

A budding problem



Amy Crowe
St Vincent's Hospital
MIDG 21/6/2011

MS

- 64 year old female
- PMHx:
 - OA
 - Hep C
 - L) TKR
 - Excessive ETOH

Acute bacterial PHJI- Debridement & Retention

- May 2009- #NOF- DHS
 - Non-union
- 16/8/2010 r/o DHS & L)THJR
- 29/8/2010
 - wound ooze
 - CRP 92
 - PHJI
- 5/9/2010, w/out (x 3)

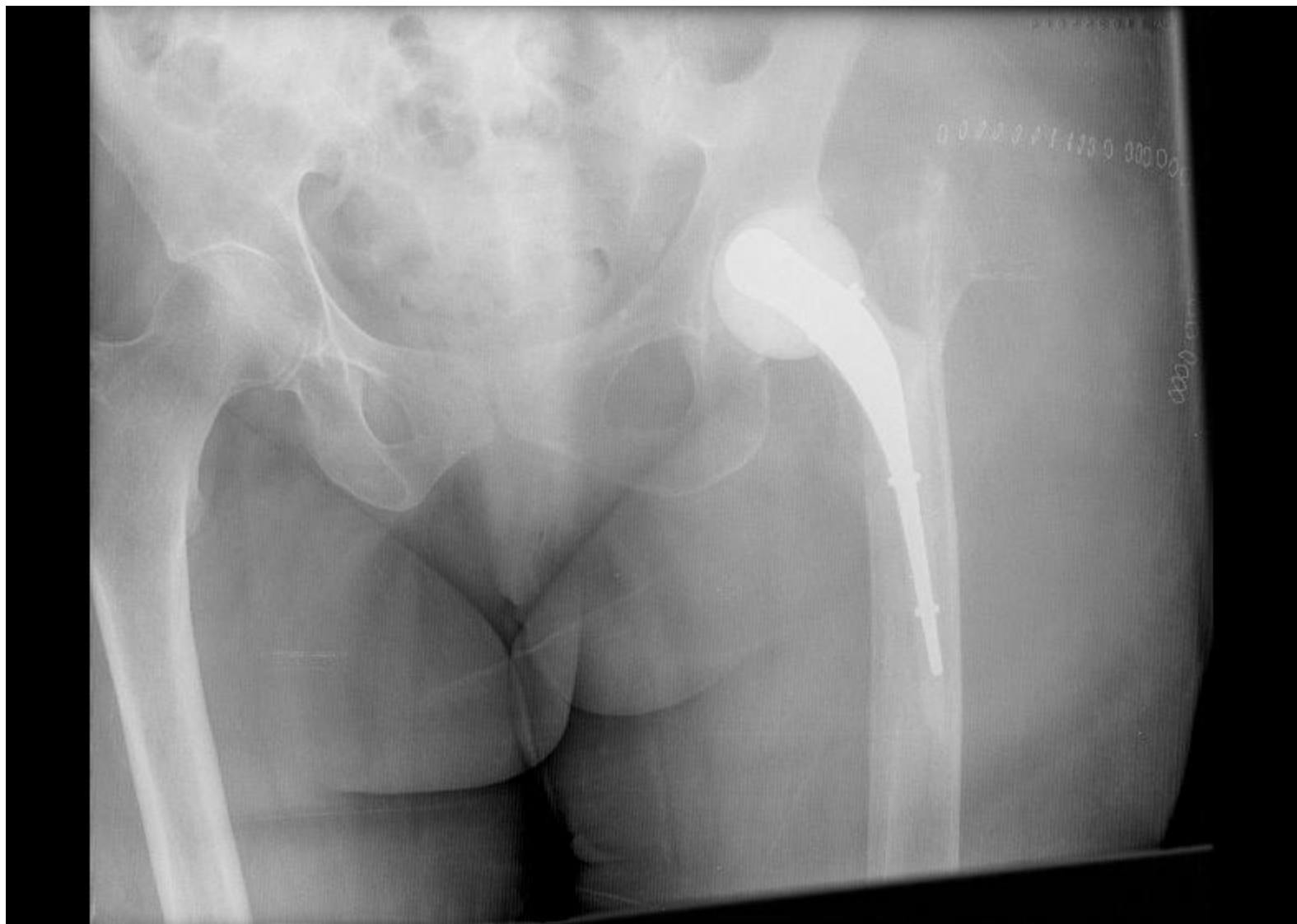
Acute bacterial PHJI- Debridement & Retention

- Histopathology- acute inflammatory infiltrate
- 5 intra-operative specimens
- *Pseudomonas aeruginosa*
 - MIC Timentin= 32
- *Enterococcus faecalis*
 - Mx; Meropenem & Benzylpenicillin 4/52
 - Plan 6/52, then Augmentin DF & Ciprofloxacin



Candida PHJI- two stage arthroplasty

- Oct 2010- represented with acute infection
 - 1st stage r/o prosthesis & I/O spacer
 - 1/1 Tissue
 - No organisms seen, poly ++
 - C.albicans
 - Fluconazole MIC <1
 - No Pseudomonas/Enterococcus isolated
 - Histopathology- chronic inflammation
 - Mx: Meropenem, Benzylpenicillin & Fluconazole
 - Ciprofloxacin, Augmentin DF & Fluconazole

