Antimicrobial Stewardship – To Whom Much is Given, Much is Demanded
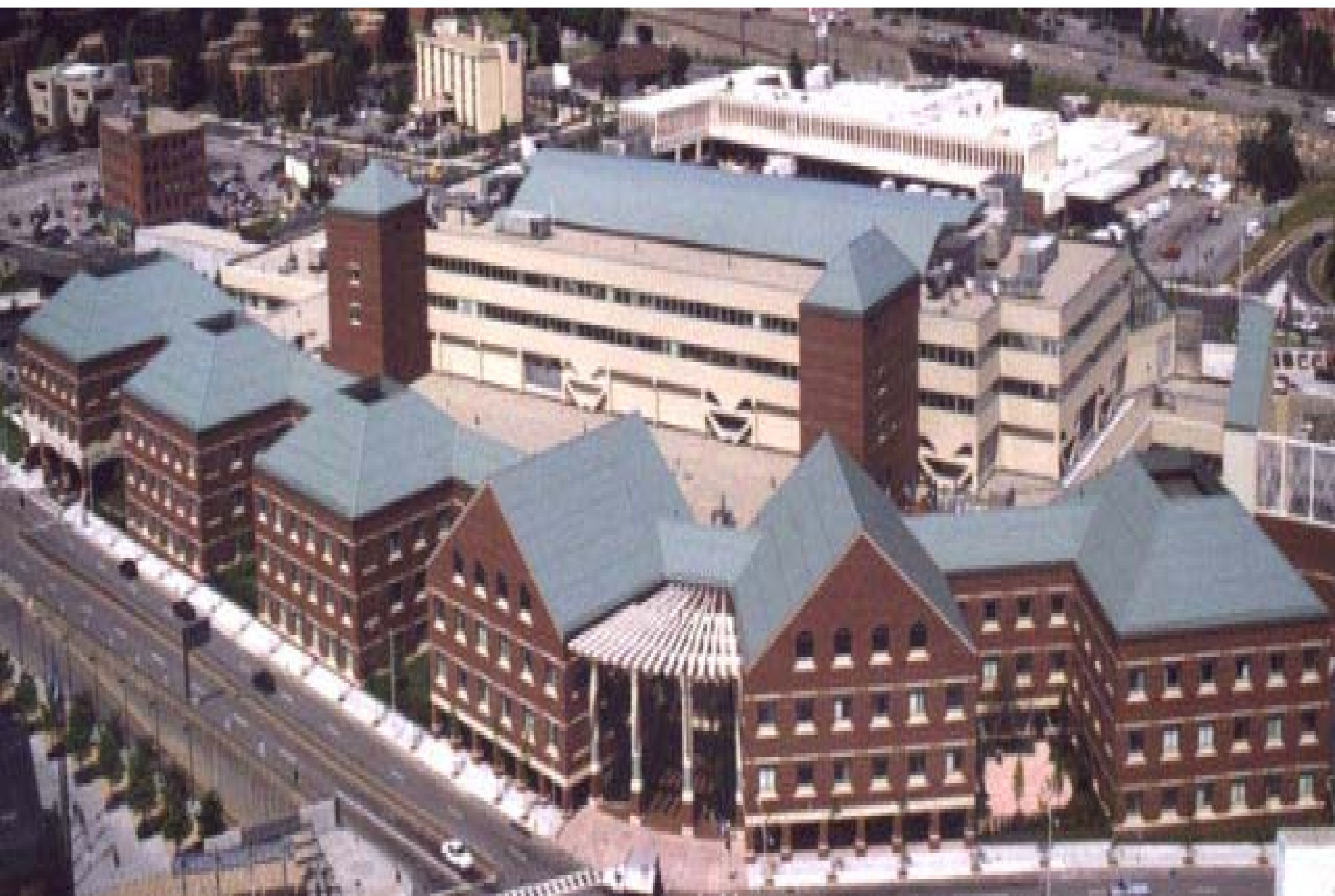
George M. Abraham, MD, MPH, FACP, FIDSA
Professor of Medicine, University of Massachusetts Medical School
Chair, Department of Medicine, Saint Vincent Hospital
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Chair, Infectious Disease Board, American Board of Internal Medicine

GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS*

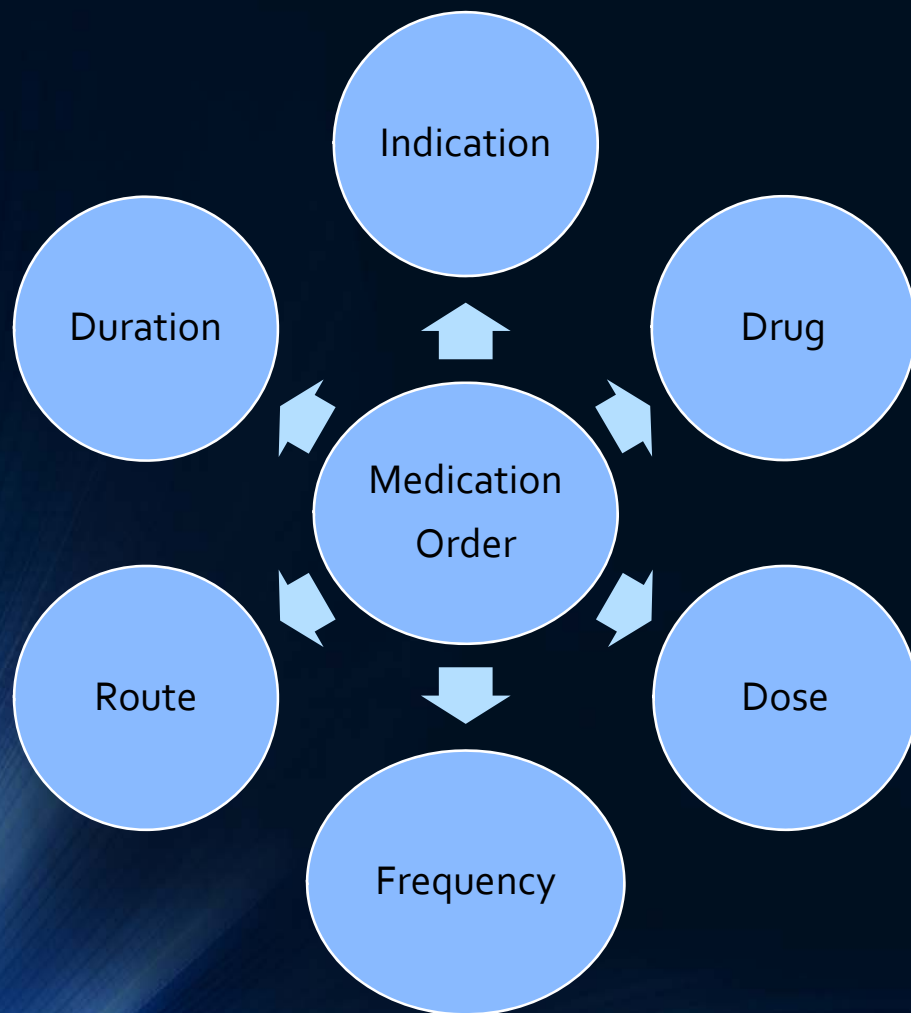## A Syndrome of Diagnostic Significance

Harold Jeghers, M.D.,† Victor A. McKusick, M.D.,‡ and Kermit H. Katz, M.D.§

GRAPES

Or a microbiologist secretly dressing a child up as gram positive cocci in clusters (Staphylococci)

Concepts of Antimicrobial Stewardship

Indication

Drug

Duration

Medication Order

Route

Dose

Frequency

Antimicrobial Stewardship Goals
- Primary
  - Maximize effectiveness
  - Minimize adverse events
  - Minimize development of resistance
- Secondary
  - Cost-savings/cost-avoidance

Barlam TF, et al. *Clin Infect Dis.* 2016;62(10):e51-e77.

Antibiotic Overuse and Deaths from Resistant Organisms

CDC: Approximately 50% of antimicrobials used in the inpatient setting are unnecessary

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses,

23,000 deaths

*bacteria and fungus included in this report

Local, National, and **GLOBAL PROBLEM!**

Centers for Disease Control and Prevention. Get smart: Know when antibiotics work. 2016.
Centers for Disease Control and Prevention. National strategy to combat antibiotic-resistant bacteria. 2014.

