Antibiotics: Managing a Medical Treasure

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Objectives

- Analyze the relationship between antibiotic use and antibiotic resistance
- Review the reasons for the dearth of new antibacterial antibiotics
- Discuss the need for antibiotic stewardship and optimizing antibiotic use
- Describe the methods for optimizing antibiotic use including the use of biomarkers, newer diagnostic tools and approaches to deescalate antibiotics

Disclosures: None

Case History

A 61 yo male s/p Whipple resection in Jan. 2009 that was complicated by duodenal stump leak with drain placement.

Pt. had fascial dehiscence and colocutaneous fistula. He was placed on **multiple antibiotics** including **imipenem**. A surgical repair was done. He was discharged in mid-April.

Re-admitted 4/27 for volume depletion, acute renal failure (ARF), and sepsis. On 5/13, a blood culture showed *K. pneumoniae* with the following susceptibility pattern:

Test(s) ordered: BLOOD CULTURE completed: May 13, 2009

*** BACTERIOLOGY FINAL REPORT => May 13, 2009**
CULTURE RESULTS: *KLEBSIELLA PNEUMONIAE*
Comment: Cross resistance to other QUINOLONES likely
COLISTIN RESULT = S (BY DISK TEST)

ANTIBIOTIC SUSCEPTIBILITY TEST RESULTS:
KLEBSIELLA PNEUMONIAE

	SUSC	INTP
AMPICLN	>= 32	R
AMPICILLIN/SUL	>= 32	R
CEFEPIME	>= 32	R
AZTREONAM	>= 32	R
CEFAZOLIN	>= 32	R
PIPERACILLIN/T	>=128	R
CEFTAZIDIME	>= 32	R
CEFTRIX	>= 64	R
CIPROFLOXACIN	>= 4	R
GENTMCN	8	I
IMIPENEM	**>= 16**	**R**
NITROFURANTOIN	>=128	R
TOBRMCN	>= 16	R
TRMSULF	>= 320	R
LEVOFLOXACIN	>= 8	R

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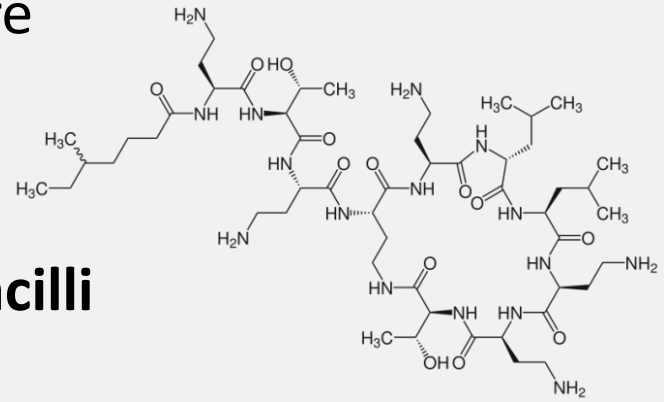
Hospital Course

After a small leak at the anastomosis was diagnosed, this patient was successfully treated with bowel rest and **colistin.**

Colistin

- A **polymyxin** antibiotic which is a mixture of cyclic polypeptides.



- Effective against most **gram-negative bacilli**
- Adverse effects: **nephrotoxicity** and **neurotoxicity**
- Available for >50 yrs — not subject to the regulations of modern drugs
    - No standardized dosing
    - No detailed trials on pharmacology or pharmacokinetics

Hospital Course

After a small leak at the anastomosis was diagnosed, this patient was successfully treated with bowel rest and colistin.

He was lucky!

Antimicrobial susceptibility patterns for *Klebsiella pneumoniae* isolates

Antimicrobial	MIC value, μg/mL	
	Patient 1: urine specimen	Patient 2: blood specimen
Amikacin	⩾64	⩾64
Ampicillin	⩾32	⩾32
Aztreonam	⩾64	⩾64
Cefazolin	⩾64	⩾64
Cefepime	32	⩾16
Ceftriaxone	⩾64	⩾64
Ciprofloxacin	⩾4	⩾4
Gentamicin	⩾16	⩾16
Piperacillin-tazobactam	⩾128	⩾128
Tobramycin	⩾16	⩾16
Trimethoprim-sulfa	⩾320	⩾320
Nitrofurantoin	256	NA
Ertapenem	⩾8	⩾8
Imipenem	⩾16	⩾R[a]
Moxifloxacin	NA	⩾R[a]
Tigecycline	⩾8	⩾8
Polymyxin B[b]	4	⩾16

NOTE. All susceptibility testing, except for polymyxin B, was done using the Vitek 2 automated system (bioMérieux). MIC, minimum inhibitory concentration; NA, not available.

[a] Antimicrobial agents indicated with "R" instead of an MIC value were read as susceptible by the automated system, but findings were modified on the basis of polymerase chain reaction testing results indicating the presence of *K. pneumoniae* carbapenemase genes.

[b] Tested using Etest.

Elemam A et al. Clin Infect Dis. 2009;49:271-274

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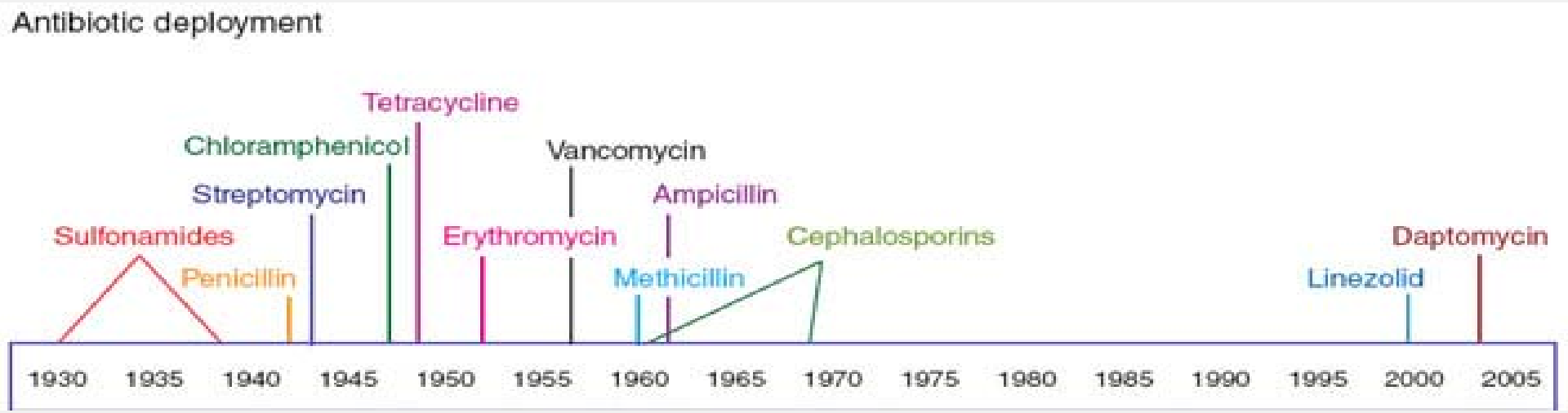
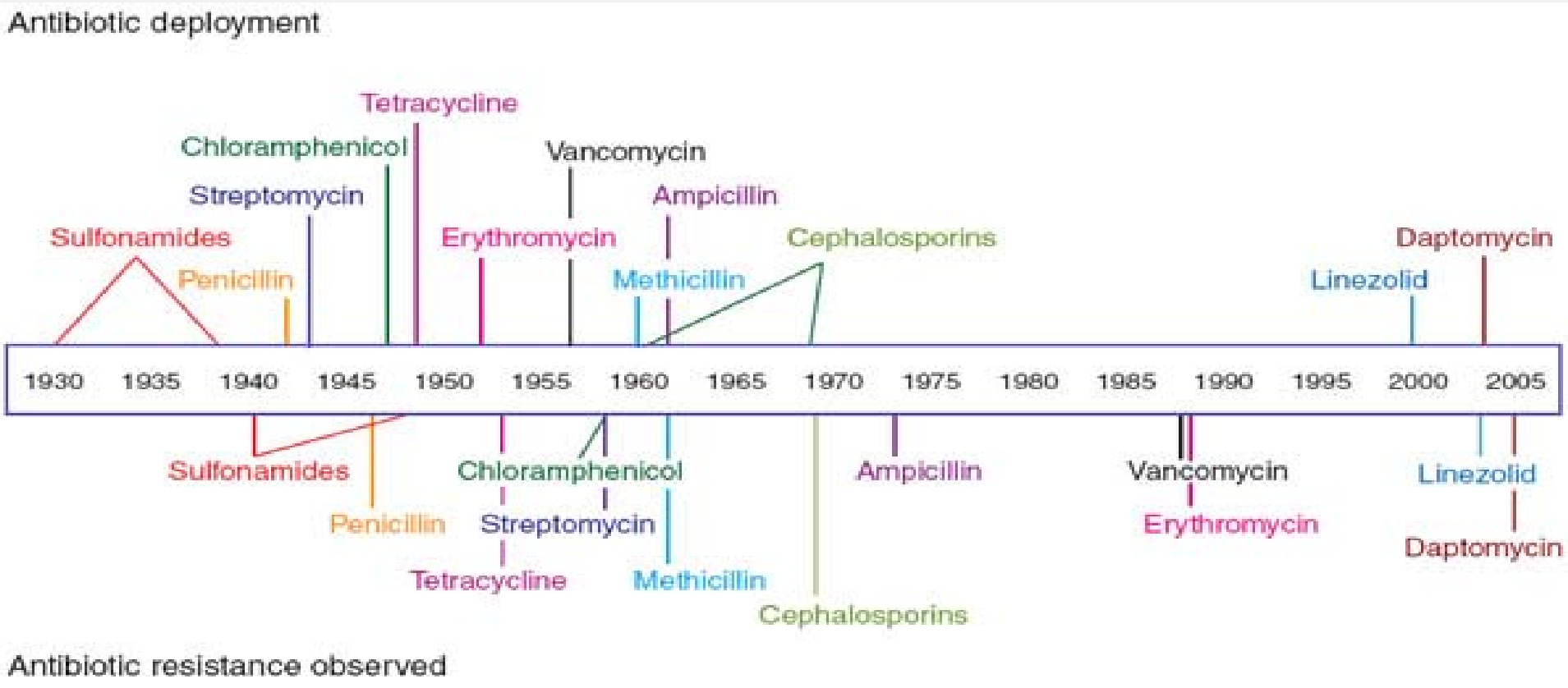
Antibiotics and Antibiotic Resistance



Clatworthy et al. *Nature Chemical Biology* **3**, 541 - 548 (2007)

