Spectrum Health

Shorter is BETTER: The Changing Paradigm of Antibiotic Duration

Liam Sullivan, DO
Spectrum Health Medical Group
Infectious Disease

Disclosures

- No financial disclosures
- I love dogs
- I am a we bit Irish

Outline

01

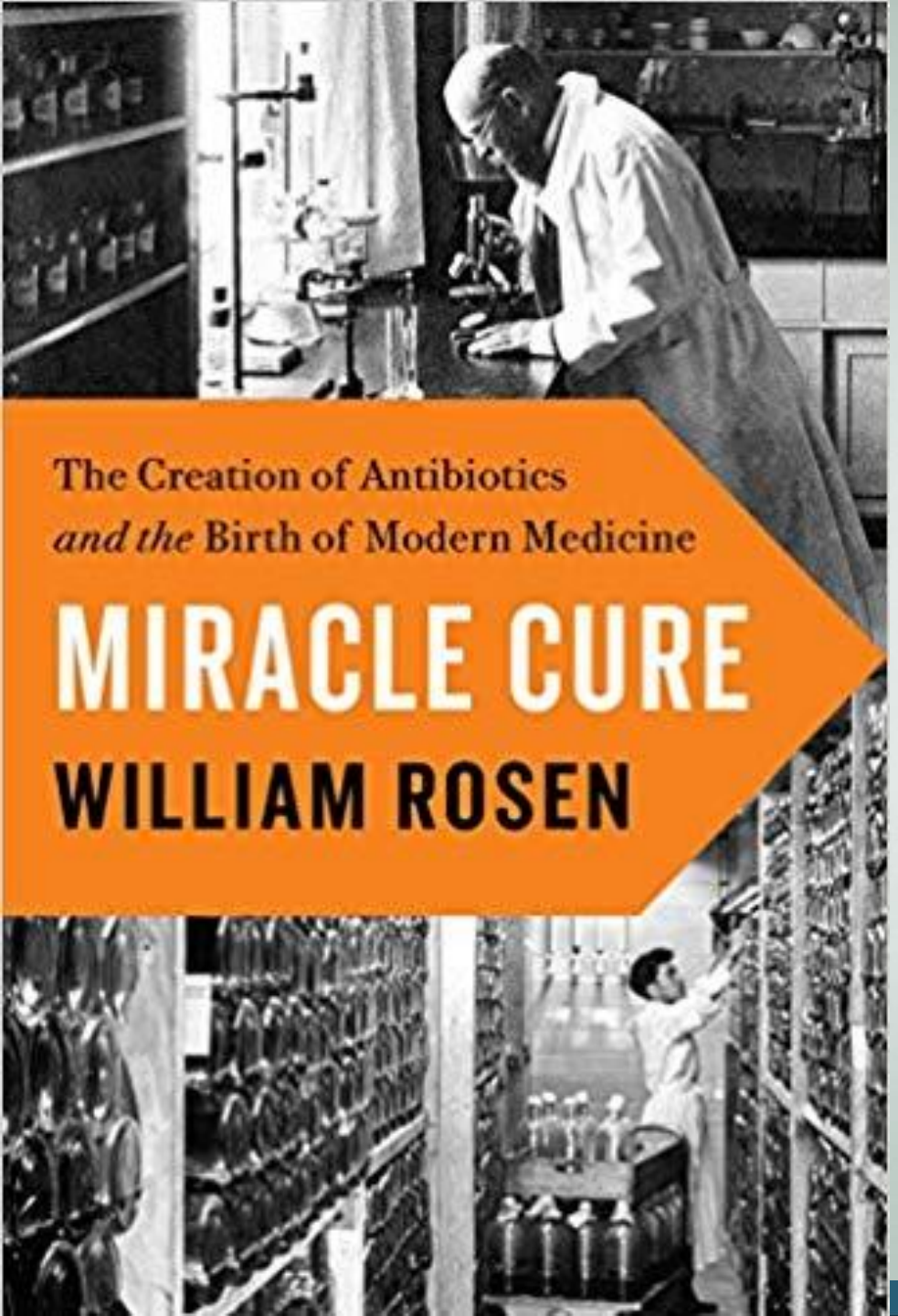
Review consequences of antibiotic overuse

