Clinical implications of fungal biofilms

Antwerpen – 29 March 2018

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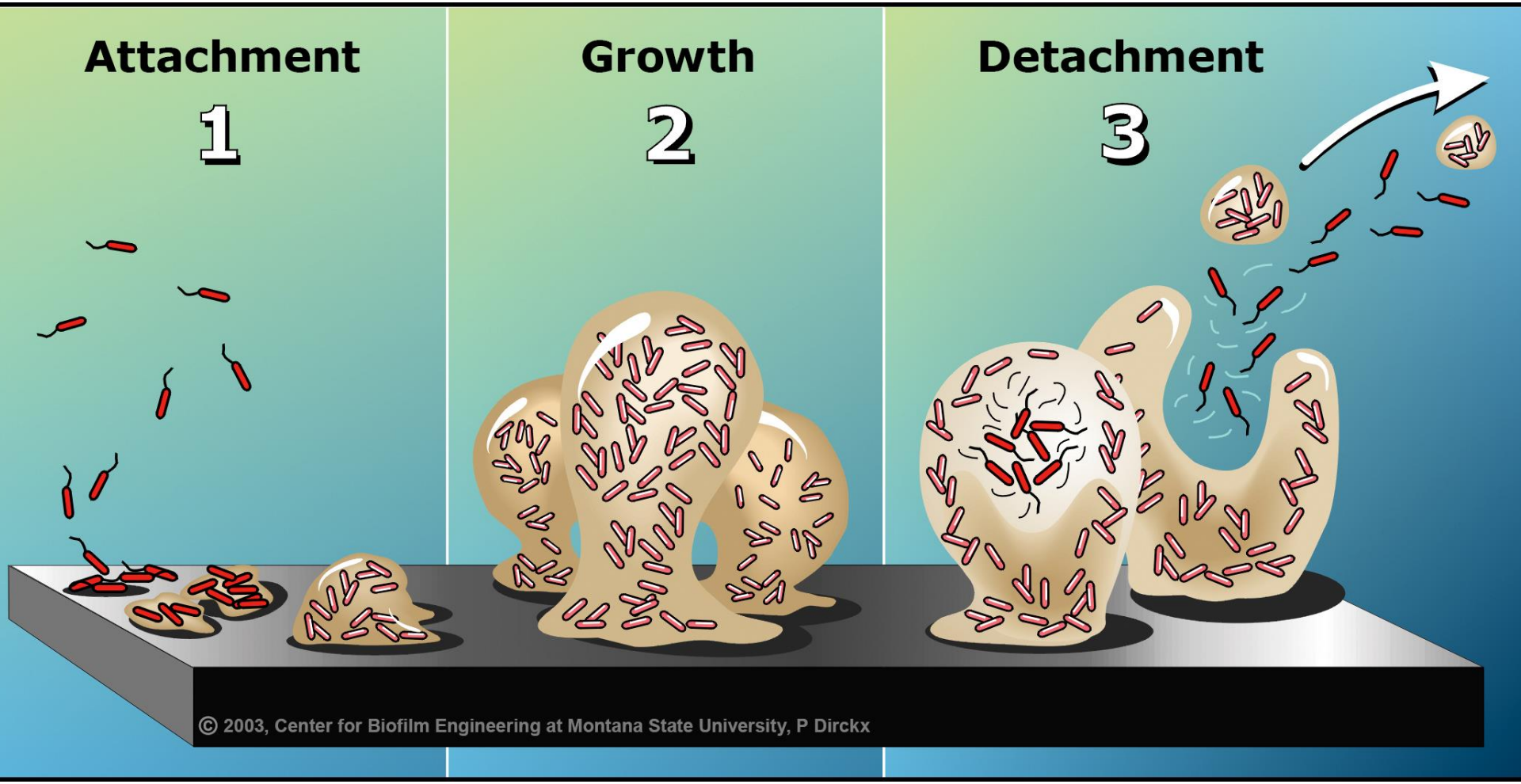
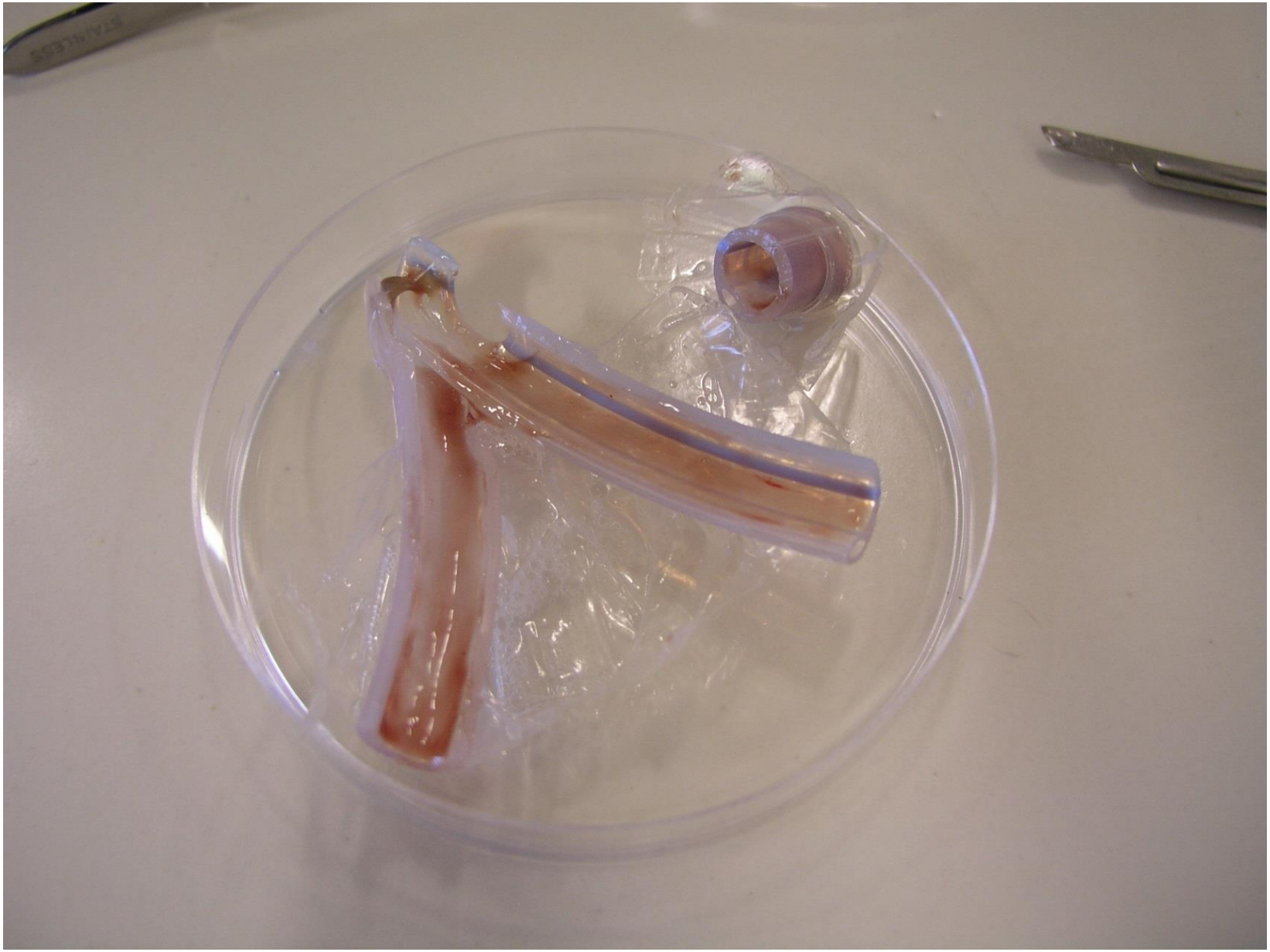
Biofilm formation



Mixed biofilms on endotracheal tubes



Mixed biofilms on endotracheal tubes
Approx. 20% contain *Candida* spp.

Assessment of Microbial Diversity in Biofilms Recovered from Endotracheal Tubes Using Culture Dependent and Independent Approaches

Ilse Vandecandelaere[1]*, Nele Matthijs[1], Filip Van Nieuwerburgh[2], Dieter Deforce[2], Peter Vosters[3], Liesbet De Bus[3], Hans J. Nelis[1], Pieter Depuydt[3], Tom Coenye[1]

