Antibiotics for Students and Others
You Pick the Ending

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Disclosures
This presentation is sponsored by Cepheid

Workshop Schedule

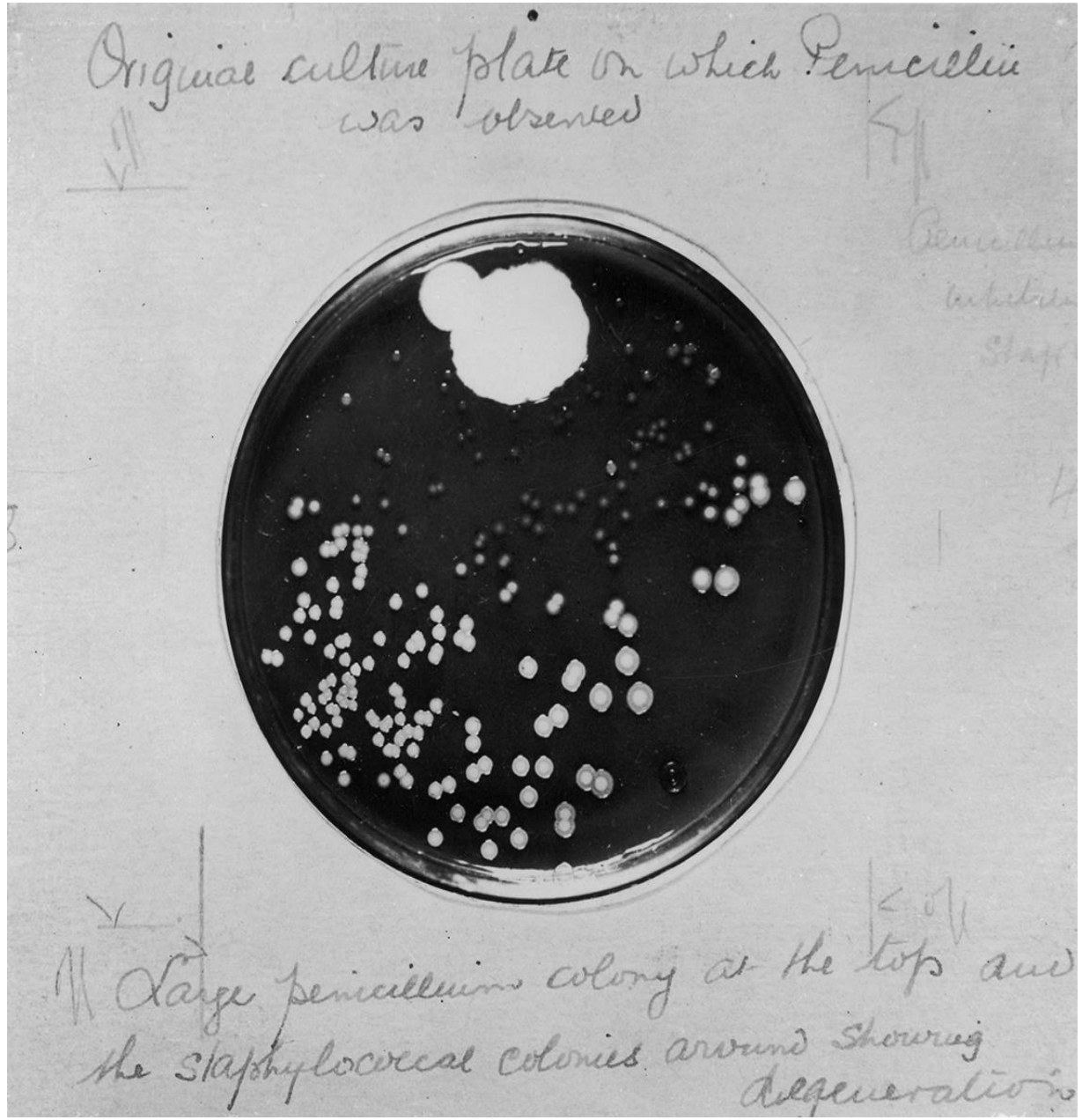
1. Introductions
2. Discussion “The Pre-Antibiotic World”
3. The Amazing Penicillin Story
4. Early Antibiotics and the end of Infectious Diseases?
5. Antibiotic Susceptibility Testing: The Basics and The Rules
6. Discussion and slides: Why and how do Bacteria become Resistant to Antibiotics?
7. Some Problematic “Bad Bugs”
8. Interesting Case Reports and Examples of Why Susceptibility Testing is Challenging
9. Some New Technologies and Some New Antibiotics
10. Discussion: You Pick the Ending

Discussion
What Did We Do BeforeAntibiotics?

Penicillin, A Football Game, A Fire, and WW II

Sir Alexander Fleming 1928

- **The prepared mind, luck or both**
  - **Fleming was going through old plates that were left out while he was on vacation for 4-5 weeks**
  - **These had been placed in detergent but a few were not covered with detergent**
  - **He observed mold growing on one of the plates and commented that the colonies of Staphylococci were not growing near the mold**
  - **At this point there are many biological facts that do not add up, but the bottom line is that he launched an investigation in to the inhibitory substance in the mold**

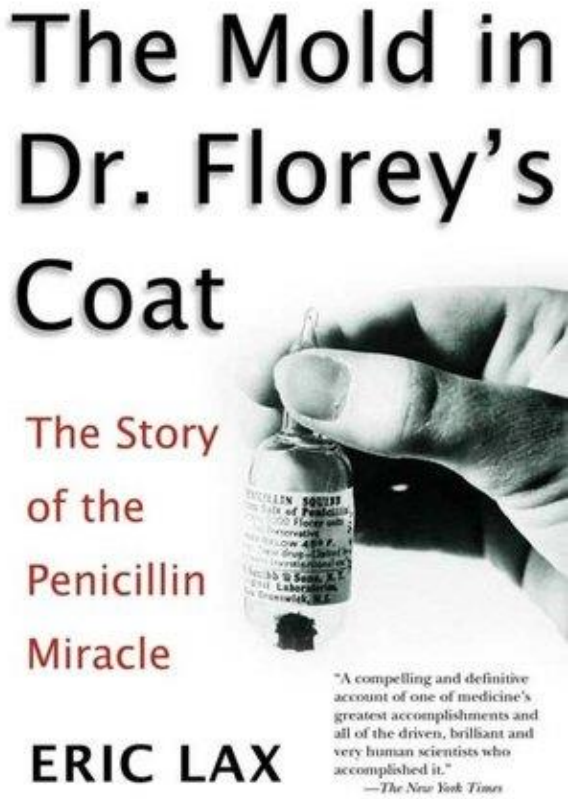

Original culture plate on which Penicillin was observed
Large penicillinin colony at the top and the staphylococcal colonies around showing degeneration

Fleming and Penicillin

- Fleming pursued the substance in the mold, which he named penicillin
- Fleming was unable to concentrate the substance from the mold due to lack of “chemical assistance”
- Although he published a few papers, he gave up his pursuit in 1935

Howard Florey **Ernest Chain** **Norman Heatley**

The War in England



During the early part of the war, Florey and others purposely contaminated lab coats with their special strain of *Penicillium* in case their lab was blown up by the Germans

https://us.macmillan.com/books/9780805077780/themoldindrfloreyscoat Accessed 7/1/22

The First Two Patients 1941

- First patient was Albert Alexander, a 43 yo constable who was septic and covered with pustules
  - Heatley: “He was oozing pus everywhere”
  - Treated, improved dramatically
  - Penicillin re-crystallized from his urine and used on another patient
- 15 yo septic patient Arthur Jones cured by using some of the re-crystallized penicillin from Alexander and the remaining supply of penicillin
  - However, Alexander relapsed and died because they ran out of penicillin

https://www.ox.ac.uk/news/science-blog/penicillin-oxford-story Accessed 7/1/22

Florey and Heatley in US

- **In 1941, Howard Florey and Norman Heatley came to America to try to convince our government to back large-scale production of penicillin because the war in England prevented further development of penicillin**
- **Heatley first worked the National Regional Research Laboratory in Peoria, Illinois and then at Merck in Rahway, NJ to help develop penicillin**
  - **In Peoria, we learned about MOLDY MARY**
- **December 1941: US enters war and penicillin is not a top priority**

Anne Miller

- **March 14, 1942, 33 year-old Anne Miller was dying of *Staphylococcal aureus* septicemia in New Haven Hospital following a miscarriage**
- **Her doctor (John Bumstead) had met another doctor (John Fulton) who was a champion of Howard Florey's penicillin research. Fulton called the Chair of the Committee on Chemotherapy in Washington, DC and he authorized a call to Merck**
- **Merck released 5.5 grams of penicillin (about a teaspoon which represented 50% of the total US supply)**
- **After a small first dose (no toxicity), she was injected every 4 hours for a few days**
- **She died, 57 years later, at age 90**

Penicillin in the United States

- Due to success with penicillin and Anne Miller, US Government saw the potential of penicillin for treating wound infections in our soldiers
- However, with our entrance into WW II, it was not a high priority
- A fire would soon change that
- But first, football

Boston College vs Holy Cross
November 28, 1942

- **BC was 8-0, ranked number 1 in the nation by AP**
  - **Had given up only 19 points all season**
- **Holy Cross was 4 and 4**
- **BC was a 3 touchdown favorite**
- **If they won this game, BC was going to be invited to the Sugar Boll as the highest ranked team in college football**
- **Game played before 41,000 fans at Fenway Park**

"The Greatest Upset of the Time"

- **Holy Cross changed up its defensive schemes and BC got "trapped"**
- **Holy Cross easily won 55-12**
- **BC players and families canceled their plans to celebrate the victory at the Cocoanut Grove nightclub in Boston's South End**
  - **The loss saved the lives of BC fans/players**

Cocoanut Grove

Dinner Specials

Complete Dinner at Price of Entree

HALF GRAPEFRUIT, SARANCHINO — FRESH FRUIT COCKTAIL, ROYAL
FILET OF MARINATED HERRING — CHILLED TOMATO, PINEAPPLE OR CRANBERRY JUICE
OYSTER, SHRIMP, CRAB MEAT OR CLAM COCKTAIL OR ANTIPASTO 50c EXTRA

MIXED PICKLES — RIPE OLIVES

CONSOMME ROYALE — SOUP DU JOUR

ROAST RIB OF BEEF, Chef's Special	1.40
BREADED VEAL CUTLETS, Spaghetti	1.60
SCALLOPINE OF VEAL au Marsala	1.60
FRESH CALF'S LIVER, Rasher of Bacon	1.75
FRESH SCALLOPS, Tartar Sauce	1.05
BOSTON SCROD Saute, Meuniere	1.50
BROILED HALIBUT STEAK	1.50
HALF BROILED NATIVE CHICKEN	2.00
LAMB CHOP MIXED GRILL	1.75
CHICKEN LIVERS AND FRESH MUSHROOMS SAUTE	1.50
SPANISH OMELETTE	1.50
PAN FRIED NATIVE CHICKEN in Sherry Wine	2.00
BONELESS CHICKEN sous Cloche, Janette	2.25
SIRLOIN STEAK, Minute	2.25
SQUAB CHICKEN en Casserole	2.00
CHICKEN A LA KING	1.50
HAM STEAK, Pineapple Ring Glace	1.50
FRESH LOBSTER A LA NEWBURG en Casserole	2.25
FRESH LOBSTER SALAD, Mayonnaise Dressing	2.25
GRENADINS OF BEEF TENDERLOIN, Bordelaise	1.75
BROILED LIVE LOBSTER	2.25
FILET MIGNON, Fresh Mushrooms	2.50
CLUB SIRLOIN STEAK, Broiled	2.50
CLUB SIRLOIN, Cocoanut Grove (Extra Thick)	

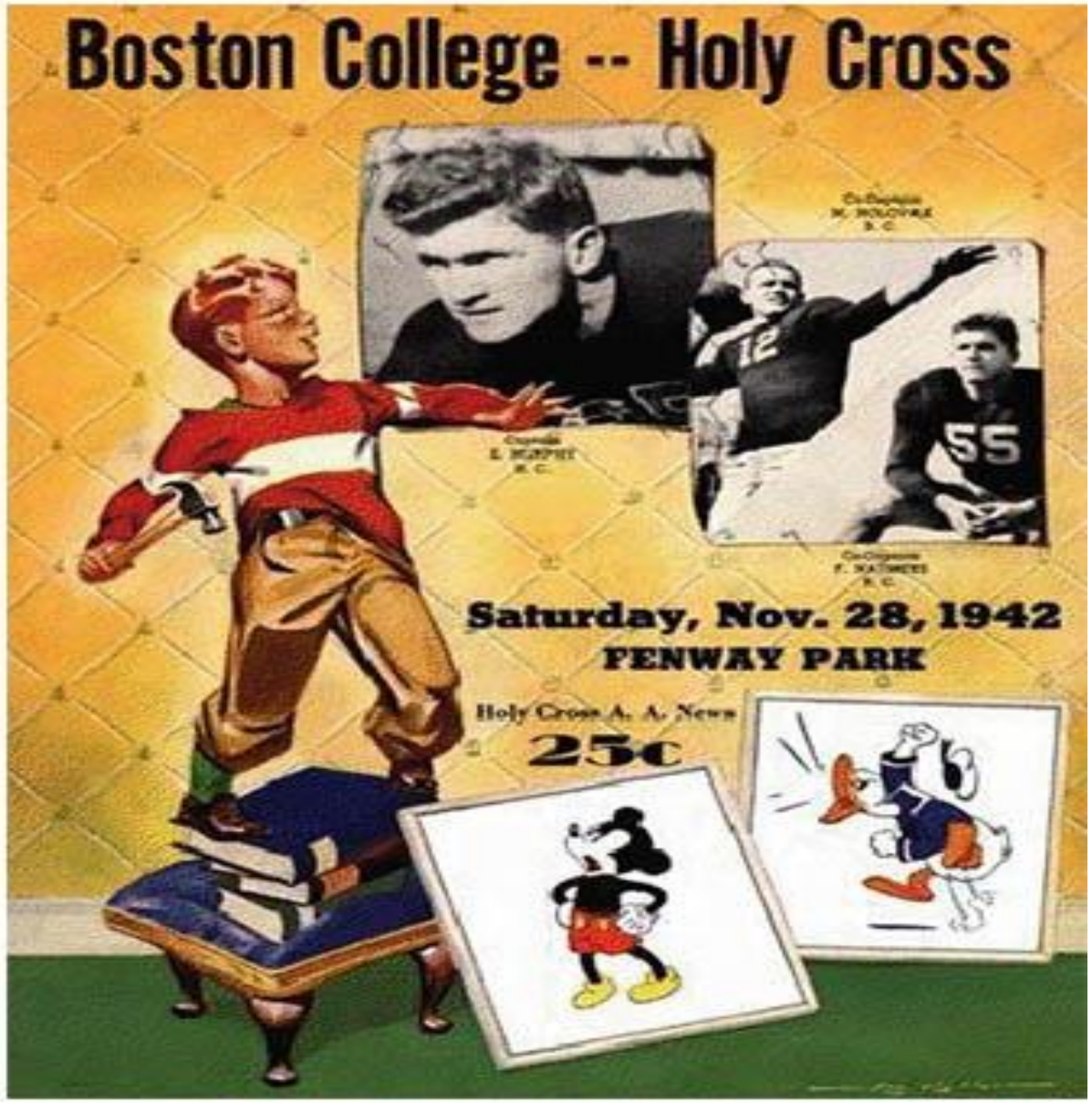
Broiled Tomato, Fresh Mushrooms 3.00

FRENCH FRIED POTATOES
NEW GREEN PEAS AU BEURRE OR VEGETABLE DU JOUR

FRESH FRUIT COCKTAIL — ASSORTED COOKIES — ORANGE SHERBET
FROZEN PUDDING, CHOCOLATE, STRAWBERRY OR VANILLA ICE CREAM
COCOANUT GROVE CHEESE, TOASTED CRACKERS