Antibiotic Pipeline and Resistance

A PERFECT STORM[1]

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

COMPANIES RESEARCHING ANTIBIOTICS: **18**

COMPANIES RESEARCHING ANTIBIOTICS: **4**

Antibiotic-resistant (%)*

Number of antibiotics approved
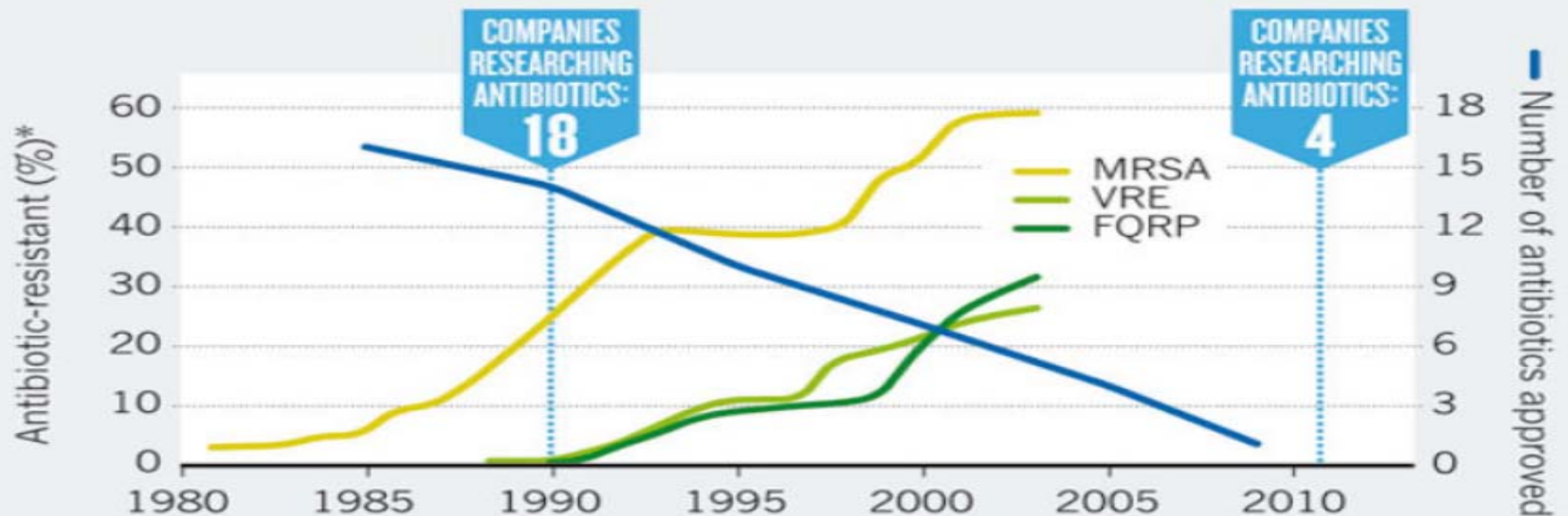
— MRSA
— VRE
— FQRP

*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

IDSA. Incentives for Antibiotic Development. 2016. Available at www.idsociety.org/AR_Policy.

How do we choose an antimicrobial regimen?

- Know the anticipated microbiology when starting empiric therapy

- De-escalation of therapy once a microbiologic diagnosis is made

Duration of therapy

- Synergistic antimicrobial therapy

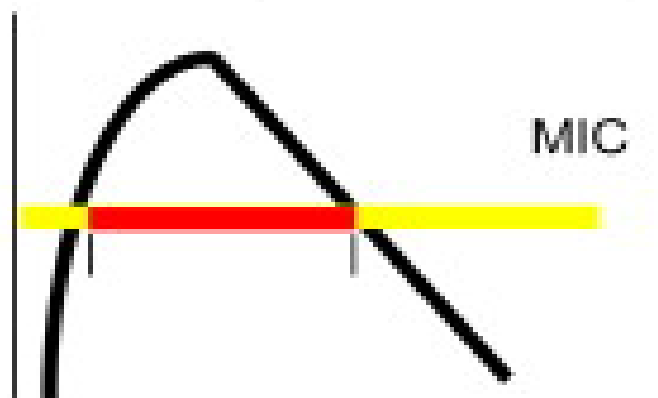- Pre-operative antimicrobial use/surgical skin preparation

- Chronic suppressive therapy in the setting of prosthetic devices

- Antimicrobial selection pressure/surveillance of resistance

Pharmacokinetic/Pharmacodynamic Profiles of Antimicrobials
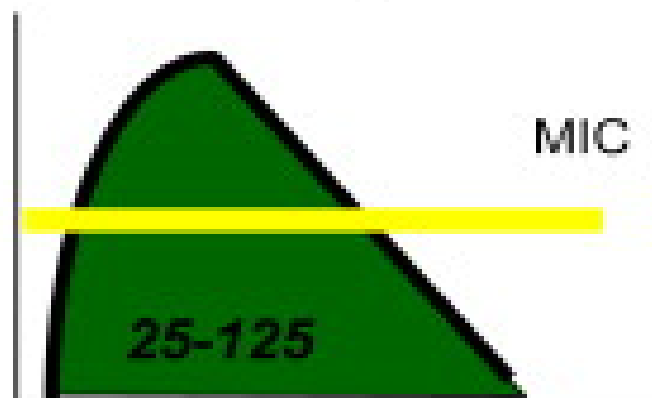
Time>MIC
time-dependent activity

