



# 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*

# Shortcuts



Case 1: [Start](#) | [Summary slide](#)

Case 2: [Start](#) | [Summary slide](#)

- **Cronobacter sakazakii** | baby formula | in adults | nosocomial pathogen?
- **Ecthyma gangrenosum** | pathogens | pathogenesis | clinical presentation

**Takeaway slide**

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# Case #1

## Case 1: HPI

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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

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## Exam

VS: 37 °C | HR **116** | BP 122/63

General: Appears **uncomfortable**

GI: NTND, **TTP** over hypogastric region & left flank

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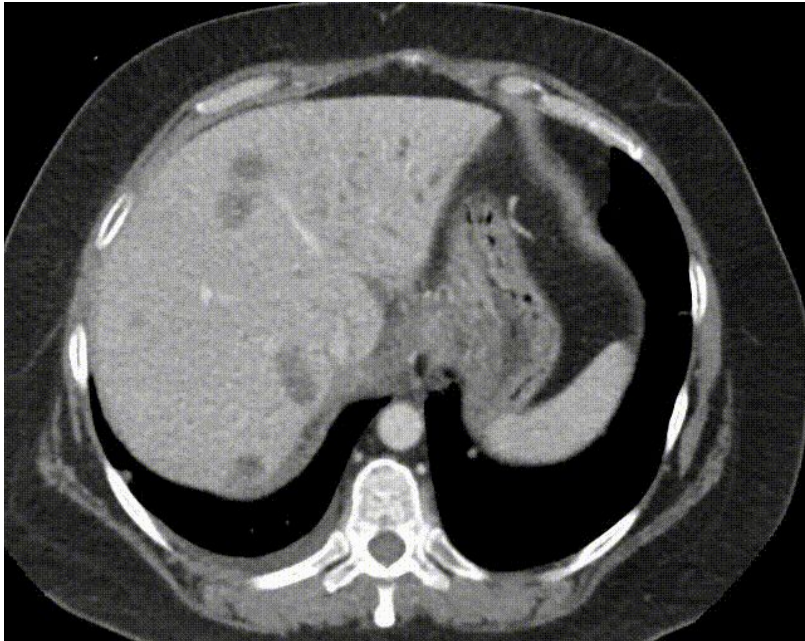
CBC: Normal (WBC 7.1)

Lipase: 753 (similar to prior admission)

