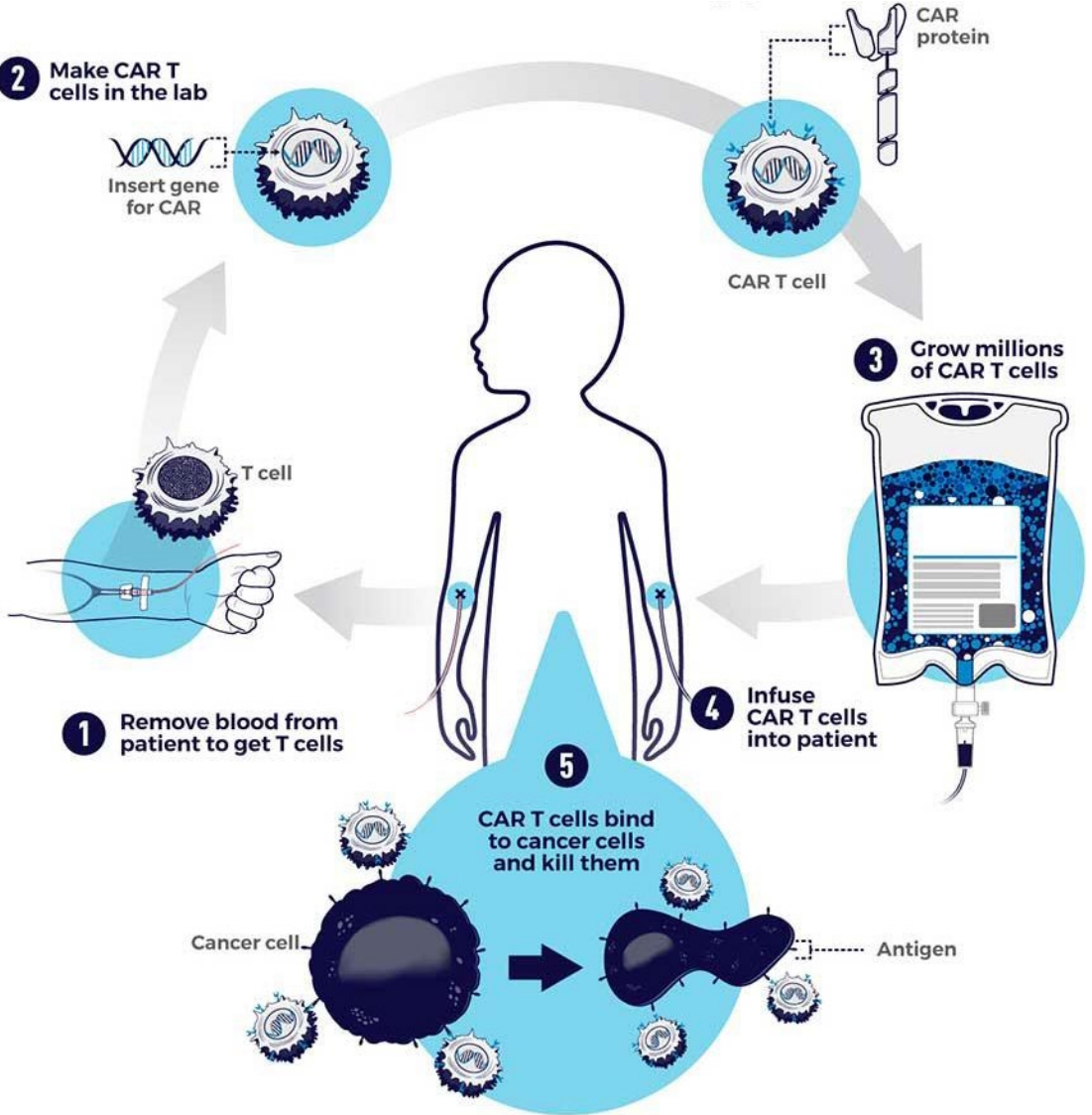


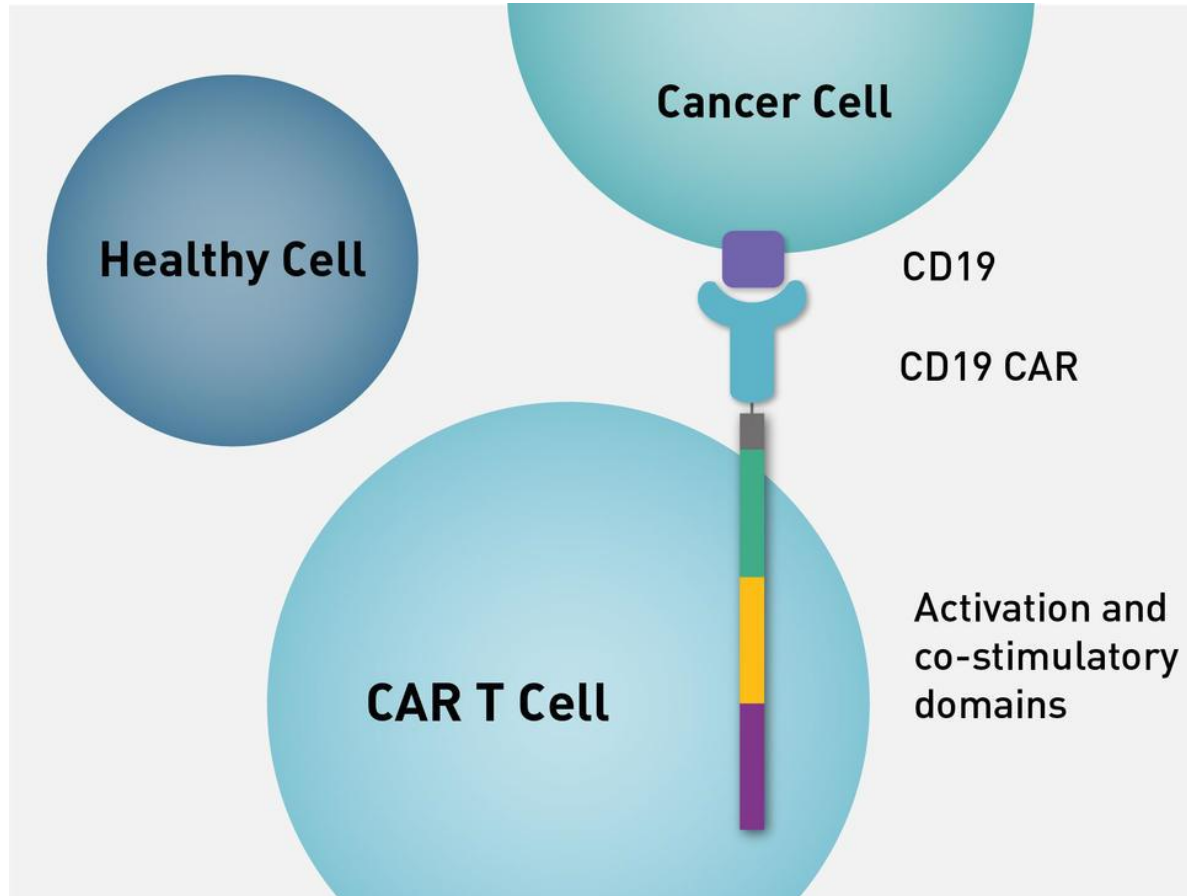
# **Multifocal bacterial infection after CAR-T cells**

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November 1, 2023

# Background: CAR-T cell therapy



# Background: CD19 CAR-T cell therapy



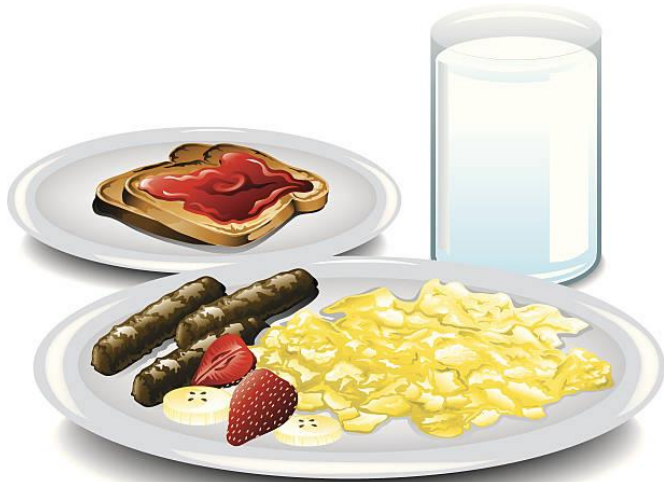
- Immunotherapy for B-cell malignancies
- CD19 = cell surface antigen in most B-lineage lymphomas and leukemias, as well as in normal B cells
- Toxicities:
  - Cytokine release syndrome (CRS)
  - Immune effector cell associated neurotoxicity syndrome (ICANS)
  - B cell aplasia
  - Hypogammaglobulinemia