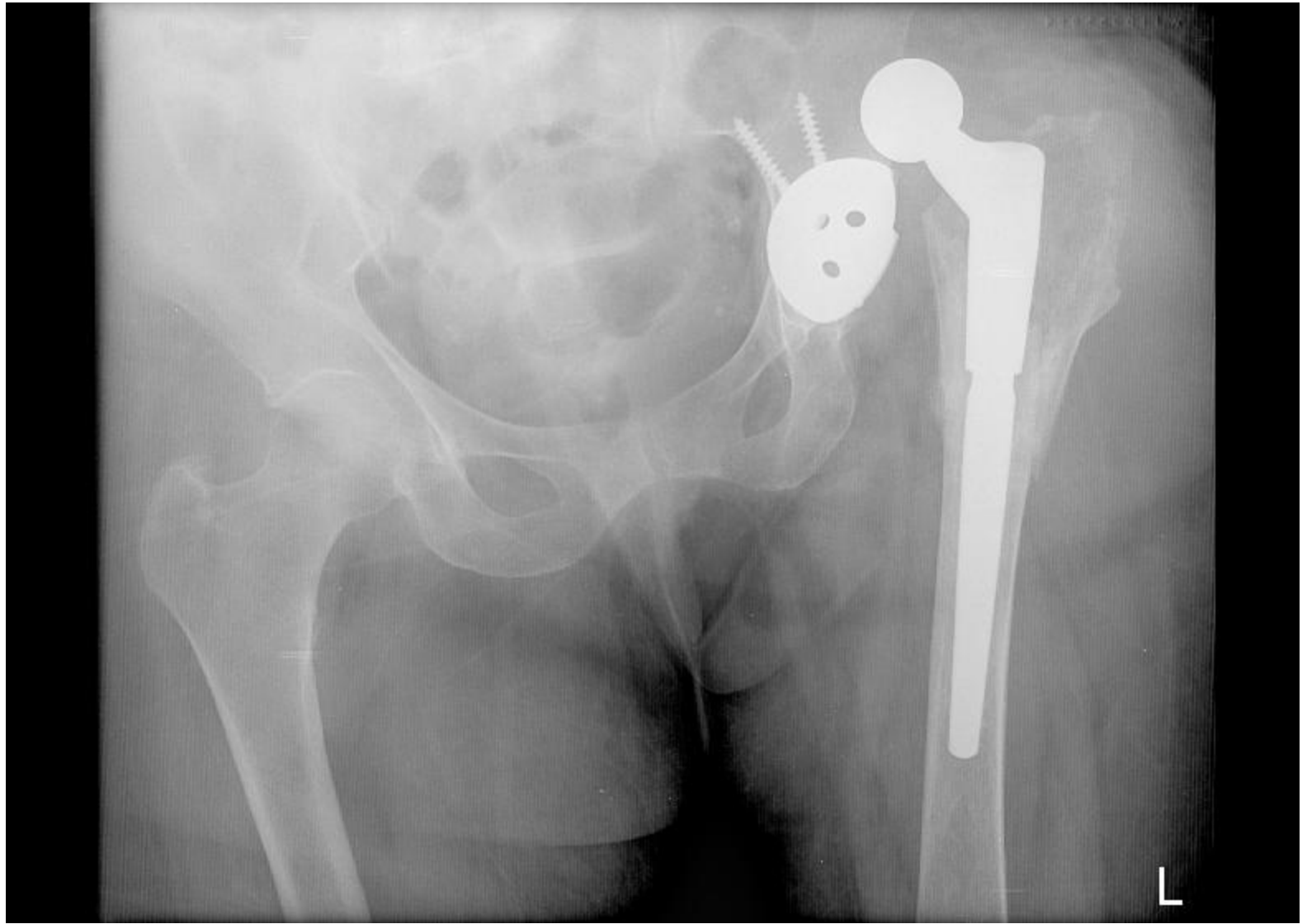


Progress post 1st stage of revision

- Poor mobility
- Bed bound & deconditioned & unable to return home
- Depression
- Derranged LFT's- Fluconazole dose reduced to 200mg daily

Reimplantation - 3 months

- Jan 2011- Second stage L) hip
 - 2 tissue specimens taken
 - 1 Specimen, Enrichment Broth, Day 2
 - C.albicans
 - Fluconazole MIC <1



- Open Reduction
- 3 tissues specimens
 - No polys, no organisms seen
 - No growth
 - Histopathology: no inflammatory infiltrate

Summary

- 64 year old
- immunocompetent host
- CPJI post bacterial PJI and prolonged antibiotic use
- recurrence CPJI post two stage revision arthroplasty (spacer) and 3/12 fluconazole.
- Eight operative procedures, lifelong suppressive fluconazole.

- Treatment Failure
 - Reduced dose Fluconazole
 - Spacer
 - Inadequate time between 1st & 2nd stage
 - Natural history & poor prognosis Candida PJI
- If I had this case again
 - Maintain high dose fluconazole or switched to another antifungal
 - Revised the use of a spacer
 - Longer duration of therapy prior to reimplantation