MIC

- Penicillins
- Cephalosporins
- Macrolides
- Clindamycin

Optimal profile:
Free serum antibiotic level exceeds
MIC for at least 40-50% of dosing interval

AUC/MIC
concentration-dependent activity

MIC

25-125

- Quinolones
- Aminoglycosides
- Azithromycin
- Ketolides

Optimal profile:
Free serum AUC/MIC ratio at least:
25-30 for Strep. or other
gram-positive bacteria, and 125 for
aerobic gram-negative bacilli

Optimizing Antimicrobial Use

- Why should we worry about antibiotic treatment length?

- Primarily collateral damage that occurs with longer courses
  - Emergence of resistance
  - Infection with toxigenic strains of *Clostridioides difficile*
  - Increased cost (more an issue in the hospital but not inconsequential in the outpatient realm particularly in the Medicare population)

Potential strategies to reduce resistance

- **Blast them**
  - Derived from early observation that multiple antibiotics were effective at preventing emergence of resistance in *Mycobacterium tuberculosis*
  - Problematic in bacteria with bacteria with moderately complex resistance, as has been shown in *Pseudomonas aeruginosa* where fluoroquinolone use can select for imipenem resistance and in *Enterococcus faecium* where cephalosporin use can select for vancomycin resistance
  - This strategy has never been shown to reduce emergence of resistance

- **Fool them**
  - Antibiotic cycling or "crop rotation"
  - Attempts to reduce selection pressure
  - No compelling data to support this approach
  - "It is a bit like offering an alcoholic the choice to rotate beer, wine, gin and whiskey as a strategy to prevent liver disease."

Potential strategies to reduce resistance

- **Stop irritating them**
  - The most reasonable strategy – reduce use of antibiotics to the bare minimum necessary to safely treat patients with serious infections
  - Should reduce selective pressure and thereby reduce prevalence of resistance

- **3 points where selective pressure can be reduced**
  - Before treatment (treat only those truly infected)
  - During treatment (avoid combinations when one antibiotic will do)
  - At end of therapy (treat only as long as required to cure)

- **The first 2 points are difficult in the inpatient setting**
  - Lots of data show delayed treatment of bacteremia and pneumonia leads to poorer outcomes than early effective therapy.
  - The imperative for early effective treatment encourages the use of combination therapy

# Potential strategies to reduce resistance

- The most viable strategy for reducing antibiotic selective pressure is to treat infections only for as long as necessary.

- However, at the time Dr. Rice gave his Lecture (2007) the evidence to do so was poor, except for 1 – 3 day courses of uncomplicated UTI in females, single dose STD treatment, and shortening endocarditis due to *Streptococcus viridans* from 4 to 2 weeks by adding an aminoglycoside to beta-lactams.

What went wrong and why did it take 60 years to get back to short courses for CAP?

- Antibiotics were a marvelous discovery that led to an attitude that we had infections on the run and soon would have an antibiotic for every infection.

- Antibiotics are by and large remarkably safe drugs (aside from collateral damage) leading to their use by a wide variety of physicians who felt little obligation to limit therapy

- There was little incentive for Pharma to sponsor research on shorter lengths of therapy on what were big money making drugs

- Prolonged courses of antibiotics have been considered to be the solution to – rather than the cause of – resistance. CDC's "Get Smart" campaign advised patients to finish the "prescription even if you feel better." This is great in order to adequately treat infection but poor advice for preventing resistance.

How did we end up with 7 & 14 day courses? Constantine units

- Durations of antibiotic therapy for most bacterial infections are based on the fact that the week has 7 days in it.

