



A man with pulmonary affection

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Man 61 y.o.

- admitted to intensive care
 - respiratory problems necessitating intubation & mechanical ventilation after splenectomy

Patient history

- **myelofibrosis**

- leukocytosis
- thrombopenia
- anemia
 - requiring blood transfusions
 - no evidence of transformation to acute leukemia

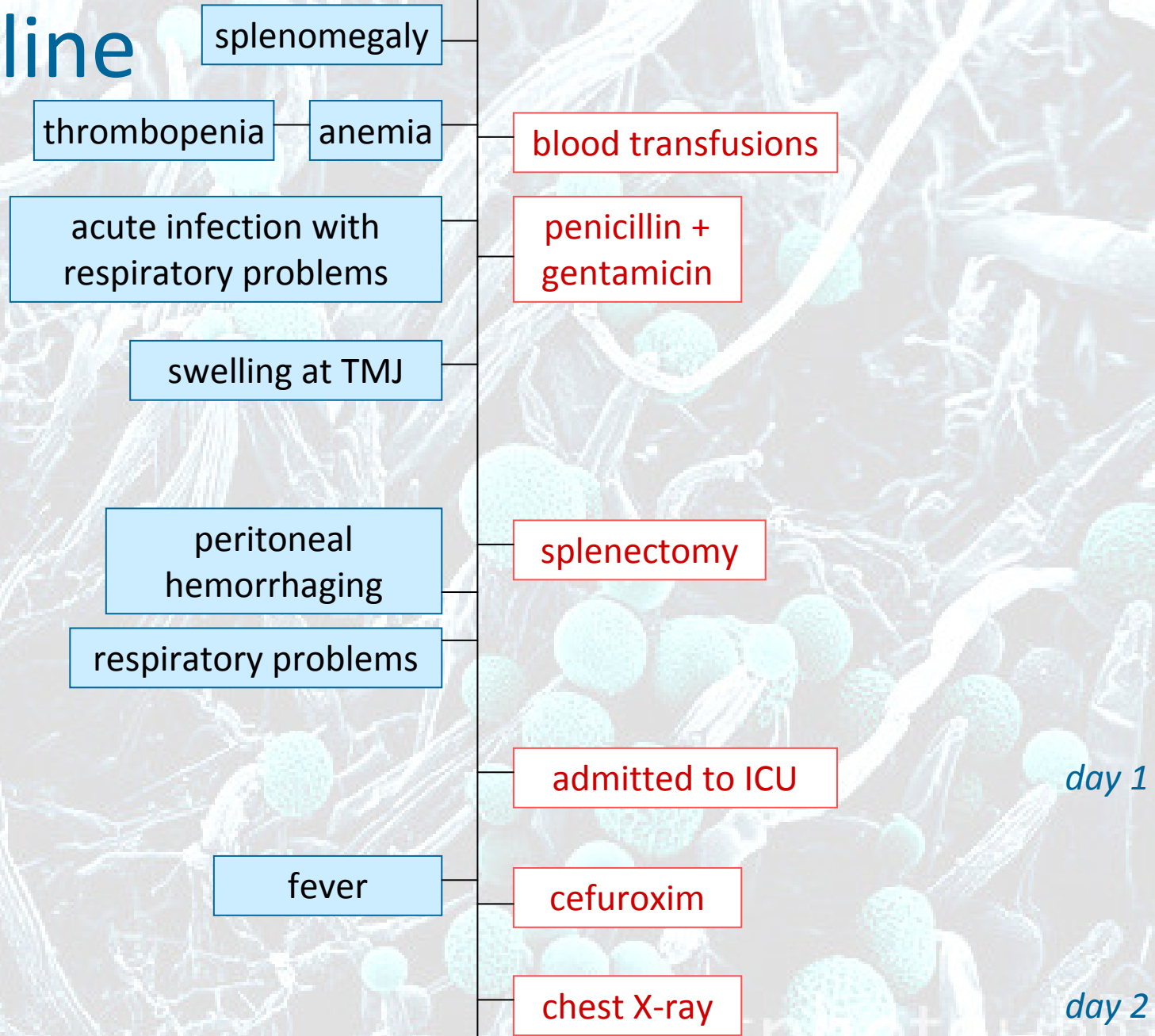
- **splenomegaly**

- *diabetes mellitus type II*
- *hypertension*
- *gout*

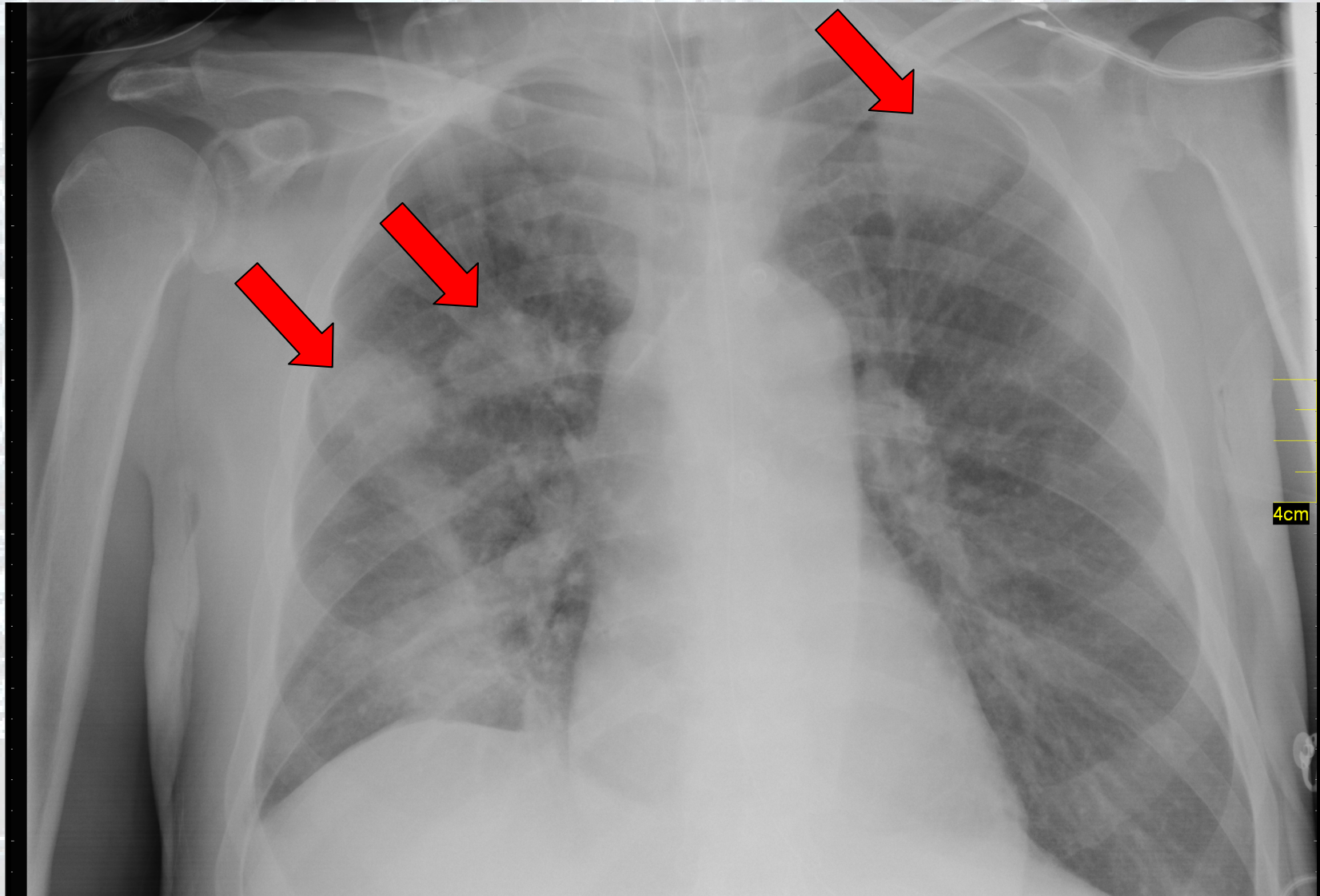
Treated with...