			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

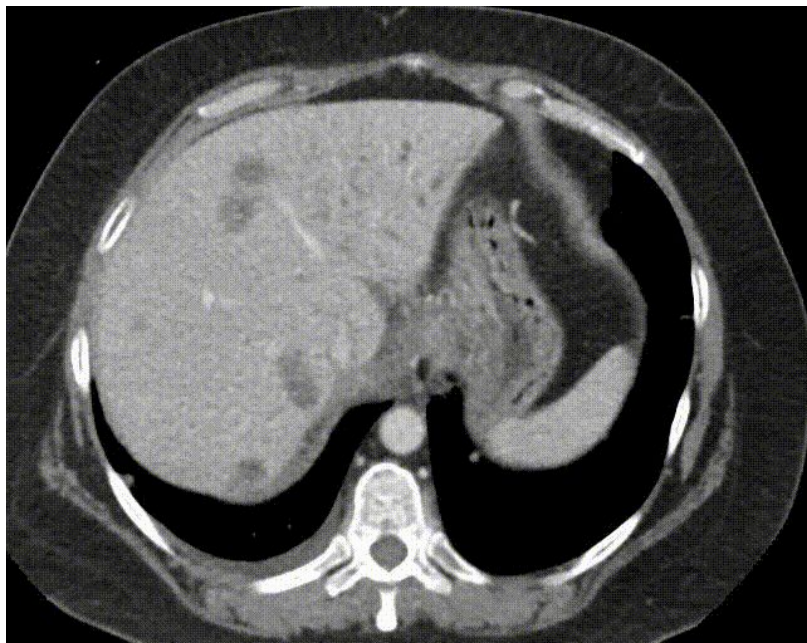
CT A/P on admission



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

## Case 1: Initial imaging

CT A/P on admission

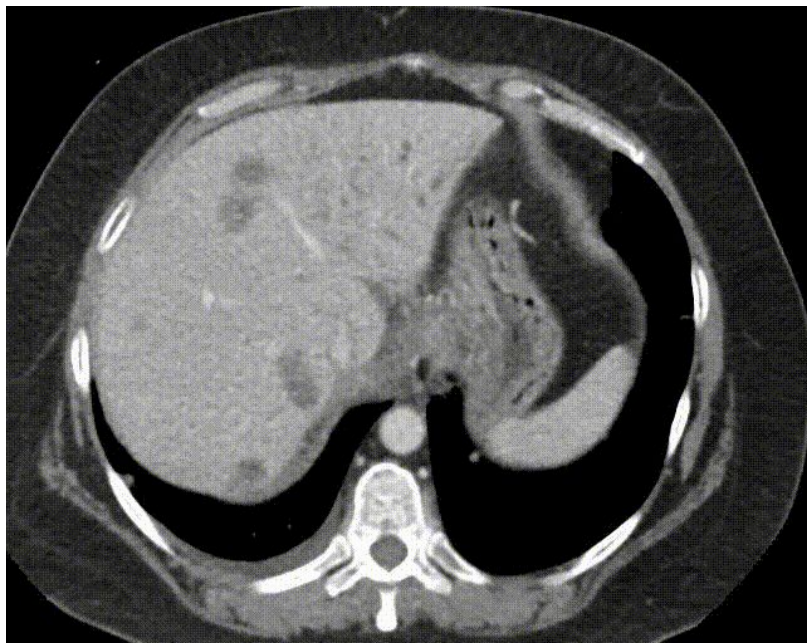


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Biliary System: Interval placement of a CBD stent with **improved but persistent biliary ductal dilatation**. There is expected associated **nondependent pneumobilia**

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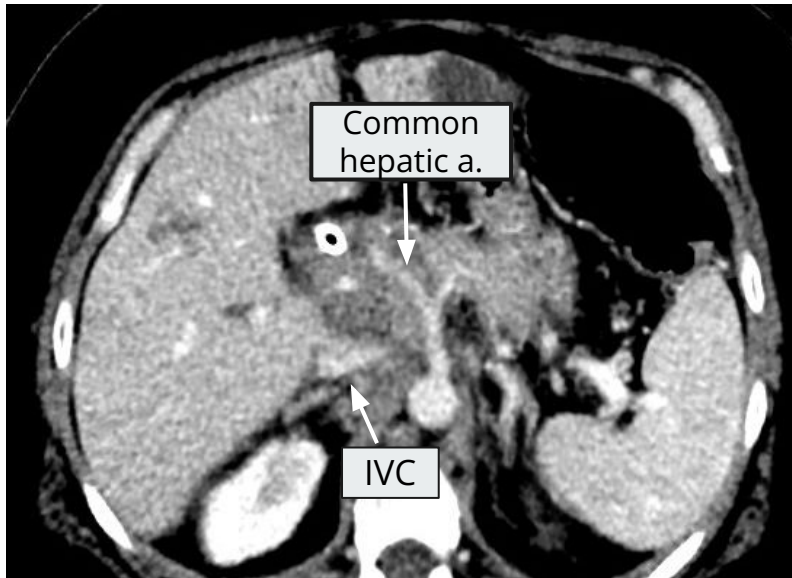
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Lymph Nodes: **Necrotic conglomerate of masses at the porta hepatis** which may reflect pathologic lymph nodes. Bulky retroperitoneal adenopathy

