Malignant fevers

CID conference
Hunter Ratliff
12/19/2024

Ages, dates, and other identifying information may have been changed
I have no conflict of interest in relation to this presentation

Case #1

Case 1: HPI

A **45 y/o F** with PMH including colorectal cancer w/ liver mets (on fruquintinib), recurrent ESBL UTIs p/w **epigastric / left flank pain**

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Oncology History

- Diagnosed w/ rectal cancer 3 yr ago
  - Mets to liver & lungs
- Recently started on fruquintinib
  - Oral VEGF inhibitor
  - Still has port
- Chemo held two weeks ago (as it can cause pancreatitis)

Case 1: Initial exam & labs

Exam
VS: 37 °C | HR **116** | BP 122/63
General: Appears **uncomfortable**
GI: NTND, **TTP** over hypogastric region & left flank

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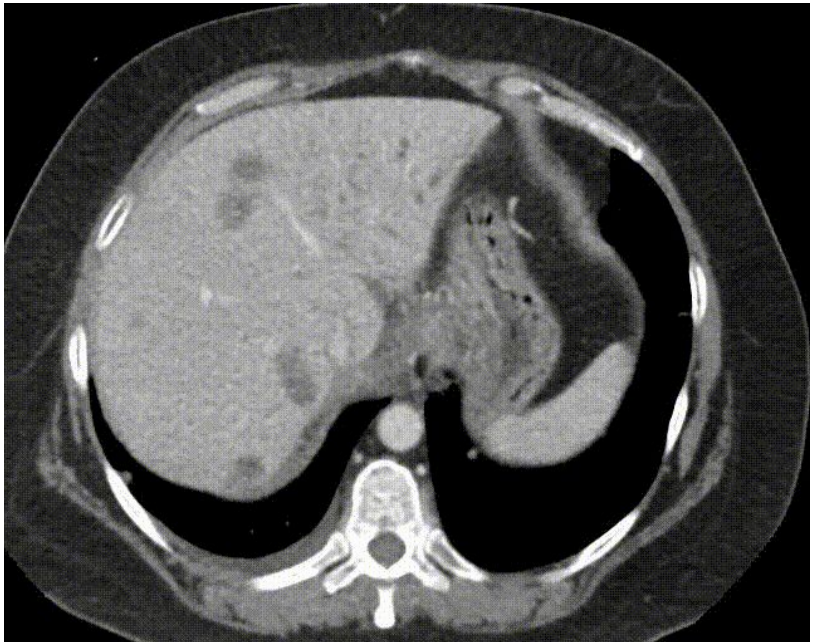
		Prior admission (-4 d)		
ALKALINE PHOSPHATASE 40 - 110 U/L	247 ^	294 ^	326 ^	300 ^
ALT (SGPT) <31 U/L	98 ^	122 ^	235 ^	270 ^
AST (SGOT) 11 - 34 U/L	77 ^	98 ^ CM	177 ^	207 ^
BILIRUBIN TOTAL 0.3 - 1.3 mg/dL	1.5 ^	1.7 ^ CM	3.2 ^ CM	5.6 ^ CM
Comment: Naproxen therapy can falsely elevate total bilirubin levels.				
BILIRUBIN DIRECT 0.1 - 0.4 mg/dL	1.1 ^	0.8 ^ CM	2.5 ^	

Case 1: Initial imaging

CT A/P on admission



Pancreas: **Edematous pancreas**. Prominent pancreatic ductal caliber, likely secondary to findings at the porta hepatis. Subtle peripancreatic stranding persists, **without peripancreatic fluid**. No solid pancreatic mass is evident

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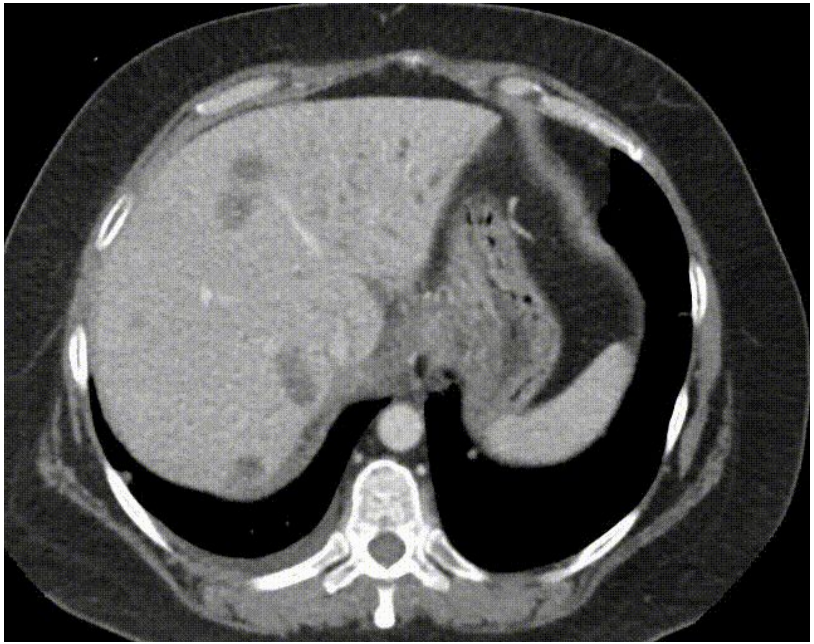

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Biliary System: Interval placement of a CBD stent with **improved but persistent biliary ductal dilatation**. There is expected associated nondependent pneumobilia