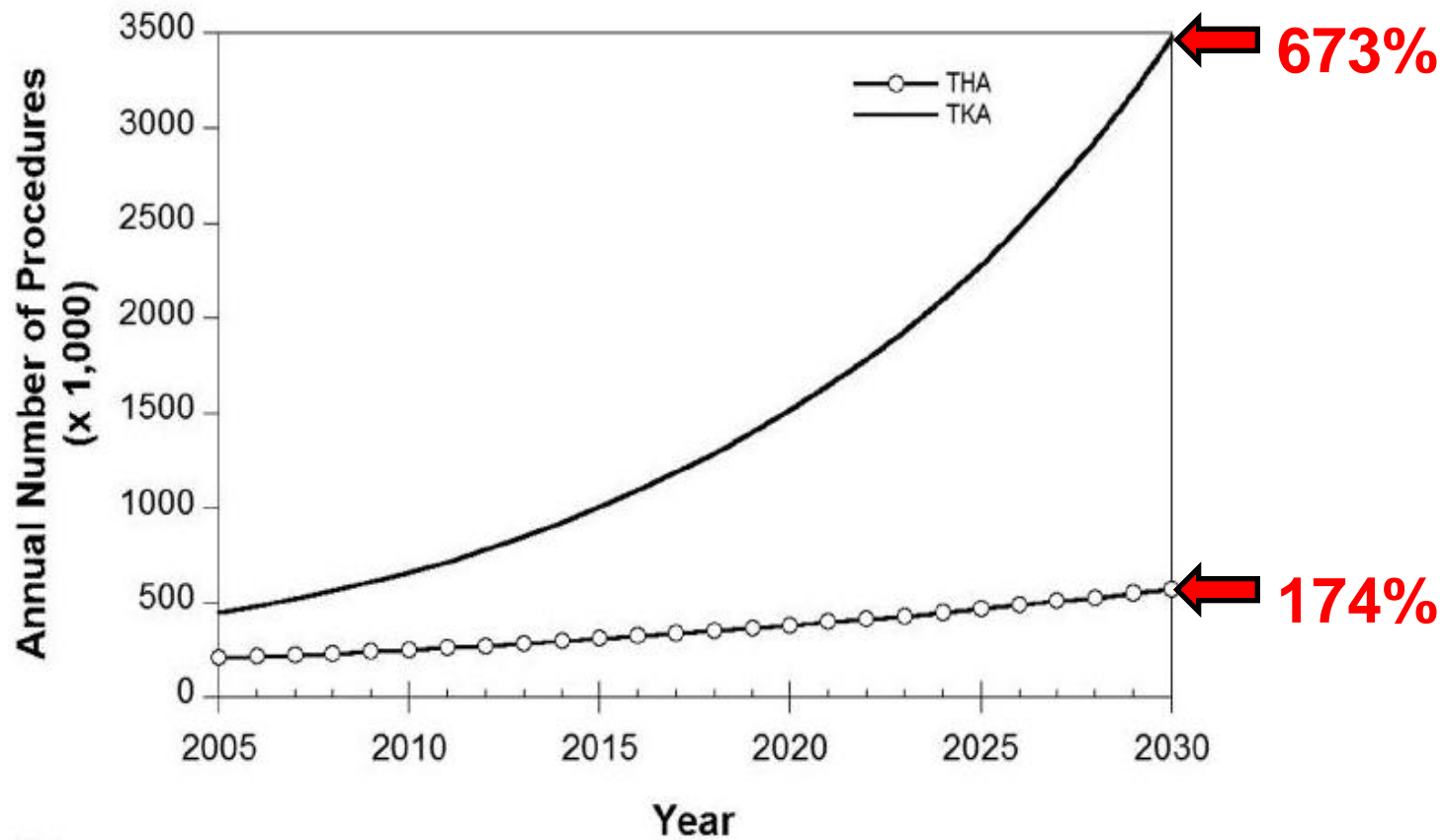
Discussion

- Epidemiology & background of CPJI
- Surgical Management
- Medical Management
- Use of Spacers
- Antifungal tissue distribution
- Role of biofilm & biofilm active agents

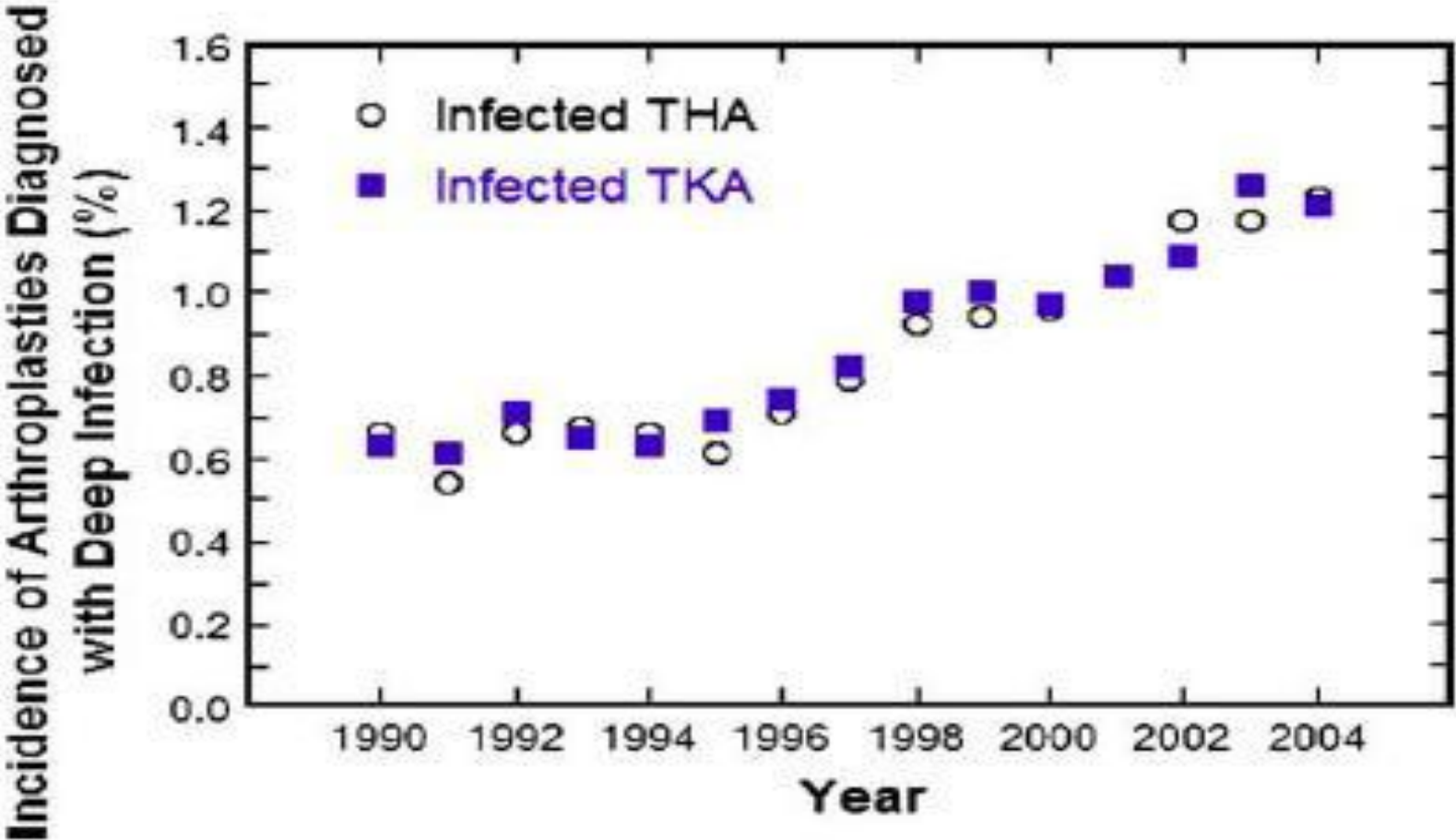
Joint Replacement Rates

- In Australia 2009¹
 - 39,200 hip replacements
 - 39,500 knee replacements

¹ Australian Orthopaedic Association National Joint Replacement Registry Annual Report 2009



