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Case presentation

- **Herein we report a 30-year-old man with FHF that underwent liver transplantation at our center.**

Case presentation

- **who underwent liver transplantation from a deceased donor.**

- **Pretransplant screenings for donor and recipient such as HIV, HBV, HCV, HDV, CMV, EBV, and syphilis for donor and HIV, HAV, HBV, HCV, HDV, CMV, EBV, VZV, PPD, IGRA, and syphilis for the recipient were negative**
- **CMV (D+,R-)**
- **No Pre-transplant bacterial infection**

Case presentation

BUN:16 mg/dL (7-20 mg/dL), Cr:0.8 mg/dL (0.6-1.1 mg/dL),

CBC:

WBC:9100 , P:64%

Hg:14.6 g/dl

Plt: 186000

MELD:40

Case presentation

- After the surgery, the patient was admitted in ICU
- Methylprednisolone, Tacrolimus, Cellcept as IS agent were initiated

Case presentation

Whats your idea about Immunosuppressive therapy?

Case presentation

- **Piperacillin/Tazobactam, Ganciclovir, Trimethoprim/Sulfamethoxazole, and Fluconazole as prophylaxis were initiated**

Case presentation

Whats your idea about CMV prophylaxis??

prophylaxis

Table 1
Risk factors for cytomegalovirus disease

	High Risk	Intermediate Risk	Lower Risk	Comments
CMV serostatus	CMV IgG D+/R−	CMV IgG D+/R+, CMV IgG D−/R+	CMV IgG D−/R−	Falsely positive (blood products, IVIG) Falsely negative (loss of antibody, CVID) Equivocal results in donor: interpret as positive Equivocal results in recipient: interpret as negative Not all serologic testing products equivalent
Immunosuppression	Antilymphocyte antibodies (thymoglobulin, alemtuzumab, OKT3)	MMF, azathioprine, tacrolimus, cyclosporine, high-dose steroids	Maintenance steroids mTOR inhibitors	Increased risk for all agents, with higher doses
Organ transplanted	Lung Pancreas Intestine	Heart composite tissue	Liver Kidney	Burden of latently infected cells Higher levels of immunosuppression
CMV-specific cell-mediated immunity	Low	Intermediate	High	Data limited May be useful at guiding prophylaxis and preemptive prevention strategies

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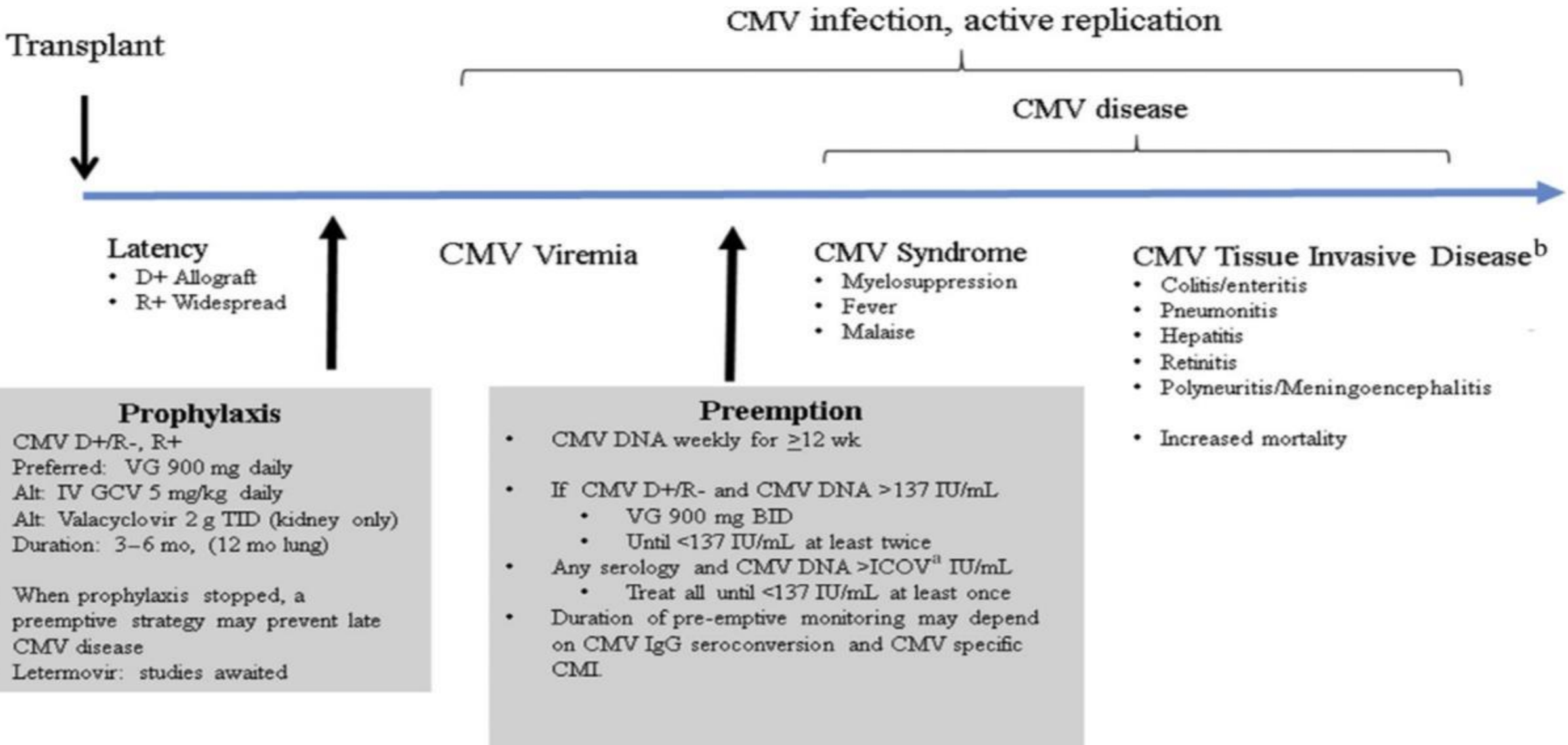
prophylaxis