02

Discuss reasons for prolonged antibiotic durations

03

Discuss evidence supporting shorter courses of antibiotics



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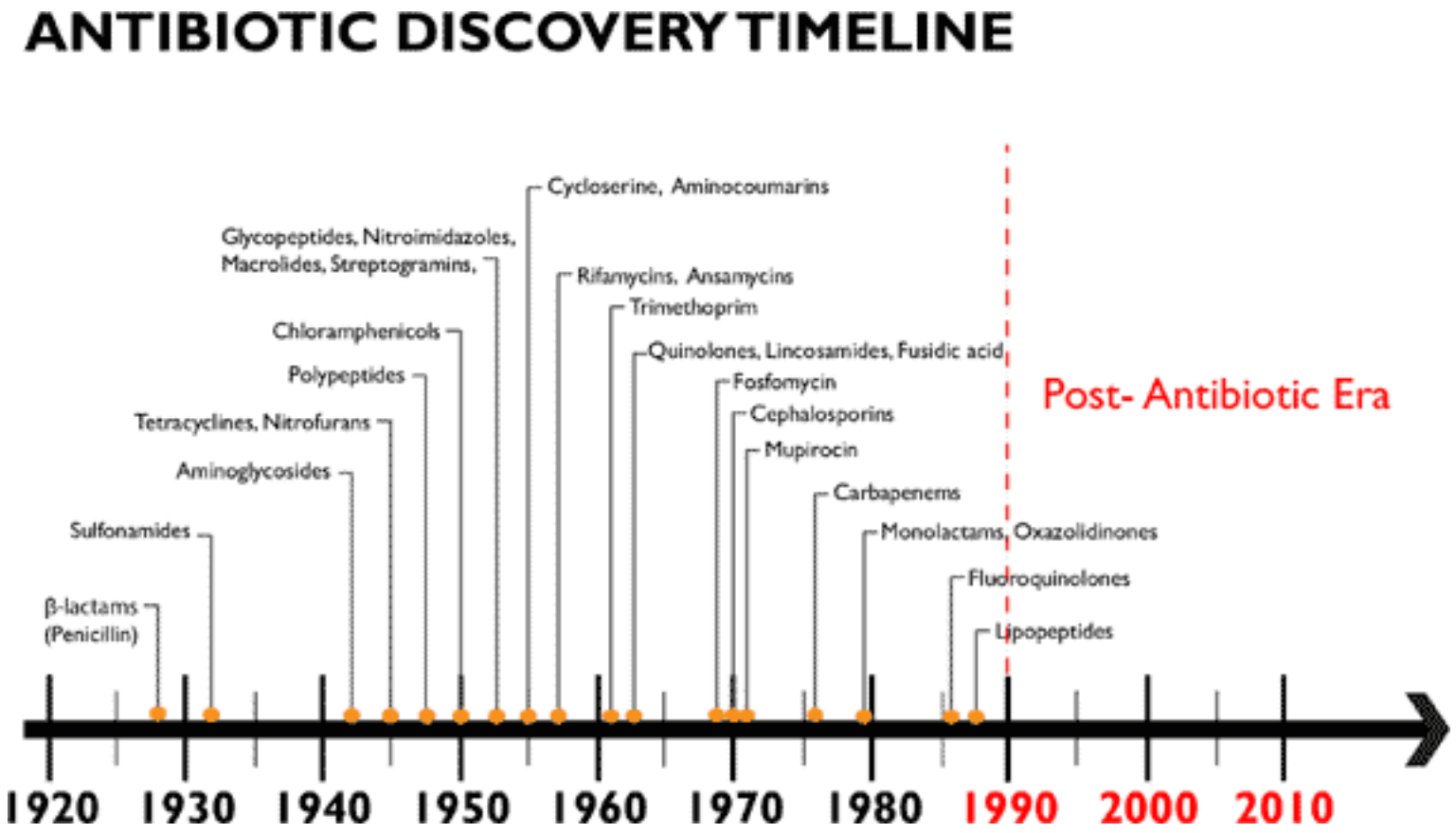
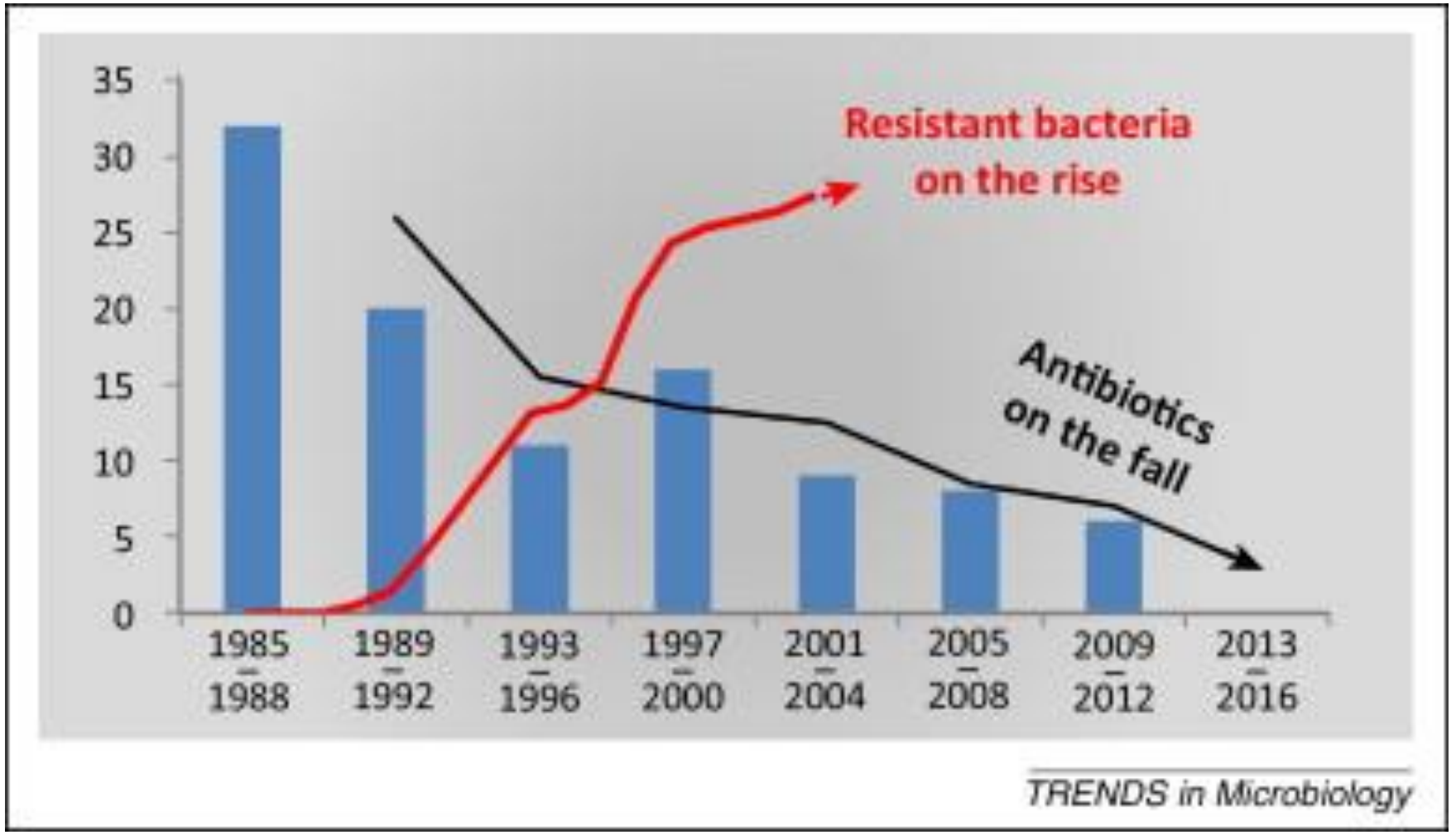
The Miracle

