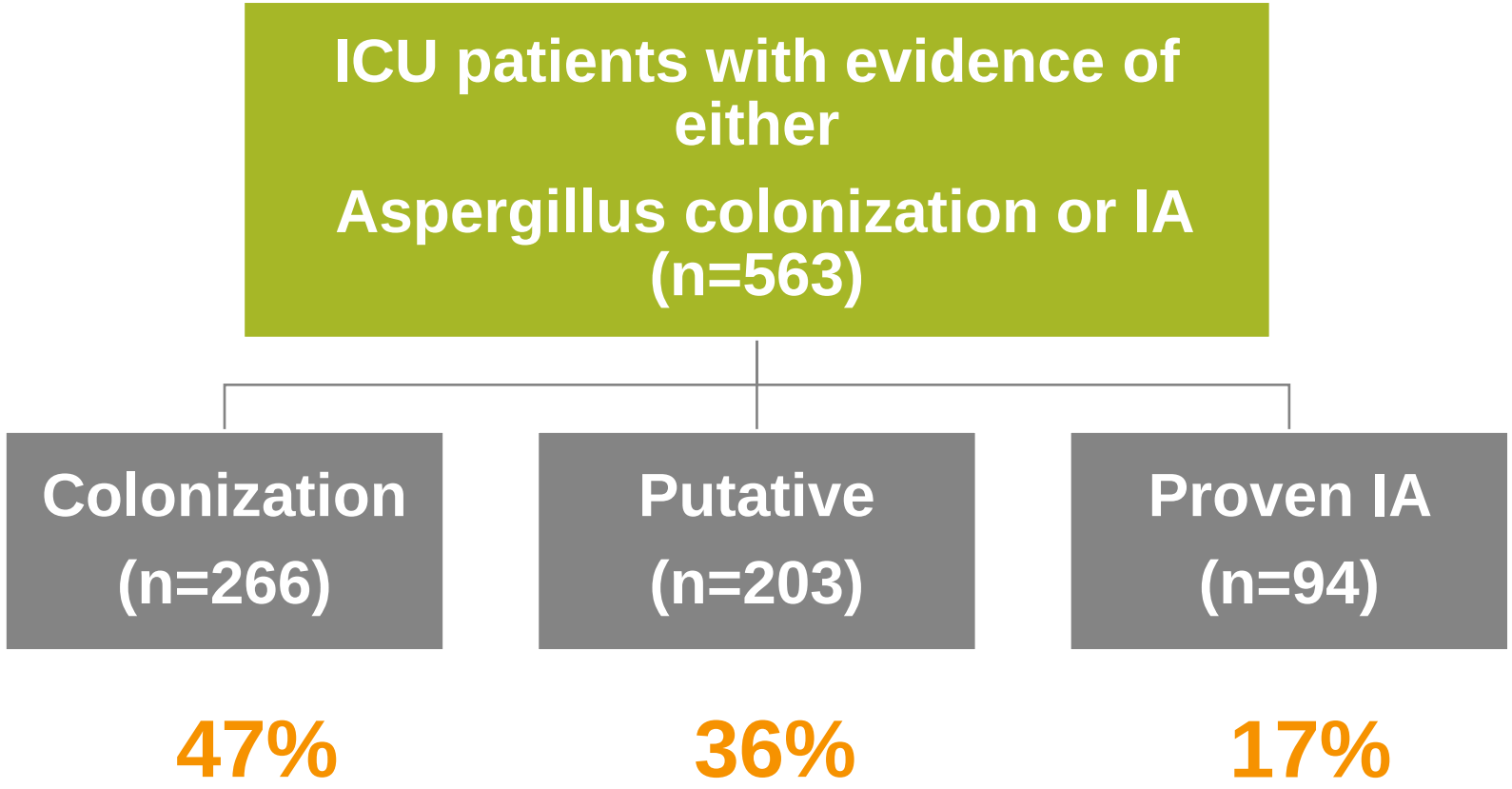
80%	1-19%
• Invasive candidiasis	• Invasive aspergillosis

診斷工具，疾病定義

Matteo Bassetti et al, Intensive Care Med (2017) 43:1225–1238

AspICU Study

A total of 563 patients from 30 ICUs in 8 countries (Belgium, France, Brazil, China, Spain, Greece, India and Portugal), 2000-2011



Taccone et al. Critical Care (2015) 19:7

在ICU，肺部是最主要IA感染部位(92%)

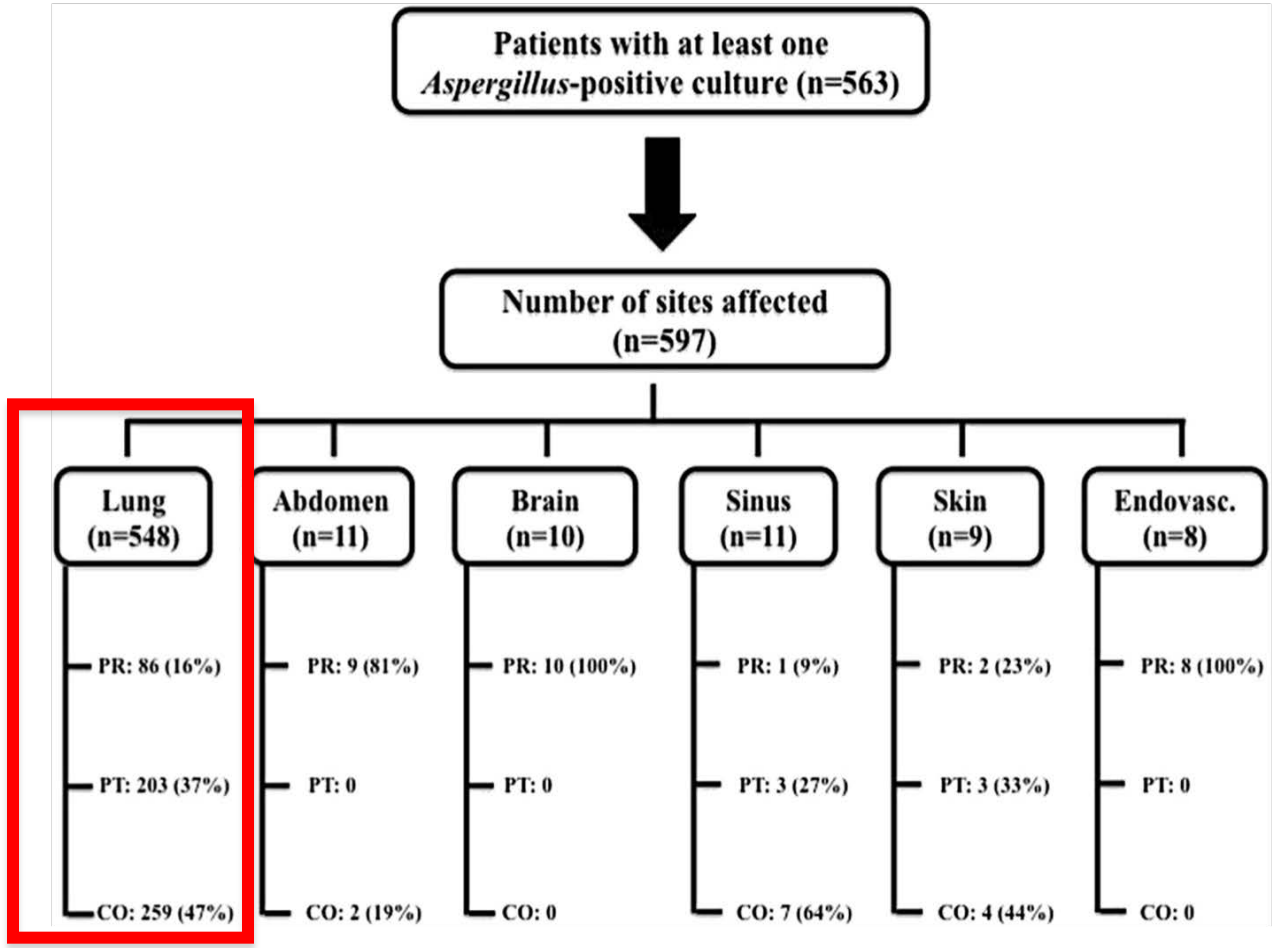
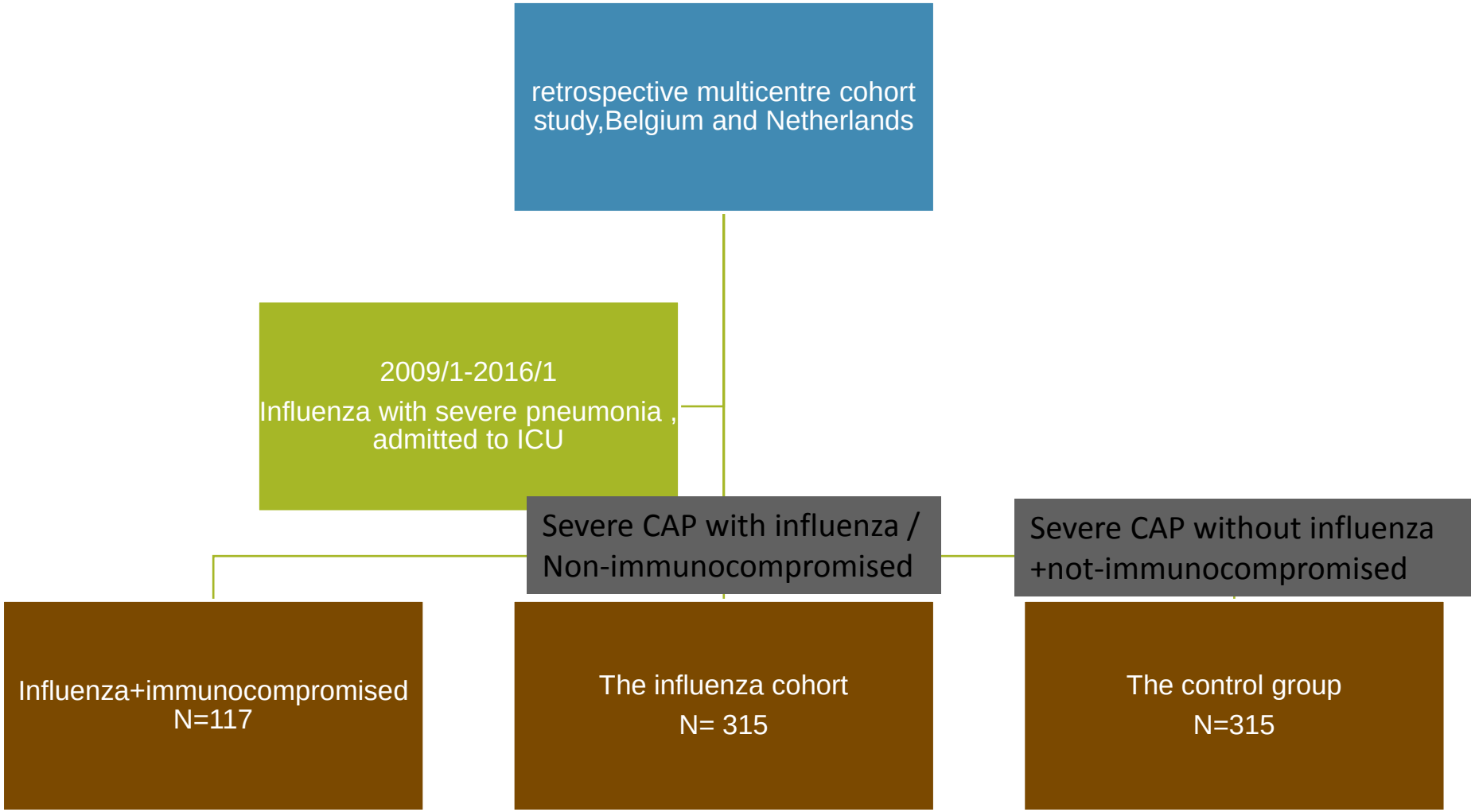


Figure 1 Number of sites affected by *Aspergillus* spp for the different diagnostic categories. Patients who had multiple sites positive for *Aspergillus* spp were counted more than once. CO, Colonization; PR, Proven; PT, Putative. Data are reported as number (%).

Taccone et al. Critical Care (2015) 19:7

Invasive aspergillosis in patients admitted to ICU



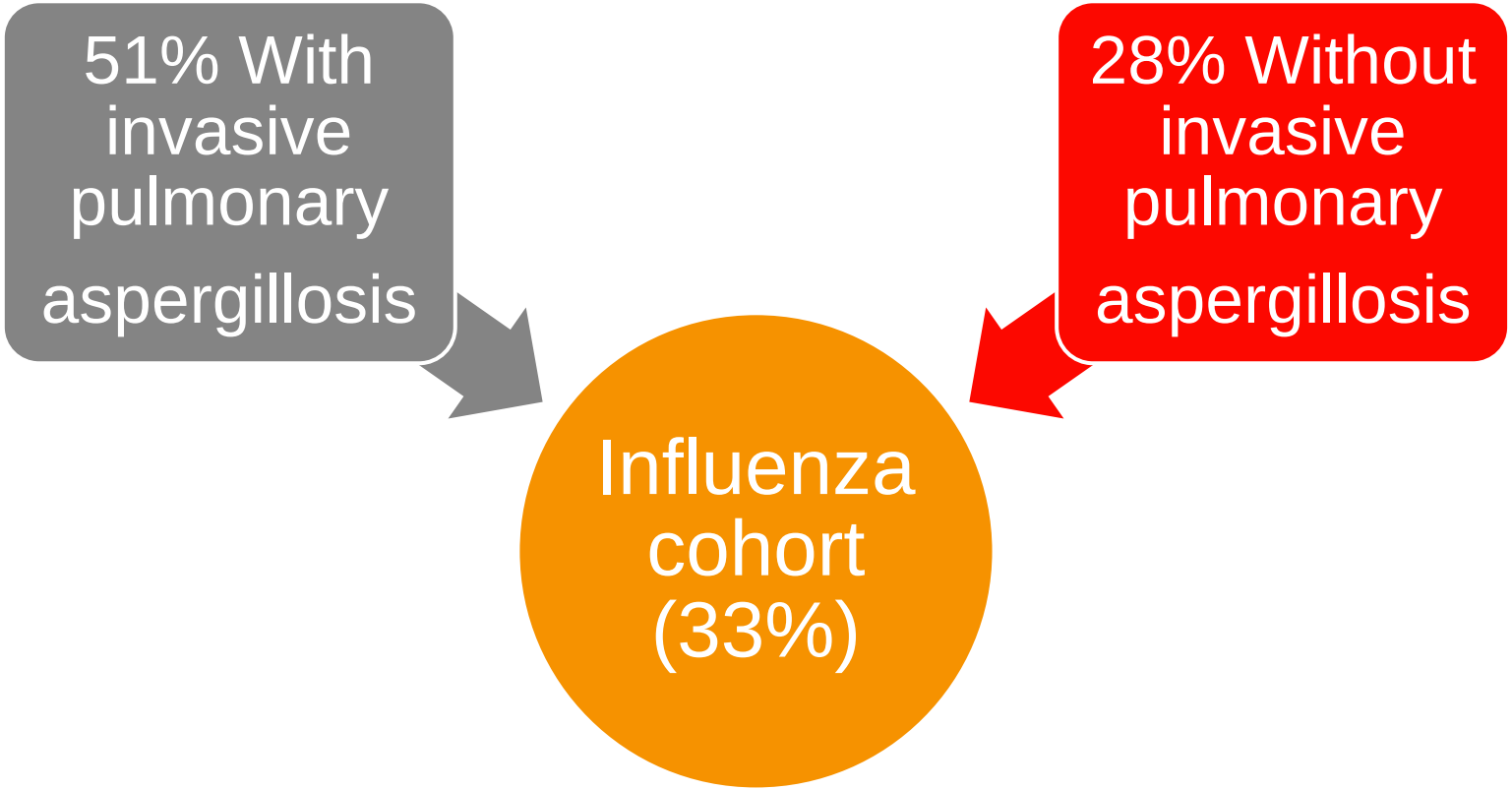
***Lancet Respir Med* 2018;6: 782–92**

Incidence of Invasive pulmonary aspergillosis

32%	14%	5%
• Flu+ • immunocompromised	• Flu+ • Non-immunocompromised	• Control group