Universal Prophylaxis for CMV

- CMV D+/R− mismatch
- Lymphocyte-depleting agents such as thymoglobulin & alemtuzumab, highdose mycophenolate mofetil & steroids
- Genetic polymorphisms in the toll-like receptor 2 gene
- Allograft rejection
- Retransplantation

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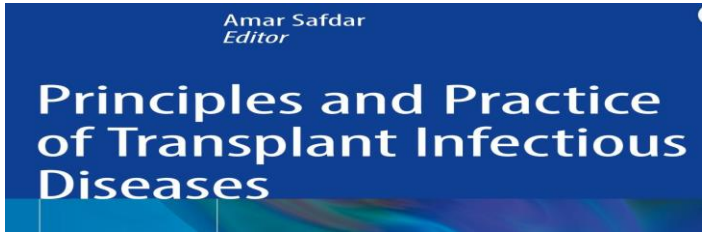
Liver	D+/R−	Antiviral prophylaxis Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir Duration: 3-6 mo	Strong, high (3-month prophylaxis) Strong, moderate (6-month prophylaxis)
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high
	R+	Antiviral prophylaxis Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir Duration: 3 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high



Case presentation

Whats your idea about fungal prophylaxis??

RF for Aspergillosis in LT

Transplant type	Risk factor
Liver transplant recipients	
Early (0-3 mo)	• Re-transplantation • Renal failure, particularly requiring renal replacement therapy • Fulminant hepatic failure • MELD > 30 • Reoperation involving thoracic or intra-abdominal cavity
Late (>3 mo)	• Cytomegalovirus infection • Creatinine > 3.3 g/dL

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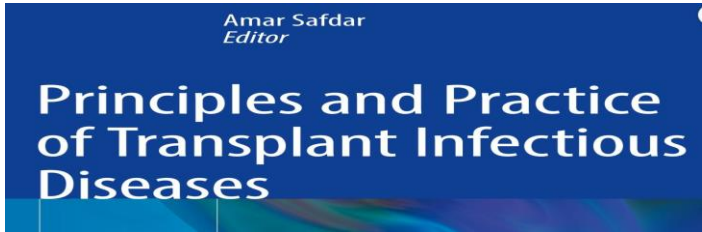
Targeted prophylaxis for Aspergillosis

- Re-transplantation (second or third liver transplant).
- Renalreplacement therapy at the time of or within 7 days of transplantation.
- Reoperation involving thoracic or intra-abdominal cavity, for example, exploratory laparotomy or any intrathoracic surgery.
- FHF
- CMV infection • prolonged intensive care unit stay • multiple invasive bacterial infections(Consider)