Annual Rate PJI 1-3 %/yr
Increasing



Candida Prosthetic Joint Infections

- Uncommon?
- 46 cases in 2002 review
- Incidence unknown, approx 1% of all PJI¹
- Increasing Incidence as overall rates of fungal infections increase

VICNISS- Hip prosthesis infection by pathogen

Organism	Frequency %
Staphylococcus aureus (MRSA)	61.6 (46.7)
Pseudomonas aeruginosa	13.7
Coagulase Negative Staphylococcus	5.5
Enterococcus faecalis (VRE)	5.5 (0)
Enterobacter spp.	2.7
Klebsiella pneumoniae	2.7
Candida albicans	1.4
Escherichia coli	1.4
Morganella morganii	1.4
Strep spp. (Group C & G)	1.4
Other	1.4

VICNISS- Knee prosthesis infection by pathogen

Organism	Frequency %
Staphylococcus aureus (MRSA)	37.2 (0)
Coagulase Negative Staphylococcus	14
Pseudomonas aeruginosa	9.3
Enterococcus faecalis (VRE)	7 (0)
Escherichia coli	7
Serratia spp	7
Enterobacter spp	4.7
Proteus spp	4.7
Candida albicans	2.3
Citrobacter spp	2.3
Enterococcus spp	2.3
Klebsiella pneumoniae	2.3

Epidemiology

- Direct Innoculation at time of surgery
- Seeding from unrecognised candidaemia
- Median time from prosthesis implantation to the onset of symptoms was 20.3 months

CPJI: Risk Factors

- **50-60% of patients will have no RF other than prosthesis itself**
- previous revision arthroplasty (60%)
- prior prosthetic joint infection (40%)
- antibiotic use within the 3 months before presentation (30%)
- use of steroids and immunosuppressive agents (20%)
- rheumatoid arthritis (20%)
- HIV Infection (10%) = 1
- Candida species isolated from a site other than blood (105) = 1

RF for invasive candida infections

- immunosuppression
- neutropenia
- chronic or prolonged use of antibiotics
- indwelling catheters
- TPN
- Malnutrition
- RA
- Cirrhosis
- Hx abdo surgery
- Hx renal tx
- burns
- IVDU

Microbiology

- Breakdown
- *C.albicans* 60%
- *C.parapsilosis* 30%
- *C.tropicalis*, *C. guilliermondii*, *C.glabrata*,
C.krusei
- Joint aspirates mostly gram negative (20% of cases had yeast/fungal elements seen on gram)

Management: Surgical

- 56.8% permanent resection arthroplasties
- 22.7% delayed reimplantation arthroplasties
- direct exchange/amputation
- medical therapy alone generally fails (two successful case reports- early)
- debridement alone generally fails one successful case report)
- no antifungal cement

Table 3. Treatment characteristics of patients with candidal prosthetic joint infection (PJI) who were treated with delayed reimplantation arthroplasty.

Patient [reference]	Site of infection	Therapy (total dose)	Reported MIC for the <i>Candida</i> isolate, $\mu\text{g/mL}$	Time from resection arthroplasty to reimplantation	Outcome	Duration of follow-up, months
1 [PR]	Hip	Resection arthroplasty; amphotericin B for 36 days (500 mg), then ketoconazole for 5 months, then fluconazole, 25 mg/day ^a for 61 days; reimplantation	—	17.7 months	Cure	73
2 [PR]	Knee	Resection arthroplasty; reimplantation	—	8 days	Cure	51
3 [PR]	Hip	Resection arthroplasty; amphotericin B for 71 days (1000 mg), then fluconazole for 269 days (400 mg); reimplantation	Fluconazole, ≤ 1.25	12.1 months	Cure	70
4 [PR]	Hip	Resection arthroplasty; fluconazole-impregnated spacer; fluconazole for 47 days (200 mg); reimplantation	Fluconazole, 0.25	2.4 months	Cure	17
5 [17]	Hip	Resection arthroplasty; amphotericin B, 35 mg/day for 6 weeks (1470 mg); reimplantation	—	5 months	Cure	24
6 [17]	Hip	Amphotericin B, 50 mg/day for 6 weeks (2100 mg), which was unsuccessful; recurrent PJI after 30 months: no antifungals given; resection arthroplasty; reimplantation	—	5 months	Cure	60
7 [12]	Knee	Resection arthroplasty and external fixation; amphotericin B (1390 mg) plus 5-FC for 6 weeks; reimplantation	Amp B, 0.08–10; 5-FC, 0.8–100	~6 months	Cure	72
8 [23]	Hip	Resection arthroplasty; 5-FC for 2 weeks plus amphotericin B, ≤ 60 mg every other day (1000 mg); reimplantation	5-FC, < 0.02	14 months	Cure	24
9 [25]	Knee	Limited excision of sinus tract and cement; amphotericin B for 6 weeks (821 mg); resection arthroplasty; reimplantation; debridement and 2 limited excisions after recurrence; resection arthroplasty/fusion	—	18 days	Treatment failure	NR
10 [15]	Knee	Resection arthroplasty; amphotericin B (880 mg), then ketoconazole given daily (400 mg); reimplantation; recurrence while receiving ketoconazole at 1 month; fluconazole maintenance, 200 mg/day for 6 months; amputation	Fluconazole, ≤ 1.25	4 months	Treatment failure	2

NOTE. Amp B, amphotericin B; 5-FC, 5-fluorocytosine; NR, not reported; PR, present report.

