Combination Therapy for Serious Gram Positive Infections

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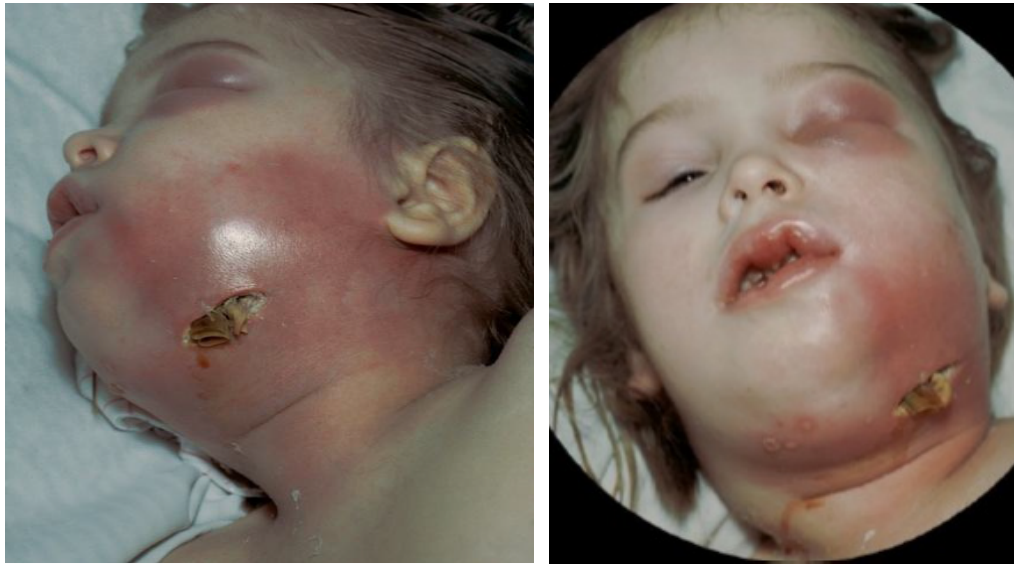
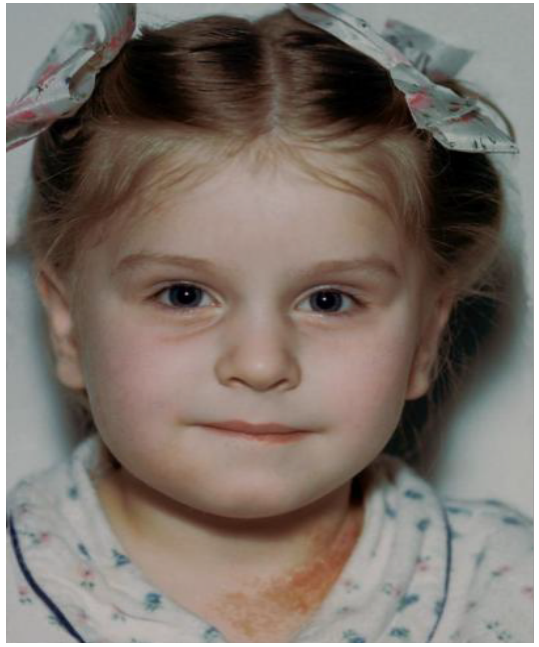
- **Consultant: Abbvie, Paratek, Ferring, Octapharma**
- **Research Grant: Octapharma**
- **Speaking: Abbvie, Paratek**

Status Quo Starting Point:
Single Antibiotic Therapy Paradigms for Bacterial Infection



1943 - 4 year old.



14 days penicillin

There was was never a comparator—does that matter?
Why 14 days?
How different were patient hosts in 1943 vs the 21st century?
How many beta-lactam resistant bacterial pathogens were clinically relevant in the 1940's?