- *Myleran (busulfan)*
- *Hydrea (hydroxyurea)*
- *Thalidomide*
- *prednisolon*

Timeline



day 2 Chest radiography

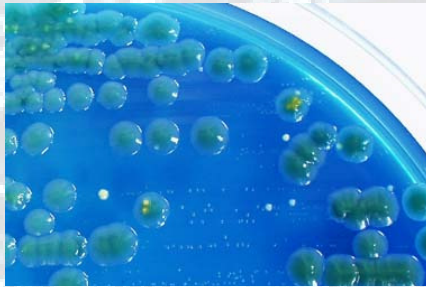


day 2 Chest radiography

- rounded consolidations bilaterally
 - left apically
 - right middle lobe x2

Timeline

contd.



Serratia marcescens

day 3

cefotaxim

extubated,
but soon returns to ICU

day 13

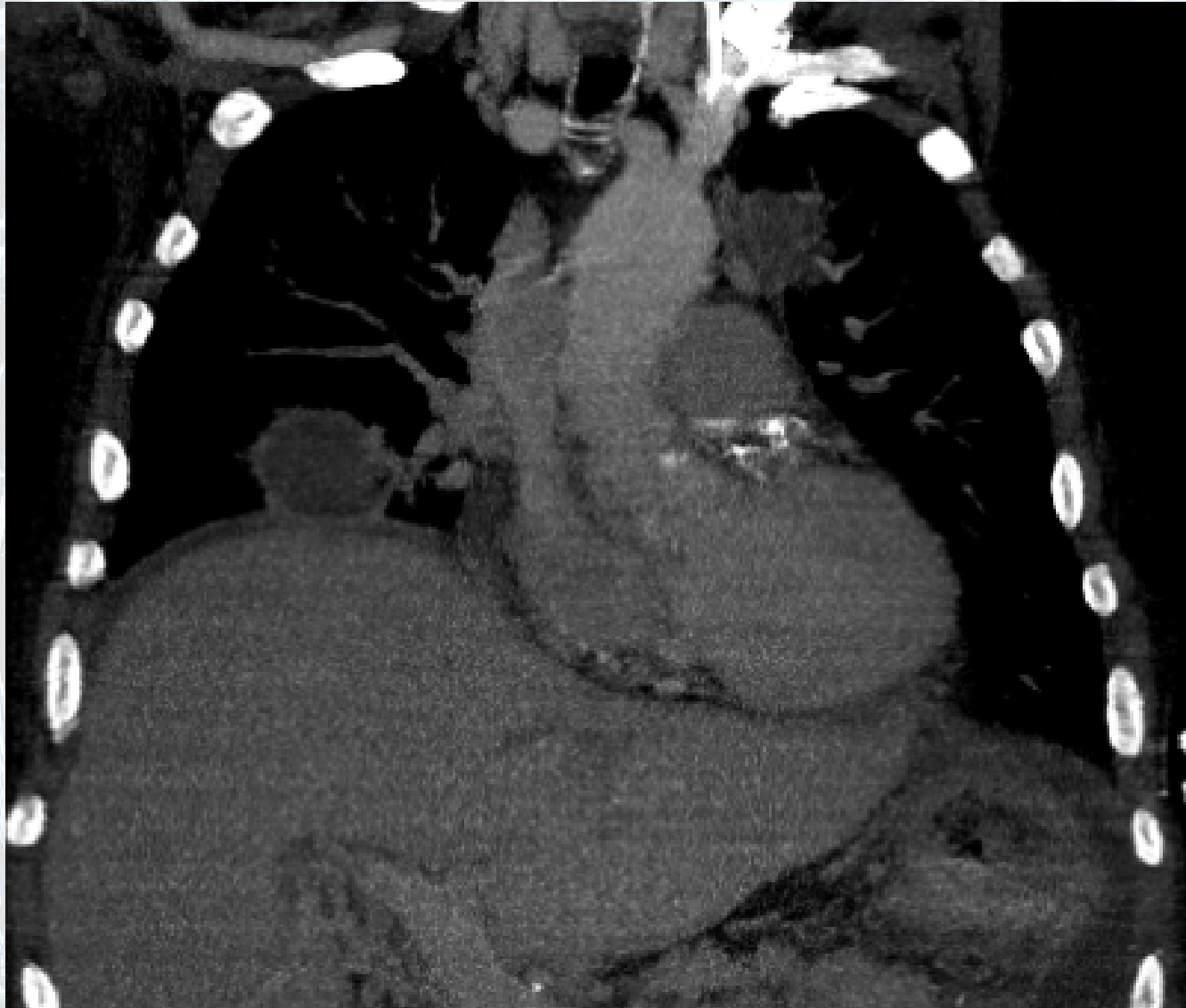
CT chest

day 14

+ metronidazol for 1 day

LIBRARY

Computer tomography of chest day 14



Computer tomography of chest day 14



Computer tomography of chest day 14

- rounded consolidations in both lungs (as seen on X-ray day 2)
 - central fluid with pockets of air
 - multiple septic emboli or fungal infection?
- multiple enlarged mediastinal lymphnodes

