

# Anaerobic Infections of the Abdomen Are Anaerobes now MDROs ?

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# Not a Needle in a Haystack, But a Case of a Needle in a Liver



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# Presentation

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- 56 y.o. former nurse presented to ED 3/22/12 with dizziness, fever, fatigue, small volume watery diarrhea for last 6 days
- PMH: pulmonary hypertension, CHF, HLD, HTN
- Travel 1 week Cancun in February
- Lives rural NY with dogs & cats; no other animals; drinks from well water
- Differential at this point ?

**Clostridium difficile**

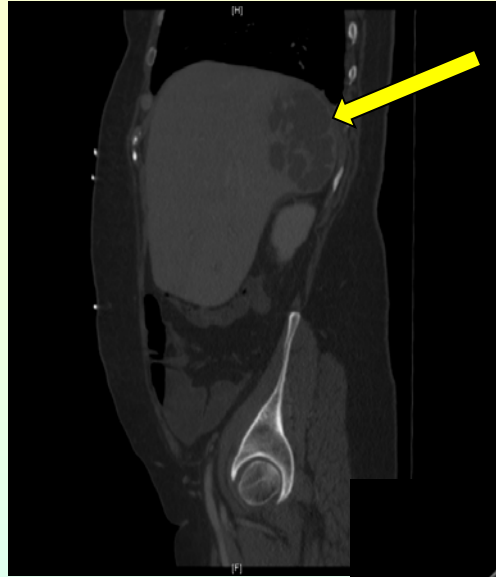
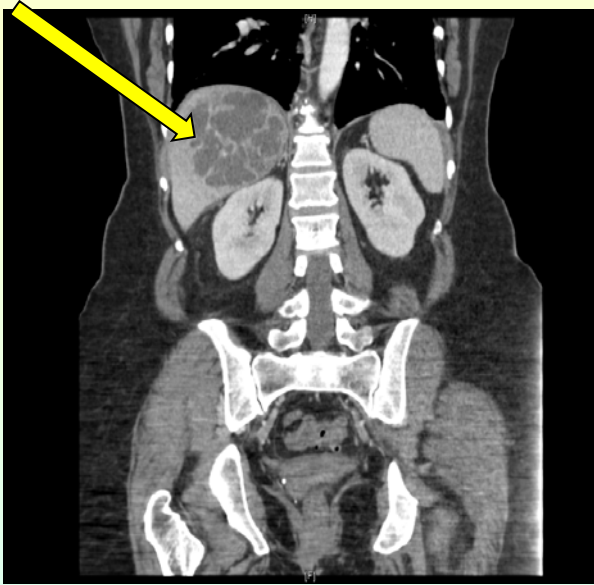
**Enteric parasite**

**Enteric bacterial pathogen**

**Viral syndrome**

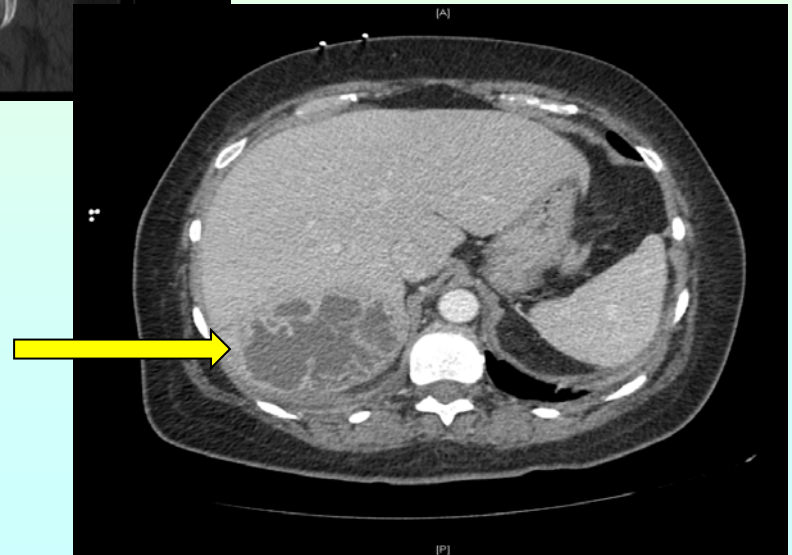
# Hospital Day 2

Mild RUQ discomfort → Abdominal CT



• Started on cipro & flagyl

• Septated rim-enhancing posterior rt. hepatic lobe lesion spanning segments VI and VII



# Hospital Day 4

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- IR guided drainage of abscess
- Courier delivers sample to Micro Lab



**Additional differential at this point ?**

**E. histolytica liver abscess  
Hydatid disease  
Pyogenic liver abscess  
Disseminated fungal disease**

# Sample is inoculated onto various media

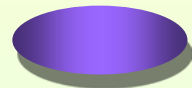
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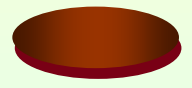
**5% Sheep blood – grows most things**



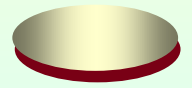
**CNA – selective for gram-positive organisms**



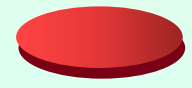
**MacConkey – grows gram-negative rods**



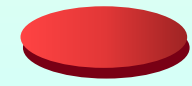
**Chocolate – grows Haemophilus + ALL**



**Anaerobic BBE (for Bacteroides)**



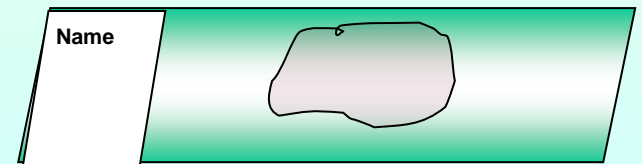
**Anaerobic Brucella**



**Anaerobic LKV**



**Anaerobic CM broth**



**And onto slide  
for Gram stain**

# Laboratory Results

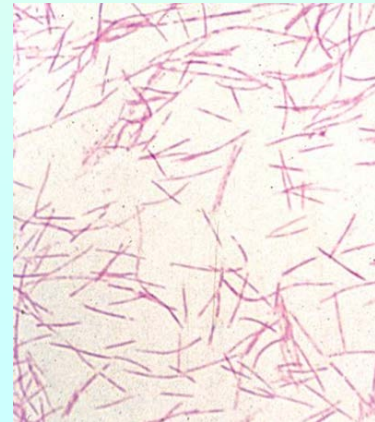
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- HCV, HAV, HIV antibodies negative
- Malaria preparations negative
- Dengue serology negative
- *Entamoeba histolytica* ab negative
- *Echinococcus* ab negative
- Urine *Histoplasma capsulatum* ab negative
- Blood cultures x 2 no growth
- *Clostridium difficile* PCR negative

# Laboratory Results continued

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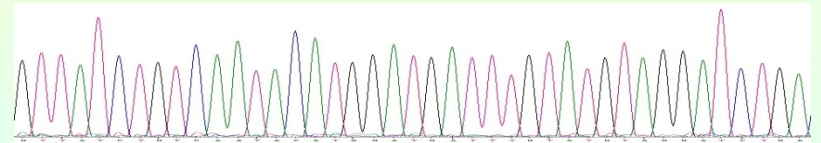
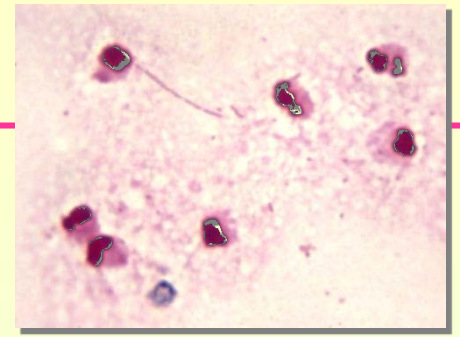
- **Stool O&P negative x 2; Stool WBCs negative**
- ***Giardia* antigen negative**
- **Stool culture negative for enteric pathogens**
- **Urine culture – 25,000 cfu/ml mixed skin flora**
- ***Helicobacter pylori* stool antigen negative**
- **Blood cultures negative x 4 more sets**
- **Abscess aspirate cultures negative**
- **Gram stain positive for rare GNRs**





# Hospital day 6

- Gram stain positive for GNRs
- Cultures negative so far
- 16s sequencing performed on original aspirate material (saved in refrig)