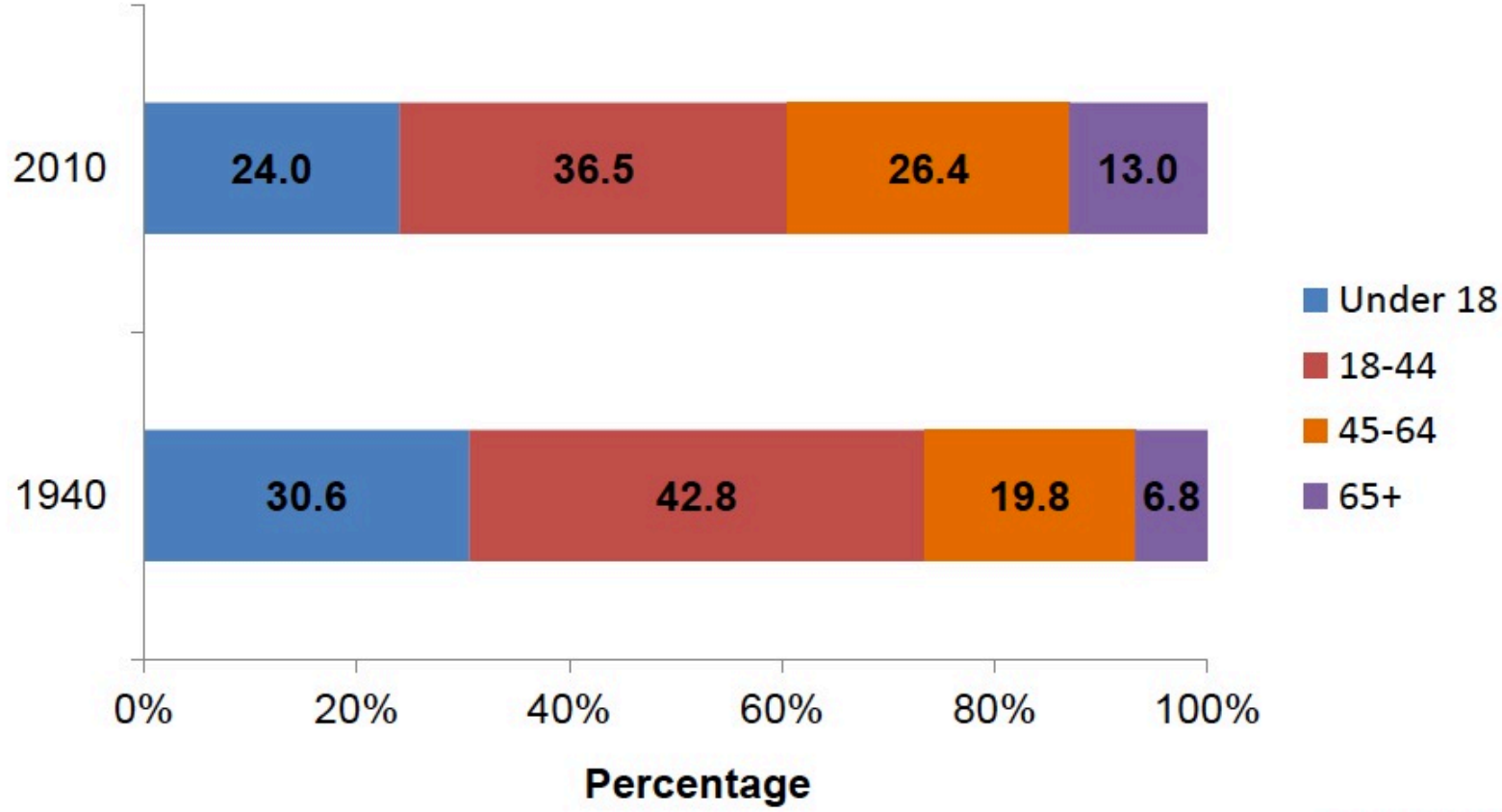
Herrell '43 Proc Staff Meetings Mayo Clinic 18:65-76

Age Distribution: 1940 and 2010

POPULATION

330 million

132 million

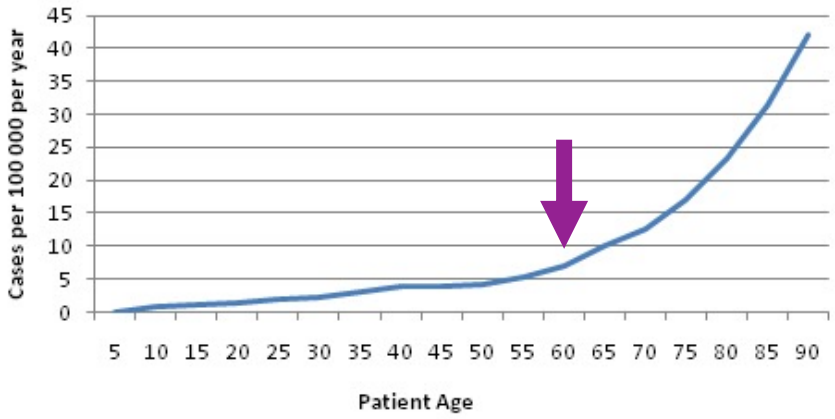


Sources: U.S. Census Bureau, *1940 Census* and *2010 Census*.

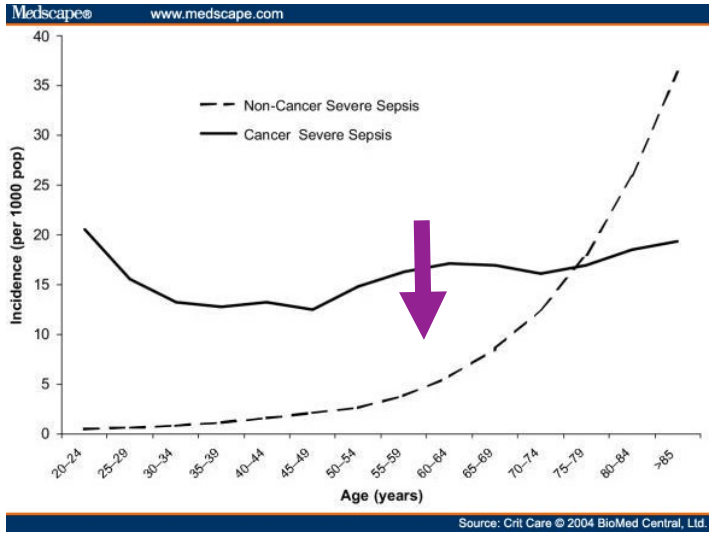
United States Census Bureau

Age >65 Years in US: 9 million-> 43 million

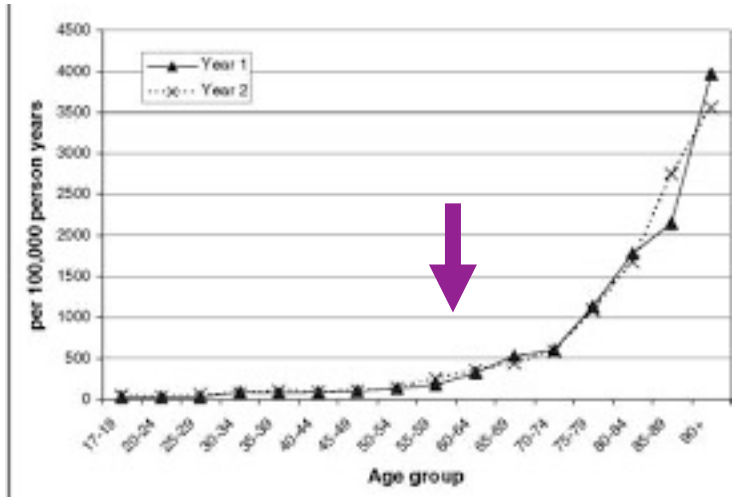
Consequence of Longevity: Senescence of Innate Immunity