# Case presentation

- 48 yo F with relapsed/refractory diffuse large B-cell lymphoma (DLBCL)
- Hx malignant pleural effusions - prior thoracenteses removed >1L
- 28 days post CD19 directed CAR T-cells (Yescarta - axicabtagene ciloleucel)
  - Cytokine release syndrome (CRS, grade 2)
    - Tocilizumab x2 and dexamethasone
  - Mold ppx - Isavuconazole
  - Hypogammaglobulinemia - Monthly IVIG

# Case presentation

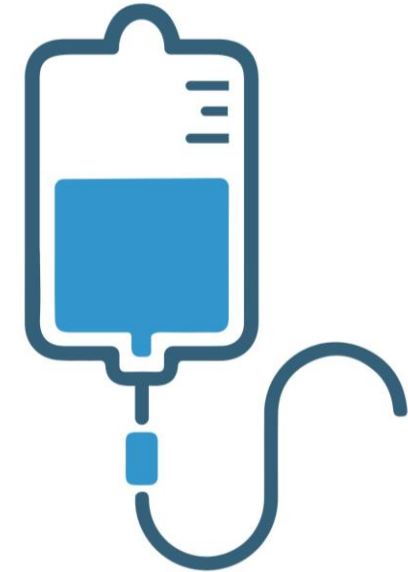
48 F with relapsed/refractory DLBCL 28 days post CD19 CAR T-cells



After breakfast



Sharp, 10/10 pain  
Radiating to back



Not relieved with IV  
hydromorphone

# Initial evaluation

## Vitals:

- Afebrile, 100/80, HR 80, RR 16, O2 100% on room air
- Pain: 3 doses hydromorphone to get pain down to a “tolerable” level

## Exam:

- Abdomen: Soft, nondistended, **very tender to epigastrium and RUQ**

## Labs:

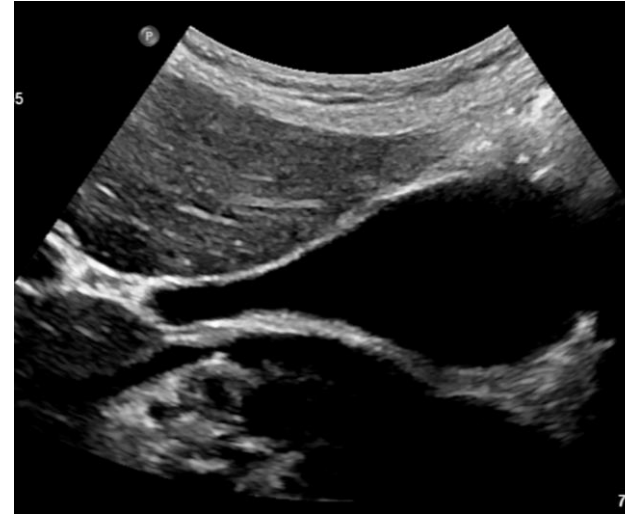
- CBC: stable pancytopenia; absolute neutrophil count ~1,000
- Normal: BMP, LFTs, lipase, LDH, troponin, lactate (1.2)
- CRP 0.3



# Initial imaging

## RUQ US

- Normal liver, no biliary dilatation
- Normal gallbladder
- Minimal perihepatic fluid



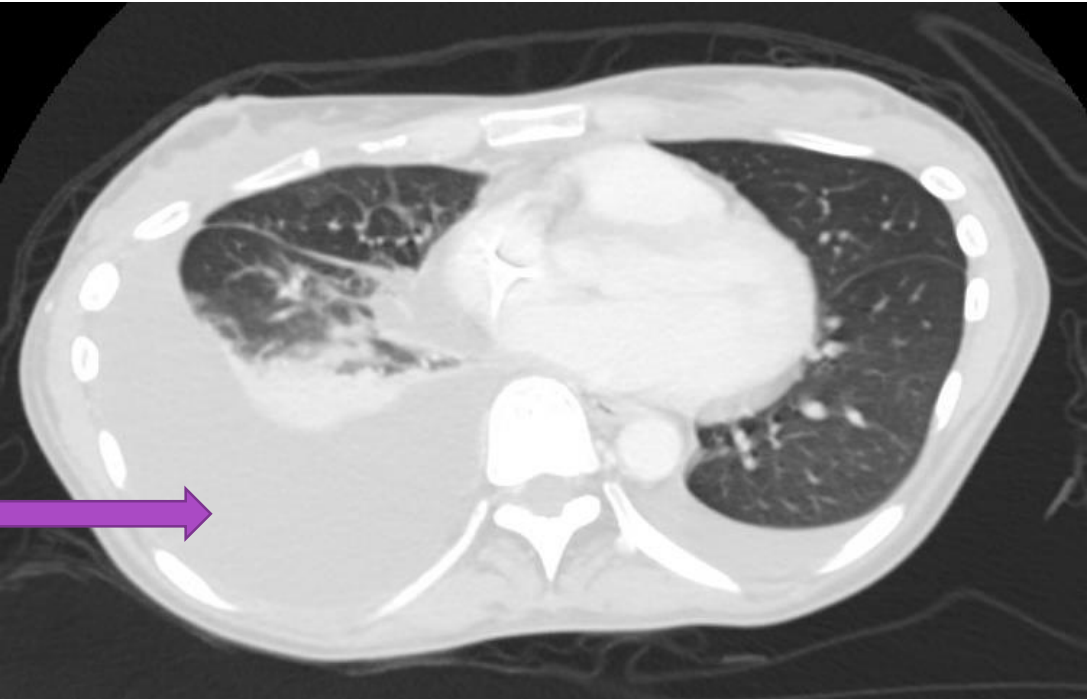
## CT A/P

- Stable lymphadenopathy
- Cholelithiasis without cholecystitis
- Distention of the stomach, no obstructing mass
- Redemonstration of peritoneal thickening



# CT chest

Admission



Before CAR-T



Previous thoracentesis:  
27,000 nucleated cells, 90% neoplastic lymphocytes



What is the most likely cause of the patient's abdominal pain?

- a) Bacterial peritonitis
- b) Mucormycosis
- c) Skin / soft tissue infection
- d) Zoster
- e) Mesenteric ischemia
- f) Empyema

# Initial management and course

- Dx: multifactorial pain - biliary colic, constipation, growing pleural effusion
  - Managed with supportive care
- 12h after admission: rigors, feeling warm, tachycardia, BP 70s/40s
  - Ceftriaxone, 1L IV fluid
- 24h after admission: Recurrent/progressive hypotension
  - Pip/tazo, 2L IV fluid
  - Repeat CT A/P ordered and thoracentesis planned
  - Norepinephrine, ICU transfer, Vancomycin