**Final identification  
Day 7**

***Fusobacterium  
nucleatum***

# Epilogue

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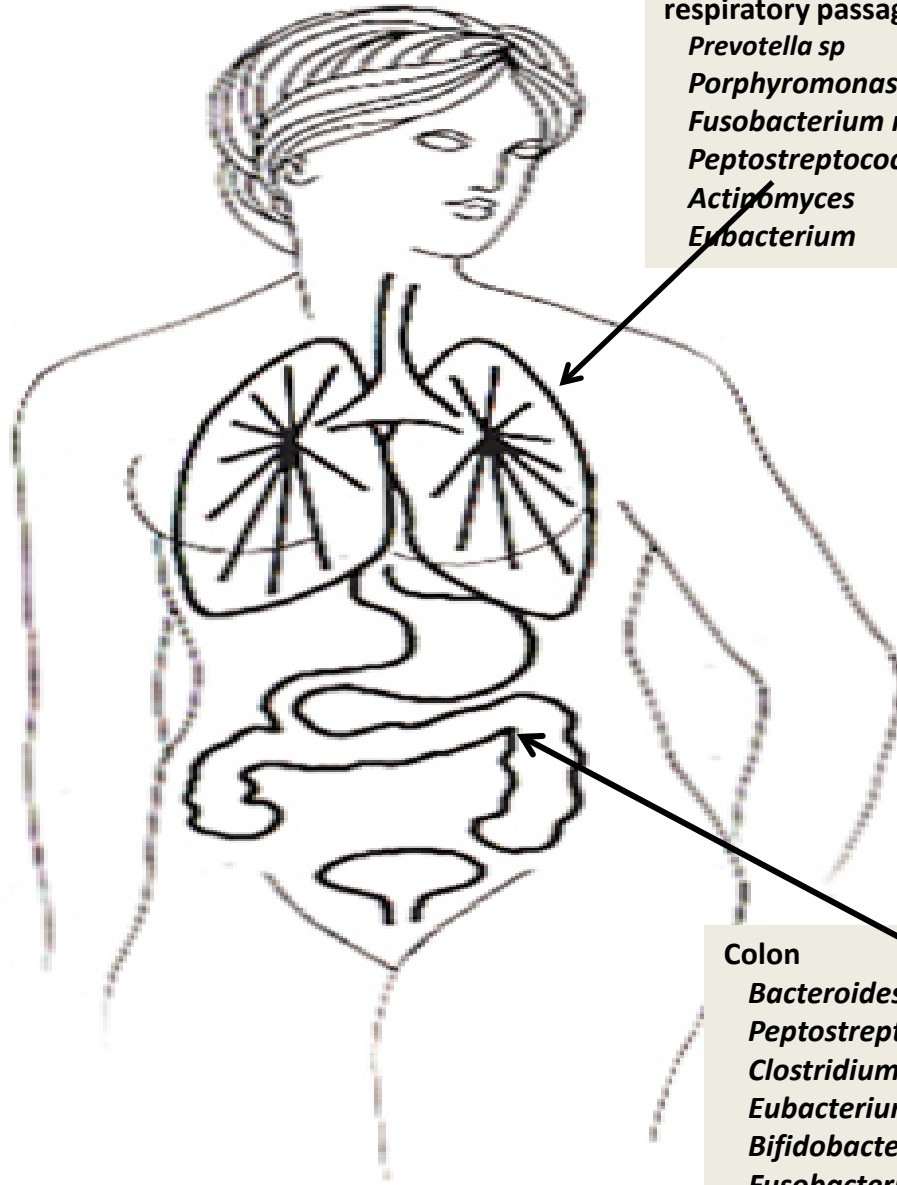
- **Meds changed to meropenem**
- **Patient had 7 crowns and 1 bridge 1 yr. ago**
- **Normal colonoscopy 1 yr. ago**
- **Day 8 – CT showed residual abscess**
- **Day 9 – IR place larger drain with tissue Plasminogen Activator**
- **Day 15 – patient discharged on P.O. flagyl & cipro.**
- **Recommended another colonoscopy.**

**Skin**

*Propionibacterium acnes*  
*Peptostreptococcus*

**Oral cavity and upper  
respiratory passages**

*Prevotella sp*  
*Porphyromonas spp*  
*Fusobacterium nucleatum*  
*Peptostreptococcus*  
*Actinomyces*  
*Eubacterium*



**Female genital tract**

*Lactobacillus*  
*Peptostreptococcus*  
*Pigmented Bacteroides*  
*Other Bacteroides*  
*Eubacterium*

**Colon**

*Bacteroides fragilis group*  
*Peptostreptococcus*  
*Clostridium sp*  
*Eubacterium*  
*Bifidobacterium*  
*Fusobacterium*

***Predominate anaerobes of the normal flora***

# Bacteroides Reclassification

## *Bacteroides*



B fragilis group

Prevotella

Other

*B fragilis*

*B thetaiotaomicron*

*B ovatus*

*B vulgatus*

*P (B) distasonis*

Porphyromonas

## A list of the related species comprising the 'B. fragilis group' at present

<b>Bacteroides</b>			<b>Parabacteroides</b>
<b>acidifaciens</b>	<b>fluxus</b>	<b>propionicifaciens</b>	<b>distasonis<sup>2</sup></b>
<b>barnesiae</b>	<b>fragilis<sup>1,2</sup></b>	<b>pyogenes</b>	<b>goldsteinii</b>
<b>caccae<sup>2</sup></b>	<b>galacturonicus</b>	<b>rodentium</b>	<b>gordonii</b>
<b>cellulosilyticus</b>	<b>gallinarium</b>	<b>salanitronis</b>	<b>johnsonii</b>
<b>chinchillae</b>	<b>graminisolvens</b>	<b>salyersiae</b>	<b>merdae<sup>2</sup></b>
<b>clarus</b>	<b>helcogenes</b>	<b>sartorii</b>	
<b>coagulans</b>	<b>heparinolyticus<sup>3</sup></b>	<b>stercoris<sup>2</sup></b>	
<b>coprocola</b>	<b>intestinalis</b>	<b>thetaitaomicron<sup>2</sup></b>	
<b>coprophilus</b>	<b>massiliensis</b>	<b>uniformis<sup>2</sup></b>	
<b>coprosuis</b>	<b>nordii</b>	<b>vulgatus<sup>2</sup></b>	
<b>dorei</b>	<b>oleiciplenus</b>	<b>xylanisolvens</b>	
<b>eggerthii<sup>2</sup></b>	<b>ovatus<sup>2</sup></b>	<b>xylanolyticus</b>	
<b>faecis</b>	<b>paurosaccharolyticus</b>	<b>zoogloformans<sup>3</sup></b>	
<b>finegoldii</b>	<b>plebeius</b>		

<sup>1</sup>The main pathogenic species of *Bacteroides* that were included in an antibiotic susceptibility study and are most frequently isolated from clinical specimens.

<sup>2</sup>The 10 *Bacteroides* species earlier comprising the *B. fragilis* group.

<sup>3</sup>Now in the genus *Prevotella*.

# Bacteroides and Parabacteroides taxonomy: incidence at St. John's Med Ctr 2006-2011

Species (N=559)	no.	% total	
<i>B. caccae</i>	28	5.0	
<i>B. cellulosilyticus</i>	3	0.5	
<i>P. distasonis</i>	23	4.1	
<i>B. dorei</i>	1	0.2	
<i>B. eggerthii</i>	1	0.2	
<i>B. fragilis</i> *	211	37.7	
<i>P. goldsteinii</i>	10	1.8	
<i>P. gordonii</i>	2	0.4	* Total 67.9%
<i>B. intestinalis</i>	2	0.4	
<i>P. johnsonii</i>	5	0.9	
<i>B. massiliensis</i>	2	0.4	
<i>P. merdae</i>	7	1.3	
<i>B. nordii</i>	3	0.5	
<i>B. ovatus</i> *	69	12.3	
<i>B. salyersiae</i>	4	0.7	
<i>B. stercoris</i>	3	0.5	
<i>B. thetaiotaomicron</i> *	100	17.9	
<i>B. uniformis</i>	35	6.3	
<i>B. vulgatus</i>	49	8.8	
<i>B. xylanisolvens</i>	1	0.2	

Citron DM. Premolecular identification: Ignorance was bliss?  
Anaerobe 18:189; 2012

# Approved list of names vs species in kit databases

Organisms	Euzeby List (16S)	RapID ANA II	Rapid 32A
Bacteroides	20	10	10
Prevotella	42	11	9
Clostridia	203	24	22
Actinomyces	45	7	5
GP cocci	20	9	5

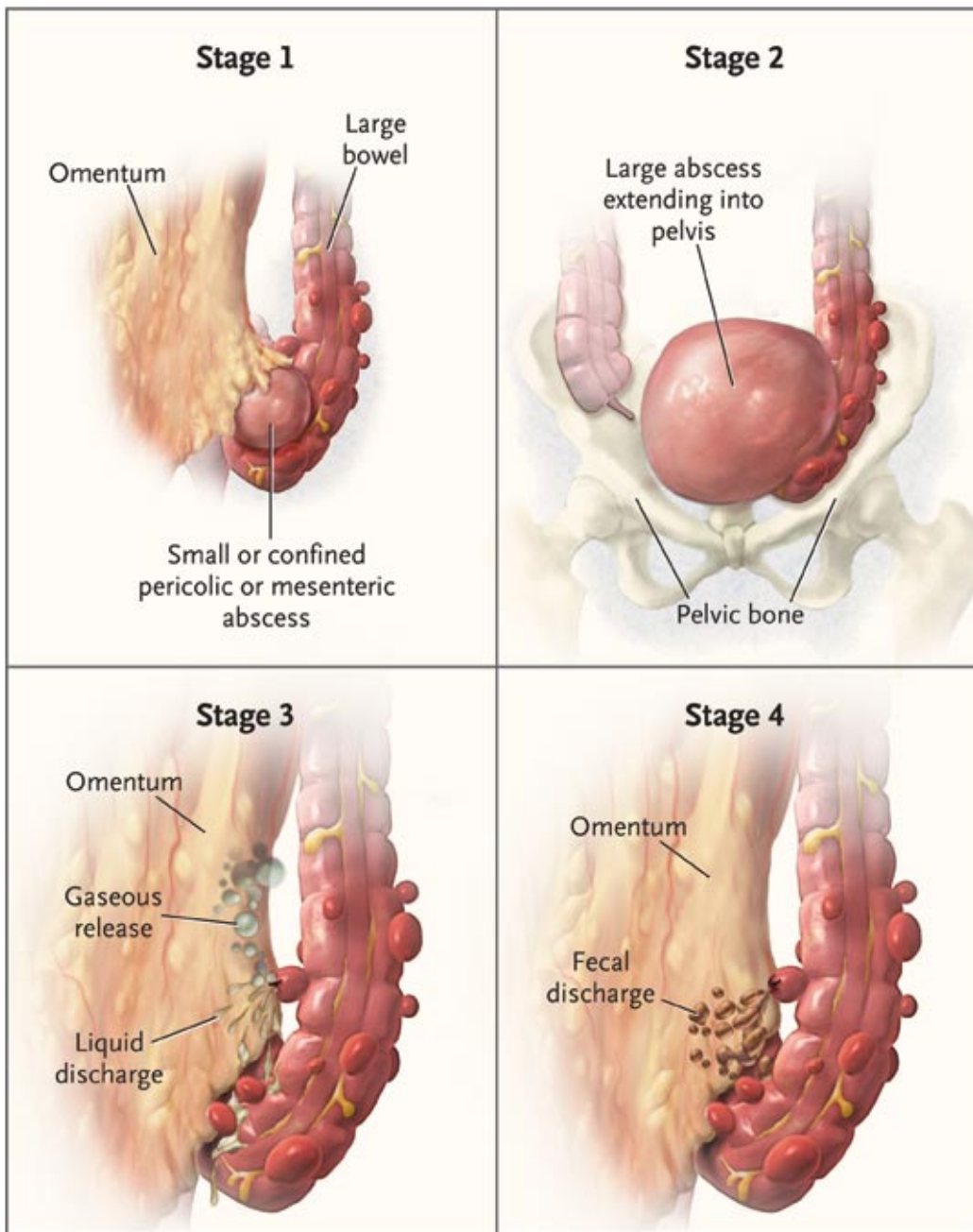
# Diverticulosis Perforated Diverticulitis