Lancet Respir Med 2018;6: 782–92

90-days mortality after ICU admission



Lancet Respir Med 2018;6: 782–92

Table 2 Risk factors for IPA in ICU patients

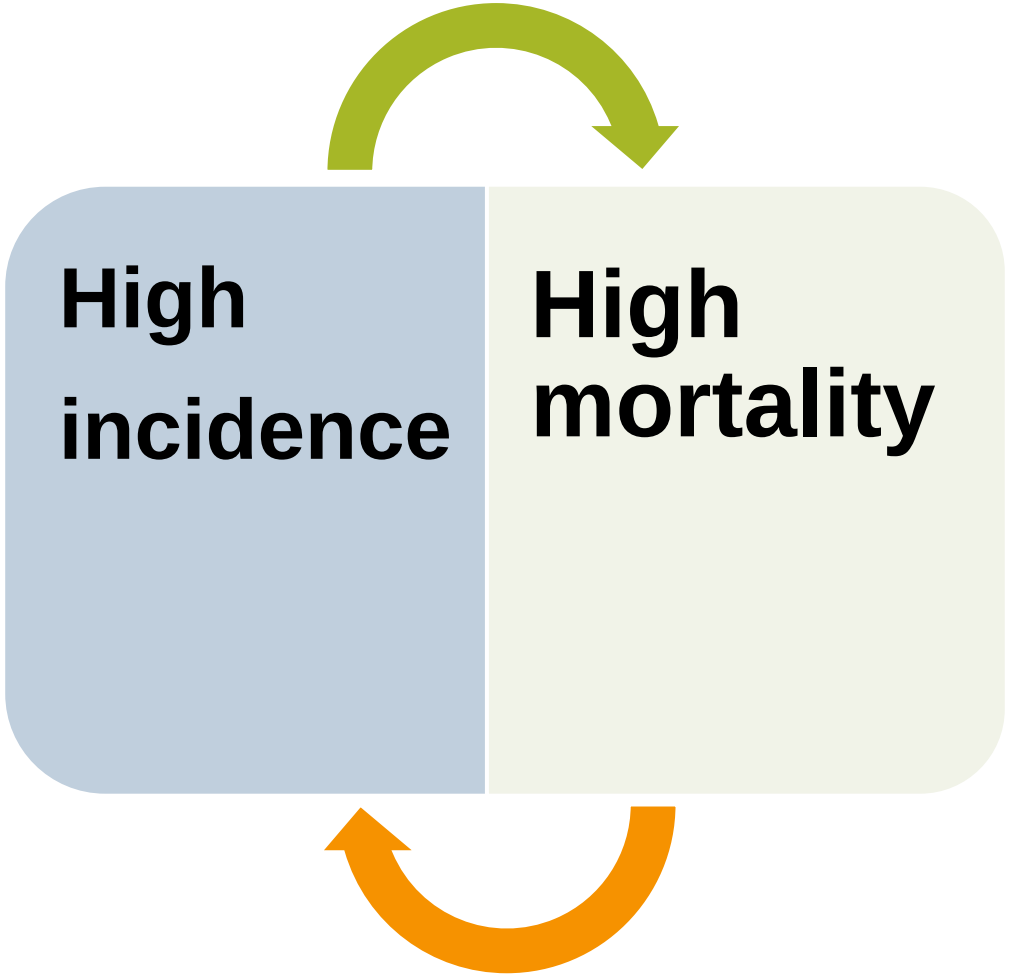
1. High risk
Neutropenia (500/mm^3)
Hematological malignancy
Allogeneic HSCT
2. Intermediate risk
Prolonged treatment with corticosteroids before admission to the ICU
Autologous HSCT
COPD
Liver cirrhosis
Solid organ cancer
HIV infection
Lung transplantation
Systemic immunosuppressive therapy
3. Low risk
Severe burns
Solid organ transplant
Steroid treatment for >7 days
Prolonged stay in the ICU (>21 days)
Malnutrition
Post cardiac surgery
Near drowning

Post influenza, post COVID-19

Intensive Care Med (2017) 43:1225–1238

IA in ICU

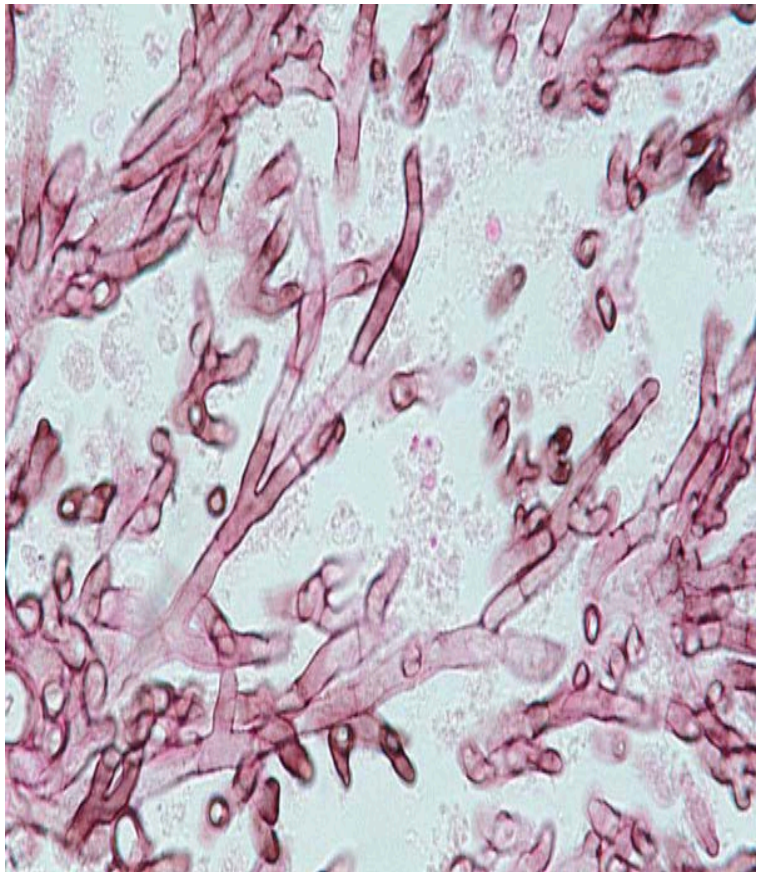
我們常常忽略了黴菌感染的可能性!



我們的挑戰

Proven invasive fungal infections

組織病理證據hyphae



新增tissue fungal PCR

Tissue Nucleic Acid Diagnosis

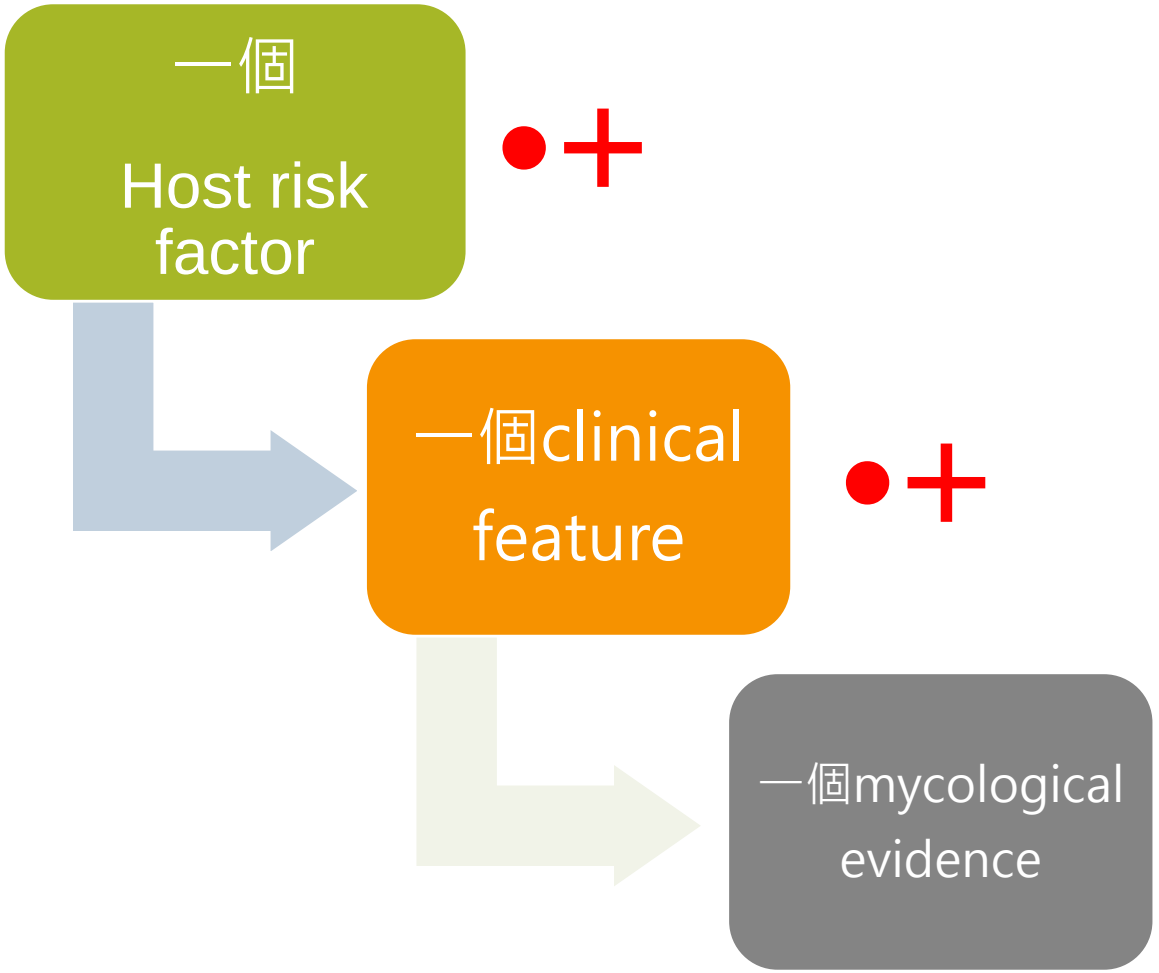
Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue

Excluding excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine

Clinical Infectious Diseases ® 2020;71(6):1367–76

Clin Infect Dis. 2008 June 15; 46(12): 1813–1821

Probable invasive fungal infection



Clinical Infectious Diseases ® 2020;71(6):1367–76

Host factors

Host factors
Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancy[a]
Receipt of an allogeneic stem cell transplant
Receipt of a solid organ transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

Clinical Infectious Diseases ® 2020;71(6):1367–76

Clinical features

Clinical features
Pulmonary aspergillosis
The presence of 1 of the following 4 patterns on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air crescent sign
Cavity
Wedge-shaped and segmental or lobar consolidation

Clinical Infectious Diseases ® 2020;71(6):1367–76

Mycological evidence

Culture	Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate
	Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold
GM	*Aspergillosis only*
	Galactomannan antigen
	Antigen detected in plasma, serum, BAL, or CSF
	Any 1 of the following:
	Single serum or plasma: ≥1.0
	BAL fluid: ≥1.0
	Single serum or plasma: ≥0.7 and BAL fluid ≥0.8
	CSF: ≥1.0
PCR	*Aspergillus PCR*
	Any 1 of the following:
	Plasma, serum, or whole blood 2 or more consecutive PCR tests positive
	BAL fluid 2 or more duplicate PCR tests positive
	At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

Clinical Infectious Diseases ® 2020;71(6):1367–76

2016 guidelines for the use of antifungal agents

Table 3 Summary of recommendations for the treatment of invasive aspergillosis (IA).

Diagnosis	Primary	Alternative[a]	Comments
Invasive pulmonary aspergillosis (IPA)	Voriconazole[b] (S/H)	L-AmB[c] (S/M) AmB-d[d] (S/M) Itraconazole[e] (W/M) Posaconazole[f] (W/M) Echinocandin[g] (W/M)	1. Primary combination therapy is not routinely recommended. 2. Treatment is continued for a minimum of 6–12 weeks and vary by site of disease, evidence of disease improvement, degree and duration of immunosuppression (S/L). 3. Surgical intervention recommended, if feasible, for pulmonary lesions in proximity to great vessels or pericardium, invasion of chest wall from contiguous pulmonary lesion, emphysema, and persistent hemoptysis from a single cavitary lesion (S/M).

1. Intravenous, or po, voriconazole 400 mg
(6 mg/kg) every 12 h for two doses on day 1 (loading), then 200 mg (4 mg/kg) every 12 h
2. Liposomal amphotericin B 3-5 mg/kg iv daily

Kung HC et al. J Microbiol Immunol Infect. (2018)

2016 guidelines for the use of antifungal agents

Invasive sinonasal aspergillosis	Similar to IPA	Similar to IPA	1. Initial therapy with polyene should be considered in the presence of risks or evidences suggestive of mucormycosis until excluded otherwise. 2. Surgical debridement should be considered as adjunctive treatment to antifungal therapy if possible (S/M).
Tracheobronchial aspergillosis	Similar to IPA	Similar to IPA	1. Therapy with aerosolized polyene for inhalation remains investigational and non-standardized.
CNS aspergillosis	Voriconazole (S/M)	L-AmB (S/M)	1. Surgical resection of the infected tissue if feasible. 2. Be aware of drug interactions between anticonvulsants and triazoles. 3. Combination therapy may be considered in selected patients with proven or probable IA.

(*continued on next page*)

Kung HC et al. J Microbiol Immunol Infect. (2018)

2016 guidelines for the use of antifungal agents

Paranasal sinuses> >lung> brain>skin

DM:Rhinocerebral mucormycosis

Pulmonary mucormycosis most common in hematologic malignancies

Table 4 Summary of recommendations for the treatment of mucormycosis.

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Invasive mucormycosis			Management should include antifungal therapy, control of underlying conditions and surgery. (S/M)
CNS	L-AmB (S/M)[b]	AmB-d (S/M)[c] Posaconazole[d] (S/M)	
Others	AmB-d (S/M)	L-AmB (S/M) Posaconazole[d] (S/M)	Surgical resection of the infected tissue is mandatory (S/M) but not recommended in disseminated cases. (W/L)

Kung HC et al. J Microbiol Immunol Infect. (2018)

2016 guidelines for the use of antifungal agents

- When facing breakthrough infections or treatment failures:

✓review the evidence of IA

✓test antifungal susceptibility

✓review potential interacting drugs

✓perform therapeutic drug monitoring

✓reduce doses of immunosuppression if feasible

✓surgical resection of necrotic tissue

✓diagnostic approach for potential new etiology

✓ switch to a different class of antifungal agent or combination therapy

Kung HC et al. J Microbiol Immunol Infect. (2018)

Therapeutic drug monitoring (TDM)

- Wild type phenotype:

✓Target plasma trough voriconazole concentrations of ≥ 1.5–2 mg/L

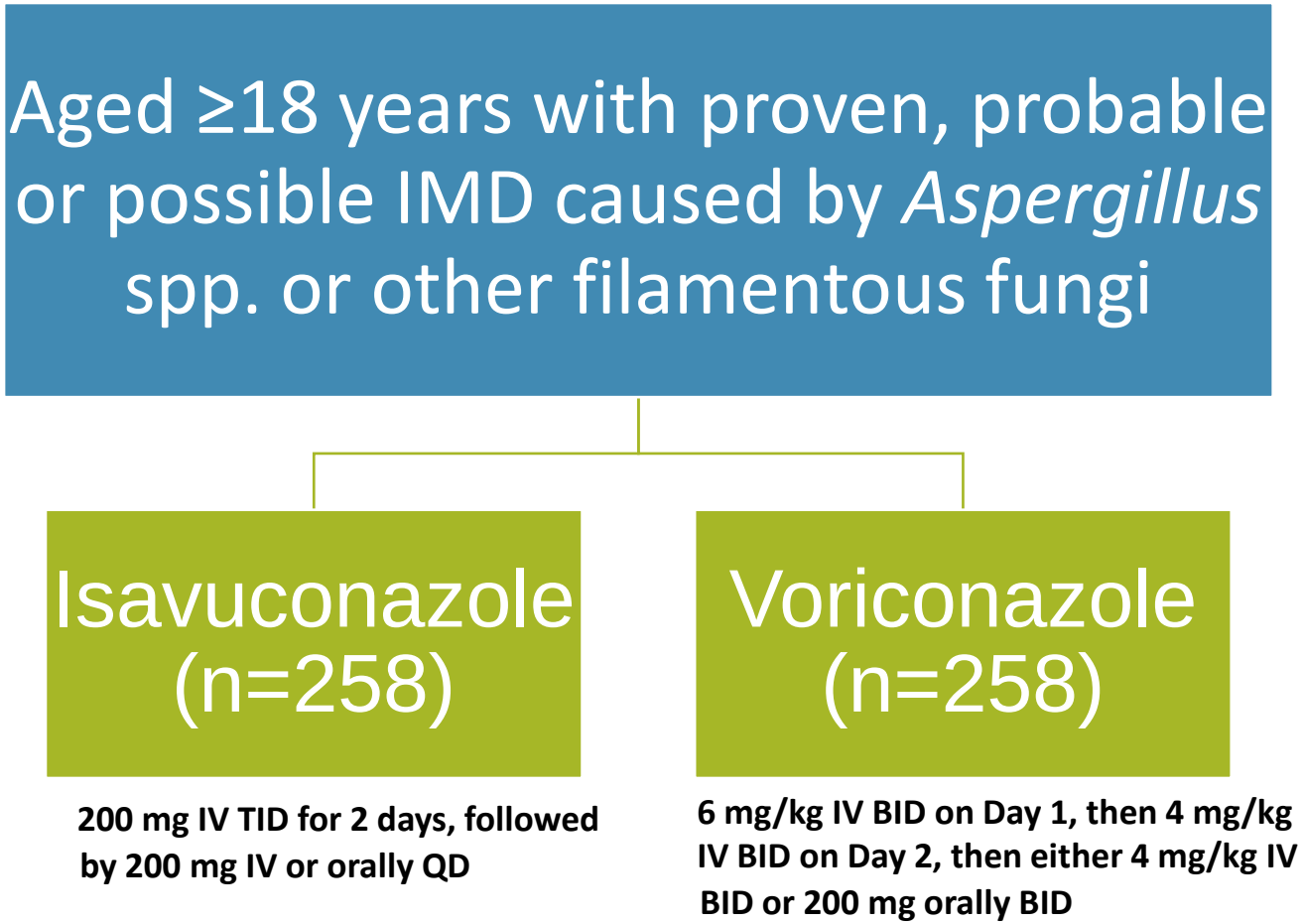
✓higher exposures (> 5.5 mg/L) increasing the risk of (neuro)toxicity

- Higher trough concentrations (> 2 mg/L) are recommended for treatment of pathogens with elevated MICs (e.g., > 0.25 mg/L)

Intensive Care Med (2020) 46:1524–1535

Isavuconazole in IA: SECURE study

Phase 3, double-blind, global multicentre, comparative-group study



Johan A Maertens, et al Lancet 2016; 387: 760–69

All-cause mortality: isavuconazole 與 voriconazole相當

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
All-cause mortality			
ITT population	258	258	
Day 42 all-cause mortality	48 (19%)	52 (20%)	−1·0% (−7·8 to 5·7)
Deaths	45 (17%)	50 (19%)	..
Unknown survival status†	3 (1%)	2 (1%)	..
Day 84 all-cause mortality	75 (29%)	80 (31%)	−1·4% (−9·2 to 6·3)
Deaths	72 (28%)	75 (29%)	..
Unknown survival status†	3 (1%)	5 (2%)	..