Antibiotics and Antibiotic Resistance



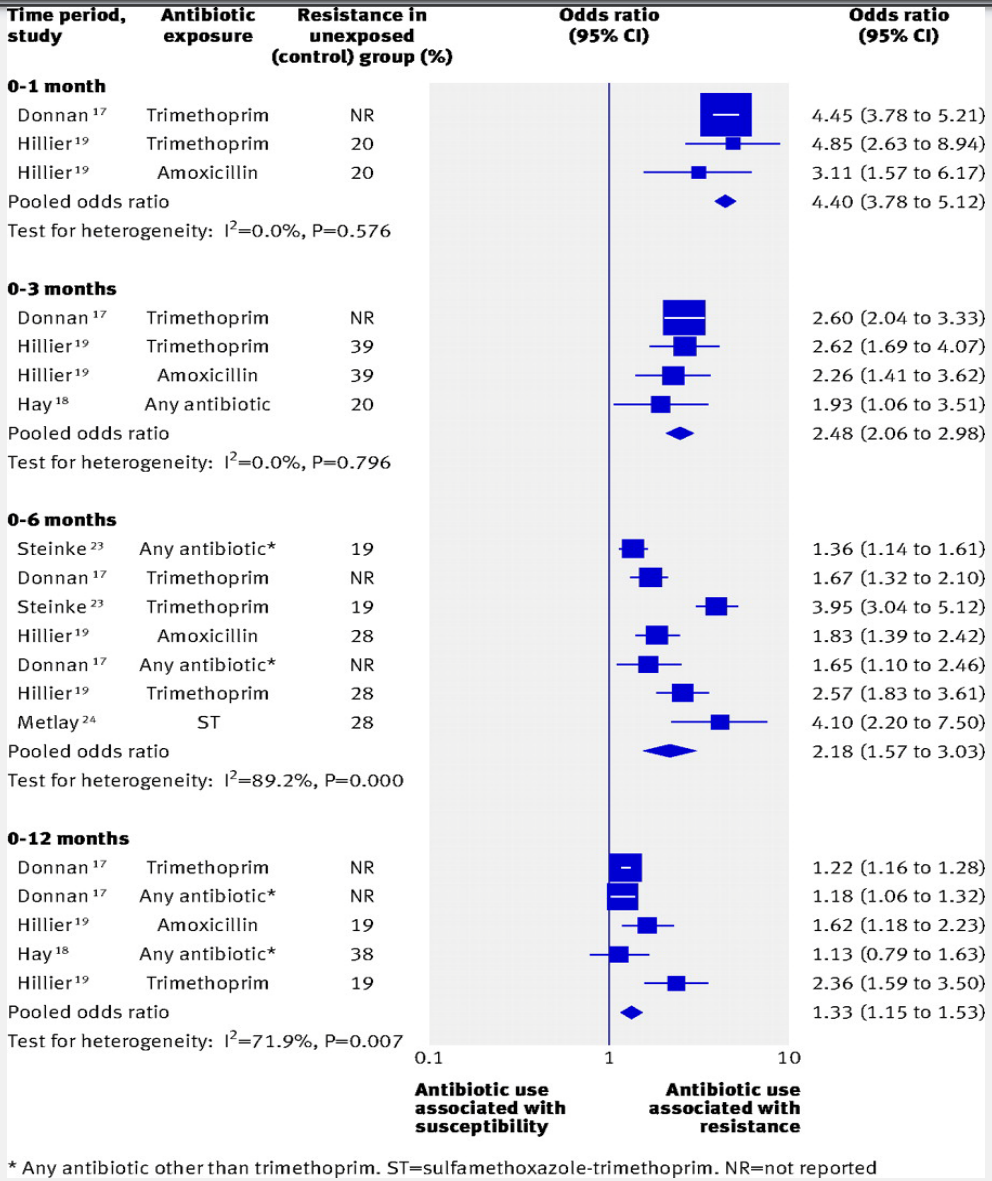
Clatworthy et al. *Nature Chemical Biology* **3**, 541 - 548 (2007)

“But I don’t usually see antibiotic resistant bacteria when I prescribe antibiotics!”

“But I don’t usually see antibiotic resistant bacteria when I prescribe antibiotics!”

The link between antibiotic use and antibiotic resistance

Forest plot : individual study and pooled ORs (log scale) for resistance in urinary tract bacteria (*E. coli*) and antibiotic exposure



* Any antibiotic other than trimethoprim. ST=sulfamethoxazole-trimethoprim. NR=not reported

Costelloe C et al. BMJ 2010;340:bmj.c2096
©2010 by British Medical Journal Publishing Group
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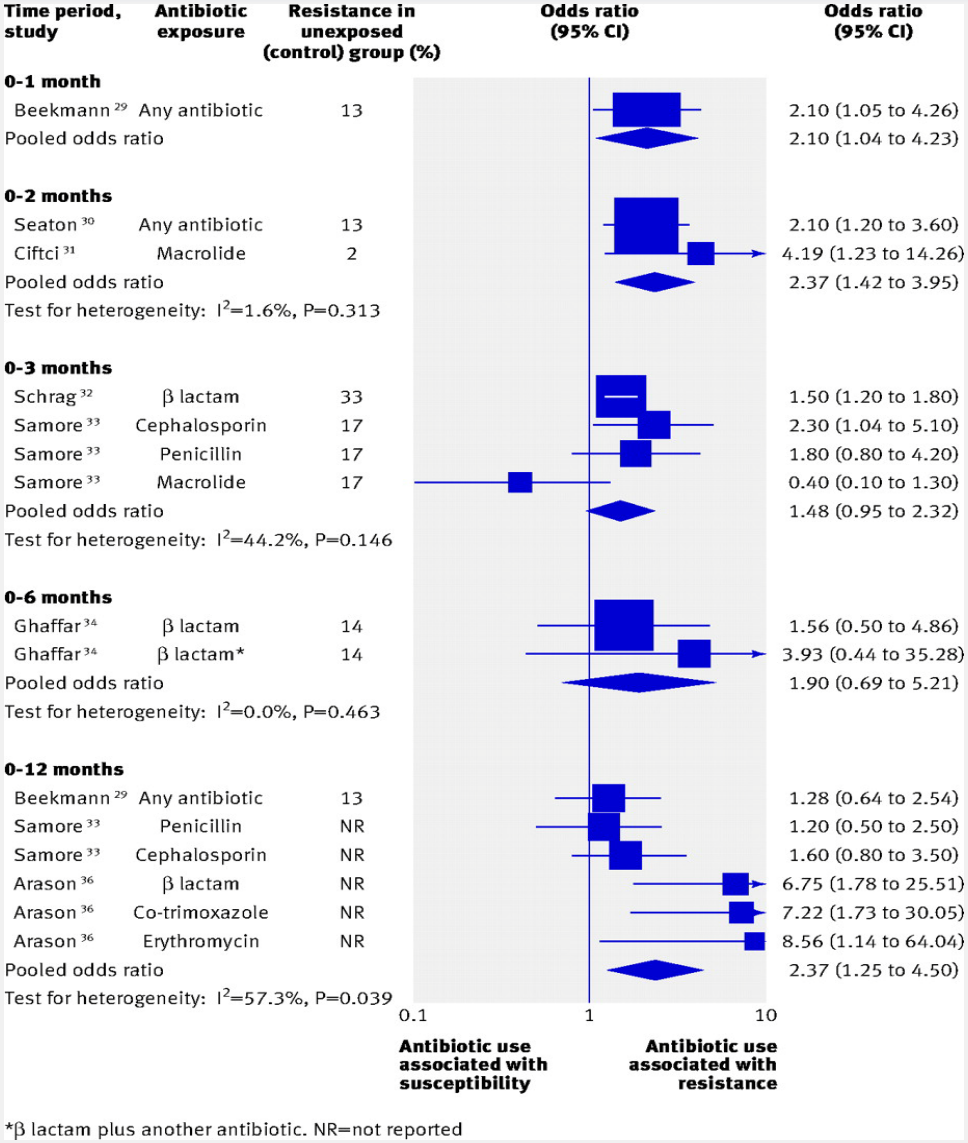
Forest plot: individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and previous antibiotic prescribing



*β lactam plus another antibiotic. NR=not reported

Costelloe C et al. BMJ 2010;340:bmj.c2096

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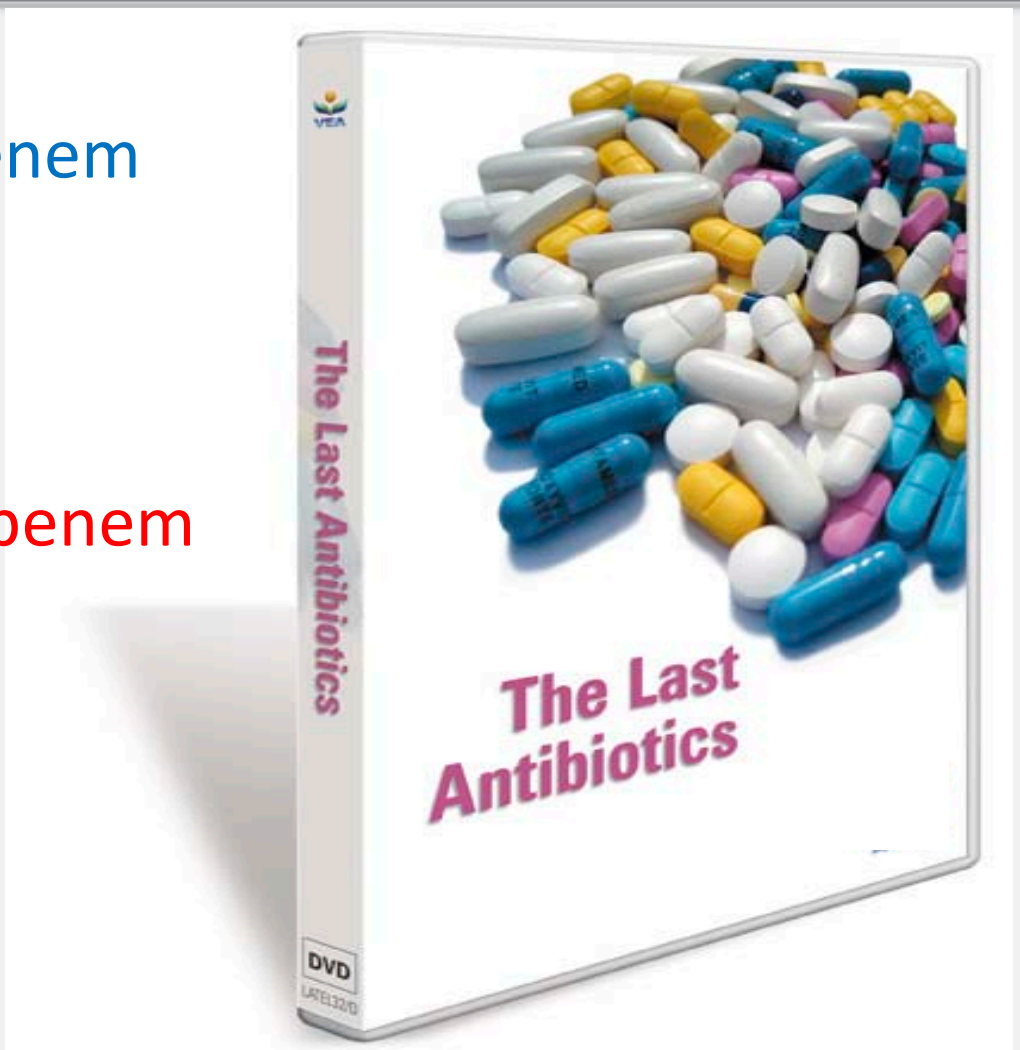
Carbapenem Use and Resistance to Carbapenems