Targeted prophylaxis for Aspergillosis

- Anidulafungin, micafungin or caspofungin in standard dose, or voriconazole is recommended for the use of targeted prophylaxis against IA in liver transplant recipients (Strong; high)
- Targeted prophylaxis with a lipid formulation of amphotericin B in dosages ranging 3-5 mg/kg may be considered (Weak; moderate)
- Targeted prophylaxis should be continued for 14-21 days (Strong; high)
- Screening with serum GM and β-D-Glucan is not recommended for preemptive therapy (Weak; low)



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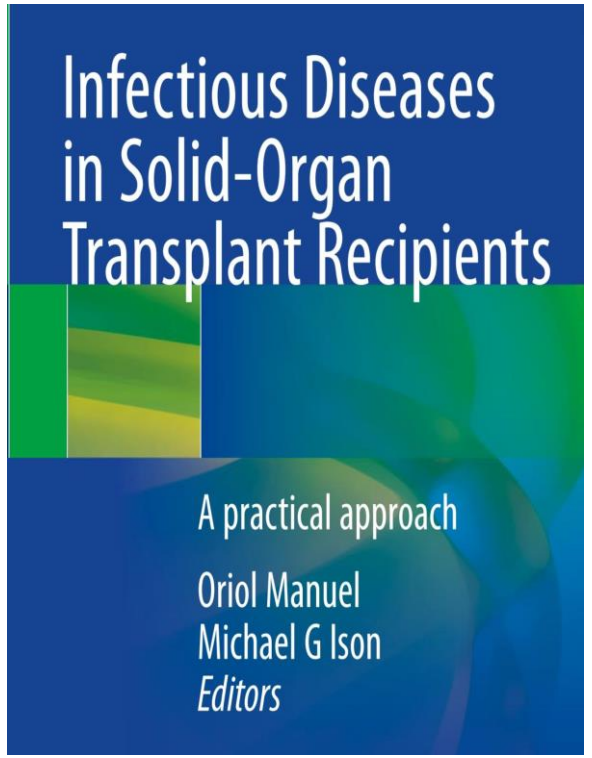
MINIREVIEWS

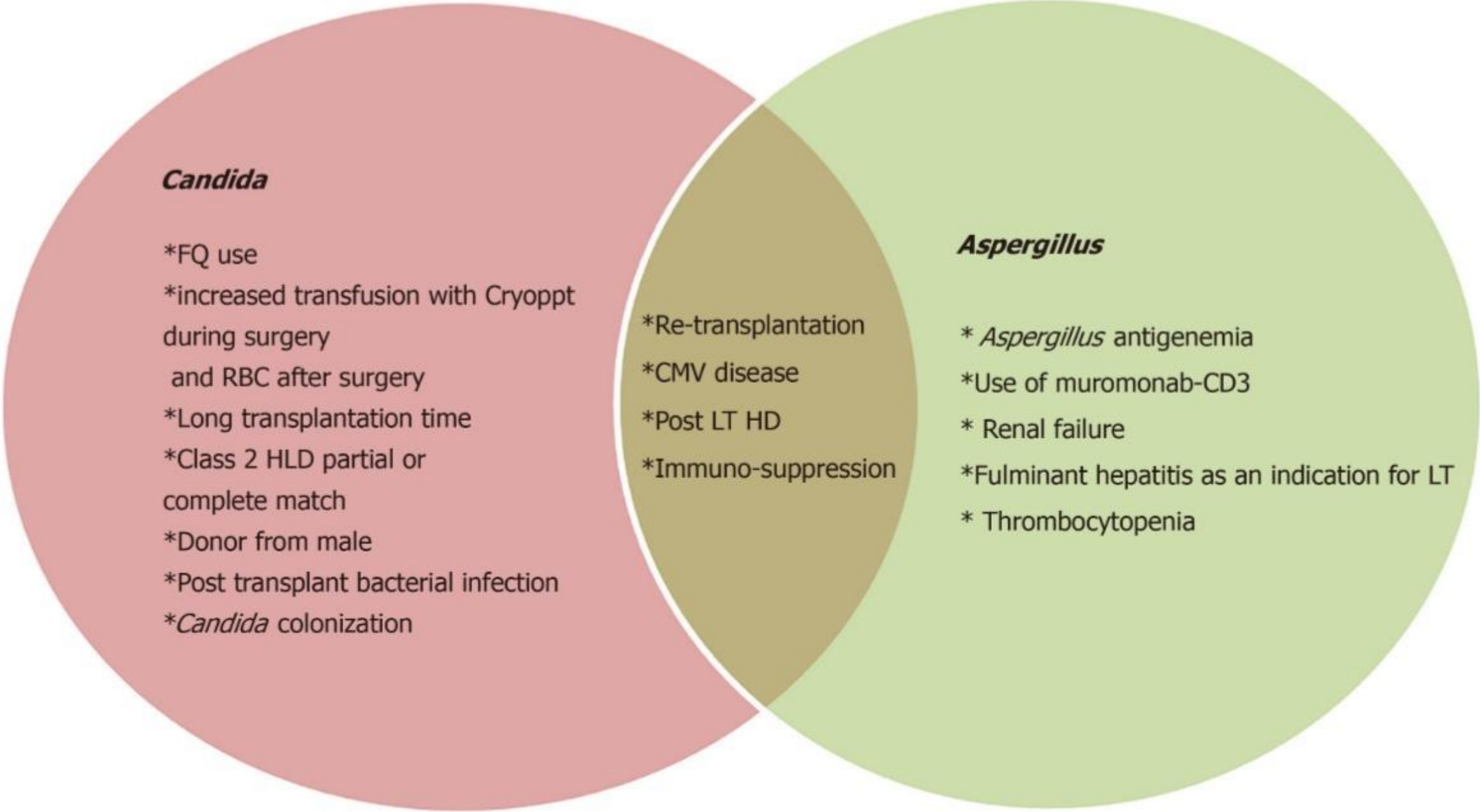
Fungal infections following liver transplantation