Johan A Maertens, et al Lancet 2016; 387: 760–69

臨床治療反應(包含mycological, image response) ：isavuconazole 與voriconazole相當

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Johan A Maertens, et al Lancet 2016; 387: 760–69

藥物副作用

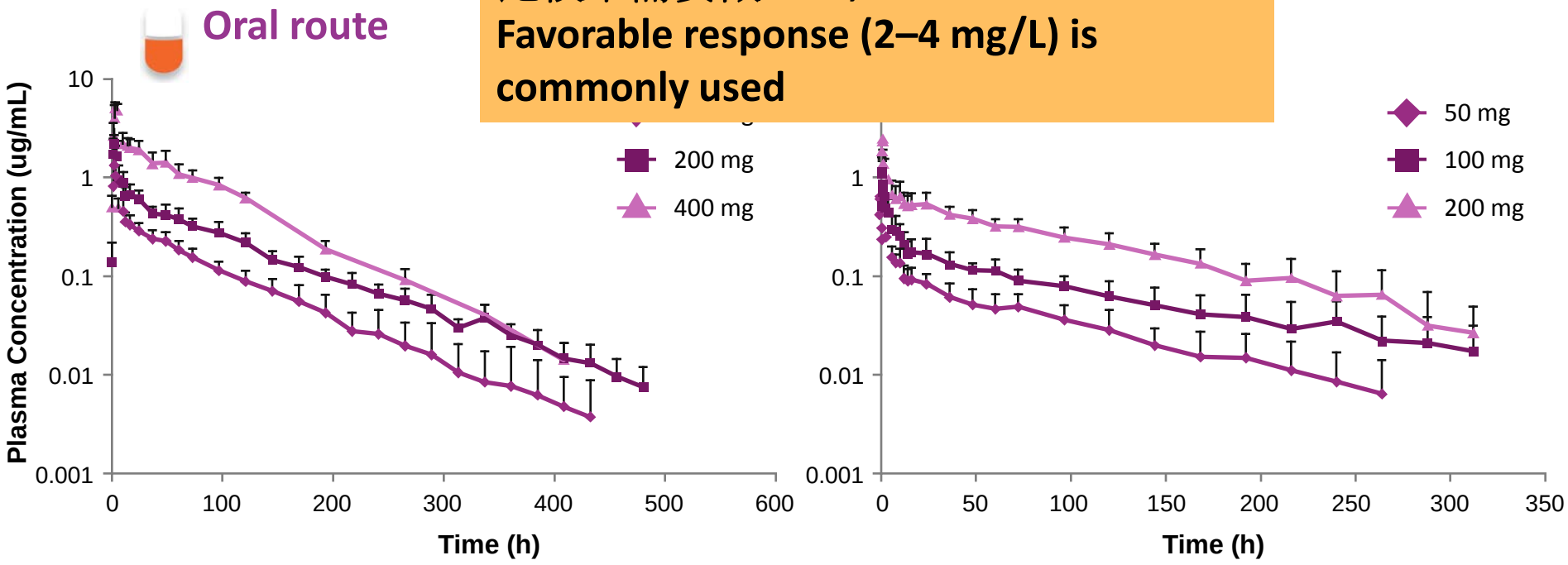
	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

Johan A Maertens, et al Lancet 2016; 387: 760–69

Isavuconazole具有線性可預測性的藥物動力學

CRESEMBA displays **linear and predictable pharmacokinetics.**

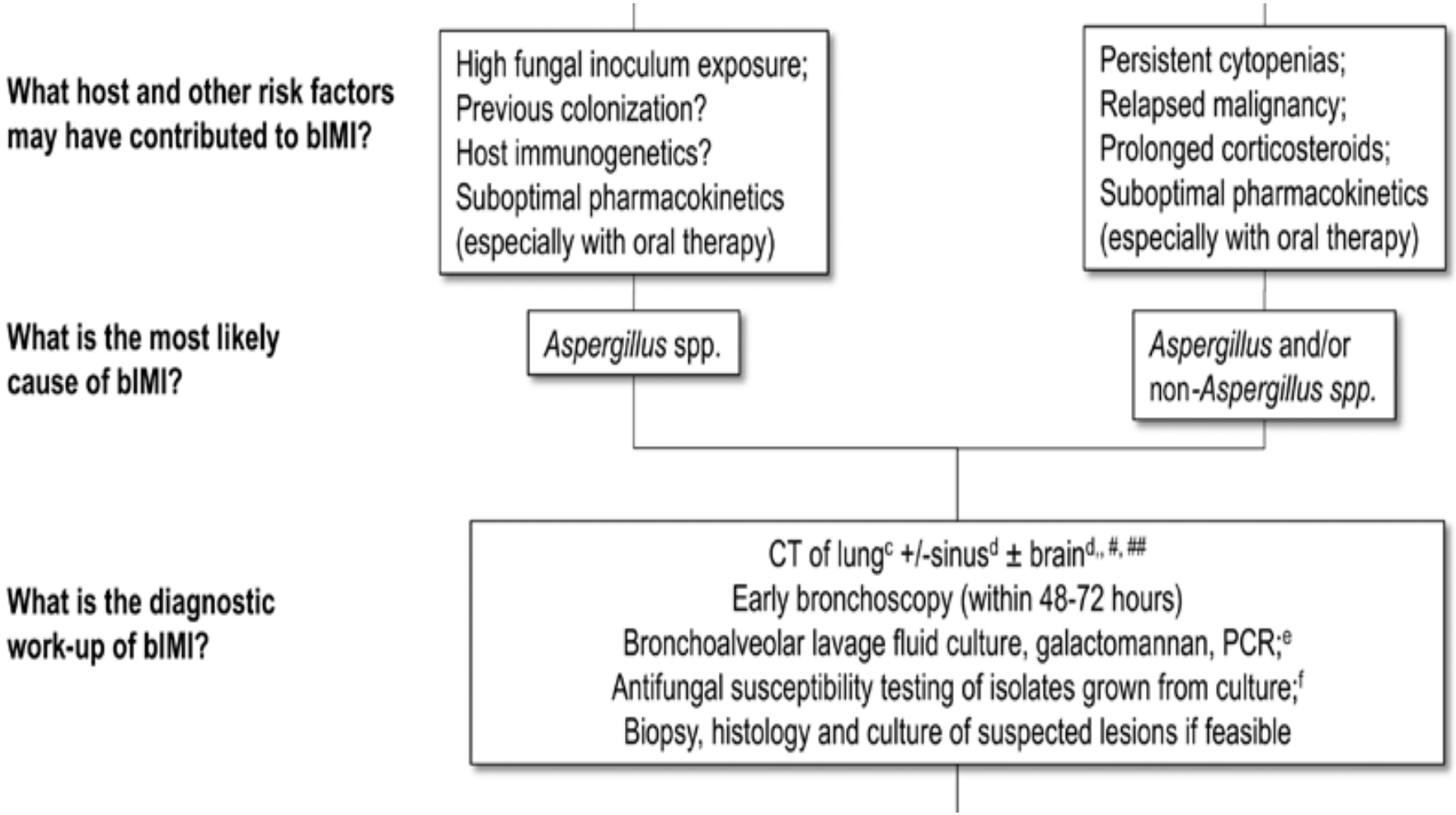
比較不需要做TDM,
Favorable response (2–4 mg/L) is commonly used



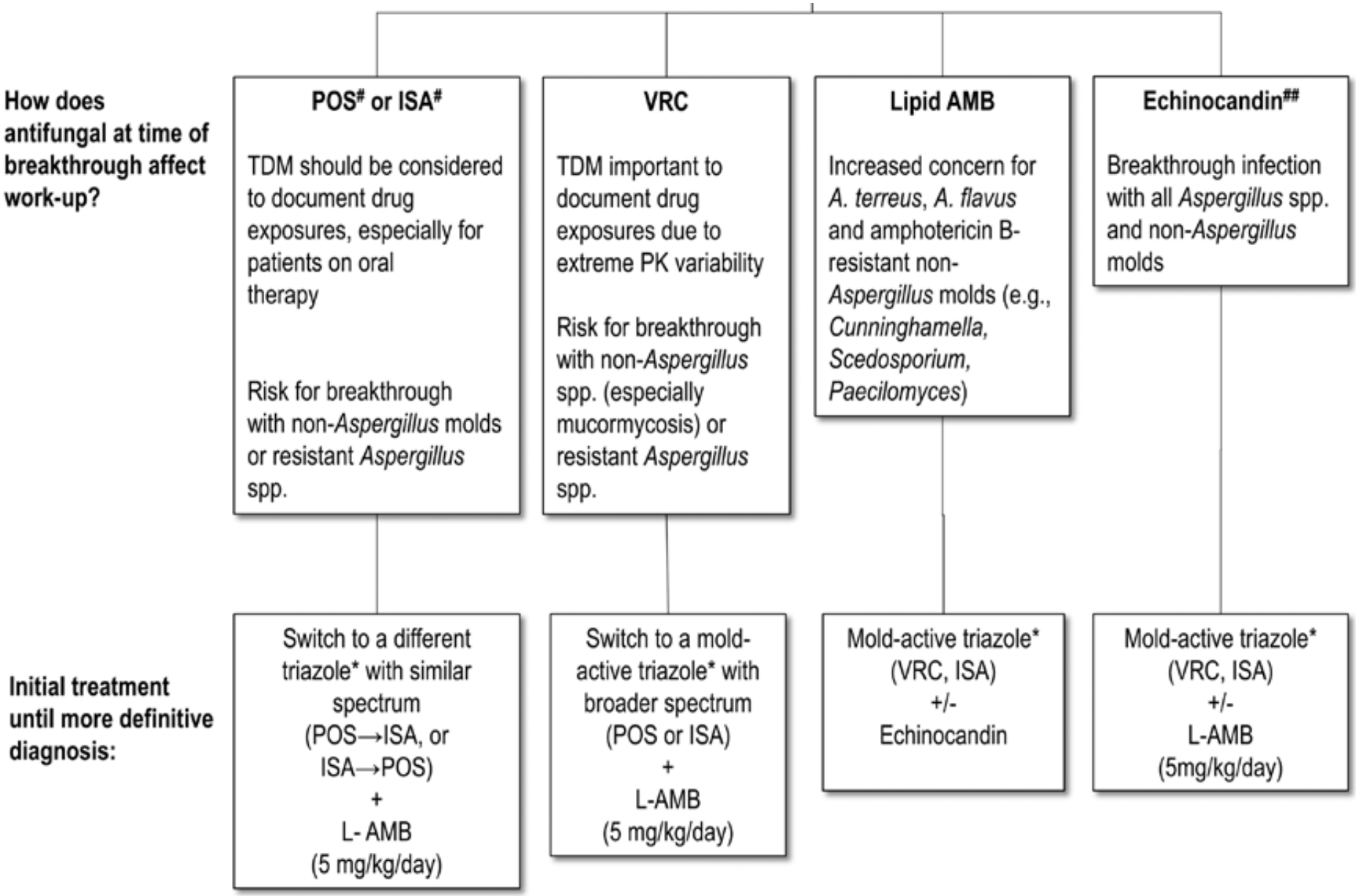
Plasma concentration in healthy volunteers after single dose CRESEMBA via oral and IV route.

- A, Mean (plus or minus SD) plasma profiles of BAL4815 after oral administration of BAL8557 (equivalent to 100 mg, 200 mg, and 400 mg BAL4815). B, Mean (plus or minus SD) plasma profiles of BAL4815 after intravenous infusion of BAL8557 (equivalent to 50 mg, 100 mg, and 200 mg BAL4815).
- Antimicrob Agents Chemother. 2006 Jan;50(1):279-85.

Flowchart for assessment and management of invasive mold infections



Clin Infect Dis. 2018 May 31.



Clin Infect Dis. 2018 May 31.

Invasive candidiasis

定義：

✓Candidaemia

✓Deep-seated candidiasis

✓Deep-seated candidiasis with associated candidaemia

Incidence of IC in ICUs

- A multinational, multicenter, retrospective study in 23 ICUs in 9 European countries
- 2015/1-2016/12
- ICU-acquired IC: candidemia and intra-abdominal candidiasis (IAC) developing at least 48 h after ICU admission

Bassetti et al. Critical Care (2019) 23:219

Cumulative incidence of IC

- 80,645 admissions and 570 episodes of ICU-acquired IC

→incidence of 7.07 episodes per 1000 ICU admissions

✓Candidemia :5.52 episodes per 1000 ICU admissions

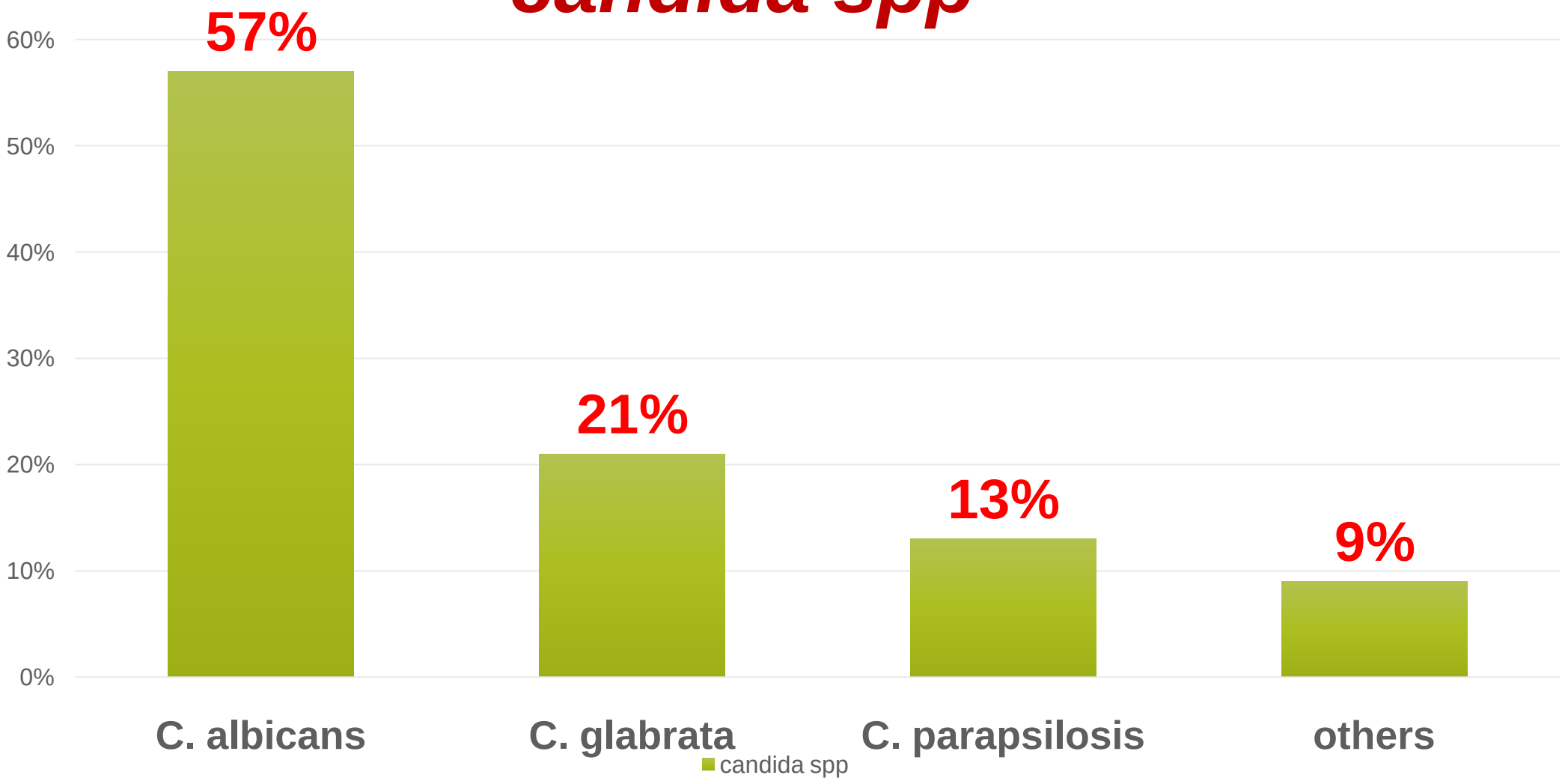
✓IAC: 1.84 episodes per 1000 ICU admissions