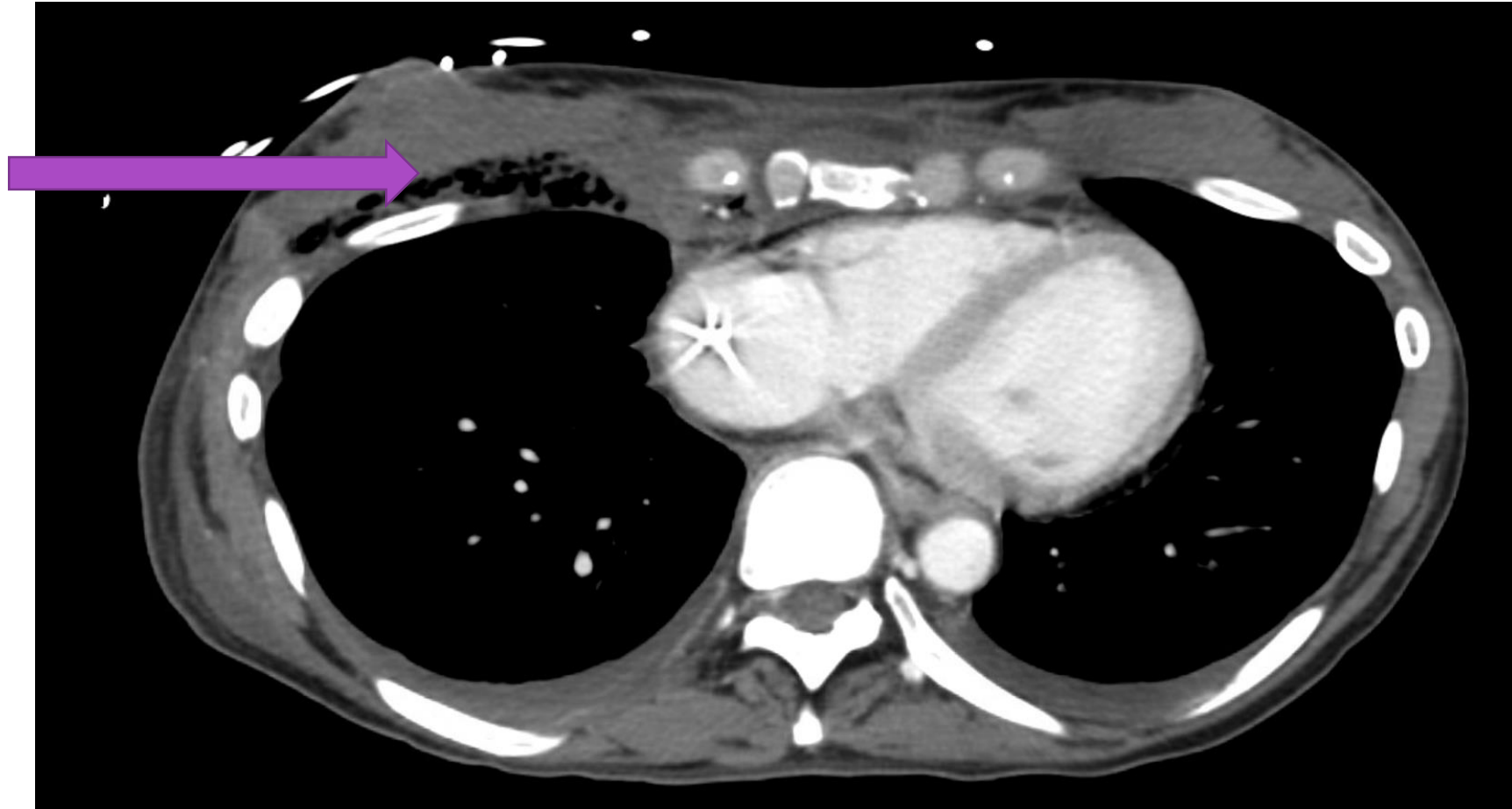
~30 hours after admission

On admission to ICU:

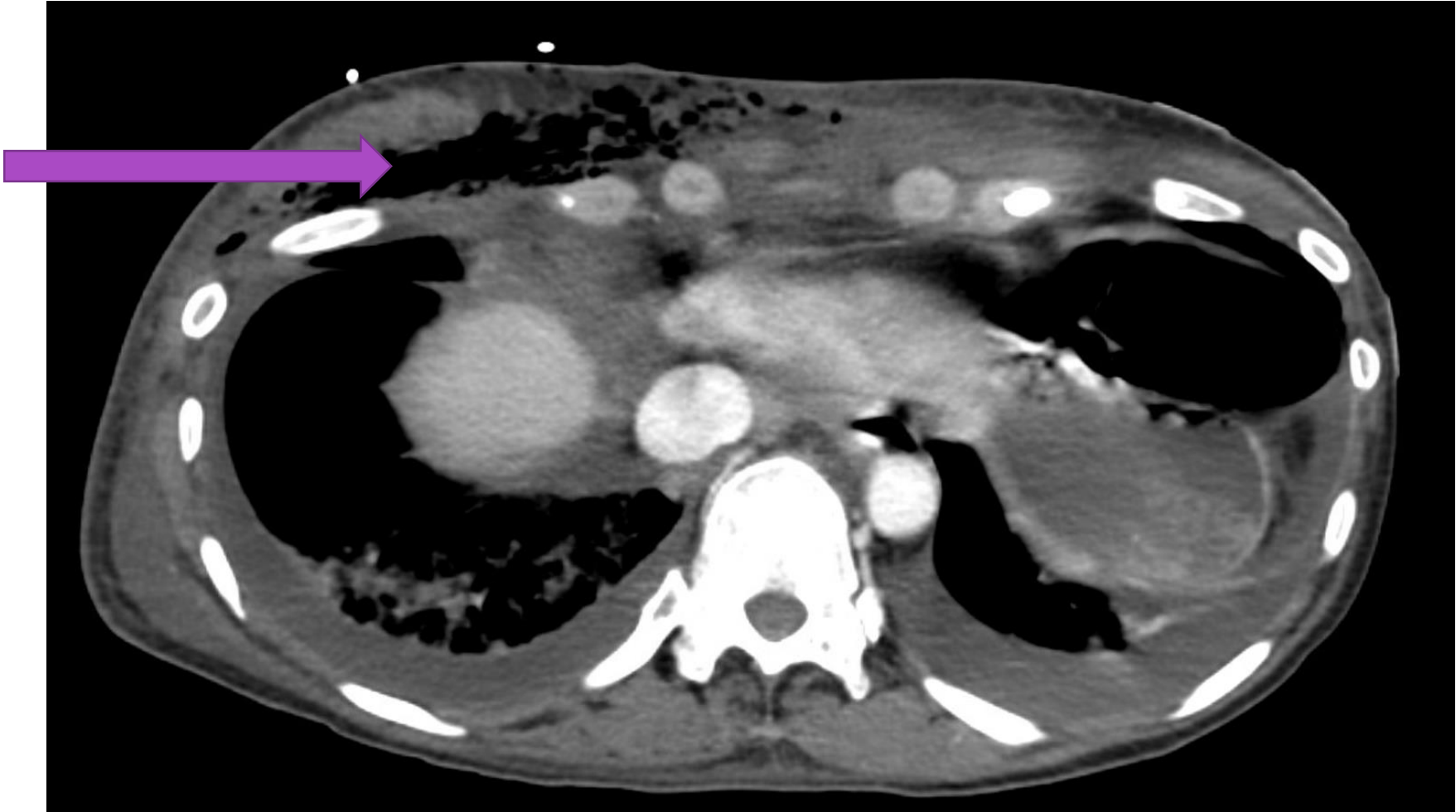
- Purpuric RUQ rash 25x10 cm with well defined border + halo of erythema
- Thoracentesis performed for R pleural effusion
  - pH 7.25, gram stain & subsequent cultures negative