Whats Operative Risk factor for invasive fungal infections????

Operative Risk factor for invasive fungal infections

- Prolonged surgical time
- Poor function of allograft
- Iron overload of recipient
- Use of corticosteroids /Use of antilymphocytic antibodies
- Fungal colonization
- Retransplantation/Reoperation
- ≥40 units of cellular blood products
- Choledochojejunostomy
- SBP prophylaxis with fluoroquinolone



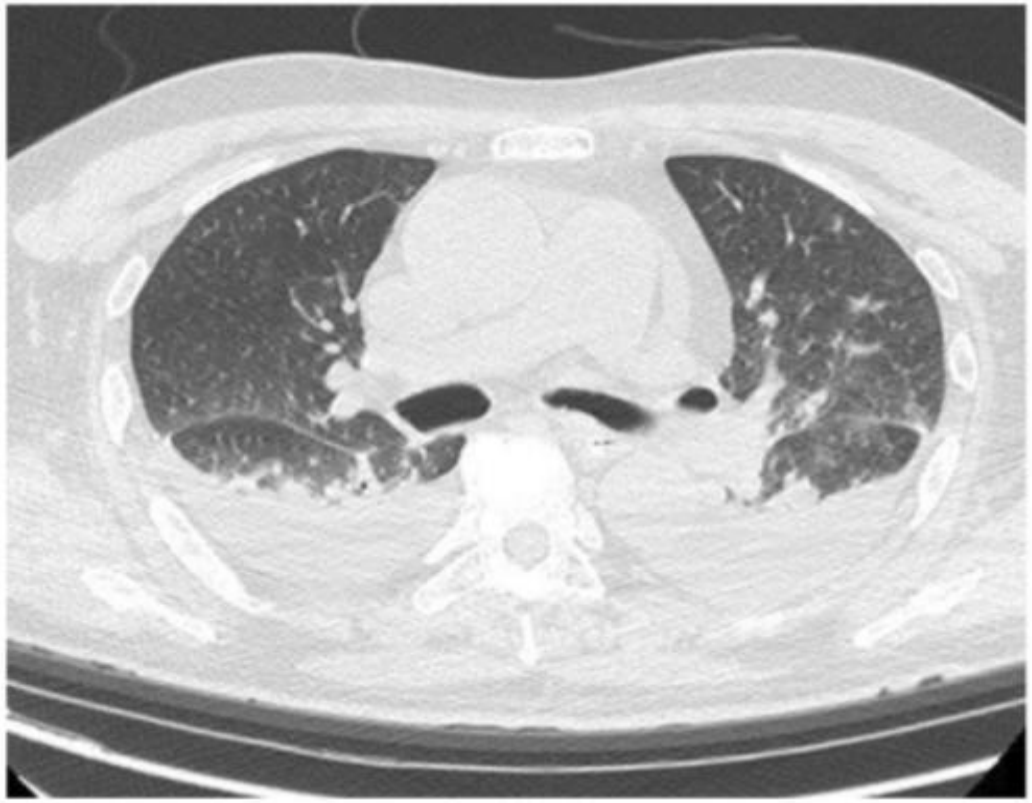

Candida
*FQ use
*increased transfusion with Cryoppt during surgery and RBC after surgery
*Long transplantation time