COFFEE, TEA OR MILK

Massachusetts Old Age Tax 5% on All Checks of $1.00 or More—Cabaret Tax 5%



Quick History of The Cocoanut Grove

- **Built in 1927 went from very popular to dormant during prohibition to the place to be seen in 1942**
- **Official capacity around 600; often >1000**
- **One of the exits was a revolving door without side doors**
- **Other exits locked with chains so patrons could not sneak out without paying**

The Fire

- **November 28th, over 1000 people packed in**
- **A busboy lit a match to make enough light to see a socket so he could replace a bulb**
- **Artificial palm tree caught fire**
- **Within 12 minutes, the club burned down**
- **Many patrons trapped by stuck revolving door and blocked exits**
- **492 deaths and many burn victims**

The Cocoanut Grove: Aftermath

"The Fire That Made Penicillin Famous"*

- **The Cocoanut Grove fire was used by local authorities as a "Rehearsal for Possible Blitz"**
  - **All emergency medical supplies and support staff were utilized**
  - **180 burn victims were shipped to Boston City Hospital and treated with conventional therapy for burns**
  - **40 others were sent to MGH**
  - **MGH team led by Dr. Oliver Cope was studying burn treatments following Pearl Harbor and the new treatments were being tested at MGH**
- **With approval from Washington, MGH received permission to contact Merck to obtain a new experimental drug**

***Sheehan,J. and Ross, R.N. Yankee Magazine, 1982**

"The Fire That Made Penicillin Famous"

- **Merck staff worked 24 hour shifts to produce as much penicillin as possible**
- **4 days after the fire, The Boston Globe reported "police escorts from 4 states accompanied a consignment of an as-yet unnamed drug rushed to the MGH early this morning from Merck for the treatment of fire victims….. A 32 liter supply of the drug will be used to prevent infections from burns."**

Sheehan, J. and Ross, R.N. Yankee Magazine, 1982

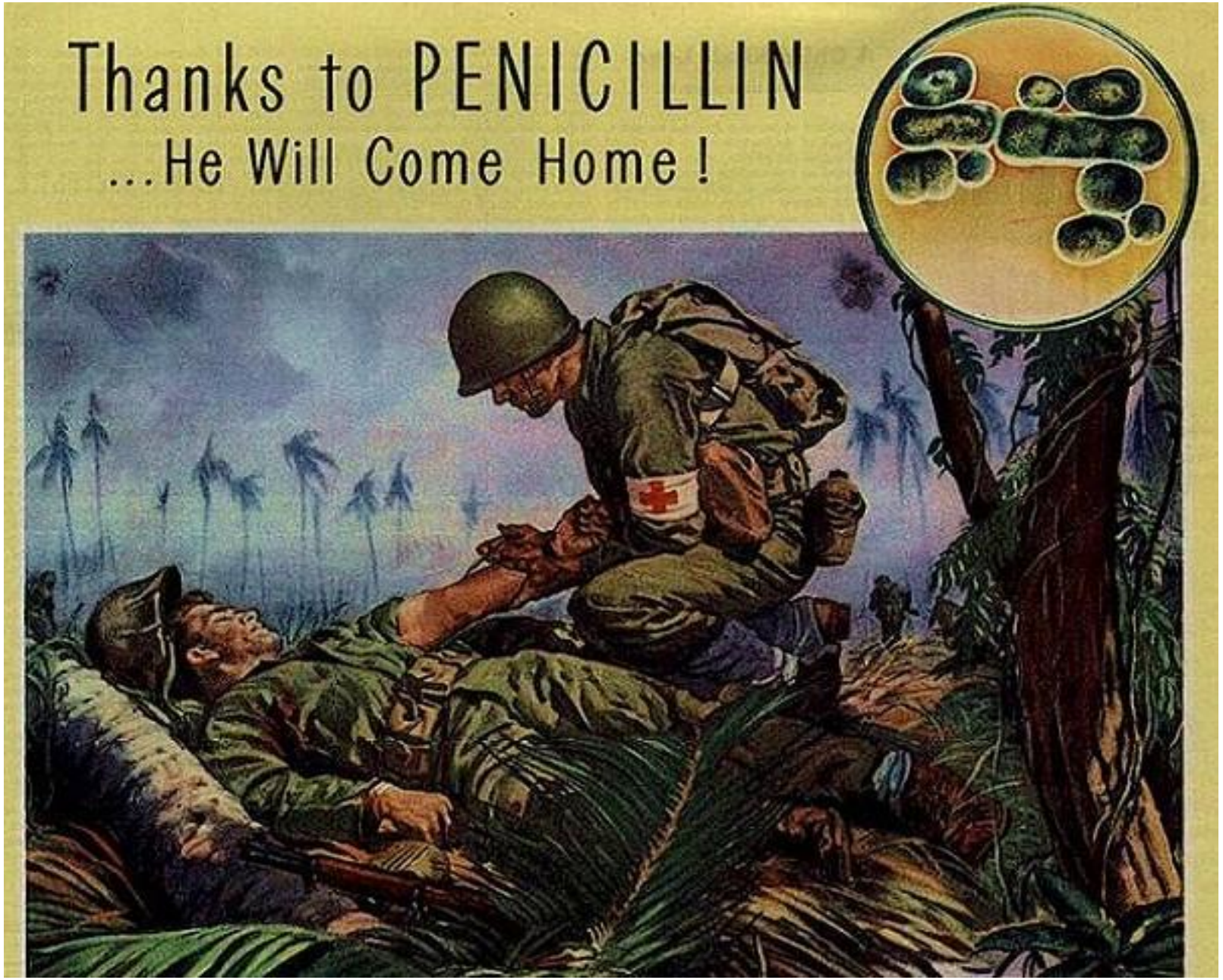
Email from Dr. Grant Rodkey
VA Surgeon Age 96

“ Steve: I never knew of this Yankee Magazine article before. It is excellent and written with real authority by John Sheehan. However, I do remember those days vividly. Most active Attending Surgeons in the city were away in military service, so a heavy burden fell on residents and medical students in the care of these patients”

“The Fire That Made Penicillin Famous”

- **Preceding the fire, less than 100 Americans had been treated with penicillin**
- **After the fire, the media brought national attention to the “miracle drug”**
- **The pharmaceutical companies began large scale production of penicillin**

Penicillin became the second highest priority of the war effort in 1943


Thanks to PENICILLIN
...He Will Come Home!

Credited with saving the lives of 10-15% of all WWII casualties!

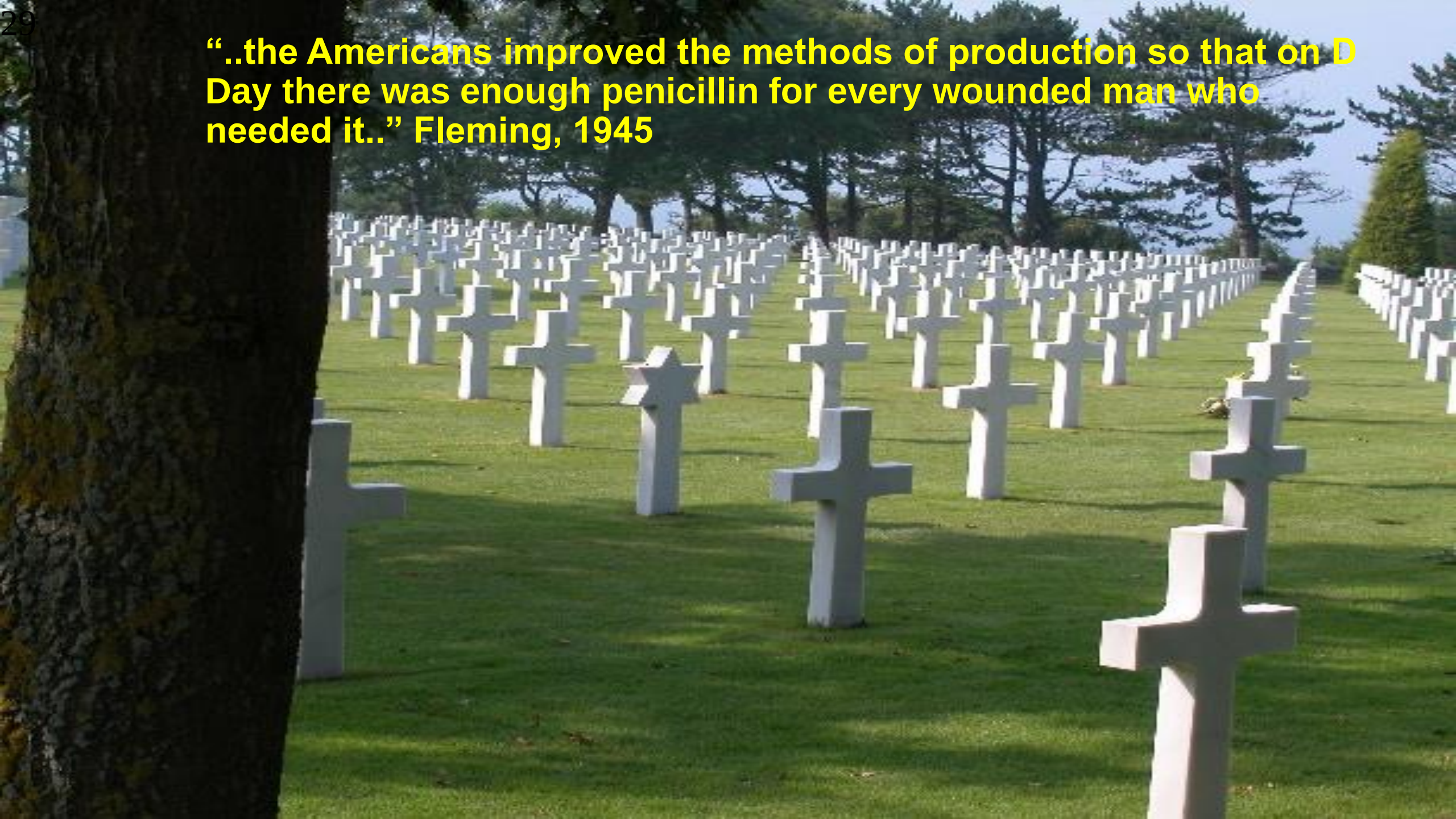
Penicillin After the Fire

From January to May 1942 US produced 400 million units of penicillin

Early dilemma: Who should get penicillin?

A severely wounded soldier or a soldier with gonorrhea

By the end of the war, US produced 650 billion units/month


“..the Americans improved the methods of production so that on D Day there was enough penicillin for every wounded man who needed it..” Fleming, 1945

Other Medical Achievements

- Skin Surface and Surgical Management
  - Gauze impregnated with boric petroleum replaced tannic acid
- Fluid Management
  - Plasma transfusion had never been done “in mass”
  - 1200 units donated the day after the fire; 3800 units were eventually donated and used
- Respiratory Management
  - Many of the victims inhaled toxic substances during the fire and new treatments were developed for respiratory management

Fire Safety Standards

- Revolving doors were outlawed and then allowed if the revolving door is placed between two outward-opening exit doors
- Exit doors had to be clearly marked and free from blockage
- Non-combustible decorations
- Emergency lighting and sprinklers

Early Warning

- Fleming was working with mutants of *S. aureus* that could be grown in the presence of increasing concentrations of penicillin
- He was concerned that if patients did not take a full course of treatment, resistant strains would appear
- Another concern: an oral form of penicillin was produced and was available without prescription

A Dire Prediction

“The greatest possibility of evil in self medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save”

Fleming quoted in the New York Times, p. 21, June 26, 1945 (as quoted in “The Antibiotic Paradox” by Stuart B. Levy, MD)

The Golden Years 1942-2000

- Scientists all over the world started working on discovering new antibiotics
- Soil samples taken from the tires of airplanes that had landed from exotic destinations and cultured for fungi
- Antibiotics were considered “Miracle Drugs”

Tuberculosis

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis

Surgeon General of the United States
William Stewart 1967

“The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.”

This was a real bummer for me as it was the year I graduated from college as a microbiology major and was looking for a job in clinical microbiology

Highlights of 60 Years of Antibiotics

The 50's: vancomycin, erythromycin, tetracycline, coliston

The 60's: methicillin, metronidazole, ampicillin, gentamicin, nalidixic acid, clindamycin

The 70's: cefazolin, amoxicillin, minocycline, fosfomycin, tobramycin, cefoxitin, ticarcillin, amikacin

The 80's: piperacillin, amoxicillin/clavulanate, ceftriaxone, ofloxacin, mupirocin, ciprofloxacin, azithromycin, moxifloxacin

The 90's: clarithromycin, levofloxacin, cefepime. pip/tazobactam quinopristin/dalfopristin

2000's: linezolid, daptomycin, ertapenem, tigecycline, doripenem,

2010's-2020's ceftaroline, fidaxomicin, ceftolozane/tazobactam, dalbavancin, oritavancin, tedazolid, ceftazidime/avibactam, meropenem/vaborbactam

Morning Coffee Break
With Exhibitors

Part II: Antibiotic Susceptibility Testing and Development of Resistance

Quantitatively We Are More Bacterial Than Human

- **Born sterile and quickly colonized by specific bacteria at specific sites**
- **We have 10^{13}-10^{14} total bacteria**
  - **Weight: about 3 pounds (same as a human brain)**
- **10,000 different species of bacteria**
- **Human genome has 23,000 genes**
- **Bacterial genome provides 4-8 million additional genes**

Role of Microbiome

- **Most bacteria are good and are essential to our well-being by aiding**
  - **Digestion**
  - **Make vitamins that are absorbed**
  - **B vitamins and vitamin K2**
  - **Protect against colonization by other organisms**
- **Part of our immune response is an effort to protect our microbiome from pathogens**

The Bacterial Paradox

- **Bacteria are so important that we:**
  - **share them by kissing those we love**
  - **use fecal bacteria to treat recurrent *C. difficile* and now other maladies**
- **So why do some of our bacteria betray us, cause disease and then become resistant to antibiotics?**

Dominance of Bugs over Drugs

- **Bacteria are the dominant species on the earth**
  - **rapid multiplication rate**
  - **natural mutation rate**
  - **ability to transfer or move genes via transformation, conjugation, transduction and transposition**
- **Collectively, these properties allow bacteria to survive, change and eventually flourish under intense selection pressure**

Why Do Bacteria Become Resistant to Antibiotics?