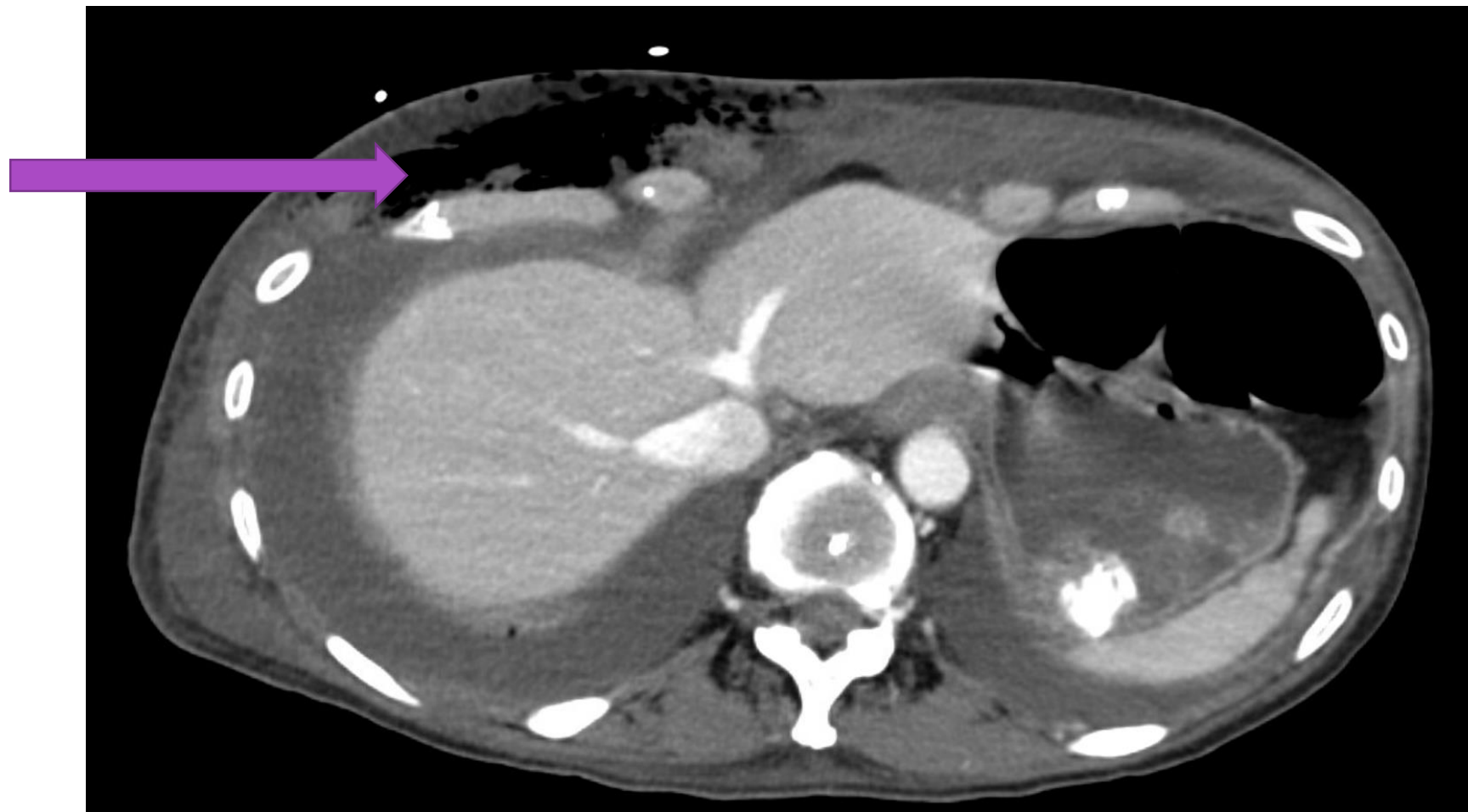
Repeat imaging 36 hours after admission



# Repeat imaging 36 hours after admission



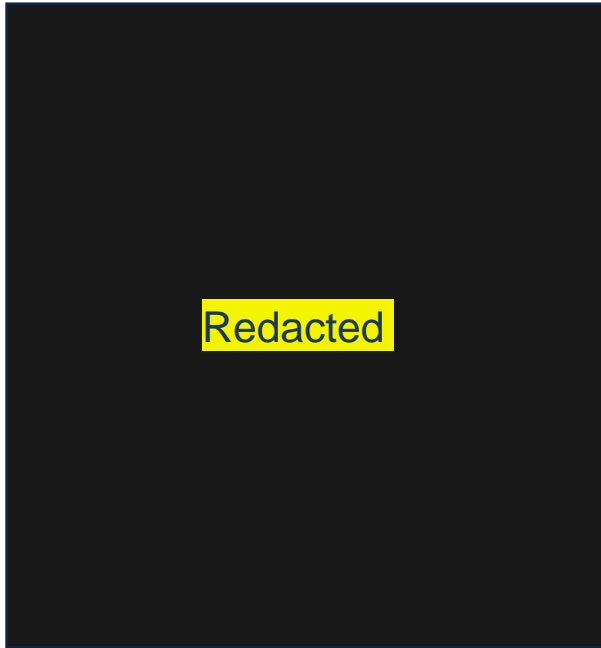
Repeat imaging 36 hours after admission



What is the most likely cause of the patient's abdominal pain?

- a) Bacterial peritonitis
- b) Mucormycosis
- c) Skin / soft tissue infection – necrotizing fasciitis
- d) Zoster
- e) Mesenteric ischemia
- f) Empyema

# Emergent operative debridement of abdominal wall



OR findings:

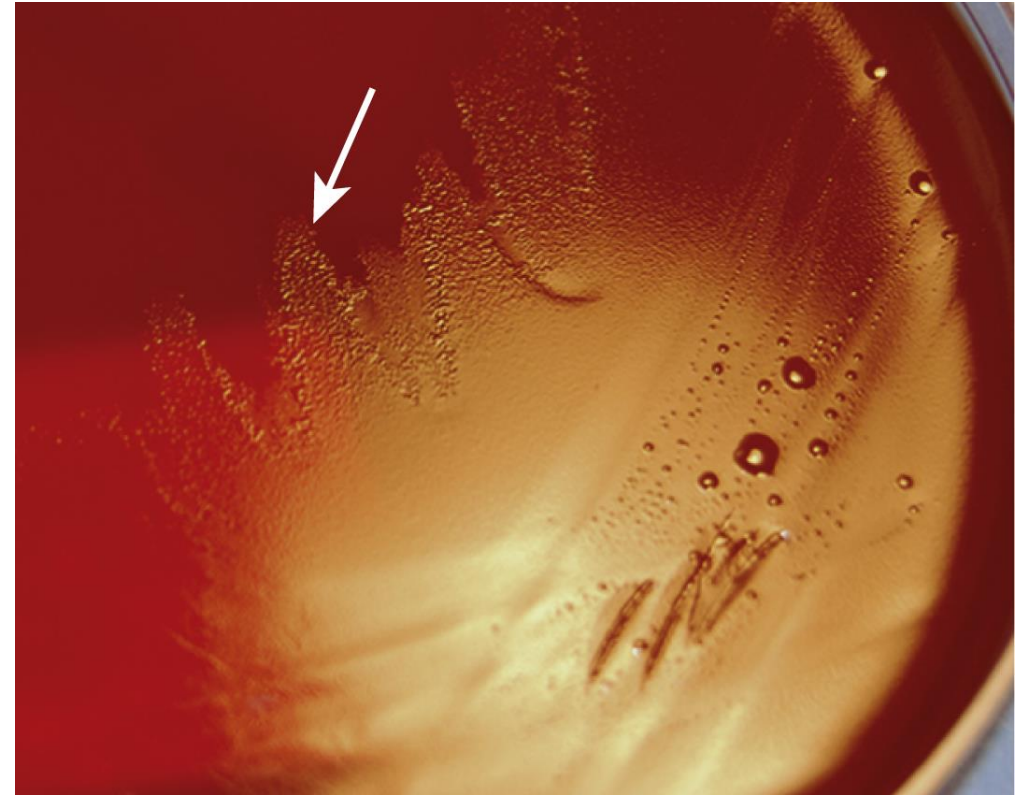
- Extensive muscular necrosis
- Necrotic skin and subcutaneous tissues
- Total area of excisional debridement: 38 x 25 x 2-3 cm.



What is/are the most likely organism(s) responsible for necrotizing fasciitis in this patient?

- a) *Pseudomonas aeruginosa*
- b) *Clostridium*
- c) Group A Strep
- d) Polymicrobial - *Escherichia coli*, *Bacteroides*, Strep
- e) *Staph aureus*
- g) *Vibrio vulnificus*

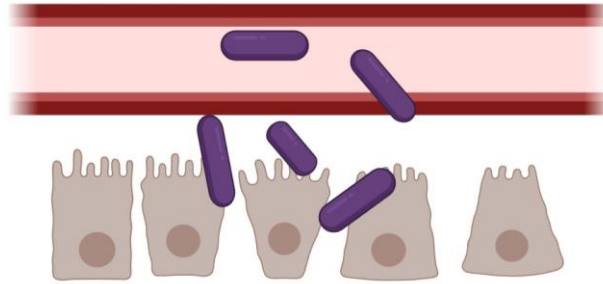
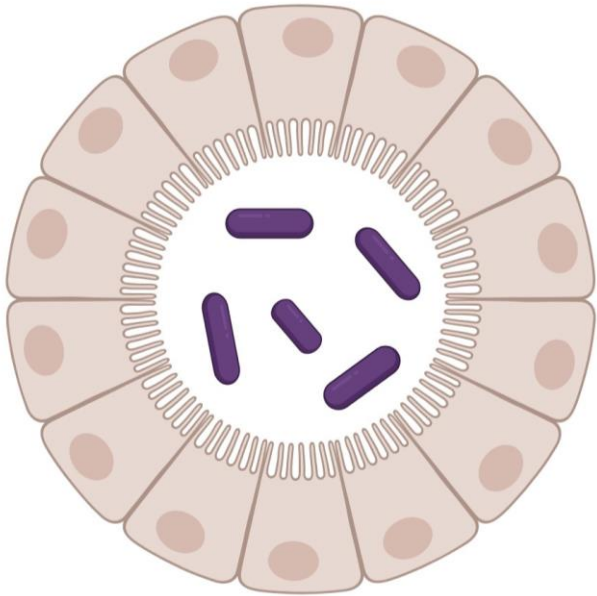
# Clostridium septicum



# *Clostridial* species

- Anaerobic, spore-forming gram-positive bacilli
- Many different species including *C. perfringens*, *C. septicum*
- Treatment of choice is penicillin +/- clindamycin (for toxin inhibition)
  - Also susceptible to vancomycin, piperacillin/tazobactam, carbapenems, metronidazole
- Among cancer patients, clostridial bacteremia is typically seen in:
  1. Solid tumor malignancies (particularly colorectal tumors)
  2. Hematologic malignancies (usually acute leukemia and in the context of neutropenia)
- Rare: median number of episodes ~3 per 1000 oncology hospital admissions
- Mortality ranges from 20% to 48%