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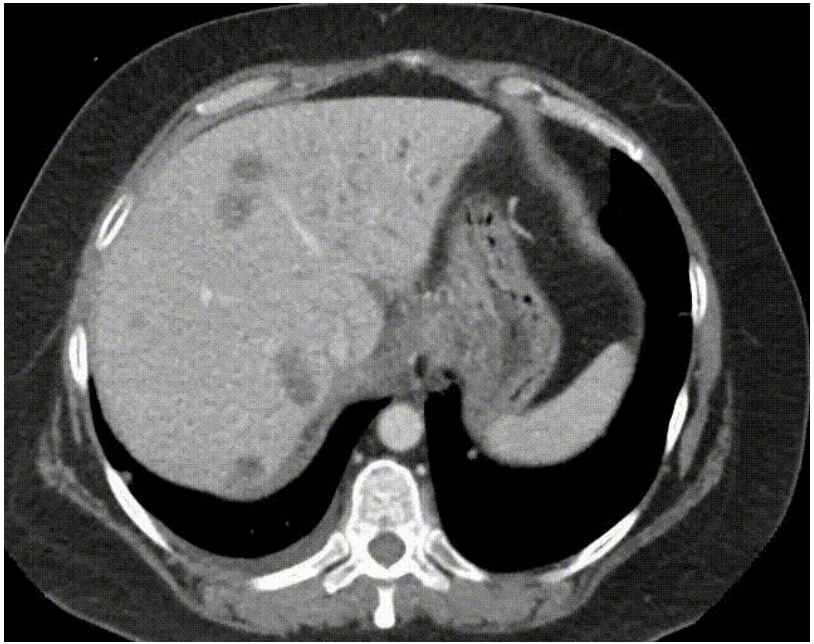

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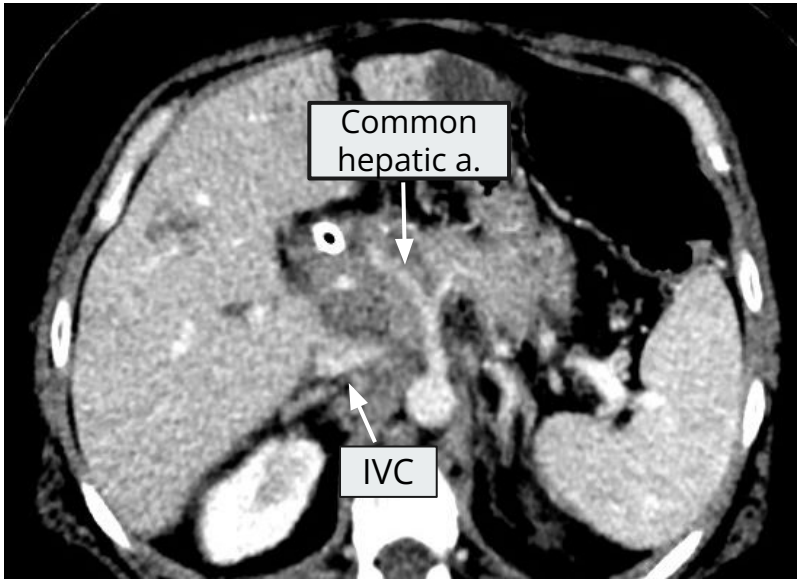
Lymph Nodes: **Necrotic conglomerate of masses at the porta hepatis** which may reflect pathologic lymph nodes. Bulky retroperitoneal adenopathy

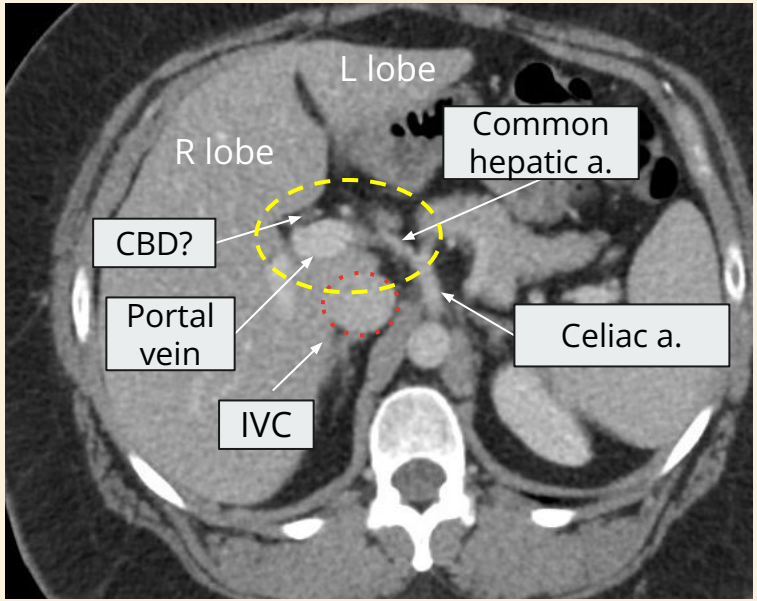
Aside: Where is the porta hepatis?

This admission



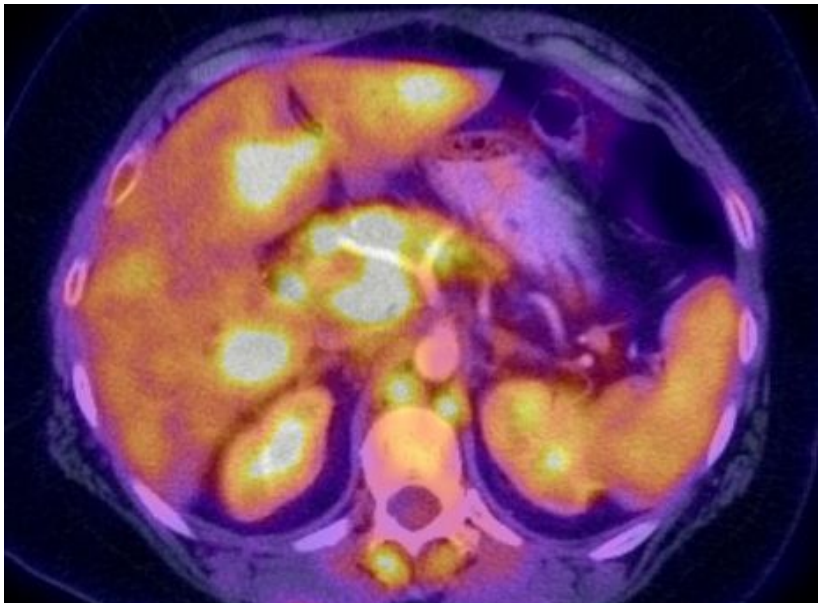
Necrotic conglomerate of masses at the porta hepatis which may reflect pathologic lymph nodes

CT from 18 months ago



Where is the porta hepatis?