Table 1 Multivariable analysis of center-level factors potentially associated with changes in the cumulative incidence of invasive candidiasis in European ICUs

Center-level variables*	Number of IC episodes	Number of ICU admissions	Cumulative incidence (IC episodes/1000 ICU admissions)	CIR (95% CI)	*p*
Year of study					0.313
2015	271	40,642	6.67	Ref	
2016	299	40,003	7.47	1.18 (0.85–1.63)	
Type of ICU					0.073
Medical ($n = 5$)	149	7828	19.03	Ref	
Surgical ($n = 3$)	51	29,087	1.75	0.10 (0.01–0.76)[§]	
Mixed (medical plus surgical, $n = 15$)	370	43,730	8.46	0.40 (0.10–1.63)	

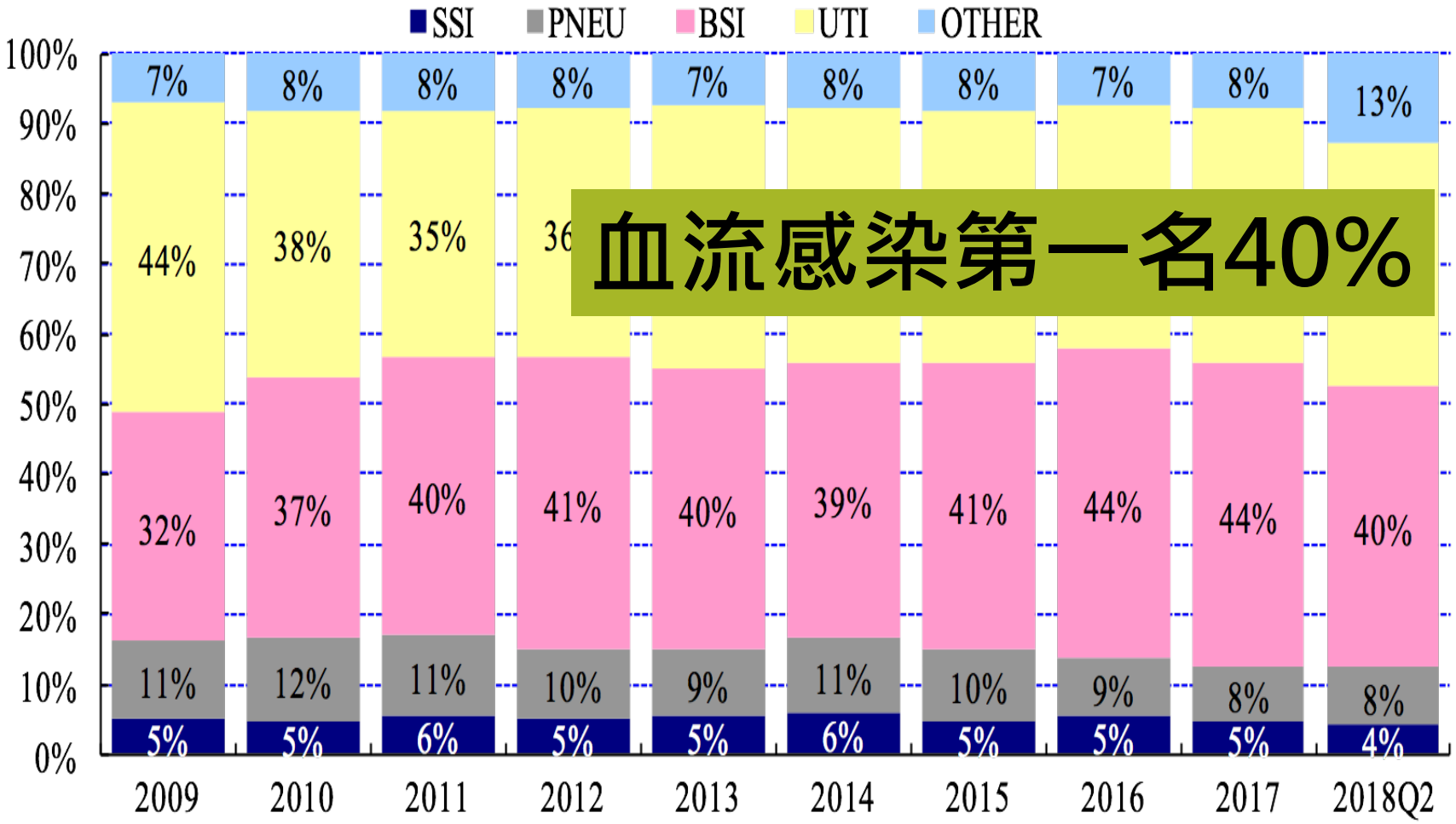
Bassetti et al. Critical Care (2019) 23:219

candida spp



Bassetti et al. Critical Care (2019) 23:219

台灣2008年至2018年醫學中心加護病房院內感染



衛生署疾病管制局--台灣院內感染監視資訊系統（TNIS）

2009至2018年第2季醫學中心加護病房BSI 感染菌種排名

BSI	2009年	2010年	2011年	2012年	2013年	2014年	2015年	2016年	2017年	2018年Q2
菌種	排名	排名	排名	排名	排名	排名	排名	排名	排名	排名
Klebsiella pneumoniae	3	3	3	2	2	2	2	3	1	1
Acinetobacter baumannii	1	1	1	1	1	1	1	1	2	3
Enterococcus faecium	10	8								
Other Candida spp. or NOS	8	9								
Candida albicans	7	7	5	9	5	6	7	8	5	5
Enterobacter species	4	4	9	4	9	7	5	6	6	7
Staphylococcus aureus	2	2	2	3	3	5	6	5	7	7
Coagulase negative staphylococci	5	5	4	6	10	8	8	9	8	10
Escherichia coli	9	10	10	11	11	10	12	7	9	9
Pseudomonas aeruginosa	5	5	6	5	6	9	9	10	10	6

*Candida albican*第五名

衛生署疾病管制局--台灣院內感染監視資訊系統（TNIS）

Proportion of the most relevant Candida spp. of candidemia

>90% invasive disease

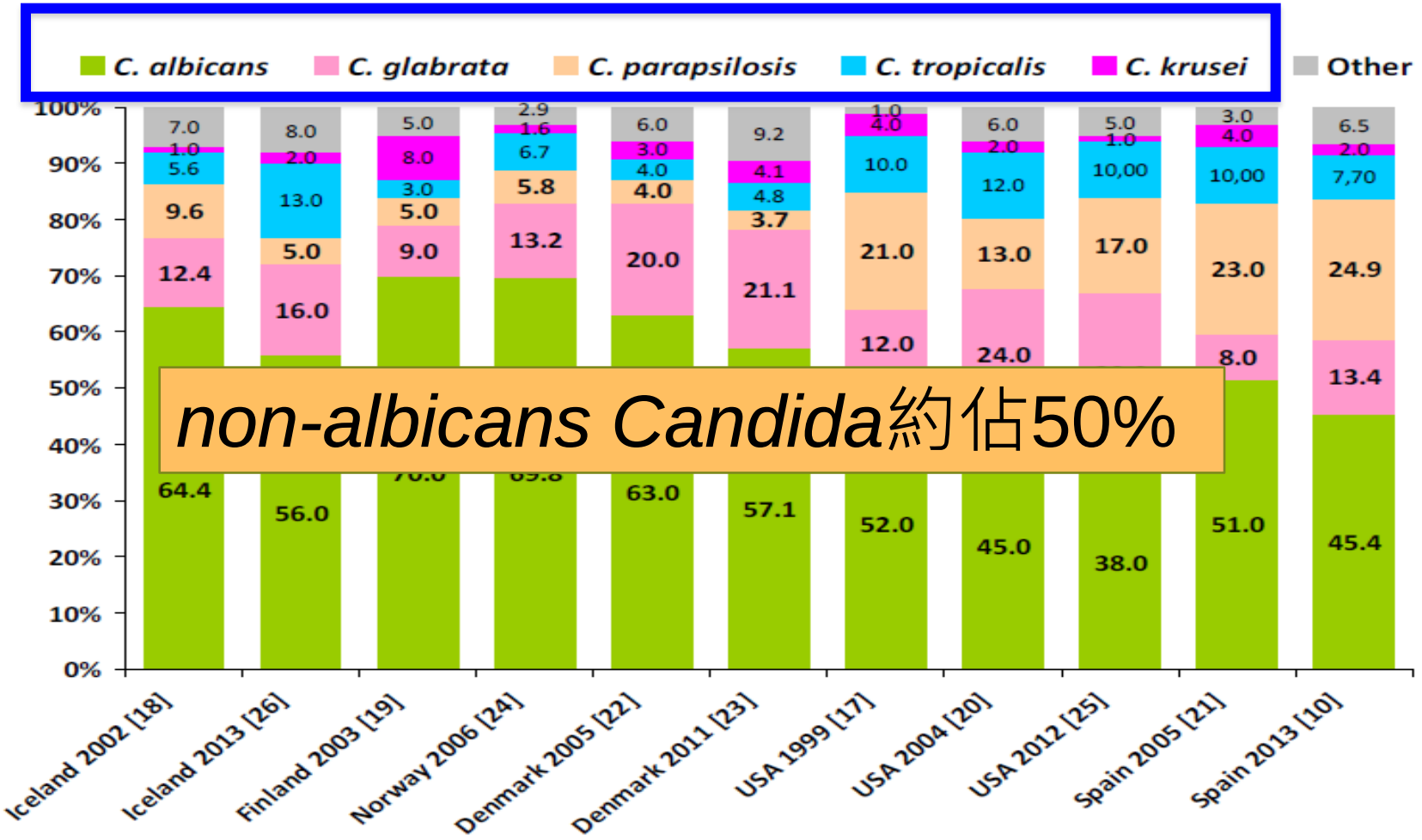
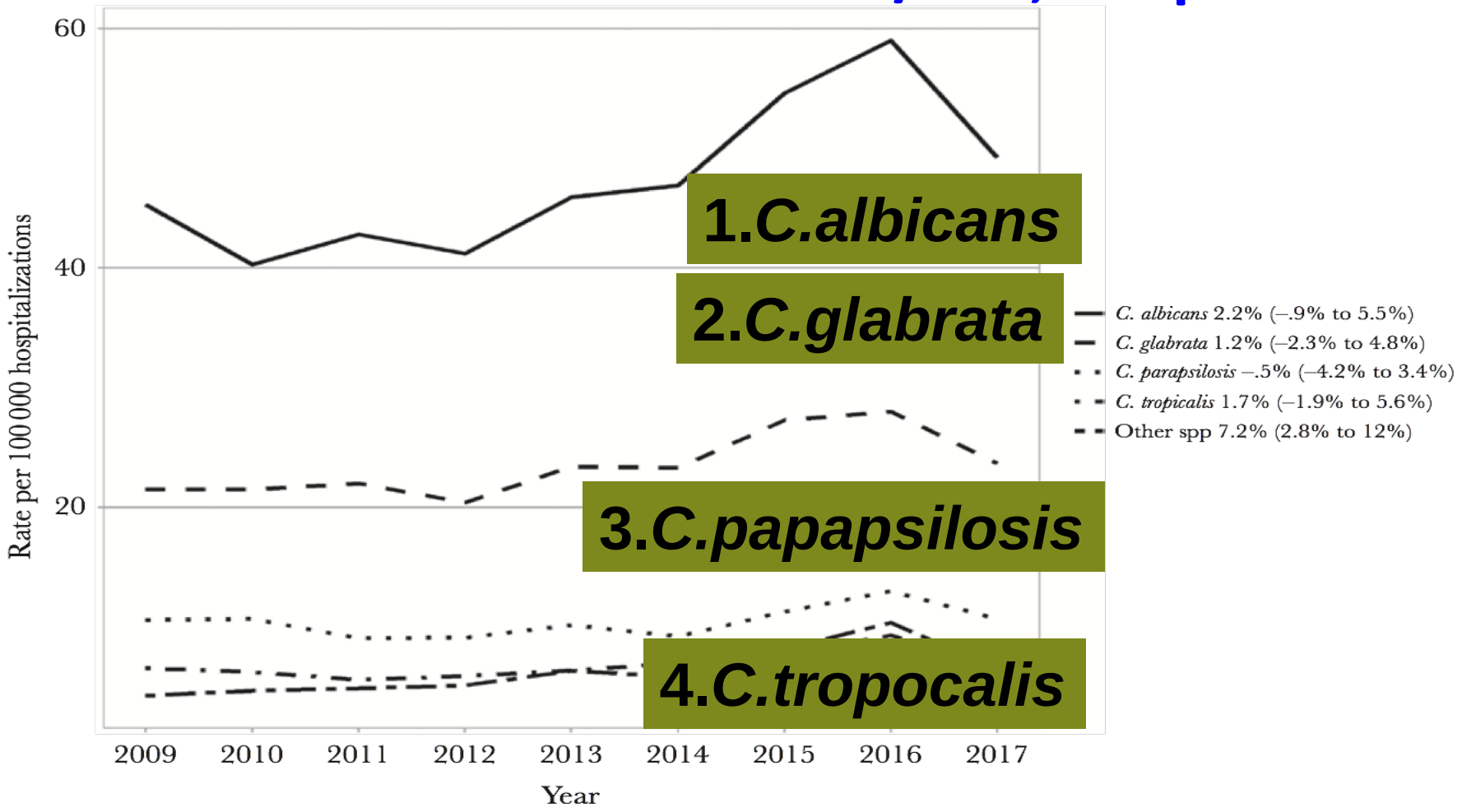


FIG. 1. Proportion of the most relevant Candida species from population-based studies reporting on candidemia in different countries.

Clin Microbiol Infect 2014; 20 (Suppl. 6): 5–10

Invasive Candidiasis Species Distribution and Trends in United States

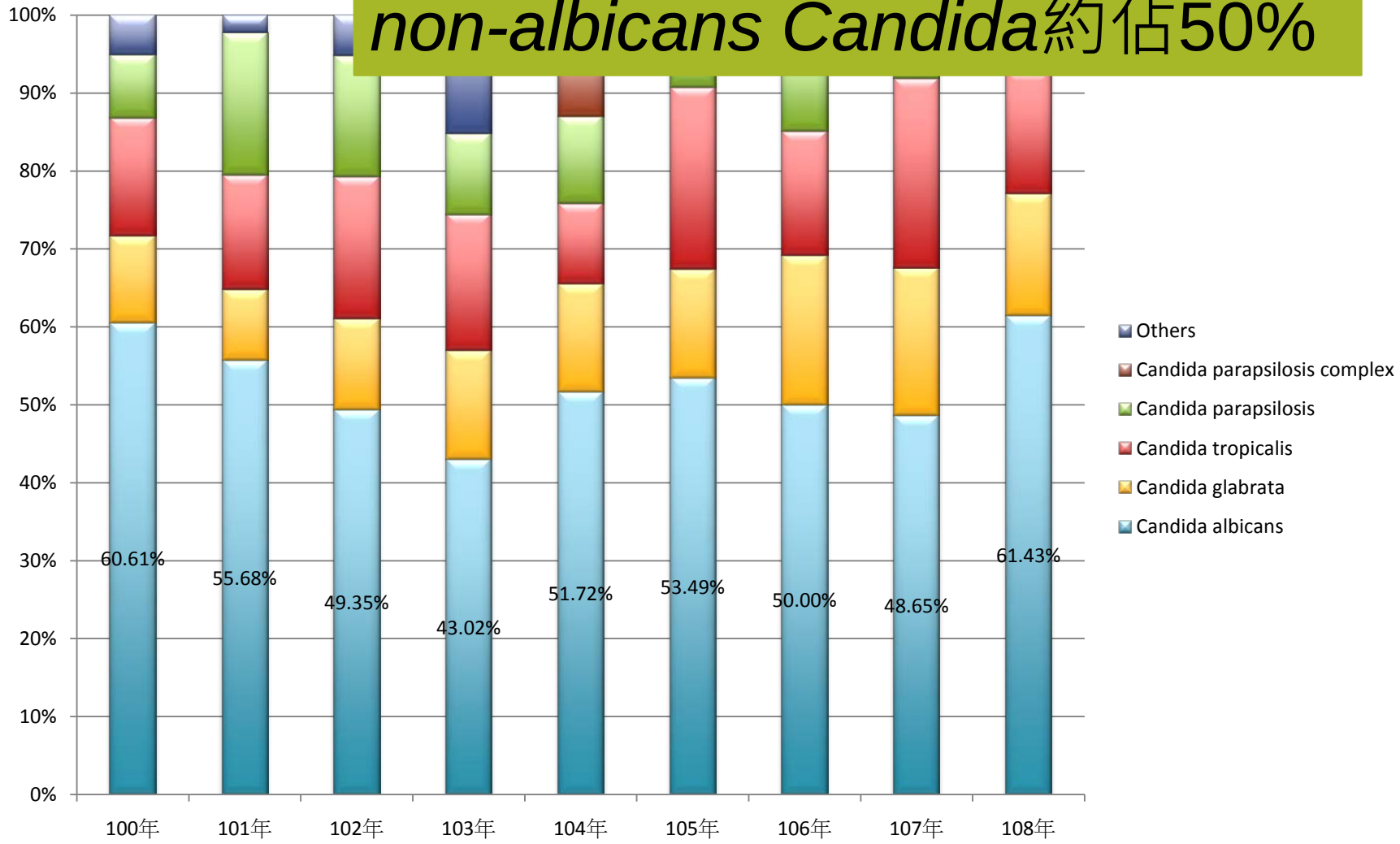
2009-2017:平均IC incidence 90/100,000 patients