- **We are trying to kill them**
- **They are trying to eat and reproduce**
- **What would you do if someone was trying to kill you while you were trying eat and/or reproduce?**
- **Bacteria are good at survival**

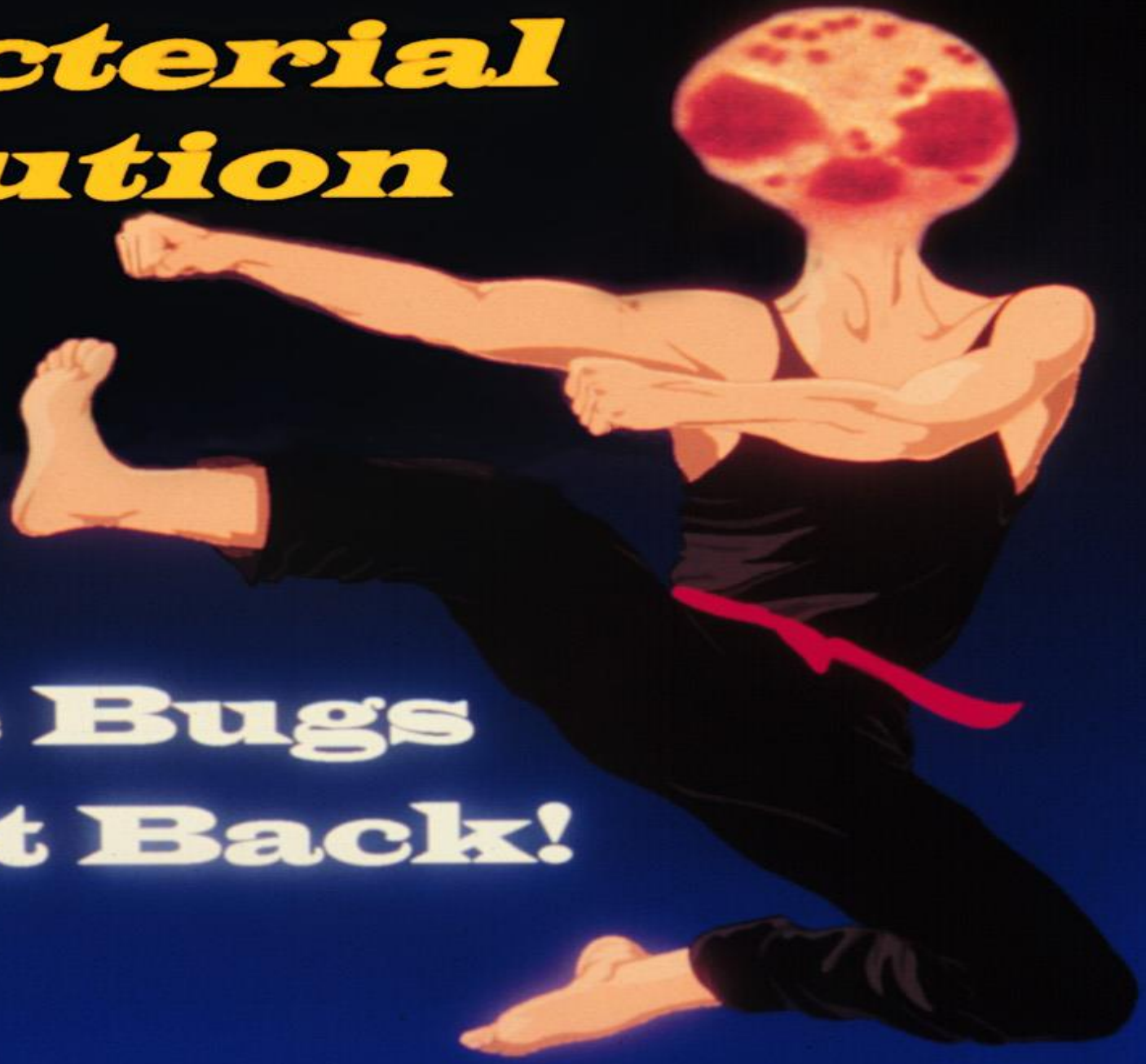
How Bacteria Become Resistant to Antibiotics

- **Make enzymes that break-down antibiotics**
  - **Beta-Lactamases break down the beta-lactam ring of penicillins and cephalosporins**
    - **There are around 3000 different ones**
    - **CREs, ESBLs, and ampCs, etc.**
- **Make porin proteins that keep bacteria from getting through the cell wall or efflux proteins that help escort antibiotics out of the cell**
- **Mutate to alter the target sites of antibiotics (e.g., protein synthesis)**
- **Mutate so antibiotics cannot interfere with DNA synthesis/replication**

CRE = Carbapenem Resistant Enterobacterales

ESBL = Extended Spectrum Beta-Lactamase

The Bacterial Revolution



The Bugs Fight Back!

Evolution: The Short Course

- 3.85 billion years old: Bacteria
- 210 million years old: Real Mammals
- 60 million years old: Human-like Mammals
- 30 million years old: Monkeys
- 2.5 million years old: Direct Ancestors
- 0.2 million years old: Neanderthals
- 0.125 million years old: Homo Sapiens
- 82 years old: Antibiotics

Methods of Detecting Antibiotic Susceptible and Antibiotic Resistant Bacteria

Phenotypic Methods of Antibiotic Susceptibility and Resistance Testing

- Disk Diffusion (Kirby-Bauer)
- Minimum Inhibitory Concentration (MIC)
  - Manual
  - Automated
- Agar Gradient Diffusion
- Agar Dilution (will not cover as it is hardly done these days)

Establishment of Interpretive Guidelines (FDA, CLSI)

- Pharmacokinetics/pharmacodynamics
- Tissue and fluid concentrations
- *In vitro* susceptibility test data
  - Quantitative methods to determine MIC
  - Qualitative correlation with disk diffusion methods
- Clinical efficacy studies
- Understanding resistance mechanisms
- Certain bug/drug combinations never work

FDA=Food and Drug Administration CLSI=Clinical and Laboratory Standards Institute

Breakpoints

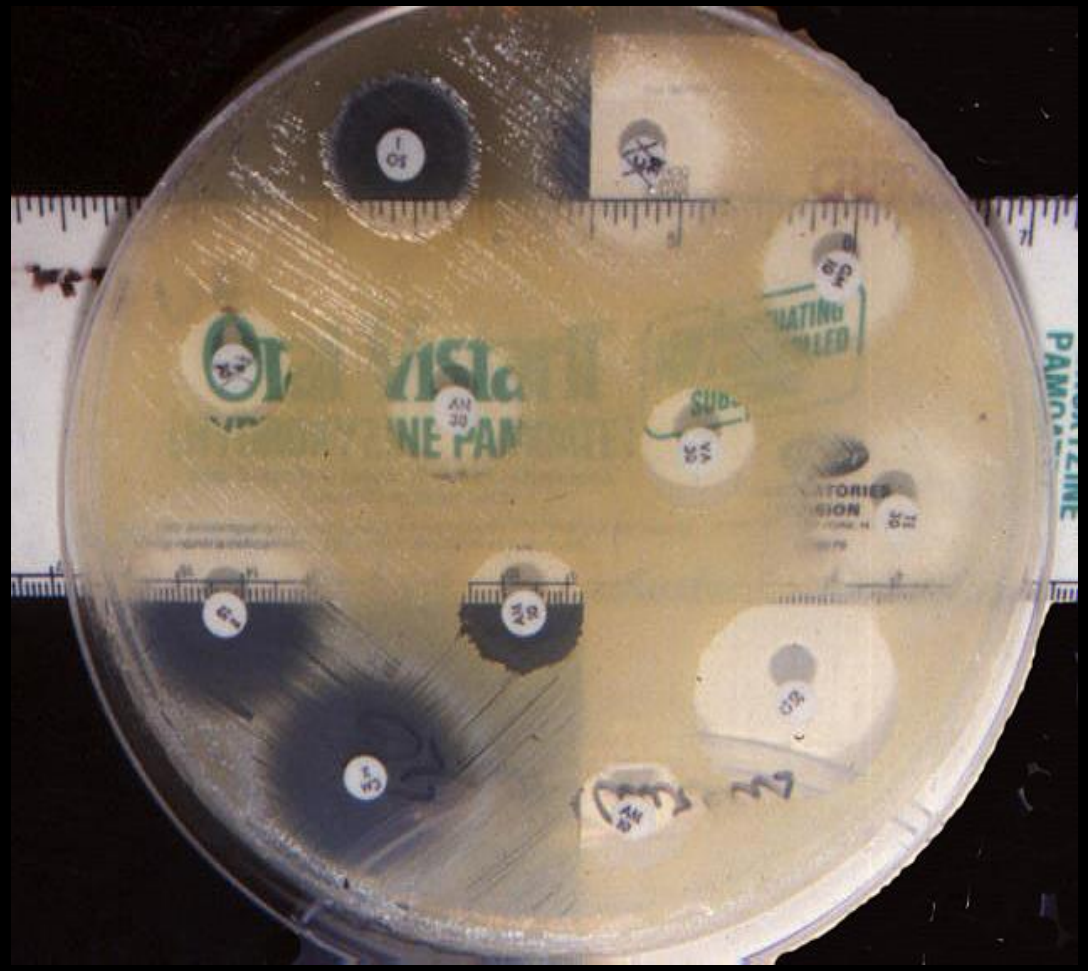
- **Breakpoints refer to the 4 categories to which we classify "bug/drug" combinations**
  - **Susceptible: Implies that the organism isolated from the infected site should be appropriately treated with the recommended dose of antibiotic**
  - **Intermediate (or SDD: Susceptible Dose Dependent): The organism may be appropriately treated if the antibiotic concentrates at the site of infection or if the drug is dosed at higher concentrations**
  - **Resistant: The organism is not inhibited by achievable concentrations of the antibiotic**

Interpretive Criteria for Antibiotic X Used For Determining Disk Diffusion Breakpoints

	Zone Diameter(mm)
Susceptible	≥20
Intermediate	15-19
Resistant	≤14

Disk Diffusion (Kirby-Bauer)

- Create “lawn” by streaking entire plate with the patient’s isolate
- Dispense up to 12 antibiotic disks on plate
- Incubate for 18-24 hours
- Measure zone of inhibition in mm



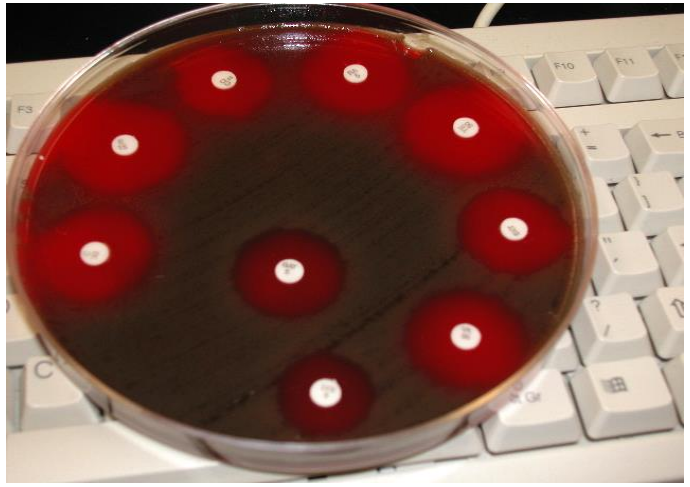
A Closer Look

- The antibiotic impregnated disk is 6 mm in diameter
- Measure the diameter of the zone of inhibition (minimum zone = 6mm)
- Go to CLSI tables and determine S, I or R

Disk Diffusion
9 Antibiotics Tested Against
S. pneumoniae

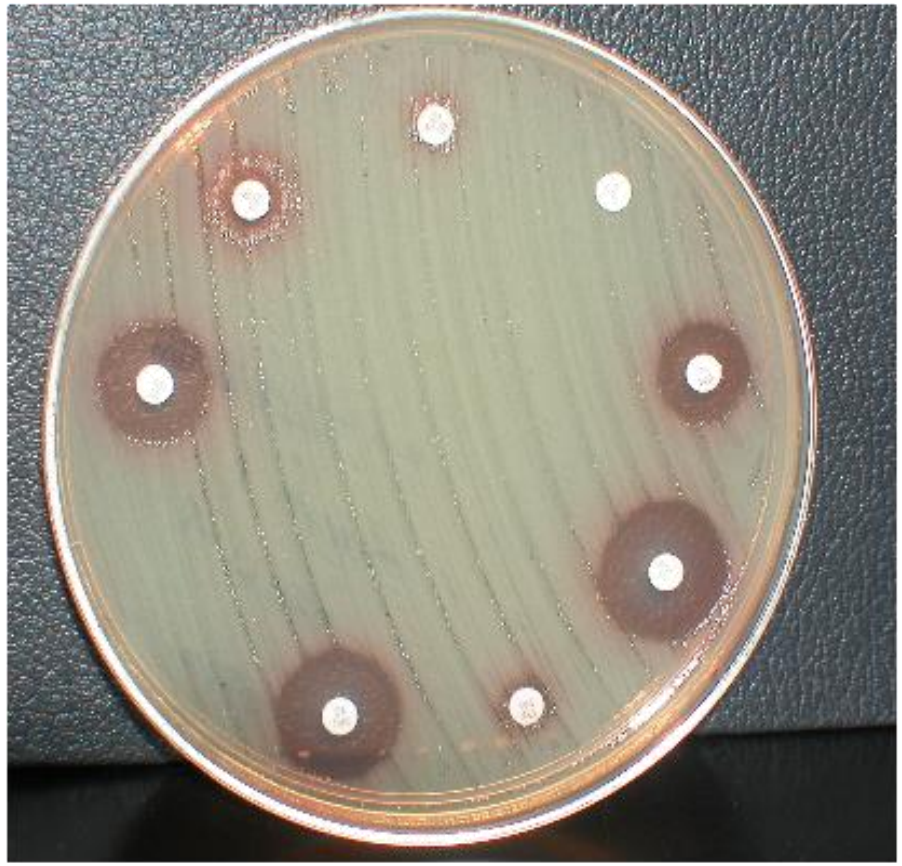
- 5% Sheep Blood Mueller-Hinton Agar plate with 9 different disks prior to incubation