PET CT from 1.5 months ago



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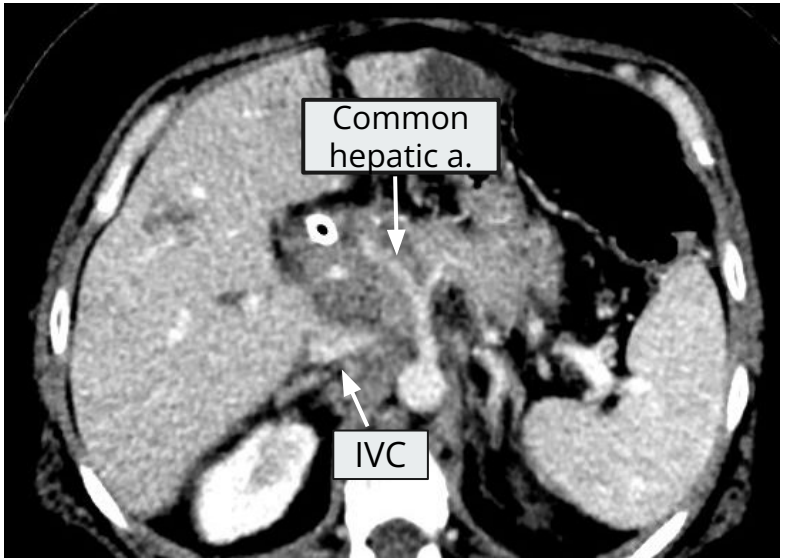

Case 1: Back to the case

A **45 y/o F** with PMH including colorectal cancer w/ liver mets (chemo -2wk), obstructive jaundice s/p recent ERCP w/ stent, recurrent ESBL UTIs p/w **abdominal pain** and admitted for suspected **ERCP induced pancreatitis** (after recent admission for *drug-induced* pancreatitis)

Hospital day 1: GI consulted, says CT looks better with the stent from last admission (low concern for obstruction)

Days 2-6: **LFTs improving**, working on pain control & advancing diet

Hospital day 7: **fevers & tachycardia**, multiple episodes of diarrhea & suprapubic pain

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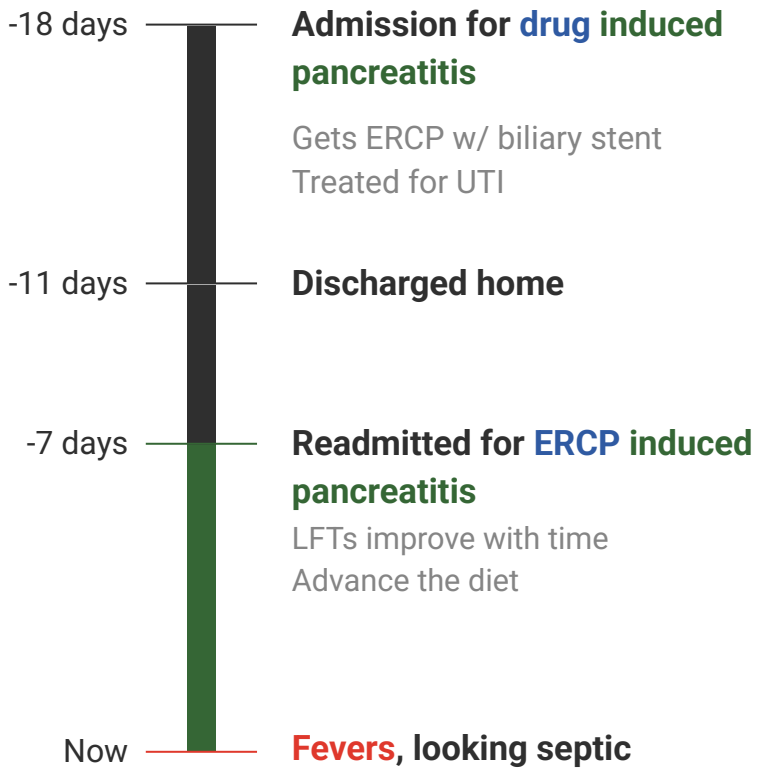
A **45 y/o F** with PMH including colorectal cancer w/ liver mets (chemo -2wk), obstructive jaundice s/p recent ERCP w/ stent, recurrent ESBL UTIs p/w **abdominal pain** and admitted for suspected **ERCP induced pancreatitis**. Fevers on hospital day 7 in the context of new diarrhea & suprapubic pain



Case 1: Hospital course

- **Blood Cx**: ???
- **Urine Cx**: ???

Guess what grew?

WBC 3.7 - 11.0 x10^3/uL	9.7
RBC 3.85 - 5.22 x10^6/uL	3.34 ↓
HGB 11.5 - 16.0 g/dL	9.6 ↓
PLATELETS 150 - 400 x10^3/uL	194
MPV 8.7 - 12.5 fL	11.0
NEUTROPHIL %	86.0

URINALYSIS, MACROSCOPIC	ⓘ
APPEARANCE	Turbid !
COLOR	Normal (Yel...
SPECIFIC GRAVITY, URINE	1.025
GLUCOSE	Negative
BILIRUBIN	Negative
KETONES	Negative
BLOOD	Moderate !
PH URINE	5.5
PROTEIN	50 !
UROBILINOGEN	2 !
NITRITE	Negative
LEUKOCYTES	Large !