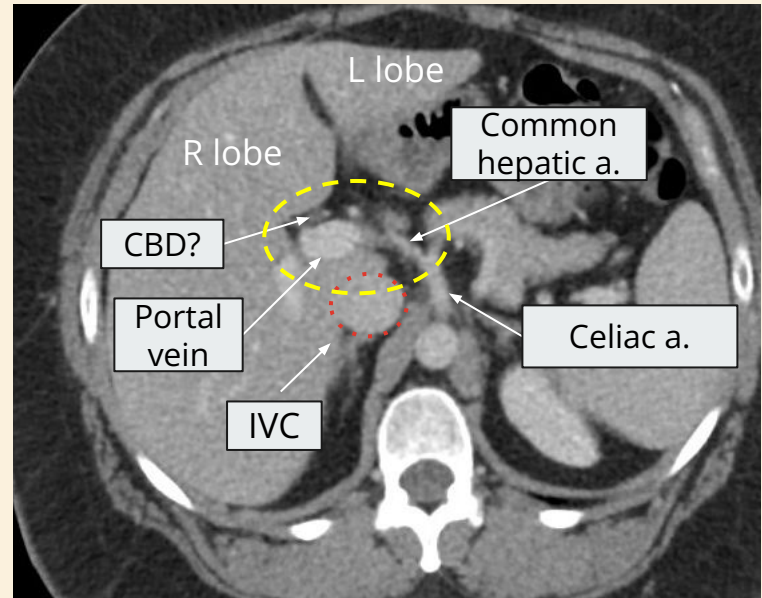
## Aside: Where is the porta hepatis?

This admission



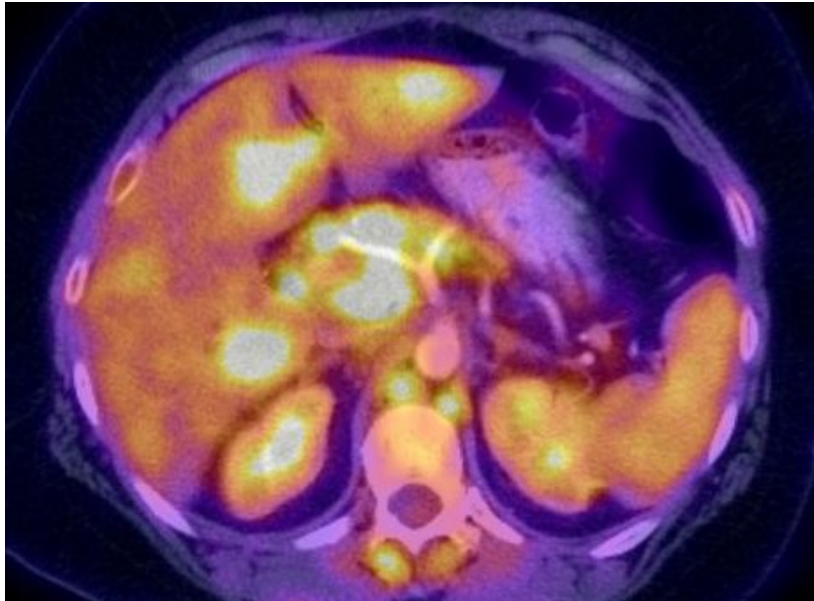
Necrotic conglomerate of masses at the porta hepatis which may reflect pathologic lymph nodes

CT from 18 months ago

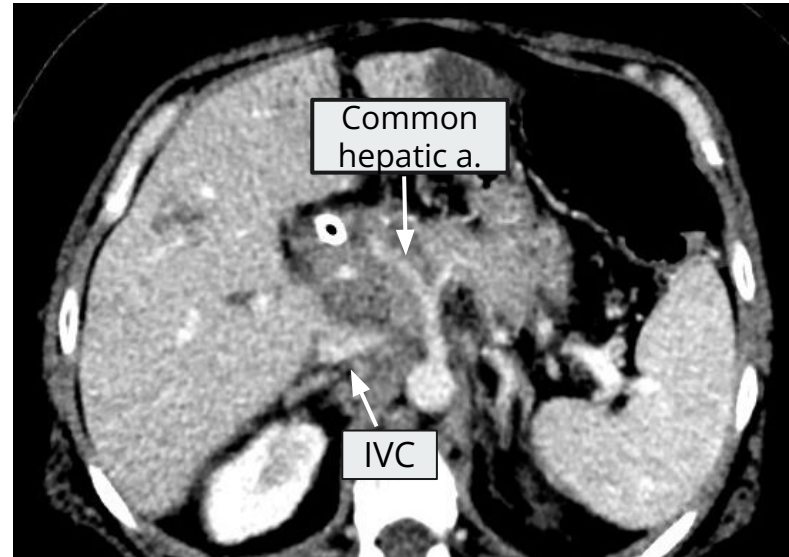


# Where is the porta hepatis?

PET CT from 1.5 months ago



This admission



## Case 1: Back to the case

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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** (after recent admission for *drug-induced* pancreatitis)