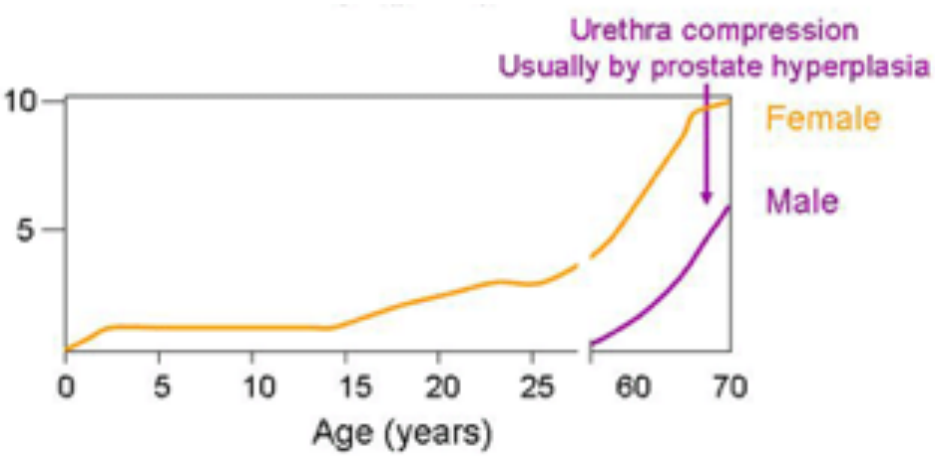
Infective Endocarditis



Sepsis

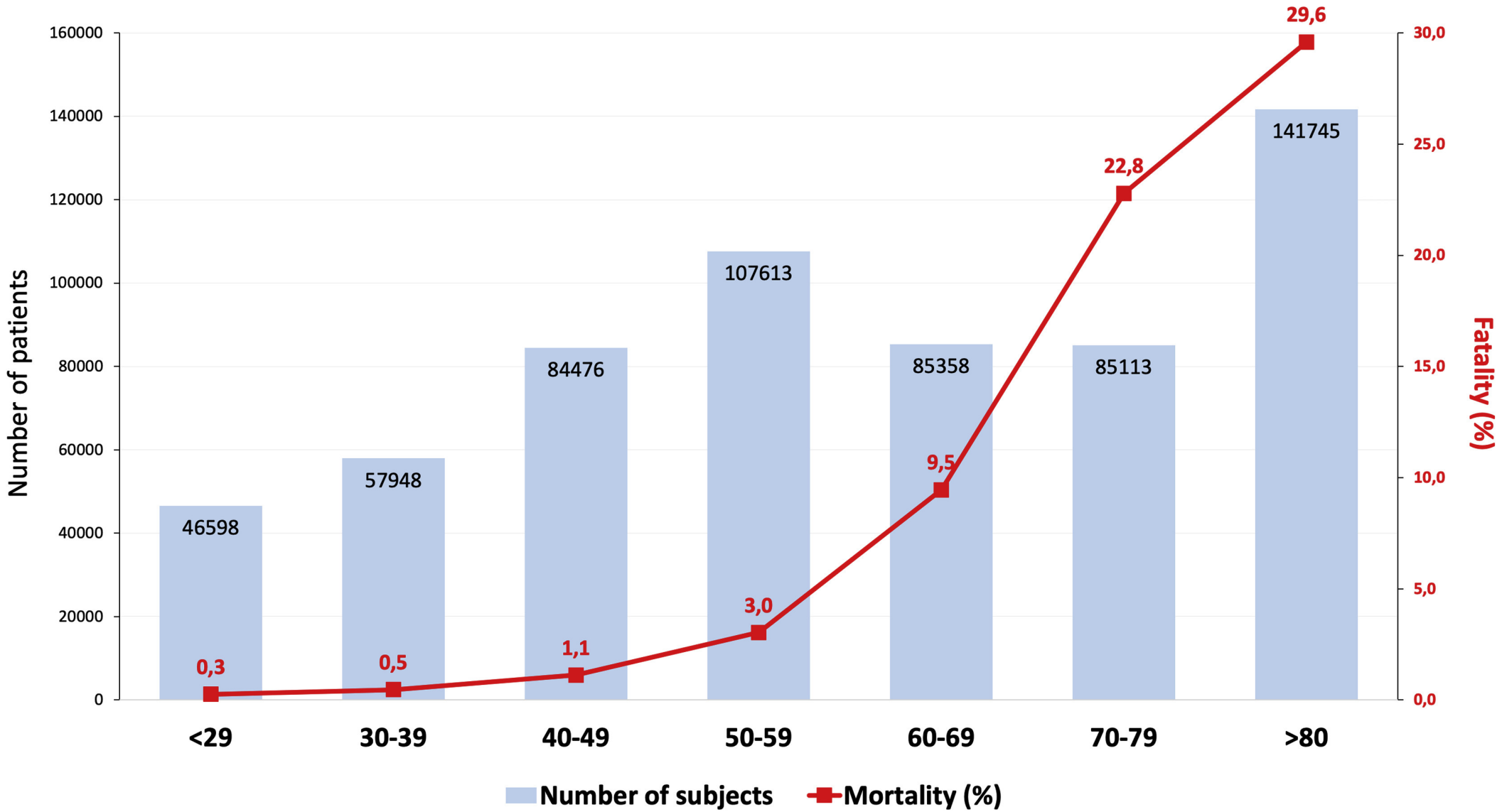


Community Acquired Pneumonia



Urinary Tract Infection

COVID-19 Mortality by Age



Factors Determining A Successful Outcome in the Treatment of Infection

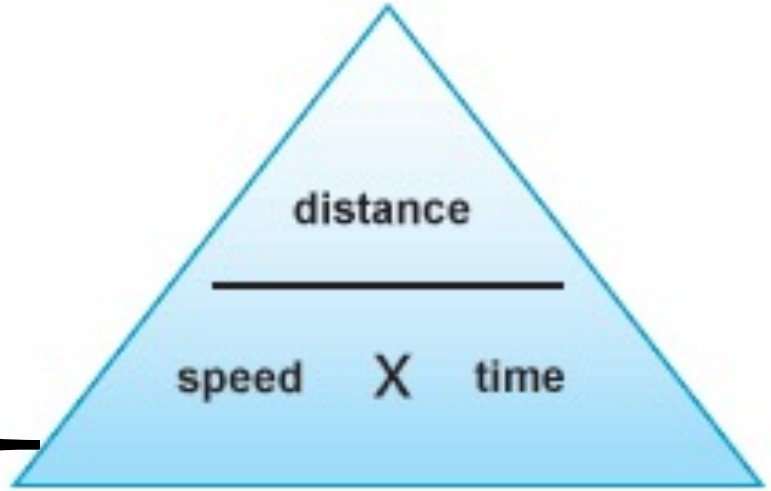
Host Immunity
- Age