- Same plate after 24 hours of incubation at 35^{o}C in 5% CO_2

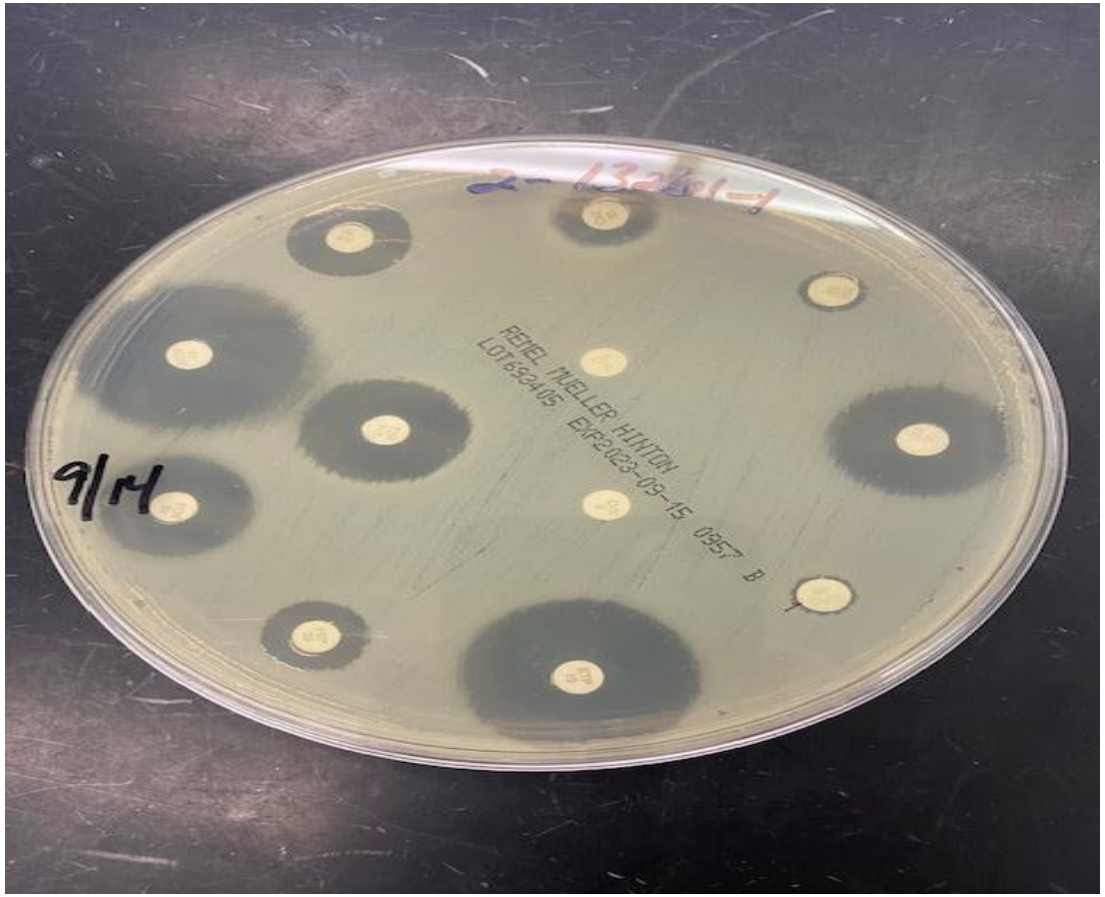


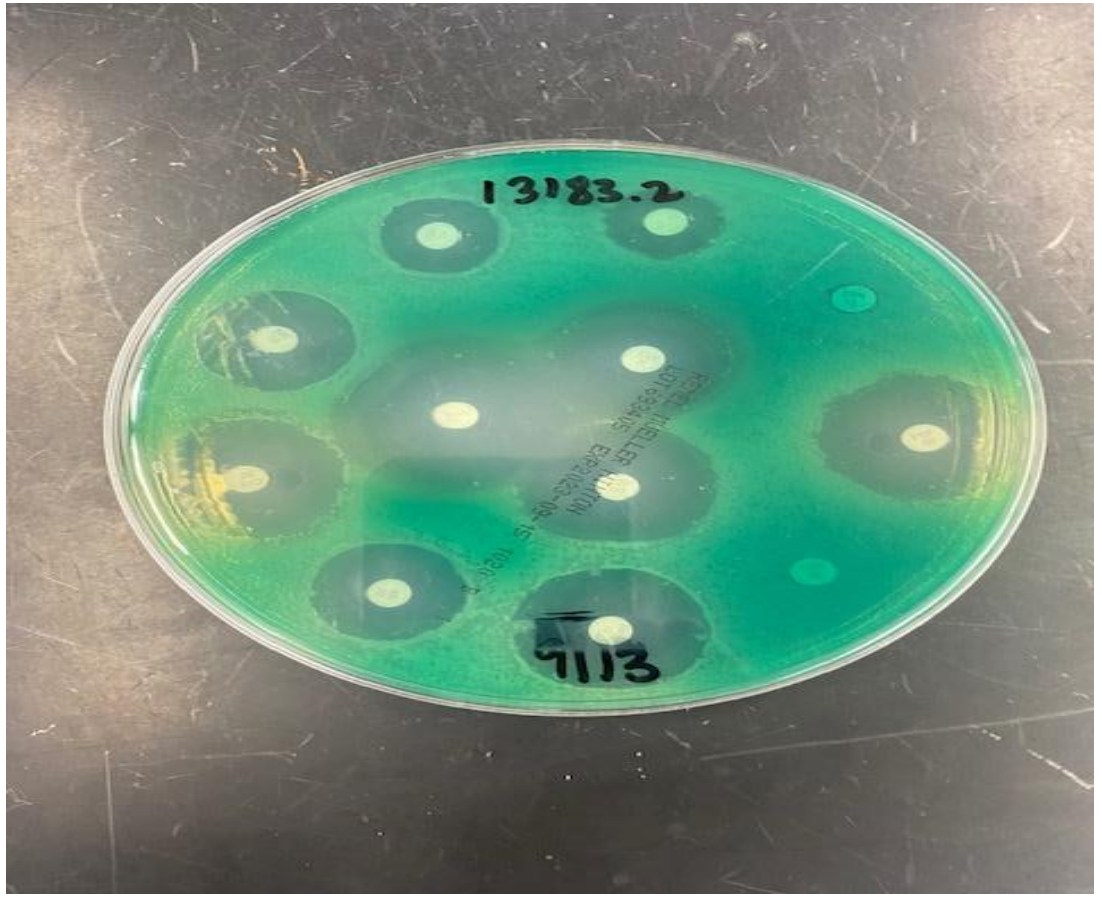
Disc Diffusion on Mueller-Hinton Agar

- Gram Negative Organism Resistant to many antibiotics
- Have to measure the zone of diameter around each disk
- Assign S, I, or R based on the size of the zone based on breakpoints in the most recent edition of CLSI/FDA



Disc Diffusion on Mueller-Hinton Agar





MICs

Minimum Inhibitory Concentration (MIC)

- **The minimum concentration of an antibiotic that will inhibit the growth of an organism *in-vitro***
- **Expressed in micrograms of antibiotic per milliliter of test media (µg/ml)**
- **Used to predict efficacy of an antibiotic *in-vivo***

Interpretive Criteria for Antibiotic X Used For Determining MIC Breakpoints

	MIC (µg/ml)
Susceptible	≤4
Intermediate	8-16
Resistant	≥32

What Does it Mean?

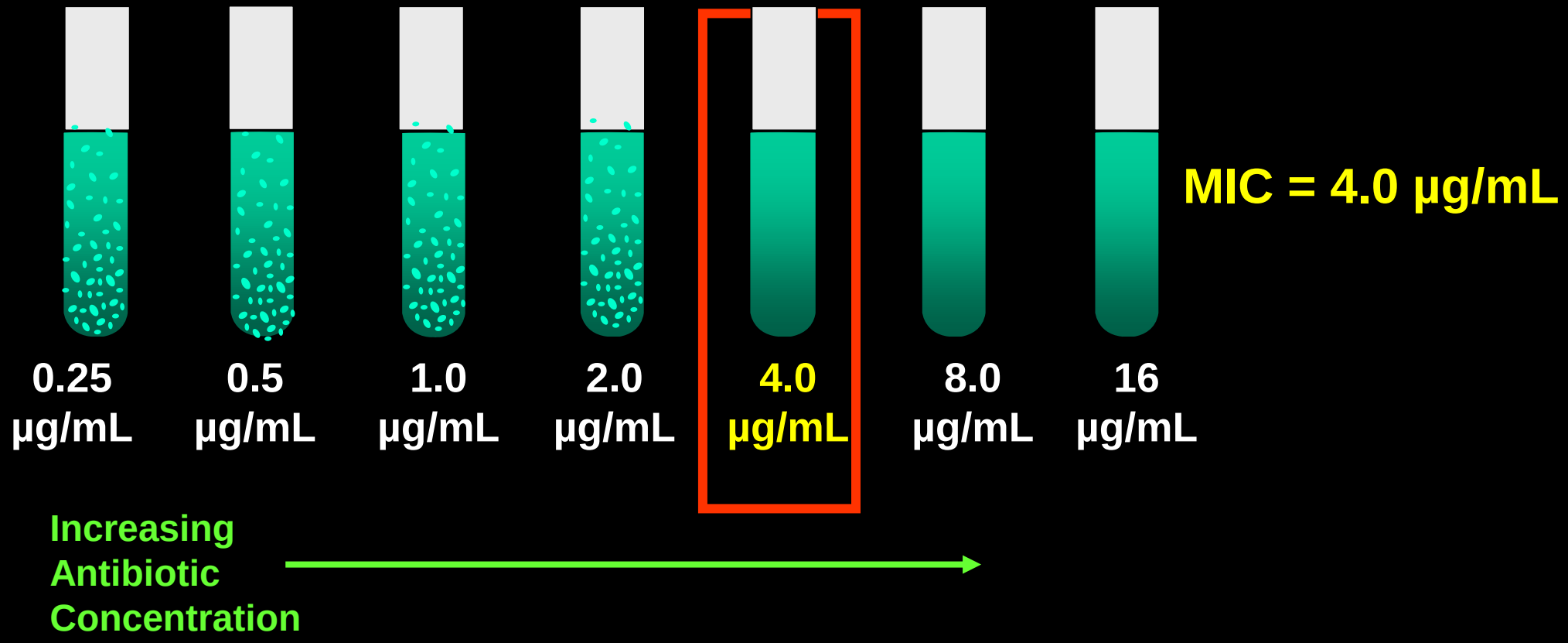
- **An individual MIC tells you the concentration of antibiotic that is needed to inhibit the growth of that organism *in-vitro***
- **That concentration can be between 0.001 and >1000 µg/ml**
- **The microbiology laboratory interprets that concentration as S, I (SDD), or R**

MIC
Ingredients

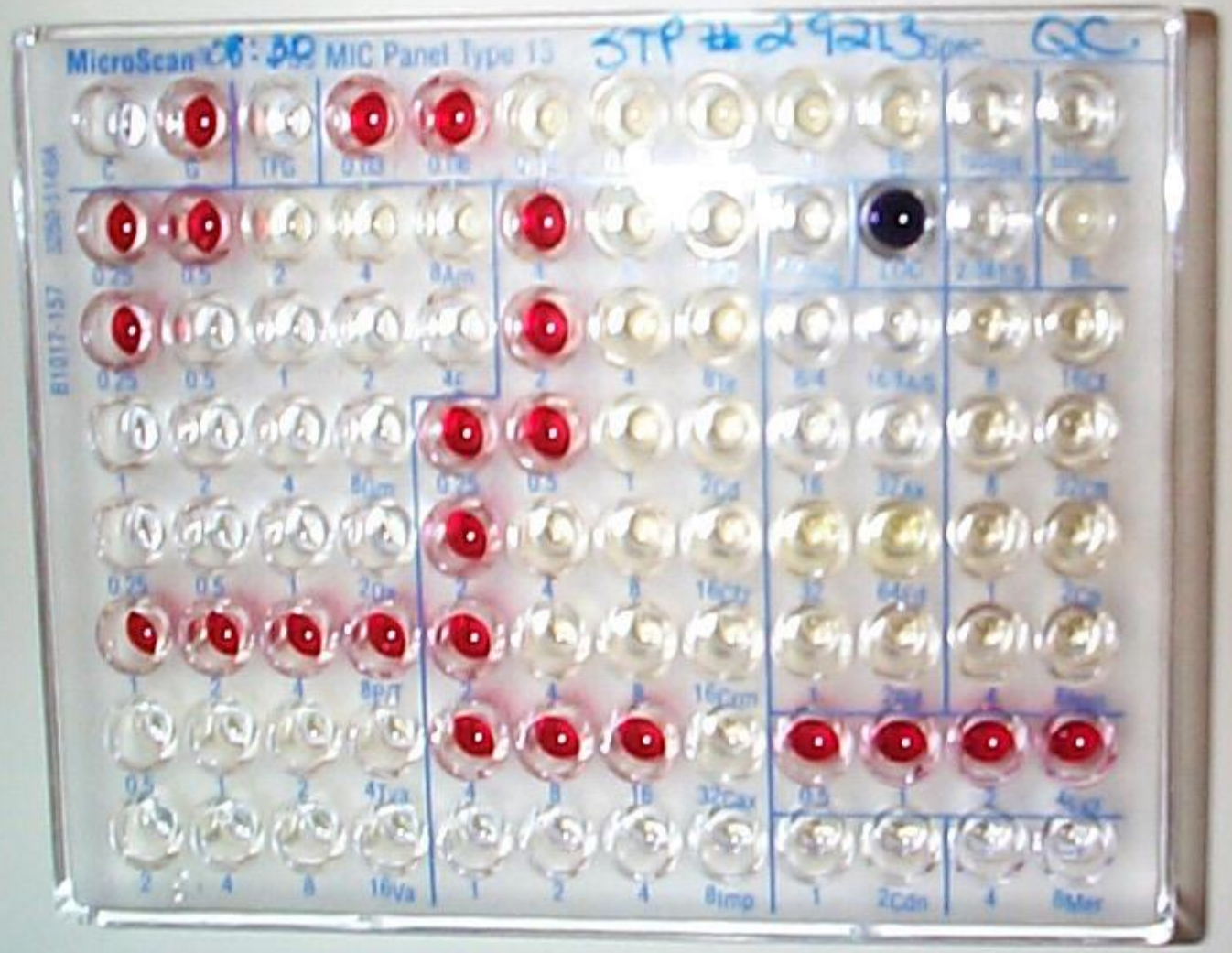
- A bacterial isolate from the patient's culture
  - (e.g., *E. coli, S. aureus, etc.*)
- Antibiotics: 1 or more antibiotics, usually many
- Method: Choice of 4 or 5 automated methods
  - Microscan, Vitek, Phoenix, Sensititre, Selux (new)
- Time: Most MIC assays take between 16-24 hours

The MIC is measured by determining lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism after overnight exposure

Known bacterial inoculum placed into each tube



Broth Dilution MIC

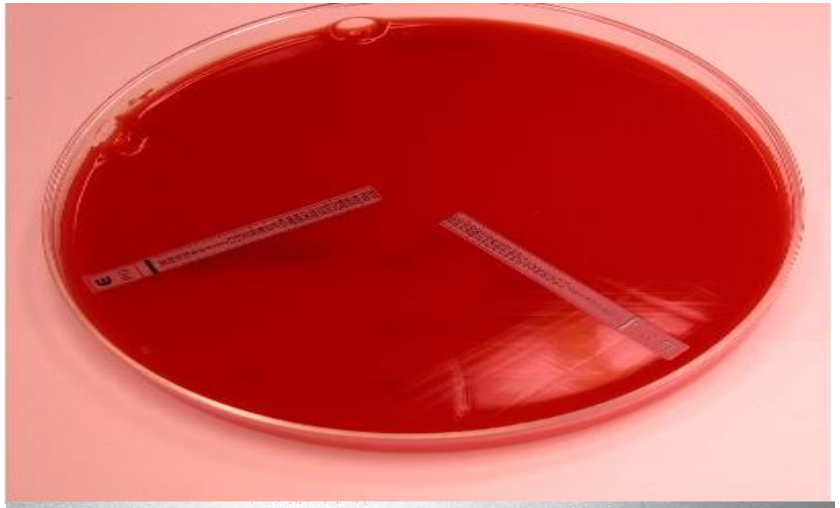


Agar Gradient Diffusion MIC

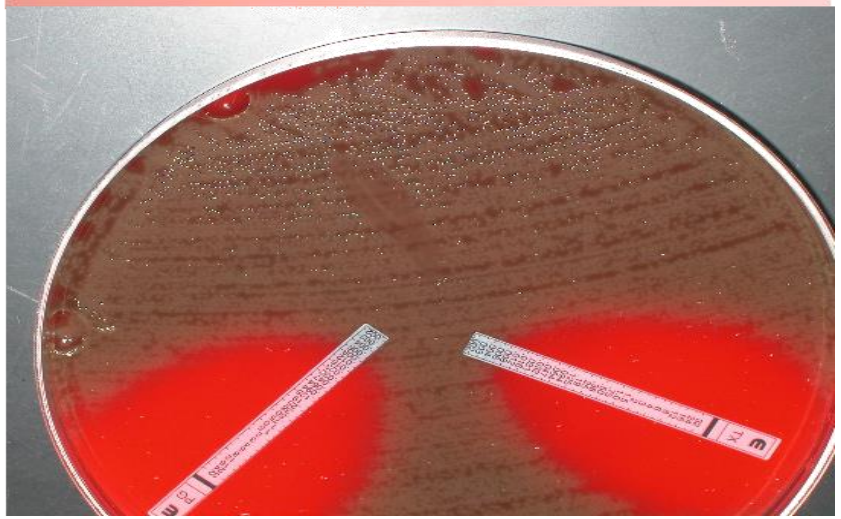
- Unique, agar gradient dilution MIC method to test multiple concentrations of one antibiotic
- Continual gradient rather than doubling dilutions

Agar Gradient Diffusion with *Streptococcus pneumoniae*

- Plate inoculated with *S. pneumoniae* and 2 different e-test strips



- Same plate after 24 hours of incubation at 35^{o} C in 5% CO_2



Can I Compare the MICs of One Class of Antibiotics to Another?