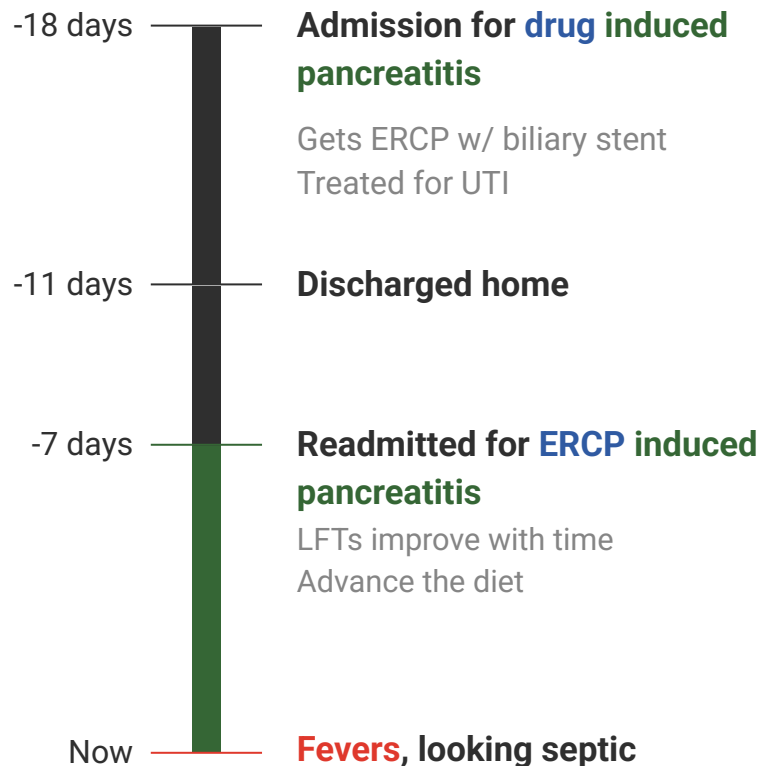
**Hospital day 1:** GI consulted, says CT looks better with the stent from last admission (low concern for obstruction)

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

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

## Case 1: Summary

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	9.7
3.7 - 11.0 x10 <sup>3</sup> /uL	
RBC	3.34
3.85 - 5.22 x10 <sup>6</sup> /uL	▼
HGB	9.6 ▼
11.5 - 16.0 g/dL	
PLATELETS	194
150 - 400 x10 <sup>3</sup> /uL	
MPV	11.0
8.7 - 12.5 fL	
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?

URINALYSIS, MACROSCOPIC	⚠
APPEARANCE	Turbid ⚠
COLOR	Normal (Yel...
SPECIFIC GRAVITY, URINE	1.025
GLUCOSE	Negative
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PH URINE	5.5
PROTEIN	50 ⚠
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# Case 1: Hospital course

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

Started on Merrem

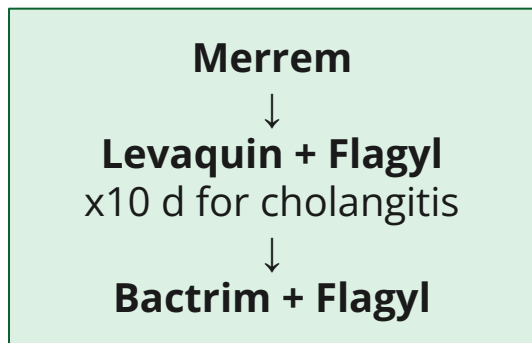
GI said maybe  
cholangitis

# Case 1: Hospital course

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

Repeat CT A/P: unchanged

48h BCx cleared



## *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

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# Discussion



Links to articles discussed  
here



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# *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**”