# Clostridium septicum



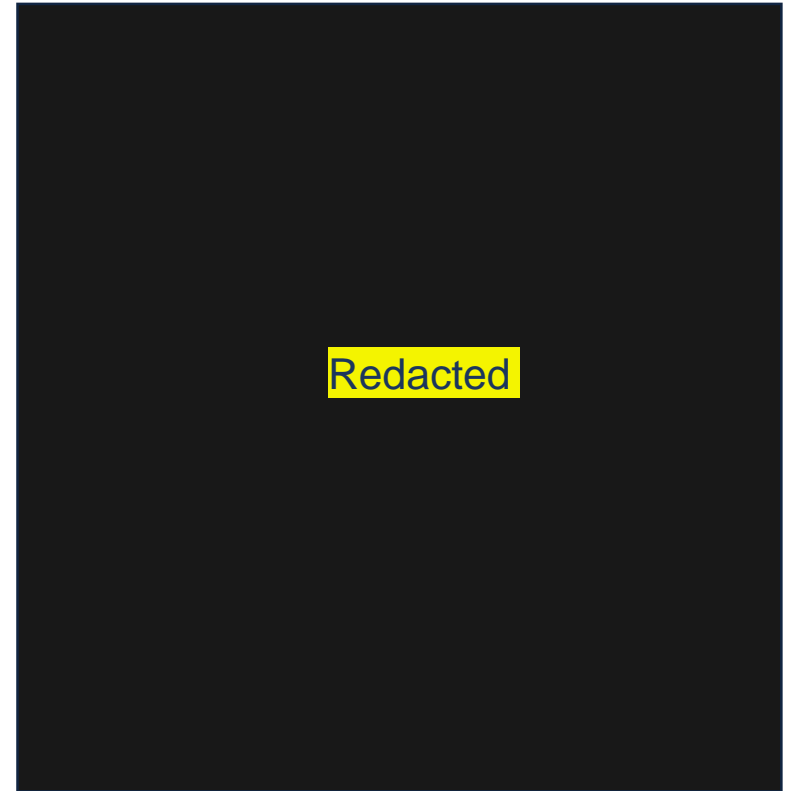
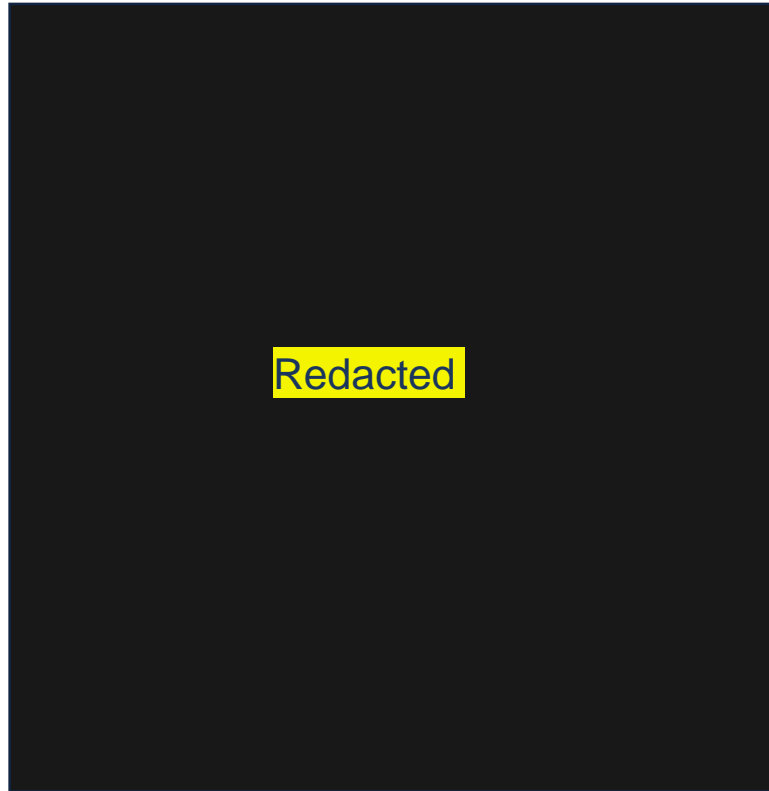
- Spontaneous, nontraumatic myonecrosis – often associated with malignancy
- Neutropenic enterocolitis / typhlitis

# Antimicrobial susceptibility & management

## Mouse studies of *C. septicum*

- High susceptibility to **penicillin, clindamycin and tetracycline**
- Much lower susceptibility to **vancomycin**
  
- Retrospective study of 52 human clinical isolates of *C. septicum*:
  - Low MICs to **penicillin, pip/tazo, clindamycin, metronidazole**
    - No EUCAST breakpoints for non-perfringens species

# Operative management



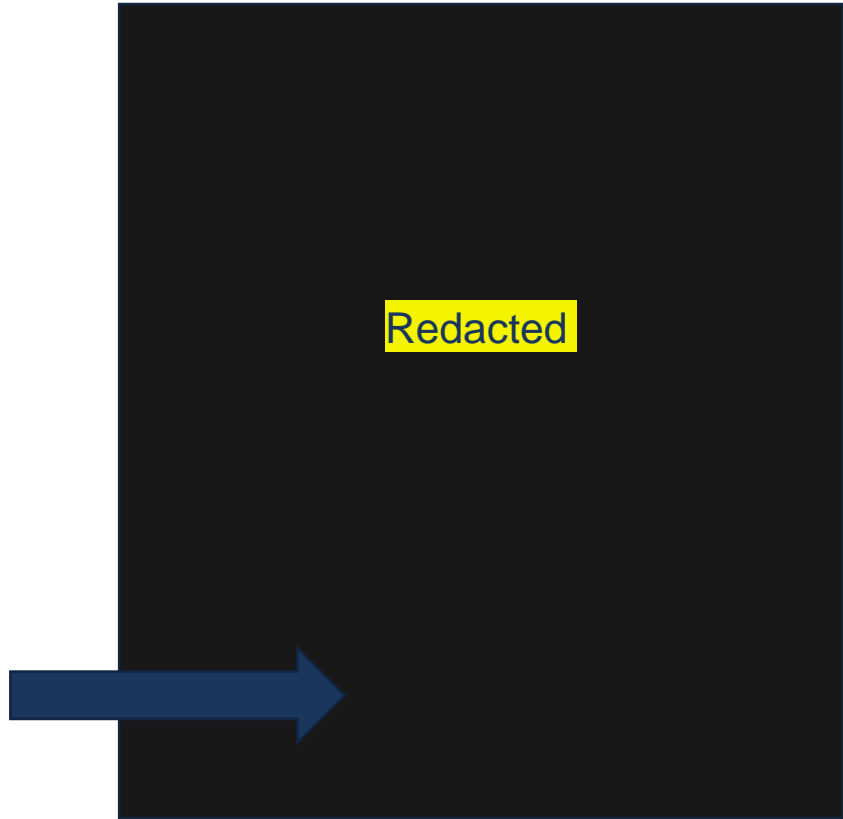
# Antimicrobial susceptibility & management

## Susceptibility

	Clostridium septicum ETEST MIC (MCG/ML)	
Amoxicillin/clavulanic acid	2/1	<b>Susceptible</b>
Ceftriaxone	1	<b>Susceptible</b>
Clindamycin	1	<b>Susceptible</b>
Meropenem	2	<b>Susceptible</b>
Metronidazole	8	<b>Susceptible</b>
Moxifloxacin	>32	<b>Resistant</b>
Penicillin	2	<b>Resistant</b>

# Day 47—recurrent fever, pain & erythema around wound

- Empiric pip/tazo + vancomycin
- Thoracentesis: negative cultures
- Rx: amox/clav x 10 days for SSI/SSTI