- Immunosuppression

Pathogen
- Virulence (invasion/evasion)
- Antimicrobial Resistance
- Infecting Site

Surgical Source Control

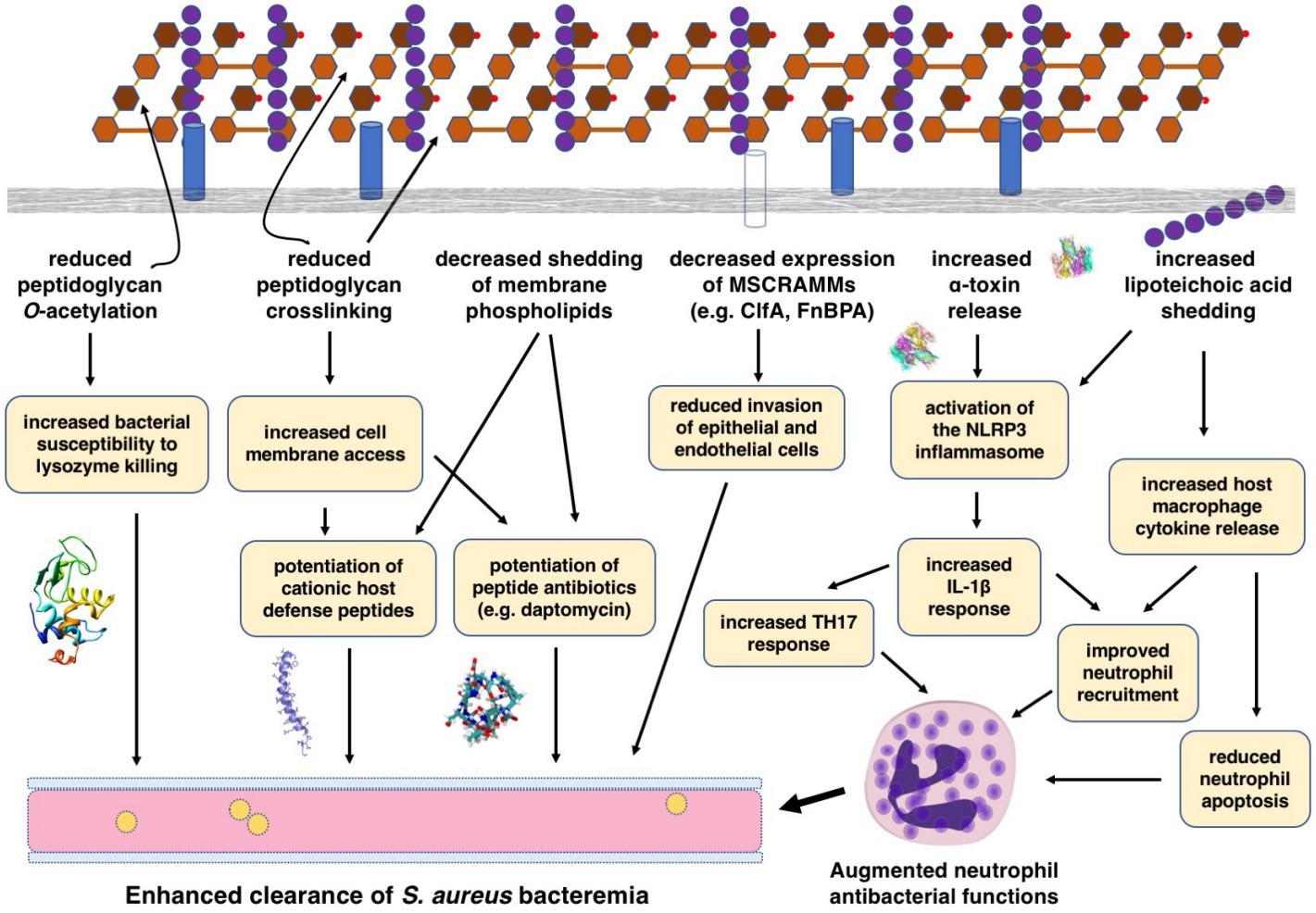
Antibiotic Properties: MIC (S vs R)
- Bactericidal vs Bacteriostatic
- PK/PD
- Penetration into biofilms
- Activity against 'inert' forms
- Synergy with Innate Immunity