Imipenem

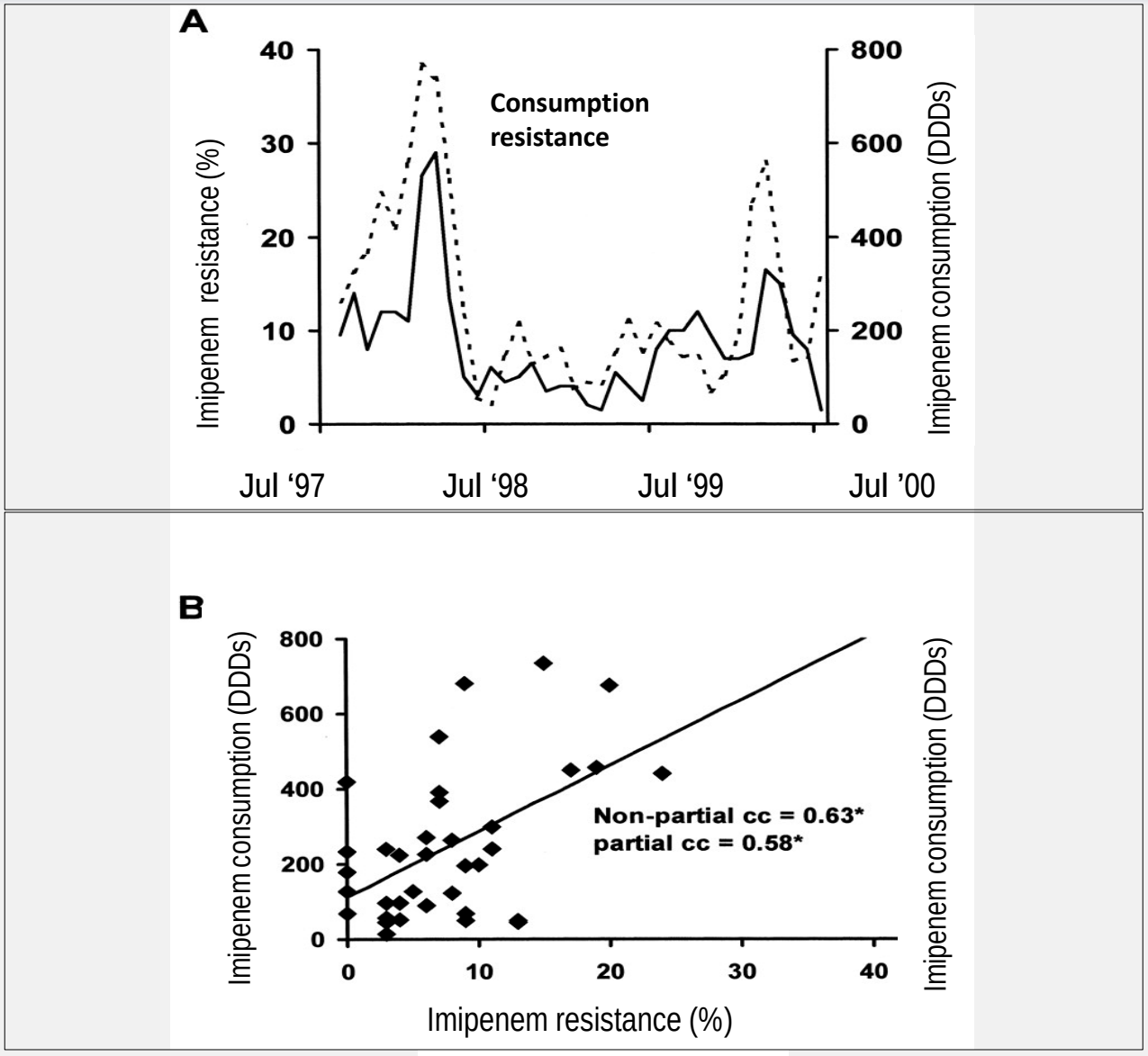
Meropenem



Doripenem

Ertapenem

Correlation between consumption of imipenem and resistant *P. aeruginosa*



Lepper, P. M. et al. 2002. 46(9):2920-2925 Antimic Agents and Chem

Carbapenemases

Carbapenem resistance in *Enterobacteriaceae* and *Acinetobacter baumannii* is primarily mediated by carbapenemases.

These carbapenemases are class A, B or D β-lactamases with the ability to hydrolyze carbapenems.

Often these carbapenemases can inactivate other β-lactam antibiotics, thus limiting the antimicrobials available to treat infections with these pathogens.

Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
Expert Rev. Anti Infect. Ther. 9(5), 555–570 (2011)

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Carbapenemases

***Klebsiella pneumoniae* carbapenemases (KPCs),** reported worldwide

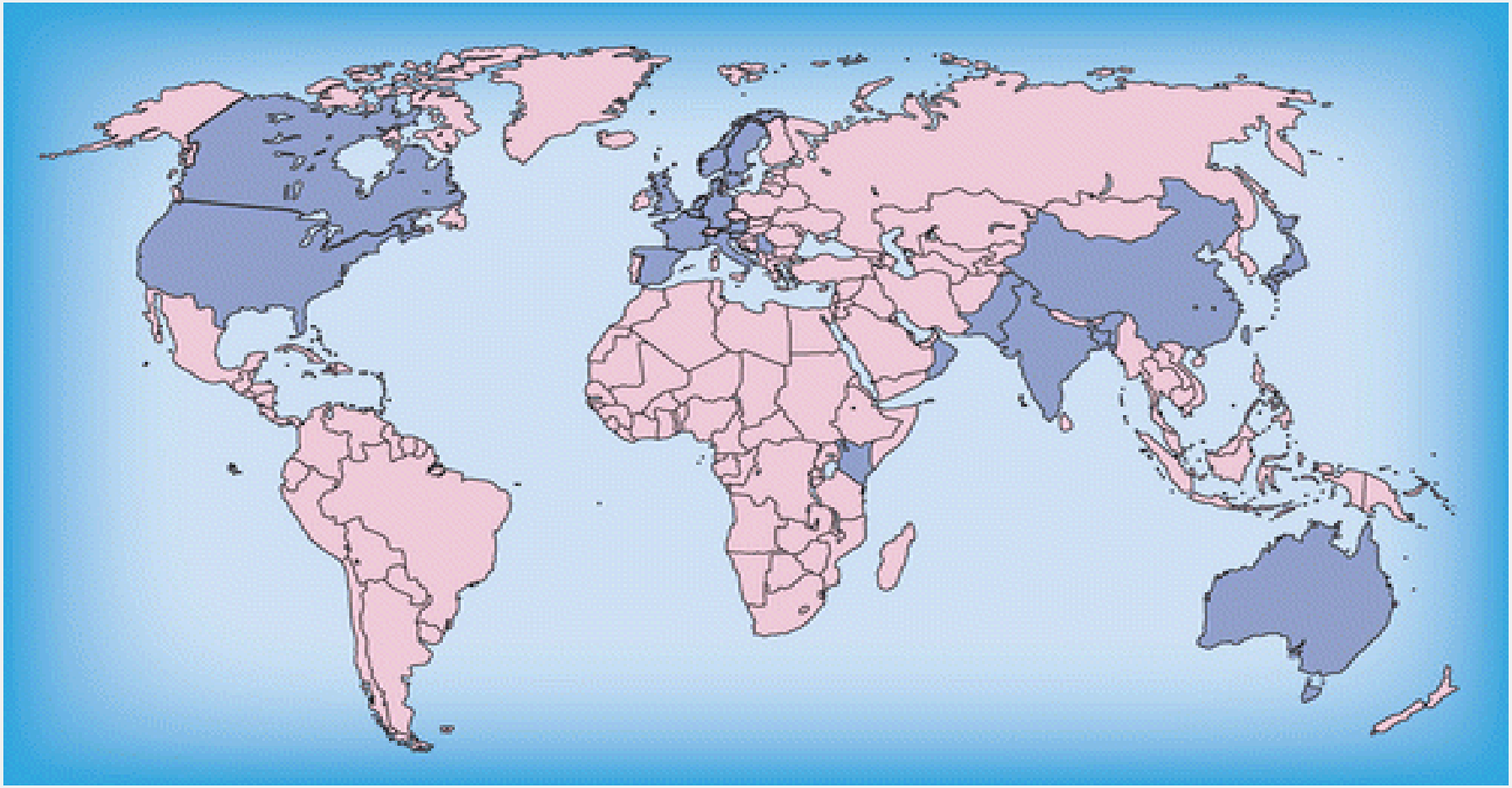
- Increasing KPC types (now up to 13) are described
- KPC-2 and KPC-3 most common

New Delhi Metallo-β-lactamases, type 1 (NDM-1), increasing worldwide

- Early cases had contact with the healthcare system in the Indian subcontinent.