Timeline

contd.

ultrasound guided
needle biopsy of the lung

day 15

discussion on anti-fungal
therapy...

meropenem

day 16

histology results
(biopsy 1)

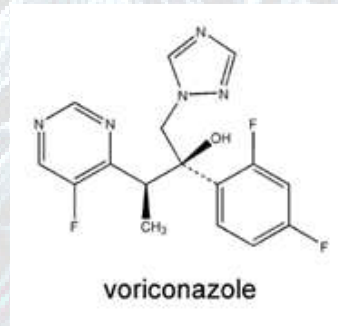
day 20

Histology (biopsy 1)

- fungal hyphae and conidia
 - mostly hyphal fragments
 - uncertain species
 - branching at 45 degree angle in a few places

Timeline

contd.



ultrasound guided
needle biopsy of the lung *day 15*

discussion on anti-fungal
therapy...

meropenem *day 16*

histology results
(biopsy 1) *day 20*

re-biopsy for new culture *day 21*

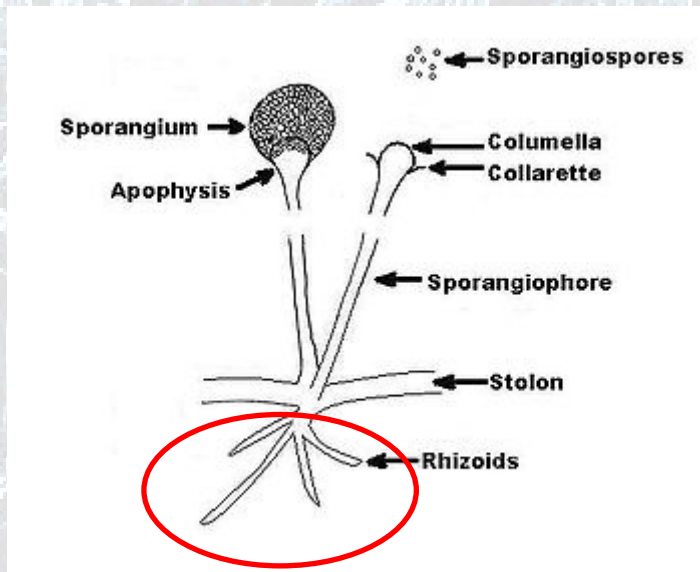
voriconazol 400mg x2

extubated →
out of ICU *day 23*

culture results
(biopsy 2) *day 24*

Culture (biopsy 2)

Mucoraceous mould
Rhizopus/ Rhizomucor



Timeline

contd.

