



C.H.U. de Charleroi

Blood stream candidiasis

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62-year-old man: clinical history

- Fever for 10 days with peaks above 39°C, cough, orthopnea
- Hospitalized 3 days before in Colmar, France:
 - hypoglycemia
 - diagnosis of sepsis from pulmonary origin
 - treatment: levofloxacin



Relevant medical history

- Diabetes type 1
- Chronic kidney failure with kidney graft in 2004
- Coronary artery bypass graft surgery in 2006, complicated by MRSA mitral endocarditis, mediastinitis and sternitis treated by sternectomy

Treatment

- Mycophenolic acid 360 mg q24h
- Everolimus 1,25 mg q12h
- Methylprednisolone 2 mg q24h
- Ambulatory insulin pump therapy
- Furosemide 20 mg q24h
- Acetylsalicylic acid 100 mg q24h
- Carvedilol 6,25 mg q24h
- Atovarstatin 20 mg q24h
- CaCO₃ 1 g q24h
- Colecalciferol 1x/month
- Pregabalin 75 mg q12h
- Zolpidem q24h



Physical examination at admission

- Blood pressure 120/70 mmHg
- Temperature 37,7°C
- Heart rythm 86/min
- Cardiac auscultation: no heart murmur
- Pulmonary auscultation: pulmonary stasis

Laboratory results and chest X ray

Parameters	Values	Normal values
Hemoglobin (g/dl)	11.5	12 - 16
WBC (/ μ l)	2 830	4 500 - 10 000
Platelets (/ μ l)	73 000	150 000 - 400 000
Glucose (mg/dl)	182.6	70 - 110
Urea (mg/dl)	65.1	20 - 40
Creatinin (mg/dl)	2.51	0.50 - 0.90
Estimated creatinin clearance (ml/min)	26	> 60
C-reactive protein (mg/dl)	8.36	< 0.75

Chest X ray: cardiomegalia without pulmonary infiltrates



Treatment and evolution

- Amoxiclav IV switched to Piperacillin tazobactam after 3 days because of recurrence of fever (39,3°C) and chills

Day 5: call from Colmar



« presence of yeasts in the blood cultures »



Candidemia in a kidney graft recipient with chronic kidney failure :

Which treatment would you give him?

- 1 - Fluconazole (400 mg q24h IV)
- 2 - Voriconazole (6mg/kg q12h IV day 1, followed by 4mg/kg q12h IV)
- 3 - Caspofungin (70 mg day 1 followed by 50 mg q24h)
- 4 - Anidulafungin (200 mg day 1, followed by 100 mg q24h)
- 5 - Amphotericin B lipid formulation (Liposomal Amphotericin B 3mg/kg q24h or Lipid complex Amphotericin B 5mg/kg q24h)
- 6 - Amphotericin B lipid formulation + Flucytosine (25-37,5 mg/kg q12h)

Candidemia in a kidney graft recipient with chronic kidney failure :

Which treatment would you give him?

1 - Fluconazole (400 mg q24h IV) | 0%

2 - Voriconazole (6mg/kg q12h IV day 1, followed by 4mg/kg q12h IV) | 0%

3 - Caspofungin (70 mg day 1 followed by 50 mg q24h) | 0%

4 - Anidulafungin (200 mg day 1, followed by 100 mg q24h) | 0%

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6 - Ampho B lipid + Flucytosine (25-37,5 mg/kg q12h) | 0%



Management

- Administration of Anidulafungin 200mg, followed by 100mg q24h
- Immunosuppressive therapy was reduced (mycophenolic acid stopped, everolimus reduced)

Additional information from Colmar

- Identification: *Candida parapsilosis*
- In vitro susceptibility¹:

Molecule	MIC ($\mu\text{g/ml}$)	Thresholds ($\mu\text{g/ml}$)	Interpretation
Fluconazole	> 256	S \leq 1; R>1	Resistant
Voriconazole	3	S \leq 1; R>2	Resistant
Caspofungin	1	S \leq 2; R>2	Sensitive
Amphotericin	0.25	S \leq 1; R1	Sensitive