# Diverticulitis

- **Western society      Common**
    - 5-10 % <45 years old
    - >80% >80 years old
    - Men = Women
    - Sigmoid and descending colon - 90%
  - **20% with pts with diverticulosis develop symptoms**
  - **130,000 US hospitalizations annually**
  - **20% of symptomatic pts < 50 years old**
- More severe in younger patients vs delay dx ?**



**Stage      Mortality**  
**Stage 1&2      < 5%**  
**Confined**  
**Stage 3      13%**  
**Perforation with**  
**peritonitis**  
**Stage 4      45%**  
**Free rupture**

# Abdominal Pain Case (1)

64 year old cardiologist

Went to a medical conference in San Francisco

Developed hard stools

While doing an angioplasty he had the sudden onset of abdominal pain referred to the penis

History Levofloxacin & metronidazole intolerance

MSSA carrier

PE: Severe left sided abdominal pain and rebound

WBC 19,400 (88% PMNs, 7 Bands) Hct. 39%, Plt. 149K

CT Abdomen/Pelvis: No Kidney Stone

Sigmoid wall thickening

Therapy: Ertapenem → Imipenem 500 mg q 6 H

Initial improvement x 48 h then deteriorates

# Abdominal Pain Case (2)

Repeat CT Scan: micro perforation & extraluminal pericolonic air

Develops rapid atrial fibrillation/flutter → cardioversion

OR: - Laparoscopic colectomy with end colostomy & Hartman pouch; HARD stool at site of perforation

- Ureteral stent placed

- Perforated diverticulitis with pelvic abscess

Culture: E coli R- Levo, Ampicillin,  
N ferm GNR S- all usual (Not Pseud)  
E. faecium  
lactobacilli  
B fragilis R- FOX, Imipenem, Pip-Tazo  
C. perfringens  
Clostridium-other

ICU → cardiac arrest; 34 day hospital stay- retires

# *Preoperative Surgical Consent*

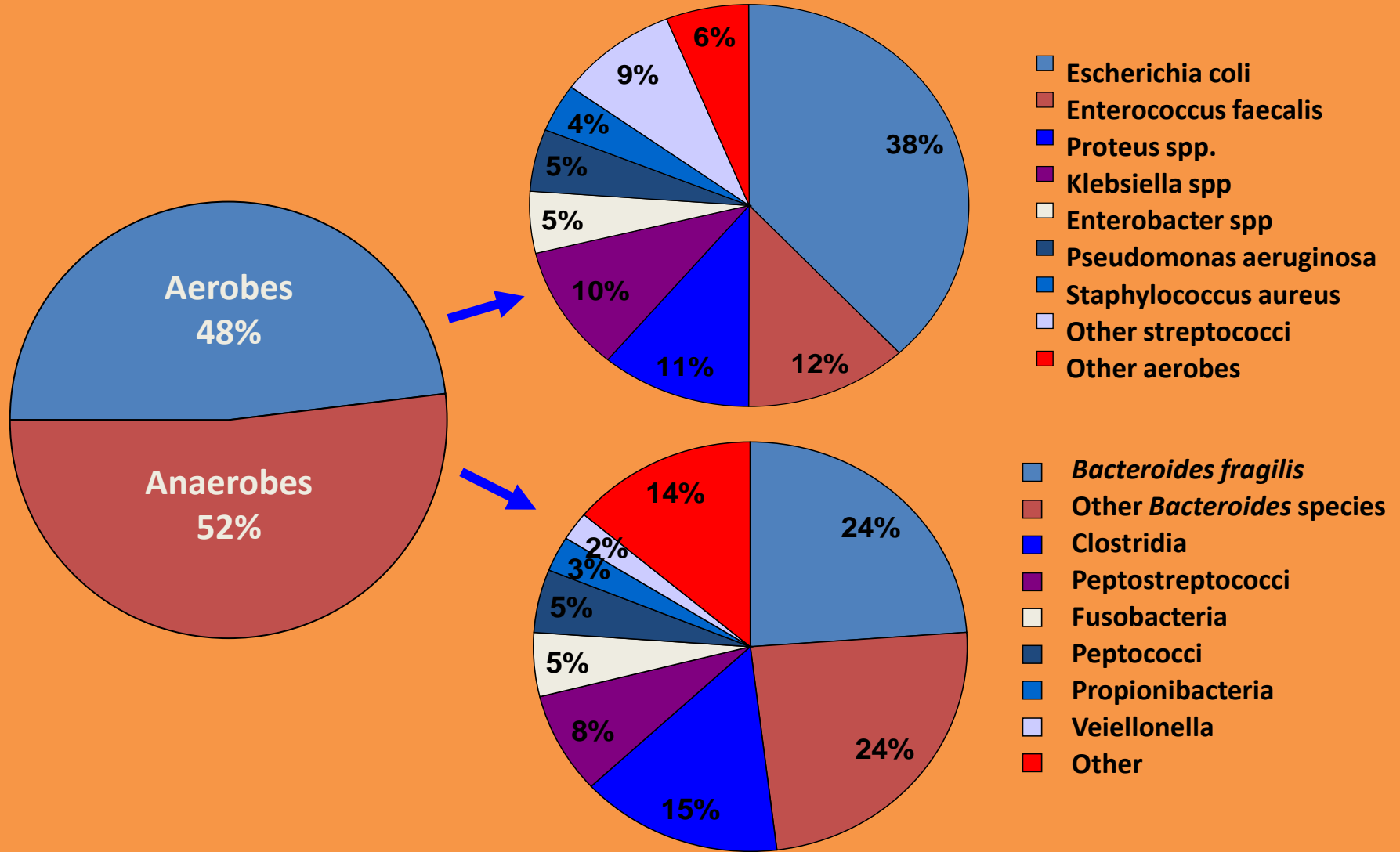




**300,000 cases/year US**  
**Lifetime incidence 7-14%**

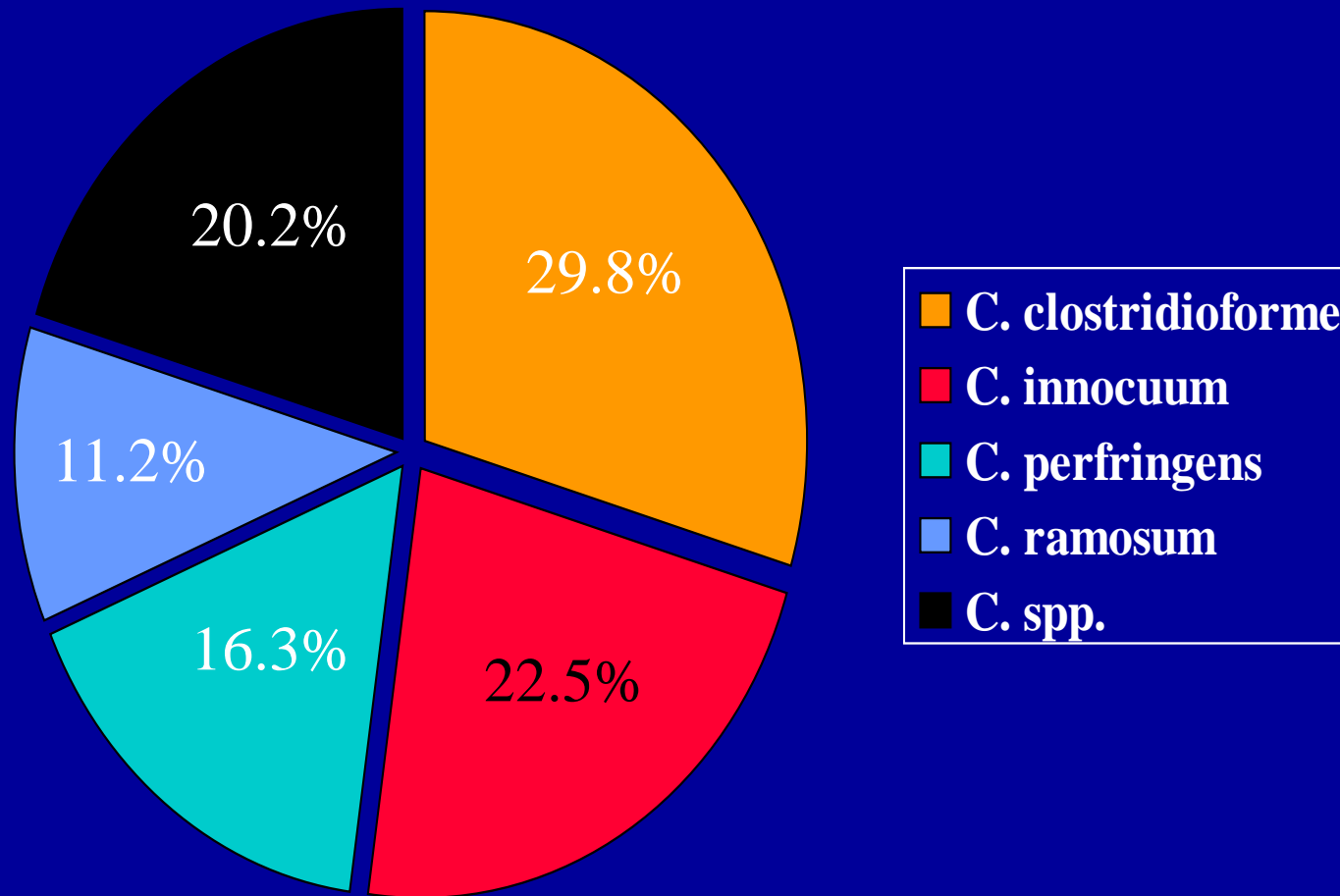
# Intra-Abdominal Infections

## Pathogens



# *Clostridium* Species from Intra-Abdominal Infections

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# Acute Appendicitis Appendectomy or Antibiotics First Common Features of Randomized Clinical Trials of “Antibiotics First” Regimens.