CT chest: large R + moderate L pleural effusions persist



# Day 61: Readmission with fever, hypotension, dyspnea

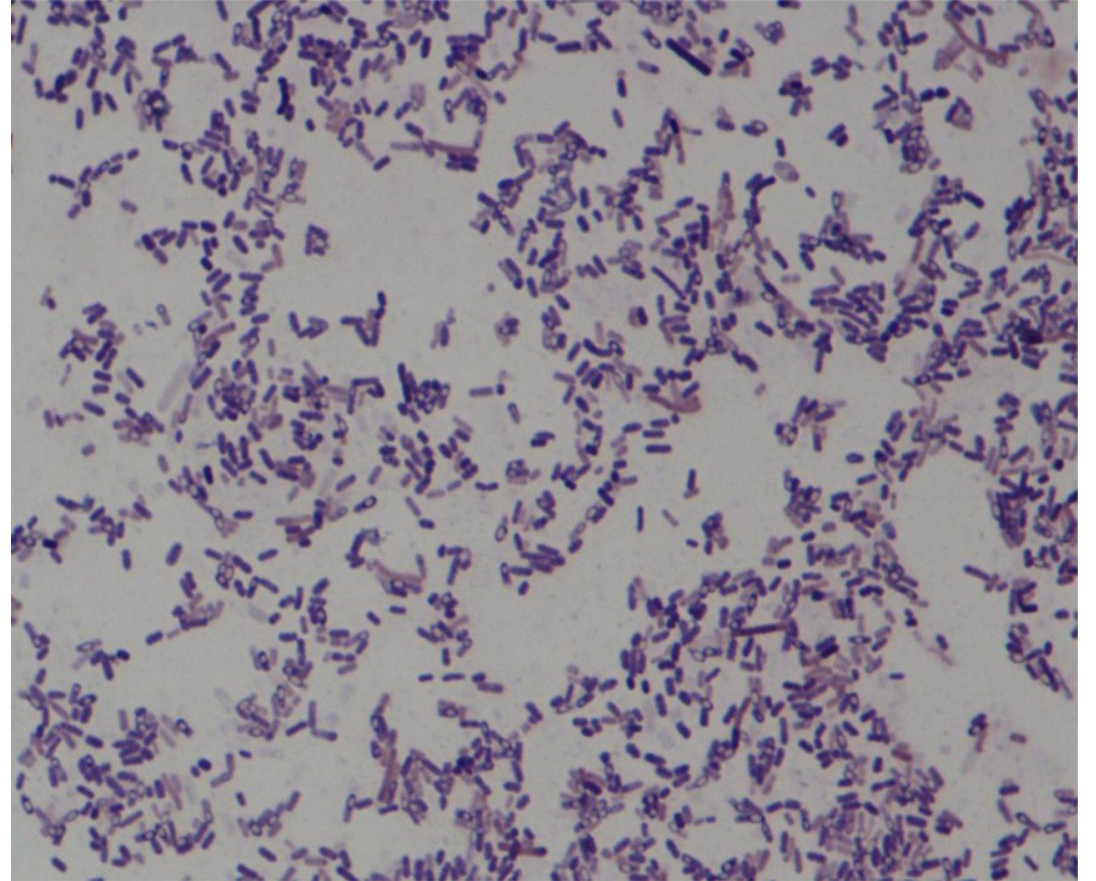


Thoracentesis: 1,880 nucleated cells, exudative, cultures pending

What is the most likely cause of this patient's pleural effusion?

- a) Malignant effusion
- b) Invasive fungal infection
- c) MDR Pseudomonas
- d) Clostridium septicum

# Empyema – VATS decortication



How long would you treat this patient's *C. septicum* empyema s/p VATS decortication?

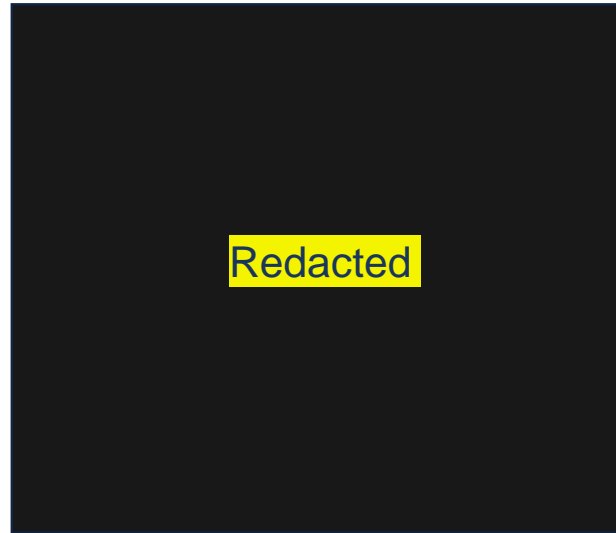
- a) 2-3 weeks
- b) 4-6 weeks
- c) 6-12 weeks
- d) Indefinitely / chronic suppression

## Day 86 erythema & fever



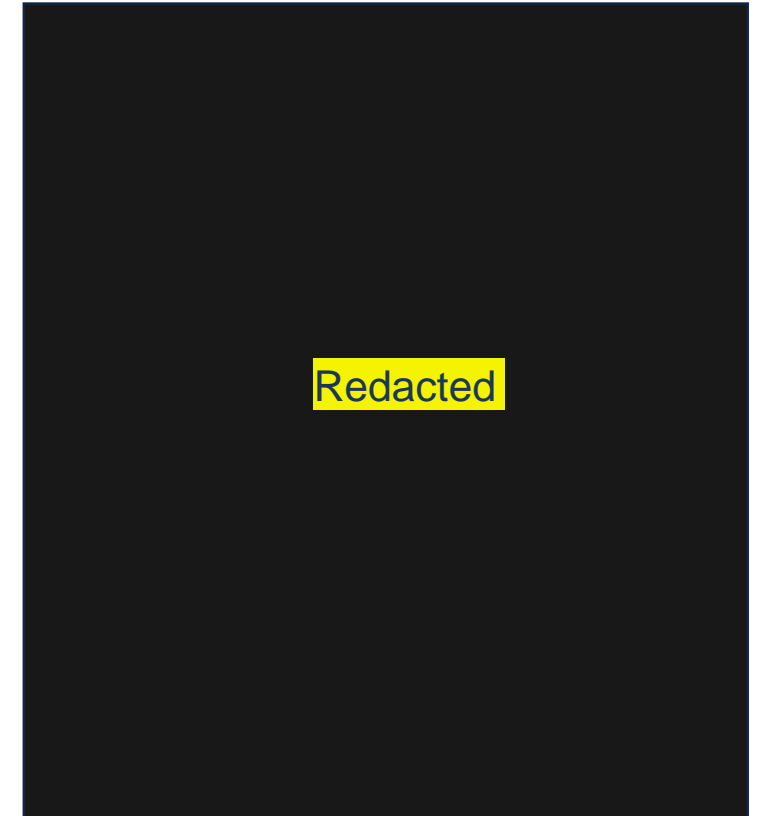
- On amoxicillin → Linezolid + meropenem
  - Repeat CT C/A/P stable
  - Vanc/CTX x 5 days; improved
- Ceftriaxone until chest tube removal
- Amoxicillin x 6 months or indefinite

## Day 98 erythema & fever



- Non-neutropenic fever, leukocytosis, elevated lactate, new erythema
- Amox → Linezolid + Meropenem
  - 2 days after bispecific Ab
  - CRP 281, IL-6 449
- CT: intramuscular abscesses in R posterolateral abdominal wall – FNA abscess – negative Cx, + Flow
- Colon - increasing pneumatosis; Surgical consult – no OR
  - Stable pleural effusions
  - Ertapenem