Golden Age of Antibiotics

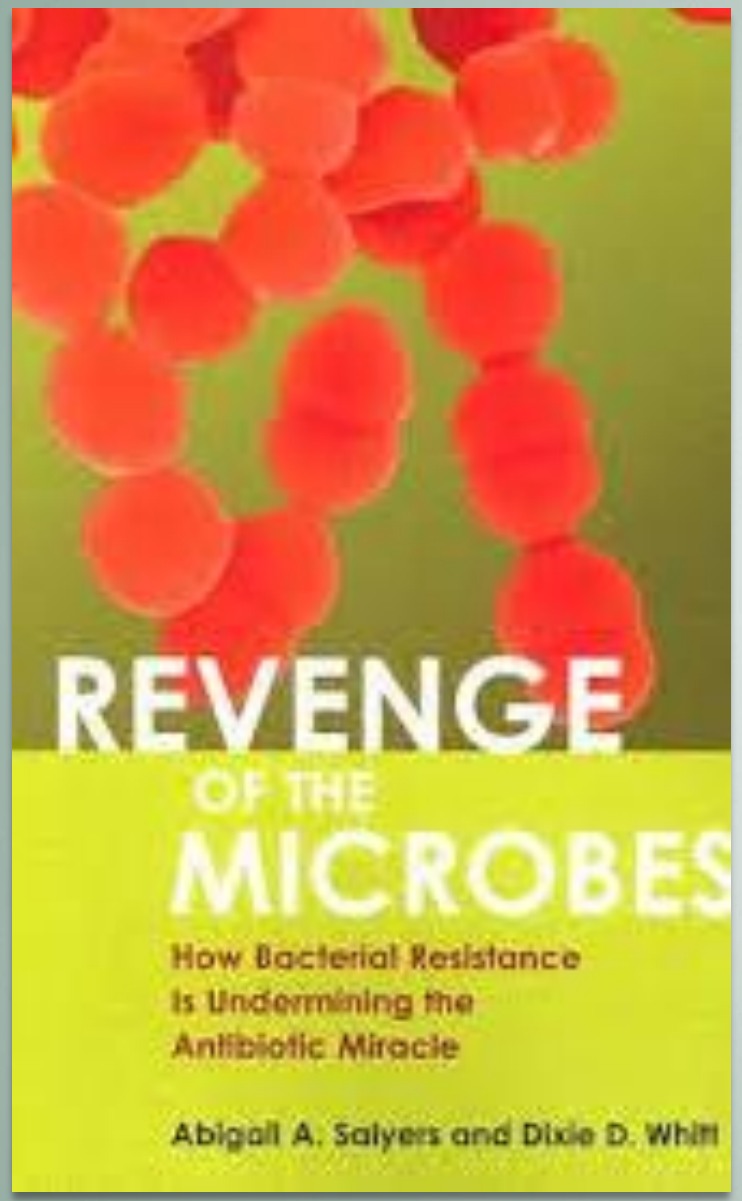


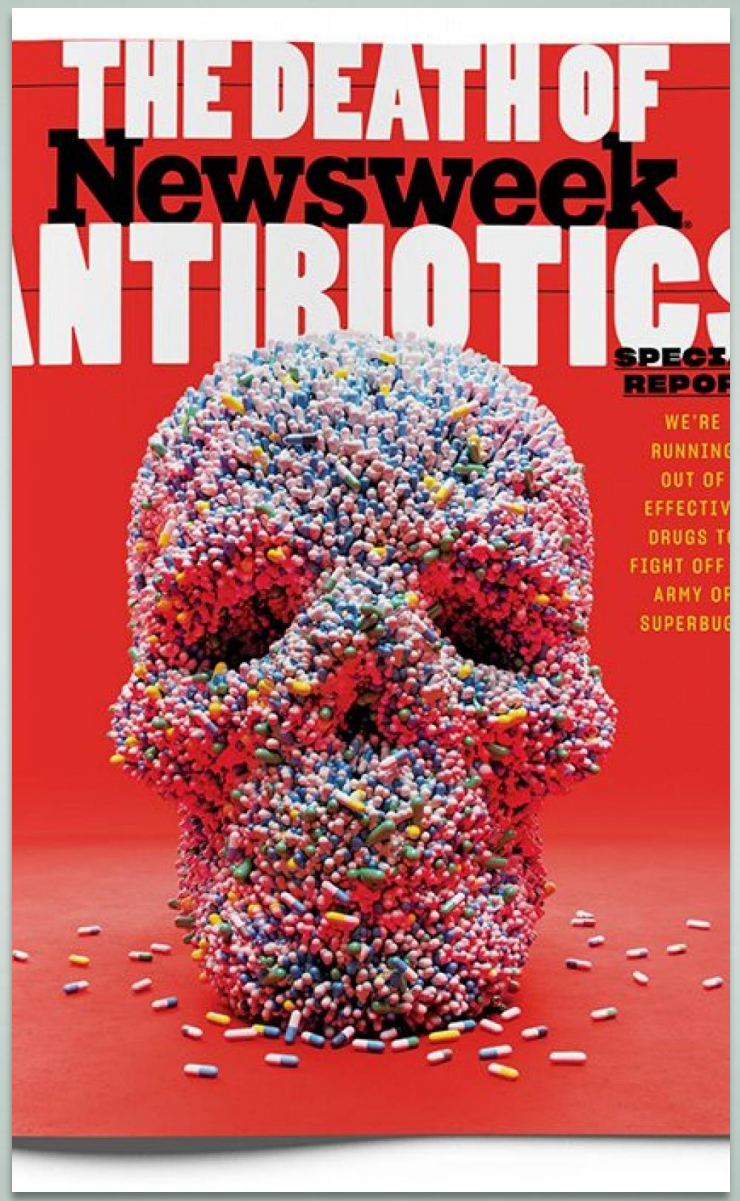
Pawar, S, et al. Current Topics in Medicinal Chemistry (2017) 17: 251.

RISE OF THE RESISTANCE



Schäberle, Till & Hack, Ingrid. Trends in Microbiology 2014 (22), 165-7.

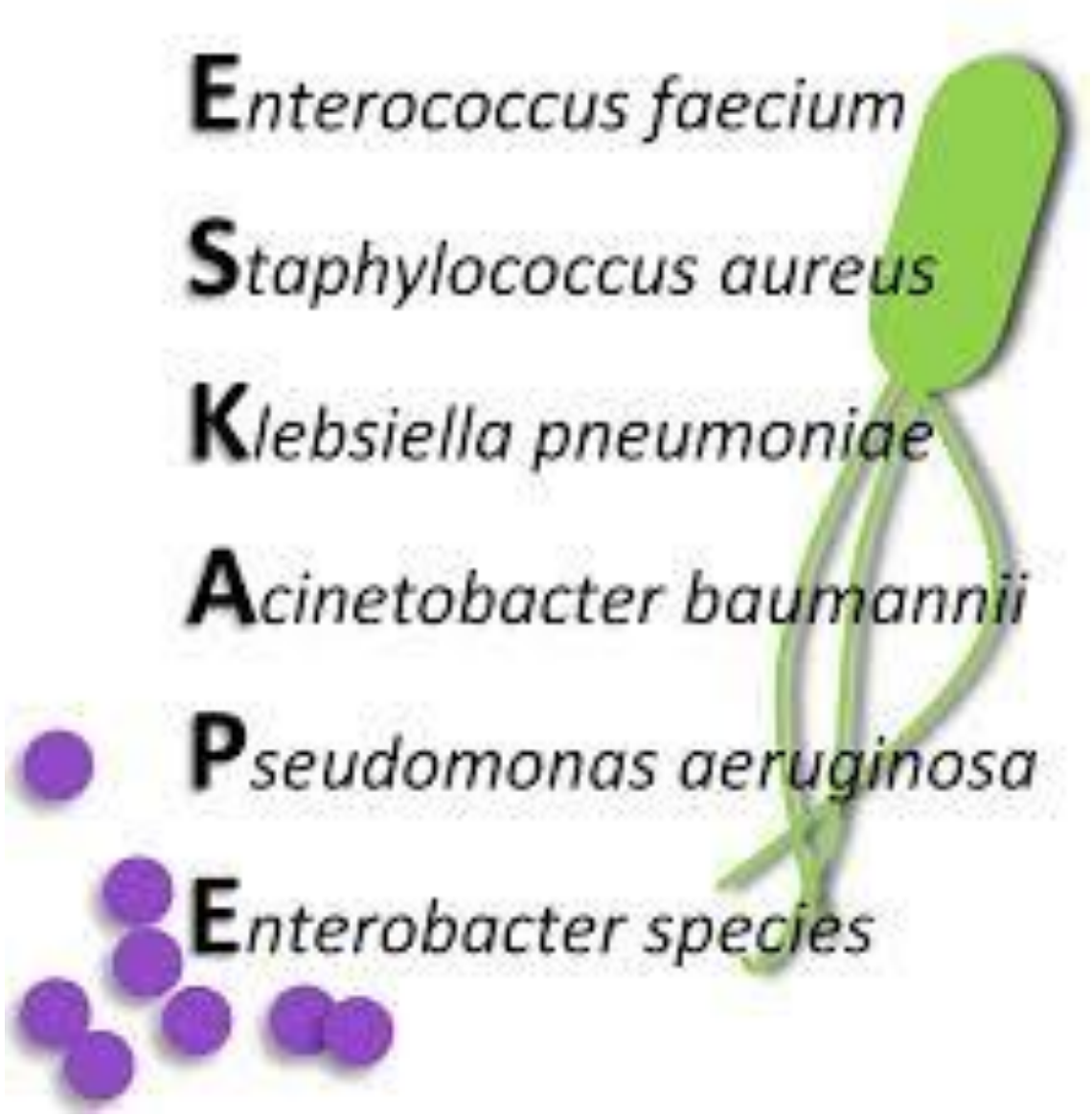

REVENGE
OF THE
MICROBES
How Bacterial Resistance
Is Undermining the
Antibiotic Miracle
Abigail A. Salyers and Dixie D. Whitt