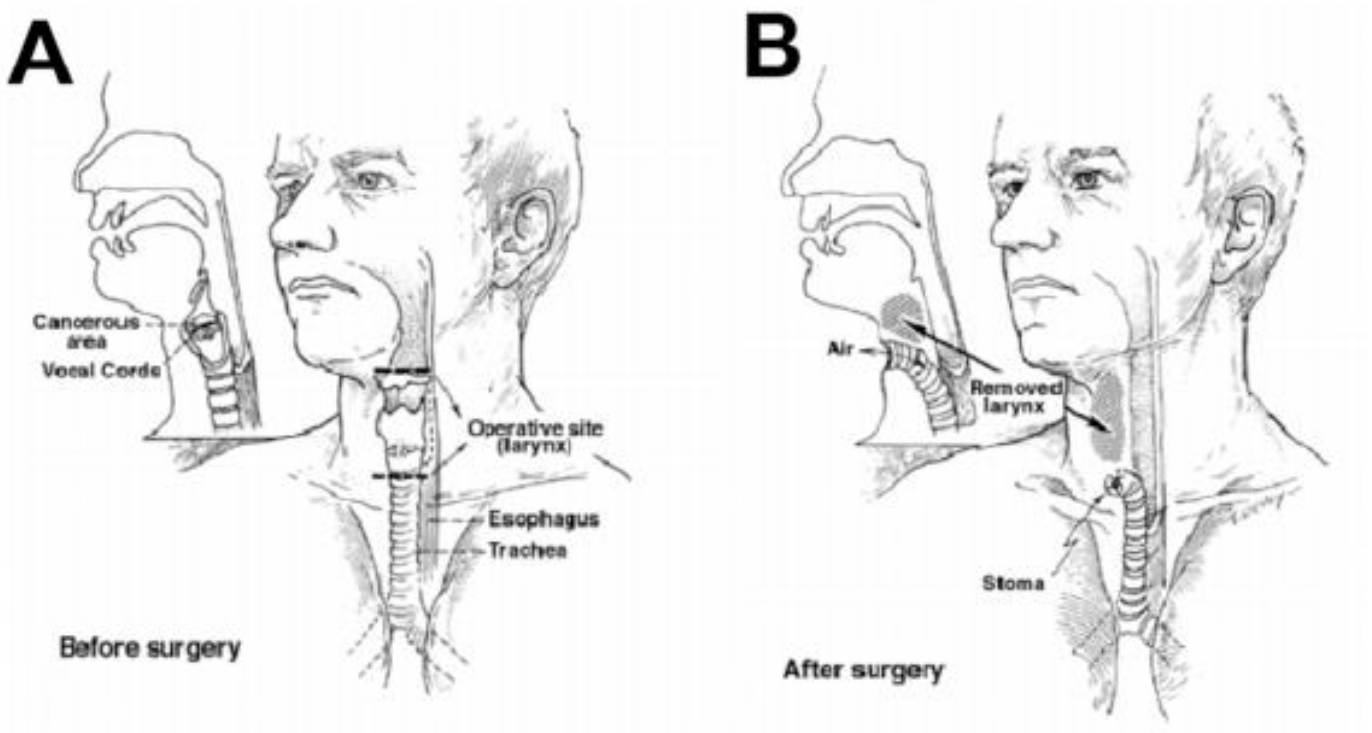
Table 2. Identification results of the ET biofilm flora of patients from whom two tubes were investigated.

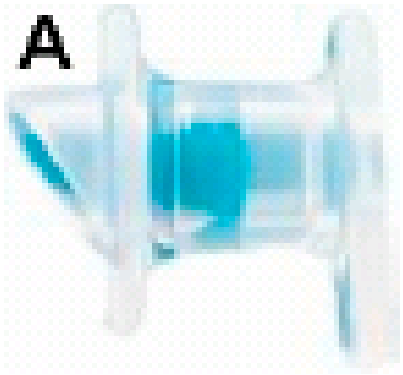
Patient	Sample	Species recovered
1	E01	*E. aerogenes, E. coli, R. ornithinolytica, S. lentus, S. capitis, C. albicans*
	E03	*R. planticola, S. epidermidis, S. xylosus, S. warneri*
24	E25	*S. epidermidis, S. saprophyticus, C. albicans, Candida* spp.
	E32	*S. epidermidis, Candida* spp.
25	E26	*E. coli, S. saprophyticus, S. epidermidis*
	E29	*E. coli*
32	E34	*C. albicans, M. luteus*
	E36	*C. albicans, S. maltophilia*

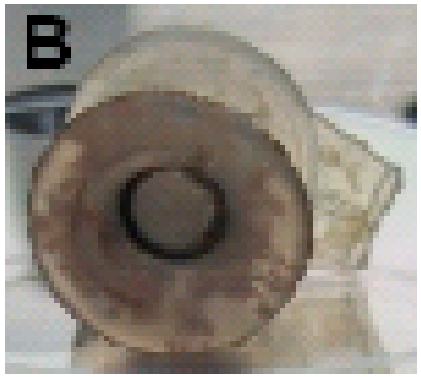
Species recovered in both samples from a given patient are underlined.

doi:10.1371/journal.pone.0038401.t002

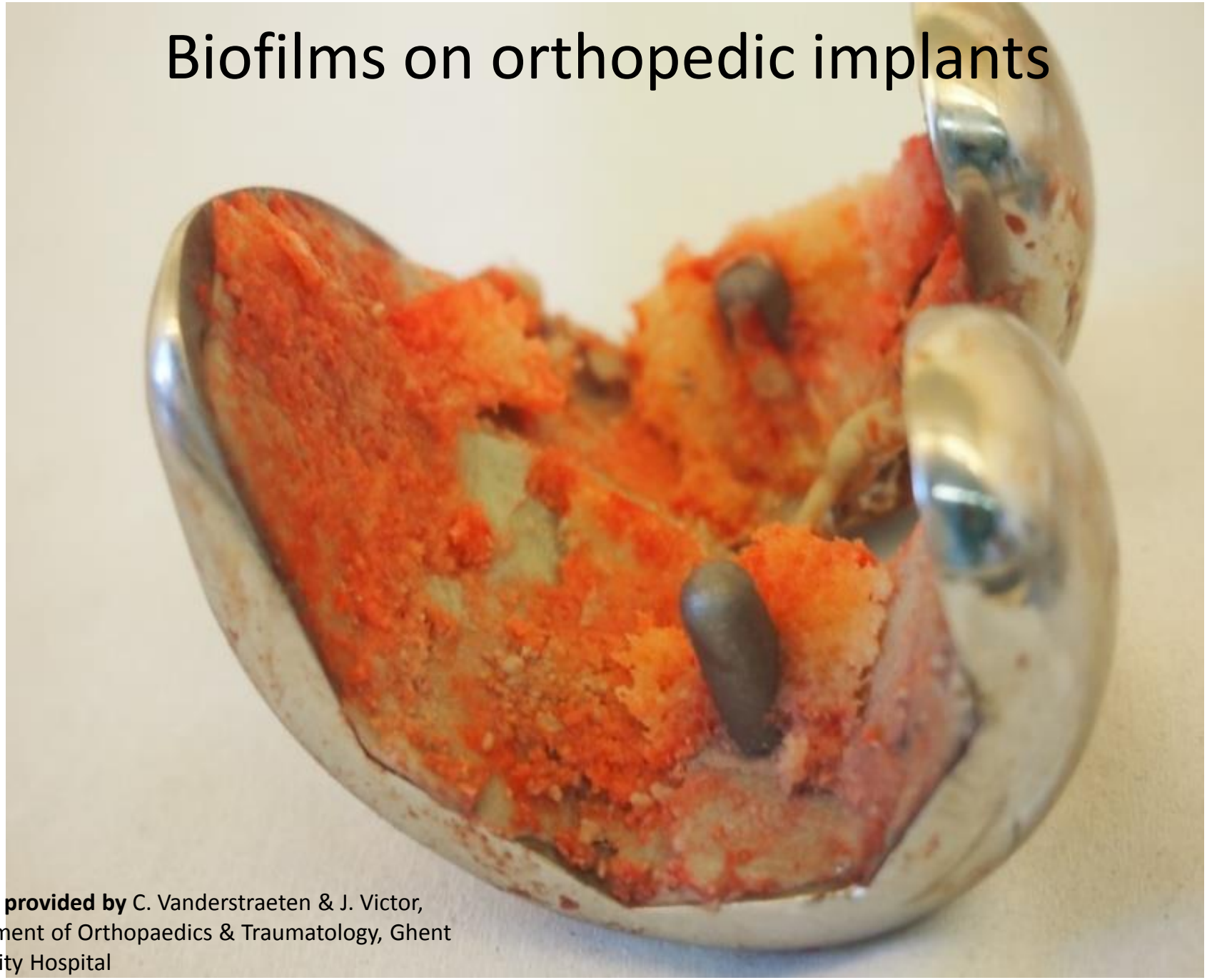
Candida albicans biofilms on voice prostheses