## Day 104 Recurrent erythema

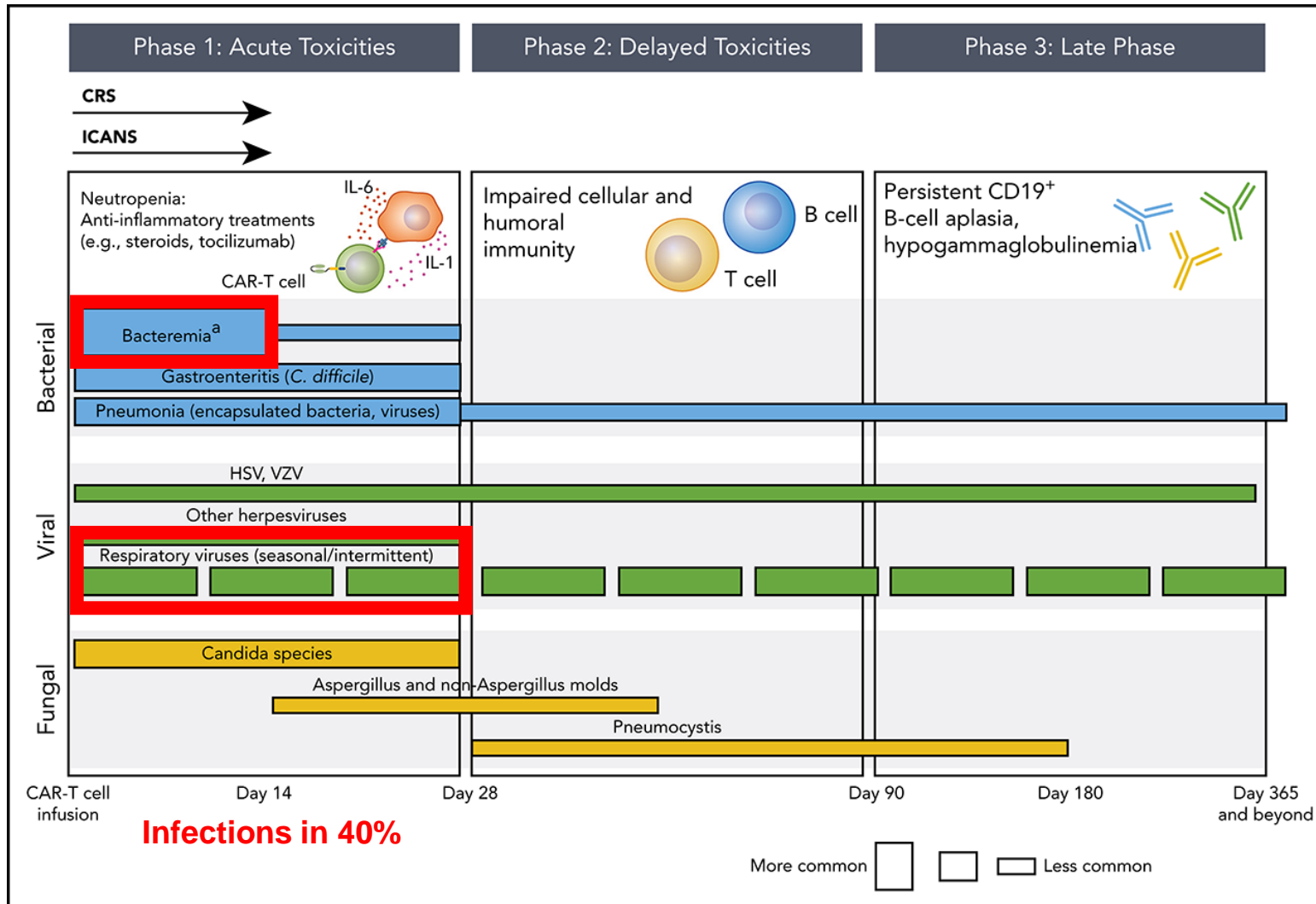


- Vancomycin + ertapenem

# Subsequent course

- Lymphoma progression – treatment with bispecific T cell engager
  - Epcoritamab – targets CD3 and CD20
- Recurrent sepsis vs CRS
- After 5<sup>th</sup> dose epcoritamab, developed fever, bradycardia, hypoxemia, hypotension, transferred to ICU
- Treated with meropenem + linezolid and tocilizumab + dexamethasone
- Worsening clinical status, GOC conversations, comfort care

# Infectious complications after CAR T-cell therapy



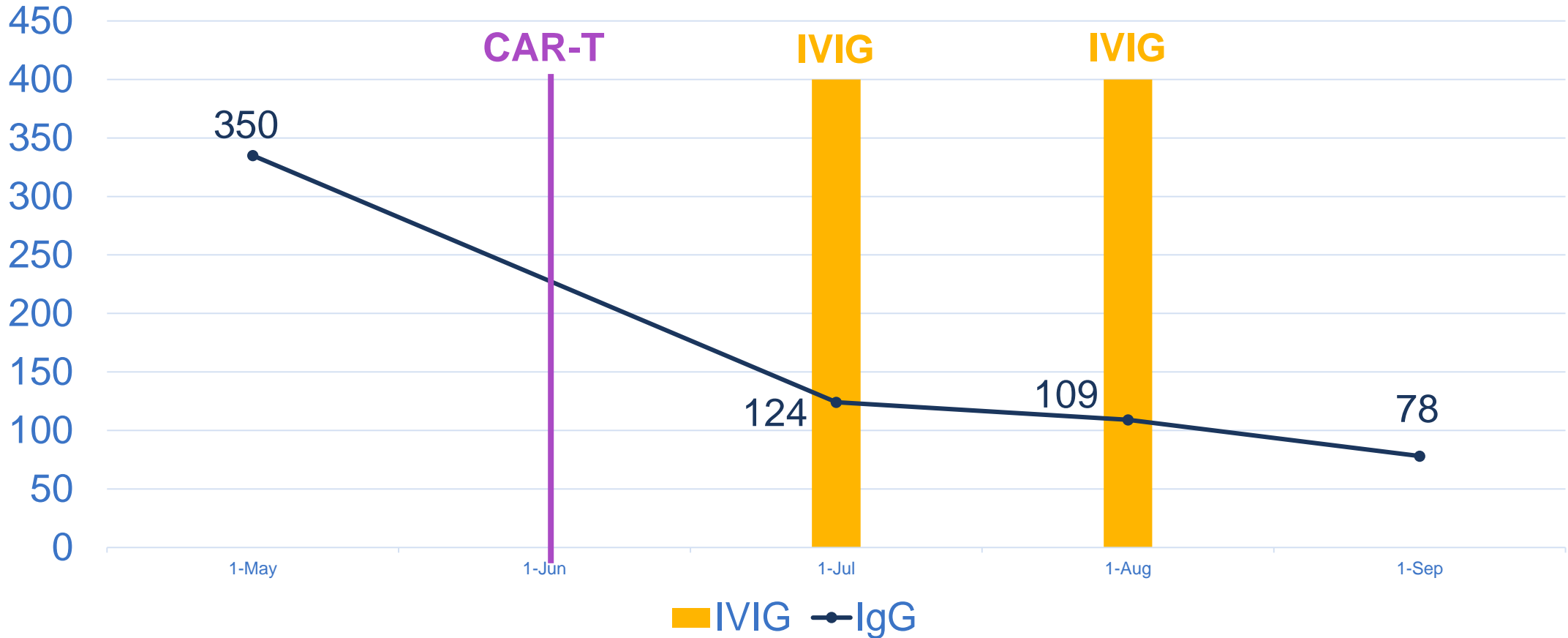
## Risk factors

- Prior HCT
- IgG <400
- Higher-severity CRS

## Clostridial infections after CAR-T

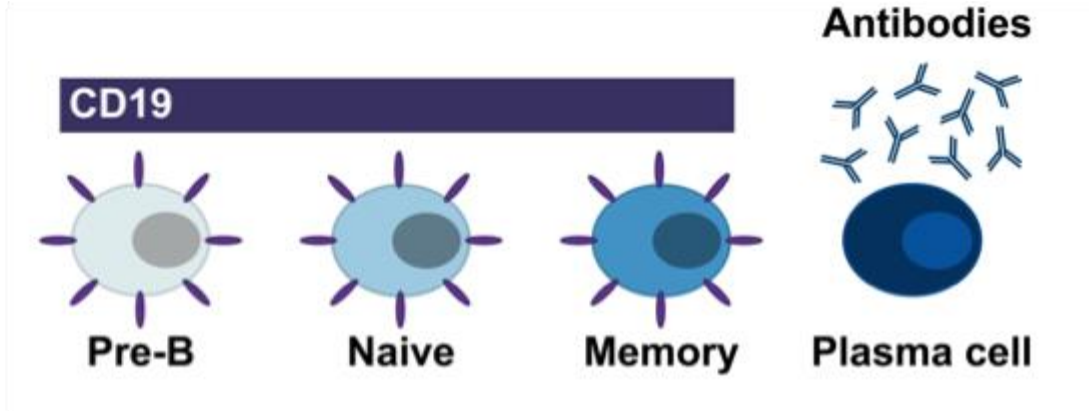
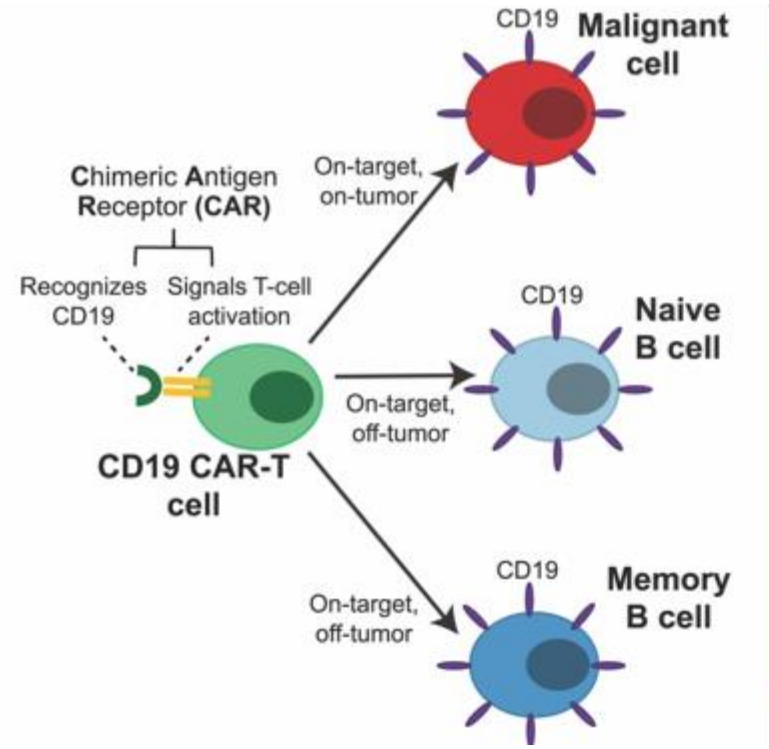
- No literature
  - 1 report of *C. tertium* bacteremia pre-CAR T
  - *C difficile*

