

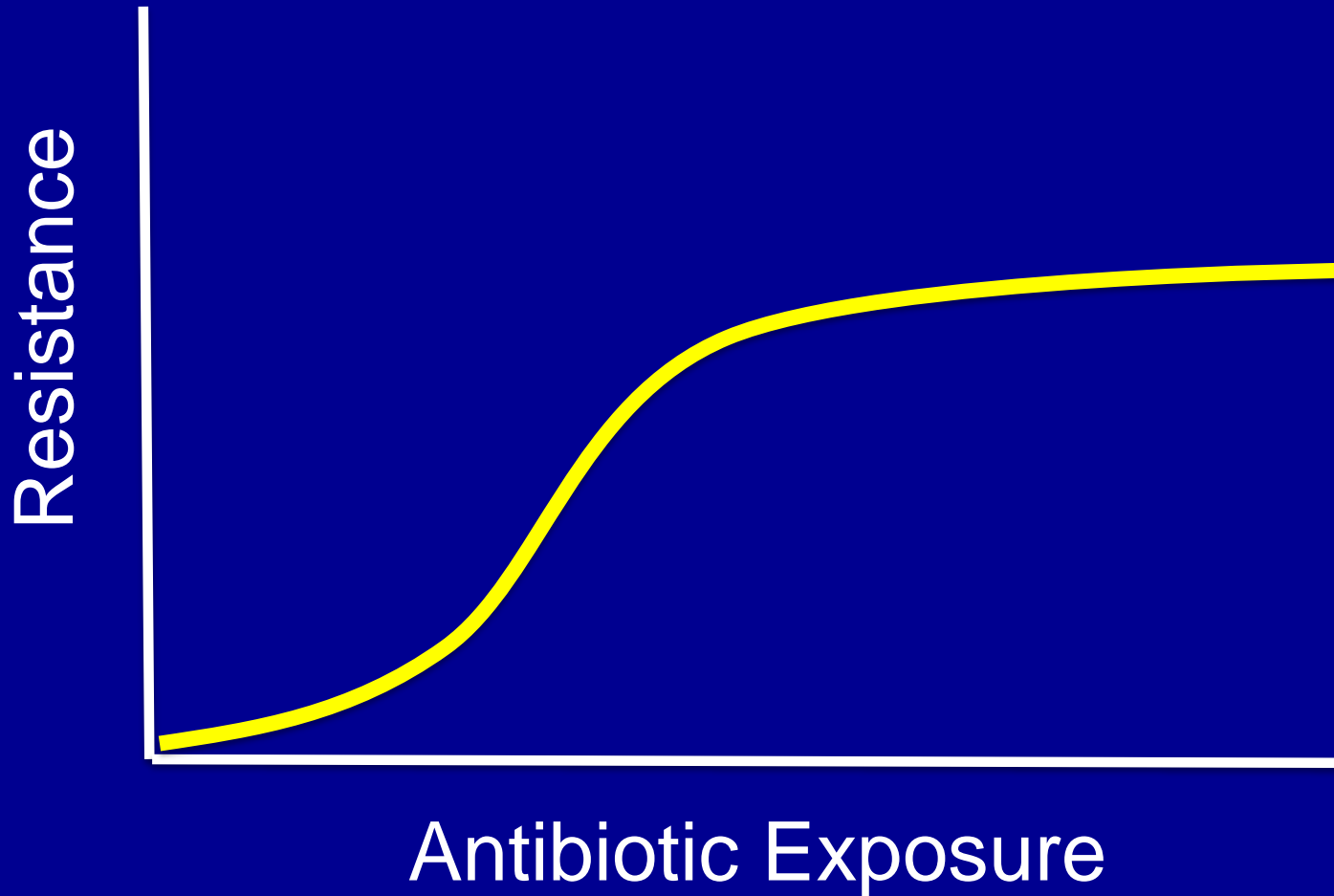
Antibacterial Resistance: Research Efforts

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Resistance Dose-Response Curve



Anti-Resistance Tool Box

- Prevention
- Immunotherapies
- Better use of antibiotics we have
 - Rapid diagnostics
 - Stewardship
 - Better treatment strategies

Rapid Diagnostics

The Promise of Rapid Diagnostics

- Minimize empirical therapy
- Allow precise targeting of pathogens
- Enable new drug discovery and development of narrow-spectrum agents
- Reduce selective pressure

Diagnosis of Chest Pain

- Electrocardiogram: 10 minutes
- Arterial blood gas: 5 minutes
- Chest radiograph: 30 minutes
- Troponin: 10 minutes

Diagnosis of Community-acquired Pneumonia

- Chest radiograph (non-specific): 30 minutes
- Microbiological testing (n=260)*
 - Sputum Gram-stain and culture (2-3 days)
 - Adequate sputum sample: 17% (82% positive)
 - Blood culture: 16% (2-3 days)
 - Urinary antigen: 20% (2-20 hours)
 - Pathogen identified in 60% overall

* Eur J Clin Microbiol Infect Dis 2005; 24:241.