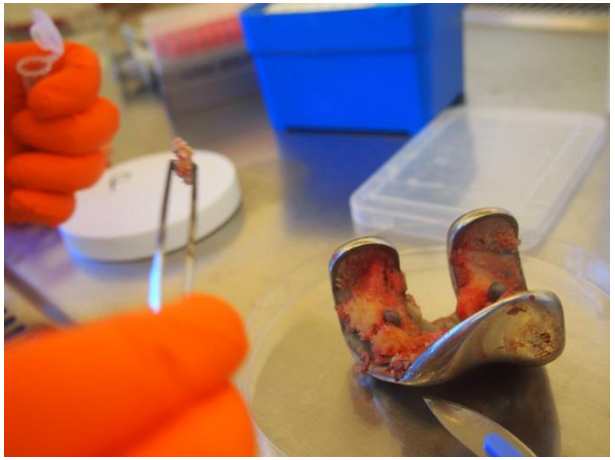




Biofilms on orthopedic implants

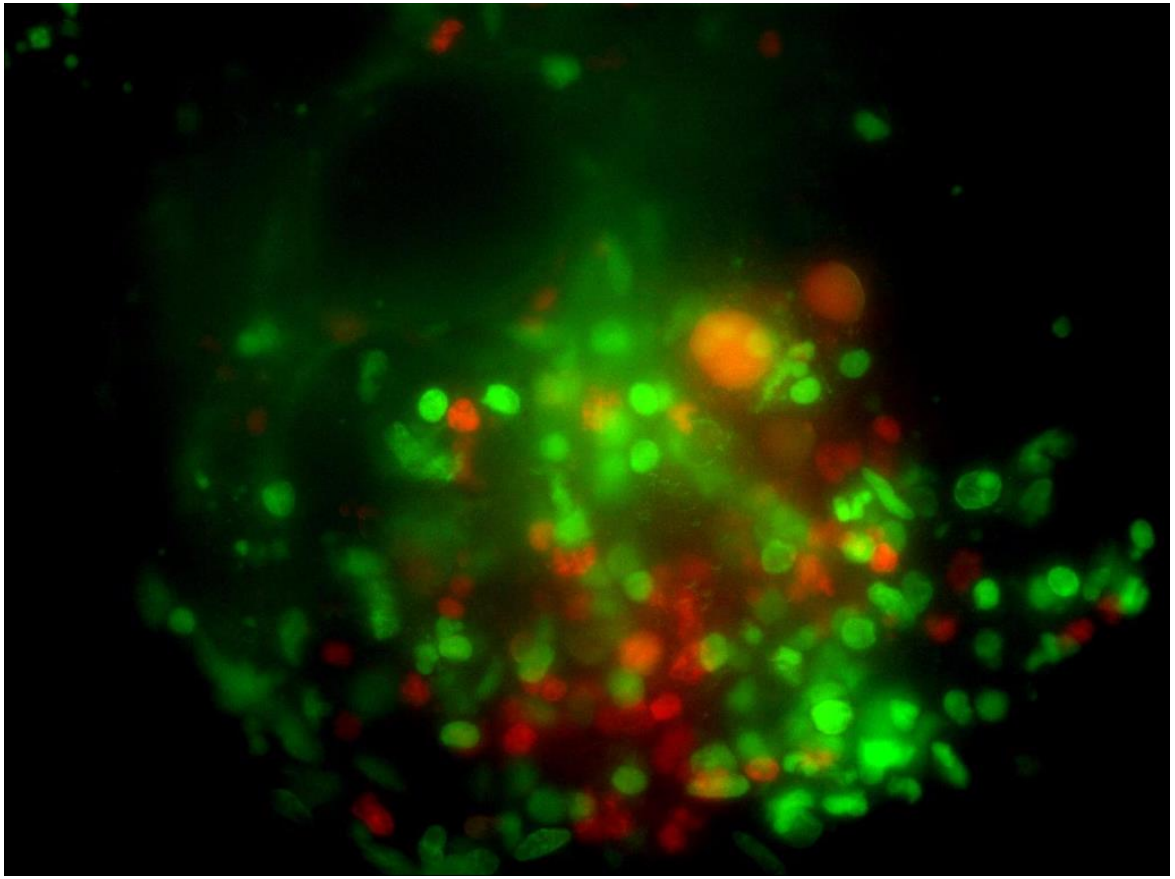


Sample provided by C. Vanderstraeten & J. Victor, Department of Orthopaedics & Traumatology, Ghent University Hospital



Stain with

Live/Dead



Fungal Biofilms, Drug Resistance, and Recurrent Infection

Jigar V. Desai[1], Aaron P. Mitchell[1], and David R. Andes[2]

- *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, …)
- *Aspergillus fumigatus*
- *Cryptococcus neoformans*
- *Trichosporon* sp.

2014

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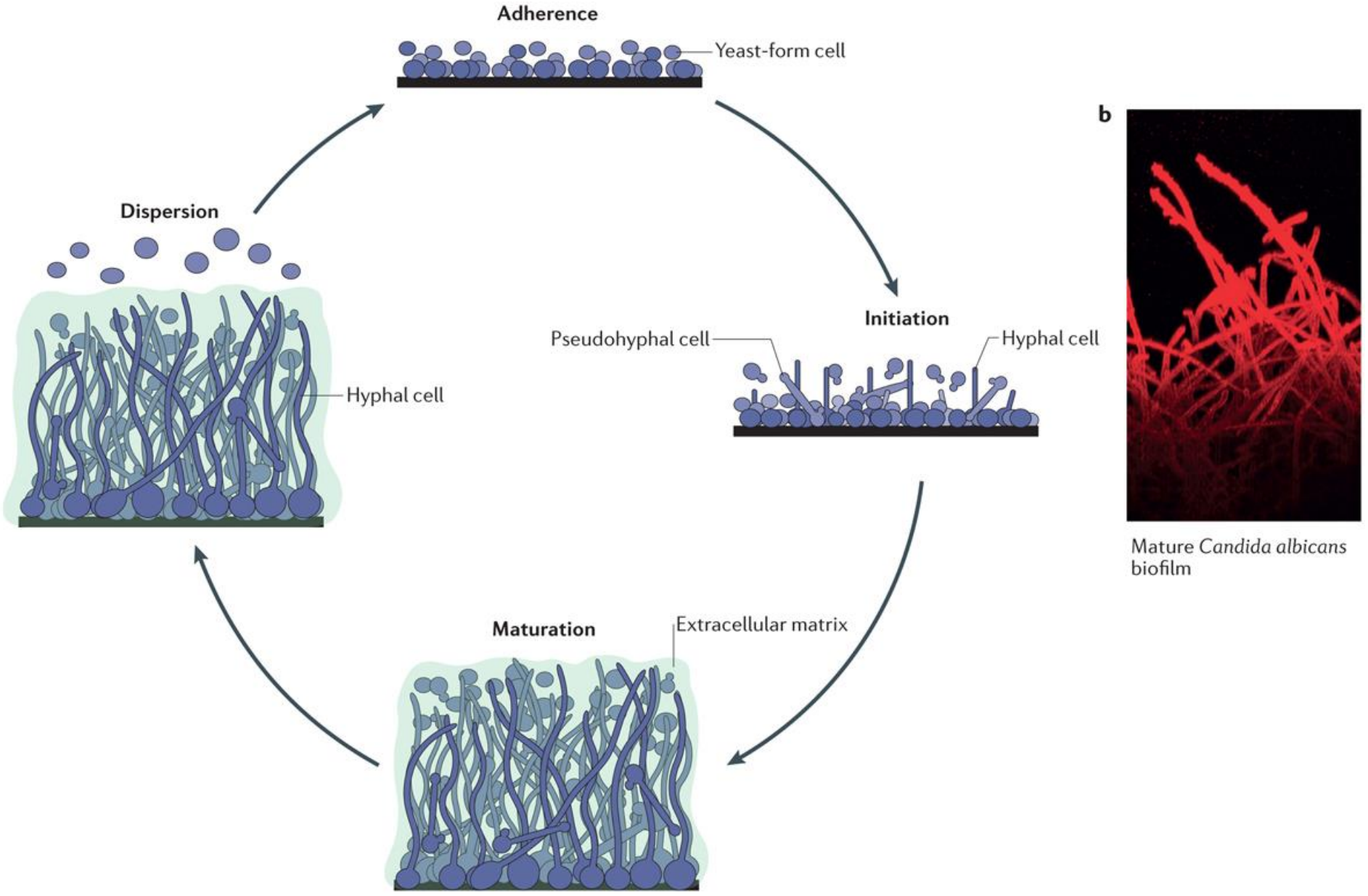
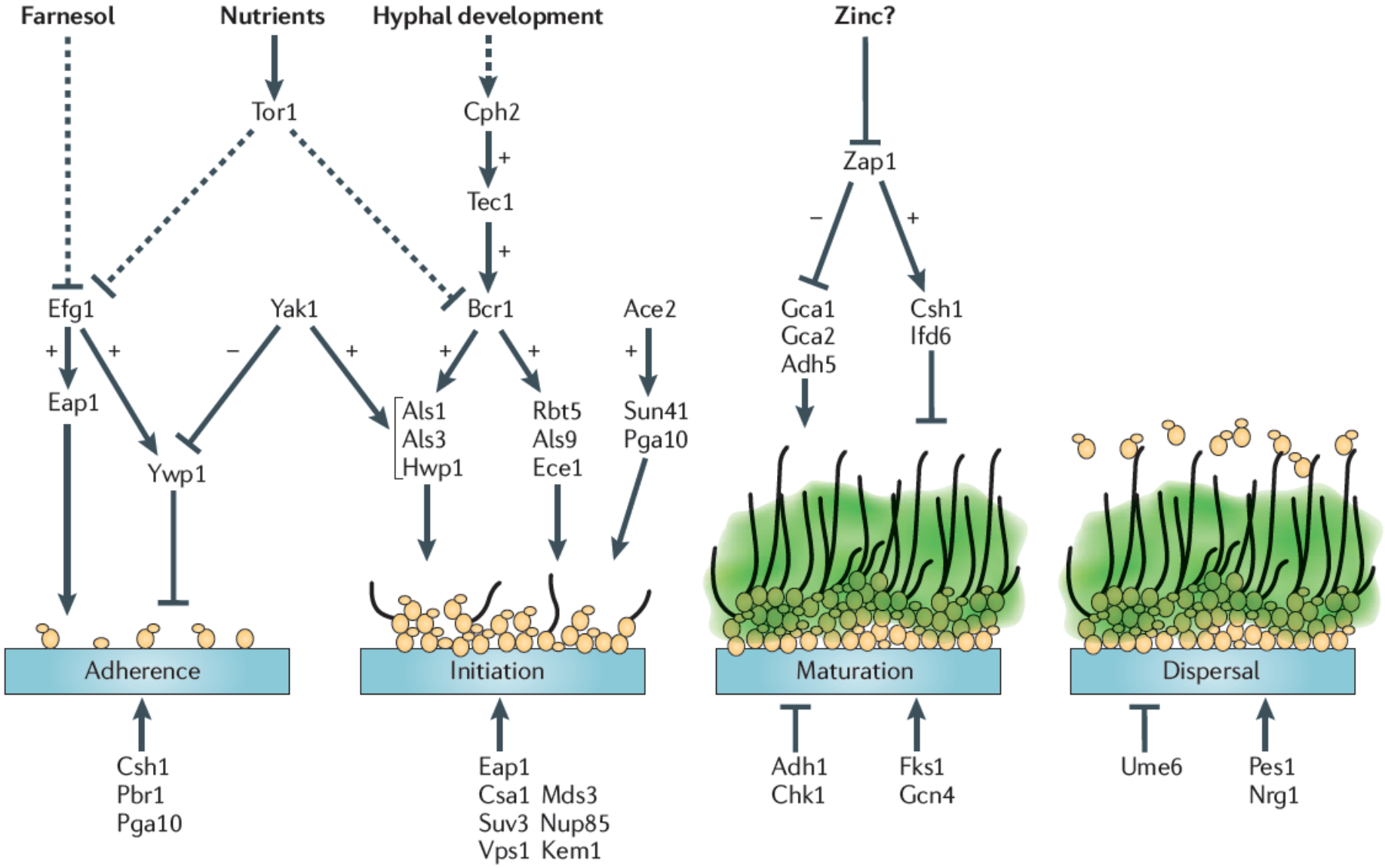
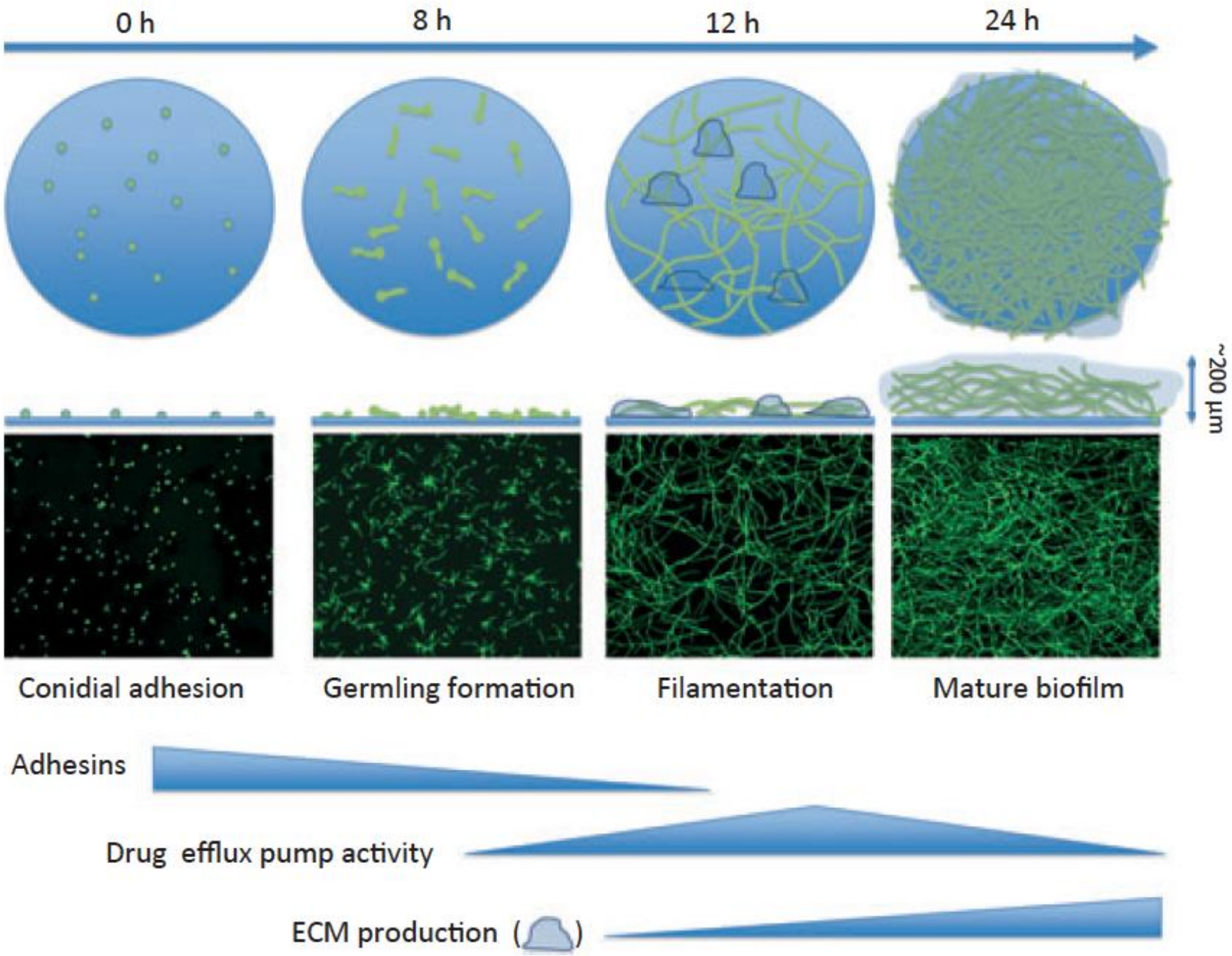