	Now	Admit
TOTAL PROTEIN	7.2	8.7 ▲
ALBUMIN	2.1 ↓	2.6 ↓
BILIRUBIN, TOTAL	1.5 ▲	1.7 ▲
BILIRUBIN,CONJUGATED	1.0 ▲	0.8 ▲
AST (SGOT)	62 ▲	98 ▲
ALT (SGPT)	65 ▲	122 ▲
ALKALINE PHOSPHATASE	215 ▲	294 ▲

Case 1: Hospital course

- **Blood Cx**: ***Cronobacter sakazakii***
- **Urine Cx**: GNR

Treatment?

Where is the source?

Additional HPI / social Hx?

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Case 1: Hospital course

- **Blood Cx**: ***Cronobacter sakazakii***
- **Urine Cx**: E coli

Started on Merrem

GI said maybe cholangitis

Case 1: Hospital course

- **Blood Cx**: ***Cronobacter sakazakii***
- **Urine Cx**: E coli

Repeat CT A/P: unchanged

48h BCx cleared

Merrem
↓
Levaquin + Flagyl
x10 d for cholangitis
↓
Bactrim + Flagyl

Cronobacter sakazakii

Amikacin	<=2 mcg/mL	Sensitive
Amoxicillin/clauvulanate	<=2 mcg/mL	Sensitive
Ampicillin		Resistant
Cefazolin	16 mcg/mL	Resistant
Cefepime	<=1 mcg/mL	Sensitive
Ceftazidime	<=1 mcg/mL	Sensitive
Ceftriaxone	<=1 mcg/mL	Sensitive
Ciprofloxacin	<=0.25 mcg/mL	Sensitive
Ertapenem	<=0.5 mcg/mL	Sensitive
Gentamicin	<=1 mcg/mL	Sensitive
Indeterminate		
Levofloxacin	<=0.12 mcg/mL	Sensitive
Tetracycline	<=1 mcg/mL	Sensitive
Tobramycin	<=1 mcg/mL	Sensitive
Trimethoprim/Sulfamethoxazole	<=20 mcg/mL	Sensitive

Discussion

Links to articles discussed here

Cronobacter sakazakii

Objectives:

- Describe the **microbiology** (*and disturbing taxonomy*) of Cronobacter sakazakii
- Compare the **clinical manifestations & risk factors** in neonates & adults
- Review the **unique methods of resistance** that makes it a food borne pathogen
- Discuss the possibility of **nosocomial spread** in adults

Microbiology & taxonomy

- **Gram negative rod** in Enterobacteriaceae family
- Unique in its **xerotolerance**, meaning it can survive in **dried food** (milk, baby formula) [1.1]
- Formerly known as
  - *Enterobacter sakazakii complex*
  - “**yellow-pigmented E. cloacae**”

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Named after **Cronus** (Titan in greek mythology) who **devoured his children**

Cronobacter in infants

- Most notorious association for Cronobacter is association with **baby formula** **& infants** [1.2]
  - May cause **bacteremia**, **meningitis** and **necrotizing enterocolitis**
- CDC estimates **2-4 cases per year** [source]
  - But not a reportable disease in all states

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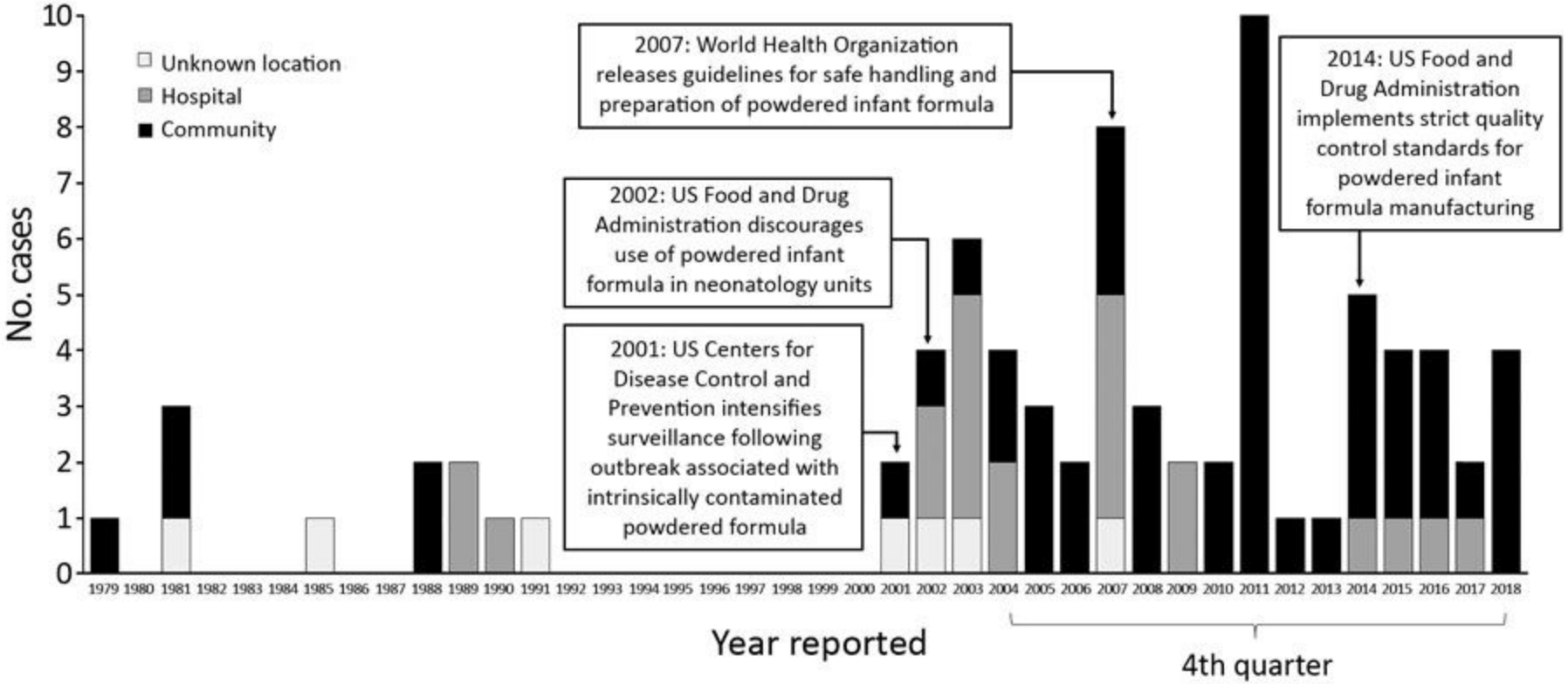
- CDC estimates 2-4 cases per year [source]
  - But not a reportable disease in all states
- In infants with invasive infections: [1.2]
  - **20-40% case fatality rate**
  - 78% had powdered formula exposure
- In the US, most cases are **community onset**
  - In part because hospitals stopped using powdered formula inpatient after a 2001 outbreak at NICU in Tennessee