**Table 2.** Common Features of Randomized Clinical Trials of “Antibiotics First” Regimens.

- Eligible patients are consenting adults who are not pregnant, do not have compromised immune function, and do not have certain implantable devices.
- Patients have no evidence of abscess or perforation on imaging.
- Patients have no evidence of sepsis or disseminated peritonitis on clinical examination.
- Patients are admitted to a hospital, and intravenous antibiotics are administered for 48 hours.
- Patients are assessed at intervals of 6–12 hours for progression of symptoms or development of sepsis.
- Patients begin oral intake of food; when pain is well controlled, patients are discharged home with 7 days of oral antibiotics.
- A patient proceeds to surgery if sepsis or shock, worsening fever, or disseminated peritonitis develops or if by 48 hours the patient’s pain or elevated white-cell count is not reduced or the patient is unable to eat.

# Appendectomy vs Abx First

**In US**, the usual treatment uncomplicated appendicitis is a prompt appendectomy.

- The laparoscopic preferred to the open approach (owing to a lower incidence of surgical-site infection and a faster return for the patient to usual activities)

**In Europe** antibiotics-first strategy is an alternative particularly in a patient who has had prior surgical complications and has a strong preference for avoiding appendectomy.

- In European randomized trials It was not associated with an increased risk of perforation (**2 studies did**) or a higher rate of complications; however, **as many as half the patients so treated will have early treatment failures**, and all have a **risk of recurrent appendicitis (10-37%) may ultimately require Appx**



# Diabetic Foot Infections

## US Multi-Center Trial

- 454 pretreatment specimens  
433 patients; 427 (+) cultures
- 83.8% Polymicrobial
  - 48% Aerobes Only
  - 43.7% Mixed  
Aerobes/Anaerobes
  - 1.3% Anaerobes only

## Bacteriology

1145 aerobes	2.7/culture
462 anaerobes	2.3/culture
<i>S aureus</i>	14.3%
MRSA	4.4%
Anaerobe GP cocci	45.2%
<i>F magna</i>	24.4%
<i>Prevotella</i>	13.6%
<u><i>B fragilis</i> gp</u>	10.2%

# Differences in Distribution & Antimicrobial Susceptibility of Anaerobes Isolated from IAIs versus DFIs

Organism/Antimicrobial Agent	MIC breakpoint	<u>% Resistant</u>	
		IAI	DF
<i>Bacteroides fragilis</i> group spp.			
amoxicillin-clavulanate	>4	8.8	19.6
cefoxitin	>16	30.5	31.4
clindamycin	>2	35.3	35.4
moxifloxacin	>2	21.3	43.1
<i>Clostridium</i> spp.			
amoxicillin-clavulanate	>4	1.9	0
cefoxitin	>16	41.1	0.5
clindamycin	>2	16.5	21.0
moxifloxacin	>2	32.3	0

Cephamiracle 3rd Generation Gorillamycin

Cephawonderful

1st Generation

Penems

Monobactams

Oxycephamycins

Macrolides

Thienamycins

Tetracyclines

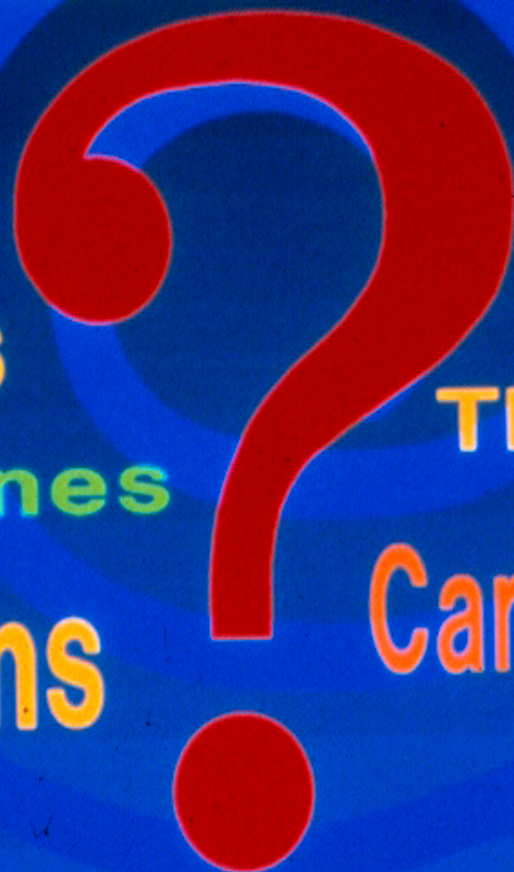
Carbapenems

Penicillins

2nd Generation

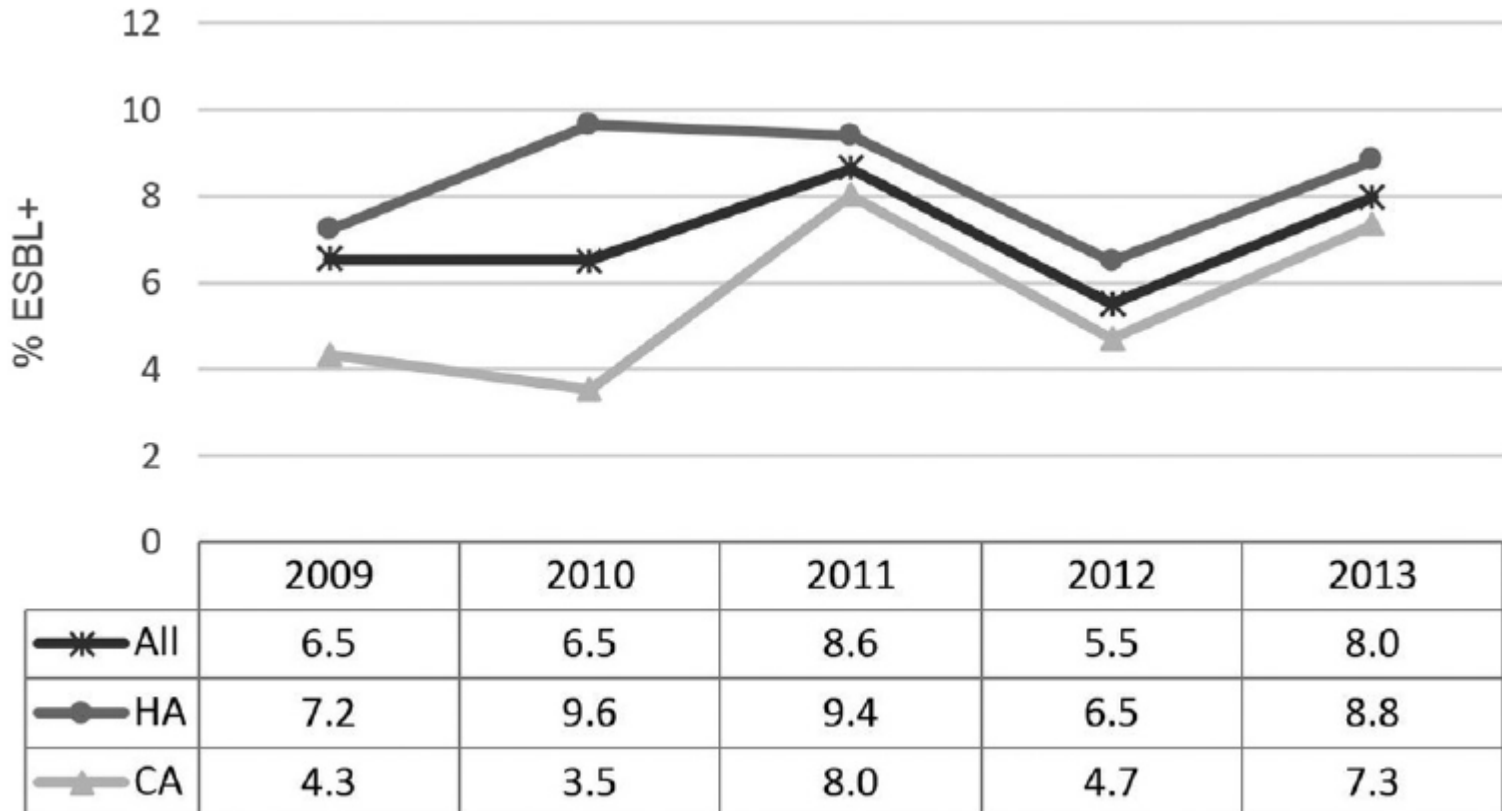
Aminoglycosides

Quinolones Penams

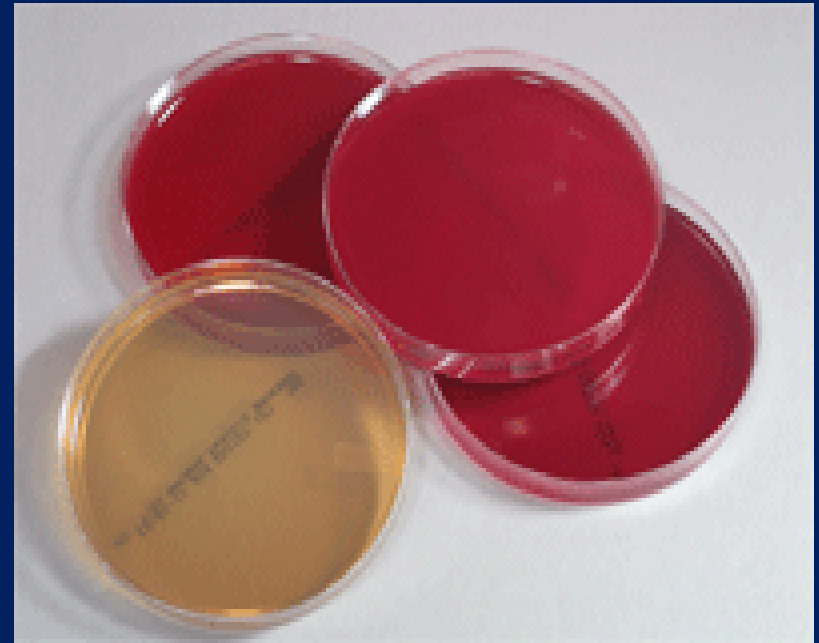


# Trends in the prevalence of genotypically ESBL-positive isolates of *E. coli* from IAIs in the United States in 2009 to 2013.