- The modern week has 7 days in it because Roman Emperor Constantine the Great said so in 321 AD.
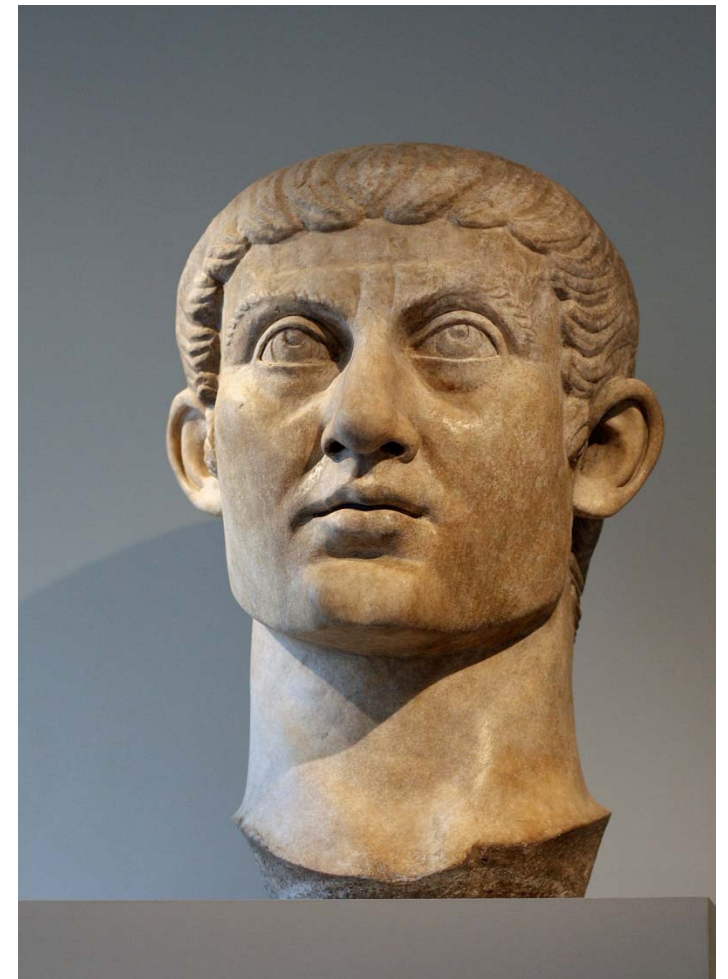
RCTs: short course vs traditional courses of antibiotics

- In every RCT published so far short-course therapy was just as effective as longer courses, often with better point estimates of clinical success, fewer adverse events and / or diminished emergence of resistance at the site of infection.

Community acquired pneumonia

- Uranga et al, JAMA Internal Medicine 2016;176:1257

    - Objective: to validate the IDSA/ATS guidelines for CAP
    - Multicenter, noninferiority trial at 4 teaching hospitals in Spain
    - 312 patients with CAP studied
    - Randomized at day 5 to intervention or control group
    - Intervention group had antibiotic stopped if they met criteria
    - Control group were treated as usual by their clinicians
    - Clinical success and CAP symptoms were identical at 10 and 30 days
    - Only 4 patients in the control group had 5 days of therapy
    - They observed most of their patients were clinically better by day 3.
    - Limitation: almost 80% of patients received quinolones so may not be generalizable to patients treated with beta-lactams

RCTs: short course vs traditional courses of antibiotics

Diagnosis	Number	Short (days)	Long (days)	Result
Community acquired pneumonia	9	3 or 5	7, 8, or 10	Equal
Hospital acquired / ventilator associated pneumonia	2	7-8	14-15	Equal
Complicated UTIs / pyelonephritis	6	5 or 7	10 or 14	Equal
Complicated / post-operative abdominal infections	2	4 or 8	10 or 15	Equal

RCTs: short course vs traditional courses of antibiotics

Diagnosis	Number	Short (days)	Long (days)	Result
Gram Negative bacteremia	1	7	14	Equal
Acute Exacerbation Chronic Bronchitis / COPD (metanalysis of 21 trials)	1	≤ 5	≥ 7	Equal
Acute Bacterial Skin and Skin Structure Infections (Cellulitis / Major abscess)	3	5-6	10	Equal
Chronic Osteomyelitis	1	42	84	Equal
Empiric Neutropenic Fever	1	Afebrile & stable 72 hrs	Afebrile & stable 72 hrs and ANC > 500	Equal

Given all this great data, how are we doing?

Macheda et al. J Antimicrob Chemother 2018;73:1084.

- Survey of 866 clinical microbiologists, ID physicians and members of antimicrobial stewardship teams in 56 countries

- Only 1 in 3 recommended short-course regimens

Who is prescribing short course regimens?

Fernandez-Lazaro et al. Clin Infect Dis Jan 2019

- Retrospective cohort analysis of family physicians in Ontario, Canada, between 1 March 2016 and 28 February 2017.