*Class 2 HLD partial or complete match
*Donor from male
*Post transplant bacterial infection
*Candida colonization
*Re-transplantation
*CMV disease
*Post LT HD
*Immuno-suppression
Aspergillus
* Aspergillus antigenemia
*Use of muromonab-CD3
* Renal failure
*Fulminant hepatitis as an indication for LT
* Thrombocytopenia

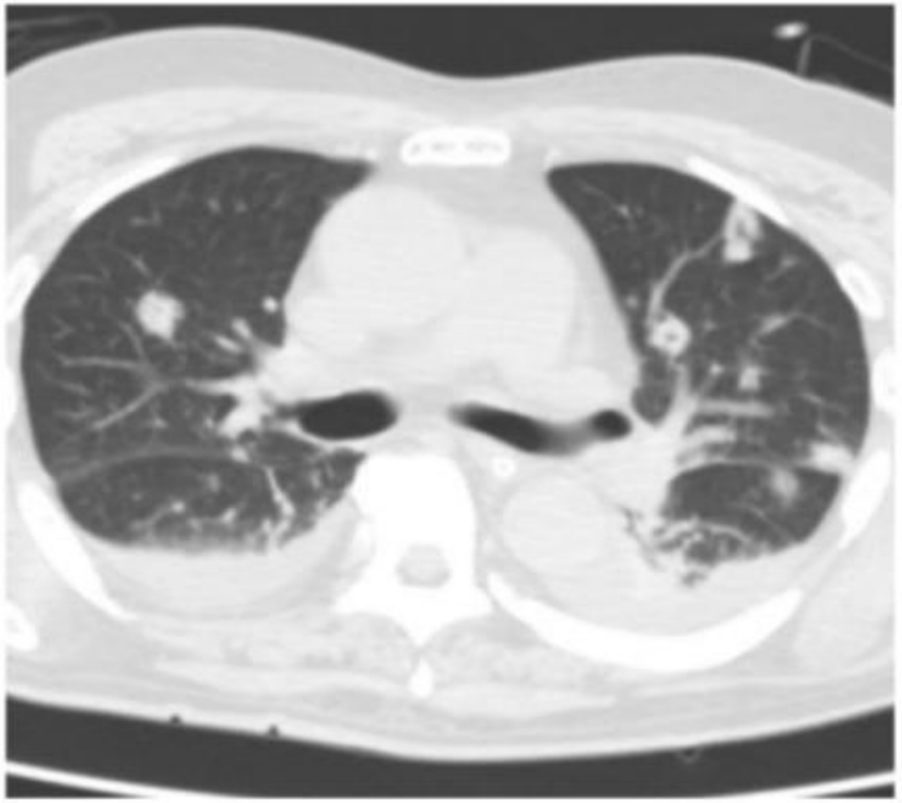
Case presentation

- After 5days post transplant **vital signs revealed a temperature of 101.2°F, pulse 98 beats per minute, respirations 30 breaths per minute, blood pressure 137/99 mm mercury, and a room air oxygen saturation of 87%.**