29 Hospitals in 17 states



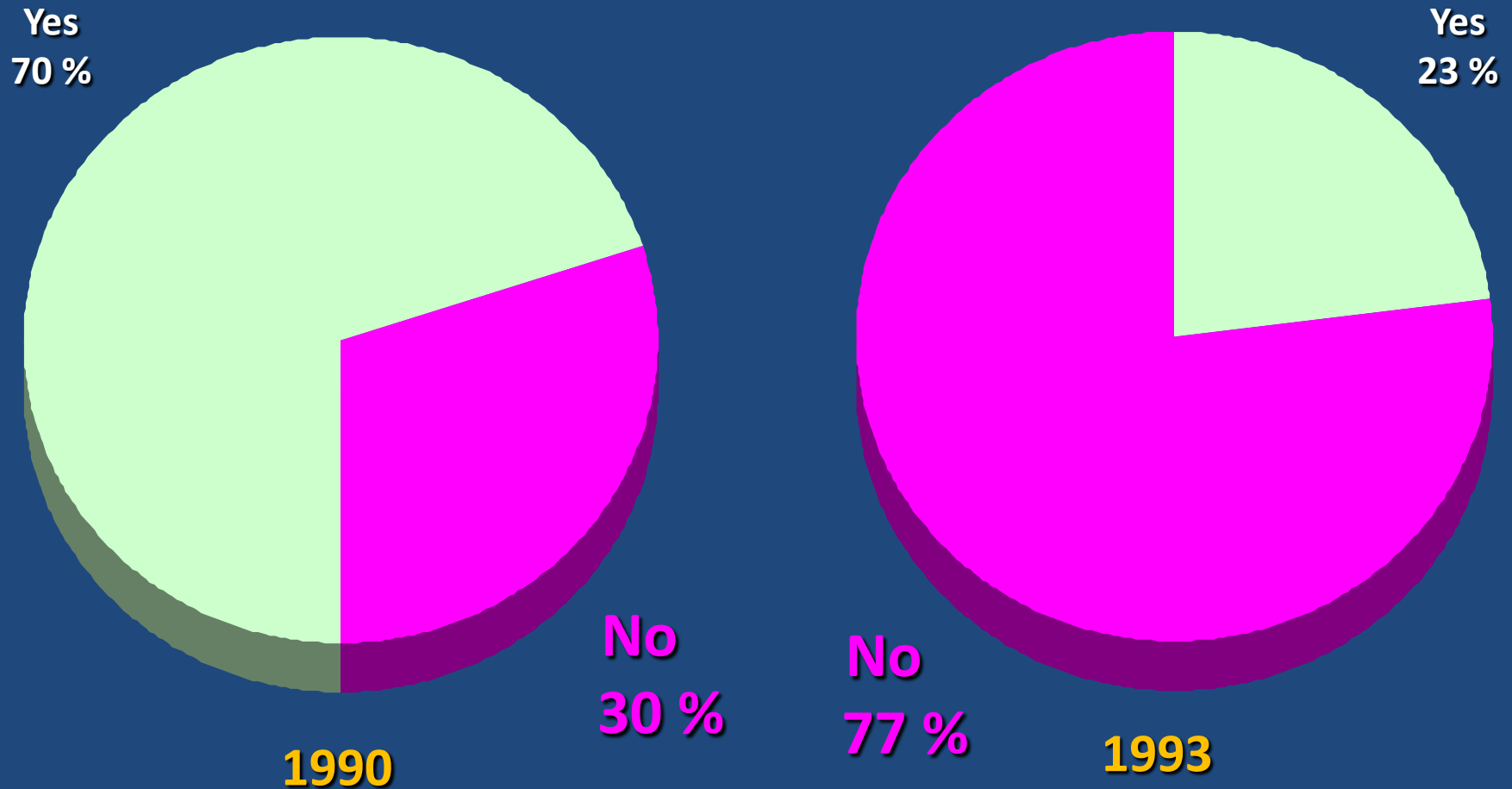
# Carry & Blair Transport





# Anaerobic Susceptibility Testing

US National Survey

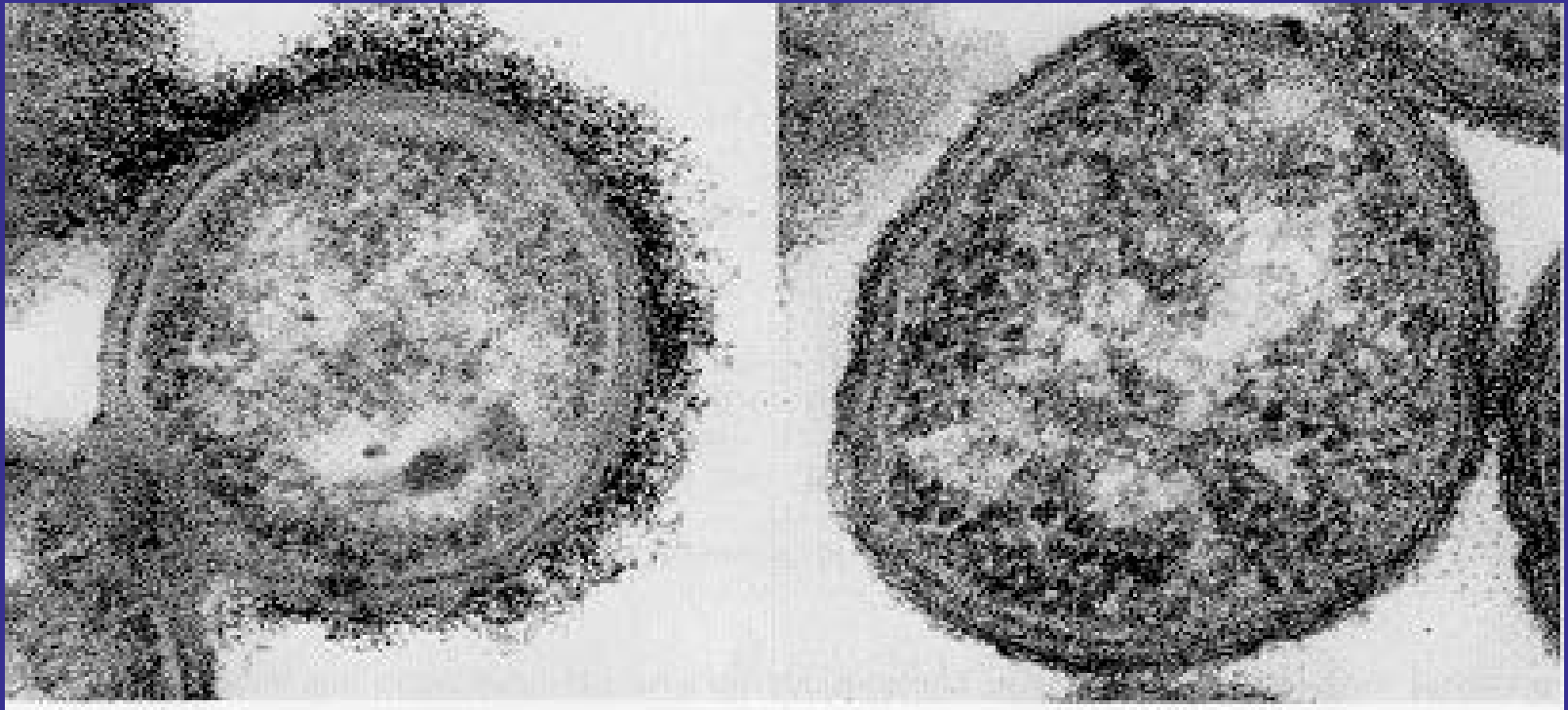


# Drugs Tested vs. Anaerobes

<b>B-lactamase only</b>	<b>29%</b> so 40% test
<b>Penicillin/Ampicillin</b>	<b>83%</b>
<b>Amp-sulbactam</b>	<b>83%</b>
<b>Clindamycin</b>	<b>100%</b>
<b>Metronidazole</b>	<b>100%</b>
<b>Cefoxitin</b>	<b>100%</b>
<b>Chloramphenicol</b>	<b>67%</b>
<b>Pip-tazobactam</b>	<b>50%</b>
<b>Imipenem/Meropenem</b>	<b>33%/17%</b>



# *Bacteroides fragilis* capsule



Rodloff et al., ZAC 4, 1985

# Bacteremia & Mortality due to B fragilis group

	<u>Chow &amp; Guze</u> (1969-72)	<u>Brook</u> (1973-85)
<i>B fragilis</i>	5/16 (31%)	28/115 (24%)
<i>B thetaiotaomicron</i>	3/3 (100%)	8/31 (38%)
<i>B vulgatus</i>	3/8 (37%)	2/5 (40%)
<i>B ovatus</i>	0/3 (0%)	1/5 (20%)
<i>P (B) distasonis</i>	1/2 (50%)	1/2 (50%)
	12/32 (38%)	40/148 (27%)

Chow Medicine 53-93-126, 1974

Brook J Clin Micro 1988

# *B fragilis* bacteremia

## Sources

- Abdomen 69%
- Soft tissue 16%
- Pelvic 5%
- Pulmonary 4%
- Other 7%

## Mortality

Matched pair study

1983-93

- Mortality 28% vs. 9%
- Attributable 19.3%
- Risk ratio 3.2
- Increased LOS 18 days

# Relationship of Treatment with Inactive Therapy and Clinical Outcome

Outcome	Active	Inactive	Fail (%)
Clinical Failure	18	9	(27%)
Clinical Success	63	2	(3%)

$p = 0.002$

# 2010 SIS/IDSA Guidelines

## Empiric Therapy- Complicated IAs

Type of therapy	<u>Agents for mild to moderate infections</u>	<u>Agents for high-severity infections</u>
<b><u>Single agent</u></b>		
Beta-lactam/beta-lactamase inhibitor combinations	(X Amp/sulbactam X) (X Cefotetan X) Ticarcillin/clavulanic acid	Piperacillin/tazobactam
Carbapenems	Ertapenem	Imipenem/cilastatin
Other	Tigecycline	Meropenem Doripenem
<b><u>Combination regimens</u></b>		
Cephalosporin-based	Cefazolin or cefuroxime + metronidazole ( X clindamycin X)	3rd/4th generation agents + metronidazole
Fluoroquinolone-based	Ciprofloxacin, levofloxacin, each + metronidazole moxifloxacin	Ciprofloxacin + metronidazole
Monobactam-based		Aztreonam + MTZ +Vanco



# Trial of Short Course Abx in cIAI

518 Patients with Adequate source control

(52.8 yo; 56% male; 75-80% white)

Abx +2 D resolution of fever, ileus, leukocytosis VS.