Lohse et al. Nat Rev Microbiol. 2018 Jan; 16(1): 19–31



Finkel and Mitchell, 2011. Nature Reviews in Microbiology



Ramage *et al*, 2011. FEMS Microbiol Lett

Biofilm formation – why do we care?

- Biofilm-related infections occur frequently
- … are difficult to treat
- … leading to failure of therapy
- … ultimately resulting in increased morbidity and mortality

Why do we care about fungal biofilms?

Table 1. Implantable devices in which *Candida* biofilms develop most frequently

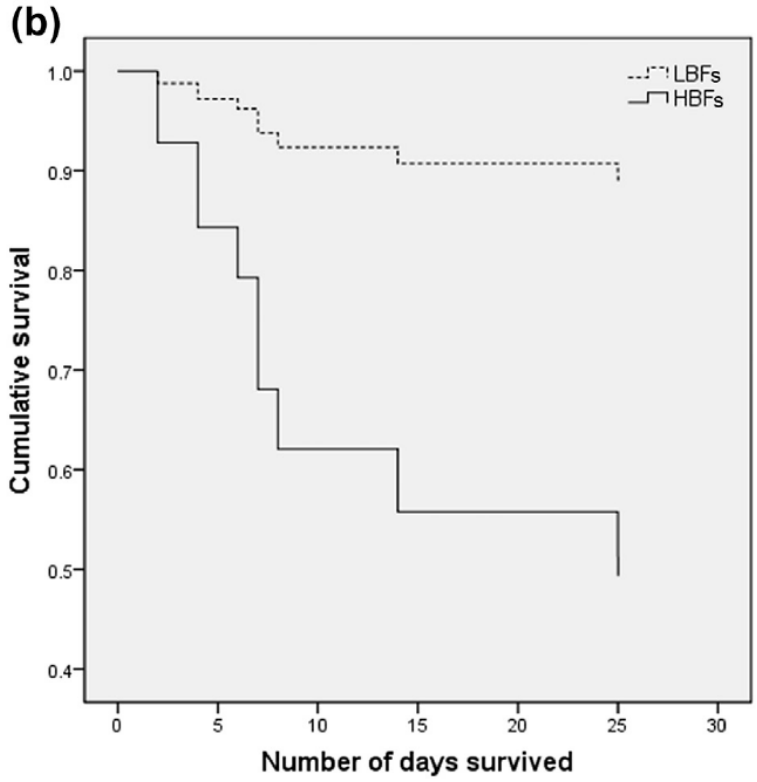
Device	Usage per year	Infection risk (%)	Main *Candida* species
Central and peripheral venous catheters	5 million	3–8	*albicans* *glabrata* *parapsilosis*
Hemodialysis and peritoneal dialysis catheters	240 000	1–20	*albicans* *parapsilosis*
Urinary catheters	Tens of millions	10–30	*albicans* *glabrata*
Endotracheal tubes	Millions	10–25	*albicans*
Intracardiac prosthetic devices	400 000	1–3	*albicans* *glabrata* *parapsilosis* *tropicalis*
Breast implants	130 000	1–2	*albicans*
Prosthetic joints	600 000	1–3	*parapsilosis* *albicans* *glabrata*
Neurosurgical shunts	40 000	6–15	*albicans*
Voice prostheses	Thousands	50–100	*albicans* *tropicalis*
Dentures	> 1 million	5–10	*albicans* *glabrata*

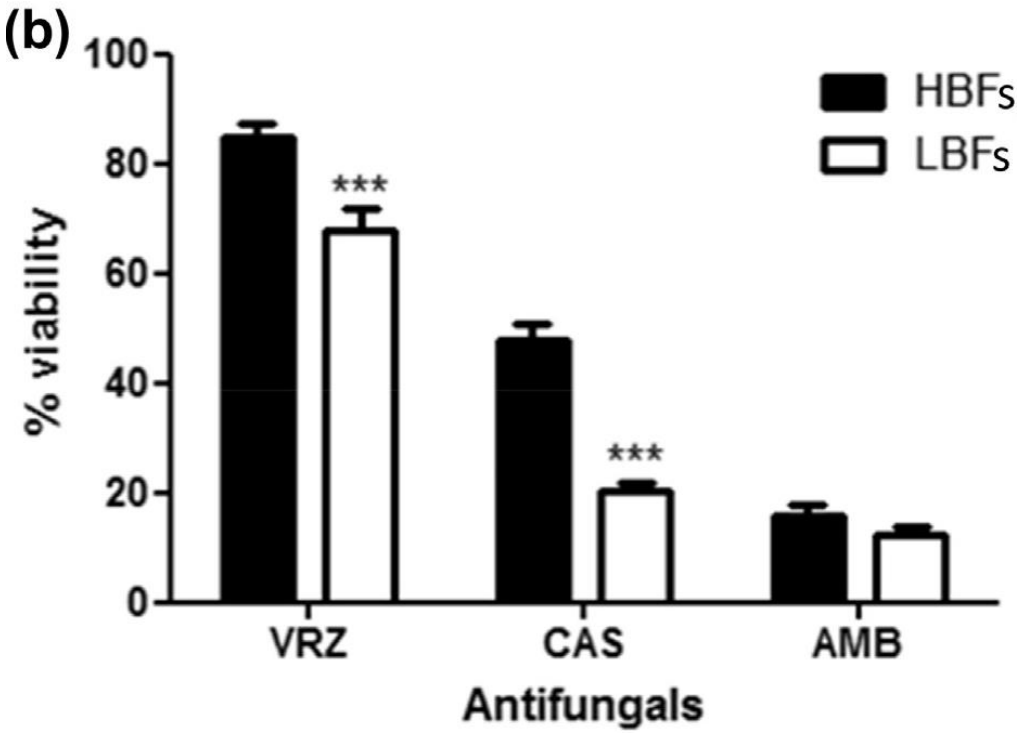
Ramage *et al*. 2006. FEMS Yeast Research.