Geographic distribution of NDM-1 carbapenemases

as of Dec. 31, 2010 (gray)



Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
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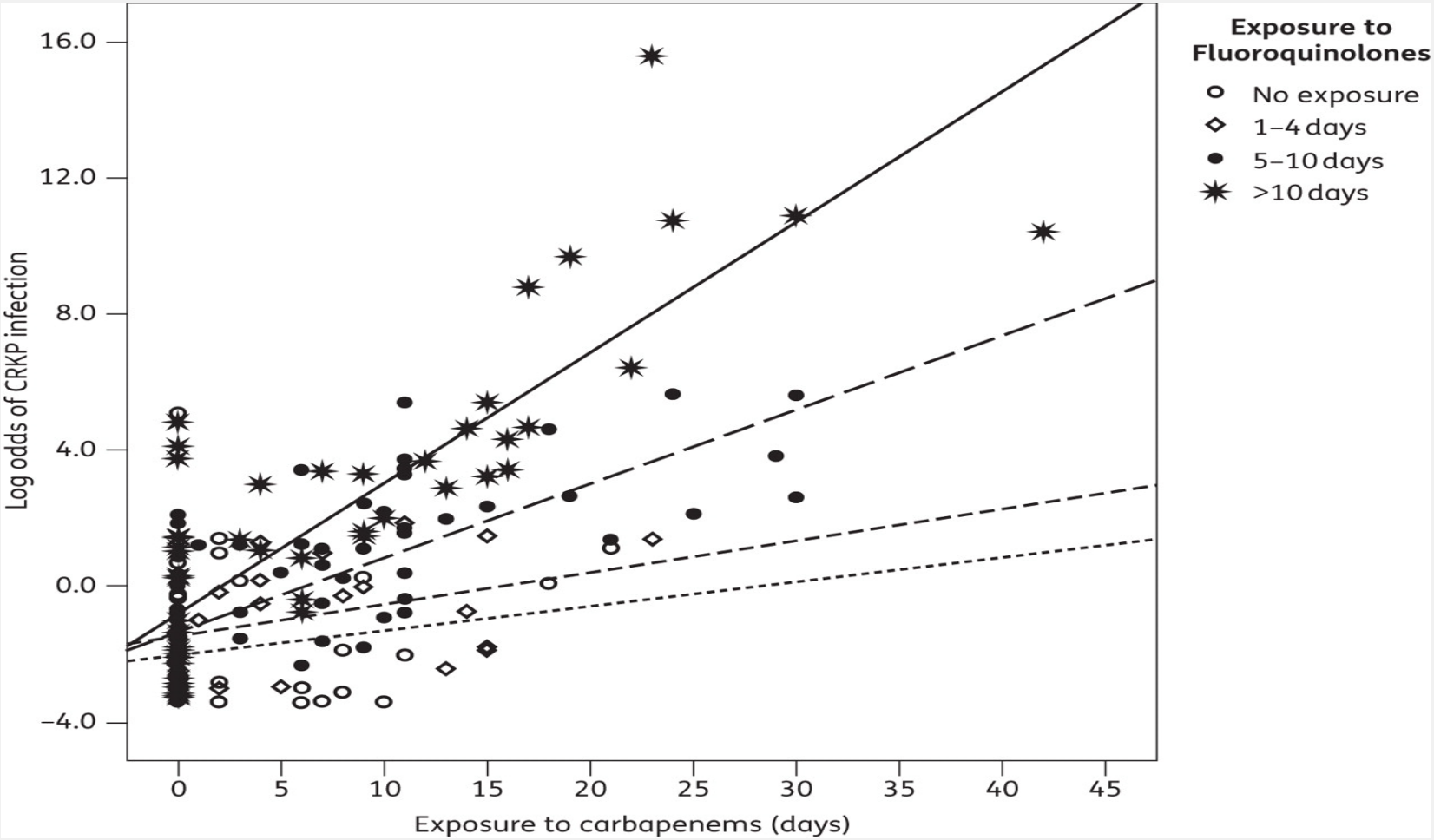
Carbapenemases

The genetic context in which these *bla* genes are encoded carry concurrent resistance determinants to other classes of antibiotics.

Exposure to other antibiotics can select for the genes carrying carbapenemases.

Interaction effect of carbapenems and fluoroquinolones on the risk of carbapenem-resistant *K. pneumoniae* (CRKP) infection



Kritsotakis E I et al. *J. Antimicrob. Chemother*. 2011;66:1383-1391

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Carbapenemases

No single agent in development demonstrates universal activity against carbapenemases

This leaves little on the horizon for patients suffering from carbapenem-resistant, Gram-negative infections.

Patel G, Bonomo R. Status report on carbapenemases: challenges and prospects
Expert Rev. Anti Infect. Ther. 9(5), 555–570 (2011)

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Evaluation of a Multi-Center Approach to Optimize Carbapenem Use

1. **Baseline data on carbapenem use (and resistance) and <u>its appropriateness</u>**

2. Assess Knowledge, Attitudes and Beliefs

3. Develop Interventions to optimize carbapenem use

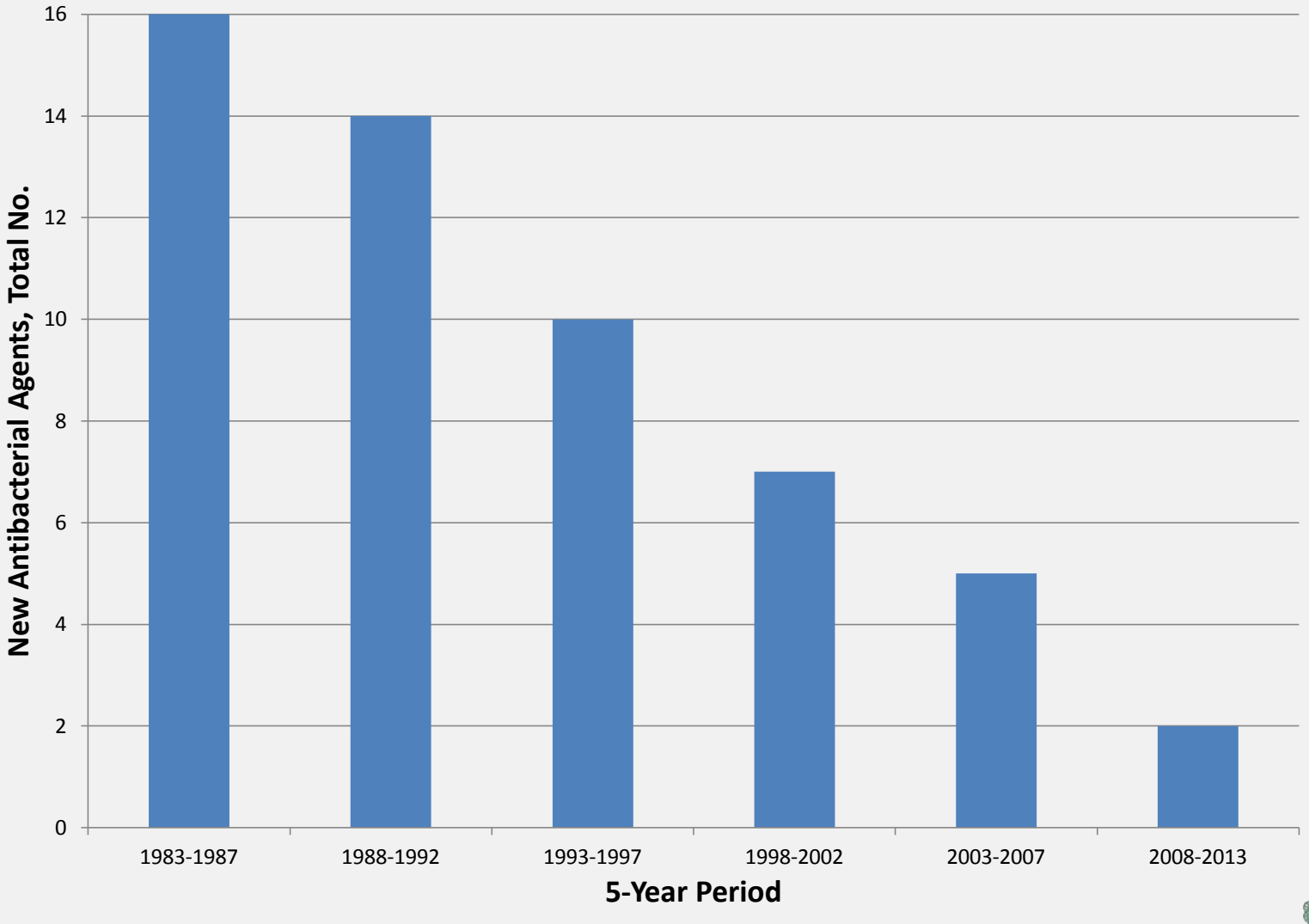
4. Follow up data to assess success

“If the patient has a carbapenemase-producing bacteria, what will be available soon to prescribe?”

The Dry Pipeline for New Antibacterial Antibiotics

- Remember: The average time from drug discovery to FDA approval is **nine** years.

New antibacterial agents approved in the U.S. per 5-year period



Adapted from: Boucher H W *et al. Clin Infect Dis*. 2009;48:1-12

“There must be SOMETHING, some antibiotic in development — Right?”

Not so much….
Progress on newer antibiotics

Many of these agents are variations on older antibiotics:

- For example, ceftobiprole, a cephalosporin with activity against MRSA, similar to ceftaroline
- Tetracycline analogs, macrolide analogs, fluoroquinolone analogs and oxazolidinone analogs are currently under investigation

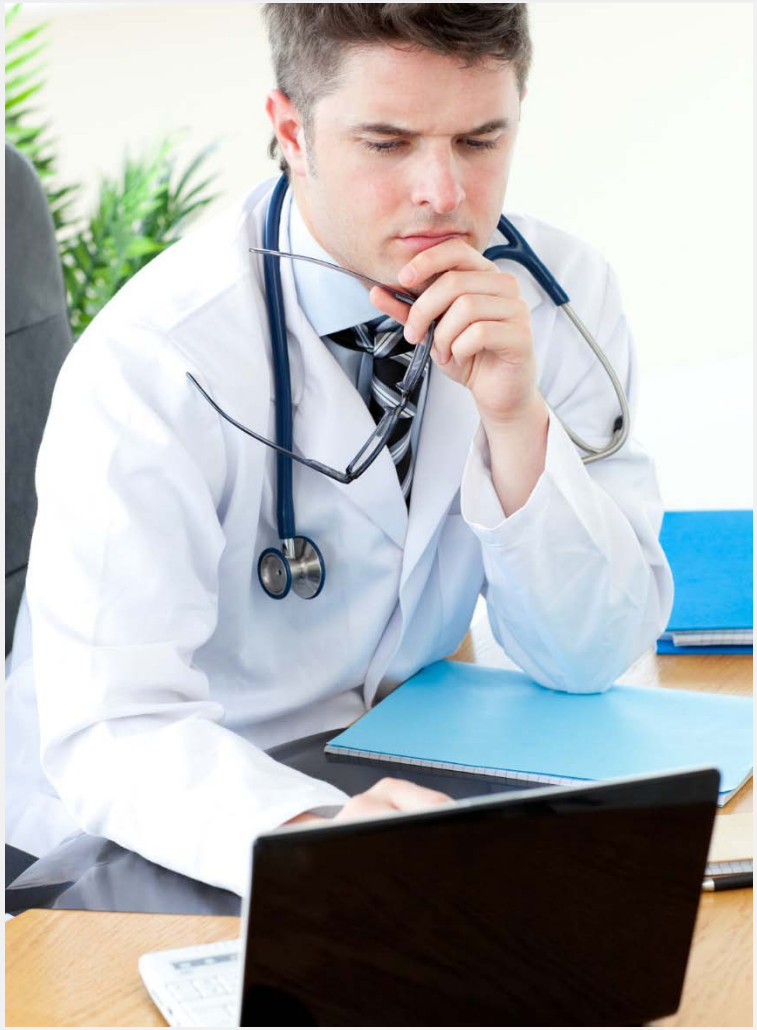
Moellering R. Discovering new antimicrobial agents.
Internation J Antimicrob Agents 2011;37:2–9.