Reported invasive Cronobacter infections among infants, United States, 1979–2018
Strysko et al (Emerging Infectious Diseases, 2020) [1.2]

Cronobacter in adults

- Case reports/series in adults [1.3] [1.5]
  - Bacteremia
  - Hepatobiliary infection
  - UTI
  - Osteomyelitis
  - Aspiration pneumonia

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Risk factors

- Age
- Malignancy
- Transplant
- Steroids, DM
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  - Bacteremia
  - Hepatobiliary infection
  - UTI
  - Osteomyelitis
  - Aspiration pneumonia
- **Empiric treatment**: depends on which study you read
  - Most say it's **more friendly than other Enterobacteriaceae** [1.4]
  - But some say high rates of resistance to ampicillin & cephalosporins [1.3]

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A nosocomial infection in adults too?

In one study of 536 patients (321 admitted, 215 outpatient) in Slovakia, Cronobacter strains were isolated from throat & sputum samples of [1.4]

- **5.3%** of **patients admitted** to the hospital
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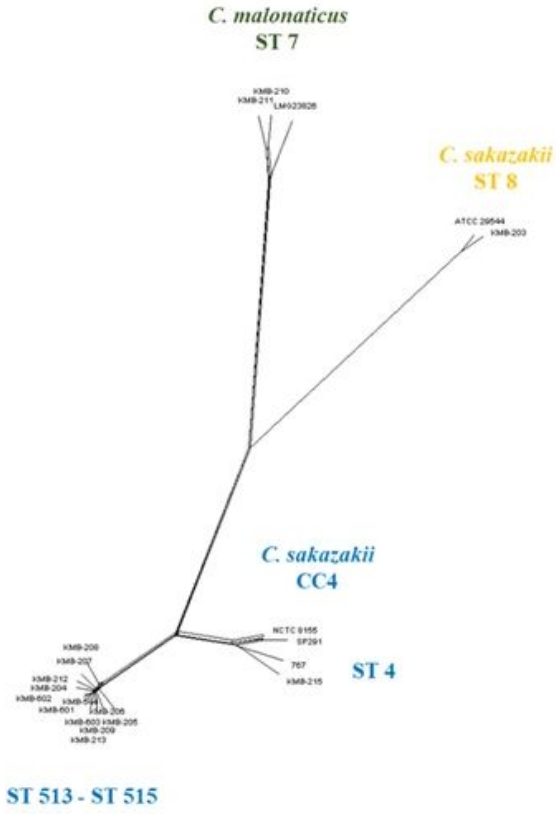
- Previous studies also found **disproportionately high rates** in the mouths of **stroke patients**
- Perhaps due to impaired swallowing

A nosocomial infection in adults too?

They did whole genome sequencing of their isolates [1.4]



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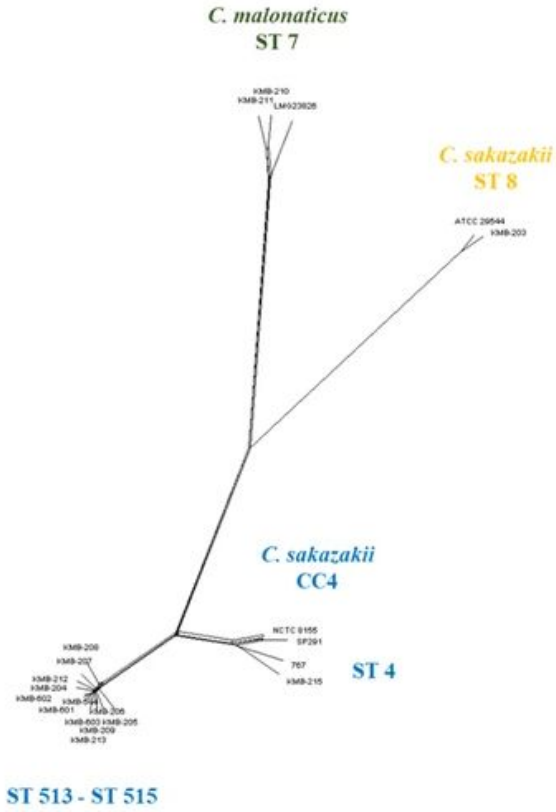

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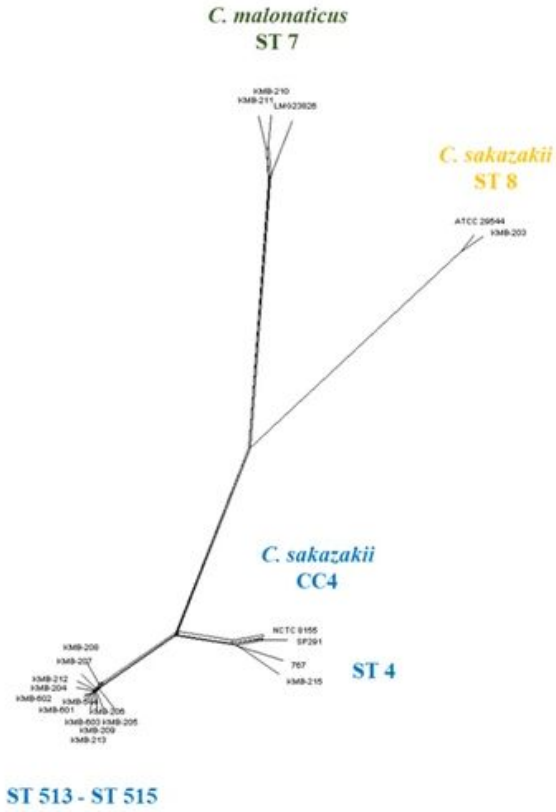