THE DEATH OF
Newsweek
NTIBIOTICS
SPECI
REPOR
WE'RE
RUNNIN
OUT OF
EFFECTIV
DRUGS T
FIGHT OFF
ARMY OF
SUPERBUG

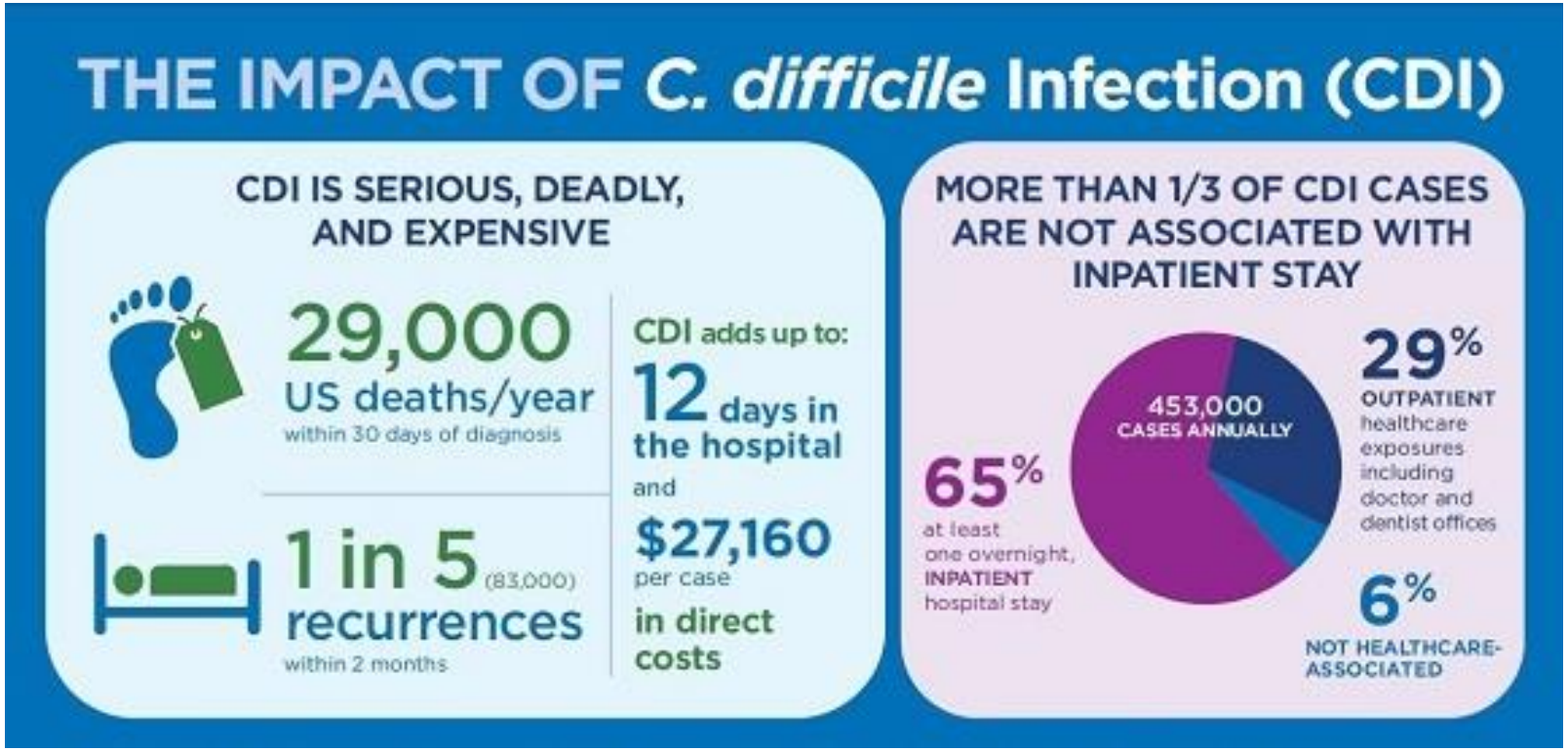
Revenge


PARTNERS IN
ANTIBIOTIC RESISTANCE

Consequences of Antibiotic Overuse

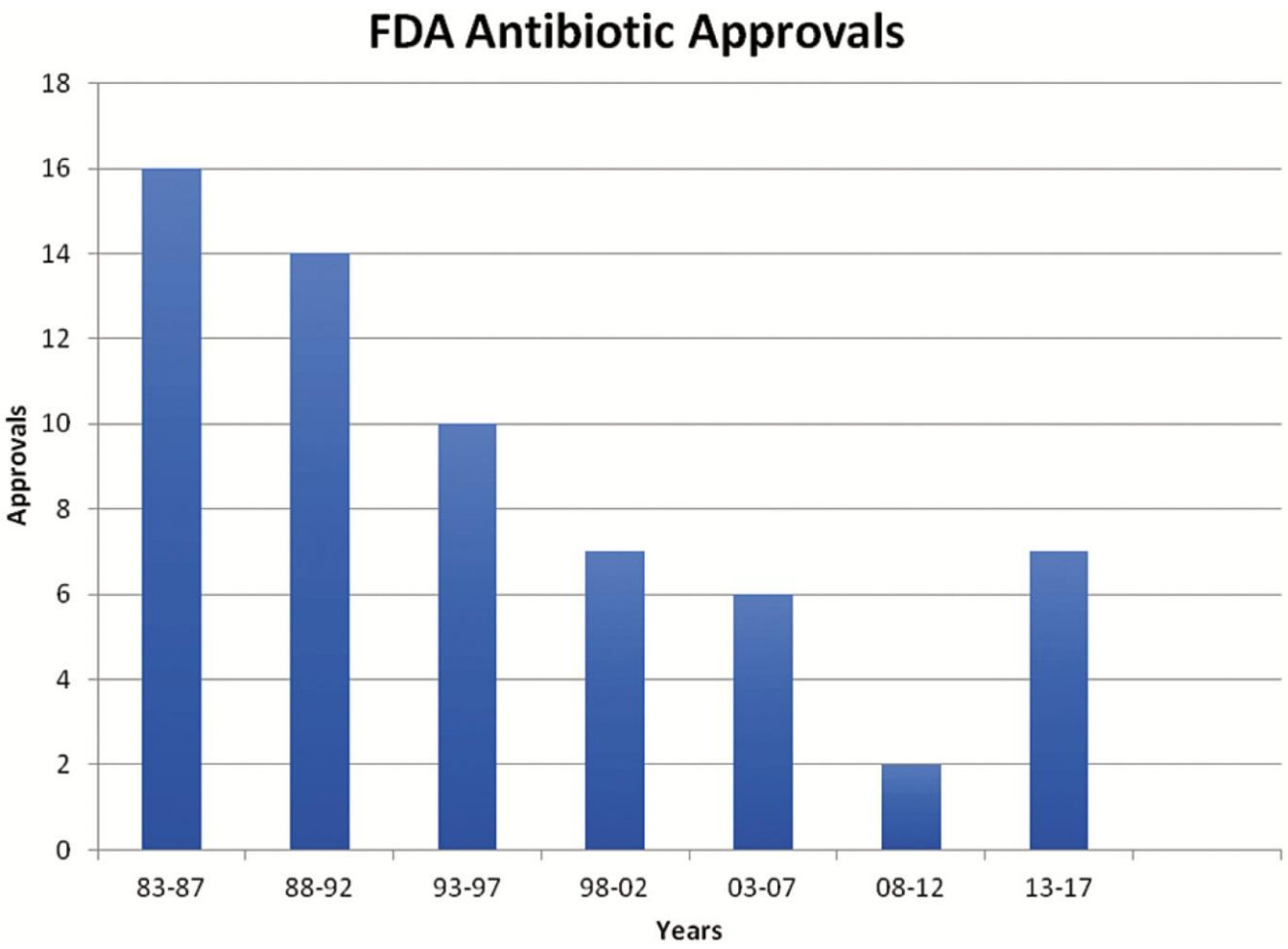


ESKAPE Pathogens



Clostridium difficile