# Microbiology & taxonomy

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- Formerly known as
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  - “**yellow-pigmented E. cloacae**”

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



# Cronobacter in infants

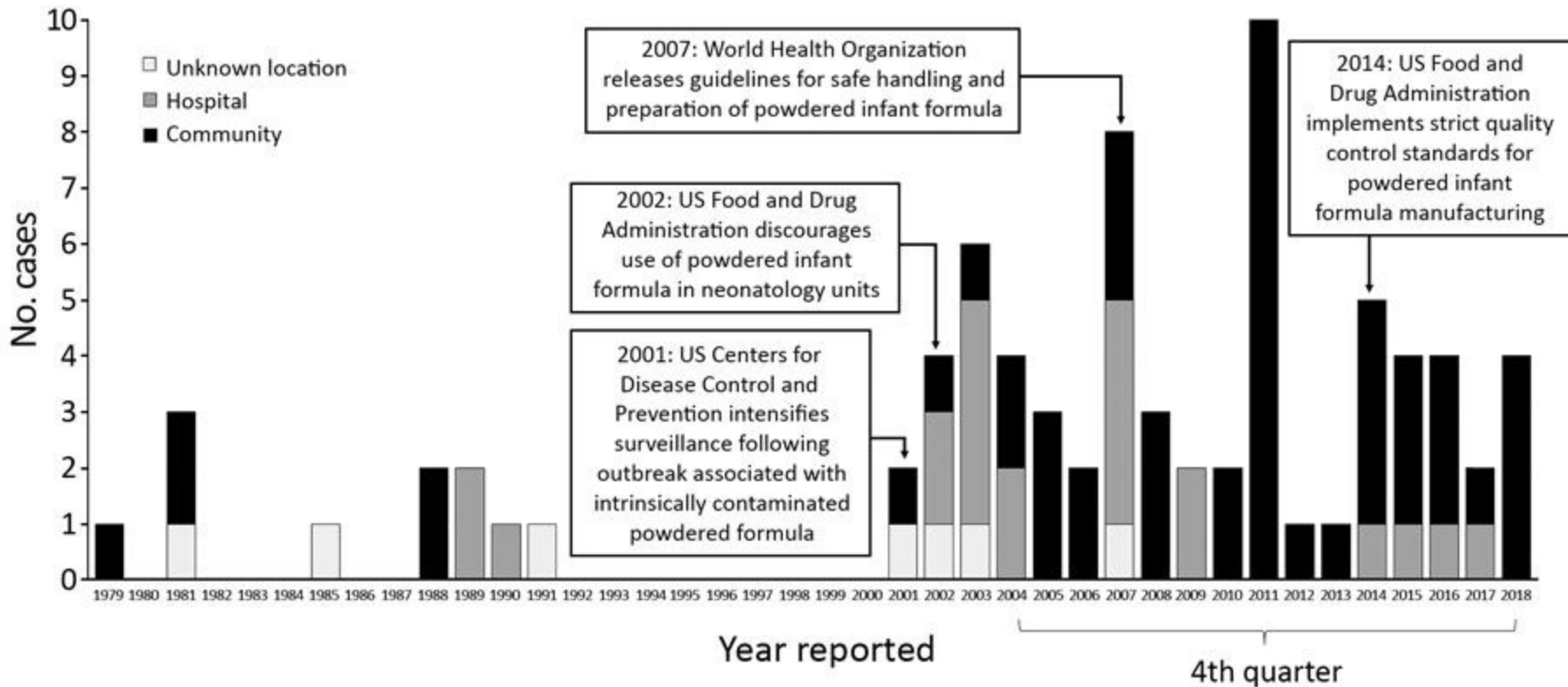
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- Most notorious association for Cronobacter is association with **baby formula & infants** [1.2]
  - May cause **bacteremia, meningitis** and **necrotizing enterocolitis**
- CDC estimates **2-4 cases per year** [[source](#)]
  - But not a reportable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