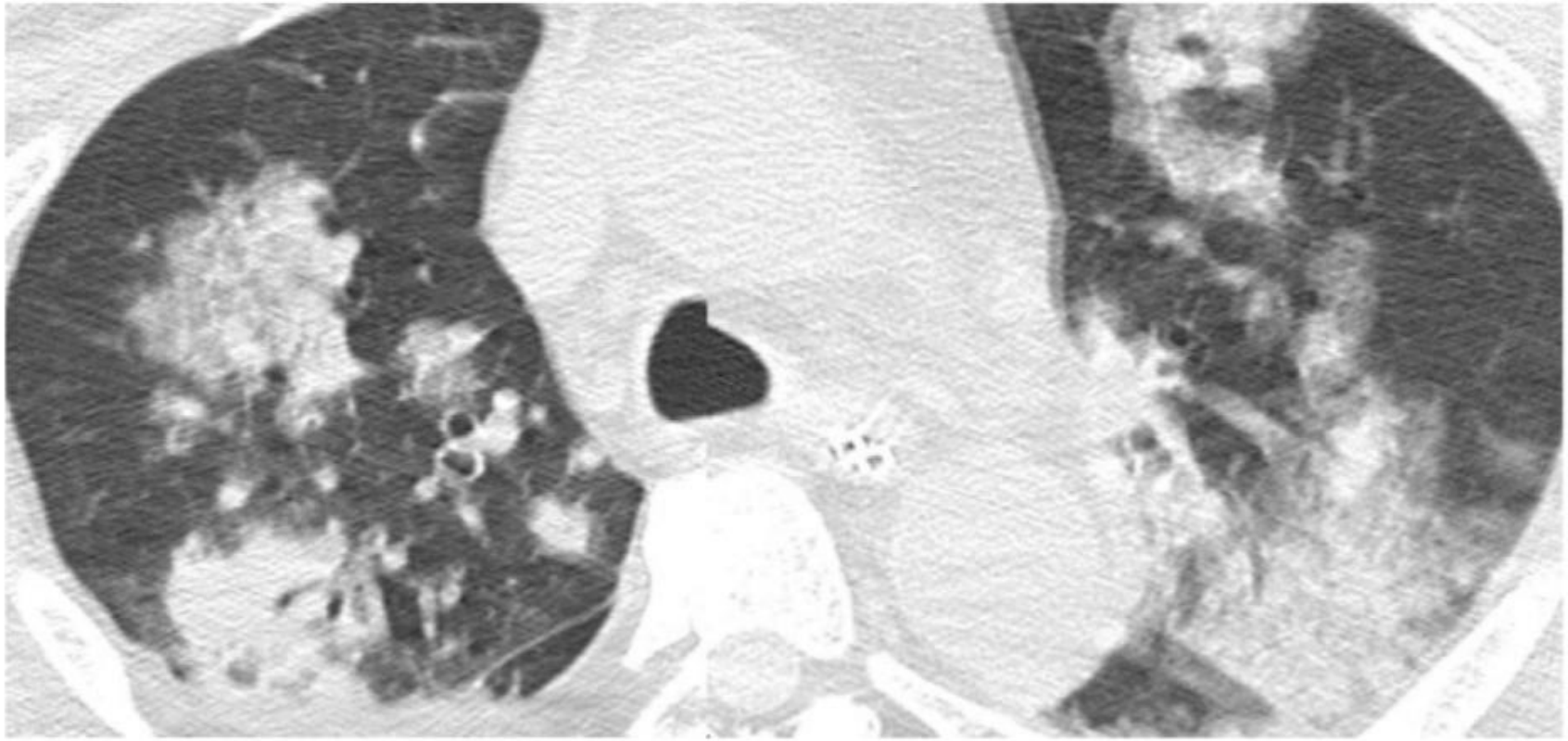
- **Chest CT scan revealed pleural effusion and nodular lesion**