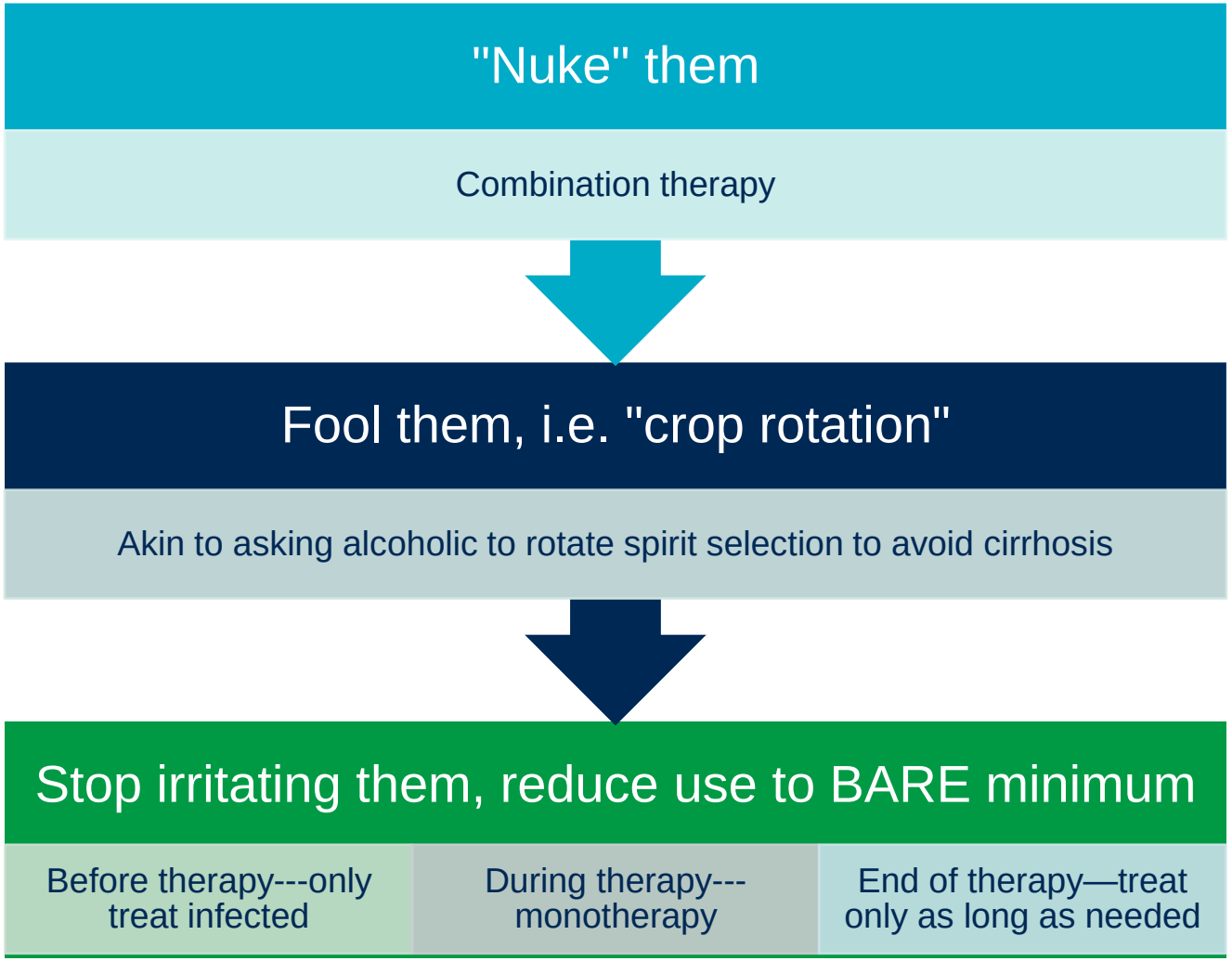
Source: NFID.org



New Antibiotic Development

Clinical Infectious Diseases, July 2019

Reducing Antibiotic Resistance



Rice, CID 2008

"Just to Be Sure"

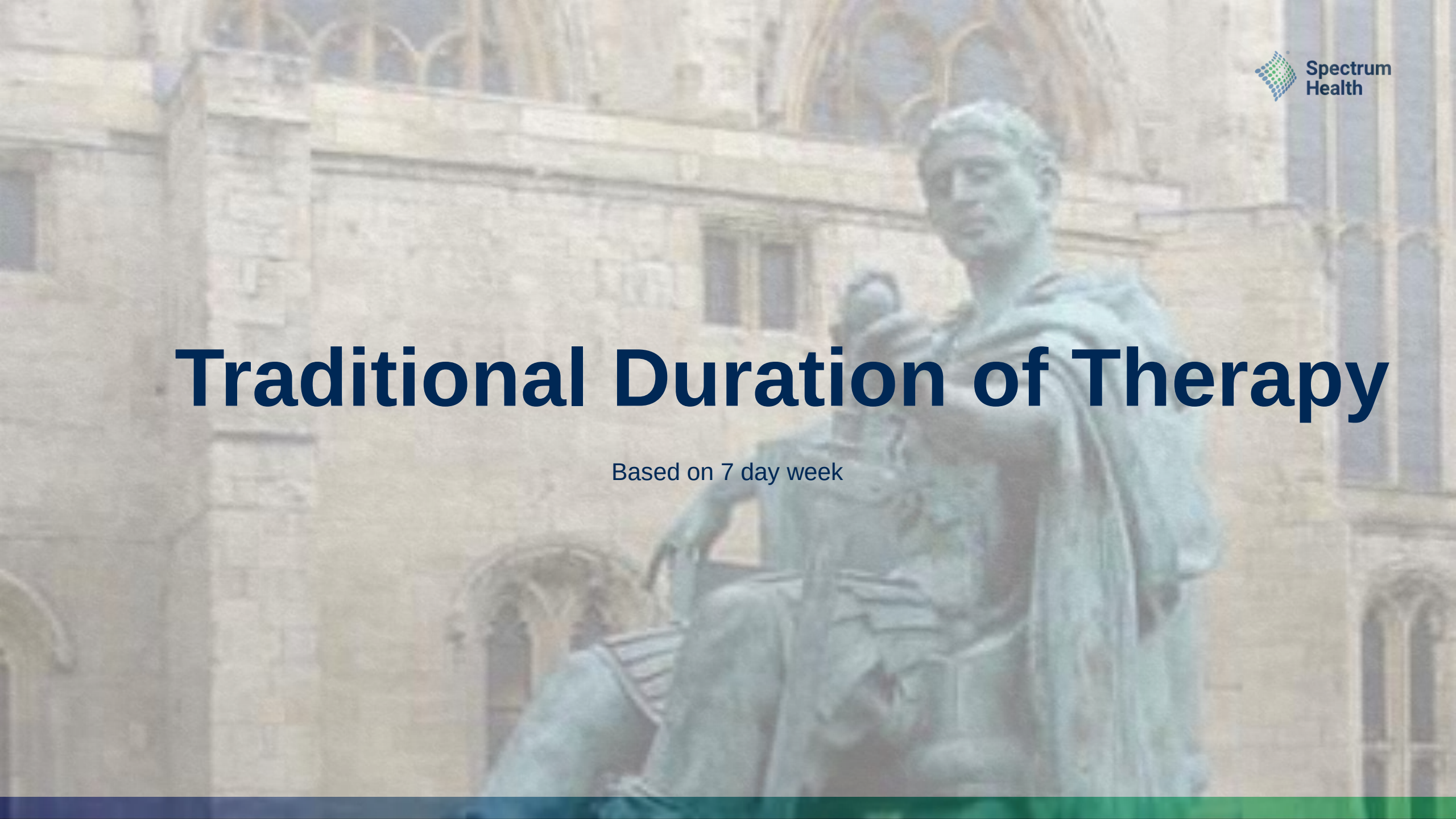
Extending courses beyond clinical improvement

"Can't hurt, might help!"