No New Antibiotics?

The *Infectious Diseases Society of America* has called for a global commitment to develop new antibacterial drugs*

* *Infectious Diseases Society of America*. The 10 x '20 initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis.* 2010;50(8):1081-1083.

“So, what do we do NOW?”



A Call to Action

"Clinicians must realize how perilously close we are to a 'post-antibiotic' era."

Jacob JT, Gaynes RP. *Expert Rev Anti Infect Ther.* 2010. 8(8):893-902

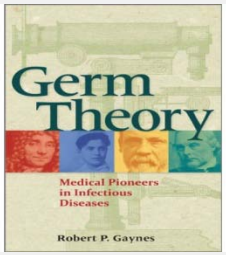
Another Inconvenient Truth: *Addressing Antibiotic Resistance*

1. Optimize antibiotic use

2. Limit the spread of resistant pathogens

Antibiotic Stewardship

No one doubts the importance of infection control practices in limiting the spread of antibiotic-resistant organisms, but optimizing antibiotic use, also known as **antibiotic stewardship**, remains essential for successful control of the antibiotic resistance.



Gaynes R. *Germ Theory: Medical Pioneers in Infectious Diseases*. 2011, Washington, DC: ASM Press.

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When you ask:

INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **39** (2009) 636–638

EDITORIAL

Why can't I prescribe that antibiotic? The role of antimicrobial stewardship programmes in modern medicine

Although all drugs may h … ysicians who do not know have an additional effec … do.'[5] damage'.[1] This refers to th … icted by Bannan *et al.* dem- biotic on the colonizing b … ior telephone approval was tion of antibiotic resistant … ibers. Nineteen per cent of suboptimal infection cor … ed to the survey believed antibiotic resistant organi … n infringement on their transmission of these org … greed that it was reasonable priate antibiotic use may … n policy. Important majori- inappropriate antibiotic … or antibiotic approval made

Autonomy in Medicine

In a recent survey, 19% of prescribers believed that Antimicrobial Stewardship Programs were an infringement on their autonomy.

Bannan A et al. Internal Med J 2009;39:662.

Doctors have not distinguished themselves when using antibiotics!

Antibiotic Use

- Patients receive an antibiotic on 80-90% of ICU days
- Patients receive an antibiotic on 40% of non-ICU days

Inappropriate Use

- 25-45% among hospitalized patients
- 20-50% among community patients

Indiscriminate Antibiotic Use is NOT an option

1. As a drug class, antibiotics are virtually unique; once an antibiotic is released for wide-scale use, its efficacy diminishes.*

2. Infections caused by antibiotic-resistant pathogens are threatening ALL progress in medicine—transplantation, surgeries, and invasive procedures.

* Gaynes R. Preserving the Effectiveness of Antibiotics. *JAMA*. 2010;303(22):2293-2294

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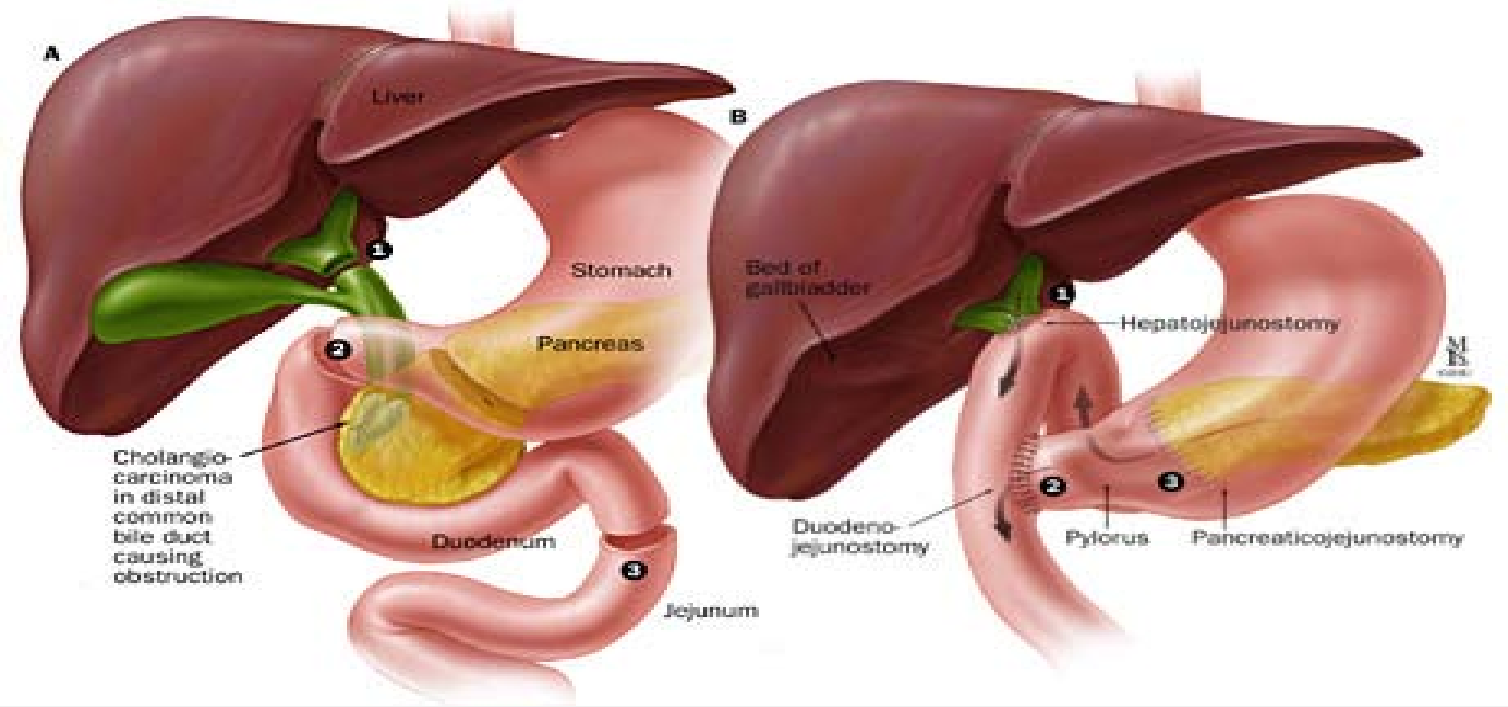
Remember our patient?

He survived a Whipple's Procedure, but nearly died from an antibiotic-resistant infection.



Ways to Optimize Antimicrobial Prescribing

- Streamlining therapy based upon microbiology culture and susceptibility results
- Dose optimization
- Antimicrobial de-escalation
- Computer-assisted decision support
- Infectious disease consultation
- Formulary restriction
- Development of guide-lines for antibiotic use
- Policies for parenteral to oral antibiotic conversion
- Prospective audit and feed-back of antibiotic use data
- Pre-approval policies

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Ways to Optimize Antimicrobial Prescribing:

What works??

Interventions to change professional practice: **Antimicrobial Stewardship**

- Cochrane reviews

  http://summaries.cochrane.org/CD003543/improving-how-antibiotics-are-prescribed-by-physicians-working-in-hospital-settings.

- Impact of antimicrobial stewardship in critical care: a systematic review

Kaki R et al. *J Antimicrob Agents Chemother* April 2, 2011

Interventions to change professional practice: **Antimicrobial Stewardship**

Generally effective:

- **Detailing**
- Computerized decision support
- Formal reassessment (or antibiotic de-escalation)
- Infectious diseases consultation
- Multifaceted interventions

A Note about Drug Detailing…

- "In the case of obtaining information from detailers, physicians' prescribing practices are less appropriate as a result of the interaction."

- Approximately 1/3 of the pharmaceutical workforce is in sales/drug detailing

Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? *CMAJ* 1993 Nov 15;149(10):1401-7.

Interventions to change professional practice: **Antimicrobial Stewardship**

Generally effective:

- Detailing
- **Computerized decision support**
- **Formal reassessment (or antibiotic de-escalation)**
- **Infectious diseases consultation**
- Multifaceted interventions

Impact of antimicrobial stewardship in critical care: a systematic review

"Studies of computer-assisted decision support, formal reassessment, and the impact of an infectious diseases consultant all demonstrated decreases in antibiotic use among several classes of antibiotics without a pronounced compensatory increase in other agents with a similar spectrum."