- The primary outcome was proportion of prolonged antibiotic course prescribed, defined as > 8 days of therapy.

- 10,616 family physicians included, prescribing a total of 5.6 million antibiotic courses. There was substantial inter-physician variability in the proportion of prolonged antibiotic courses (median 33.3%, interquartile range 21.9-47.2%, interdecile range 13.5-60.3%).

Who is prescribing short course regimens?

Fernandez-Lazaro et al. Clin Infect Dis Jan 2019

- In the multivariable regression model, later physician career stage, rural location, and a larger pediatric practice were significantly associated with greater use of prolonged courses.

- Prolonged courses were <u>more likely</u> to be prescribed by <u>late-career physicians</u> (adjusted odds ratio 1.48, 95% confidence interval 1.38-1.58) and mid-career physicians (1.25, 1.16-1.34) when compared to early-career physicians.
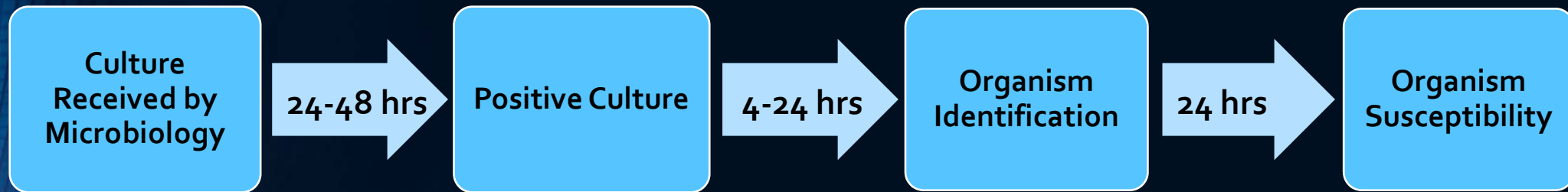
Shorter is Better

- Although the concept is 'new' there is now more than 25 years of RCT data across multiple different types of infections supporting the safety and efficacy of shorter-course antibiotic treatment regimens.

Antibiotic Resistance a Public Health Crisis

- Bad Bugs, No Drugs, No ESKAPE!

  - Call for increased antibiotic development, with incentives for production, to treat particularly resistant organisms
    - E: *Enterococcus faecium*, including VRE
    - S: *Staphylococcus aureus*, including MRSA
    - K: *Klebsiella pneumoniae*
    - A: *Acinetobacter baumanii*
    - P: *Pseudomonas aeruginosa*
    - E: *Enterobacter* species

Boucher HW, et al. *Clin Infect Dis.* 2009;48:1-12.

Organism Identification: Conventional Methods

Culture Received by Microbiology → **24-48 hrs** → Positive Culture → **4-24 hrs** → Organism Identification → **24 hrs** → Organism Susceptibility
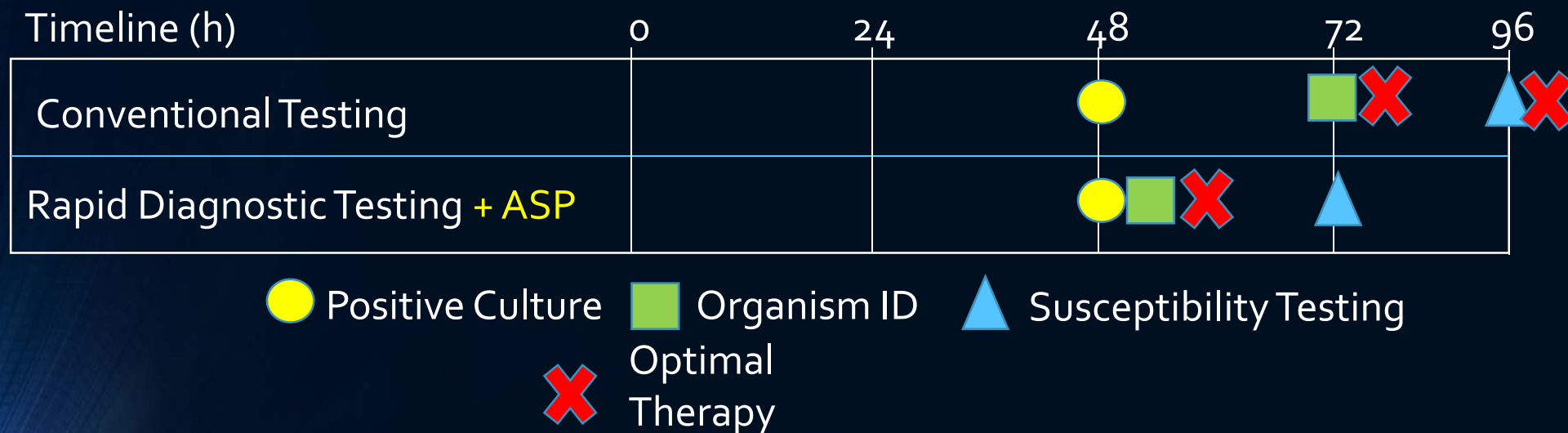
Current and Future Rapid Diagnostic Technologies