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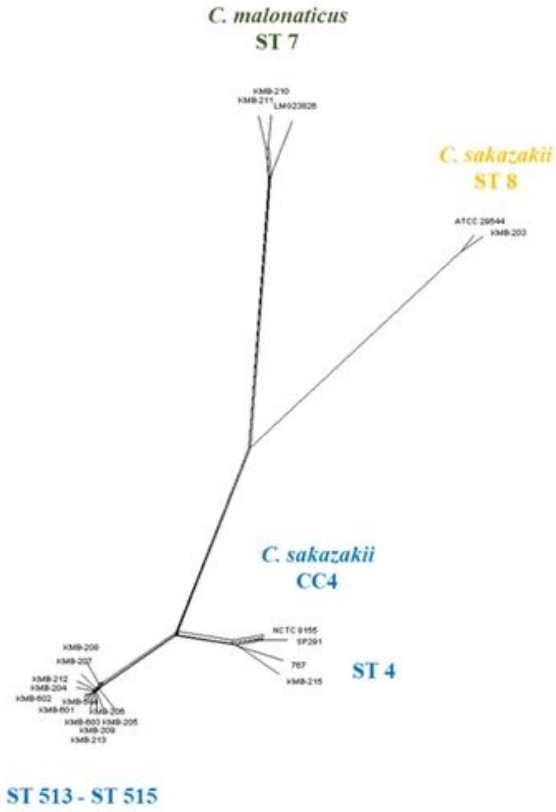
The implication being the same clonal complex was probably:

- Circulating in the hospital environment
- Spread by food transmission



Case #2

Case 2

A **29 y/o F** with PMH including extraskeletal Ewing sarcoma on chemo p/w **fevers**

Case 2: HPI

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  - No swelling
  - Full range of motion

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Got new chemo **8 days prior** to admission (via PICC)

- D1 trabectedin
- D2 and D4 irinotecan
- D5 pegfilgrastim

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A **29 y/o F** with PMH including extraskeletal Ewing sarcoma on chemo (8 days ago got trabectedin, irinotecan via PICC) p/w **fevers** x1 day

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Sarcoma in pelvis caused **hydronephrosis**, so got ureteral stent (two weeks ago)

ESBL E coli in urine 4 months ago

Case 2: HPI

A **29 y/o F** with PMH including extraskeletal Ewing sarcoma on chemo (8 days ago got trabectedin, irinotecan via PICC) , hydronephrosis s/p ureteral stent (two weeks ago), Hx ESBL UTI p/w **fevers** x1 day

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Negative ROS

- Oral lesions
- Nausea or vomiting
- Diarrhea
- Blood in stool
- Urinary changes (dysuria, frequency, incontinence)

Case 2: Social History, Exposures, Risk Factors

Geographic & Occupational: The patient lives in Paden City, West Virginia **w/ her daughter**. She denies recent travel.

Substance: They deny alcohol use and she does not use tobacco . They report no recreational drug use

Environmental exposures: They deny soil/landscaping/dust exposure.

Animal Exposures: The patient denies farm animal exposures or other animal exposure (aside from their pet hamster).

Tattoos & Piercing: They have have not gotten unprofessional piercings or tattoos .

Infectious PMH: They deny previous intolerances/allergies to antimicrobials; she denies recent antimicrobial use. They deny history of C. diff infections.

Case 2: Exam

Vitals: Tmax **100 °F** (at home) | BP **93/58** | HR 92 | SpO2 98% | BMI 24.64 kg/m^2
Gen: alert and oriented, NAD, vitals reviewed
Head/Neck: NCAT; trachea midline, no gross LAD
ENT: EOMI grossly, anicteric sclerae; MMM
Resp: normal respiratory effort, CTAB
CV: RRR; extremities perfused
GI: non-distended; no rebound or guarding
Ext: no clubbing, cyanosis, or edema
Skin: **Anterior L knee scab** with some erythema
Neuro/MSK: **L knee FROM w/o TTP or effusion**
Psych: normal mood; appropriate affect

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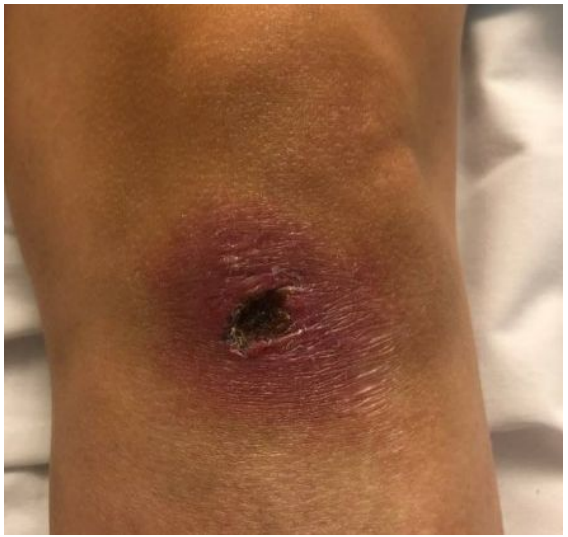