Emily E. Ricotta,et al. J Infect Dis. 2020 Aug 15

Candidemia in TCVGH

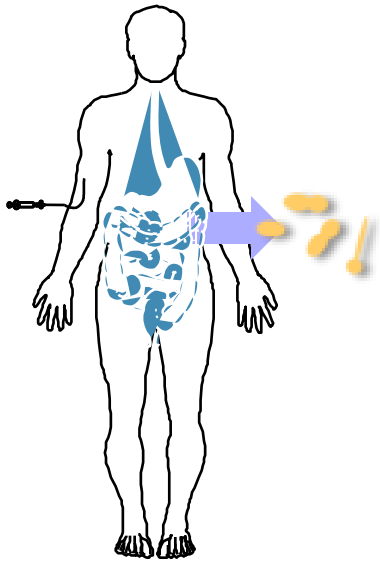
*non-albicans Candida*約佔50%



Risk factors for invasive candidiasis

Immunosuppression

Neutropenia
glucocorticoids
diabetes



Barriers/ Integument

broad spectrum antibiotics
mucosal barrier injury (mucositis)
GI perforation or surgery
TPN
catheters
hemodialysis
IV drug use
pancreatitis

Surgical ICU:
Gastroduodenal perforations, anastomotic leaks, necrotizing pancreatitis

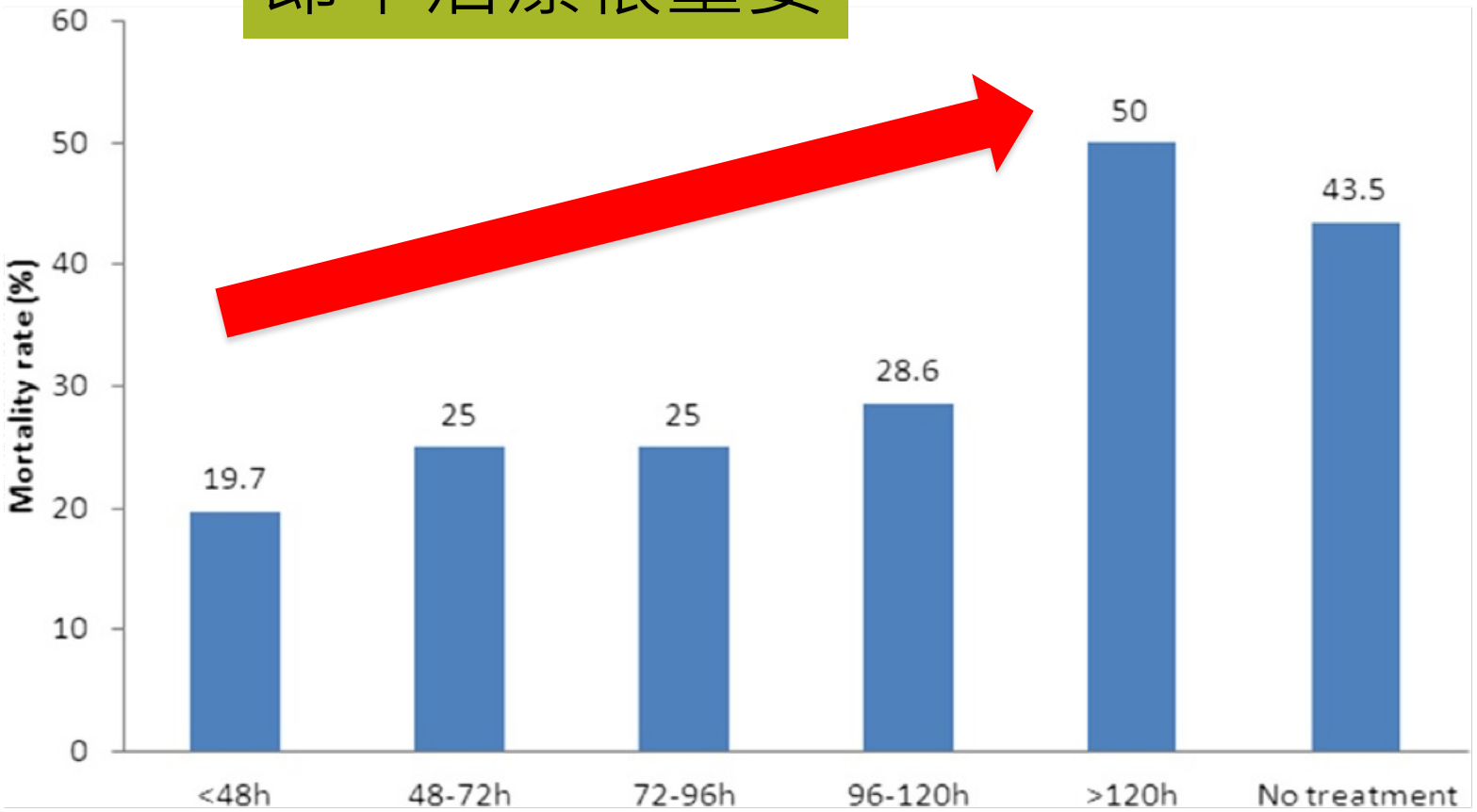
Time

Length of stay in hospital/ ICU
Duration of surgery
Duration of broad spectrum antibiotic therapy (colonization)
Severity of illness

Crit Care 2010;14:244
Eur J Clin Microbiol Infect Dis 2007;26:271–6
Clin Infect Dis 2001;33:177–86

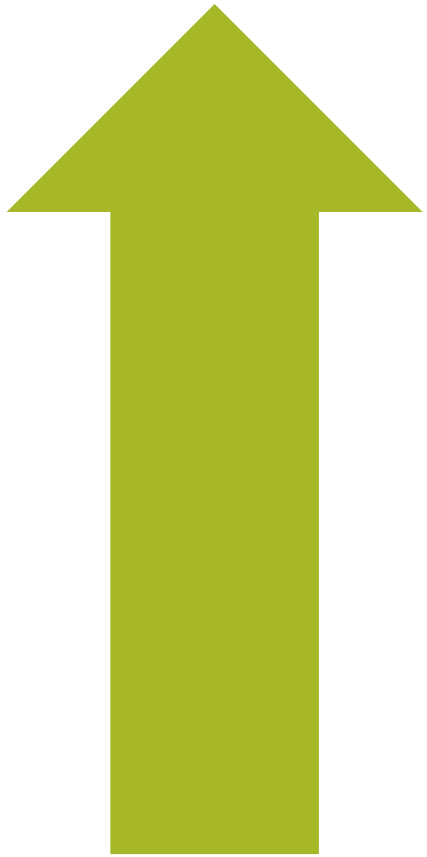
Relationship between hospital mortality (28-day) and the timing of antifungal treatment

即早治療很重要



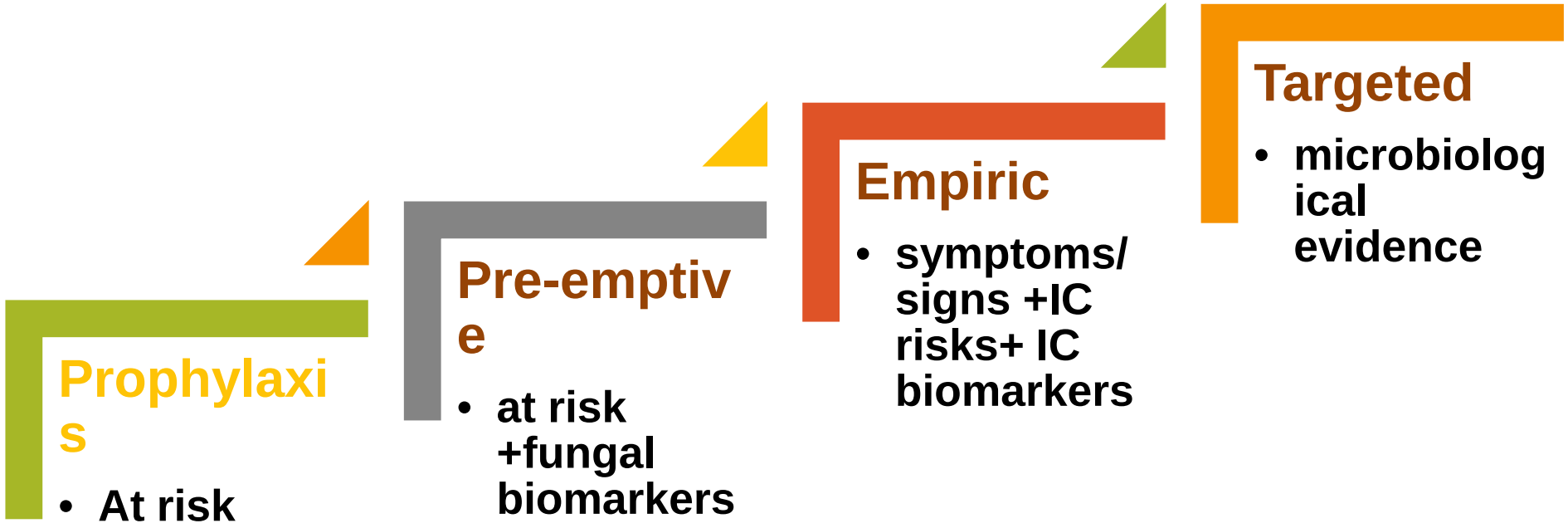
Yang et al. BMC Infectious Diseases 2014, 14:241

Antifungal therapy



When to start ?

Antifungal prescribing strategies



✓ European Society of Intensive Care Medicine (ESICM)
✓ European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

診斷IC

- **Gold standard**

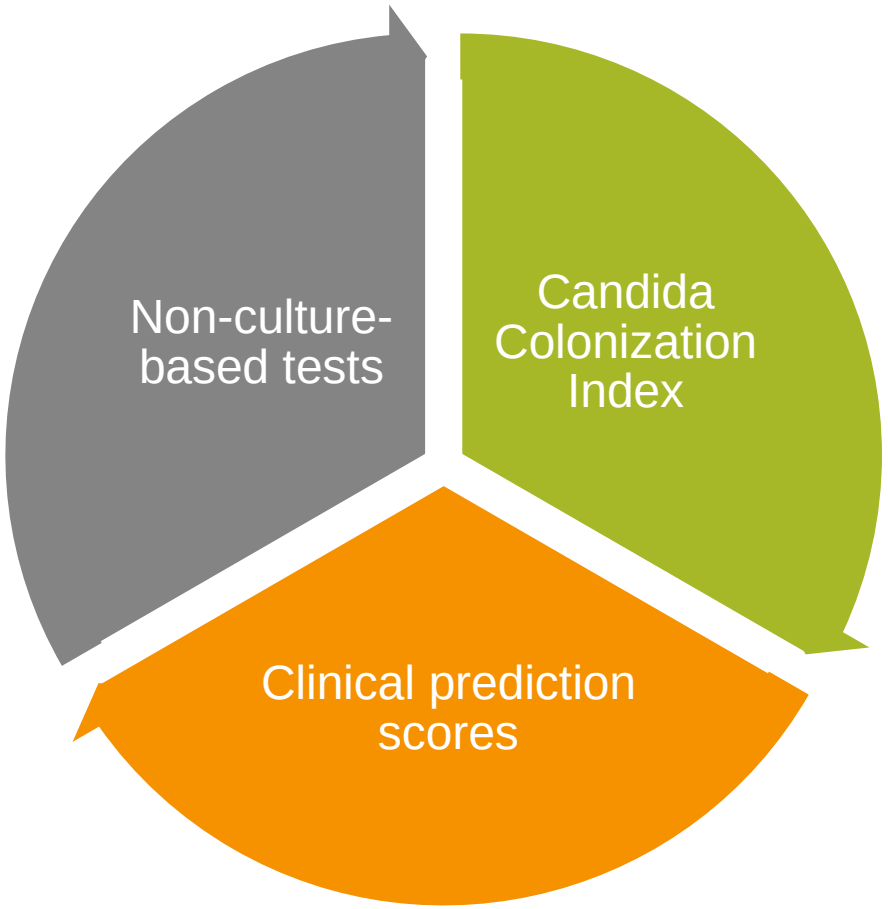
✓Blood culture: 1 colony-forming unit (CFU)/mL

✓Sensitivity is suboptimal (~ 75% in bloodstream infection, ~ 5–20% in abdominal candidiasis)

✓Time to culture positivity prolonged (2–3 days)

✓容易延誤治療時間

Three tools for early identification of IC
早期診斷



C. Logan, et al. Intensive Care Med 2020

Candida colonization as a predictor of invasive candidiasis in non-neutropenic ICU patients with sepsis

- Predicting invasive candidiasis in ICU patients

→9825 patients were studied across the 10 included studies

→3886 (40%) were colonized by a Candida species

→462 (4.7%) developed invasive candidiasis

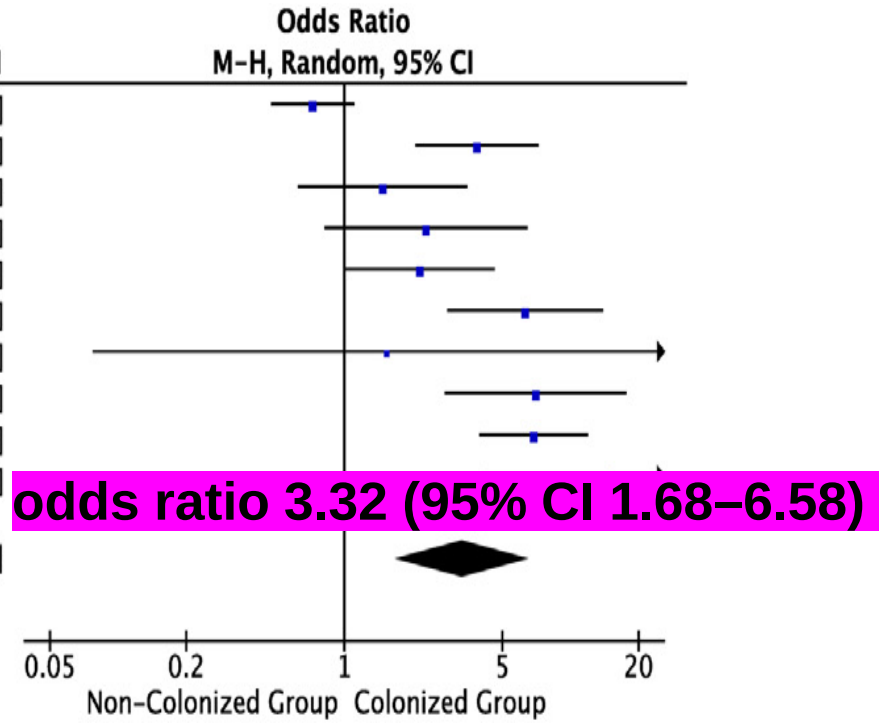
International Journal of Infectious Diseases 102 (2021) 357–362

加護病房sepsis 病人，colonized with candida 比起 non-colonized 病人，有3.32倍的風險未來變成 invasive candidiasis

Study or Subgroup	Colonization Group Events	Total	No Colonization Group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bailly et al. 2017	64	344	48	200	12.1%	0.72 [0.47, 1.11]
Blumberg et al. 2001	26	1280	16	2996	11.4%	3.86 [2.06, 7.22]
Chander et al. 2013	14	102	10	103	10.5%	1.48 [0.62, 3.50]
Gaspar et al. 2015	11	50	7	64	9.8%	2.30 [0.82, 6.44]
Han et al. 2010	14	37	35	159	10.9%	2.16 [1.01, 4.63]
Jorda-Marcos et al. 2007	56	1008	7	757	10.8%	6.30 [2.86, 13.91]
Kautzky et al. 2015	5	58	0	7	3.7%	1.54 [0.08, 30.79]
Leon et al. 2009	53	684	5	423	10.3%	7.02 [2.78, 17.71]
Patolia et al. 2013	34	296	22	1187	11.7%	6.87 [3.95, 11.94]
Vardakas et al. 2009	23	27	12	43	8.9%	14.85 [4.24, 52.03]
Total (95% CI)		**3886**		**5939**	**100.0%**	**3.32 [1.68, 6.58]**
Total events	300		162			

Heterogeneity: $Tau^2 = 0.96$; $Chi^2 = 67.34$, df = 9 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: Z = 3.45 (P = 0.0006)



diasis among ICU patients with sepsis.

International Journal of Infectious Diseases 102 (2021) 357–362

Candida Colonization

Candida Colonization Index

Candida Colonization Index	Ratio of the number of (non-blood) sites colonized with *Candida* spp /total number of sites cultured Threshold = 0.5	PPV = 66% NPV = 100%

雖然candida colonization會增加IC risk，但是其中只有約5-30%會真正變成IC

Pittet D,et al. Ann Surg 1994 220:751–758.