Burden of Infection (inoculum)



Duration of Therapy

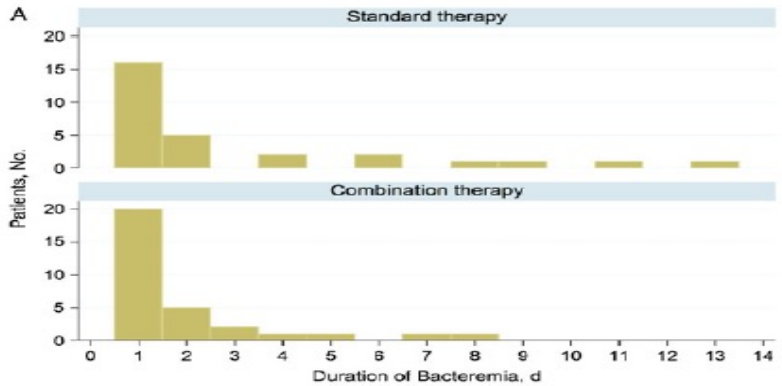
Indirect Immunological Effects of Beta-Lactams on *S. aureus* Not Reflected in MIC Testing



Sakoulas G, Geriak M, Nizet V. Clin Infect Dis 2018 Jul 9. doi: 10.1093/cid/ciy557. [Epub ahead of print]

CAMERA-2 Study: A Rigorous Look At Combination Therapy for MRSA

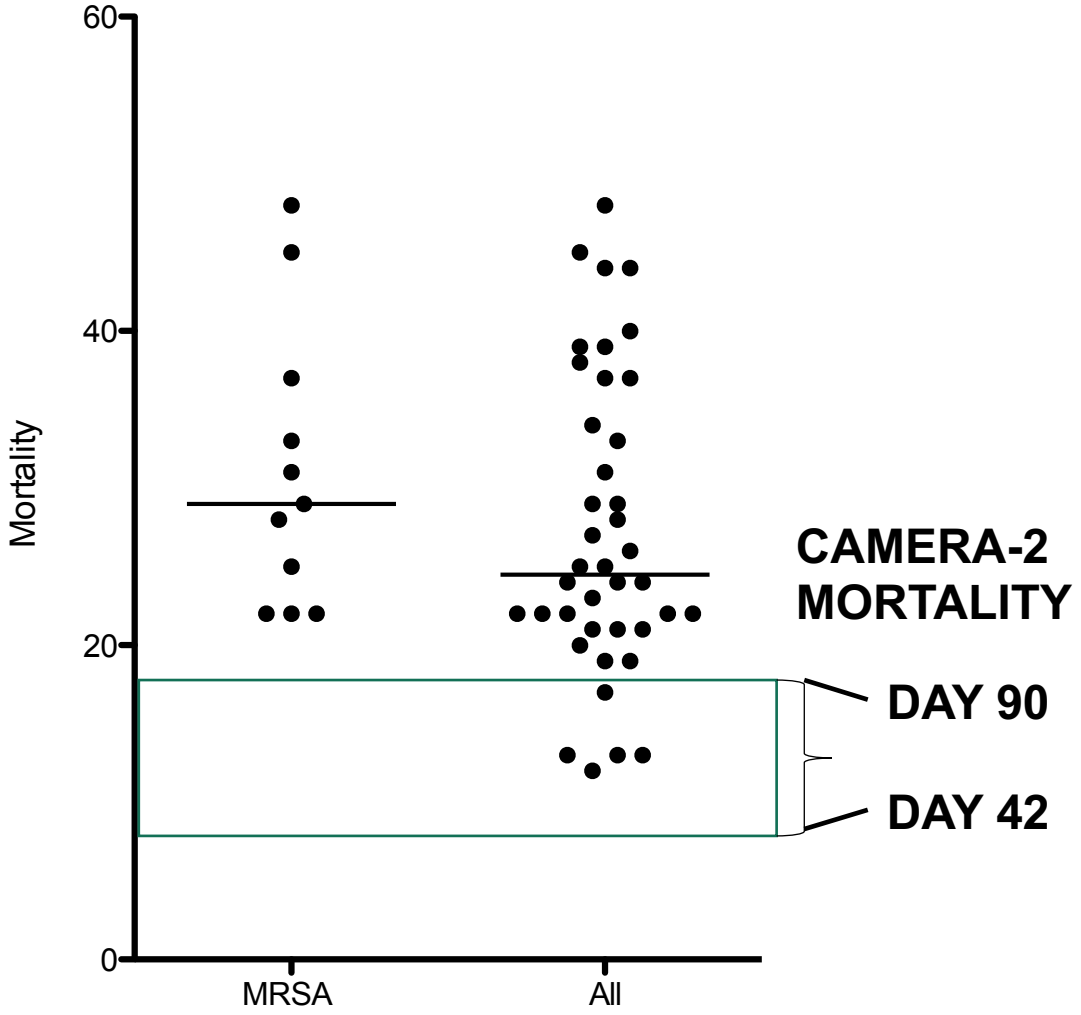
- MRSA Bacteremia Study Follow-up to CAMERA-1
- August 2015 - July 2018, 352 adults, 27 sites ,4 countries (Australia, New Zealand, Singapore, and Israel)
- Vancomycin or Daptomycin WITH/WITHOUT Combination with anti-staphylococcal β-lactam (flucloxacillin, cloxacillin, or cefazolin)
- Vast Majority of combination received vancomycin +flucloxacillin
  - 171/174 (98%) combination group
  - 178/178 (100%) monotherapy group
- Stopped Early Due to Safety Concerns
- 30% developed acute kidney injury vs 9% in the standard therapy arm
- Increased 90-day mortality in the combination arm vs the standard therapy arm (21% vs 16%)
- Combination arm had less bacteremia persistence, consistent with CAMERA-1