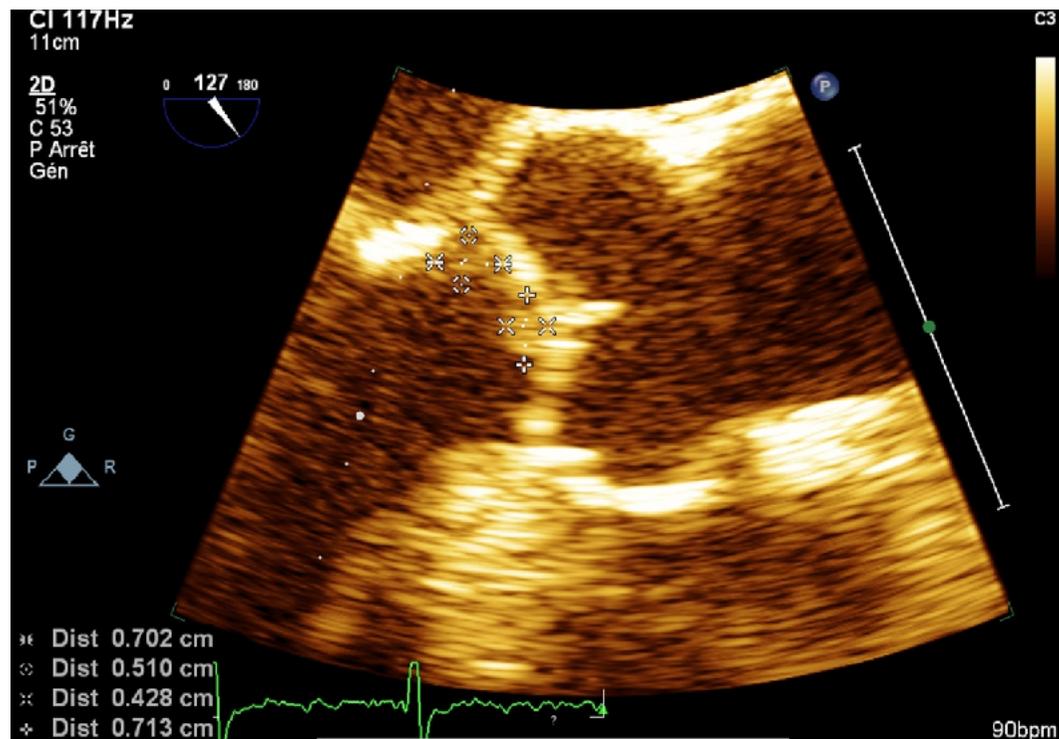
MIC: minimal inhibitory concentrations

S: sensitive

R: resistant

¹Laboratoire de parasitologie et mycologie, Strasbourg, France

Transoesophageal echocardiography



- 2 vegetations on the aortic valve (4x7 mm and 5x7mm)
- Mild aortic insufficiency
- Good ventricular function (FEVG 65%)



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Endocarditis due to Azole resistant *C. parapsilosis*.

Which treatment would you give him now?

- 1 - Caspofungin (70 mg day 1 followed by 50 mg q24h)
- 2 - Anidulafungin (200 mg day 1, followed by 100 mg q24h)
- 3 - Amphotericin B lipid formulation (Liposomal Amphotericin B 3mg/kg q24h or Lipid complex Amphotericin B 5mg/kg q24h)
- 4 - Amphotericin B lipid formulation + Flucytosine (25-37,5 mg/kg q12h)
- 5 - Echinocandin with higher dosage (Caspofungin 150mg q24h or Anidulafungin 200mg q24h)
- 6 - Another combination therapy (like Caspofungin + Flucytosine, or Caspofungin + Amphotericin B lipid complex...)

Endocarditis due to Azole resistant *C. parapsilosis*: Which treatment would you give him now?

- | | |
|--|----|
| 1 - Caspofungin (70 mg day 1 followed by 50 mg q24h) | 0% |
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Evolution

- Anidulafungin was maintained
- Biological improvement
- Clinical improvement but recurrence of fever and increasing lumbar pain
- lumbar imaging suggestive of spondylodiscitis Th12-L1



Bone scintigraphy



CT scan

Evolution

- Blood cultures: Positive for *Candida parapsilosis* on day 5, 13 and 18 after starting anidulafungin
- in vitro susceptibility results ¹ ²:

Molecule	MIC (µg/ml)	Interpretation
Fluconazole	>64	Resistant ¹
Itraconazole	0,125	Sensitive ²
Voriconazole	4	Resistant ¹ ²
Caspofungin	>2	Resistant ¹
Amphotericin	0,25	Sensitive ²
Flucytosine	0,125	Sensitive ²

¹ CHU Charleroi (Disk diffusion method. Interpretation following CLSI criteria)

² Institute of Public Health



Endocarditis due to Echinocandin and Azole Resistant *C.parapsilosis* in a kidney graft recipient with chronic kidney failure: which treatment now?