Case presentation





Case presentation



Case presentation

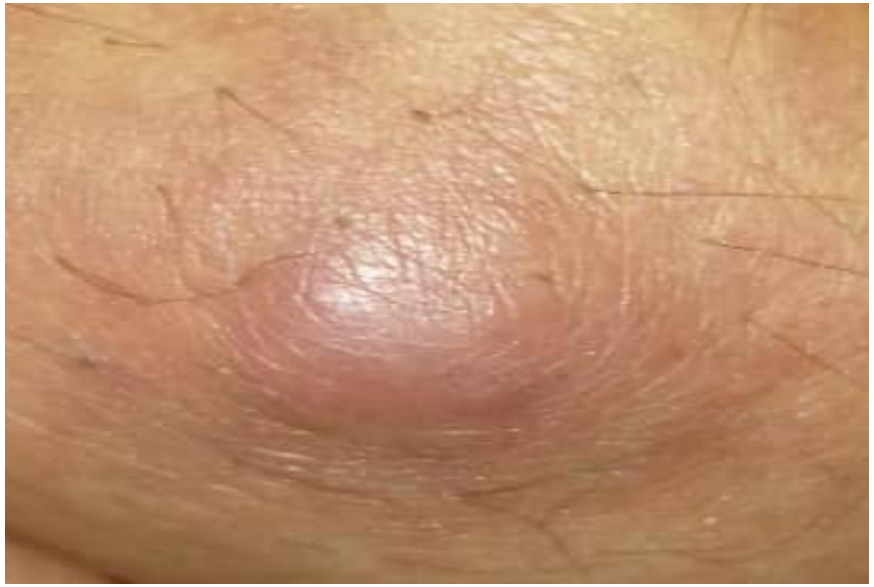
- What disease entities should be considered to explain this patient's clinical syndrome of acute respiratory illness?

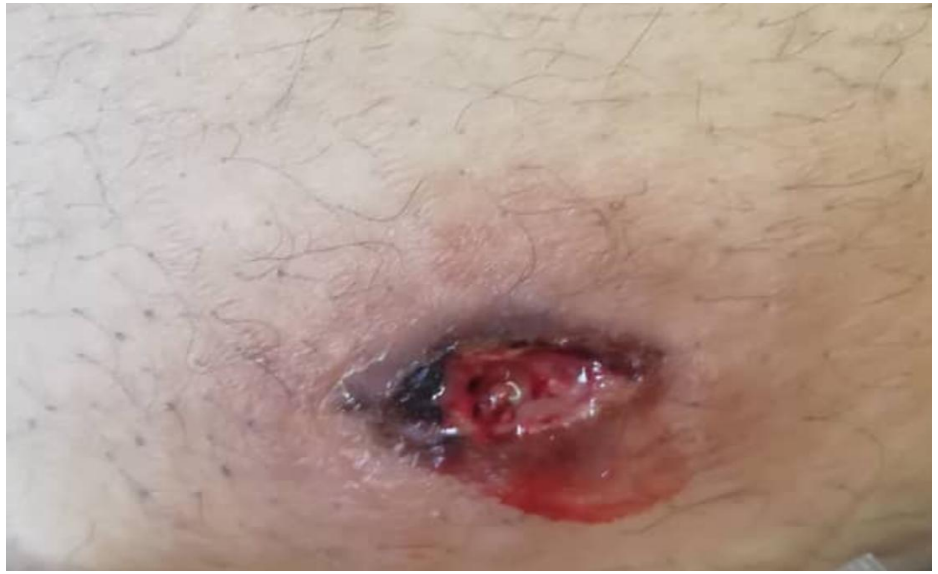
Case presentation

- CMV?
- PCP?
- RVI?
- IFI?

Case presentation

- Simultaneously he had skin ulcer on abdomen





- Whats your DDx?
- Whats your plan for treatment??