Why do we care about <u>fungal</u> biofilms?

Biofilm formation is a risk factor for mortality in patients with *Candida albicans* bloodstream infection—Scotland, 2012–2013

R. Rajendran[1], L. Sherry[1], C. J. Nile[1], A. Sherriff[1], E. M. Johnson[2], M. F. Hanson[3], C. Williams[4], C. A. Munro[5], B. J. Jones[6] and G. Ramage[1]





Clin Microbiol Infect 2016; 22: 87–9

Why do we care about fungal biofilms?

Candida species	Patients infected by biofilm–positive isolate		Patients infected by biofilm–negative isolate		OR (95% CI)	*P*[a]
	Total no.	No. (%) who died	Total no.	No. (%) who died		
C. albicans	38	32 (84.2)	130	65 (50)	3.90 (1.72–8.83)	<0.001
C. parapsilosis	14	10 (71.4)	50	14 (28)	4.16 (1.46–11.82)	0.003
C. tropicalis	20	8 (40)	8	4 (50)	0.88 (0.54–1.45)	0.62
C. glabrata	6	4 (66.6)	20	11 (55)	1.46 (0.32–6.62)	0.61
Other[b]	2	2 (100)	6	4 (66.6)		0.34
Total	80	56 (70)	214	98 (45.7)	2.76 (1.55–5.00)	<0.001

Tumbarello *et al.* 2007. J. Clin. Micro. 45: 1843-1850.

Reduced susceptibility in fungal biofilms

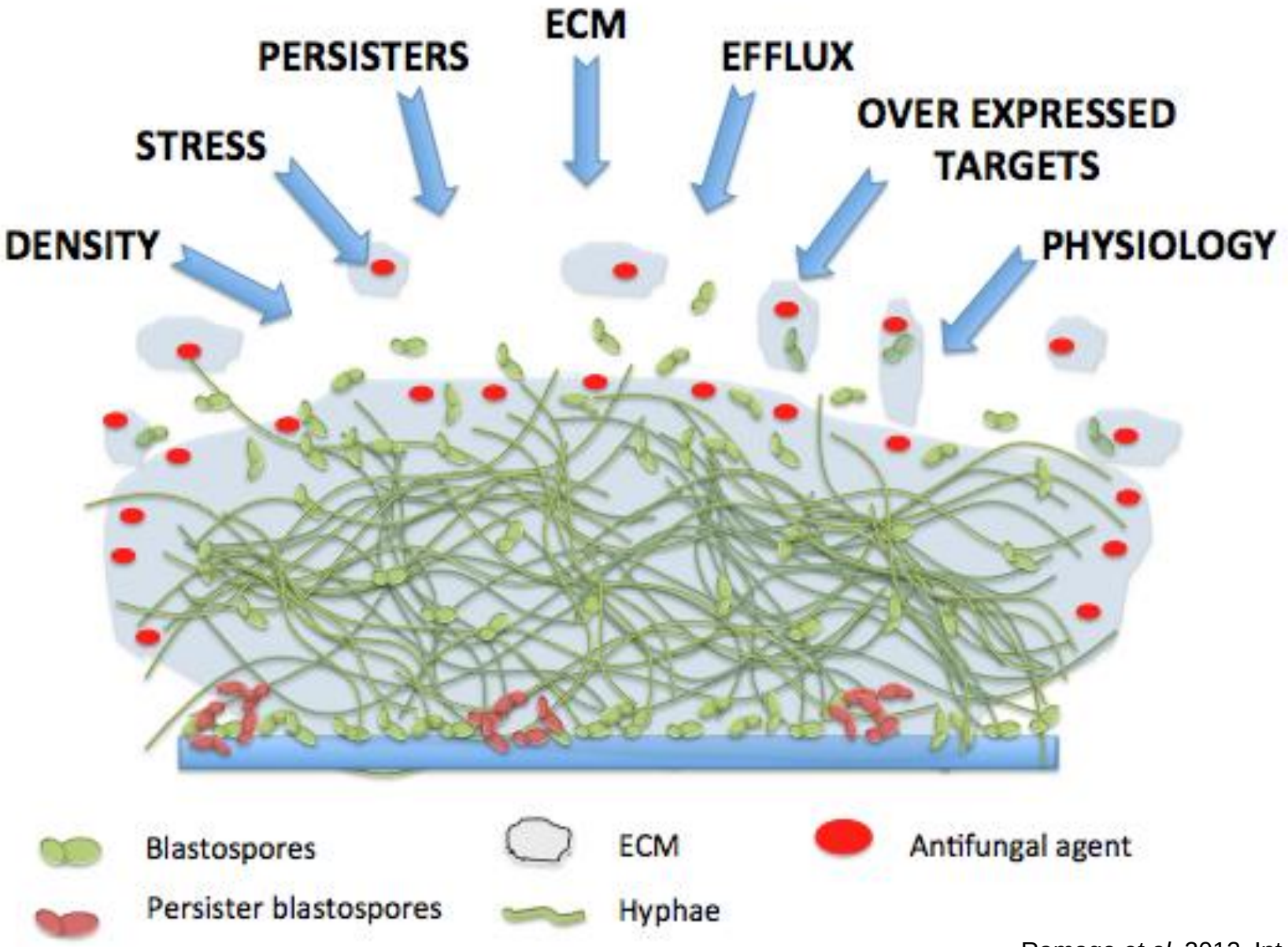
N = 34	FLZ		VRZ		ITZ		CSP		AMB		NYS	
	PMIC	SMIC	PMIC	SMIC	PMIC	SMIC	PMIC	SMIC	PMIC	SMIC	PMIC	SMIC
MIC_{50}	0.5	>128	<0.0625	>128	0.0625	>128	<0.0625	<0.0625	0.0625	2	2	16
MIC_{90}	2	>128	<0.0625	>128	0.125	>128	<0.0625	0.0625	0.125	4	2	32
low	0.0625	>128	<0.0625	>128	0.0625	>128	<0.0625	<0.0625	<0.0625	1	1	16
high	4	>128	1	>128	4	>128	0.25	0.0625	0.25	8	4	32

FLZ = fluconazole; VRZ = voriconazole; ITZ = itraconazole; CSP = caspofungin; AMB = amphotericin B; NYS = nystatin

PMIC = planktonic minimum inhibitory concentration (CLSI); SMIC = sessile minimum inhibitory concentration.

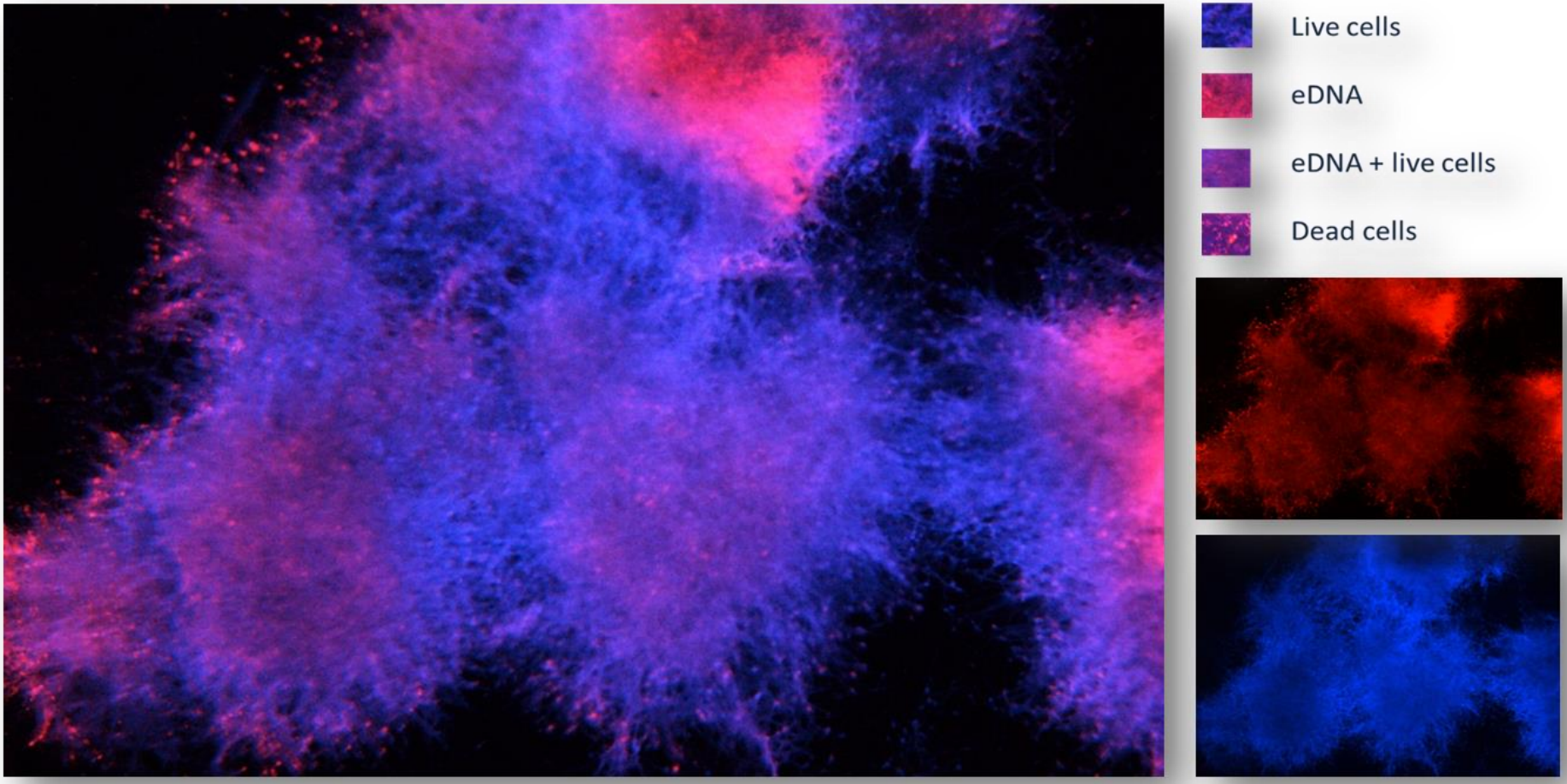
Choi *et al*. 2007. AAC. 51, p 1520-1523