Ambi-Some 5 mg/kg/d

day 24

Cancidase (caspofungin) 70 mg

Ambi-Some 10 mg/kg/d

day 28

fever

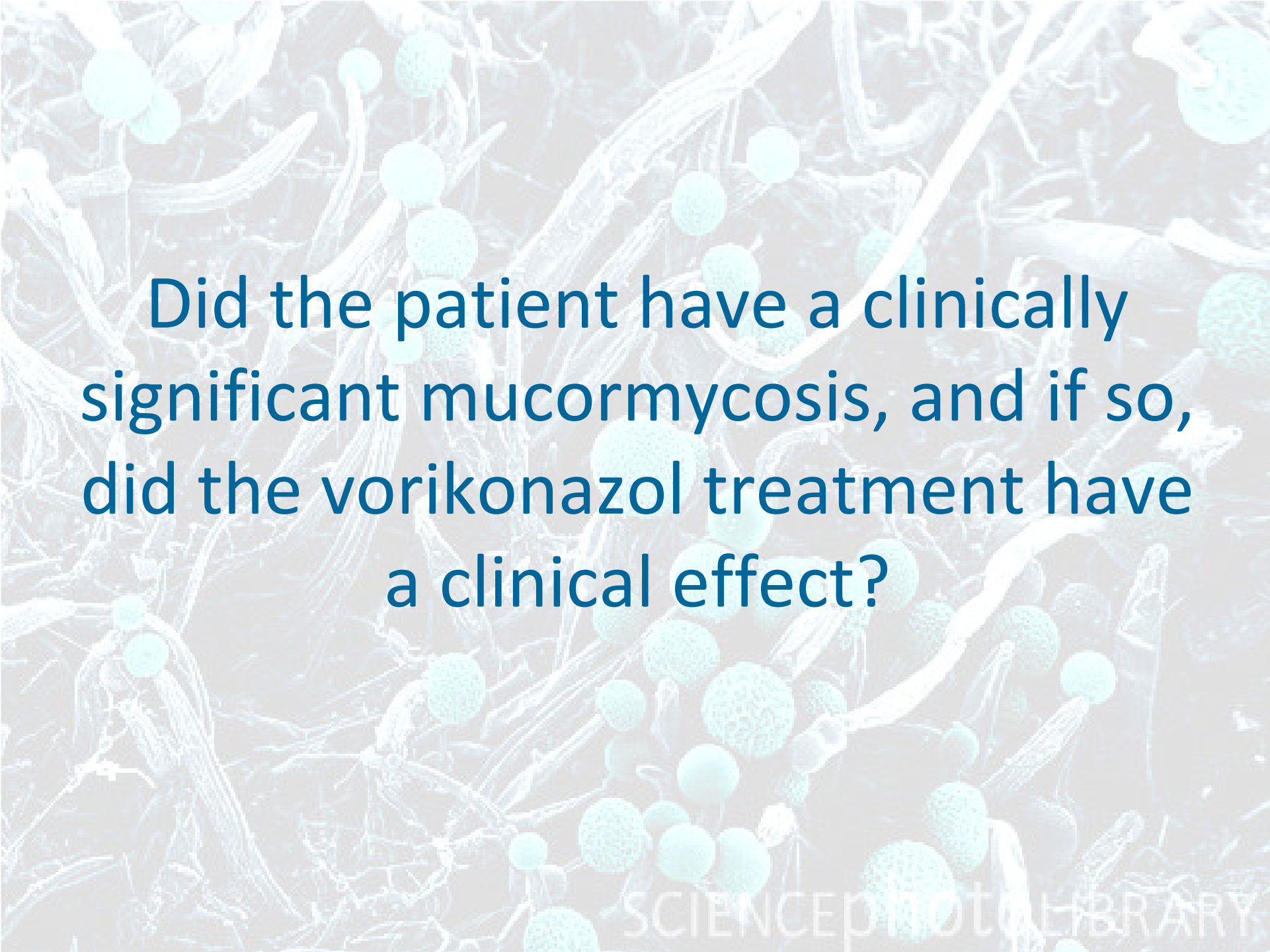
saturation 85%

day 32

ad mortem



day 33



Did the patient have a clinically significant mucormycosis, and if so, did the vorikonazol treatment have a clinical effect?