Organism Identification Technologies

- Peptide nucleic acid fluorescent in situ hybridization (PNA FISH)

- Polymerase Chain Reaction (PCR)

- Multiplex PCR

- Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF)
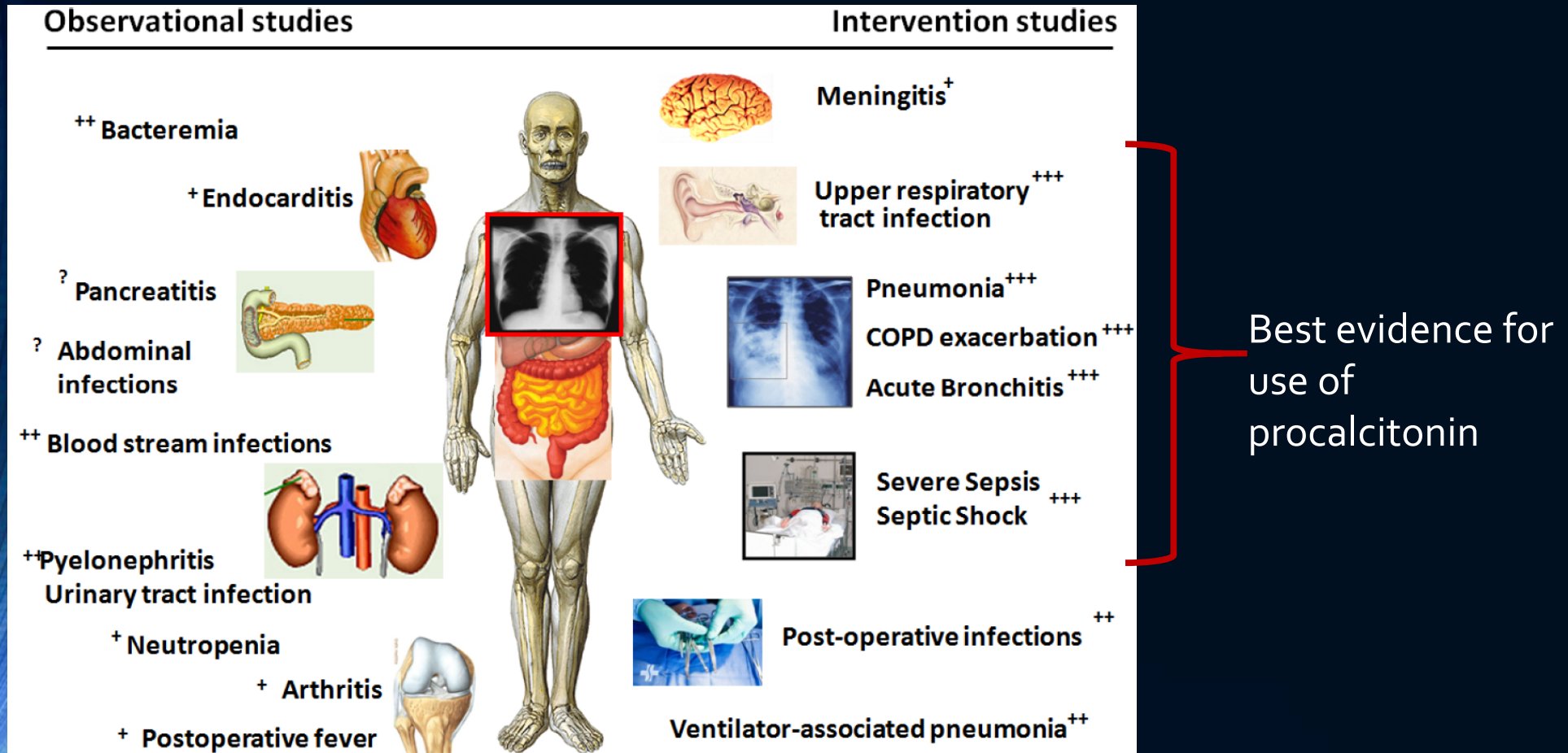
Bauer, et al. *Clin Infect Dis.* 2014;59(S3):S134-45.