Case presentation

- **Broad spectrum antibiotic & Antifungal were started**

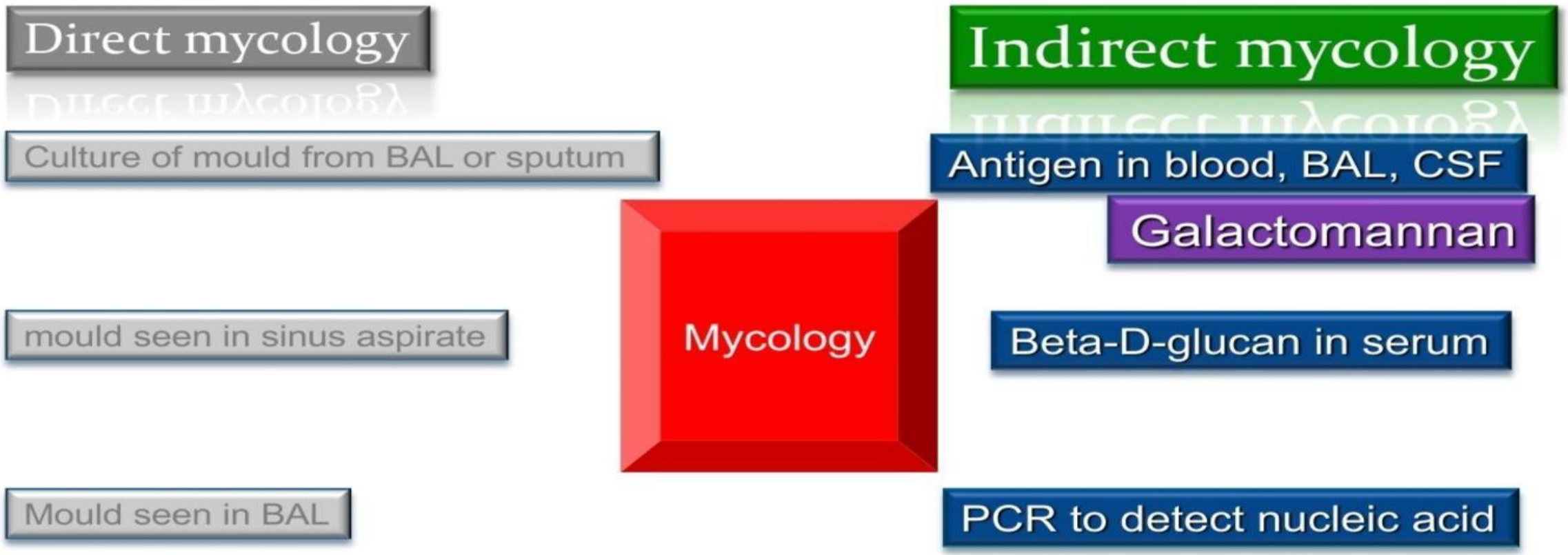
Case presentation

- **Skin biopsy** of abdomen revealed cutaneus ulcer with supputative granoloma and fungal element with septated hyphae that was compatible with **Aspergillosis**.

- **Bronchoalveolar** lavage demonstrated: Positive for **Aspergillosis PCR & GM**

EORTC/MSG Consensus Group definitions:

Proven IFI	Probable IF	Possible IFI
Histological or culture evidence (in sterile material)	Host factors (neutropenia, immunosuppressants) + **Mycological criteria** (direct - cytology, culture of non sterile material - or indirect tests - GM or βDG) + Clinical criteria (+CT/MRI, FBS, retinal)	Host factors + **Clinical criteria**



Definitions of Invasive Fungal Disease • cid 2020:71 (15 September)

Probable Invasive Pulmonary Mold Diseases

- 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

Definitions of Invasive Fungal Disease • cid 2020:71 (15 September)

Probable Invasive Pulmonary Mold Diseases

- 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

Definitions of Invasive Fungal Disease • cid 2020:71 (15 September

MANAGEMENT

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- Serum GM is not recommended to diagnose IA in SOT recipients (Strong; moderate)
- BAL GM is the preferred sampling method for the diagnosis of IPA in SOT recipients (Strong; high quality)
- BAL GM index value cutoff of ≥1.0 is preferred for the diagnosis of IA and in combination with other fungal diagnostic modalities (eg, chest CT scan, culture) (Strong; moderate)
- Standardized BAL Aspergillus PCR can be used in combination with other fungal diagnostic modalities (eg, chest CT scan, BAL GM, culture) for the diagnosis of IA. (Strong; low)

TREATMENT

Voriconazole	AI	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	AI	As effective as voriconazole and better tolerated
Liposomal amphotericin	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	

- Voriconazole is the treatment of choice in most patients; isavuconazole, posaconazole, and L-AmB are important alternative agents.

- Combination therapy can be used in select patients with more extensive infection and in those with significant and ongoing immunosuppression.

Infect Dis Clin N Am 35 (2021) 415–434

Duration of therapy

- The optimal duration of therapy for IA depends upon the:
- Response to therapy
- The patient's underlying disease(s)
- Immune status.

- Treatment is usually continued for 12 weeks

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Case presentation

- At the end of 2 weeks therapy with VOR we have imaging and clinical response.
- He was discharged with continued oral antifungal treatment.
- The patient did not show any relapses for up to 18 weeks.

Take home message

- Fungal infections following liver transplantation remain an influential cause of morbidity and mortality in these patients, despite the low incidence.
- Identification of high-risk patients based on risk factors and starting an appropriate prophylactic antifungal regimen based on R is the first step in avoiding dealing with this evasive disease.

Thank You!