- Breakpoints are based on achievable levels of the antibiotic in blood, tissue, urine, etc
- Dosing is based on the route of administration, the half-life of the antibiotic in the body, and the concentration of unbound antibiotic
- An MIC of 1.0 to a given antibiotic may be essentially the same as an MIC of 4.0 to another antibiotic
- In general, lower is better

So, Can I Compare the MICs of One Class of Antibiotics to Another

The Answer is NO

MICs are Antibiotic Specific

E.coli and a few antibiotics

Drug	S	I	R
Ciprofloxacin	≤0.25	0.5	≥1.0
Levofloxacin	≤0.5	1.0	≥2.0
Ppiperacillin	≤8/4	16/4-32/4	≥32/4

You Make the Call

An *E. coli* from blood has the following MIC results expressed in µg/ml

- **Ampicillin 4**
- **Ciprofloxacin 1**
- **Levofloxacin 1**
- **Piperacillin/tazo 8/4**
- **Cefepime 8**
- **Tigecycline 0.25**

What antibiotic would you use and why?

We Make the Call for You

- That *E. coli* from blood has the following MIC results with our guideline based interpretations
  - Ampicillin 4 S
  - Ciprofloxacin 1 R
  - Levofloxacin 1 I
  - Piperacillin/tazo 8/4 S
  - Cefepime 8 SDD
  - Tigecycline 0.25 Should not have been reported

Emerging Resistance Means Changing Rules

- Antibiotic susceptibility and resistance testing breakpoints change because bacteria are moving targets (mutate/acquire DNA) and do not “read” our rules
- Regulatory agencies meet often to review breakpoints
- Breakpoint changes enable labs to detect emerging antibiotic resistance but implementing these changes is often difficult. Why?
  - New College of American Pathologists regulations with respect to changes (Discuss)

MICs Change as Bacteria Change Carbapenem Breakpoint Changes

Enterobacterales

Agent	CLSI 2009			CLSI 2020		
	S	I	R	S	I	R
Doripenem	-	-	-	≤ 1	2	≥ 4
Ertapenem	≤ 2	4	≥ 8	≤ 0.5	1.0	≥ 2
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4

CLSI = Clinical and Laboratory Standards Institute

Full Range MIC Testing or Small Range Breakpoint Testing

- **Full Range MIC Testing**
  - **Wide range of antibiotic concentrations tested**
    - **For example, 0.5 to 32 (0.5, 1.0, 2.0, 4.0, etc.)**
    - **Breakpoint changes may be easier to implement**
- **Small Range Breakpoint Testing**
  - **Small range of concentrations tested (around the breakpoints)**
  - **Test only 2-3 concentrations of the antibiotic**
- **Why do you need to choose?**
  - **Limited wells on testing plates**
  - **So, choice is to test more antibiotics with a smaller range of antibiotic concentrations or test fewer antibiotics with a larger range of antibiotic concentrations**

What Method(s) Should I Use? Considerations

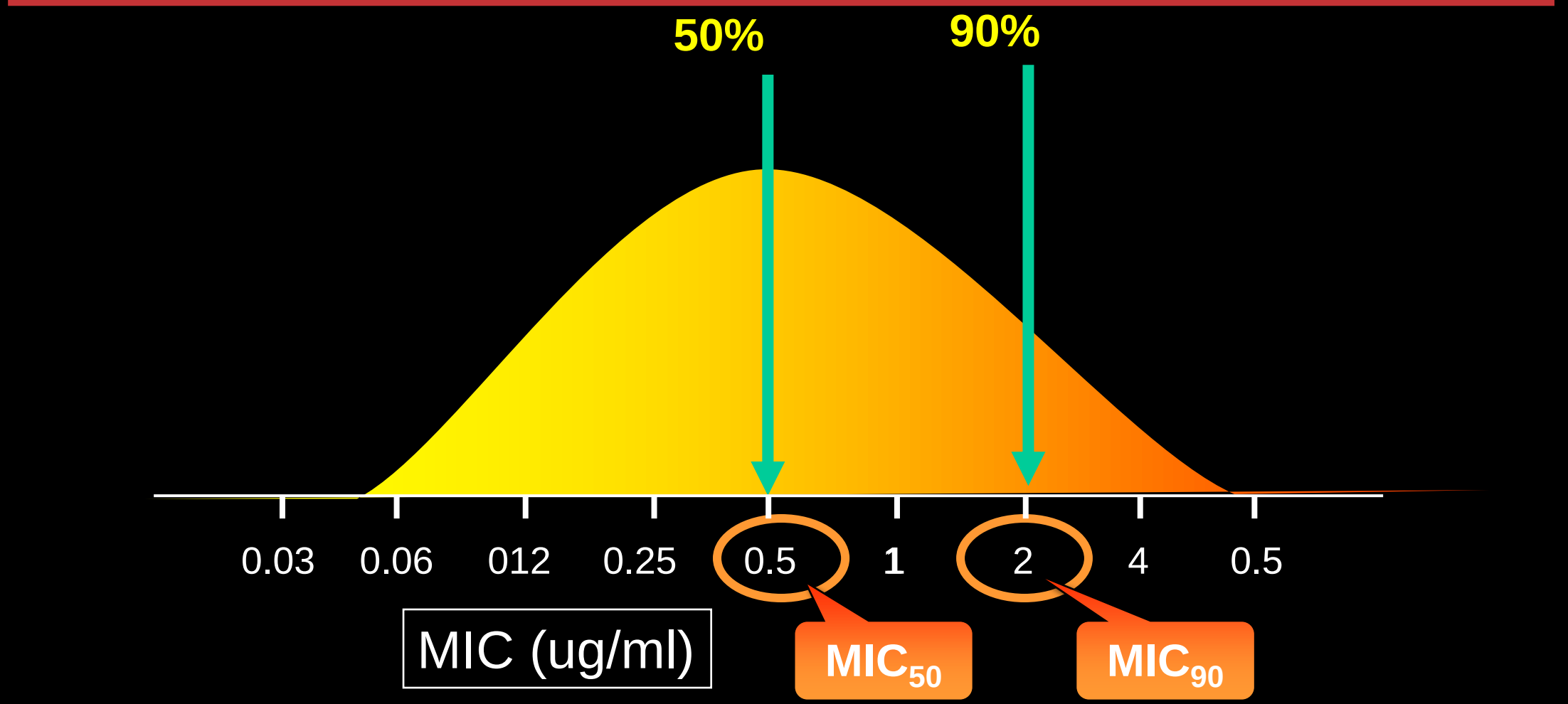
- Cost
- Ease of use
- Does system software keep up with CLSI/FDA changes?
- Does system hardware keep with with CLSI/FDA changes?
- Does system easily interface with hospital or company IT system?
- Do you have a MALDI system for identification?
- Can you use more than 1 method?
  - e.g., automated system and disk diffusion and agar gradient diffusion

Determining Mode, MIC_{50} and MIC_{90} Raw Data

Isolate #	MIC(µg/ml)
1	.03
2	.03
3	.03
4	.03
5	.03
6	.03
7	.06
8	.06
9	.06
10	.12

MIC_{50} and MIC_{90} unimodal population

Like golf: the lower-the better



What Does it Mean?

- An MIC_{50} tells you that 50% of a population of organisms has an MIC of X or below
- An MIC_{90} tells you that 90% of a population of organisms has an MIC of Y or below

Genotypic Detection of Antibiotic Resistance

- A single or multi-plex assay called a Polymerase Chain Reaction (PCR) that detects the presence of a gene or multiple genes associated with antibiotic resistance
- Genotypic PCR results, mostly, but do not always, agree with phenotypic assay results.
- We will look at a few cases in which we got discrepant results after we discuss some problematic bacteria

Common Targets for PCR Assays

- ***mec*A in *Staphylococcus spp.***
  - Major gene associated with methicillin/oxacillin resistance
- ***van*A/*van*B**
  - Genes associated with vancomycin resistance in Enterococci
- **Carbapenemase genes (KPC, NDM, etc.)**
  - Multiple genes associated with carbapenem resistance
- **Combined bacterial identification targets with antibiotic resistance gene targets**

Antibiograms

- Microbiology Laboratory compiles S, I, and R data on isolates on a yearly basis (1/1 to 12/31)
- Data based on unique isolates
- Very useful document for big picture thinking but only a guide for use in an individual patient

Sample Antibiogram
Gram-Negatives (1 year)

Gram Negative Organisms	# Isolates*	Ampicillin	Ampicillin/sulbactam	Cefazolin	Amikacin	Gentamicin	Tobramycin	Trimethoprim/sulfa	Ciprofloxacin	Levofloxacin	Imipenem	Ertapenem	Ceftazidime	Ceftriaxone	Cefuroxime	Tigecycline	Piperacillin/tazobactam	Cefepime
Acinetobacter baumannii	6		100		100	100	100	100	83	100	100		100	83				100
Citrobacter freundii	29				97	97	97	97	90	93	100	97	76	76		100	93	100
Enterobacter aerogenes	45				100	98	98	96	96	98	100	100	82	78		100	93	98
Enterobacter cloacae	73				100	97	97	90	97	97	100	97	79	79		99	84	96
Escherichia coli	553	54	73	86	99	89	92	76	76	76	100	99	95	92	89	100	98	93
Klebsiella oxytoca	51		80	57	99	96	96	96	96	98	100	100	100	98	94	100	96	98
Klebsiella pneumoniae	261		82	88	99	95	94	88	92	93	100	100	91	91	87	99	96	92
Morganella morganii	33				100	91	97	79	79	82	21	100	85	85			94	97
Proteus mirabilis	172	65	90	92	100	76	90	71	51	57		100	100	99	99		100	99
Providencia stuartii	12		42		100			83	50	58	58	92	100	100			100	100
Pseudomonas aeruginosa	178				97	94	97		80	76	89		91				90	94
Serratia marcescens	45				100	100	100	100	96	98	100	100	100	96		96	100	100
Stenotrophomonas maltophilia	23							91		96			30					

* Individual patient isolates.

Numbers in antibiotic columns represent the percentage of susceptible isolates

Some Tricks of the Trade Questions

- Why don't we report erythromycin and clindamycin on Staph isolates from urine? SXT on enterococci?
- Why don't we report tigecycline on blood isolates?
- Can I use ceftaroline for a MRSA in blood or sputum?
- Why don't we report daptomycin for a MRSA in a tracheal aspirate/bronchial specimen/sputum?
- Do we test but not report certain antibiotics?
- How do you respond when a physician asks you to test something unusual?

Short Break

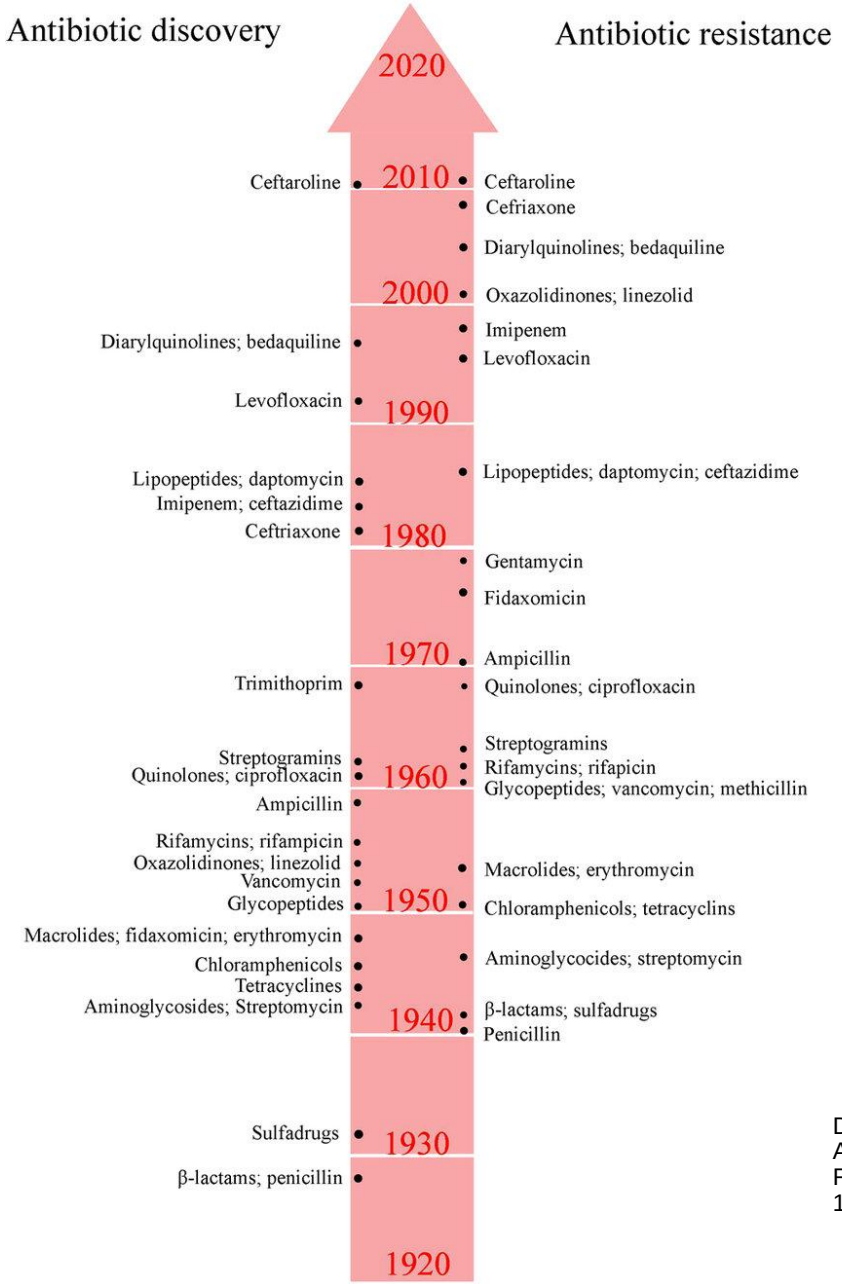
Bad Bugs

Resistance

Happens

Resistance Happens

- Penicillin resistance happened in moments
- 4 generations of cephalosporins and cephalosporin resistance
  - Early beta-lactamases, then ESBLs and ampCs
- Macrolide and tetracycline resistance
- Fluoroquinolone resistance
- Now carbapenem resistance
- A few haven’t happened!! Name one



Dahal, Ram Hari & Chaudhary, Dhiraj. (2018). Microbial Infections and Antimicrobial Resistance in Nepal: Current Trends and Recommendations. The Open Microbiology Journal. 12. 230-242. 10.2174/1874285801812010230.