Often done to treat physician anxiety

Fallicy that longer = less resistance

Rice, CID 2008



Traditional Duration of Therapy

Based on 7 day week

Why Does Duration Matter?

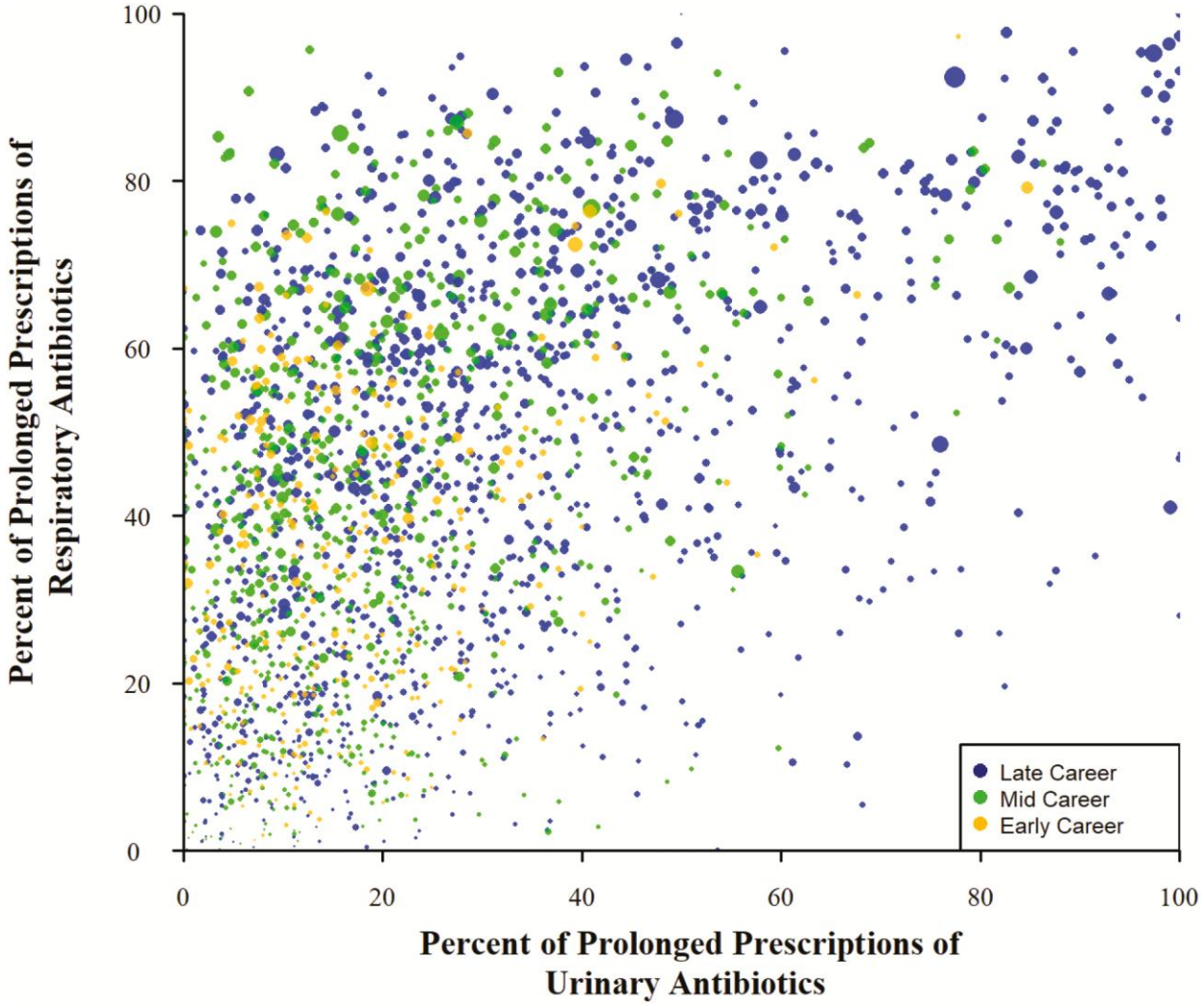
Longer exposure to antibiotics drives resistance

Longer exposure to antibiotics increases risk of adverse events

Longer exposure to antibiotics increases risk of C diff

Predictors of Prolonged Therapy

- 10K Family physicians
- Proportion prolonged antibiotic courses (>8 d)
- Predictors
  - Late career physicians
  - Rural location
  - Comorbid conditions
- Brad Spellberg:
  - ***"We <u>ALL</u> perform poorly, some worse than others."***



Fernandez-Lazaro, CI et al. CID 2109

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EDITORIAL

The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

Revised Thinking

Spellberg, JAMA Internal Med, 2016

Evidence for Shorter is Better

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

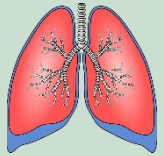
Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

Spellberg, JAMA Internal Med, 2016

Community Acquired Pneumonia

6 prospective RCTs



Mild-moderate CAP

Hospitalized patients

PSI IV-V

Treatment duration:

3-5 days vs 8-10 days

Clinical success equal

NOT agent specific

Spellberg, JAMA Internal Med, 2016

2016 CAP Study

- Multicenter, non-inferiority
- 312 hospitalized patients
- Randomized at day 5
  - Control → continued treatment
  - Intervention → stopped treatment
- Primary outcome
  - Clinical success at day 10 & 30

Uranga, et. al., JAMA Internal Med, 2016

Table 1. Baseline Characteristics of Study Participants[a]

Characteristic	Control Group (n = 150)	Intervention Group (n = 162)
Age, mean (SD), y	66.2 (17.9)	64.7 (18.7)
Sex		
Male	95 (63.3)	101 (62.3)
Female	55 (36.7)	61 (37.7)
Tobacco		
Current smoker	32 (21.3)	36 (22.6)
Never smoker	68 (45.3)	71 (44.7)
Former smoker	50 (33.3)	52 (32.7)
Alcohol consumption (yes)	24 (16.1)	17 (10.5)
Comorbidities		
Liver disease	4 (2.7)	4 (2.5)
Heart disease	38 (25.3)	39 (24.1)
Congestive heart failure	14 (9.3)	12 (7.4)
Cerebrovascular disease	16 (10.7)	9 (5.6)
Renal disease	12 (8.0)	12 (7.4)
COPD	21 (14)	27 (16.7)
Diabetes	25 (16.7)	21 (13.0)
Charlson Comorbidity Index, median (IQR)	1 (0-2)	1 (0-2)
Charlson Comorbidity Index, categorized		
0	61 (40.7)	70 (43.2)
1	37 (24.7)	47 (29.0)
>1	52 (34.7)	45 (27.8)
Katz Index, mean (SD)[b]	0.6 (1.6)	0.4 (1.3)
PSI class		
I-III	89 (59.3)	102 (63.0)
IV-V	61 (40.7)	60 (37.0)
PSI score, mean (SD)	83.7 (33.7)	81.8 (33.8)

Primary Outcome

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	*P* Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)[a]			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%)[a]			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

Uranga, et. al., JAMA Internal Med, 2016

Secondary Outcomes

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure[b]	2 (1.5)	3 (2.1)	>.99
Respiratory failure[c]	26 (19.0)	31 (21.2)	.64
Severe sepsis[d]	7 (5.1)	8 (5.5)	.89
Renal failure[e]	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

Uranga, et. al., JAMA Internal Med, 2016

CAP: Does 3 days work?