- 1 - Amphotericin B lipid formulation
- 2 - Amphotericin B lipid formulation + Flucytosine
- 3 - Echinocandin high dosage + Voriconazole
- 4 - Another combination therapy (like Caspofungin + Flucytosine, or Caspofungin + Amphotericin B lipid complex...)
- 5 - I really don't know; let's call Pr Aoun!

Endocarditis due to Echinocandin and Azole Resistant *C.parapsilosis* in a kidney graft recipient with chronic kidney failure: which treatment now?

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| 1 - Amphotericin B lipid formulation | 0% |
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| 5 - I really don't know; let's call Pr Aoun! | 0% |



Would you perform cardiac surgery?

NB: CABG in 2006, complicated by MRSA mitral endocarditis, mediastinitis and sternitis treated by sternectomy

- 1 - Yes, it is the only curative approach
- 2 - It will depend on the evaluation of the operative risk by the surgical team
- 3 - Only if antifungal therapy alone fails
- 4 - No, the risk is too high

Would you perform cardiac surgery?

NB: CABG in 2006, complicated by MRSA mitral endocarditis, mediastinitis and sternitis treated by sternectomy

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|--|----|
| 1 Yes, it is the only curative approach | 0% |
| 2 It will depends on the evaluation of the operative risk by the surgical team | 0% |
| 3 Only if antifungal therapy alone fails | 0% |
| 4 No, the risk is too high | 0% |

Further management

- Liposomal Amphotericin B progressively increased to 250mg q24h, associated with Flucytosine 2g q12h
- No cardiac surgery performed;
 - risk estimated too high by the surgical team
 - no valvular dysfunction, no uncontrolled sepsis, no new definite embolic events
 - satisfactory evolution under medical therapy
- Liposomal Amphotericin B administered for 3 months
- Flucytosine ongoing (chronic suppressive therapy)



Evolution and potential portal of entry

- No more vegetations observed by TEE after 2 months of combination therapy and also after 1 year of suppressive therapy
- Renal function stable
- Patient is doing well today

- Presence of *Candida parapsilosis* in an urine culture 1 year before admission: is urinary tract the portal of entry of this infection?

Discussion

- *C. parapsilosis* have reduced susceptibility to echinocandin¹.
- Development of resistance during treatment with Caspofungin for a prosthetic valve endocarditis have been described ².
- Mortality of *C. parapsilosis* endocarditis in an historical review of 72 cases was 53% for medical therapy alone, and 33% for medical therapy combined with surgery ³.
- However in a recent series of 27 *Candida* endocarditis, mortality was similar in both groups (27% with medical therapy alone, and 33% with combined therapy) □.
- Liposomal Amphotericin B and Flucytosin were well tolerated and no nephrotoxicity was observed.

1. Munro CA. Fungal echinocandin resistance. F1000 Biology Reports 2010, 2:66

2. Moudgal V et al. Multiechinocandin- and multiazole resistant *C. parapsilosis* isolates serially obtained during therapy for prosthetic valve endocarditis. AAC, Feb 2005 p767-69

3. Garzoni C et al. *C. parapsilosis* endocarditis: a comparative review of the literature, Eur J Clin Microbiol Infect Dis (2007) 26:915

4. Baddley JW et al. *Candida* infective endocarditis. Eur J Clin Microbiol Infect Dis (2008) 27: 519



Conclusion

- Amphotericin B lipid formulation and Flucytosin are still the Gold Standard treatment of *Candida* endocarditis
- Nephrotoxicity of Liposomal Amphotericin B is not systematic
- Flucytosin has been used as suppressive agent with success
- Surgery is not always mandatory in case of candida endocarditis
- The role of Echinocandins in the management of Candida endocarditis requires further evaluation
- Cross boarder communication from our French colleagues was remarkable



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- Thank you for your attention