Clinical prediction scores

Clinical prediction scores		
Candida Score	Candida Score = TPN (1 point), surgery (1 point) severe sepsis (2 points), Multifocal Candida colonization (1 point). Threshold = 2.5	Sensitivity = 81% Specificity = 74% PPV = 16% NPV = 98%
Ostrosky-Zeichner Clinical Prediction Rule	Mechanical ventilation ≥ 48hours AND Systemic antibiotic AND CVP (on any of day 1–3 of ICU admission) plus ≥1 of: any major surgery (days 7–0), pancreatitis (days 7–0), use of steroids/other immunosuppressive agents (days 7–0), use of TPN (days 1–3), or dialysis (days 1–3)	Sensitivity = 50%, Specificity= 83% PPV = 10% NPV = 97%

León C, et al. 2006 Crit Care Med 34:730–737.

Ostrosky-Zeichner L, et al. 2011 Mycoses 54:46–51

Can we recommend the use of risk prediction models in daily clinical practice?

Risk prediction models, because of their simplicity and high negative predictive values, should be used for identifying high-risk patients (Strong recommendation, low-quality evidence)

→ **for ruling out the presence of IC in specific high-risk patients**

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Non culture-based tests

Non-culture-based tests		
1,3-β-d-glucan (BDG)*	detection of (1–3)-beta-d-Glucan (BDG), a pan-fungal (incl *Candida* and *Aspergillus*) cell wall	Sensitivity ~ 75–80% Specificity ~ 60–85%
Candida mannan and anti-mannan*	Detection of mannan antigen (MAg) (a cell wall component) and anti-mannan IgG antibodies (Anti-Mn) in serum	Combined MAg and Anti-Mn Sensitivity ~ 79–87% Specificity ~ 80–90%
Candida albicans germ tube antibody (CAGTA)*	Detects antibodies to antigens located on the cell wall of *Candida albicans*	Sensitivity ~ 59–73% Specificity ~ 58–88%
Multiplex *Candida* real time polymerase chain reaction (PCR)*	Detection of *Candida* DNA by polymerase chain	Sensitivity ~61–95%
T2-magnetic resonance *Candida* assay (T2Candida)*	Miniaturized magnetic resonance technology to identify and speciate whole *Candida* cells of the five most common *Candida*: *albicans, glabrate, parapsilosis, tropicalis* and *krusei*	Sensitivity ~88–94% Specificity ~93–95%

Candida spp., Aspergillus spp., Furarium spp, PJP

lack of validation and standardization,>5 colony-forming unit (CFU)/mL

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The T2 Magnetic Resonance (T2MR)

FDA approved in 2014 for the diagnosis of candidemia

Nuclear magnetic resonance +PCR molecular assay

Figure 1. T2Dx Instrument.

- 只能驗以下**5**株

✓**3 CFU/mL for C. albicans and C. tropicalis**

✓ **2 CFU/mL for C. krusei and C. glabrata**

✓ **1 CFU/mL for C. parapsilosis**

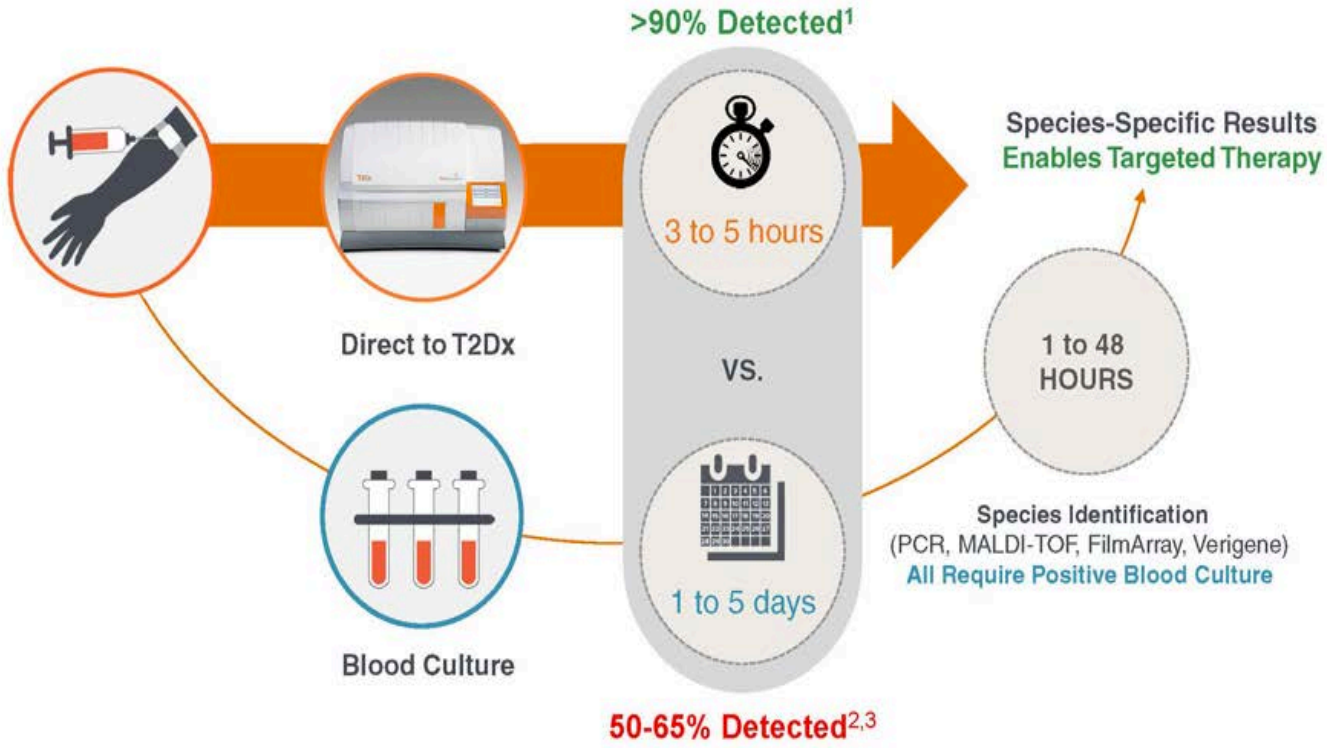
J. Fungi 2018, 4, 45; doi:10.3390/jof4020045

The T2 Magnetic Resonance (T2MR)

T2MR: Establishing a New Standard in Sepsis Pathogen Detection

T2Biosystems®

T2Sepsis diagnostics provide a faster and more accurate solution for sepsis pathogen detection



1. Mylonakis, E., Clancy, C. J., Ostrosky-Zeichner, L., Garey, K. W., Alangaden, G. J., Vazquez, J. A., ... & Zervou, F. N. (2015). T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. *Clinical Infectious Diseases*, ciu959.
2. Clancy, C. J., & Nguyen, M. H. (2013). Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clinical infectious diseases, 56(9), 1284-1292.
3. Cockerill III, F. R., Wilson, J. W., Vetter, E. A., Goodman, K. M., Torgerson, C. A., Harmsen, W. S., ... & Wilson, W. R. (2004). Optimal testing parameters for blood cultures. Clinical Infectious Diseases, 38(12), 1724-1730.

The T2 Magnetic Resonance (T2MR)

- T2MR demonstrated a sensitivity and specificity of 91.1% and 98.1%
- T2MR is expected to allow timely initiation of antifungal therapy and help with anti-fungal stewardship

J. Fungi 2018, 4, 45; doi:10.3390/jof4020045

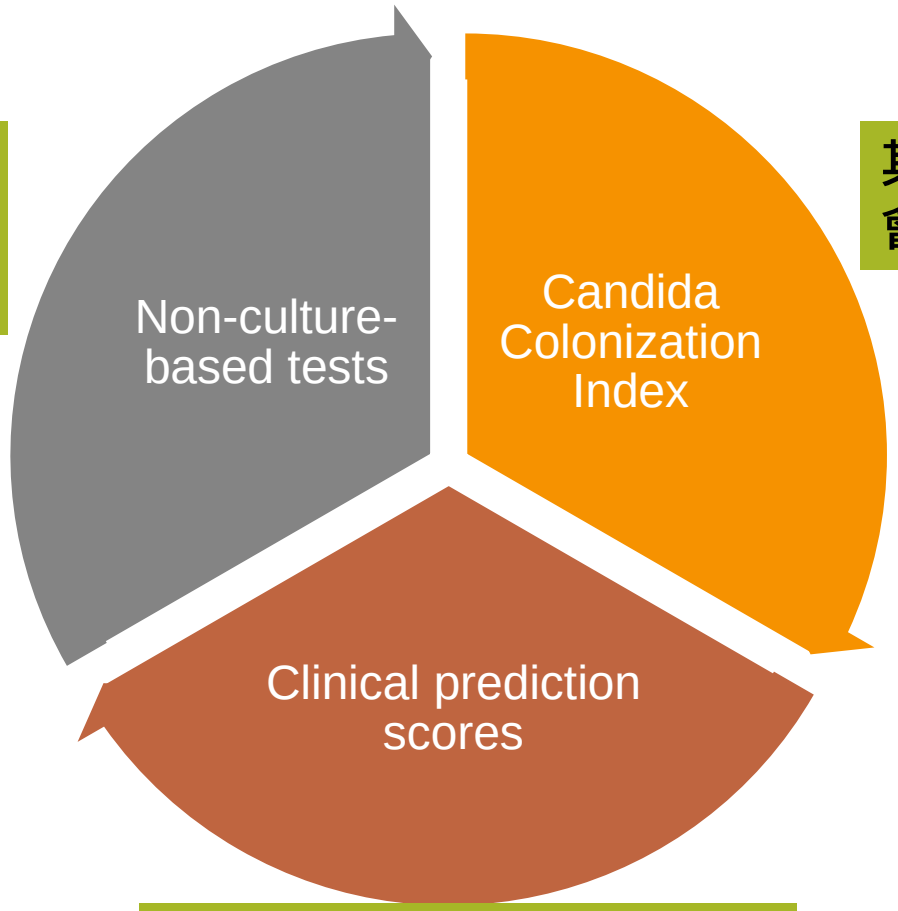
What conventional and non-culturebased microbiological techniques are available for diagnosing IC?

The panel agrees that PCR-based tests and miniaturized-magnetic resonance-based technology perform well. However, the lack of standardization and of large-scale validation precludes their clinical use without ancillary testing (weak recommendation, low quality of evidence)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Three tools for early identification of IC
早期診斷

Sensitivity/specificity不高
T2MR明日之星

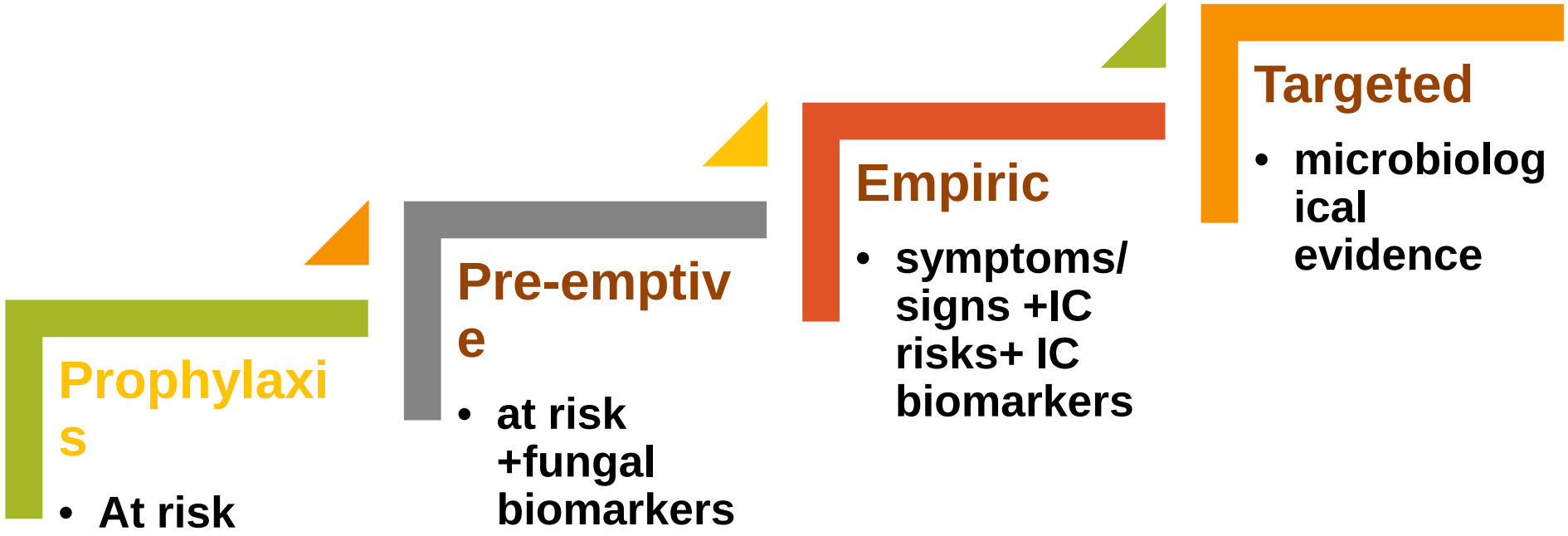


其中只有約5-30%會真正變成IC

Positive predictive value (PPV)低

C. Logan, et al. Intensive Care Med 2020

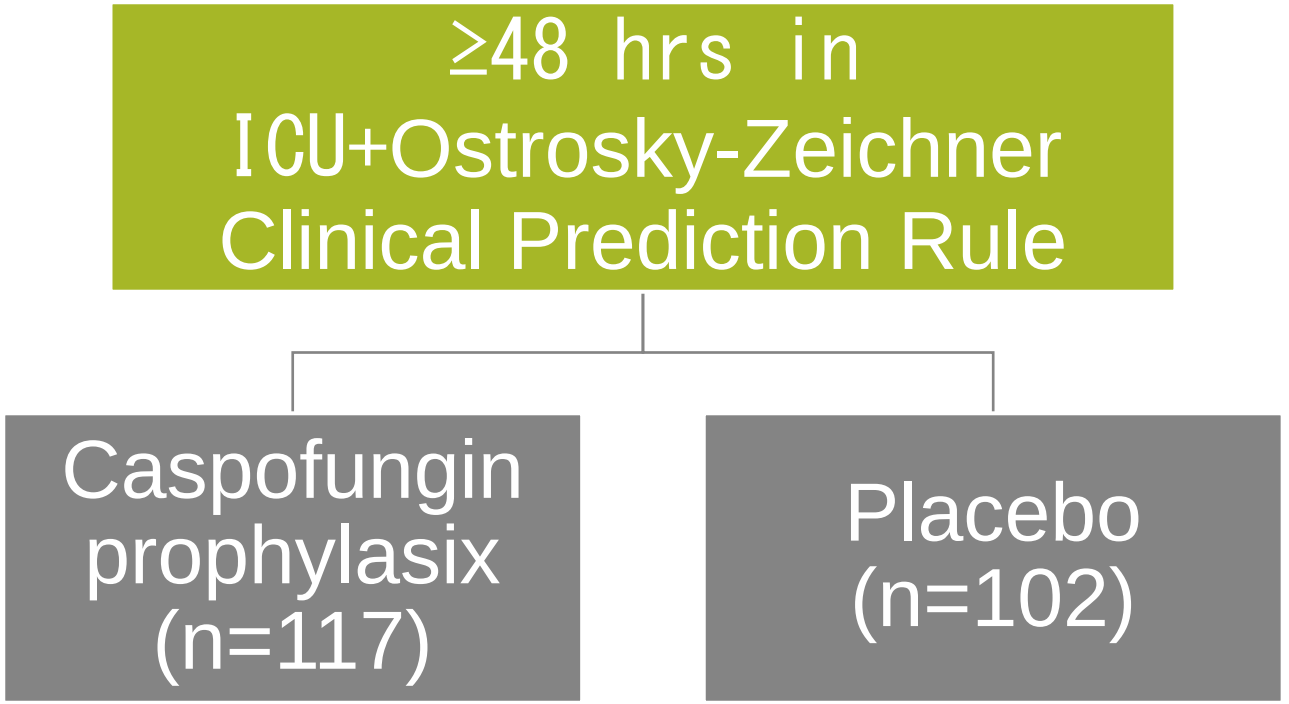
Antifungal prescribing strategies



ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

MSG-01：caspofungin prophylaxis

multicenter, randomized, double-blind, placebo-controlled study, USA



Luis Ostrosky-Zeichner,et al. Clinical Infectious Diseases 2014;58(9):1219–26

Caspofungin在ICU high risk 病人預防性使用，未來產生IC incidence, mortality與placebo相當

Table 3. Study Endpoints and Outcomes

	Prophylaxis/MITT Population		
Variable	Caspofungin (n = 102)	Placebo (n = 84)	*P* Value
Incidence of proven or probable IC by DRC, %	9.8	16.7	.14
Incidence of proven IC by DRC, %	1.0	4.8	.11
Use of antifungals within 7 d EOT, %	13.7	17.9	.35
All-cause mortality within 7 d EOT, %	16.7	14.3	.78

Abbreviations: DRC, data review committee; EOT, end of therapy; IC, invasive candidiasis; MITT, modified intention to treat.

Luis Ostrosky-Zeichner,et al. Clinical Infectious Diseases 2014;58(9):1219–26

Should antifungal prophylaxis be used in critically ill patients?