From Kaki R *et al*. *J Antimicrob Agents Chemother* April 2, 2011

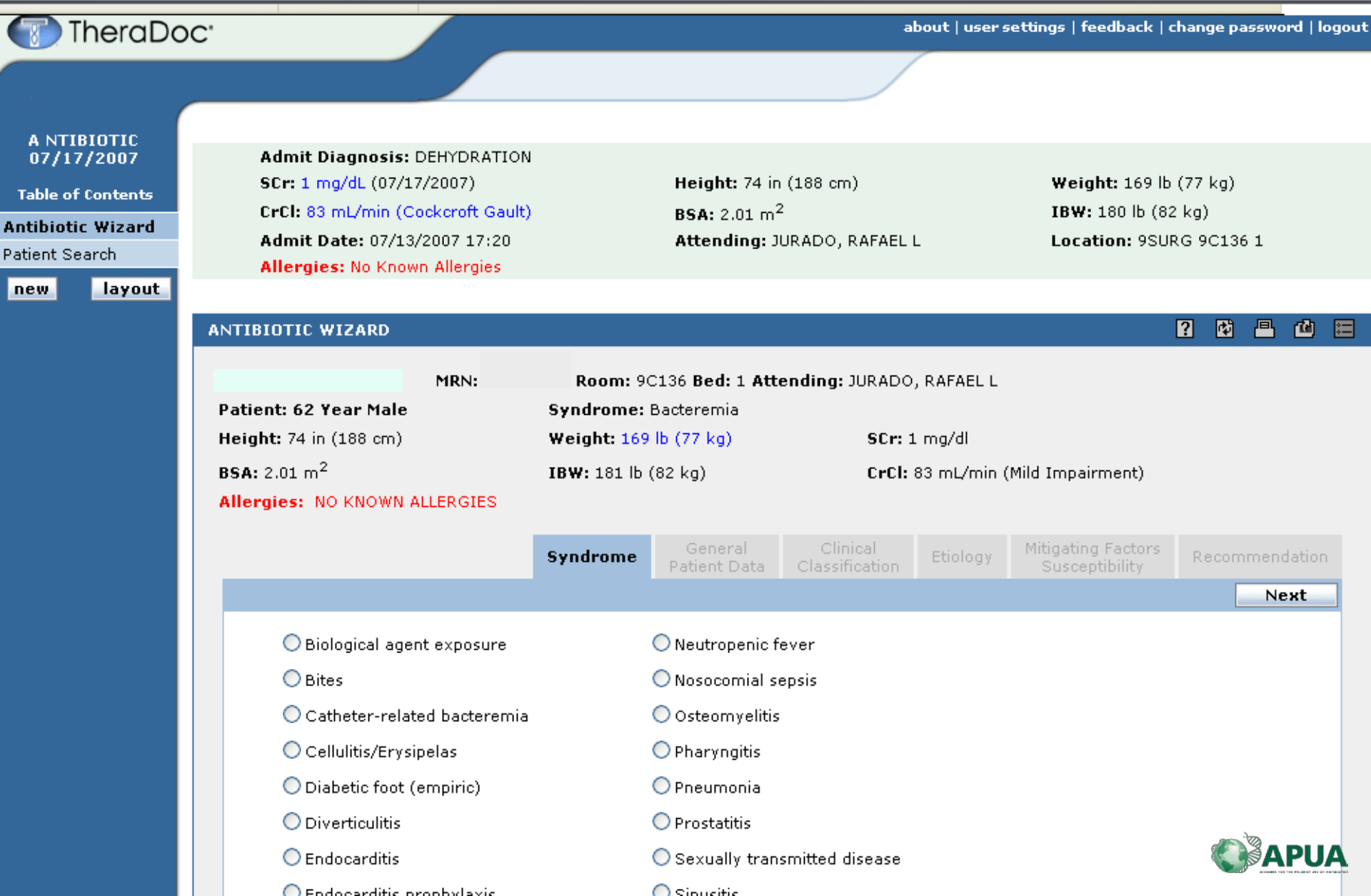
Computerized Decision Support

- Computerized Protocols

  - ✓Dynamic
  - ✓Explicit
  - ✓**Patient-specific**
  - ✓**Point-of-care**

Annals Int Med 2000;132:373-83

Theradoc's Antibiotic Wizard



Antimicrobial De-escalation

What is it actually??

- *Is the patient actually infected at all?*
- *Is the patient actually infected with bacteria?*
- *How long do you need to treat with antimicrobials?*

Antimicrobial De-escalation

Is the patient actually infected with bacteria?

- Pathogens are isolated in a minority of cases where infection is suspected and antibacterial antibiotics are used.

Gaynes R, et al. A Multicenter Study on Optimizing Piperacillin Tazobactam Use: Lessons on Why Interventions Fail. *Infect Control Hosp Epidemiol* 2009; 30:794-6

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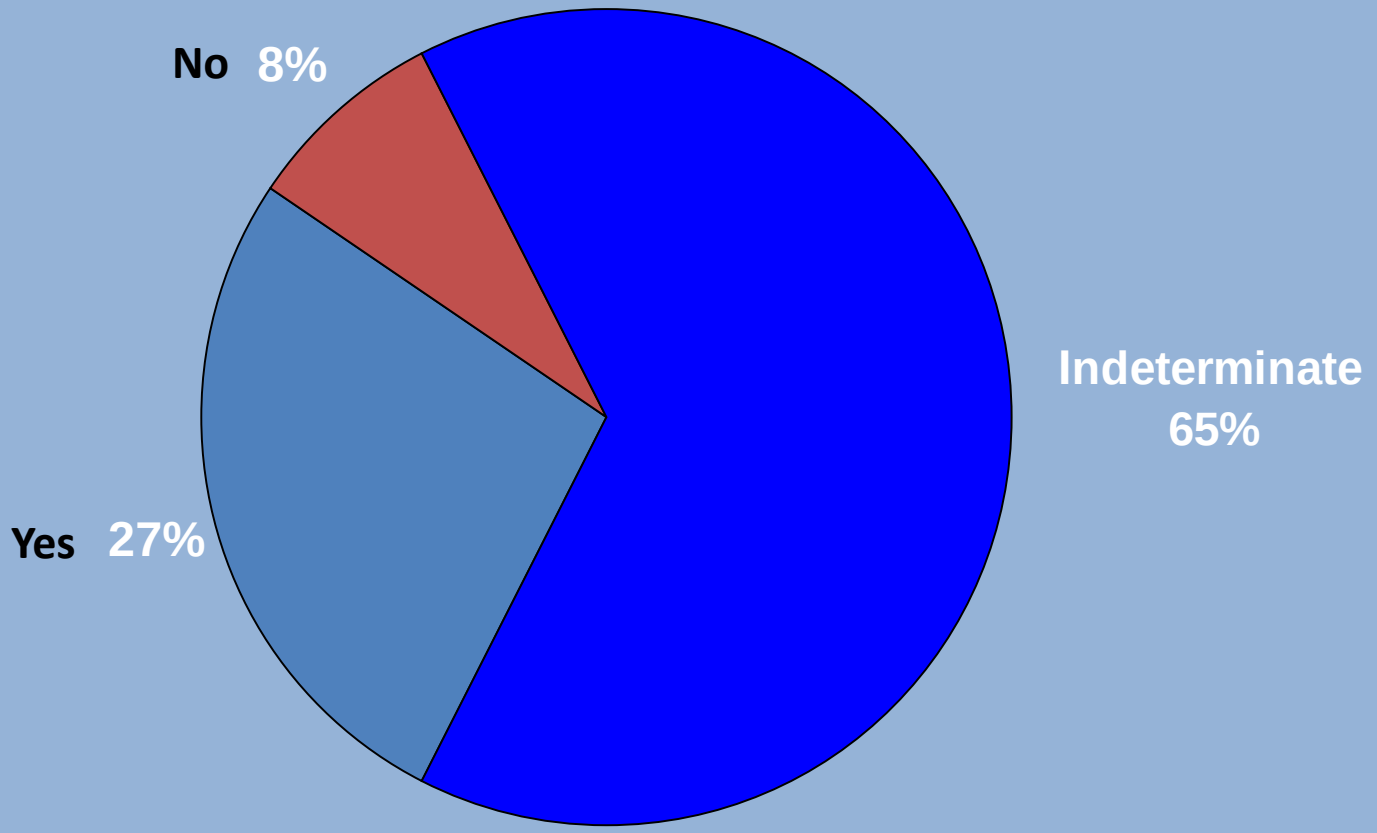
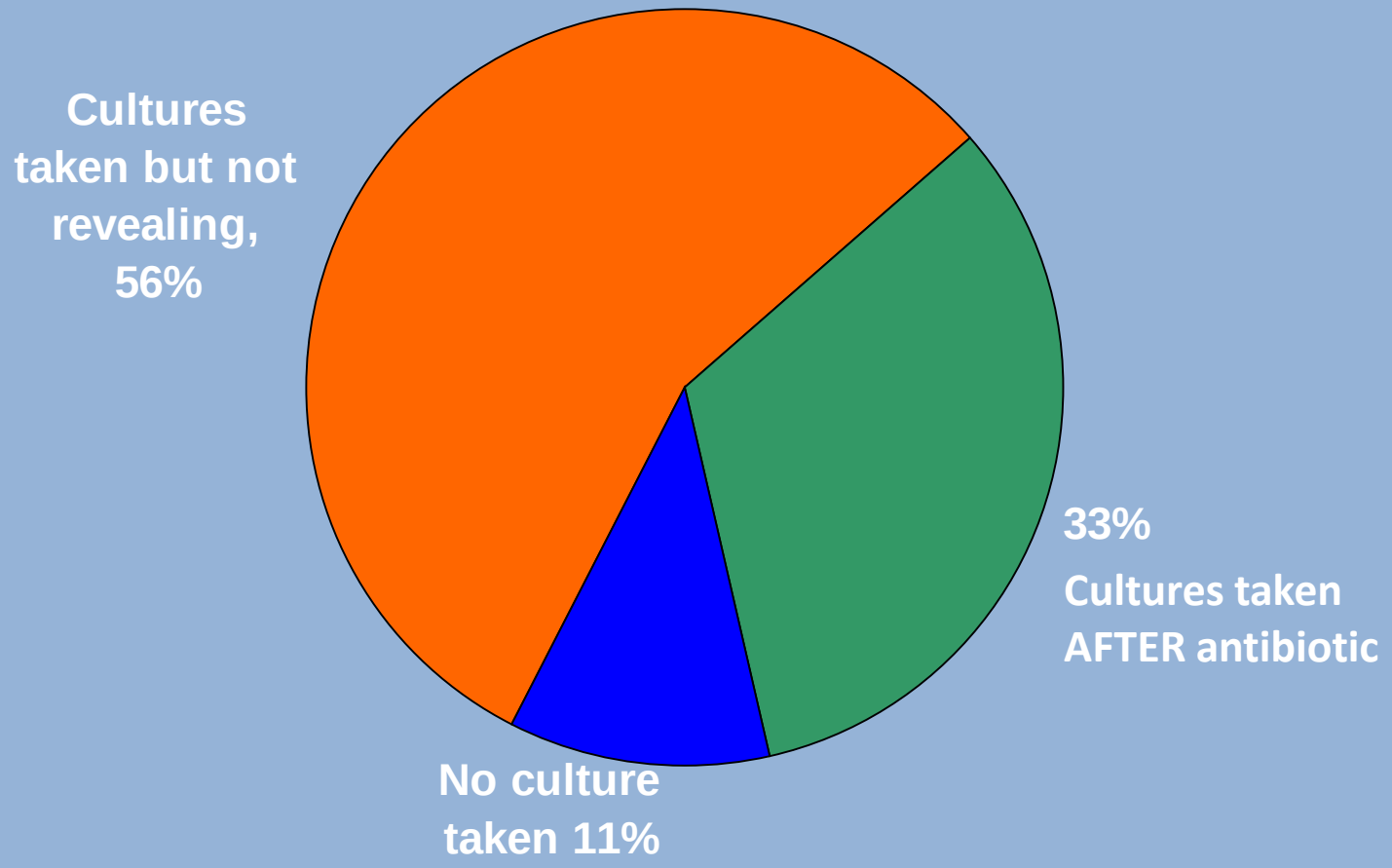
Was therapy altered at 72 hrs using microbiology cultures when Pip/Tazo was appropriate empiric therapy?
(N=135 cases)



Gaynes R, et al. *Infect Control Hosp Epidemiol* 2009; 30:794-6

Why empiric therapy was NOT altered at 72 hrs

(N=88 Indeterminate cases)



Antimicrobial De-escalation

Is the patient actually infected with bacteria?

Use of BIOMARKERS

- The biomarker, Procalcitonin, is a precursor of calcitonin and is rapidly released in blood in presence of an infection.

- Antimicrobial therapy has been discouraged with low levels of procalcitonin for lower respiratory tract infections with no difference in outcome but significant reductions in antibiotic use.*

* Gilbert D. Clin Infect Dis 2011;52(Suppl 4):S346-350

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Antimicrobial De-escalation

Is the patient actually infected with bacteria?