Fixed course 4+1/- 1 Day abx

	<b>Long</b>	<b>Short</b>
<b>Abx duration</b>	<b>8 days</b>	<b>4 days</b>
<b>Surgical Site Inf</b>	<b>8.8%</b>	<b>6.6%</b>
<b>Recurrent IAI</b>	<b>13.8%</b>	<b>15.6%</b>
<b>Resistant Pathogen</b>	<b>3.5%</b>	<b>2.3%</b>
<b>C difficile Inf</b>	<b>1.2%</b>	<b>1.9%</b>

# ***IDSA IAI Guidelines 2016***

## ***Issues***

**Most studies are Appx (60%)**

**Duration of Therapy**

**Resistance rates**

**- MRSA**

**- ESBLs**

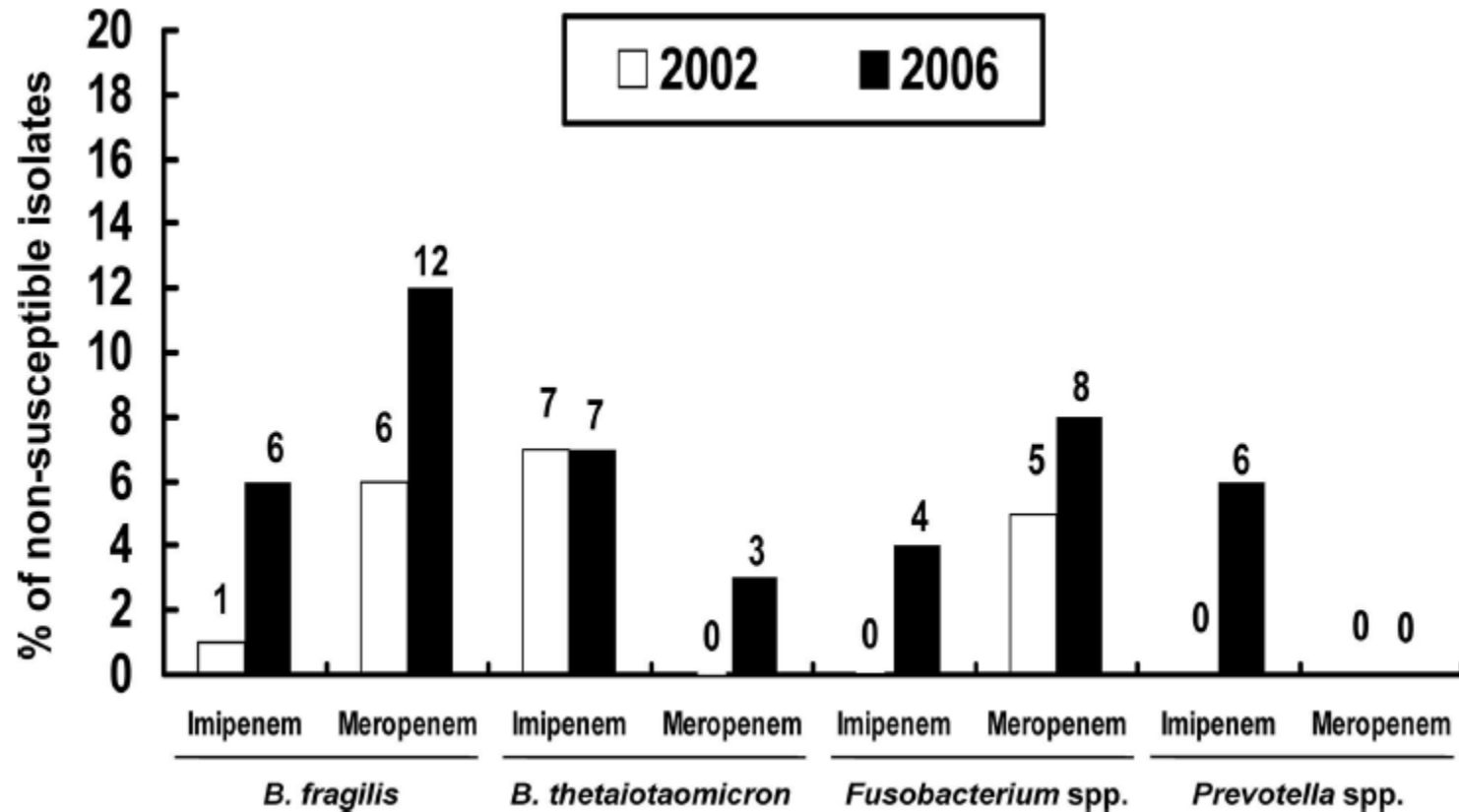
**CLSI vs EUCAST Breakpoints**

**Old Agents/ Old Studies**

**New Agents**

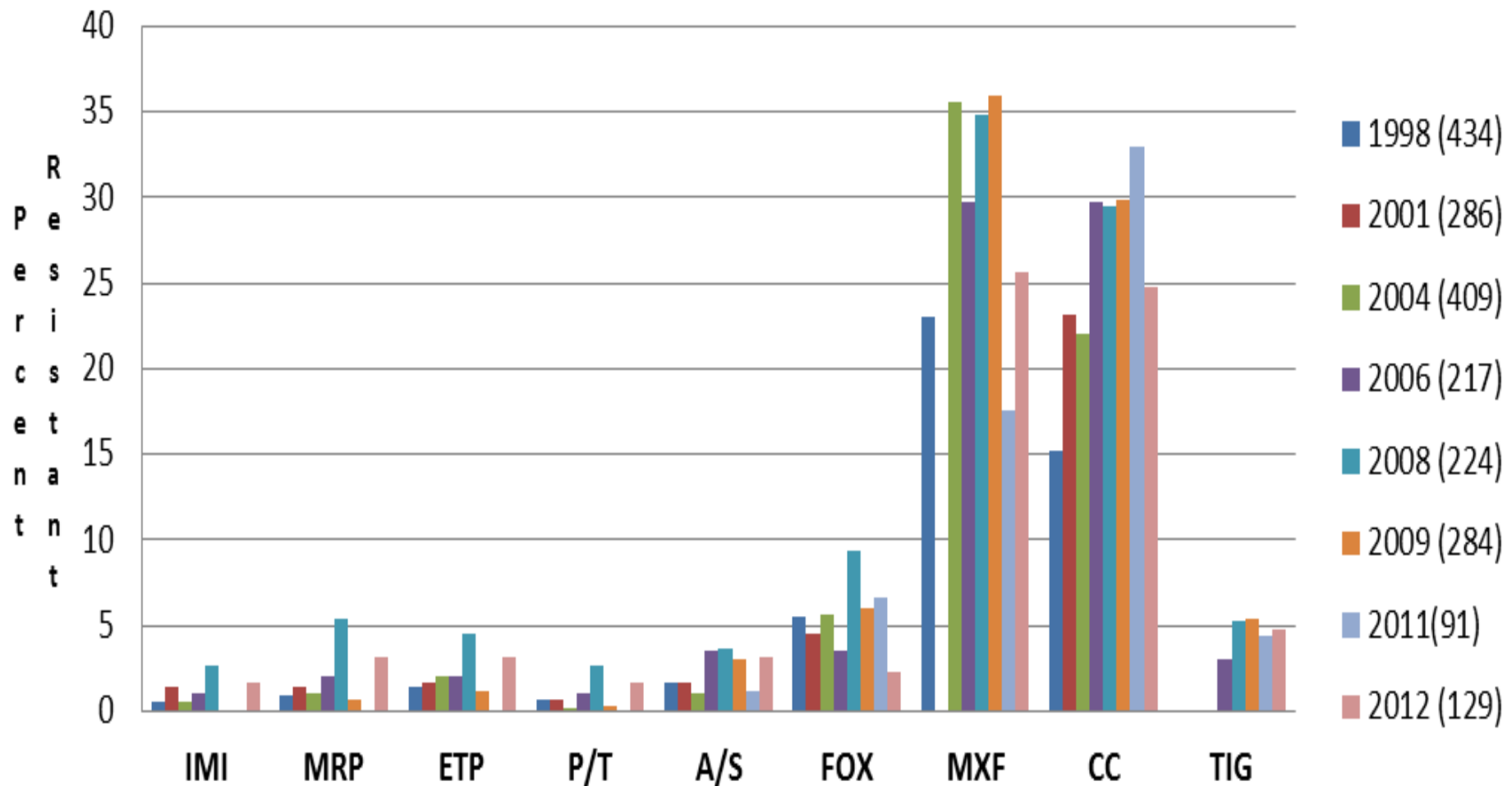
**Lack of Clinical Outcome Data**

**Differences in rates of non-susceptibility to imipenem and meropenem for selected clinical isolates of anaerobes isolated between 2002 and 2006 at National Taiwan University Hospital.**



[number of isolates above the bars.]