^a Dose reduced secondary to renal failure.

Table 3. Treatment characteristics of patients with candidal prosthetic joint infection (PJI) who were treated with delayed reimplantation arthroplasty.

Patient [reference]	Site of infection	Therapy (total dose)	Reported MIC for the <i>Candida</i> isolate, $\mu\text{g/mL}$	Time from resection arthroplasty to reimplantation	Outcome	Duration of follow-up, months
1 [PR]	Hip	Resection arthroplasty; amphotericin B for 36 days (500 mg), then ketoconazole for 5 months, then fluconazole, 25 mg/day ^a for 61 days; reimplantation	—	17.7 months	Cure	73
2 [PR]	Knee	Resection arthroplasty; reimplantation	—	8 days	Cure	51
3 [PR]	Hip	Resection arthroplasty; amphotericin B for 71 days (1000 mg), then fluconazole for 269 days (400 mg); reimplantation	Fluconazole, ≤ 1.25	12.1 months	Cure	70
4 [PR]	Hip	Resection arthroplasty; fluconazole-impregnated spacer; fluconazole for 47 days (200 mg); reimplantation	Fluconazole, 0.25	2.4 months	Cure	17
5 [17]	Hip	Resection arthroplasty; amphotericin B, 35 mg/day for 6 weeks (1470 mg); reimplantation	—	5 months	Cure	24
6 [17]	Hip	Amphotericin B, 50 mg/day for 6 weeks (2100 mg), which was unsuccessful; recurrent PJI after 30 months: no antifungals given; resection arthroplasty; reimplantation	—	5 months	Cure	60
7 [12]	Knee	Resection arthroplasty and external fixation; amphotericin B (1390 mg) plus 5-FC for 6 weeks; reimplantation	Amp B, 0.08–10; 5-FC, 0.8–100	~6 months	Cure	72
8 [23]	Hip	Resection arthroplasty; 5-FC for 2 weeks plus amphotericin B, ≤ 60 mg every other day (1000 mg); reimplantation	5-FC, < 0.02	14 months	Cure	24
9 [25]	Knee	Limited excision of sinus tract and cement; amphotericin B for 6 weeks (821 mg); resection arthroplasty; reimplantation; debridement and 2 limited excisions after recurrence; resection arthroplasty/fusion	—	18 days	Treatment failure	NR
10 [15]	Knee	Resection arthroplasty; amphotericin B (880 mg), then ketoconazole given daily (400 mg); reimplantation; recurrence while receiving ketoconazole at 1 month; fluconazole maintenance, 200 mg/day for 6 months; amputation	Fluconazole, ≤ 1.25	4 months	Treatment failure	2

NOTE. Amp B, amphotericin B; 5-FC, 5-fluorocytosine; NR, not reported; PR, present report.

^a Dose reduced secondary to renal failure.

Spacers in CPJI

Tabla 2 Aspectos microbiológicos y terapéuticos tras el diagnóstico de infección por <i>Candida</i> spp.							
Especie	Cultivos positivos / cultivos practicados	Tratamiento quirúrgico	Tratamiento antifúngico	Evolución	Cirugía definitiva	Evolución definitiva	Tiempo de seguimiento (meses)
<i>C. parapsilosis</i>	3 / 6	D	Fluconazol	Fracaso	—	TSF	63
<i>C. albicans</i>	6 / 6	R2T	Fluconazol y caspofungina	Fracaso	AR	Éxito	24
<i>C. albicans</i>	8 / 8	R2T	Fluconazol	Fracaso	AR	Éxito	2
<i>C. albicans</i>	3 / 3	D	Fluconazol	Fracaso	AR	TSF	67
<i>C. glabrata</i>	4 / 4	R2T	Fluconazol	Fracaso	AR	Éxito	10
<i>C. albicans</i>	5 / 5	R2T	Fluconazol	Fracaso	D	Curación	65
<i>C. albicans</i>	3 / 6	R2T	Fluconazol	Fracaso	AR	Curación	17
<i>C. tropicalis</i>	6 / 6	D	Fluconazol	Fracaso	AR	TSF	9
<i>C. tropicalis</i>	3 / 3	R2T	Anidulafungina y fluconazol	Fracaso	AR	TSF	10
<i>C. albicans</i>	4 / 4	R2T	Fluconazol	Fracaso	AR	TSF	43

D: Desbridamiento; R2T: Recambio en 2 tiempos. AR: artroplastia de resección. TSF: tratamiento supresivo con fluconazol.

Conclusion: Prosthetic joint infection was associated with long-term antibiotic treatment and multiples previous surgeries. Treatment with fluconazol and debridement or two-stage replacement with a spacer was associated with a high failure rate.

Table 3. Treatment characteristics of patients with candidal prosthetic joint infection (PJI) who were treated with delayed reimplantation arthroplasty.