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  - May cause **bacteremia, meningitis** and necrotizing enterocolitis
- 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  
 Stryko et al (Emerging Infectious Diseases, 2020) [1.2]

# Cronobacter in adults

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

# Cronobacter in adults

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## Risk factors

- Age
- Malignancy
- Transplant
- Steroids, DM
- Cirrhosis, EtOH

# Cronobacter in adults

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- Case reports/series in adults [1.3] [1.5]
  - 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]

## Risk factors

- Age
- Malignancy
- Transplant
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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
- **None** of the **outpatients**

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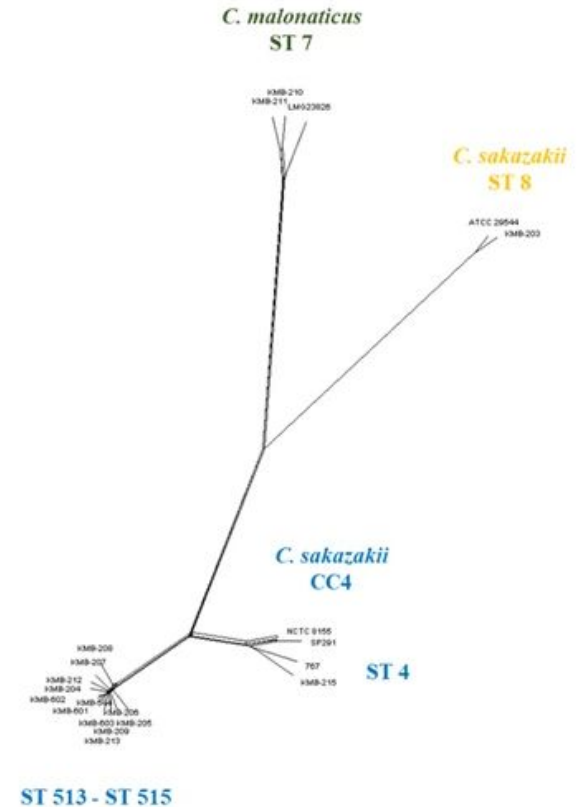
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- Previous studies also found **disproportionately high rates** in the mouths of **stroke patients**
- Perhaps due to impaired swallowing

# A nosocomial infection in adults too?

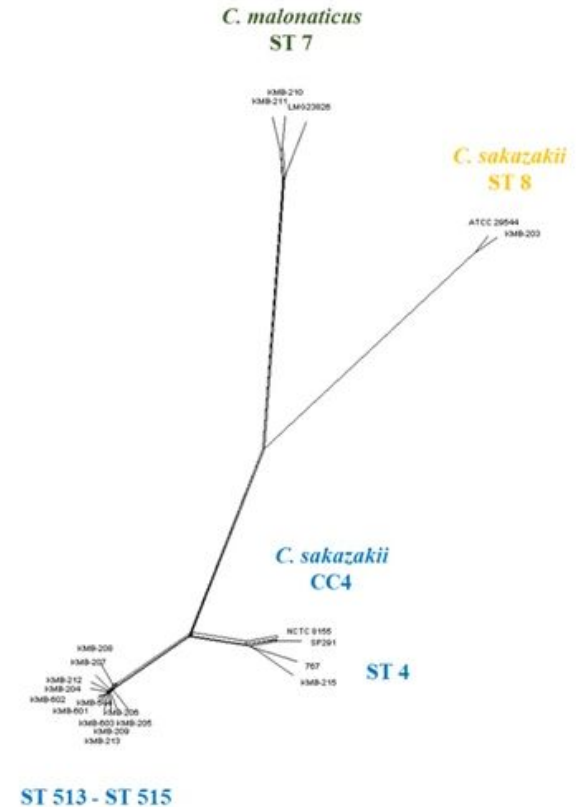
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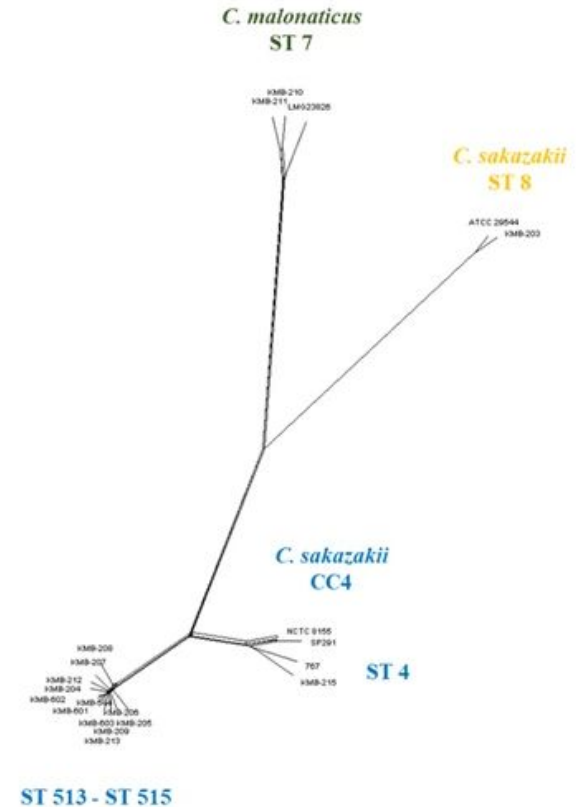
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- Some strains had **increased xerotolerance**, **thermotolerance**, and resistance to osmotic stress (all encoded by the **same genomic island**)