Reduced susceptibility in fungal biofilms



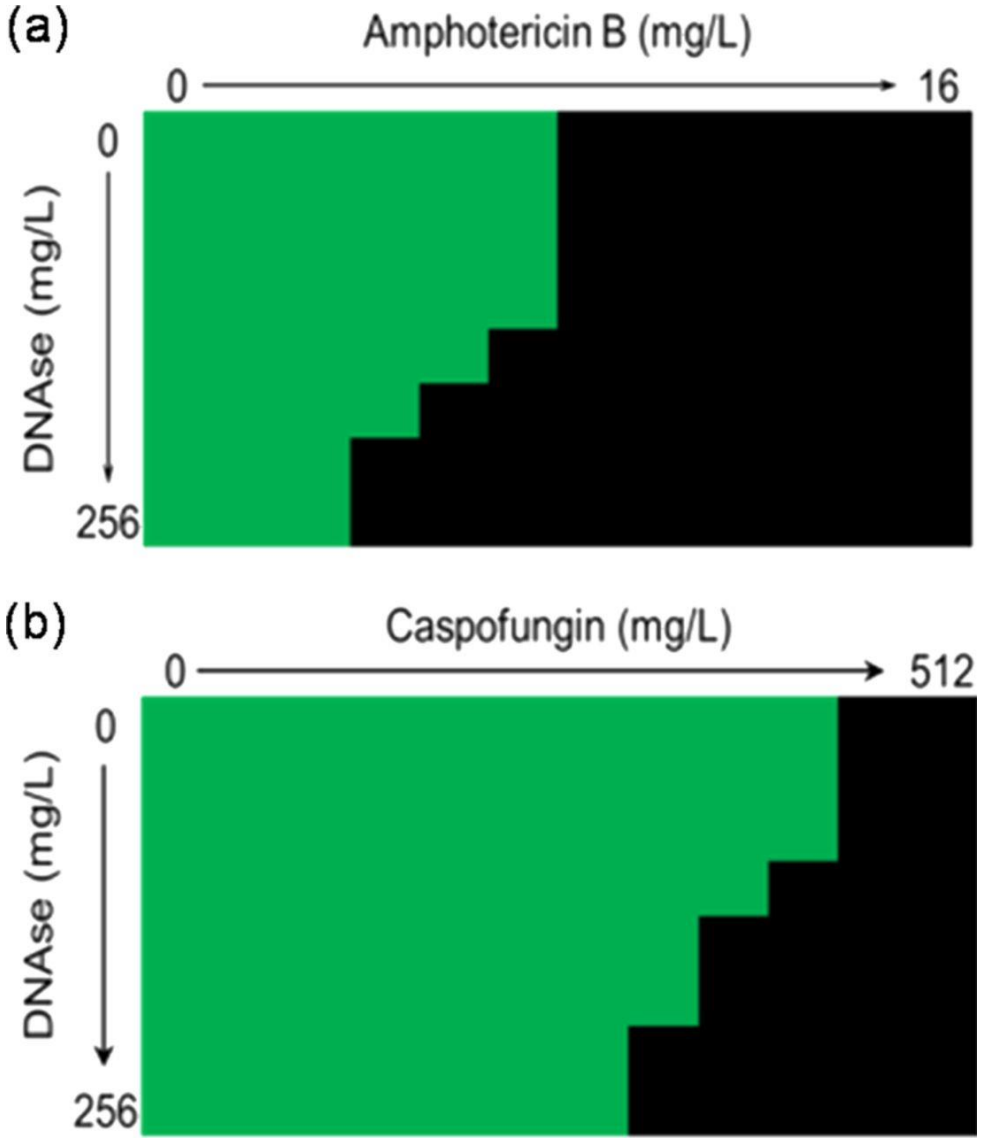
Ramage *et al*, 2012. Int. J. Micro.

Role of the matrix in *A. fumigatus* biofilms



Rajendran et al. Eukaryotic Cell 2013;12:420-429

Role of the matrix in *A. fumigatus* biofilms

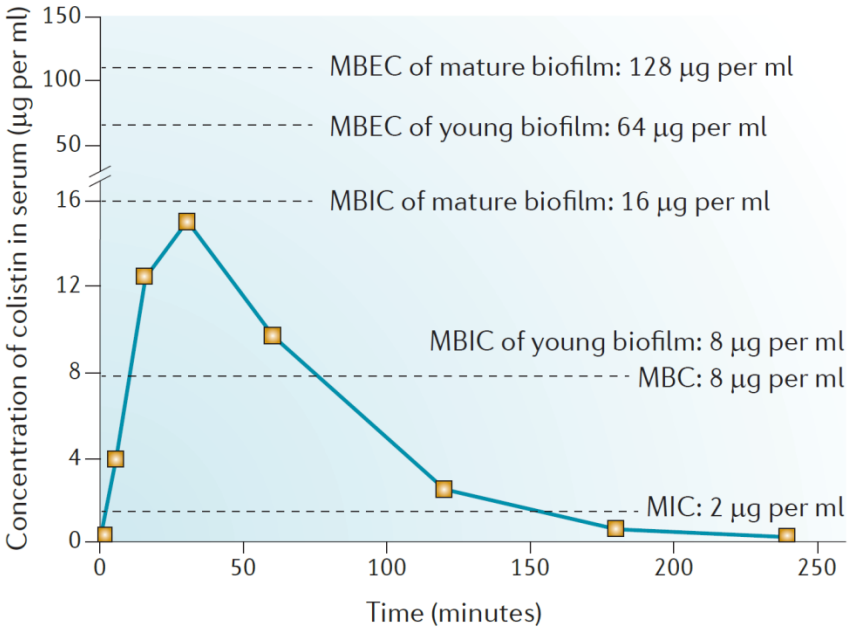


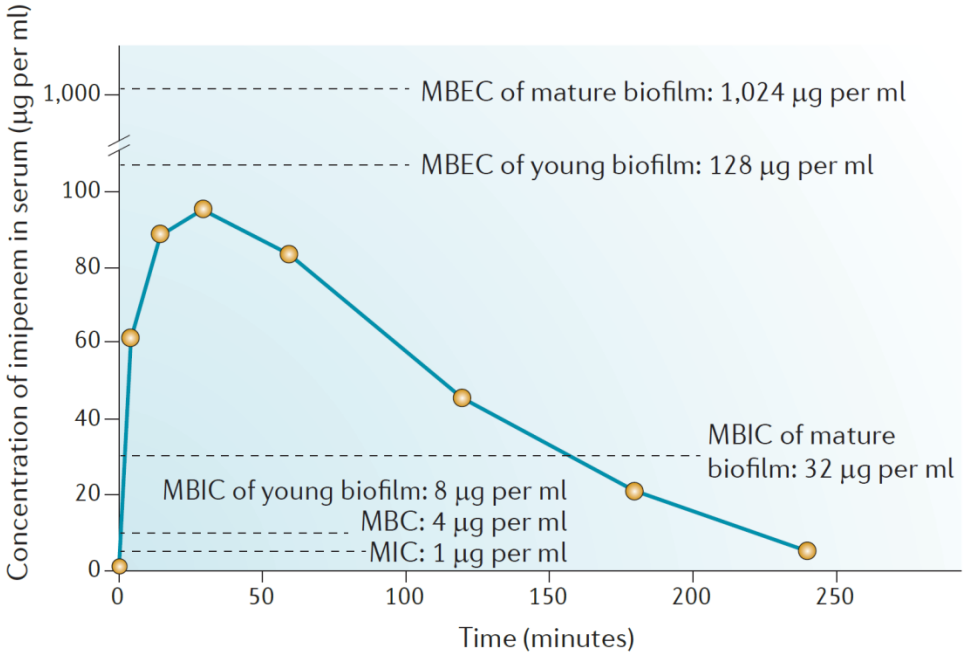
Strain	sMIC (mg/liter) at 24 h		FC
	−DNase	+DNase	
Af293	128	32	4
YHCF1	128	16	8
YHCF2	64	8	8
YHCF3	64	8	8
YHCF4	64	16	4
YHCF5	64	16	4

Rajendran et al. Eukaryotic Cell 2013;12:420-429

Implications for treatment: from *in vitro* to *in vivo*

In vivo PK/PD in a mouse model of biofilm lung infections





!!! Inhibition =/= eradication !!!