Patient [reference]	Site of infection	Therapy (total dose)	Reported MIC for the <i>Candida</i> isolate, $\mu\text{g/mL}$	Time from resection arthroplasty to reimplantation	Outcome	Duration of follow-up, months
1 [PR]	Hip	Resection arthroplasty; amphotericin B for 36 days (500 mg), then ketoconazole for 5 months, then fluconazole, 25 mg/day ^a for 61 days; reimplantation	—	17.7 months	Cure	73
2 [PR]	Knee	Resection arthroplasty; reimplantation	—	8 days	Cure	51
3 [PR]	Hip	Resection arthroplasty; amphotericin B for 71 days (1000 mg), then fluconazole for 269 days (400 mg); reimplantation	Fluconazole, ≤ 1.25	12.1 months	Cure	70
4 [PR]	Hip	Resection arthroplasty; fluconazole-impregnated spacer; fluconazole for 47 days (200 mg); reimplantation	Fluconazole, 0.25	2.4 months	Cure	17
5 [17]	Hip	Resection arthroplasty; amphotericin B, 35 mg/day for 6 weeks (1470 mg); reimplantation	—	5 months	Cure	24
6 [17]	Hip	Amphotericin B, 50 mg/day for 6 weeks (2100 mg), which was unsuccessful; recurrent PJI after 30 months: no antifungals given; resection arthroplasty; reimplantation	—	5 months	Cure	60
7 [12]	Knee	Resection arthroplasty and external fixation; amphotericin B (1390 mg) plus 5-FC for 6 weeks; reimplantation	Amp B, 0.08–10; 5-FC, 0.8–100	~6 months	Cure	72
8 [23]	Hip	Resection arthroplasty; 5-FC for 2 weeks plus amphotericin B, ≤ 60 mg every other day (1000 mg); reimplantation	5-FC, < 0.02	14 months	Cure	24
9 [25]	Knee	Limited excision of sinus tract and cement; amphotericin B for 6 weeks (821 mg); resection arthroplasty; reimplantation; debridement and 2 limited excisions after recurrence; resection arthroplasty/fusion	—	18 days	Treatment failure	NR
10 [15]	Knee	Resection arthroplasty; amphotericin B (880 mg), then ketoconazole given daily (400 mg); reimplantation; recurrence while receiving ketoconazole at 1 month; fluconazole maintenance, 200 mg/day for 6 months; amputation	Fluconazole, ≤ 1.25	4 months	Treatment failure	2

NOTE. Amp B, amphotericin B; 5-FC, 5-fluorocytosine; NR, not reported; PR, present report.

^a Dose reduced secondary to renal failure.

Antifungal Use in CPJI

- Amphotericin alone
- Azole Alone
- Amphotericin and Azole
- Amphotericin and Flucytosine
- Echinocandin

Management: Medical

Table 4. Summary of medical therapy for patients with candidal prosthetic joint infection who were treated at the Mayo Clinic or described in the literature.

Therapy	Patient group		All (n = 10)
	Mayo Clinic (n = 4)	Literature (n = 6)	
Monotherapy	1 (25)	3 (50)	4 (40)
Amphotericin B	0 (0)	3 (50)	3 (30)
Fluconazole	1 (25)	0 (0)	1 (10)
Combination therapy	2 (50)	3 (50)	5 (50)
Amphotericin B plus 5-FC	0 (0)	2 (33)	2 (20)
Amphotericin B, then fluconazole	1 (25)	0 (0)	1 (10)
Amphotericin B, then ketoconazole, then fluconazole	1 (25)	1 (17)	2 (20)
No therapy	1 (25)	0 (0)	1 (10)
Fluconazole-impregnated spacer	1 (25)	0 (0)	1 (10)
Median dose, mg (range)			
Amphotericin B	750 (500–1000)	1195 (821–2100)	1000 (500–2100)
Fluconazole	200 (25–400)	200	200 (25–400)
Duration of therapy, median days (range)			
Amphotericin B	53.5 (36–71)	42.0 (32.0–42.0)	42 (42–71)
Fluconazole	61 (47–269)	182.5 ^a	122 (47–269)

NOTE. Data are no. (%) of patients, unless otherwise indicated. 5-FC, 5-fluorocytosine.

^a Duration of maintenance fluconazole prior to amputation.

- Doses
 - Amphotericin B 1145mg (mean total), 42 days
 - Fluconazole 200mg (mean total), 122 days
- 40% Adverse Event rate (mostly ARF)

Antifungal- tissue penetration

- AMB: joint fluid levels approx 50% of serum levels¹
- Fluconazole: good joint fluid penetration
 - 80-90% in some studies
 - 72% of serum levels in a case of medical therapy alone²
- Echinocandin ?

1.Kucers, 2010

2. Cushing, Journal of Arthroplasty, 1997

Role of biofilm in device associated infections



- Adherence
- Support network & nutrition for sessile cells
- Increased antibacterial/antifungal resistance
- Ongoing nidus for infection

Biofilm Structure

- Sessile & Planktonic forms
- Stages; adherence, maturation and dispersion

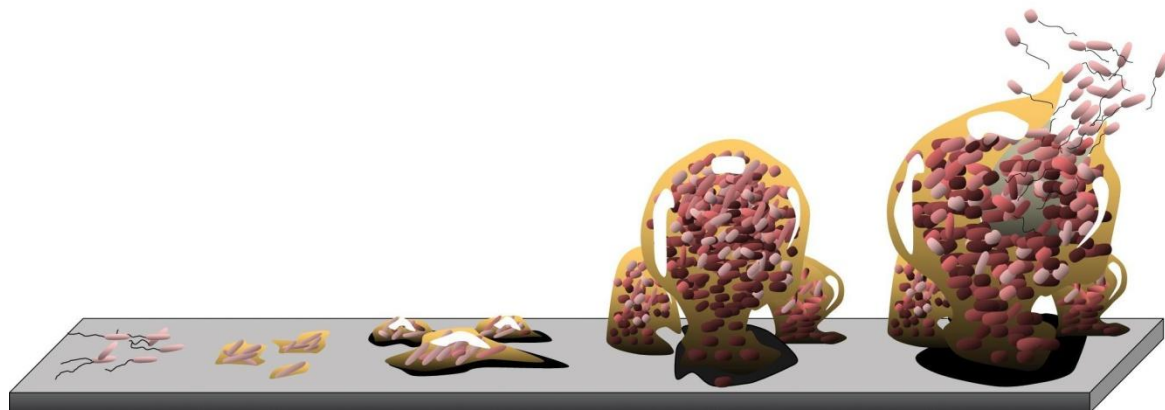


TABLE 2-7 -- Biofilm-Associated Microorganisms Isolated from Indwelling Medical Devices