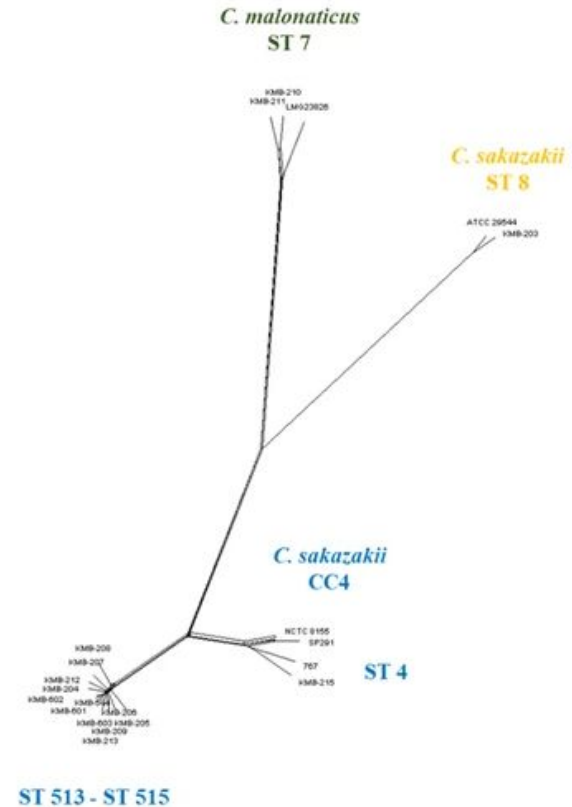
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The implication being the same clonal complex was probably:

- Circulating in the hospital environment
- Spread by food transmission



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# Case #2

## Case 2

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

## Case 2: HPI

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- **Onset of fevers last night**, came to ED within 8 hours

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

- D1 trabectedin
- D2 and D4 irinotecan
- D5 pegfilgrastim

## Case 2: Background

---

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

**ESBL E coli** in urine **4 months ago**

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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) , 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

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**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<sup>2</sup>

**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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- **Febrile** (100 at home)
- **L axillary fullness**
- Left knee **slightly warm** with **rash** but no pain, swelling

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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

	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

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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

	PMN ABS
% Units	1.70 - 7.00 x
18:07	0.10 ▼
14:27	0.40 ▼
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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

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



## Case 2: Hospital course

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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) , 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

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# Discussion



Links to articles discussed  
here



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# 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	<i>P. aeruginosa</i>	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