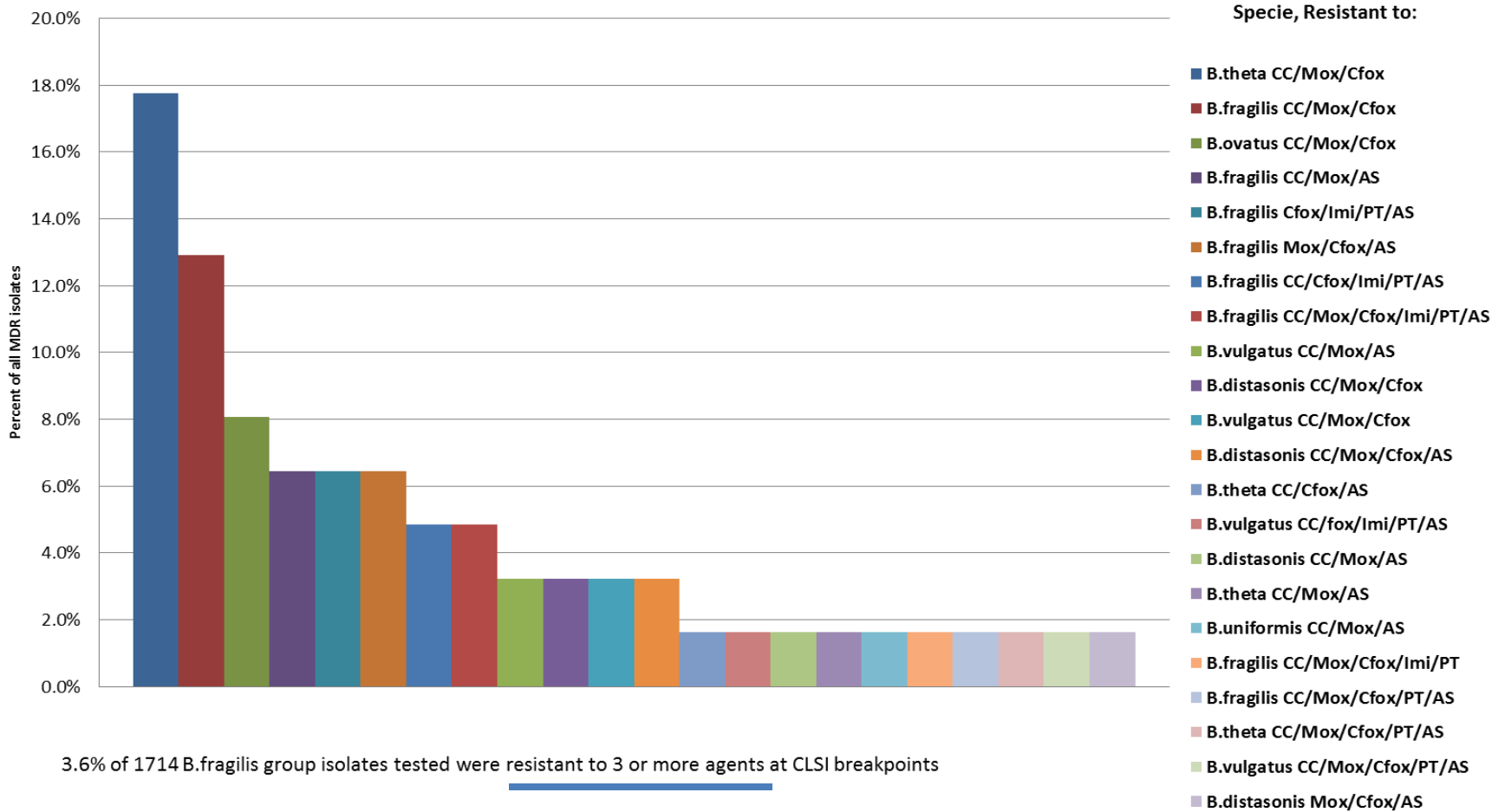
# Variation in Resistance by Species: US National Surveillance: *B. fragilis*



3.6% were resistant to  $\geq 3$  drugs

Snydman D et al. ICAAC 2014- submitted AAC 2015

## *B. fragilis* group Isolates 2008-2012 MDR (n=62)



## Percent Resistance of other Antibiotics vs *B. fragilis* in Germany (2007), Spain, Europe and Belgium

	Germany	Spain *		Europe	Belgium
		(08)	(12)		
<b>Moxifloxacin</b>	<b>13.9</b>	<b>25</b>	<b>NT</b>	<b>14</b>	<b>30</b>
<b>Tigecycline</b>	<b>NT</b>	<b>6.5</b>	<b>NT</b>	<b>1.8</b>	<b>NT</b>
<b>Clindamycin</b>	<b>22.7</b>	<b>47.9</b>	<b>45</b>	<b>28.5</b>	<b>23</b>
<b>Metro</b>	<b>0</b>	<b>0</b>	<b><u>6.3</u></b>	<b>0.5</b>	<b>0</b>

Seifert H, et al. JAC 2010; 65: 2405-10; Betriu C, et al AAC 2008; 52:2686-90;  
 Nagy E, et al. Clin Micro and Infection 2011; 17:371-9.  
 Trevino M, et al. Anaerobe 2012;18:37-43.  
 Weybo I, et al. JAC 2014; 69: 155-61

# Resistance Genes in Spanish Study of Carbapenem Resistant Bacteroides

- 6 carbapenemase producing strains showed *cfiA* genes
- 5 *B. fragilis*, 1 *P. distasonis*
- All carbapenemase producing isolates had multiple drug resistances, including some to piperacillin-tazobactam (4), clindamycin (3), cefoxitin (4), metronidazole (1) and tigecycline (2)
- Clonally unrelated

# Metronidazole Resistant *B fragilis*

- 206 human isolates from UK \* (2004)
- 50/206 (24%) + *nim* gene (A-F exist)
  - MICs 1.5->256 ug/ml
- 24 of these (11.6% total) MIC >16 ug/ml
- 10/26 with MICs  $\leq 8$  had slow growing subpopulations with MICs 8->256 ug/ml
- Conclusions: *nim* genes presence does not always confer resistance

## Other mechanisms of resistance exist

-Overexpression of a DNA repair protein (RecA) increases Mtz resistance \*\*

- Efflux Pumps \*\*\*

- Gal & Brazier JAC 2004;54:109 \*\* Steffens LS et al. Res Microbio 2010;161:346
- \*\*\* Wexler H Anaerobe 2012; 18:200



## The 5-nitroimidazole resistance *nim* genes of interest for *Bacteroides*

<i>Nim</i> gene type	Carrying genetic element	Activating IS	No. of isolates <sup>1</sup>
<b><i>nimA</i></b>	pIP417 (7.7 kb)	IS1168	0 <sup>[02, 4, 5]</sup>
	10 kb uncharacterized plasmid	IS1168	2 <sup>[02]</sup>
	8.2 kb uncharacterized plasmid	IS614	1 <sup>[02]</sup>
	chromosomal	IS1168 or unknown	3 <sup>[02]</sup>
	unknown	IS1168	2 <sup>[5]</sup>
	unknown	IS1169	1 <sup>[6]</sup>
<b><i>nimB</i></b>	chromosomal	IS1168 or IS612 or IS614	8 <sup>[02, 4]</sup>
	unknown	IS1168	3 <sup>[6]</sup>
<b><i>nimC</i></b>	pIP419 (0 kb)	IS1170	4 <sup>[5]</sup>
	chromosomal	IS1170	2 <sup>[02]</sup>
	unknown	IS1170	2 <sup>[63, 6]</sup>
<b><i>nimD</i></b>	pIP421 (7.3 kb)	IS1169	1 <sup>[02, 7]</sup>
	chromosomal	unknown	1 <sup>[02]</sup>
	unknown	IS1169	6 <sup>[6]</sup>
<b><i>nimE</i></b>	pBF388c (pWAL60, 8.3 kb)	ISBf6	5 <sup>[02, 8]</sup>
<b><i>nimF</i></b>	chromosomal	unknown	[6]
<b><i>nimG</i></b>	unknown	unknown	[63]
<b><i>nimH</i></b>	unknown	unknown	— <sup>2</sup>

<sup>1</sup>The number of isolates with the given genotypes are indicated with references.

<sup>2</sup>Taken from GenBank (www.ncbi.nlm.nih.gov, acc. no. FJ969397)

# Clinical Metronidazole Resistance

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<u>Reference</u>	<u>Year</u>	<u>Country</u>	<u>Isolate Source</u>	<u>Mtz Tx</u>
Turner	(95)	UK	<i>B fragilis</i>	Blood ?
Caudhry	(01)	India	B fragilis	Blood ?
Schapiro	(04)	US	<i>B fragilis</i>	Ankle -
Wareham	(05)	UK	<i>B fragilis</i>	Blood +
Katsandri	(06)	Greece	<i>B vulgatus</i>	Abd +
Hecht	(07)	US	<i>B fragilis</i>	Abd +
Sherwood	(11)	US	B fragilis	Wound +
Kalapila	(13)	US	B fragilis	Blood/Abdomen +

**Several other unpublished cases are known to have occurred**

Goldstein, Citron & Hecht in Antimicrobial Resistance 2008;  
Sherwood et al. Anaerobe 2011; MMWR 62:No34; 694,2013

## The insertion sequence elements involved in the up-regulation of antibiotic resistance genes in *Bacteroides*


IS Family <sup>1</sup>	Group <sup>a</sup>	IS2	Activated genes
IS4	ISPep	IS943	<i>cfiA</i>
		ISBf8	<i>cfxA</i>
IS5	IS5	IS1186 (IS1168)	<i>cfxA, cfiA, nimA, nimB</i>
		IS1169	<i>cfiA, nimA, nimD</i>
	IS1031	ISBf6	<i>nimE</i>
IS21	—	ISBf1	<i>cepA</i>
IS982	—	IS1187	<i>cfiA</i>
IS31380	IS942	IS942	<i>cfiA</i>
		IS1170	<i>nimC</i>
		IS612	<i>cfiA, nimB</i>
		IS613	<i>cfiA</i>
		IS614	<i>cfxA, cfiA, nimB</i>
		IS615	<i>cfiA</i>
		-	
		IS1188	<i>cfiA</i>
		IS4351	<i>ermF, cfiA</i>
		IS616	<i>cfiA</i>

<sup>1</sup>The IS families and the subgroups within them (taken from IS Finder)<sup>77</sup>;

– indicates no further classification;

<sup>2</sup>The species of IS elements activating the resistance genes of *Bacteroides* spp.; the mosaics and isoforms are not indicated.

IS: Insertion sequence.