Indwelling Medical Device	Organisms
Central venous catheter	Coagulase-negative staphylococci, <i>Staphylococcus aureus</i> , <i>Enterococcus faecalis</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i>
Prosthetic heart valve	Viridans streptococci, coagulase-negative staphylococci, enterococci, <i>S. aureus</i>
Urinary catheter	<i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>Proteus mirabilis</i>
Artificial hip prosthesis	Coagulase-negative staphylococci, hemolytic streptococci, enterococci, <i>P. mirabilis</i> , <i>Bacteroides</i> species, <i>S. aureus</i> , viridans streptococci, <i>E. coli</i> , <i>P. aeruginosa</i>
Artificial valve prosthesis	<i>C. albicans</i> , <i>Streptococcus mitis</i> , <i>Streptococcus salivarius</i> , <i>Rothia dentocariosa</i> , <i>Candida tropicalis</i> , <i>Streptococcus sobrinus</i> , <i>S. epidermidis</i> , <i>Stomatococcus mucilaginosus</i>
Intrauterine device	<i>S. epidermidis</i> , <i>Corynebacterium</i> species, <i>S. aureus</i> , <i>Micrococcus</i> species, <i>Lactobacillus plantarum</i> , group B streptococci, <i>Enterococcus</i> species, <i>C. albicans</i>

Reprinted from Donlan RM. Biofilm formation: A clinically relevant process. *Clin Inf Dis*. 2001;33:1387-1392, with permission.

Biofilm activity & Bacterial PJI

- Staphylococcus biofilm long recognised to play an important role in Staphylococcus PJI
- Improved rates of success with debridement & retention approach using biofilm active agents
- Partnered Rifampicin use in CoNS and Staph.aureus device related infections prototype

Candida spp & biofilm

- Thought to be produced by all species
- C.albicans > C.tropicalis
>C.glabrata >C.parapsilosis

Candida spp & biofilm

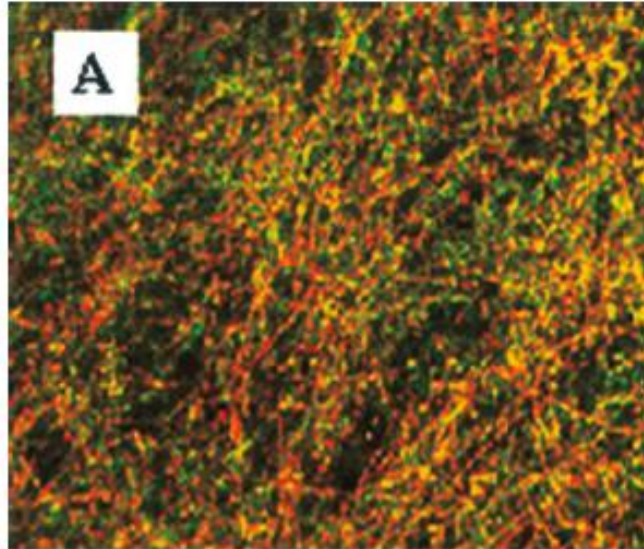
- Recalcitrant to Rx with conventional azole therapies
- C.albicans sessile forms high level of resistance to fluconazole
- Less resistance to Amphotericin
- Least resistance to Caspofungin

Sessile Cells MIC₅₀

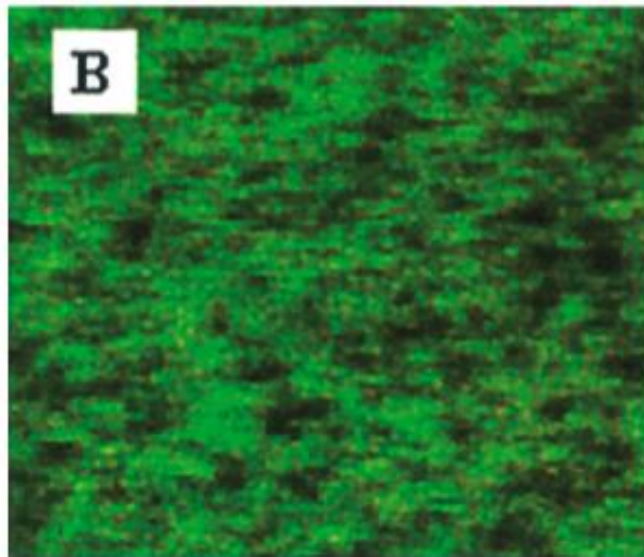
- **Sessile cells** in biofilms exhibit drastic phenotype differences to cells in planktonic form
- Fluconazole >64µg/mL
 - (cf: Planktonic MIC 0.25-64µg/mL)
- Caspofungin 0.0625µg/mL
 - (cf: Planktonic MIC 0.25-1µg/mL)

Candida spp. biofilms & Caspofungin activity

- Reduced biofilm resistance
- Reduces viable cells in biofilm
- Reduced amount of biofilm
- Reduces dispersion of cells from biofilm

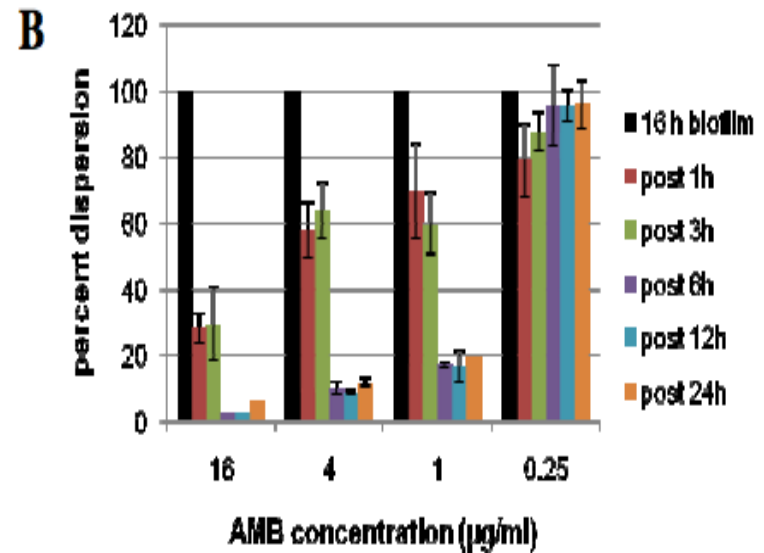
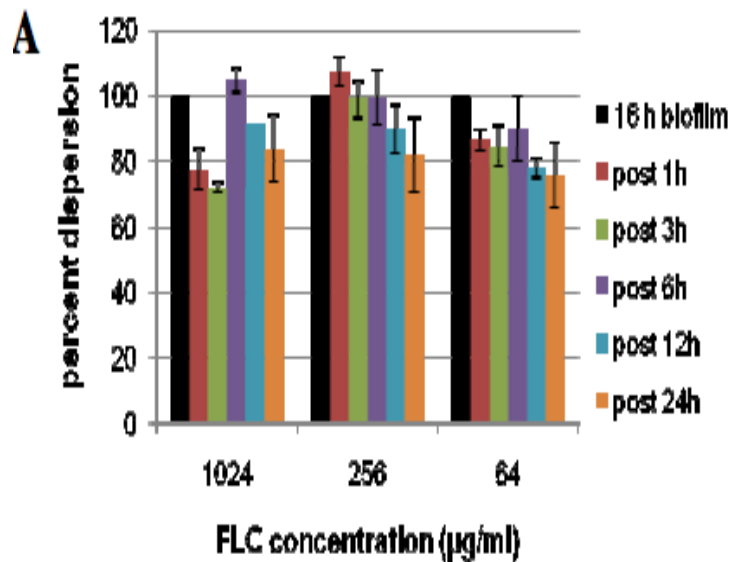