Bjarnsholt et al. Nat Rev Drug Discov 2013 12:791-808

Implications for treatment: value of standardized biofilm susceptibility in the lab?

Should standardized susceptibility testing for microbial biofilms be introduced in clinical practice?

Standardized biofilm models **more predictive** than planktonic cultures viz.

- → Antibiotic activity against sessile bacteria
- → Resistance and tolerance mechanisms in biofilms

Data interpretation with **caution** due to *in vitro/in vivo* differences in biofilm biology

Not predictive of clinical success due to differences in

- → Underlying biofilm biology
- → Environment (flow, shear stress)
- → Matrix composition
- → Interplay with host

Possible applications

- → Drug/device registration
- → Drug/device comparisons
- → Support to move forward with a clinical trial
- → Basic biology of biofilms

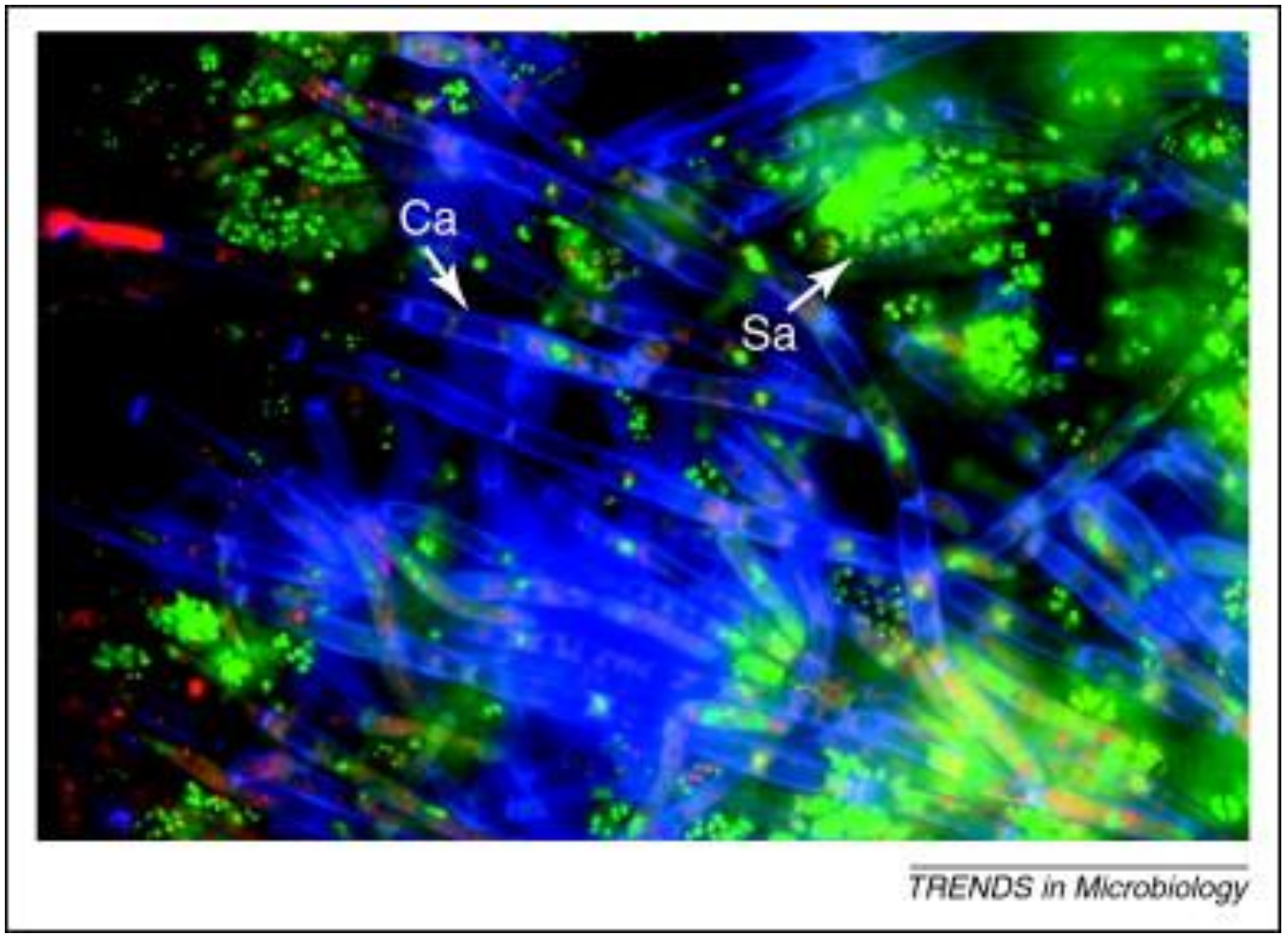
Modulation of drug activity by PK/PD parameters, host (e.g. immune response, host tissue) and environmental factors (e.g. oxygen, nutrients)

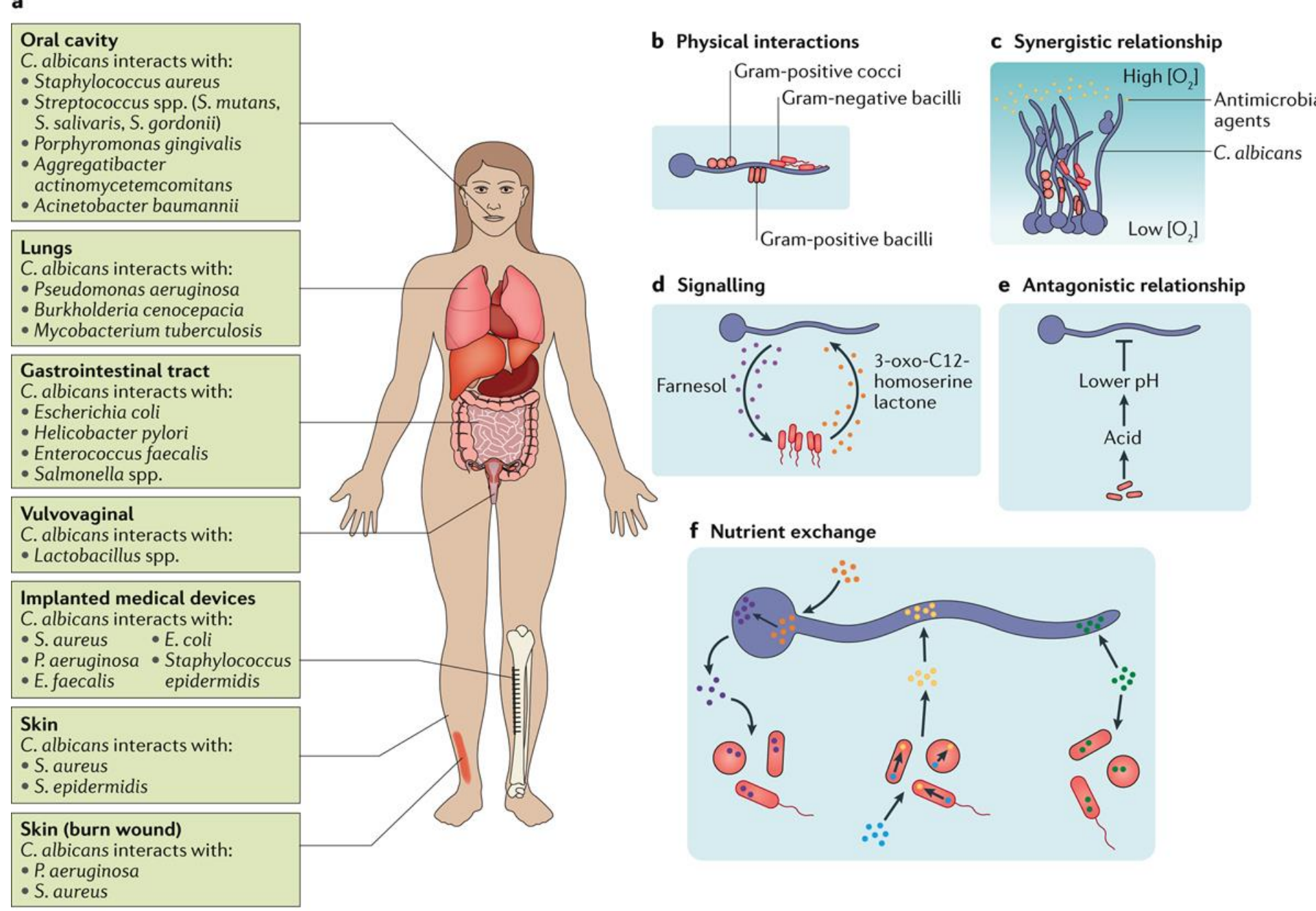
PK/PD issues limiting applicability

- → Access of drugs to biofilms in deep tissues
- → Effective antibiotic concentration not achievable
- → Drug tolerant phenotypes

Importance of *Candida*–bacterial polymicrobial biofilms in disease

Melphine M. Harriott[1] and Mairi C. Noverr[2,3]