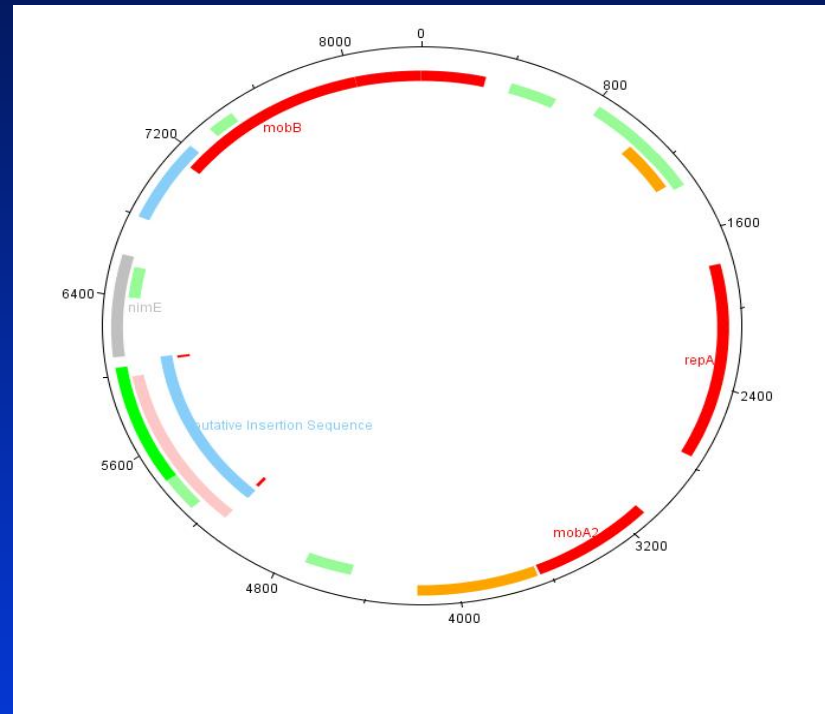
- 
- **Efflux mechanisms** confer a low to moderate level of intrinsic resistance
  - Low level resistance allows the organisms to survive long enough to acquire mutations that result in high level resistance
  - Concomitant expression of several pumps can lead to high level resistance phenotypes
  - Efflux may cooperate with other mechanisms to confer not only **high level** but **broad spectrum** resistance
  - Efflux pumps may be induced by a wide variety of stressors, including O<sub>2</sub>, bile, antimicrobial agents, and a wide variety of commonly used cleansers and microbicides.

# *B fragilis* plasmid (8.8 kb)

## Resistance to Carbapenems & Metronidazole

Rings: outer→inner

- 1-DNA co-ordinates
- 2-forward strand coding sequences
- 3-inner strand coding
- 4-Insertion sequence ISBf6



Class III BFP35 plasmid described by Soki, et al (Plasmid 63:86-97, 2009); isolate also contained 5.5 kb pHAG (W1) plasmid, *cfiA* gene and *nimE* gene.

Sherwood et al. Anaerobe (2011)

# Recent Worldwide Surveys of *B fragilis*

## Susceptibility & Resistance

- **Europe:** Eitel Z et al Anaerobe 2013;21:43
  - 161 strains 2008-2009 *cepA* in 70.8% but its presence did not correlate with ampicillin MIC values
- **Argentina:** Canagia L et al AAC 2012;56:1309
  - 363 isolates 17 Centers 2006-2009
    - 1.1-2.3% resistance to a carbapenem 8/23 isolates *cfiA* +
- **Canada:** Karlowsky et al AAC 2012;56:124
  - 387 isolates 9 Centers 2010-2011
  - 8%<sup>®</sup> Ertapenem; 2.3% Imipenem
  - One *B. thetaiotaomicron*<sup>®</sup> metronidazole
  - Two *B fragilis*<sup>®</sup> Imipenem & Pip-Tazo
- **Japan:** Tran C et al J Infect Chemo 2013;19:279
  - 702 isolates from 27 medical centers (2010)
  - 2.9%<sup>®</sup> Pip/Tazo & Imipenem
  - IAI- Resistance genes studied 2 *cfiA* (+) *B fragilis* did not produce the protein product
- **Taiwan:** Wang et al EJCMID 2014; 33:2041-52 (2008-2010)
  - *B fragilis* 13.5%<sup>®</sup> Ertapenem
- **Russia:** Shilnikova Anaerobe 2014; epublished doi:10.1016/j.anaerobe.2014.08.003
  - 3 *B fragilis*<sup>®</sup> metronidazole & Imipenem (2004-2014)

# Risk Factors for Resistance to $\beta$ L/ $\beta$ LIs & Ertapenem in *Bacteroides* sp. Bacteremia 2007-2013

Retrospective case-control study 159 Pts.

1,051 Tertiary Care Center (Hopkins)

- **Bacteremia associated with**
  - **Recent surgery**
  - **Malignancy**
  - **Immunosuppression**
- **16% (26/159) had resistance**
  - Amoxicillin clavulanate **11.5%**
  - Ertapenem **7.0%**
  - Piperacillin/Tazobactam **6.8%**

Duration of exposure to  $\beta$ L/ $\beta$ LI was the ONLY independent risk factor

Each additional day of therapy was associated with a 2.5% increased risk of resistance development

# **B fragilis is now an MDRO**

79 yo male travels India goes back to Seattle for cancer therapy (MMWR 62:694, 2013)

*B. fragilis* Blood & Abdominal fluid

® Metronidazole, Imipenem, Pip-tazo

Steve Jenkins (Cornell, NYC)

**15 *B fragilis* isolates over three years (2011-14)**

® Imipenem, Pip-Tazo

Michael Jacobs (Case U, Cleveland) (2014)

*B fragilis* ® Imipenem



# *Bacteroides fragilis*

Both a gut commensal and a virulent pathogen

**Horizontal Gene Transfer in the GI Tract means “any gene in any bacterium can be mobilized” and transferred**

- **Regional variation in susceptibilities continues**
- **Carbapenems and piperacillin/ tazobactam** remain the most active *B-lactam* agents
- There is a modest trend among carbapenems and other *β-lactam* agents for increasing resistance over time
- Resistance to **clindamycin** and **moxifloxacin** continues to rise from elevated levels seen in the 1990s although the past 2 years have shown modest declines
- **Tigecycline** resistance is increasing
- Rare **metronidazole** resistance is seen although recent Spanish study is worrisome

# Some Take Home Messages on Species and Drug Combinations

- *B. ovatus* more resistant for carbapenems
- *B. vulgatus* more resistant for Pip-tazo
- *P. distasonis* more resistant for Amp-Sulb and Cefoxitin
- *B. ovatus* and *B. uniformis* very resistant to moxifloxacin as well as *B. vulgatus* ( $\geq 50\%$ )
- *Bacteroides non-fragilis* more resistant to tigecycline than *fragilis*
- *Bacteroides fragilis* in general more susceptible compared to other species for all drugs

## Appendix D. Cumulative Antimicrobial Susceptibility Report for *Bacteroides fragilis* Group Organisms

Isolates collected from selected US hospitals  
1 January 2007 – 31 December 2009<sup>a</sup>

Anaerobic Organisms	Number of Strains	Ampicillin-sulbactam		Piperacillin-tazobactam		Cefoxitin		Ertapenem		Imipenem		Meropenem		Clindamycin		Moxifloxacin		Metronidazole <sup>b</sup>	
		%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R	%S	%R
Percent Susceptible (%S) and Percent Resistant (%R) <sup>c</sup>																			
Breakpoints in µg/mL		≤ 8/4	≥ 32/16	≤ 32/4	≥ 128/4	≤ 16	≥ 64	≤ 4	≥ 16	≤ 4	≥ 16	≤ 4	≥ 16	≤ 2	≥ 8	≤ 2	≥ 8	≤ 8	≥ 32
<i>B. fragilis</i>	872	89	4	98	1	85	6	96	2	98	2	97	2	64	28	53	38	100	0
<i>B. thetaiotaomicron</i>	342	86	3	92	2	32	13	96	2	99	0	99	1	27	56	44	34	100	0
<i>B. ovatus</i>	67	93	2	93	2	37	15	98	0	100	0	100	0	54	39	43	39	100	0
<i>B. vulgatus</i>	70	67	6	100	0	83	4	98	2	98	2	98	2	49	51	43	46	100	0
<i>B. uniformis</i>	60	87	2	93	0	42	13	97	0	100	0	98	0	35	52	35	50	100	0
<i>B. eggerthii</i>	58	95	0	100	0	98	2	100	0	100	0	100	0	29	55	28	55	100	0
<i>Parabacteroides distasonis</i>	111	69	11	91	2	41	16	97	0	100	0	99	0	30	41	54	38	100	0
<i>B. fragilis</i> group without <i>B. fragilis</i>	708	83	4	93	1	40	12	97	1	99	0	99	0	33	42	43	40	100	0
<i>B. fragilis</i> group (all 7 species listed)	1580	86	4	95	2	65	9	97	1	98	1	98	1	50	39	49	39	100	0

<sup>a</sup>Data were generated from unique isolates from patient specimens submitted to three referral laboratories: Tufts New England Medical Center, Boston, MA; Loyola University Medical Center, Maywood, IL; and R.M. Alden Research Laboratory, Culver City, CA. Testing was performed by the agar dilution method.

<sup>b</sup>Resistance to metronidazole occurs infrequently.

<sup>c</sup>Intermediate category is not shown, but can be derived by subtraction of %S and %R for each antimicrobial agent from %100.

# Resistance Studies on Other Anaerobes (Not *B. fragilis*)

- **Fusobacterium:** clindamycin 20%, moxifloxacin 30%, other studies with no resistance to clindamycin or ampicillin-sulbactam
- **Prevotella:** clindamycin 30%, moxifloxacin 20%, rare metronidazole resistance, in contrast other studies with clindamycin 4%
- **Clostridial species:** clindamycin 20%, moxifloxacin 35%
- **Anaerobic Gram positive cocci:** moxifloxacin 20%, clindamycin 20%
- **Anaerobic Gram positive bacilli:** metronidazole 75%, moxifloxacin 7%, clindamycin 15%

A night-time photograph of the Nashville skyline, featuring the AT&T Building and other illuminated skyscrapers. The sky is a deep purple and blue, with city lights reflecting on the water in the foreground.

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