Control
Red= Metabolic
Uptake

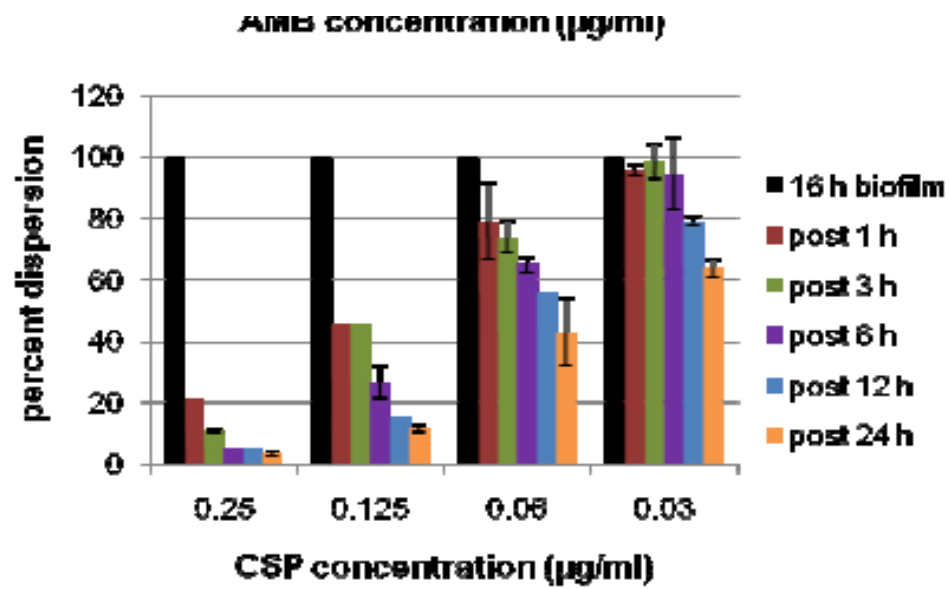


Caspofungin
Red=
Metabolic
Uptake

Biofilm & Dispersion of Planktonic forms



C



Drug	Concentration ($\mu\text{g/ml}$)	Non-viable dispersed cells (%)				
		1 h	3 h	6 h	12 h	24 h
FLC	1024	16.5 \pm 4.8	31.3 \pm 3.2	48.7 \pm 3.8	47.0 \pm 4.2	66.8 \pm 2.3
	256	9.5 \pm 6.2	16.2 \pm 2.6	26.5 \pm 2.7	27.3 \pm 4.9	37.5 \pm 2.9
	64	5.5 \pm 2.2	11.6 \pm 1.4	15 \pm 5.6	16.9 \pm 4	14.5 \pm 7.7
AMB	16	13.8 \pm 3.9	15.7 \pm 0.0	34.5 \pm 0.7	50 \pm 14.1	64.2 \pm 6
	4	0.0 \pm 0.0	11.8 \pm 3.8	14.2 \pm 8.0	46.6 \pm 0.0	63.4 \pm 10.3
	1	0.0 \pm 0.0	0.0 \pm 0.0	3.8 \pm 0.0	44.0 \pm 0.0	38.0 \pm 8.9
	0.25	10.9 \pm 4.6	9.0 \pm 1.4	6.1 \pm 1.2	46.1 \pm 8.8	40.8 \pm 6.5
CSP	0.25	23.6 \pm 1.8	68.5 \pm 4.0	74.5 \pm 7.7	92.2 \pm 0.3	98.2 \pm 0.1
	0.125	1.3 \pm 1.8	51.7 \pm 2.4	40.0 \pm 4.0	81.2 \pm 1.7	81.4 \pm 1.9
	0.06	6.6 \pm 0.0	2.6 \pm 3.7	22.2 \pm 4.7	34.3 \pm 4.4	46.7 \pm 2.3
	0.03	2.0 \pm 1.0	1.6 \pm 2.3	3.8 \pm 5.3	11.4 \pm 7.7	17.4 \pm 2.2

Could debridement & retention be a viable option for CPJI with use of echinocandins?

CASE REPORTS

Micafungin plus Fluconazole in an Infected Knee with Retained Hardware due to *Candida albicans*

Christopher M Bland and Sanil Thomas

Summary: CPJI

- An uncommon cause of PJI (1%-2%)
- Majority of cases-resection arthroplasty
- Antifungal agent (Amphotericin B or Fluconazole)
- Two stage revision success rate up to 80%
- Avoid Spacers!
- Echinocandins superior biofilm activity invitro
- Use in clinical setting of CPJI area requiring ongoing review

Acknowledgements

- Dr Trish Peel, SVHM