The panel recommends against the routine and universal administration of antifungal prophylaxis in critically ill patients (weak recommendation, moderate quality of evidence)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

IFI prophylaxis

Table 1. Antifungals approved for IFI prophylaxis

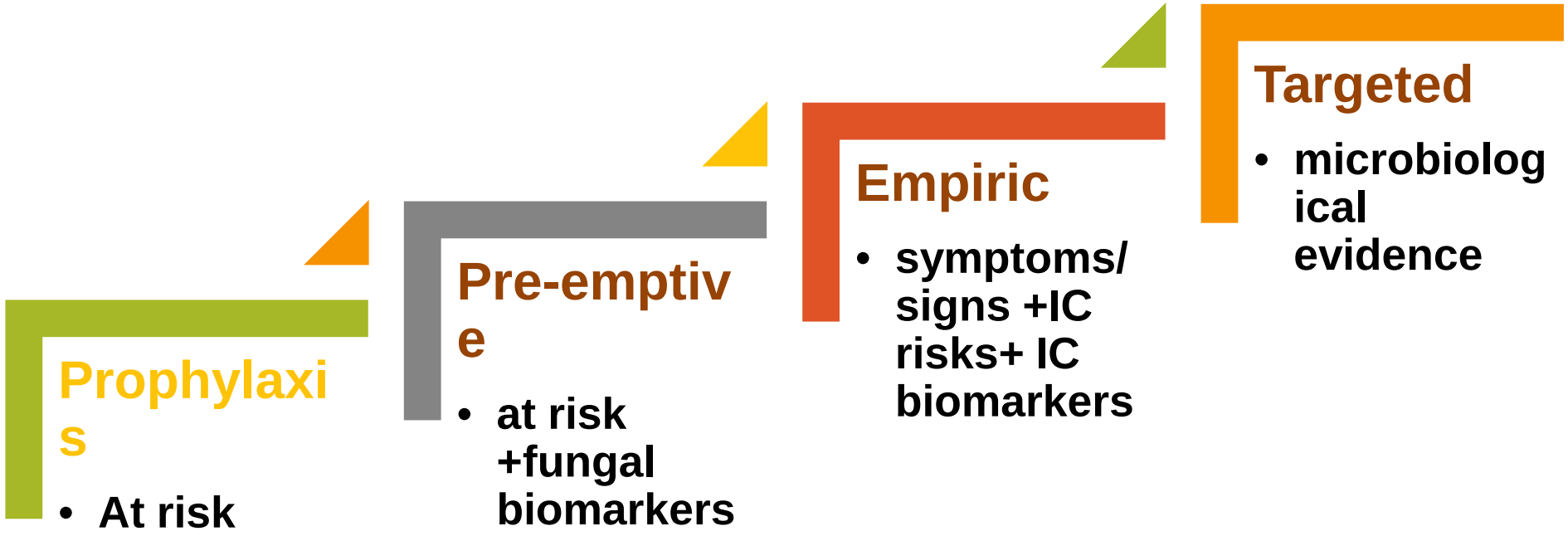
Parameter	Fluconazole	Posaconazole	Micafungin
FDA-approved indication	Prevention of candidiasis in patients undergoing HCT receiving cytotoxic chemotherapy and/or radiation therapy	Prevention of invasive *Aspergillus* and *Candida* infections in patients at high risk due to immunocompromise, such as HCT recipients with GvHD or those with haematological malignancies and prolonged chemotherapy-associated neutropenia	Prevention of *Candida* infections in patients undergoing HCT
Year approved for any indication	1992	2006 (suspension); 2013 (delayed-release tablet); 2014 (iv solution)	2006
Generic	Yes	No	No
Doses and formulations	Oral tablet: 50 mg, 100 mg, 150 mg, 200 mg Oral suspension: 10 mg/mL (35 mL), 40 mg/mL (35 mL) iv solution: 100 mg (50 mL), 200 mg (100 mL), 400 mg (200 mL)	Oral suspension: 40 mg/mL (105 mL) Delayed-release tablet: 100 mg iv solution: 300 mg (16.7 mL)	iv solution for reconstitution: 50 mg, 100 mg

J Antimicrob Chemother 2018; 73 Suppl 1: i60–i72

Condition	Antifungal	Duration
Acute leukaemia/MDS	Posaconazole[a] delayed-release tablets OR Micafungin iv[b]	Starting 24–48 h after chemotherapy until neutrophil recovery
Autologous HCT	Fluconazole 400 mg orally daily[c] OR Micafungin iv[d] **PJP prophylaxis** Trimethoprim/sulfamethoxazole[e]	From admission until neutrophil recovery, off antibiotics, off short course steroids (<3 weeks) From day +30 until 6 months post HCT
Allogeneic HCT	Peri-engraftment, all patients Micafungin iv daily Switch to a mould-active azole[f] by day+7 or when steady-state levels of immunosuppressants are reached[g] Post engraftment • **High risk for mould[h]** Voriconazole OR Posaconazole delayed release tablets • **Low risk for mould** Fluconazole 400 mg po daily **PJP prophylaxis, all patients** Trimethoprim/sulfamethoxazole[i]	From day of admission until neutrophil engraftment Until at least day +75 and cessation of immunosuppression Until day +30-75 Start ~day +21 until immune reconstitution

J Antimicrob Chemother 2018; 73 Suppl 1: i60–i72

Antifungal prescribing strategies



ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

INTENSE trial

Randomized, double-blind, placebo-controlled trial, multi-center Europe and Israel

Community or nosocomially acquired intra-abdominal infection requiring surgery and ICU stay

preemptive antifungal therapy，開刀後48hrs內(NAI),72-120hrs(CAI)給藥

Micafungin 100mg/d (n=117)

Placebo (n=124)

Wolfgang Knitsch,et al. Clinical Infectious Diseases ® 2015;61(11):1671–8

在IAI開刀後預防性給micafungin，未來發生IC incidence,與median time to IC機率與placebo相當

Table 2. Incidence of Invasive Candidiasis in the Full Analysis Set and Per-Protocol Set for All Patients

IC Incidence	Patient With IC/Total Patients, No. (%)		
	Placebo	Micafungin[b]	Treatment Difference (Micafungin – Placebo), % (95% CI)
All patients (FAS)			
IDRB-confirmed IC	11/124 (8.9)	13/117 (11.1)	2.24 (–5.52 to 10.20)
Investigator-confirmed IC[a]	20/121 (16.5)	16/116 (13.8)	–2.74 (–11.92 to 6.56)
Any-confirmed IC[a]	20/120 (16.7)	17/115 (14.8)	–1.88 (–11.24 to 7.58)
All patients (PPS)			
IDRB-confirmed IC	5/88 (5.7)	5/79 (6.3)	0.65 (–7.17 to 8.95)

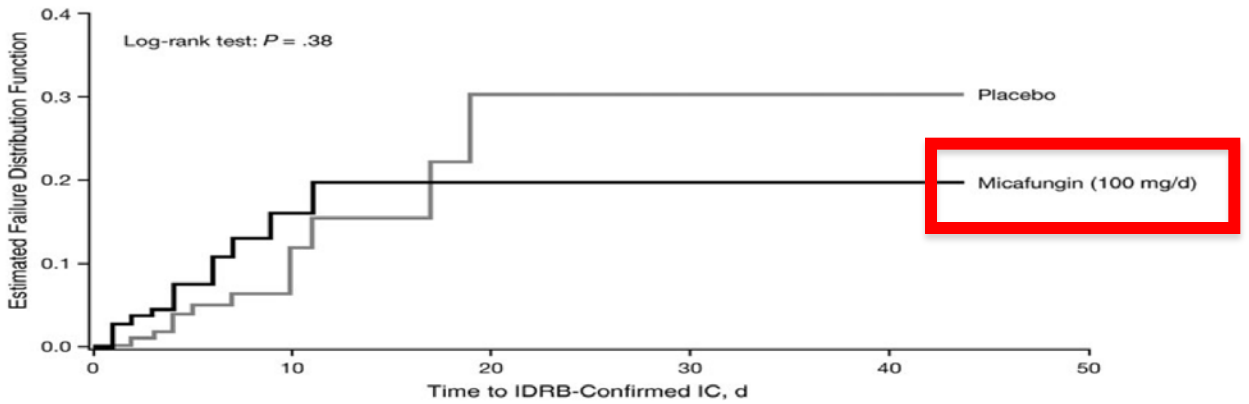


Figure 2. Kaplan–Meier failure curves of time to independent data review board (IDRB)-confirmed invasive candidiasis (IC) (full analysis set).

Wolfgang Knitsch,et al. Clinical Infectious Diseases ® 2015;61(11):1671–8

Should pre-emptive therapy be used in critically ill patients?

Criteria for starting empirical antifungal therapy in nonneutropenic patients were poorly defined

→Pre-emptive therapy subsequently disappeared from the recently revised 2016 IDSA guidelines

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

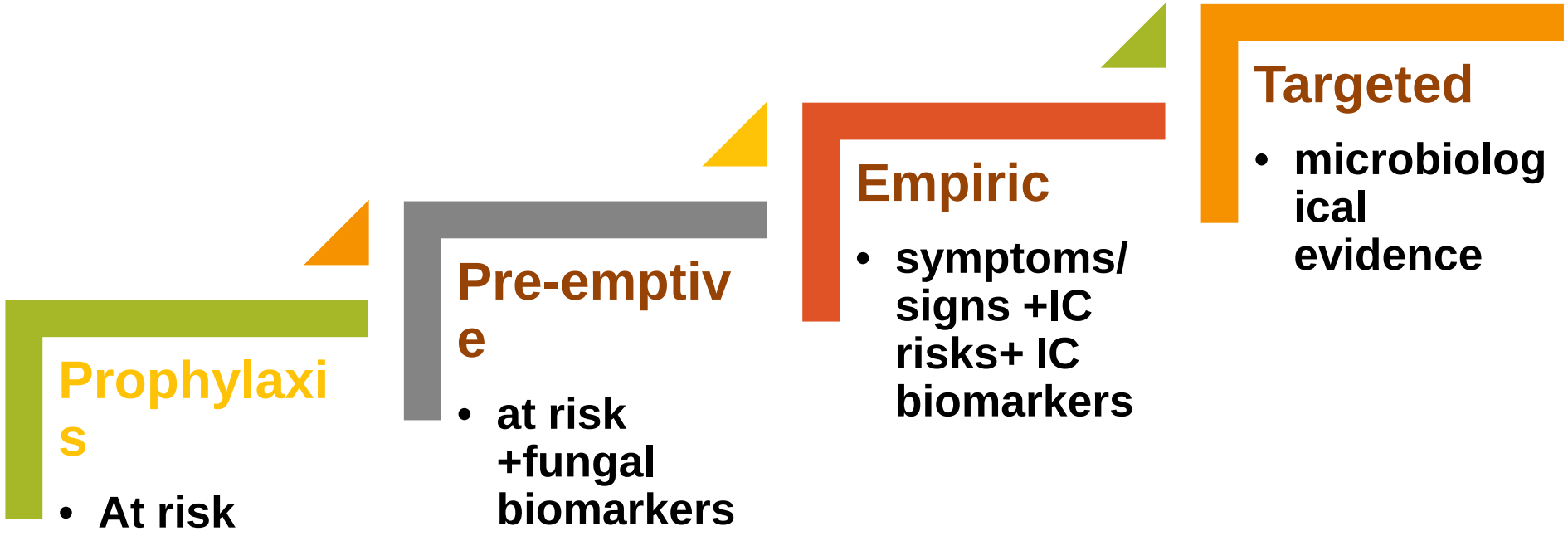
Should pre-emptive therapy be used in critically ill patients?

The panel does not recommend the use of pre-emptive antifungal therapy in critically ill patients (weak recommendation, low-quality evidence)

→more studies are needed

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

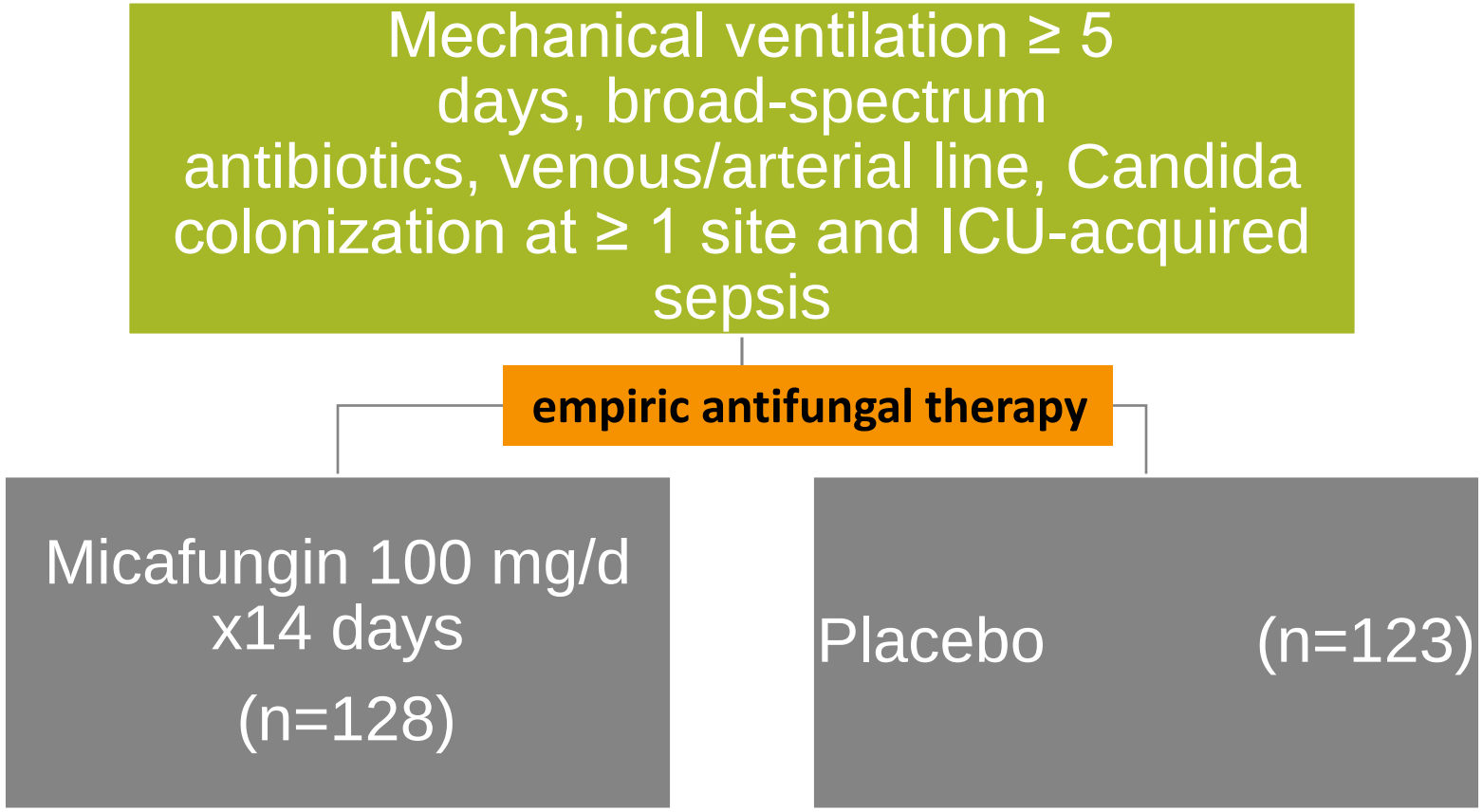
Antifungal prescribing strategies



ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

EMPIRICUS trial

Multicenter double-blind placebo-controlled study, France

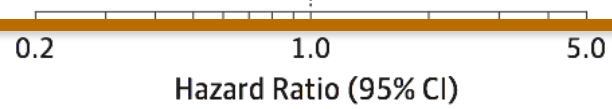


Timsit JF,et al.JAMA. 2016;316(15):1555-1564..

Day28, fungal infection free survivial rate micafungin (68%) VS placebo (60%)

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo				
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	Favors Placebo / Favors Micafungin	P Value
All patients	87	128	74	123	1.35 (0.87-2.08)		.18
SOFA score							
≤8	51	66	52	68	1.11 (0.53-2.33)		.78
>8	36	62	22	55	1.69 (0.96-2.94)		.07
Admission category							
Surgical	22	34	16	31	1.56 (0.67-3.70)		.64
Medical	65	94	58	92	1.43 (0.83-2.50)		.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)		.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)		.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)		.21
(1-3)-ß-D-glucan, pg/mL[c]							
>250	14	21	14	25	1.52 (0.47-5.00)		.48
>80	58	91	47	84	1.41 (0.85-2.33)		.19
≤80	29	37	27	39	0.98 (0.30-2.94)		.97

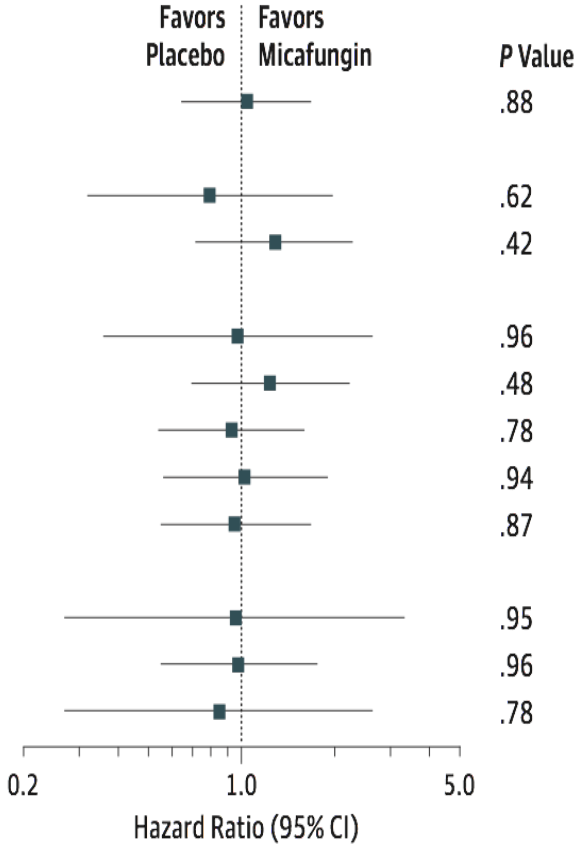


Timsit JF,et al.JAMA. 2016;316(15):1555-1564..