Global Burden of Bacterial Antibiotic Resistance in 2019: A Systematic Analysis[1]

- Mega study of millions of individual records from 2019. Using predictive statistical modeling there were 4.95 million deaths associated with antimicrobial resistance (AMR) and 1.27 million deaths attributable to bacterial AMR
- The 6 leading pathogens for death associated AMR were
  - *E. coli, S. aureus, S. pneumoniae, K. pneumoniae, A. baumannii,* and *Ps. aeruginosa*
  - MRSA was associated with more than 100,000 deaths while six more pathogens were attributable to 50,000 to 100,000 deaths each
    - Multi-Drug Resistant tuberculosis
    - Third generation cephalosporin-resistant *E. coli* and *K. pneumoniae*
    - Carbapenem-resistant *A. baumannii* (CRAB) and *K. pneumoniae*
    - Fluoroquinolone-resistant *E. coli*

1. www.thelancet.com Published online 1.20.2022 https://doi.org/10.1016/S0140-6736(21)02724-0 (Accessed 2/3/22)

MRSA = Methicillin-resistant *Staphylococcus aureus*

Attacking The Persistent Pathogen *Staphylococcus aureus*

S. aureus Resisting Antibiotics Over the Years

- Penicillin(1941)
  - moments to get first resistant strain
  - 2023: 92-97% of isolates are resistant to penicillin
- Methicillin (1959)
  - 2 years to get first resistant strain (1961)
  - now 70-30% resistant, CA-MRSA
- Vancomycin (1950's)
  - 1995: VISA
  - 2002: first VRSA
- Linezolid (2000)
  - CLSI designated "R" Breakpoint 2010
- Daptomycin (2003)
  - Resistance reported in 2005; No "R" breakpoint yet

MSSA *vs* MRSA

- In the 1960's methicillin (oxacillin) resistance emerged in *S. aureus*
- We spend a lot of time and money tracking the percentage of patient isolates that are methicillin resistant
- How has that percentage changed over the years?
- How important is it to know quickly if *mec*A (meaning methicillin resistance) is present?
  - **Genotypic vs Phenotypic detection of resistance: Quick discussion**
- Is there a difference in patient outcomes if the *S. aureus* is MSSA or MRSA?

MSSA=Methicillin Susceptible *Staphylococcus aureus*
MRSA=Methicillin Resistant *Staphylococcus aureus*

Screening for MRSA is Important Because

- It identifies colonized patients
- It reduces the transmission
- It helps select appropriate initial antibiotic therapy if the patient goes from colonization to infection
- It identifies clearance of colonization

Screening Anterior Nares for MRSA
The Queen's Method of Specimen Collection

The VA MRSA Bundle

- The VA MRSA bundle included
  - Universal nasal surveillance for MRSA
  - Contact precautions for positives
  - Hand hygiene
  - Infection control oversight
- The rate of healthcare associated MRSA infections fell
  - 62% in ICUs
  - 45% in non-ICUs

Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. N Engl J Med. 2011;364(15):1419-1430.

S. aureus at the Boston VA

Influence of Screening and IC/IP

Year	% Resistant
2000	**69%**
2002	69%
2004	60%
2006	56%
2008	56%
2010	48%
2012	47%
2014	41%
2016	41%
2020	**39%**
2021	**35%**

IC= Infection Control

IP=Infection Prevention

Internal Data – yearly antibiogram data from the Microbiology lab VA Boston Healthcare System

S. aureus Bacteremia Mortality Differences MSSA Vs. MRSA

2139 Adult Patients With *S. aureus* Bacteremia

Time Interval	MSSA (%)	Mortality (%)	MRSA (%)	Mortality (%)
2007-2009	55	18	45	25
2010-2012	59	18	41	25
2013-2015	63	13	37	26

MSSA=Methicillin Susceptible *Staphylococcus aureus*
MRSA=Methicillin Resistant *Staphylococcus aureus*

Austin ED, Sullivan SS, Macesic N, et al. Reduced Mortality of *Staphylococcus aureus* Bacteremia in a Retrospective Cohort Study of 2139 Patients: 2007-2015. Clin Infect Dis. 2020;70(8):1666-1674.

S. aureus Bacteremia Mortality Differences MSSA Vs. MRSA

- MSSA bacteremia was easier to successfully treat than MRSA bacteremia
- This research implies that it is important to prevent MRSA colonization as colonization precedes infection
- Time to targeted therapy was a key factor
  - Average time to susceptibility data went from 3.7 days at beginning of study to 2.2 days by the end of the study (initiated Cepheid and BioFire PCRs on positive blood cultures)

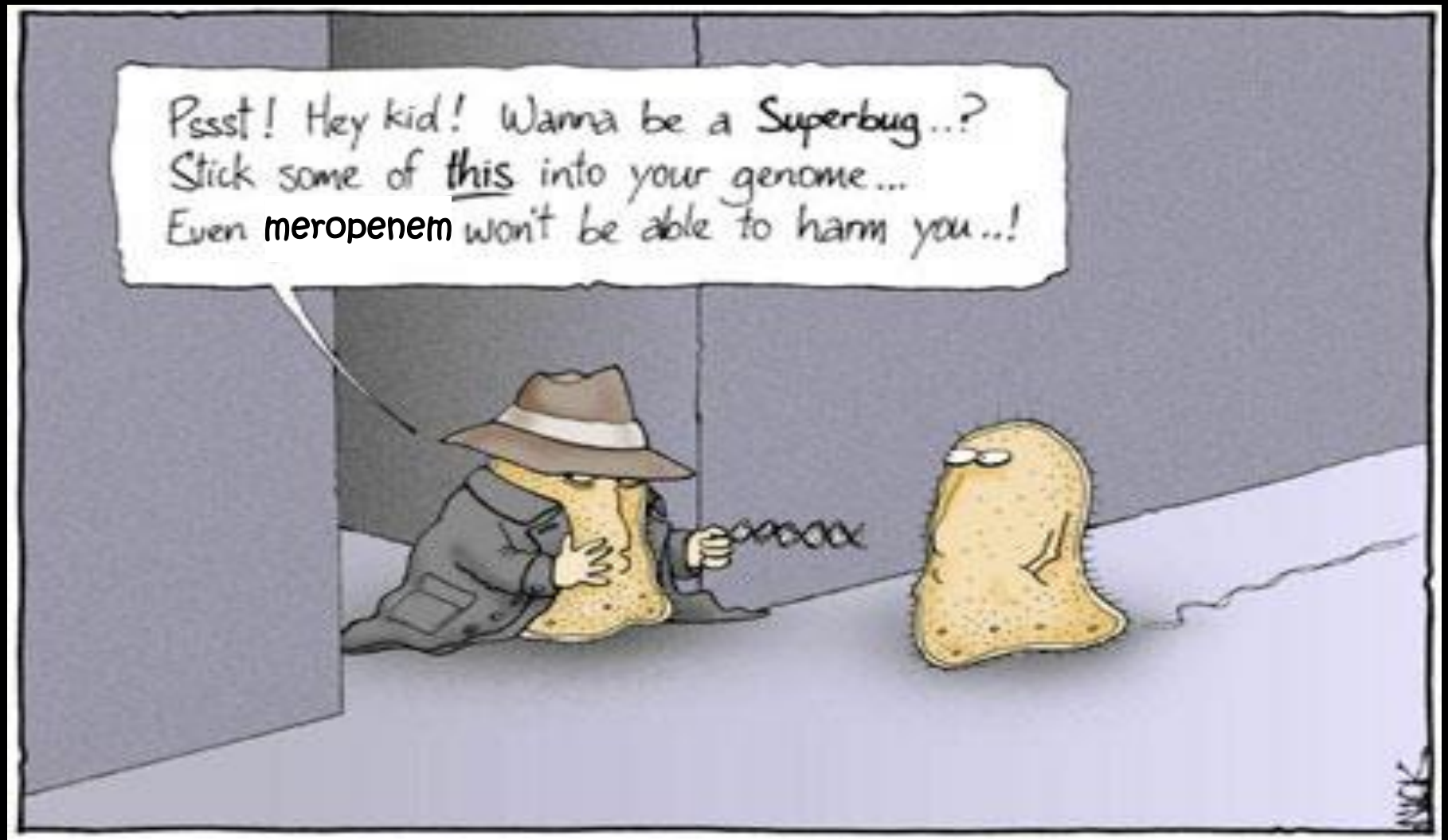
Austin ED, Sullivan SS, Macesic N, et al. Reduced Mortality of *Staphylococcus aureus* Bacteremia in a Retrospective Cohort Study of 2139 Patients: 2007-2015. Clin Infect Dis. 2020;70(8):1666-1674.

Other Gram-Positive Bacteria (Observations)

- ***Enterococcus faecalis*** 10x more common than ***E. faecium***
  - *E. faecium* much more antibiotic resistant (especially to vancomycin and ampicillin)
- ***Streptococcus pneumoniae*** infections have decreased over the past few years, most likely due to the vaccines
- ***Streptococcus pyogenes*** (Group A Strep): Increased antibiotic resistance (not penicillin)
- ***Streptococcus agalactiae*** (Group B Strep): Same as above
- ***Corynebacterium spp.***: Some species very antibiotic resistant

Challenging Section

Multi-Drug Resistant
and
Carbapenem Resistant
Gram-Negatives



It was on a short-cut through the **Surgical and Medical ICU** that Albert was first approached by a member of the Antibiotic Resistance.

Gram-Negative Organisms of Concern

- Enterobacterales and *Pseudomonas aeruginosa* with Extended Spectrum Beta-Lactamases (ESBLS)
- Enterobacterales (especially Citrobacter, Serratia, Enterobacter, and Klebsiella) and *Pseudomonas aeruginosa* with ampC Beta-Lactamases
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophila*
- *Acinetobacter baumannii* Complex including CRAB
- **Any Gram-Negatives that produce carbapenemases**
- Of concern, bacteria can have more than one antibiotic resistance genes

CRAB = Carbapenem Resistant *Acinetobacter baumannii*

Multi-Drug Resistance Gram-Negatives Organisms

- We have combined Extended-Spectrum Beta-Lactamases (ESBLs), ampCs, and other multi-antibiotic resistant organisms in to one group for infection prevention/infection control
  - They are now called Multi-Drug Resistant Organisms (MDROs)
  - Infection prevention guidelines vary dependent on the number of classes of antibiotics that are resistant
  - The most pressing concerns are gram negatives that produce carbapenemases

Carbapenemases

- Carbapenemases are enzymes that break-down the structure of Carbapenem Antibiotics
  - Imipenem
    - Meropenem
      - Doripenem
        - Ertapenem
- There are many different carbapenemases and resistance can be mediated by mechanisms other then through these enzymes

Resistance Patterns in *Klebsiella pneumoniae*

	Typical	ESBL	ampC	CRE
Ampicillin	R	R	R	R
Cefepime	S	R	S	R
Ceftriaxone	S	R	R	R
Ceftazidime	S	R	R	R
Cefoxitin	S	S	R	R
Pip/Tazo	S	S/R	S/R	R
Imipenem	S	S	S	R
Ertapenem	S	S	S	R

MRSA is a Picnic Compared to CRE

MRSA	CRE
1 organism - 1 Major Resistance Gene - *mec*A	Found in Multiple Gram-Negative Organisms Multiple Carbapenemase Resistance Genes
Easy to grow and usually easy to detect resistance	Easy to grow organisms; not always easy to detect resistance
Carried on Anterior Nares so screening is easy	Carried in GI Tract so screening is more invasive
We have made significant progress in controlling MRSA	CRE are increasing significantly world-wide

MRSA = Methicillin Resistant *Staphylococcus aureus.* CRE = Carbapenem Resistant Enterobacterales

A Most Concerning Issue is Carbapenemase Resistance

CRE

Found in multiple organisms (*Enterobacterales, Pseudomonas aeruginosa, Acinetobacter baumanii)* comprising many different carbapenem resistance genes (~500)
Multiple classes (A, B, and D), treatment issues/differences

Current problem: isolates that are genotypically resistant but phenotypically susceptible

Carried in GI tract and can be silently spread

Easy to transmit/difficult to eliminate from GI tract

CRE = Carbapenem Resistant Enterobacterales
GI = Gastrointestinal

Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed July 14, 2021.

Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the infectious disease society of america and the american society for microbiology. Clin Infect Dis. 2018;67(6):e1-e94.

The Wake Up Call[1]

- In Israel in 2006, there was an isolate of *K. pneumoniae* in a neonatal intensive care unit that turned out to harbor a Carbapenemase
- By mid 2007, there were 1275 additional cases and 10,000 patients (estimate) were colonized[2]
- This outbreak impacted and eventually changed the national infrastructure for infection control in Israel[2,3]

1. Navon-Venezia, S. et al. 2009. AAC. 53: 818-820
2. Schwaber MJ and Carmeli, Y. 2017. Clin Inf Dis. 65: 2144-2149
3. Fabre, V. and Cosgrove, S. 2017. Clin Inf dis. 65: 2150-2152

Class A CP-CREs

- **Most common are plasmid-mediated *Klebsiella pneumoniae* carbapenemases (KPC)**
  - **There are 24 distinct KPCs**
- **Mostly found in *K. pneumoniae* and *E. coli* but also in other enteric bacteria**
- **Hydrolyze all of the β-lactam antibiotics including cephalosporins, monobactams, as well as the carbapenems**
- **SME, IMI, NMC, GES subclasses as well as KPC**

Class B Plasmid-Mediated Metallo-β-Lactamases

- **Metallo: requires zinc; multiple types (NDM, VIM, IMP, etc.)**
- **NDMs (16 so far): New Delhi metallo-β-lactamase**
- **The first 3 *bla*$_{NDM-1}$ isolates detected in US were in *E. coli, Enterobacter cloacae, Klebsiella pneumoniae* and were associated with medical tourism**
- **Confers resistance to all β-lactams except aztreonam**

Class C Beta-Lactamases (ampC)

- **Common in Enterobacter, Serratia, Citrobacter, and *K. aerogenes* (formerly *Enterobacter aerogenes*)**
  - **Induced by beta-lactam antibiotics so patient's isolate goes from low level constitutive beta-lactamase production to inducible high-level beta-lactamase production**
  - **Not inhibited by clavulanate or tazobactam**
  - **Hydrolyze cephamycins and most cephalosporins, except cefepime (so cefoxitin R and cefepime S)**
  - **May hydrolyze carbapenems at very low rates**
  - **Most ampC genes are on chromosomes (non-transferable) but now some are on plasmids (transferable)**

Class D Carbapenemases

- Originally described as OXA Beta-lactamases that could hydrolyze oxacillin and cloxacillin, but they also hydrolyze carbapenems
- 5 OXA Families
  - Multiple enzymes in each family
- Primarily found in Acinetobacter, Pseudomonas and Enterobacteriaceae
- Lower MICs than other carbapenemases but still a problem, especially mucoid *K. pneumoniae* OXA-48

So How Do We Handle CRE?