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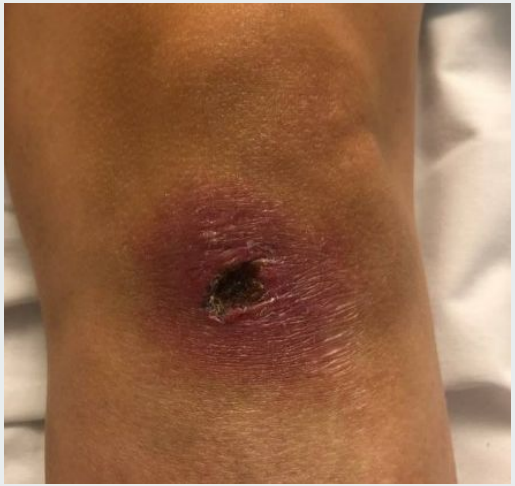

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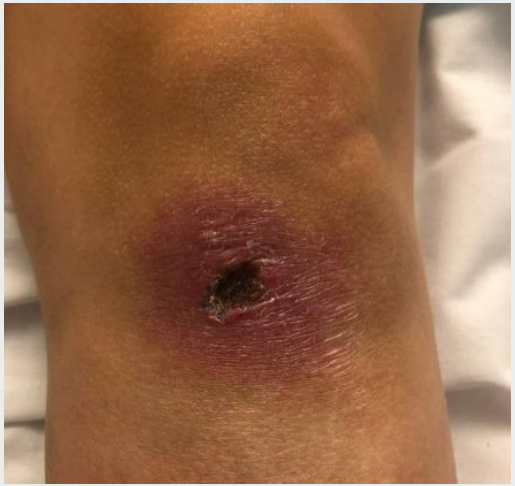

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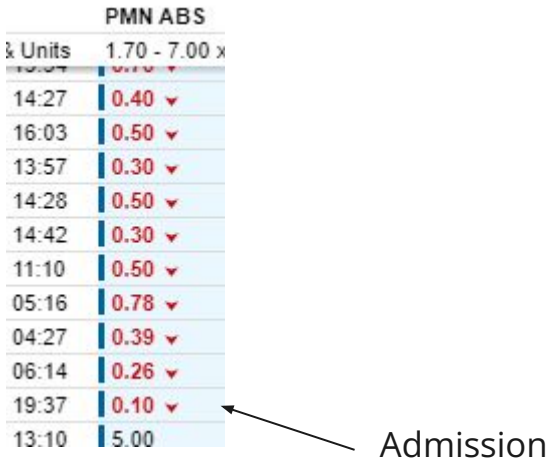
- Additional questions?
- DDx?
- Empiric treatment?

Case 2: Additional HPI & Data

Notably she states she was giving her daughter a bath 24h prior to onset of fever. During the bath, she states that **she saw bath water get under the left PICC dressing**. Following that, she felt L axillary fullness and fevers so came to ED



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	PMN ABS
& Units	1.70 - 7.00 x
14:27	0.40
16:03	0.50
13:57	0.30
14:28	0.50
14:42	0.30
11:10	0.50
05:16	0.78
04:27	0.39
06:14	0.26
19:37	0.10
13:10	5.00

Admission

BLOOD CULTURE, ROUTINE	Pseudomonas aeruginosa !
	Anaerobic Bottle (Culture)
	No Growth aerobic bottle at 5 days

Collection Side:	Left
Collection Method	Central Line
Site Description:	Arm/Antecubital
Central Line Type: (If Applicable)	PICC

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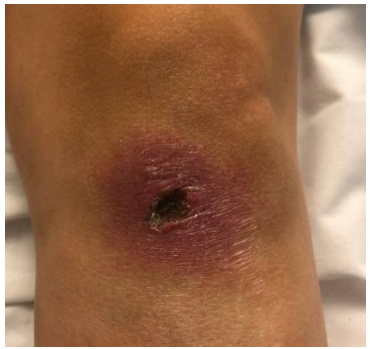
Timeline for the rash

- She fell and injured her left knee approximately 2-3 weeks
- Has had the scab since then (i.e. before developed neutropenia)
- Erythema around the scab has been stable



Case 2: Hospital course

A **29 y/o F** with PMH including extraskeletal Ewing sarcoma on chemo (8 days ago got trabectedin, irinotecan via PICC) , hydronephrosis s/p ureteral stent (two weeks ago), Hx ESBL UTI p/w **fevers** x1 day in the context of **neutropenia** & getting **bathwater** under PICC dressing

- Started on Merrem given Hx of ESBL
- PICC removed
- BCx from PICC grew Pseudomonas, peripheral culture NGTD
    - Got single dose tobramycin pending susceptibilities
- Treated for 14 days with cipro 750 BID

Discussion

Links to articles discussed here

Ecthyma gangrenosum

Even though the patient did not have it

- Describe the **pathogenesis** of Ecthyma gangrenosum
- Identify the common (and uncommon) **causative pathogens**
- Review the **clinical presentation** and progression of lesions

Pathogens causing ecthyma gangrenosum

Classically thought to only occur:

1. With **Pseudomonas**
2. In **immunocompromised**

Review of 167 cases found

- 73% were *P aeruginosa*
- 17% other bacteria
- 15% fungal

Immune status	**Septicemia**	**P. aeruginosa**	**Bacterial**	**Fungal**
Compromised	Yes	32	2	2
Compromised	No	41	15	11
Healthy	Yes	38	0	0
Healthy	No	12	12	2
Total		123 (73%)	29 (17%)	15 (9%)

Adapted from Vaiman et al (2014) [2.1]

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Bacterial

- Other Pseudomonas (P cepacia, P maltophilia, P stutzeri)
- Aeromonas hydrophila
- E coli
- Kleb pneumoniae
- Citrobacter freundii
- Staph aureus
- Staph epi
- S maltophilia
- Strep spp
- NTMs