Rapid Diagnostics

It is going to take a while to figure this one out.

- Host or the bug or both?
- Genotype versus phenotype?
- How rapid is rapid enough?

Introducing the Diagnost-o-matic[®]

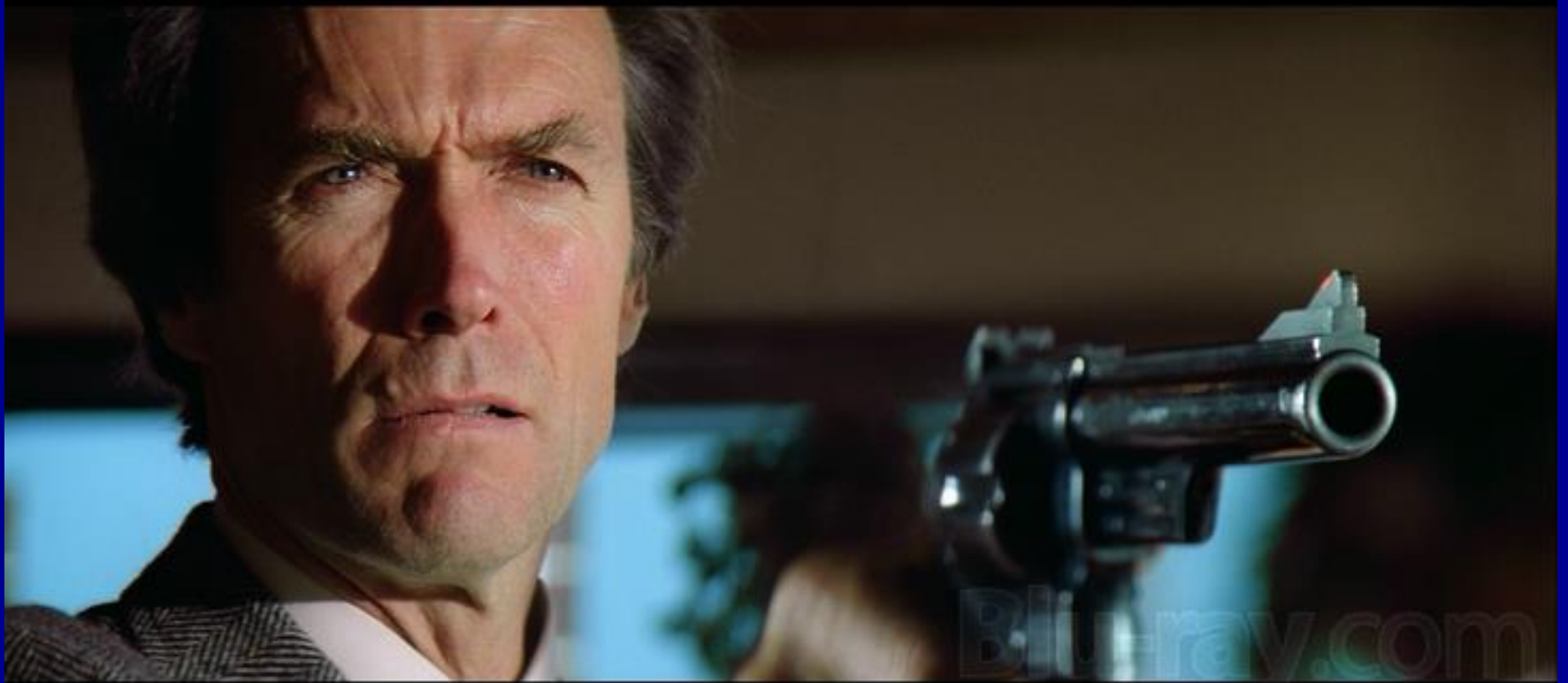
Antimicrobial Stewardship

Goals of Antimicrobial Stewardship

- To ensure effective treatment for patients with bacterial infection
- To reduce unnecessary use and minimize collateral damage

How best can we achieve these goals?

Go ahead. Make my day.



Name calling and wall building?



#&%@
you!

We shall never know all the good
that a simple smile can do.