- Is a positive Carbapenemase Producing-CRE in a clinical culture a panic/critical value?
- Do we close ICUs? Transplant units?
- Huge challenge for Infection Preventionists

Screening for CRE

- If you have CRE in your hospital, who, when, what and how should you screen?
  - Helps to know specific type of CRE (possible outbreak if all isolates are the same type)
- What do you do with screen results?
- Is it possible to eliminate CRE from the hospital? From an individual carrier?
  - Use antibiotics?
  - Fecal transplants
- For screening, there are rapid genotypic PCRs and less rapid phenotypic methods
  - One of the PCRs will pick up 90 or so most common CREs

Some Case Reports

Case Study

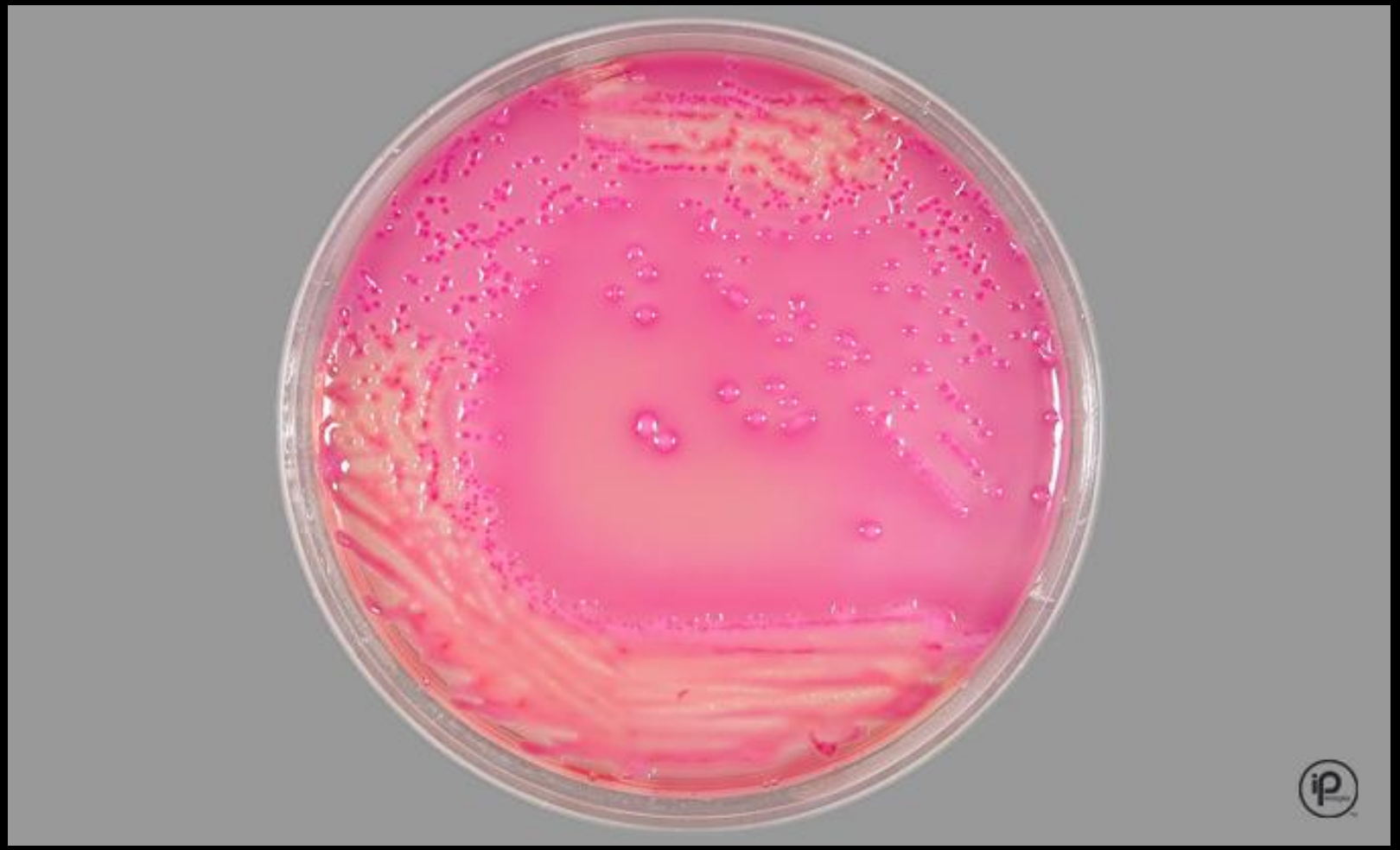
- **A 48 year-old female was admitted for elective knee replacement surgery following an automobile accident**
- **Post-surgery she developed idiopathic heparin-induced thrombocytopenia**
- **Loss of perfusion to her intestines resulted in a small bowel transplant**
- **Post-surgery # 2 she developed acute respiratory distress syndrome (ARDS) and was placed on a ventilator**
- **Her condition continued to deterioate and she developed nosocomial pneumonia**

Case and slides courtesy of Dr. Stephen Jenkins

Case Study

A gram-negative rod was recovered from her bronchial lavage, her empyema collection, her urine, and from her blood cultures

Klebsiella pneumoniae



Antibiotic Susceptibility Testing
Klebsiella pneumoniae

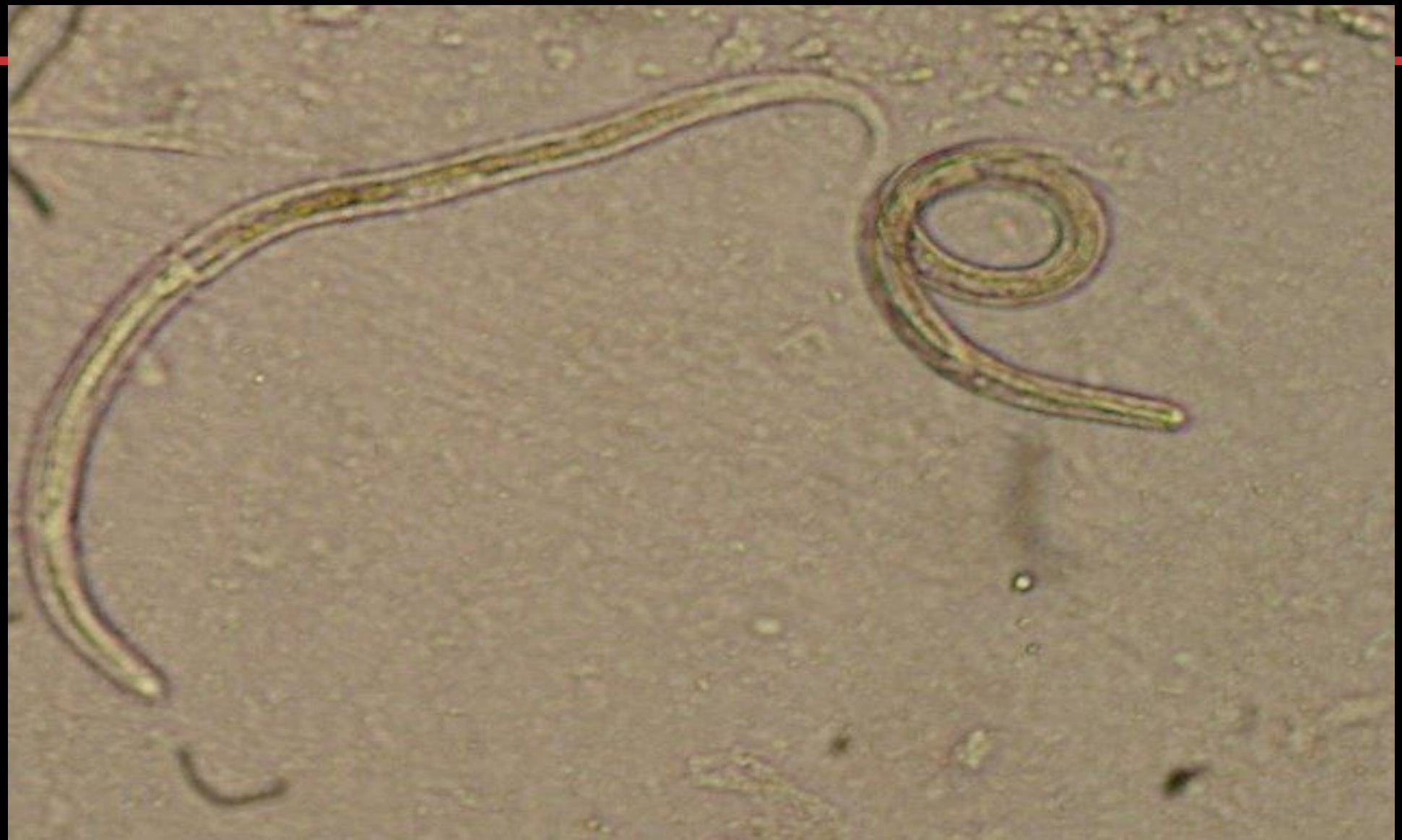
ANTIBIOTICS (μg/mL)	MIC	
• Ampicillin	>16	R
• Aztreonam	>16	R
• Ceftriaxone	>32	R
• Ceftazidime	>16	R
• Cefotaxime	>32	R
• Cefazolin	>16	R
• Ciprofloxacin	>2	R
• Cefepime	>16	R
• Cefuroxime	>16	R
• Amikacin	32	R
• Imipenem	>8	R
• Meropenem	>8	R
• Ertapenem	>4	R
• **Polymyxin B**	**2**	**S (?)**
• Gentamicin	8	R
• Levofloxacin	>4	R
• Meropenem	>8	R
• Trimethoprim-Sulfa	>2/38	R
• Tetracycline	>8	R
• Tobramycin	>8	R

S = Susceptible
R = Resistant

Case Study

- Polymyxin B MIC = 2 μg/mL (Susceptible?)
- Patient treated with tigecycline and polymyxin B - responded
- Reports in the literature of successful treatment of this organism with polymyxin B plus rifampin and combinations of agents that include imipenem and/or an aminoglycoside

The Patient Developed a Second Pneumonia Related to:

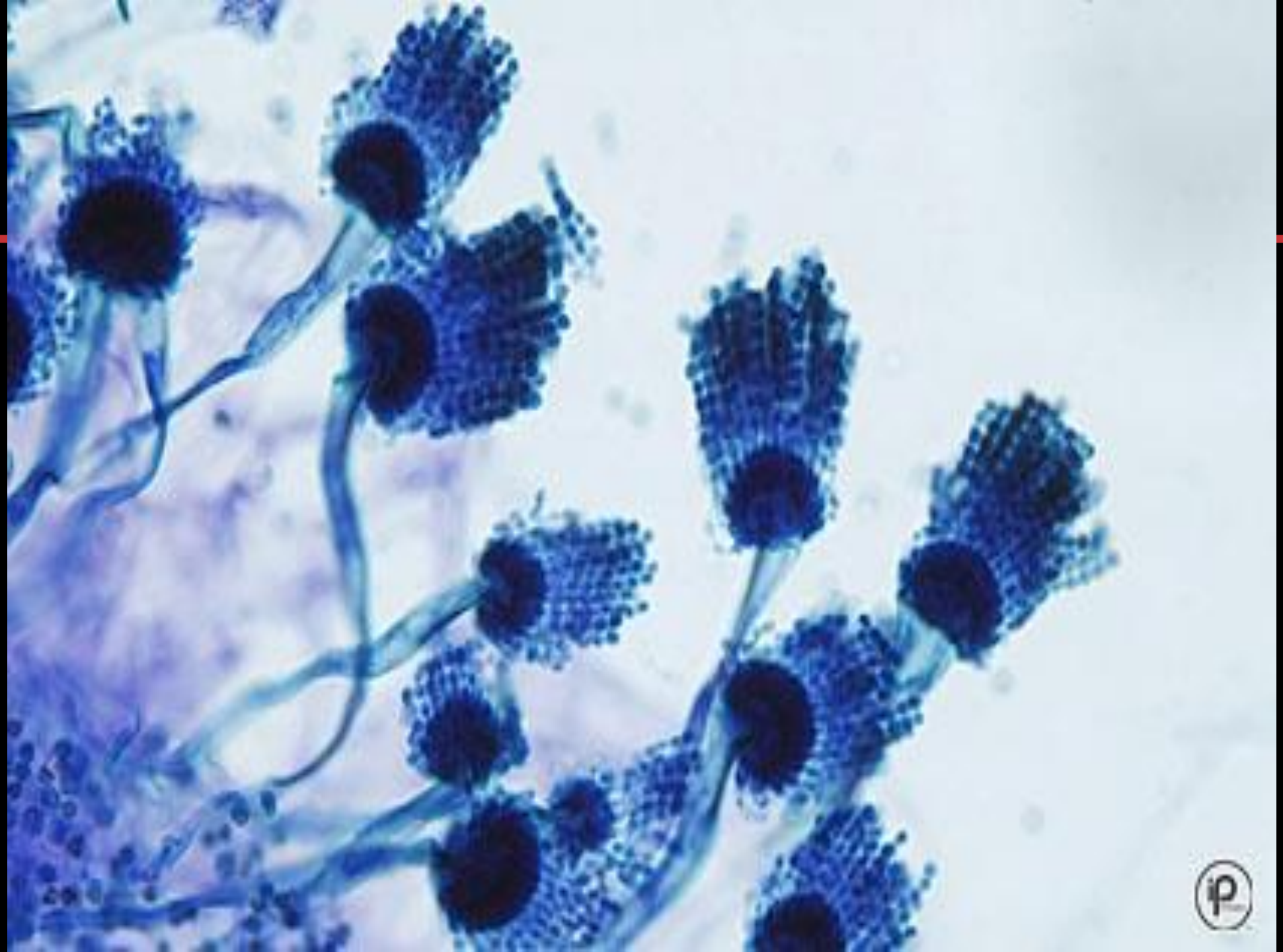


Follow-up

Hyperinfestation with *Strongyloides stercoralis*

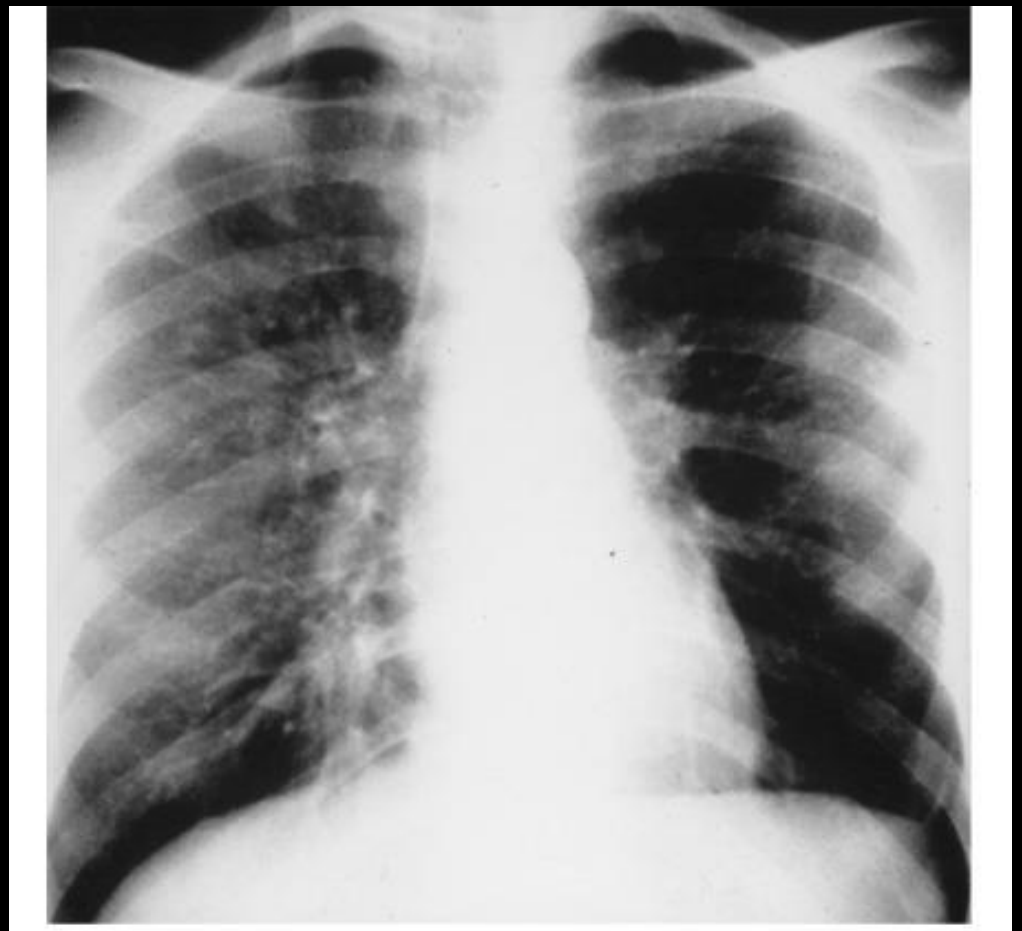
Follow-up

Treated and recovered, only to develop a new pneumonia with:



Follow-up

- *Aspergillus fumigatus*
- Again responded to therapy (voriconazole), but developed bilateral CMV pneumonia



Follow-up

Controlled with high-dose gancyclovir, but became septic with:

Multi-drug resistant strain of *Acinetobacter baumannii*

- Resistant to β-lactams, imipenem, aminoglycoside, and fluoroquinolone
- Patient expired 13 months after initial surgery

Case Report: Genotypic vs Phenotypic Resistance

- 34 year-old male with a 6-month history of transverse myelitis and anti-phospholipid syndrome developed a urinary tract infection with *Citrobacter freundii*
- Initial susceptibility testing revealed some antibiotic resistance, most likely due to the presence of an ampC beta-lactamase (resistance to cefoxitin, ceftazidime, ceftriaxone, and cefepime). It tested as susceptible to **ertapenem and meropenem**. Treated with ertapenem
- Two weeks later, the patient developed a kidney abscess and spiked a fever. Blood cultures grew a *Citrobacter freundii* **that tested phenotypically susceptible to carbapenems but was genotypically resistant** based on the detection of the bla_{KPC} gene (Cepheid Carba R and BioFire BCID PCR panel)
- Treatment with meropenem-vaborbactam (5 weeks) and amikacin (2 weeks followed by 6 weeks) resulted in negative cultures at the 3 infected sites (urine, kidney, blood)

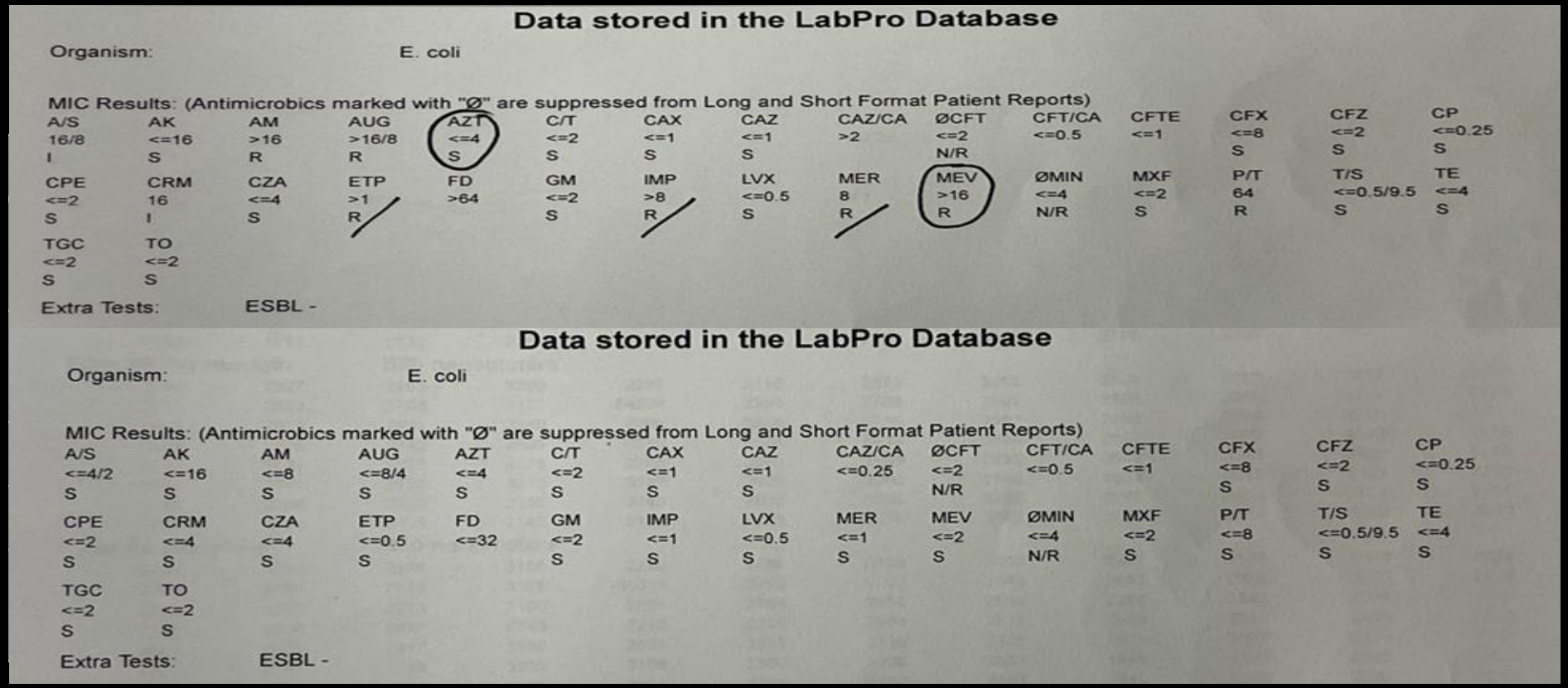
Differences in the MICs of 5 *C. freundii* Isolates[1]

Sample	Ceftazidime (µg/ml)	Ceftriaxone (µg/ml)	Cefepime (µg/ml)	Cefoxitin (µg/ml)	Pip/Tazo (µg/ml)	Ertapenem (µg/ml)	Meropenem (µg/ml)	Carbapenemase gene detected [a]
Urine	16 R	>32 R	16 R	≥16 R	64/4 R	≤0.5 S	≤1 S	KPC
BC-1 (day 1)	≤1 S	≤1 S	≤2 S	≥16 R	≤16/4 S	≤0.5 S	≤1 S	KPC
BC-2 (day 1)	4 S	2 I	≤2 S	≥16 R	≤16/4 S	≤0.5 S	≤1 S	KPC
K-1 (day 1)	16 R	32 R	8 SDD	≥16 R	64 I	≤0.5 S	≤1 S	KPC
K-2 (day 3)	4 S	8 R	≤2 S	≥16 R	≤16/4 S	≤0.5 S	≤1 S	KPC

Interpretation of MICs from CLSI M100 S31 2021. MIC = Minimum Inhibitory Concentration
S=Susceptible I=Intermediate SDD=Susceptible Dose Dependent R=Resistant
[a]KPC target identified on the Xpert Carba-R assay (Cepheid)

1. Brecher, SM., Tickler, I., and Tenover, FC. 2023. Ann of Clin Microbiol Antimicrob. https:/doi.org/10.1186/s12941-023-00579x

The Importance of Knowing When Something is Wrong: Same Organism/Different Results



Data stored in the LabPro Database

Organism: E. coli

MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

A/S	AK	AM	AUG	AZT	C/T	CAX	CAZ	CAZ/CA	ØCFT	CFT/CA	CFTE	CFX	CFZ	CP
16/8	<=16	>16	>16/8	<=4	<=2	<=1	<=1	>2	<=2	<=0.5	<=1	<=8	<=2	<=0.25
I	S	R	R	S	S	S	S		N/R			S	S	S

CPE	CRM	CZA	ETP	FD	GM	IMP	LVX	MER	MEV	ØMIN	MXF	P/T	T/S	TE
<=2	16	<=4	>1	>64	<=2	>8	<=0.5	8	>16	<=4	<=2	64	<=0.5/9.5	<=4
S	I	S	R		S	R	S	R	R	N/R	S	R	S	S

TGC	TO
<=2	<=2
S	S

Extra Tests: ESBL -

Data stored in the LabPro Database

Organism: E. coli

MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

A/S	AK	AM	AUG	AZT	C/T	CAX	CAZ	CAZ/CA	ØCFT	CFT/CA	CFTE	CFX	CFZ	CP
<=4/2	<=16	<=8	<=8/4	<=4	<=2	<=1	<=1	<=0.25	<=2	<=0.5	<=1	<=8	<=2	<=0.25
S	S	S	S	S	S	S	S		N/R			S	S	S

CPE	CRM	CZA	ETP	FD	GM	IMP	LVX	MER	MEV	ØMIN	MXF	P/T	T/S	TE
<=2	<=4	<=4	<=0.5	<=32	<=2	<=1	<=0.5	<=1	<=2	<=4	<=2	<=8	<=0.5/9.5	<=4
S	S	S	S		S	S	S	S	S	N/R	S	S	S	S

TGC	TO
<=2	<=2
S	S

Extra Tests: ESBL -

Data from Dr. Niaz Banaei September, 2023
Clinmicronet used with permission

Conclusions

Susceptibility testing is challenging

Often repeat testing and multiple methods are needed

The Laboratory of the Future

Increased Automation

Molecular Methods

Improved Turn Around Times

Total Clinical Microbiology Laboratory Automation

- Larger size microbiology labs are becoming automated
- Much more difficult than automation in chemistry and hematology
  - Why?
- Needed due to the shortage of medical technologists

Molecular Epidemiologic Approaches

Rapid PCR

- Screening of a limited number of resistance genes has been very valuable
- Multi-Plex PCR increases the number of targets
- Need to update targets periodically

Next Generation Sequencing

- Potential to yield data about any resistant gene or mutation present
- Sequence bacteria which are difficult or impossible to culture from clinical samples
- May pick up novel resistance mechanisms

Slide courtesy of Dr. Audrey Schuetz, modified by Dr. Brecher 9.2023

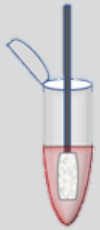
Improved Turn Around Time
Do Faster Results Improve Patient care?

- Susceptibilities directly from blood positive cultures (Accelerate)
- Susceptibilities in 5-6 hours rather than 18-24 hours and 384 well plates (Selux)
- Susceptibilities directly from specimen (AtbFinder, not FDA approved)

AtbFinder® (all-in-one, prefabricated kit) Selects The Most Effective Treatment in 4 Hours

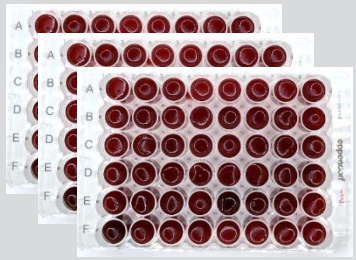
4 SIMPLE AND EASY STEPS LOW-SKILL SAMPLE PREP WORKFLOW

1



Clinical sample

2

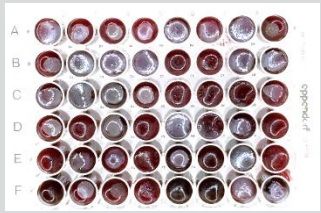


Clinical sample directly plated to the AtbFinder®

3

4h incubation

4



Read and interpret results (visually/scanner)

SAVING LIVES AND MONEY

DIFFERENCES:

- Does not require isolation of pure bacterial cultures
- No changes to existing hospital infrastructure

EASY TO USE:

- No need for special equipment

VALIDATION:

Sensitivity >99%
Specificity >98%
NPV >99%
PPV >98%

New Antibiotics

- Eravacycline and Omadacycline (tetracycline derivatives)
- Plazomycin (new aminoglycoside)
- Meropenem-Vaborbactam
- Ceftazidime-Avibactam
- Imipenem-Relabactam
- Cefiderocol
- Lefamulin (new class)
- Dalbavancin and Oritavancin (long half-life)
- Sulbactam-Durlobactam

Antibiotics in the Pipeline

- Aztreonam-avibactam
- Ceftaroline-avibactam
- Sulopenem and tebipenem
  - oral carbapenems (Not FDA approved 2023

With all these new antibiotics, we must be in great shape

- We are in terrible shape
- Big pharma is sprinting away from antibiotics
- Small pharma answered the call but many of these companies have gone bankrupt
- Why in the world (other than need) would you invest (at this time) in antibiotics?
- **Discussion:** Why is big pharma getting out of the antibiotic business?

The Future of Antibiotics and Resistance[1]

From the World Economic Forum 2013[2]

"Arguably the greatest risk….to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall"

1. Spellberg et al. 2013. NEJM.368: 299-302
2. Howell, L. ed. Global risks 2013. 8th edition: World Economic forum. 2013

But we have too many illusions that we can, by writ, govern the remaining vital kingdoms, the microbes, that remain our competitors of the last resort for dominion of the planet. The bacteria and viruses know nothing of national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor

Joshua Lederberg Ph.D. JAMA.260:684-685. 1988

Will We Have Antibiotics in 100 Years?

At this point, with the time left today, let's discuss the future of antibiotics

Your ideas?

What can we do?

How can we do it?

Alternatives to antibiotics

Antibiotic Stewardship

Thoughts