Double blind RCT 3 vs 8 days

310 non-critically ill adults

Abx stopped at clinical stability

No differences in 3 vs 8 days

- Cure
- Adverse events
- Mortality

Dinh, A et al. **Lancet 2021; 397: 1195–203**

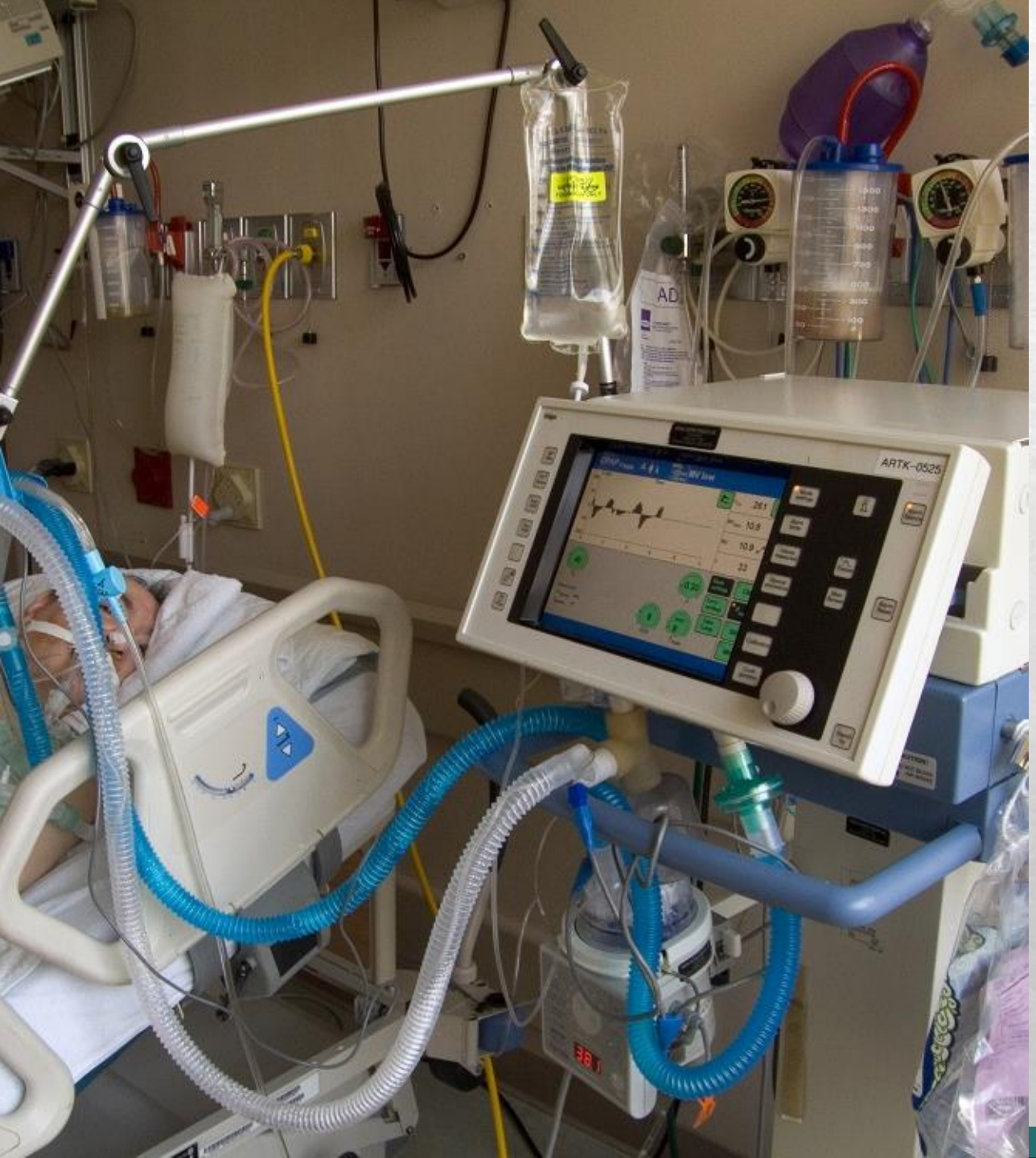
CAP: Excess Duration & Adverse Events

- Multicenter retrospective study in Michigan
- Primary outcome
  - Rate of excess antibiotic treatment duration
- Results
  - 2/3 pts received excess therapy (median: 8 days)
  - 93% excess therapy at discharge
- No differences in mortality or readmission
- Increase antibiotics associated AE in excess duration group

Table 3. Association of Excess Antibiotic Treatment Duration With 30-Day Adverse Outcomes (n = 6481)*

Outcomes at 30 Days	Appropriate Duration (n = 2090), n (%)†	Excess Duration (n = 4391), n (%)‡	Unadjusted OR per Excess Day (95% CI)§	Unadjusted *P* Value§	Adjusted OR per Excess Day (95% CI)§	Adjusted *P* Value§
Mortality‖	40 (1.9)	88 (2.0)	0.99 (0.94–1.03)	0.52	1.01 (0.97–1.05)	0.60
Readmission‖	294 (14.1)	497 (11.3)	0.99 (0.96–1.02)	0.48	1.00 (0.98–1.03)	0.92
Emergency department visit‖	238 (11.4)	480 (10.9)	0.97 (0.94–1.00)	0.021	0.98 (0.95–1.01)	0.166
Antibiotic-associated adverse event¶	72 (3.4)	210 (4.8)	1.04 (1.01–1.07)	0.012	1.03 (1.00–1.06)	0.038
Clostridioides difficile infection**	11 (0.5)	22 (0.5)	0.92 (0.81–1.05)	0.21	0.93 (0.81–1.07)	0.30
Provider-documented††‡‡	43 (2.1)	87 (2.0)	1.00 (0.94–1.05)	0.86	0.99 (0.94–1.05)	0.85
Patient-reported††§§	26/1132 (2.3)	114/2460 (4.6)	1.05 (1.02–1.08)	<0.001	1.05 (1.02–1.08)	0.001
Composite adverse outcome‖	499 (23.9)	897 (20.4)	0.98 (0.96–1.00)	0.078	0.99 (0.97–1.01)	0.40

Vaughn, et. al., Annals of Int Med, 2019



What About Ventilator Associated Pneumonia?