Mucoraceous moulds

<i>Insertia sedis</i>	Mucoromycotina (Zygomycetes)	Mucorales	Cunninghamellaceae	<i>Cunninghamella</i>
			Lichtheimiaceae	<i>Lichtheimia (Absidia)</i>
			Mucoraceae	<i>Apophysomyces</i>
				<i>Mucor</i>
				<i>Rhizopus</i>
				<i>Rhizomucor</i>
			Saksenaeaceae	<i>Saksenaea</i>
			Syncephalastraceae	<i>Syncephalastrum</i>
			Thamnidiaceae	<i>Cokeromyces</i>
	Mortierellales	Mortierellaceae	<i>Mortierella wolfii</i>	

Mucormycosis

Invasive mucormycosis is characterised by the rapid development of tissue necrosis as a result of vascular invasion and subsequent thrombosis.

Increasing incidence

- *transplant recipients*
- *neutropenia*
- ***diabetes***

- rhinocerebral
 - cutaneous
 - pulmonary
 - gastrointestinal
- disseminated

Pulmonary mucormycosis

Presentation

- rapidly progressive pneumonia
 - usually fatal in 2-3 weeks
 - fever refractory to antibiotics
- hematogenous dissemination
- brain

Risk factors

- hematological malignancies
 - lymphoma
 - leukemia
 - voriconazole prophylaxis
- severe / long-term neutropenia
- immunosuppressive therapy
 - chemotherapy
 - corticosteroids
 - organ transplantation
- AIDS
- diabetes mellitus
- desferrioxamine therapy or iron overload
- malnutrition

Mucormycosis Treatment

- **Reversal of underlying risk factors** when possible
 - reduction of immunosuppression
 - restoration of euglycemia and acid-base balance
- **Antifungal therapy**
 - >6 d delay = doubled mortality at 12 weeks
- **Surgical debridement**

Mortality rate in patients with disseminated disease still
95-100%

Mucormycosis

Antifungal Treatment

<i>Antifungal</i>	<i>Response rate</i>
amphotericin B liposomal	39-95%
amphotericin B deoxycholate	25-61%
<i>posaconazole</i>	14-83%
<i>voriconazole</i>	NA
<i>echinocandins</i> (<i>caspofungin, anidulafungin, micafungin</i>)	NA

Mucorales: Common MICs (mg/l)

<i>Anti-fungal</i> Species	<i>amphotericin B</i>	<i>itraconazol</i>	<i>vorikonazol</i>	<i>posakonazol</i>
<i>Typical serum concentration</i> <i>Therapeutic range mg/l</i>	0.5-2	0,5-2,2 >1	1-6 0,5-2	0.1-4 >1.5
Mucor spp.	0.03-4	0.125-8	8- >64	0.06-8
Rhizomucor pusillus	0.06-0.25	0.03-0.25	2-16	0.06-0.25
Rhizopus spp.	0.03-4	0.25-8	4- >64	0.03-8
Apophysomyces elegans	0.03-2	0.03-8	8- >64	0.03-4
Absidia (Lichtheimia)	0.03-2	0.03-2	2- >64	0.03-1
Cunninghamella	0.125-8	0.125-4	8- >64	0.03-1
Saksenaea vasiformis	0.125-2	0.015-0.03	0.5-4	0.015-0.25

Culture (biopsy 2)

Rhizopus spp (microsporus group)

- MICs
 - amphotericin 0.5
 - anidulafungin >32
 - caspofungin >32
 - itraconazol >32
 - vorikonazol 4
 - posakonazol 0.5

Vorikonazol and mucormycosis

- Voriconazole prophylaxis was significantly associated with "breakthrough" mucormycosis in haematological and solid organ transplant patients
 - but also seen with caspofungin and other azoles without effect against Mucorales!

Possible future treatments for mucormycosis

Antifungal/ synergistic effect of immunosuppressants

- tacrolimus / ciclosporin
 - calcineurin
- sirolimus / everolimus
 - mTOR

Antifungal effects

- colistin / polymyxin E
- statins

- iron chelating agents
 - desferasirox

- hyperbaric oxygen

- granulocyte transfusion
 - GM-CSF
 - interferon gamma