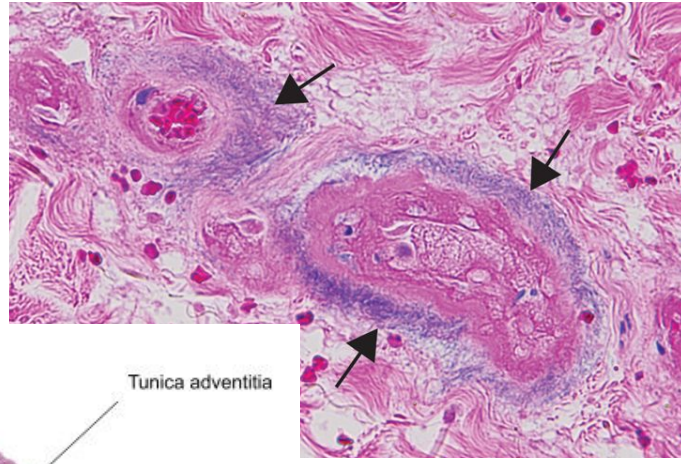
Fungal

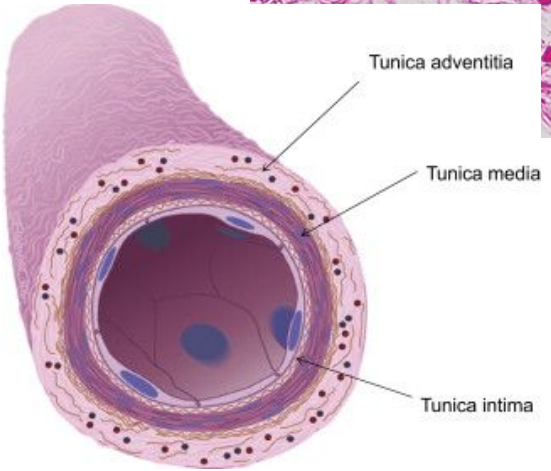
- Candida (C albicans, C tropicalis)
- Mucor pusillus
- Fusarium spp
- Scytalidium dimidiatum
- Metarhizium anisopliae

[2.1][2.2]

Pathogenesis of ecthyma gangrenosum

- Source: Either bacteremia or local infection (breakdown of skin)
- Bacteria invade the tunica media & adventitia of blood vessels → causes thrombosis & ischemic necrosis
- In the case of *Pseudomonas*, it is thought that toxins play a direct role in tissue necrosis





Basophilic bacterial rods around necrotic vessels (arrows)

doi:10.12788/cutis.0373

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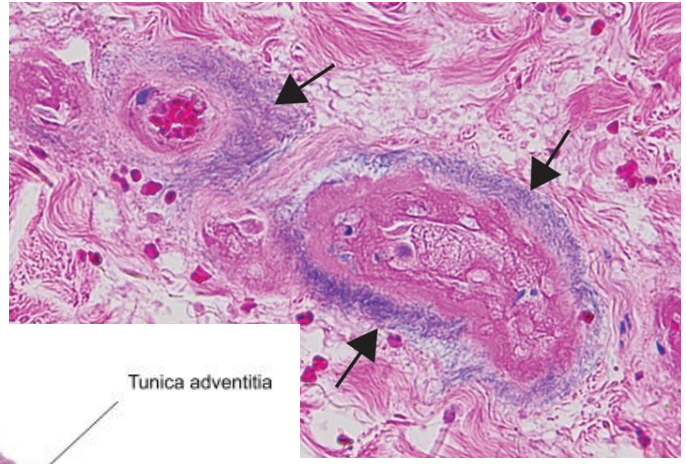
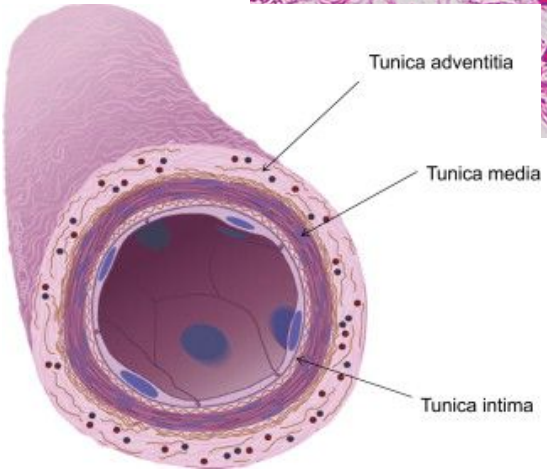
  - **Phospholipase C** breaks down phospholipids in cell membranes
  - **Pyocyanin** produces reactive oxygen species
  - **Elastase** degrades elastin and other structural proteins
  - **Exotoxin A** inhibits protein synthesis that cells use to repair tight junction proteins





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Clinical presentation

- Most often painless, erythematous macules that rapidly progress to **hemorrhagic bullae** and necrotic ulcers with a **central black eschar**
- Predisposition to some areas more than others: [2.3]
    1. Anogenital / perineal (most common)
    2. Axillary / inguinal
    3. Extremities
    4. Truncal lesions are rare (but have been reported)
- As discussed before, immunocompromise (especially **neutropenia**) is the classic risk factor, but has been seen in immunocompetent hosts [2.1] [2.3]

Learning points & take aways

Learning points & take aways

- ***Cronobacter sakazakii*** is a ubiquitous pathogen that can survive in very dry (**xerotolerance**) and high heat (**thermotolerance**) environments
  - Including dried food products (e.g. **infant formula**)
- **Immunocompromise**, including the **extremes in age** (neonates, elderly) predispose to infections. It is particularly deadly for infants
- *Cronobacter* can cause **invasive** (bacteremia) and **gastrointestinal disease** (cholangitis, necrotizing enterocolitis) in both adults and neonates

- Although classically associated with **neutropenic pseudomonal infections**, **ecthyma gangrenosum** can be seen in immunocompetent hosts and non-pseudomonal **bloodstream infections**
  - **Fusarium** spp, **staph aureus**, candida, aeromonas, among others
- Ask your patients how long they have had any rashes

Slides available on hunterratliff1.com/talk/; Citations available via QR code or via the "citations" button on the website