Day 28兩組死亡率相當

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	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



Timsit JF,et al.JAMA. 2016;316(15):1555-1564..

Which patients should receive empirical antifungal treatment?

The panel suggests that empirical antifungal therapy might be considered only in patients with septic shock and multi-organ failure (MOF) who have more than 1 extra-digestive site (i.e. urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, operative site) with proven Candida species colonization (strong recommendation, low quality of evidence)

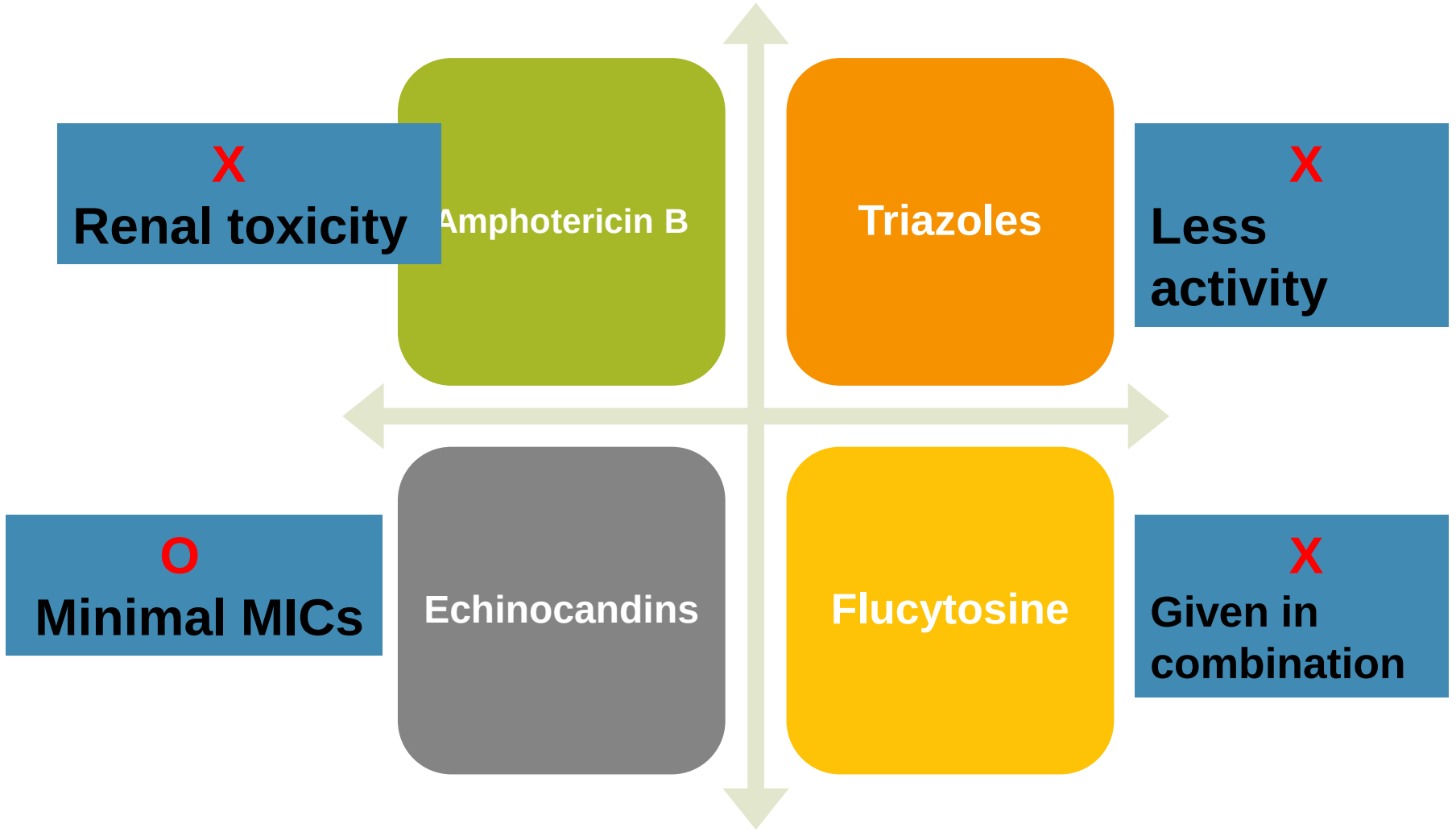
ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Which patients should receive empirical antifungal treatment?

The panel recommends not starting empirical antifungal therapy in patients without septic shock and MOF (strong recommendation, low quality of evidence)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Antifungal agents

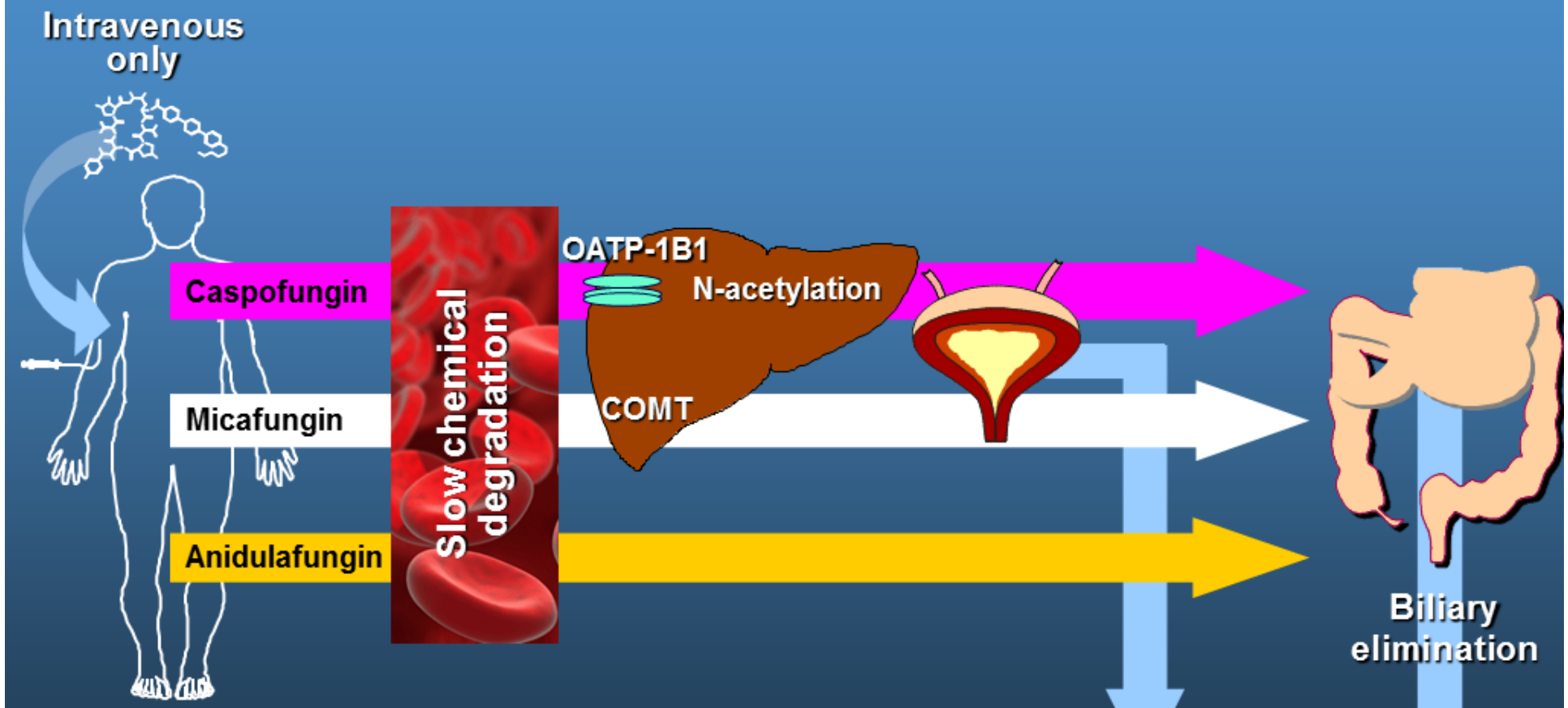


Echinocandins

- Preferred agents for most episodes of candidemia and invasive candidiasis (exception of CNS, eye and UTI)
- Strong safety profile, convenience, early fungicidal activity
- The emergence of azole-resistant Candida species
- *C. parapsilosis*: less responsive to the echinocandins

2016 IDSA guidelines

Anidulafungin metabolism and elimination differs from other echinocandins



OATP=Organic anion-transporting polypeptide.

COMT=Catechol-O-methyltransferase.

Eraxis (anidulafungin IV)

Data from the TAW package insert of Eraxis/ Mycamine/ Cancidas.

ERA-FM-1008005

Echinocandin Antifungals	Caspofungin	Anidulafungin	**MYCAMINE (Micafungin)**
儲存	冷藏2-8保存	冷藏2-8保存	**室溫15-30保存**
Loading Dose	需要	需要	不需要
稀釋總輸液量 (成人)	將調配過之適量藥物稀釋到250mL	100 mg為130mL 200 mg為260mL (負荷劑量)	100 mL 0.9%氯化鈉或5%葡萄糖注射液
用法用量及輸注時間 (成人)	一天一次	一天一次	一天一次
	起始劑量70mg 約60分鐘	負荷劑量200mg 約180分鐘	不需負荷劑量 約60分鐘
	維持劑量50mg 約60分鐘	維持劑量100mg 約90分鐘	
重度腎功能不全	不須調整劑量	不須調整劑量	無須調整劑量
重度肝功能不全	尚無嚴重肝功能不全成人患者的臨床使用經驗	不須調整劑量	不須調整劑量

Micafungin® 藥品仿單；Anidulafungin® 藥品仿單；Caspofungin® 藥品仿單。

Risk factors for mortality in candidemia

22 tertiary care medical centers in Brazil, 2003-2014
640 candidemia patients in ICU

Table 5 Factors associated with 30-day mortality[a] among 640 ICU patients with candidemia by multivariate analysis

Variable	Odds ratio	95 % Confidence interval	*p* value
Receipt of corticosteroids	4.00	1.98–8.13	<0.001
Period 1	2.49	1.22–5.08	0.01
APACHE II score[b]	1.05	1.01–1.09	0.03
Age	1.03	1.01–1.05	0.003
Treatment with an echinocandin	0.20	0.07–0.58	0.003

2003–2007, period 1;
2008–2012, period 2

Arnaldo L. Colombo,Intensive Care Med (2014) 40:1489–1498

What is the preferred first-line empirical therapy in a non-neutropenic critically ill patient with invasive candidiasis?

The panel recommends that echinocandins should be used as the first treatment option in critically ill patients with septic shock and MOF with IC (weak recommendation, low quality of evidence)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

What is the preferred first-line empirical therapy in a non-neutropenic critically ill patient with invasive candidiasis?

The panel recommends that fluconazole should be considered the first treatment option for critically ill patients with low severity of disease (i.e. without septic shock and/or MOF) in settings with low fluconazole resistance (strong recommendation, low quality of evidence)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

In non-neutropenic critically ill patients, does de-escalation of antifungal therapy yield similar outcomes (in terms of clinical success and mortality) as ongoing treatment with first-line antifungal agents?

The panel recommends de-escalating from an echinocandin to fluconazole when the patient is clinically stable and the isolate is susceptible to fluconazole (Strong recommendation, moderate quality of evidence.)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

In non-neutropenic critically ill patients, does de-escalation of antifungal therapy yield similar outcomes (in terms of clinical success and mortality) as ongoing treatment with first-line antifungal agents?

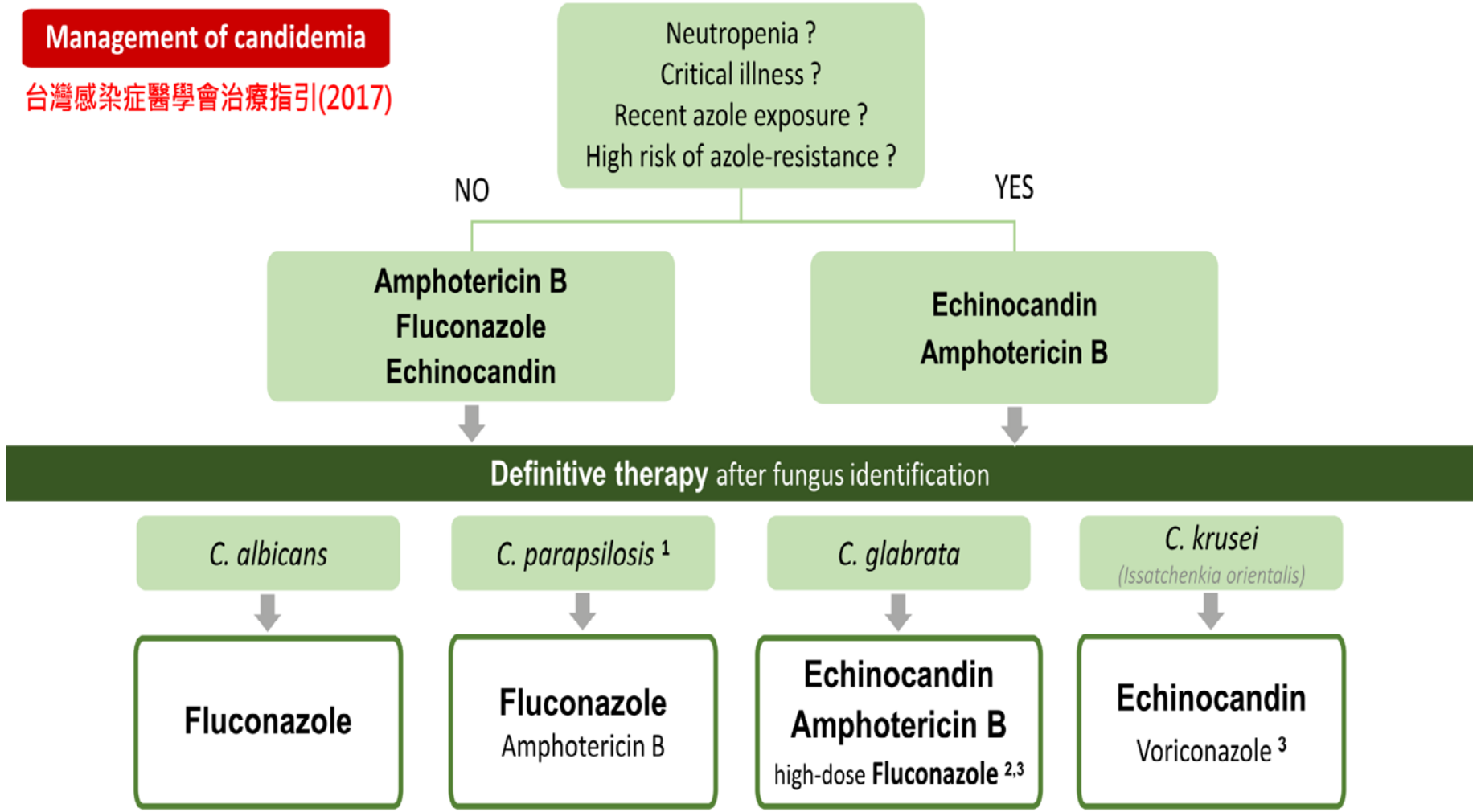
1. **Echinocandins should not be de-escalated if central venous catheter or any other foreign material has not been removed**

2. **Antifungal treatment should be stopped in patients with suspected (but not proven) IC with negative blood cultures and/or other negative culture specimens taken from suspected infectious foci before starting antifungal therapy (best practice statement)**

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Management of candidemia

台灣感染症醫學會治療指引(2017)



1. If an echinocandin is used initially, consider changing to FCZ.
2. Continue FCZ if the patient clinically improves, and whose follow-up blood culture results are negative.
3. Changing to FCZ or VCZ is not recommended without confirmation of isolate susceptibility.

J Microbiol Immunol Infect. 2017 Jul 25. pii: S1684-1182(17)30146-9.

What is the recommended duration of antifungal treatment in patients with candidemia and IC?

1. **The panel recommends that candidemia should be treated for at least 14 days after the first negative blood culture (strong recommendation, low quality of evidence)**
2. **The panel recommends that adequate source control (catheter removal, appropriate drainage, surgical control) should be performed early, if clinically feasible, in every critically ill patient with IC (strong recommendation, moderate quality of evidence)**

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

What is the recommended duration of antifungal treatment in patients with candidemia and IC?

The panel recommends that in critically ill patients with IC and inadequate source control, the treatment duration for deep-seated infection due to Candida species (including endocarditis) should be individualized and based on a multidisciplinary approach (best practice statement)

ESICM/ESCMID, Intensive Care Med (2019) 45:789–805

Successful treatment of IC