Come to Jesus



Enlightenment





Dr. Neil Gaffin

The Valley Hospital and
Ridgewood Infectious
Disease Associates,
New Jersey

TO THE EDITOR—I sat at a Pharmacy and Therapeutics meeting and listened to an oncologist argue for formulary approval of an expensive new drug for advanced prostate cancer. As an infectious diseases specialist, I would never prescribe the medicine as the complexities of its use are beyond the scope of my expertise. As I considered this, I thought about the use of antimicrobials and the fact that all physicians can prescribe them. Not only prescribe them, but also determine the dosing, spectrum, and duration of treatment.

Stewardship

- A restrictive approach more effective than persuasive, at least for a while
- Decreases unnecessary antibiotic prescribing
- Microbial outcomes
 - In-patient: improved
 - Out-patient: no data
- Clinical outcomes
 - In-patient: mostly not worse
 - Out-patient: high quality lacking
- Insufficient cost data

Compelling Data that Are Lacking in Stewardship Trials

- Improved patient outcomes
- Improved bottom line

Better Strategies Better Trial Designs

Strategy Trials to the Rescue

Community-Acquired Pneumonia

- Empirical treatment, non-inferiority
 - Beta-lactam monotherapy
 - Beta-lactam–macrolide combination therapy
 - Fluoroquinolone monotherapy
- Funding by Netherlands Organization for Health Research and Development
- Outcomes
 - Difference in 90-day mortality of 0.6 to 1.9%
 - LOS: 6 days all regimens
 - Time to oral therapy 3-4 days all therapies

Postma, et al. N Engl J Med 2015;372:1312.

Strategy Trials to the Rescue

Intraabdominal Infection

- Open-label, non-inferiority study of standard of care (SOC) vs 4 days (4D) of antimicrobial therapy for cIAI
- Outcomes (SOC vs 4D)
 - SSI, recurrent infection, death: 58/260 (22.3%) vs 56/257 (21.8%)
 - SSI or recurrent infection with resistant organism: 9 (3.5%) vs 6 (2.3%)
 - Extraabdominal infections with resistant organism: 6 (2.3%) vs 2 (0.8%)

Scott Evans



- Senior Research Scientist, Harvard School of Public Health
- Director of the Statistical and Data Management Center for the Antibacterial Resistance Leadership Group
- Teaches clinical trials

RADAR: An Innovative Trial Design

- Response Addjusted for Days of Antibiotic Risk
- Global assessment of overall outcome based on benefits and harms
 - Uses outcomes to analyze patients instead of patients to analyze outcomes
 - Patients are ranked based on Desirability of Outcome Ranking (DOOR)

Strategy Trial for MRSA Bacteremia

- 3 treatment groups
 - 1) Daptomycin
 - 2) Ceftaroline
 - 3) Combo
- Hypothesis: 60% probability of better overall outcome with combo than with daptomycin or ceftaroline alone
- Outcomes: mortality, relapse/new metastatic foci of infection, adverse events, duration of bacteremia

DOOR for MRSA Bacteremia Trial

Score*	Alive	Relapse, etc	AEs
1	Yes	No	No
2	Yes	No	Mod
3	Yes	Yes	No
4	Yes	Yes	Mod
5	Yes	No	Severe
6	Yes	Yes	Severe
7	No	N/A	N/A

* Can further differentiate rank based on duration of bacteremia

DOOR FOR MRSA BACTEREMIA TRIAL

Pt.	Alive	Relapse	AE	Score	Days +	DOOR
A	Yes	No	No	1	3	1
C	Yes	No	No	1	5	2
F	Yes	No	Mod	2	1	3
D	Yes	Yes	Mod	4	7	4
E	Yes	No	Severe	5	3	5
B	No	N/A	N/A	7	N/A	6

Advantages of RADAR

- Clinical meaningful global outcomes
- Superiority design, reduced sample size, ITT analysis
- Incorporates competing risks, adverse events, adherence
- Minimizes impact of “administrative failures”

Concluding Thoughts

- Let drug companies bring antibiotics to market
- Delink the market from indications and strategies of medical need
 - Public funding for pragmatic clinical trials of serious infections caused by antibiotic resistant bacteria (ones that pharmaceutical companies will never do)
- Minor details to be worked out
 - Who sets the priorities (CARB?)
 - Who reviews proposals and allocates money (NIH?)
 - Who designs the trials and how are the trials conducted?

Meeting the challenge of resistance.....

We can do this with

- Improved diagnostics
- Stewardship, data driven, evidence-based, and mandatory
- Smarter strategies and trials design
- (and some new antibiotics wouldn't hurt either!)