# Hypogammaglobulinemia after CAR-T





# Hypogammaglobulinemia after CAR-T



# Necrotizing fasciitis in heme malignancies


- Necrotizing fasciitis after CAR-T: no data
- Necrotizing fasciitis after HSCT: **very** limited data

Annals of Hematology (2020) 99:1741–1747  
<https://doi.org/10.1007/s00277-020-04061-y>

ORIGINAL ARTICLE



## Necrotizing fasciitis in haematological patients: a different scenario

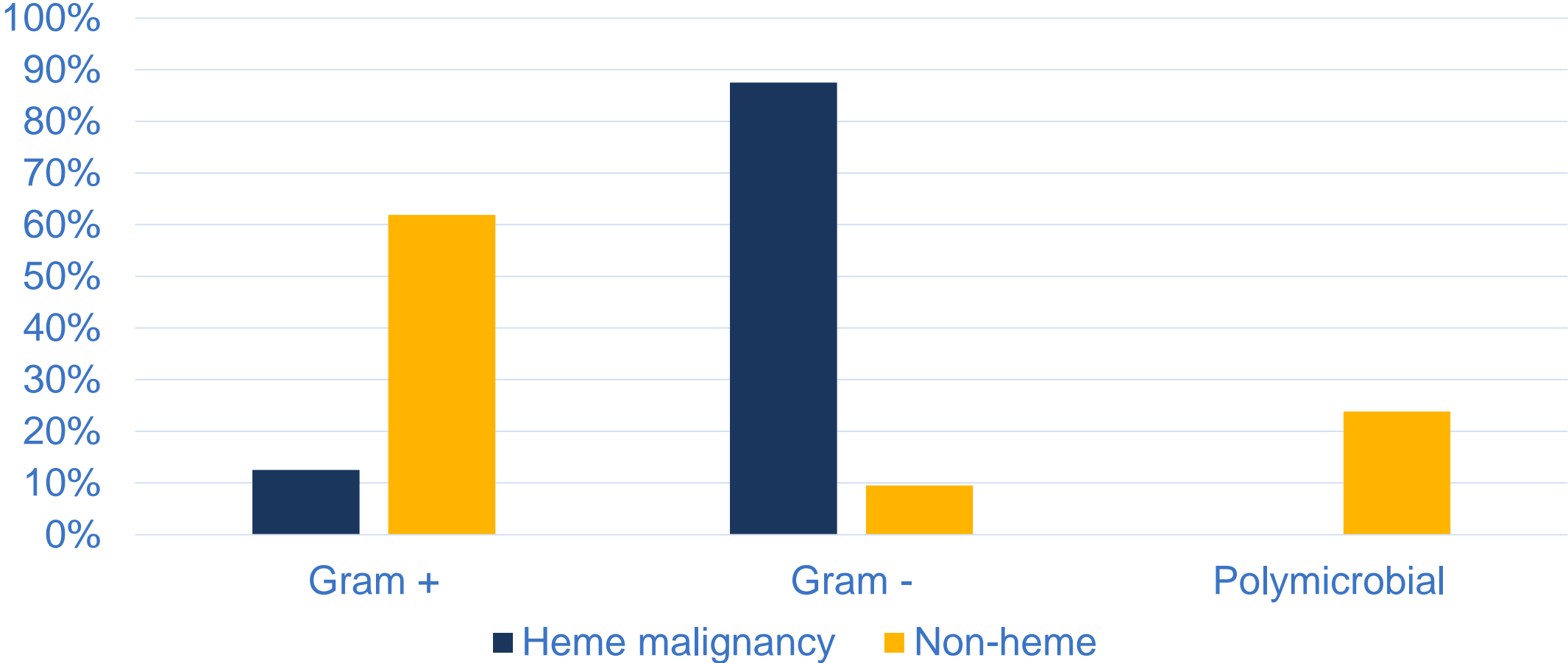
A. Albasanz-Puig<sup>1,2</sup> · D Rodríguez-Pardo<sup>1,2</sup>  · C. Pigrau<sup>1,2</sup> · M. Lung<sup>3</sup> · E. Roldan<sup>4</sup> · P. S. Corona<sup>2,5</sup> · B. Almirante<sup>1,2</sup> · I. Ruiz-Camps<sup>1,2</sup>

Received: 10 February 2020 / Accepted: 27 April 2020 / Published online: 12 May 2020

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**21 controls, 8 heme patients including 3 allo HSCT and 2 auto**

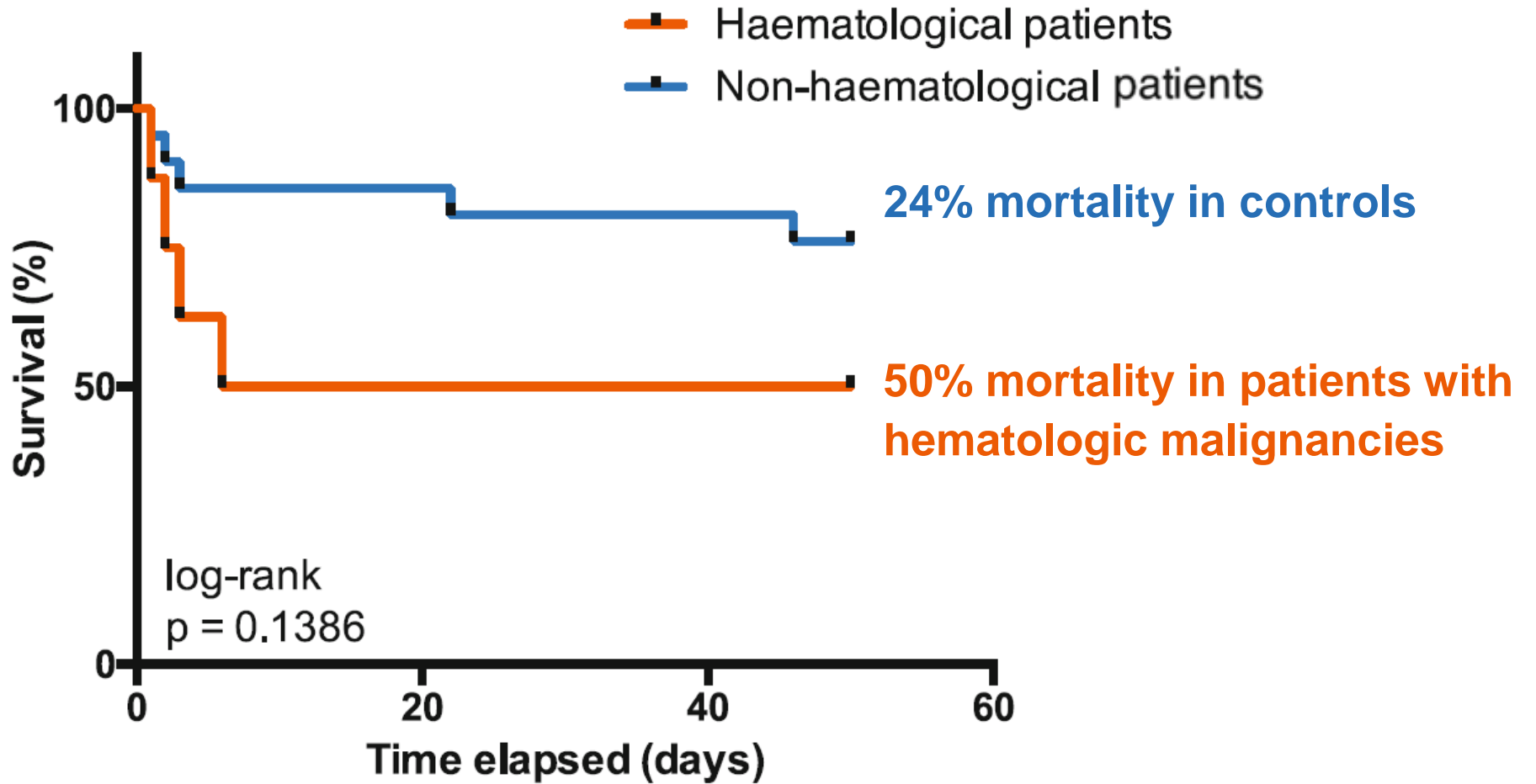
# Necrotizing fasciitis in patients with hematologic malignancies



# Necrotizing fasciitis in heme malignancies

## Summary:

- Paucity of data
- Gram negatives predominate
- Early and high mortality



Have you seen several post-CAR T clostridium infections at your center?



# Acknowledgements



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