Table 1. Randomized Controlled Trials That Used Procalcitonin (PCT) Serum Levels to Guide Antibiotic Therapy in Adult Patients With Respiratory Tract Infections

Use of Procalcitonin

Reference	Clinical syndrome(s)	Study site (location)	No. of evaluable patients		Percentage of patients who started antibiotic therapy		Duration of antibiotic therapy, mean days	
			Control group	PCT group	Control group	PCT group	Control group	PCT group
[21]	Pneumonia, AECOPD, acute bronchitis	Emergency department (Basel, Switzerland)	119	124	77.3	44.4	12.8	10.9
[22]	Community-acquired pneumonia	Emergency department (Basel, Switzerland)	151	151	99	85	12	5
[23]	AECOPD	Emergency department (Basel, Switzerland)	106	102	72	40	...	...
[24]	Rhinosinusitis, tonsillitis, pharyngitis, acute otitis media, tracheobronchitis, AECOPD, community-acquired pneumonia	General practices at multiple outpatient facilities (Switzerland)	226	232	97	25	7.1	6.2
[25]	Community-acquired pneumonia	Hospitals (Denmark)	107	103	79	85	6.8	5.1
[26]	Acute bronchitis, AECOPD, community-acquired pneumonia	Emergency departments at 6 hospitals (Switzerland)	688	671	87.9	75.4	3.8	3.2

NOTE. AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Gilbert D. *Clin Infect Dis* 2011;52(Suppl 4):S346-350

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Antimicrobial De-escalation

How long do you need to treat with antimicrobials?

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Gilbert D. *Clin Infect Dis* 2011;52(Suppl 4):S346-350

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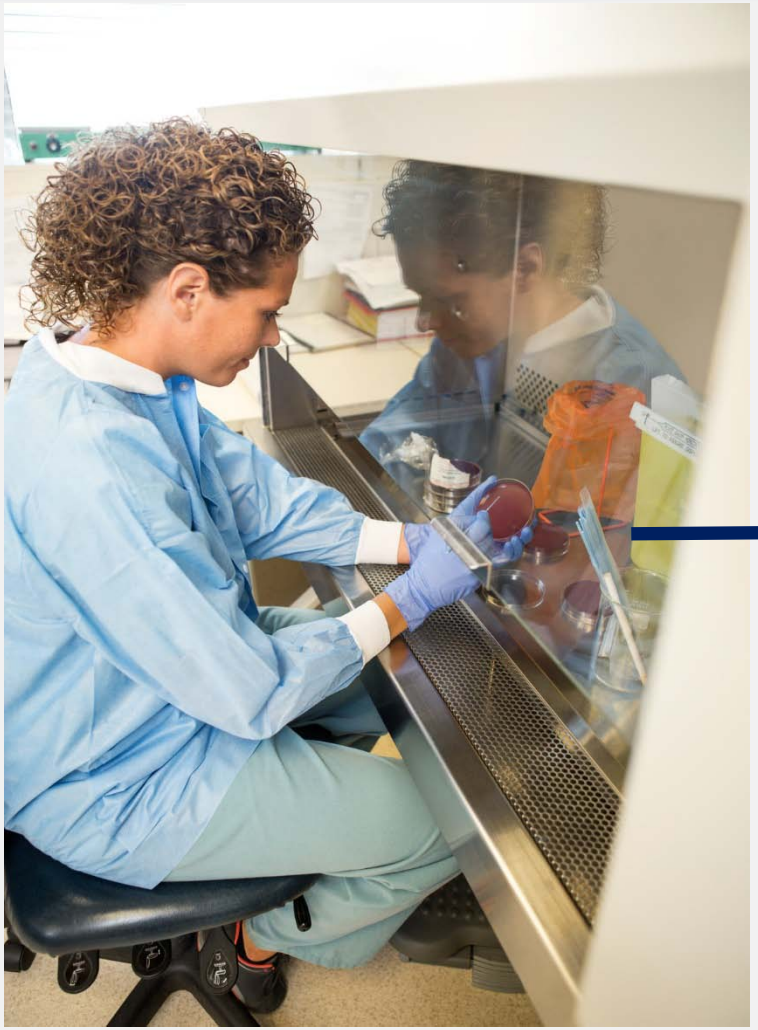
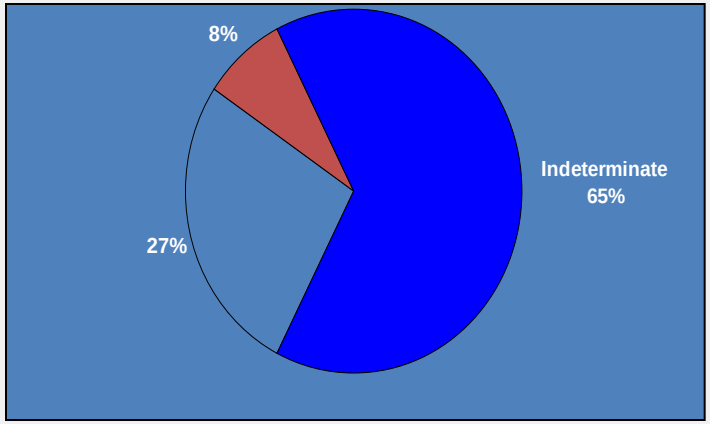
Is the patient infected with bacteria?

More help is on the way…

Illustration by Arthur Shilstone

Rapid diagnostics for identifying and characterizing the pathogen





Rapid Antigen Assays

Test	Technology	Disease/agent detected	Test sample	Detection time
Urinary antigen test	Immunochromatographic membrane test (ICT) for pneumococcal antigen	Community-acquired *S. pneumoniae* in adults	Urine	15 mins
		Streptococcal meningitis	CSF	
Urinary antigen test	Immunochromatographic membrane test (ICT) for *Legionella pneumophila* sero-group 1 antigen	*Legionellla pneumophila (Legionnaire's disease)*	Urine	15 mins
Strep A	Immunochromatographic assay	*Streptococcus pyogenes* Group A (pharyngitis)	Throat swab	<10 mins
Staph aureus	Immunochromatographic assay	*S. aureus* bacteraemia	Blood with clustered cocci	30 mins
MRSA	Immunochromatographic assay for penicillin binding protein 2a (PBP2a)	Methicillin-resistant *S. aureus*	Plated cfu	6 mins
C. difficile	Rapid Enzyme Immunoassay cartridge	Toxin-positive *C. difficile*	Feces	<30 mins
Influenza	Immunochromatographic assay for influenza A & B nucleoproteins	*Influenza A, influenza B*	Nasal swab	15 mins

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Antimicrobial De-escalation

Can the broad-spectrum antimicrobials be narrowed?

Multiplex polymerase chain reaction (PCR) panels for *S. pneumoniae, Legionella pneumophila, Haemophilus influenzae, Streptococcus pyogenes, Mycoplasma pneumoniae*, and *Chlamydohila (Chlamydia) pneumoniae* were compared with conventional cultures.*

- The sensitivity and specificity varied from 93% to 100%
- Multiplex PCR Panels can also detect viruses

*Morozumi M, et al. J Clin Microbiol 2006; 44:1440–6.

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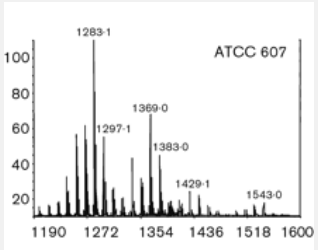
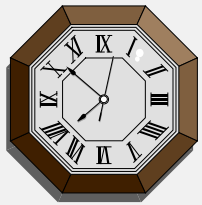
Antimicrobial De-escalation

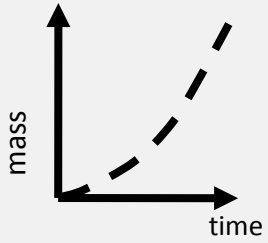
Rapid Microorganism Identification by MALDI-TOF*



Data analysis
– organism identification

Detector





Time of Flight Mass Analysis
(Mass to charge ratio)

Voltage Potential

Desorbed sample and
matrix ions

Pulsed Laser Beam
N_2 50 Hz variable repetition

UV-adsorbing matrix
mixed with sample

Sample holder

*Matrix-assisted laser desorption/ionisation-time of flight

Antimicrobial De-escalation

Can the broad-spectrum antimicrobials be narrowed?

Disadvantages of broad-spectrum antibiotics:

- Interrupt or destroy normal flora of the host
  - Opportunistic pathogens, e.g., *Candida* spp.
  - Superinfection, e.g., *Clostridium difficile*
- Development of Resistance
- Cost

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Remember: Antibiotic use is NOT always benign!!

Antimicrobial De-escalation

How long do you need to treat with antimicrobials?

Few studies or guidelines illustrate the required lengths of therapy for bacterial infections.*

- Traveler's Diarrhea (3 days)
- Meningitis (7-21 days)
- Lower extremity infections in diabetics (1-6 wks)

CAP: "*We are not aware of any controlled trials that have specifically addressed the questions of how long pneumonia should be treated.*"**

* Rice L. *Clin Infect Dis*. 2008;46:491-6
** Mandell LA, et al. *Clin Infect Dis* 2007;44 (Suppl 2):S27-72.

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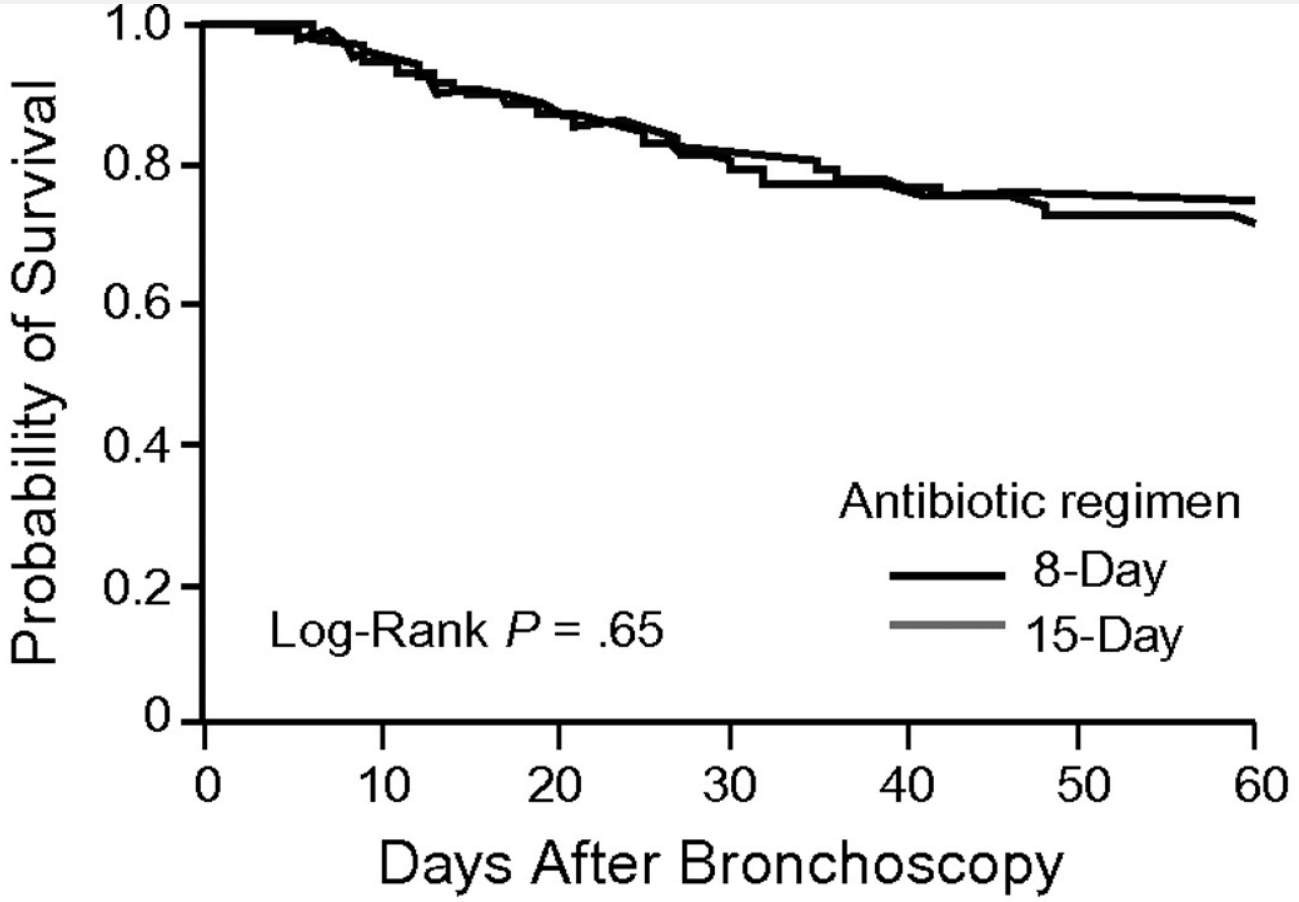
Probability of survival for 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia