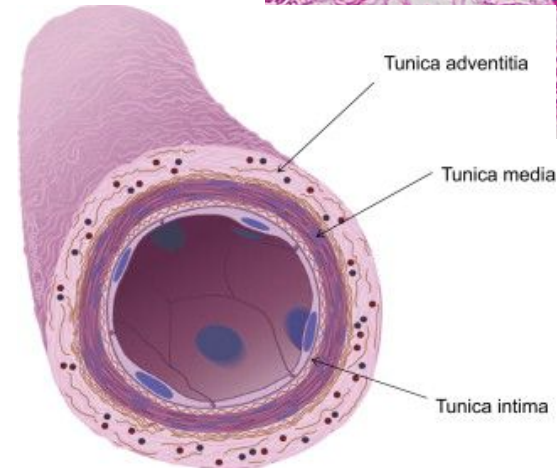
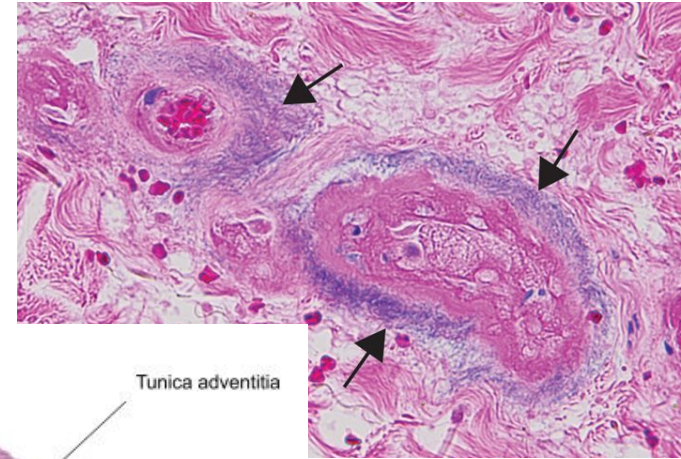
## Fungal

- *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

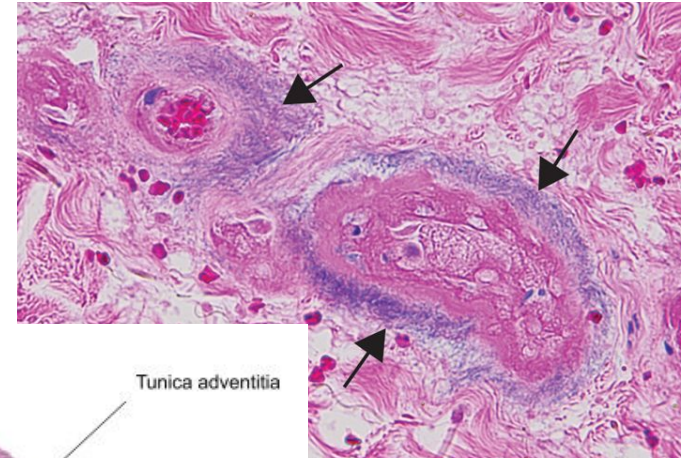
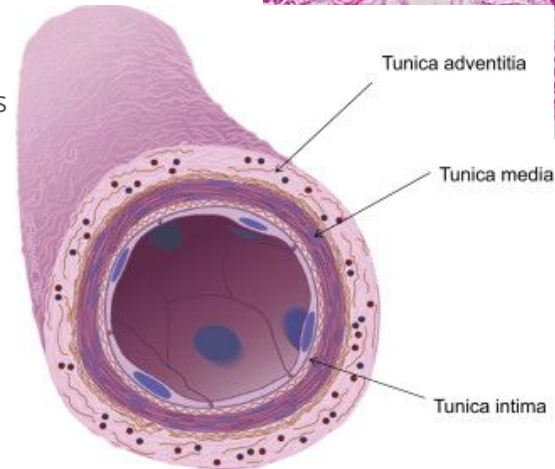


Basophilic bacterial rods around necrotic vessels (arrows)

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



Basophilic bacterial rods around necrotic vessels (arrows)

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# Clinical presentation

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- 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]

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# Learning points & take aways



# Learning points & take aways

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- ❖ *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