Tong S et al. CID 2016
Tong S et al. JAMA Feb 2020

Mortality in MRSA Bacteremia: CAMERA 2 vs Prior Studies

"Putting the 'CAMERA' Under the Microscope"



Van Hal S etal. Clin Microbiol Rev 2012. https://doi.org/10.1128/CMR.05022-11
Tong et al. JAMA 2020 Feb 11;323(6):527-537

Mortality in MRSA Bacteremia: CAMERA 2 vs Prior Studies

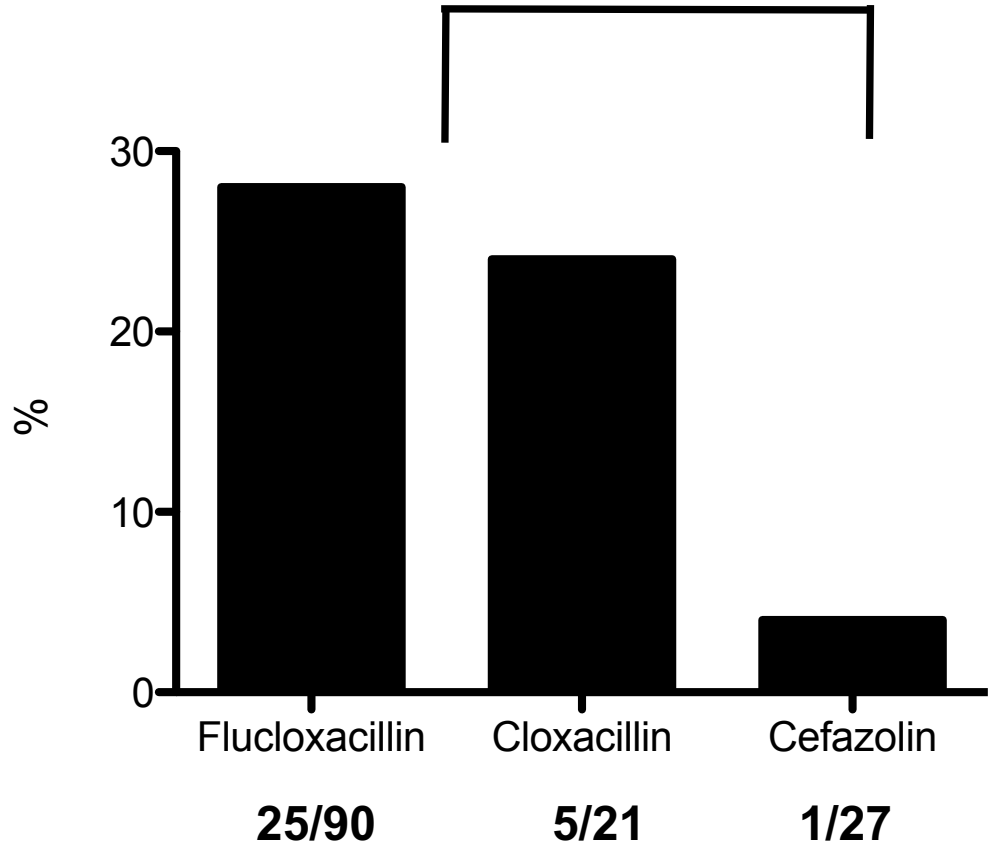
Introduction

In 2017 in the United States, there were an estimated 120 000 cases of *Staphylococcus aureus* bacteremia resulting in 20 000 deaths.[1] The mortality from *S aureus* bacteremia is higher for methicillin-resistant *S aureus* (MRSA) than for methicillin-susceptible *S aureus* (MSSA), typically at 20% to 25%.[1,2] Despite the heavy burden of *S aureus* bacteremia, there is a paucity of evidence to guide treatment. Overall, there have been fewer than 2500 patients enrolled in published randomized clinical trials for *S aureus* bacteremia in the past 20 years, and fewer than 450 for MRSA bacteremia.[3]

All-cause mortality[d]	VAN		VAN+ FLUCLOX			
Day 14	13/174	(7%)	13/170	(8%)	0.2 (-5.4,5.8)	0.95
Day 42	19/174	(11%)	25/170	(15%)	3.8 (-3.3,10.8)	0.29
Day 90	28/174	(16%)	35/170	(21%)	4.5 (-3.7,12.7)	0.28