Traditional duration 14-21 days

2 RCTs: 8 vs 15 days

Similar clinical outcomes & mortality

Significant reduction MDR pathogen in shorter treatment group

No specific studies for HAP

Hanretty, A. and J. Gallagher, Pharmacotherapy, 2018
Chastre J, et al. JAMA, 2003
Capellier G, et al. PLoS One, 2012

STOP-IT: Short Course for Intra-Abdominal Infections

- Typically treated until resolution of SIRS
  - 7-14 days most common
- Evidence for optimal duration scant & poor
- 2015 NEJM study: STOP-IT trial
  - Prospective, randomized, open label
  - Source control procedure
  - Treatment duration: 4 days after source control vs 2 days after resolution of SIRS
  - Primary outcome: SSI, recurrent IAI or death at 30 days
    - 56/257 in experimental group
    - 58/260 in control group

Table 2. Primary and Major Secondary Outcomes.*

Variable	Control Group (N = 260)	Experimental Group (N = 257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99
Time to event — no. of days after index source-control procedure			
Diagnosis of surgical-site infection	15.1±0.6	8.8±0.4	<0.001
Diagnosis of recurrent intraabdominal infection	15.1±0.5	10.8±0.4	<0.001
Death	19.0±1.0	18.5±0.5	0.66

Sawyer, et. al., NEJM 2015

Septic Arthritis

- 154 cases
  - 2/3 hand & wrist
  - 30% *Staphylococcus aureus*
  - Infected implants excluded
- Median length of IV therapy: 1-2 days
- Median surgeries: 1
- Cure rate equivalent in both arms
  - Median follow up 6 mths
- 2 weeks arm decreased LOS

CLINICAL SCIENCE

Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial

Ergys Gjika,[1] Jean-Yves Beaulieu,[1] Konstantinos Vakalopoulos,[1] Morgan Gauthier,[1] Cindy Bouvet,[1] Amanda Gonzalez,[1] Vanessa Morello,[1] Christina Steiger,[1] Stefanie Hirsiger,[1] Benjamin Alan Lipsky,[2,3] Ilker Uçkay[2,4]

Gjika, et. al., Ann Rheum Dis, 2019

Gram Negative Bacteremia

- 604 patients, prospective, randomized, open label, non-inferiority
- 7 d vs 14 d
- Primary outcome
  - 90 day mortality, clinical failure & readmission
    - 7 days: 45.8%
    - 14 days: 48.3%

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

[1]Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, and [2]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel; [3]Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Italy; [4]Infectious Diseases Institute, Rambam Health Care Campus, Haifa, [5]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, [6]The Ruth and Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, and [7]Department of Medicine B, [8]Department of Medicine C, and [9]Department of Medicine F, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel

Yahav, et al, CID 2018

What about Pseudomonas, shouldn't that be longer?

- Fabre, et. al. CID 2019
  - 249 pt Pseudomonas bacteremia
    - Short course (7-11 days) vs long course
  - Propensity matched retrospective cohort
    - Excluded: osteoarticular, endovascular & CNS infections
    - **Included: immunocompromised**
  - Outcome:
    - Recurrent Pseudomonas bacteremia or death at 30 days
  - Results
    - No outcomes difference short vs long course
    - ~1/3 transition to oral FQ day 5-6
    - **Short course: 4 fewer days average LOS**

Clinical Infectious Diseases

BRIEF REPORT

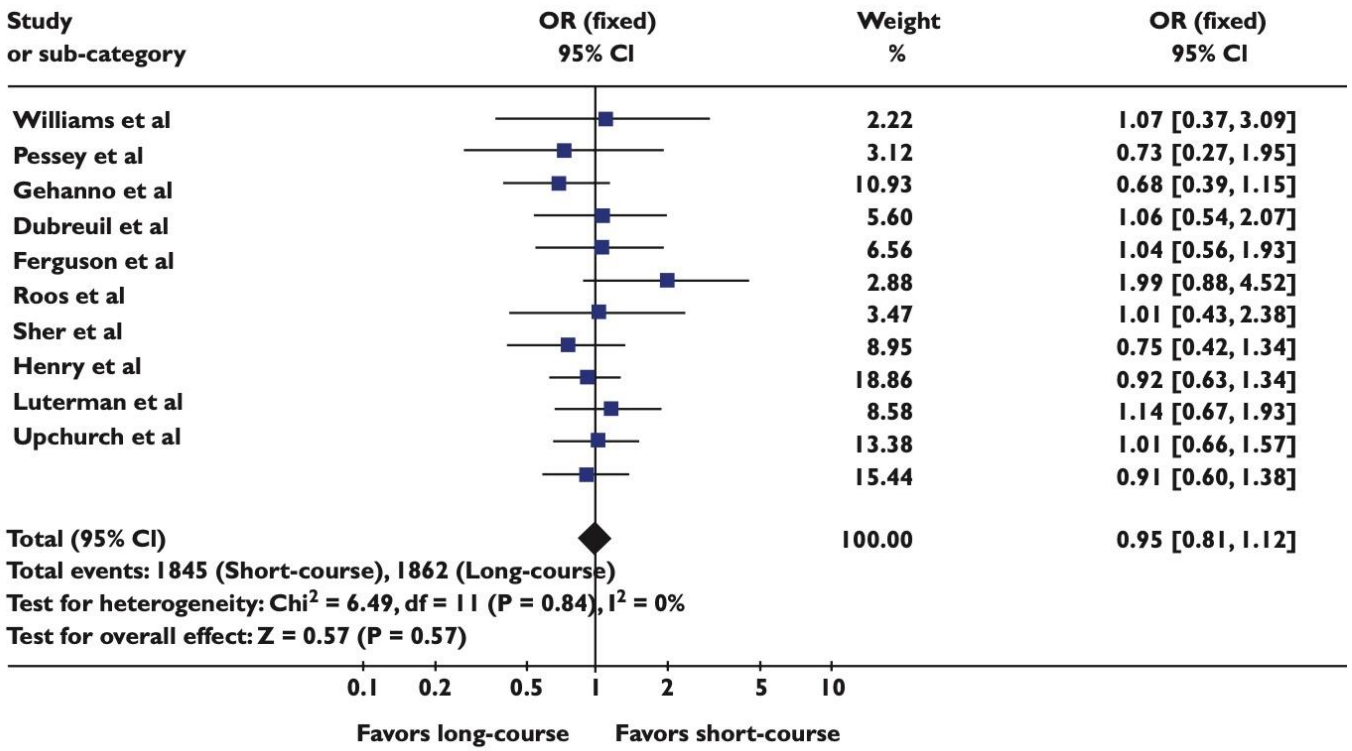
Antibiotic Therapy for *Pseudomonas aeruginosa* Bloodstream Infections: How Long Is Long Enough?

Valeria Fabre,[1] Joe Amoah,[2] Sara E. Cosgrove,[1] and Pranita D. Tamma[2]

[1]Division of Infectious Diseases, Department of Medicine, and [2]Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland

Fabre, et al, CID 2019

Acute Bacterial Sinusitis



M. E. Falagas et al. Br J Clin Pharmacol, **67**:161–171

Uncomplicated Cellulitis

- 2004 study: 5 vs 10 days
- Randomized, double blind, prospective
- Primary outcome: resolution at 14 days, no relapse at 28 days
- 87 patients
  - 43---10 days therapy
  - 44---5 days therapy
- Result: no difference at 14 & 28 days

Hepburn, et al. Arch Intern Med. 2004;164:1669-1674

Summary

- Excessively long durations of antibiotic therapy contribute of antibiotic overuse & its unintended consequences
- Traditional antibiotic durations most often are excessively long & have traditionally been based on arbitrary numbers (e.g. 7 day week)
- Over the last 20 yrs, numerous studies of many commonly encountered infections have time & again demonstrated shorter courses of antibiotics are equivalent & often superior to longer courses of antibiotics
- Shorter is Better is an essential antimicrobial stewardship mantra that ALL clinicians should embrace & practive

The Bottom Line

Questions?