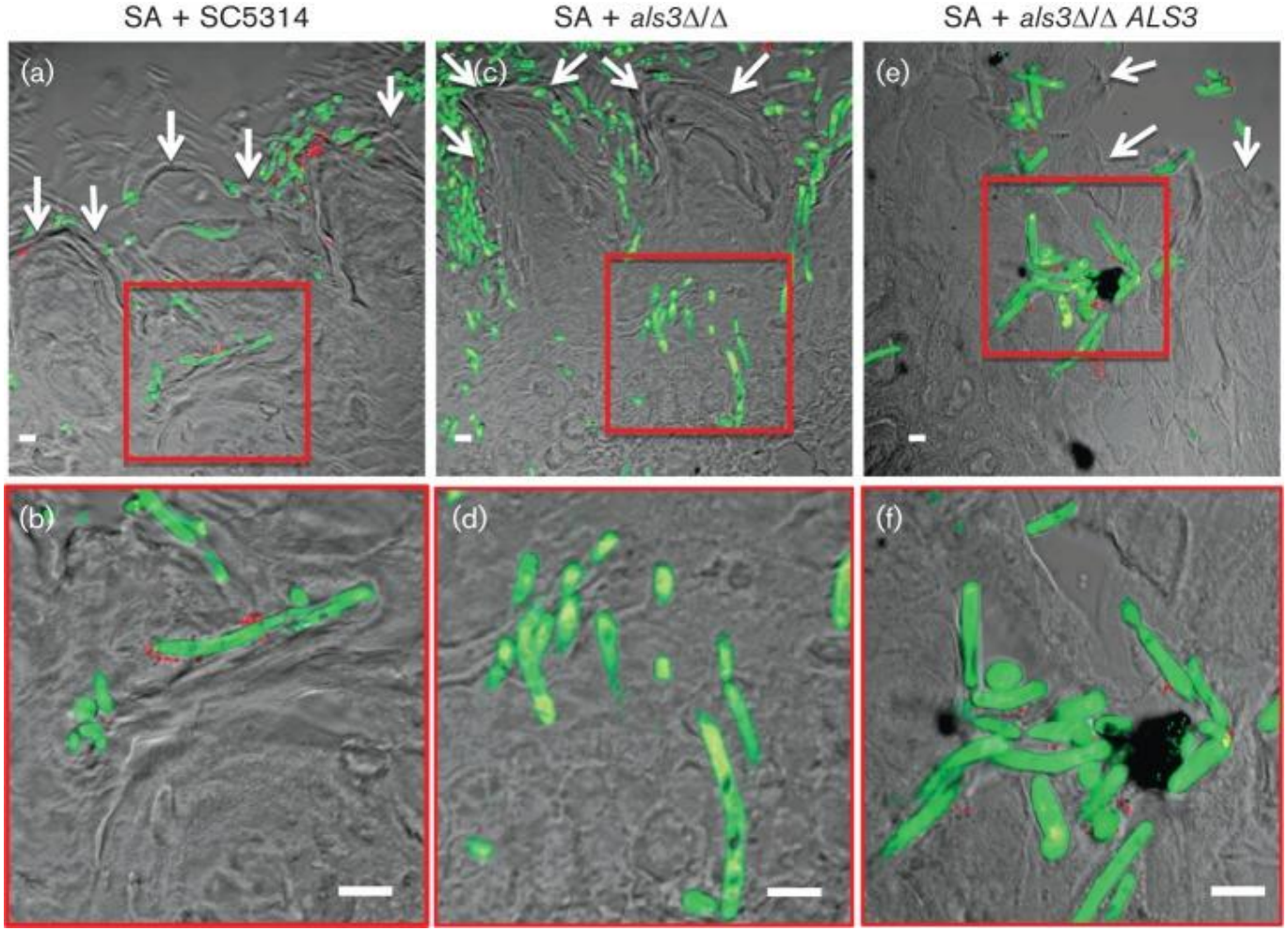


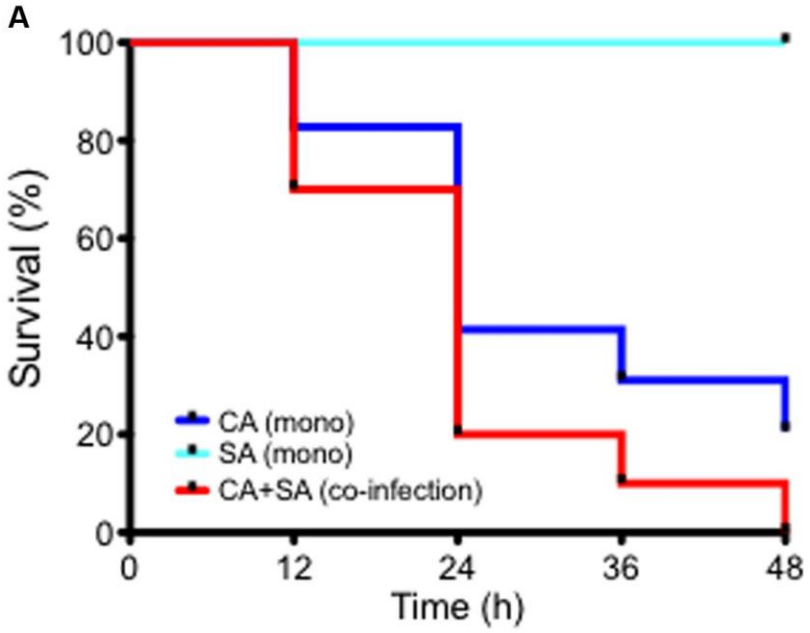


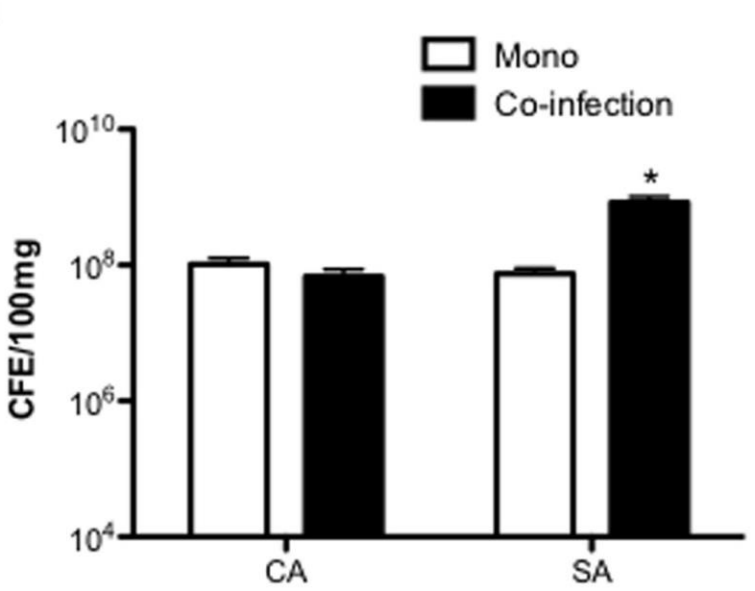
Lohse et al. Nat Rev Microbiol. 2018 Jan; 16(1): 19–31

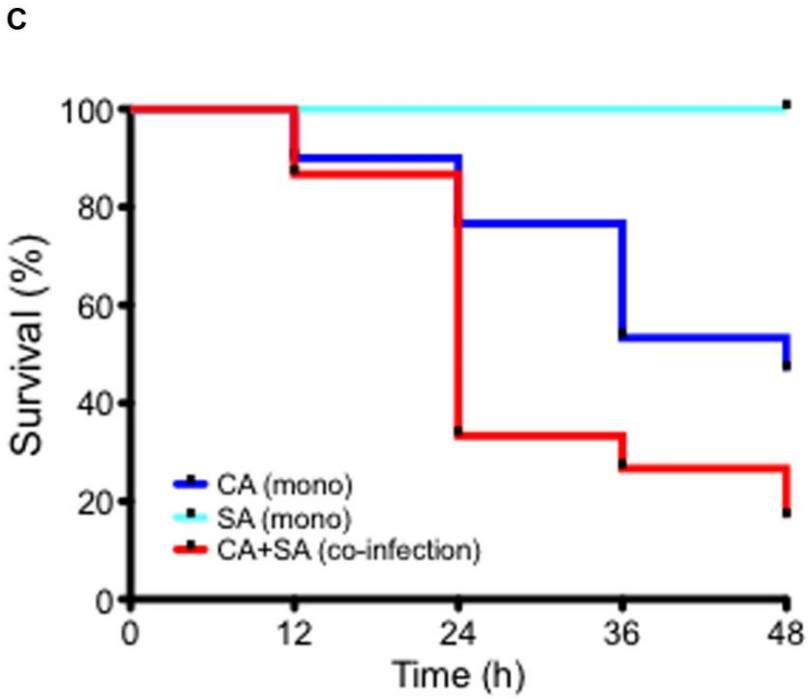
Systemic *Staphylococcus aureus* infection mediated by *Candida albicans* hyphal invasion of mucosal tissue

Lisa Marie Schlecht,[1,2]† Brian M. Peters,[2,3]† Bastiaan P. Krom,[4] Jeffrey A. Freiberg,[2,3] Gertrud M. Hänsch,[5] Scott G. Filler,[6] Mary Ann Jabra-Rizk[7,8]‡ and Mark E. Shirtliff[2,8]‡









No miconazole

With miconazole

Kearn et al. Front Microbiol 2017

Why do we care about fungal biofilms?

- Fungal biofilm-related infections occur frequently
- Fungal cells in a biofilm show reduced susceptibility and antifungal concentrations that are active against biofilms may be difficult to achieve *in vivo*
- Many fungal biofilms are polymicrobial
- Polymicrobial interactions in biofilms influence virulence and susceptibility

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