Comparison of Rapid Diagnostic Technologies to Conventional Methods

Timeline (h)	0	24	48	72	96
Conventional Testing			⬤ (Positive Culture)	🟩 ❌	🔺 ❌
Rapid Diagnostic Testing + ASP			⬤ 🟩 ❌	🔺	

⬤ Positive Culture 🟩 Organism ID 🔺 Susceptibility Testing

❌ Optimal Therapy

RDT in the setting of stewardship decreased risk of death by 36%

NNT to prevent 1 death from bloodstream infection = 20

Banerjee, et al. *Clin Infect Dis.* 2015;61(7):1071-80.
Timbrook, et al. *Clin Infect Dis.* 2017;64(1):15-23.

Use of Biomarkers: Procalcitonin

Schuetz, et al. *BMC Medicine.* 2011;9:107.

Use of Biomarkers: Procalcitonin

- Ubiquitously produced upon exposure to endotoxin or other endogenous substances (IL-6, IL-1β, TNF-α)

- Specific biomarker for bacterial infection

- Release inhibited by mediators during viral infections

- Concentration rapidly increases within 6 to 12 hours of stimulation, and declines rapidly upon adequate control of infection

- Higher levels correlated with higher bacterial loads and severity of infection

- Elevated procalcitonin is not, on its own, sufficient evidence for diagnosis of an infection

- PCT may also be elevated following trauma or cardiac shock

- Infectious source, signs, and symptoms should always be assessed

Schuetz, et al. *BMC Medicine.* 2011;9:107.

Reasons for Antibiotic Overuse : Conclusions from 8 Focus Groups

Patient Concerns

- Want clear explanation
- Green nasal discharge
- Need to return to work

Physician Concerns

- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure
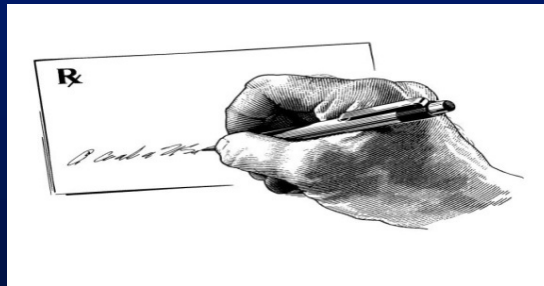
Antibiotic Prescription

Barden L.S. Clin Pediatr 1998;37:665

(Generation Gap)

The Global Crisis of Antimicrobial Production

The Return on Investment (ROI) on Antimicrobials

Risk-adjusted net present value (NPV_R)

(Return in future $$ after adjustment for the investment and any lost income expressed in millions of $$)

- *Oncologic agents NPV_R 300*
- *Neurologic agents NPV_R 720*
- *Musculoskeletal agents NPV_R 1125*
- *Hyperlipidemia and hypoglycemic agents NPV_R 1500*
- *Antibiotics NPV_R 100*

The GAIN Act

The Generating Antibiotic Incentives Now (GAIN) Act was passed in an attempt to incentivize the development of new antibiotics—a response to both growing rates of microbial resistance to antibiotics and a dearth of new antibiotic products in manufacturers' pipelines.

One of the GAIN Act's main provisions is Section 505E, which grants companies an additional five years of market exclusivity if they develop an antibiotic intended for a "qualified infectious disease."
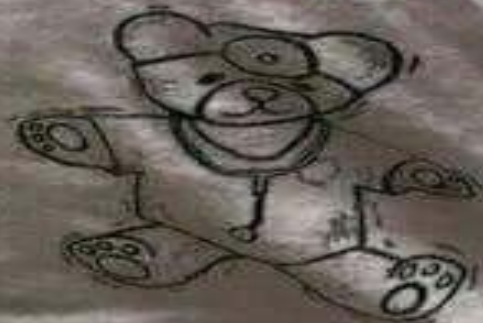
Make Antibiotics Great Again

DOING A GOOD JOB HERE

Is Like Wetting Your Pants
In A Dark Suit

YOU GET A WARM FEELING
BUT NO ONE ELSE NOTICES

Applause!!

QUESTIONS??