Tong et al. 2020 Feb 11;323(6):527-537

Major Message of CAMERA-2: AKI With Vancomycin and Beta-Lactams



Tong et al. 2020 Feb 11;323(6):527-537

P=0.008 Cefazolin vs Flucloxacillin+ Cloxacillin

P=0.007 Cefazolin vs Flucloxacillin

P= 0.07 Cefazolin vs Cloxacillin

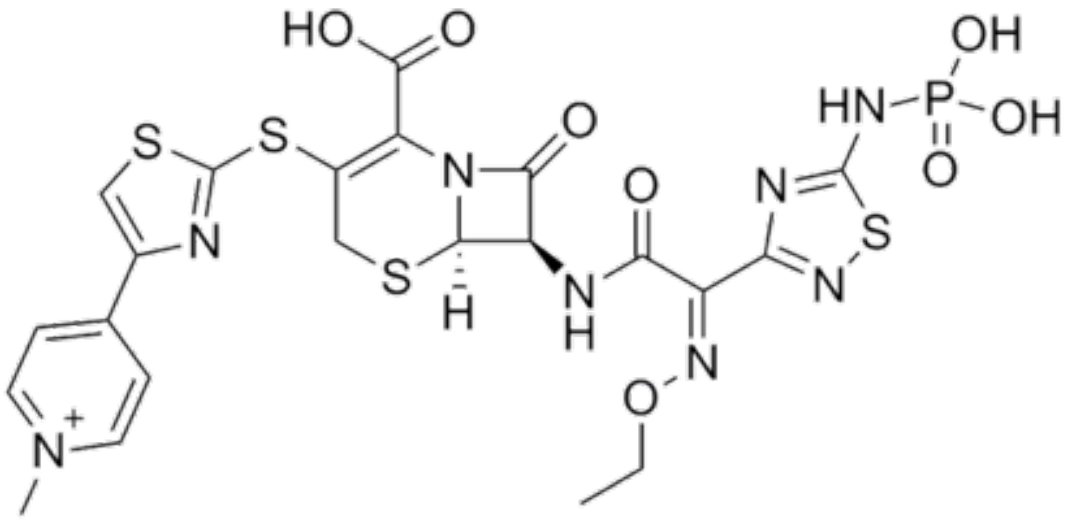
1521-009X/41/4/791–800$25.00
DRUG METABOLISM AND DISPOSITION
http://dx.doi.org/10.1124/dmd.112.049569
Drug Metab Dispos 41:791–800, April 2013

Organic Anion Transporter 3 Interacts Selectively with Lipophilic β-Lactam Antibiotics

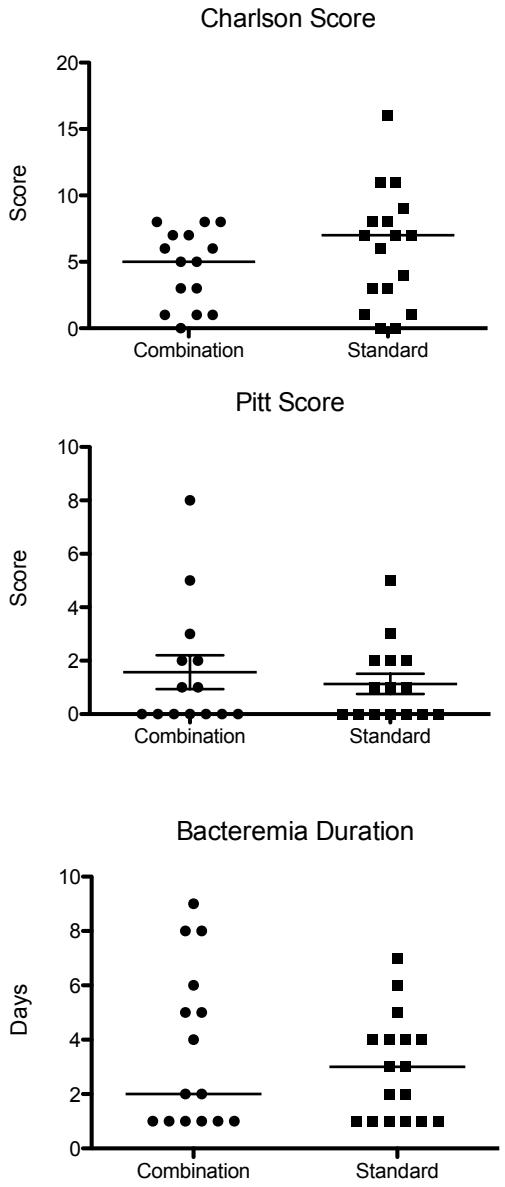
Aaron T. Wolman, Michael R. Gionfriddo, Gregory A. Heindel, Paran Mukhija, Sarah Witkowski, Ajay Bommareddy, and Adam L. VanWert

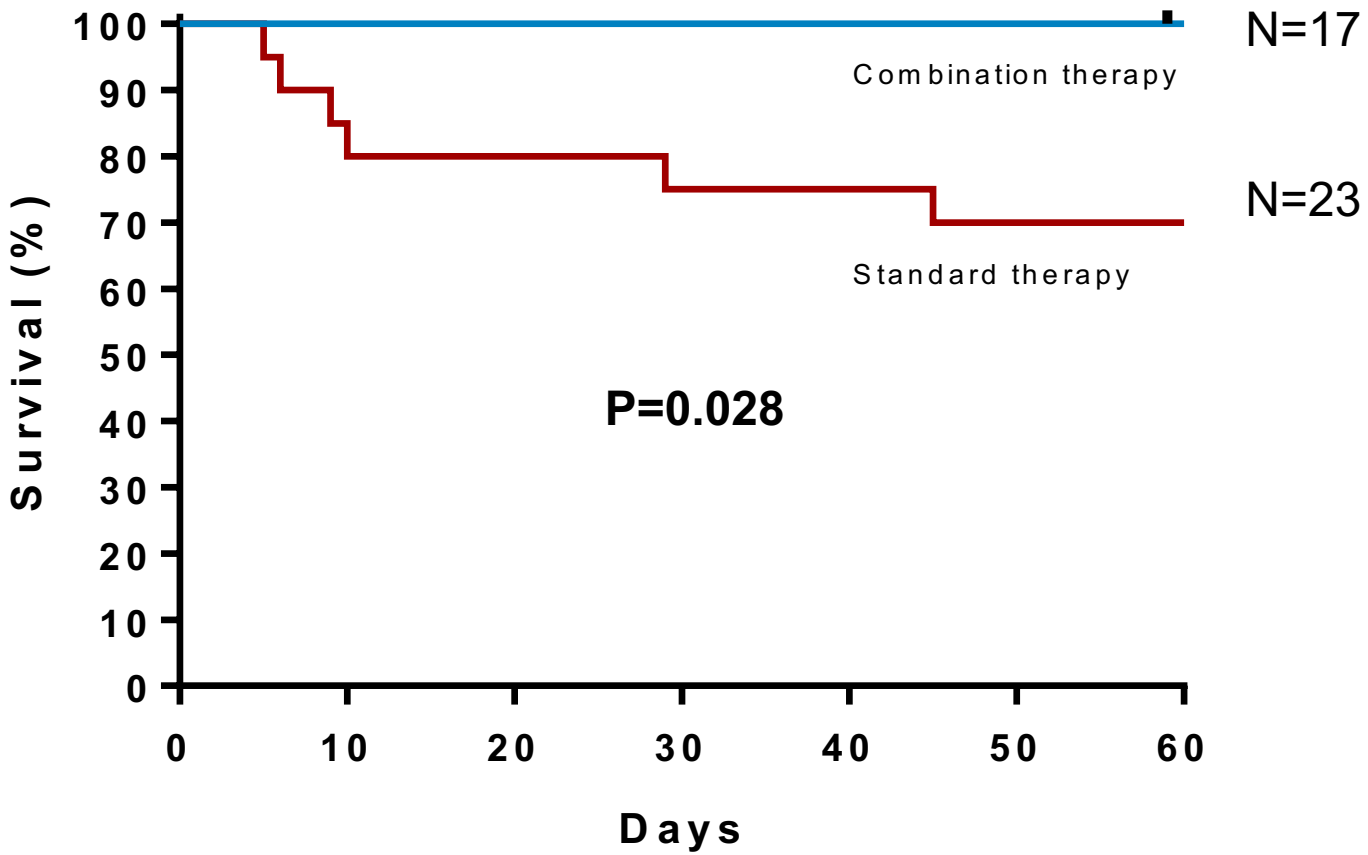
Department of Pharmaceutical Sciences, Nesbitt College of Pharmacy and Nursing, Wilkes University, Wilkes-Barre, Pennsylvania (A.T.W., G.A.H., P.M., S.W., A.B., A.L.V.); and Knowledge and Evaluation Research Unit, Clinical and Translational Sciences, Mayo Graduate School, Mayo Clinic, Rochester, Minnesota (M.R.G.)