(Kaplan-Meier estimates)



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

Kollef M H et al. *Clin Infect Dis*. 2011;53:S33-S55

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RCTs on Antimicrobial Duration in Typical Infectious Diseases in Adults

Type of Infection	Number of Studies	Short vs. Long Duration (days)	Outcome
Community-acquired pneumonia	9 studies	5 vs. 7-10 days	No difference or non-inferiority in all studies
Ventilator-associated pneumonia	1 study	8 vs. 15 days	No difference in mortality
Infective endocarditis	1 study	14 days with combination Rx vs. 28 days w/single Rx	No difference in clinical cure rate and microbiological eradication
Acute pyelonephritis	4 studies	5-7 days vs. 10-14d	No difference or non-inferiority in all studies

Adapted from Hayashi Y, Peterson D. *Clin Infect Dis.* (2011) 52 (10): 1232-1240.

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Optimizing Antibiotic Use

1. *Is the patient infected with bacteria?*
2. *Can the broad-spectrum antimicrobials be narrowed?*
3. *How long do you need to treat with antimicrobials?*

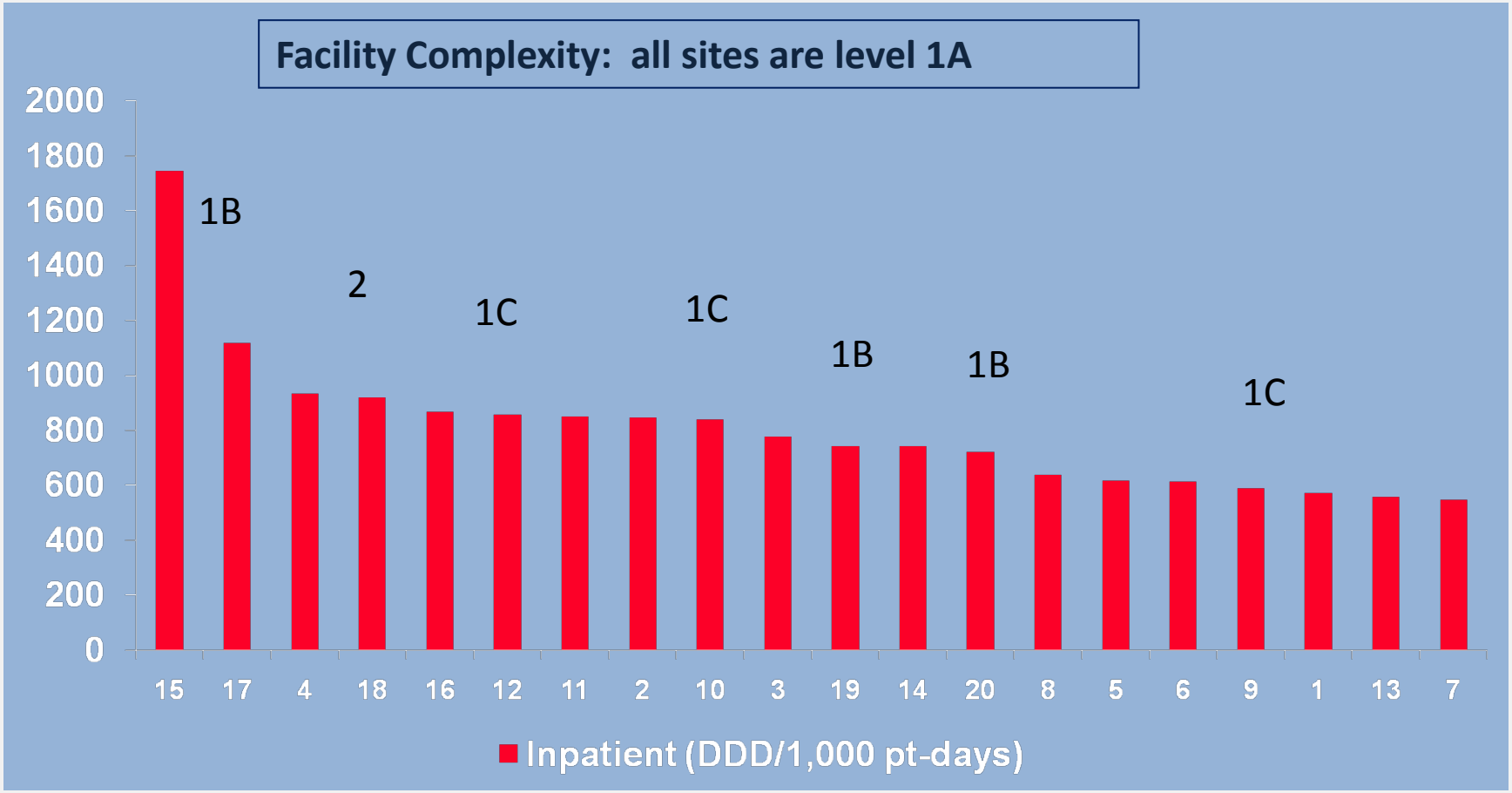
Antimicrobial Agents: Overriding Premise for Use

- Because of the potential to develop resistance, antimicrobials are fundamentally different from all other classes of pharmacotherapy

- Antimicrobials should be viewed as medical treasures and a precious resource

THE END

Finding Benchmarks:
Inpt Antibiotic Use Per Pt - FY2009
20 Largest VA Hospitals



Antibacterial Antibiotic Drug Discovery

Since the beginning of 2008, the US Food and Drug Administration has approved only 2 new antibacterial antibiotics:

- Telavancin
- Ceftaroline

“Why no antibiotic drug discovery?”

Why no antibiotic drug discovery?!

No Guarantee of Success

Finding new antimicrobial compounds, particularly new classes of antibiotics, has always been exceedingly difficult,

e.g., penicillin

Why no antibiotic drug discovery?!

Fewer pharmaceutical companies are looking

- Due to consolidations, in the last 25 years, the number of pharmaceutical companies performing drug discovery has dropped from 70 to 12.

- Only **6** companies are working on antibiotic drug discovery!

Why no antibiotic drug discovery?!

Lack of profitability:

The profitability of any drug can be expressed as its 'NPV_R': the return in future dollars after adjustment for the investment and any lost income, expressed as the # of millions of dollars

- Antibiotics NPV_R of 100
- Oncologic drugs NPV_R of 300
- Neurologic drugs NPV_R of 720
- Musculoskeletal drugs NPV_R of 1150

Stewart JJ *et al.* Putting a price on biotechnology. *Nat Biotechnol* 2001;19:813-817

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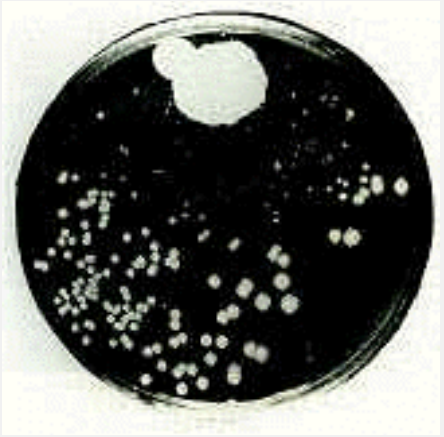
Why no antibiotic drug discovery?!

Need for Constant Marketing

Need for antibiotic marketing works against pharmaceutical efforts in antibacterial antibiotics since these drugs must be ‘marketed’ to prescribers each time an infection occurs. In contrast, an anti-hypertensive or lipid-controlling drug usually requires one-time marketing since they are often lifelong agents.

Penicillin's Discovery and Production

- In 1929, Alexander Fleming found a *Penicillium* mold growing a on plate of staphylococci, but he could not purify the compound.

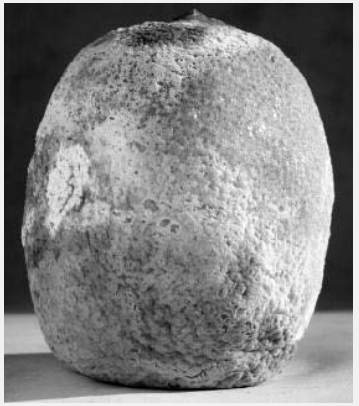


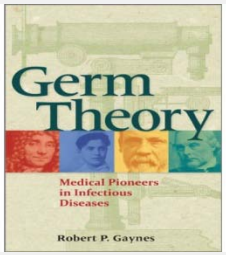
- A team of Oxford scientists finally did purify penicillin 10 years later, but had to go to the U.S. for large-scale production.

- In 1941, two members of the Oxford team headed to a U.S. agriculture station in Peoria, Ill where Charles Thom identified Fleming's strain as *Penicillium notatum*.

Penicillin Production

- Of 1,000 *Penicillium* strains in Charles Thom's collection, only 3 produced penicillin:
  - Fleming's strain
  - one in Thom's collection
  - a strain from a spoiled cantaloupe, which produced six times more than other strains and was the one used in large-scale penicillin production.





Gaynes R. Germ Theory: Medical Pioneers in Infectious Diseases. 2011, Washington, DC: ASM Press.

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