Using Ceftaroline as the Beta-Lactam in Daptomycin Combination Therapy in MRSA Bacteremia



Prospective Randomized Study of Vancomycin vs DAP+CPT in MRSA Bacteremia





Geriak M et al. Antimicrob Agents Chemother 2019 Apr 25;63(5):e02483-18.

Expensive

- **Limitations on Disposition**
- **Third Party Payors**
- **Subacute Nursing Facilities**

Cumbersome

- **Many Doses**

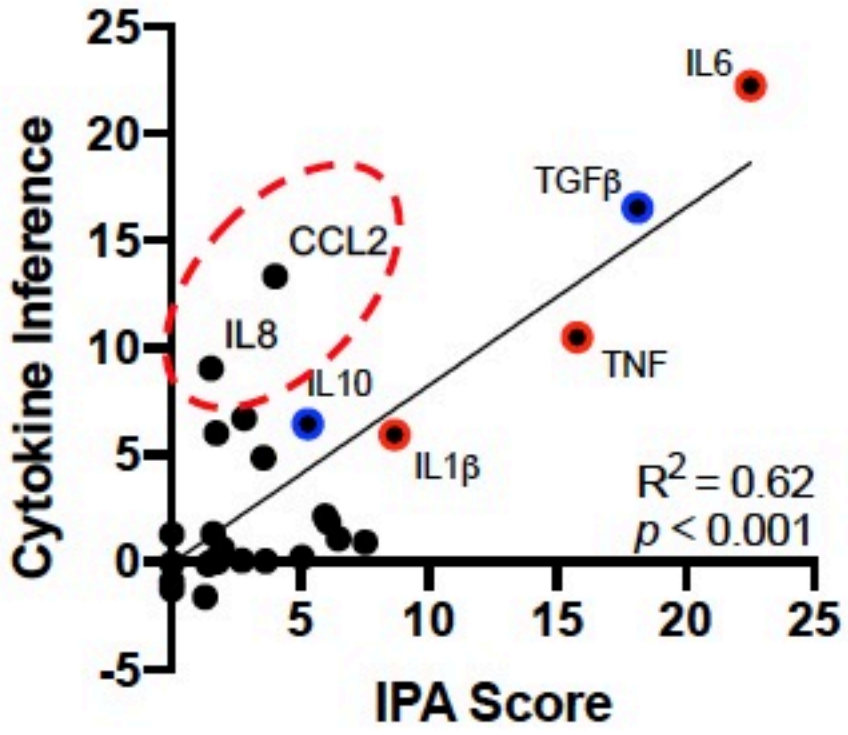
More drugs=more risk of medical errors and AE's

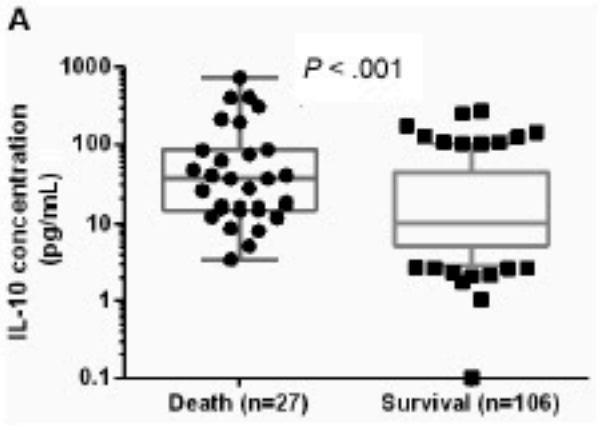
CAN DAP+CPT BE TARGETTED TO HIGH-RISK PATIENTS?

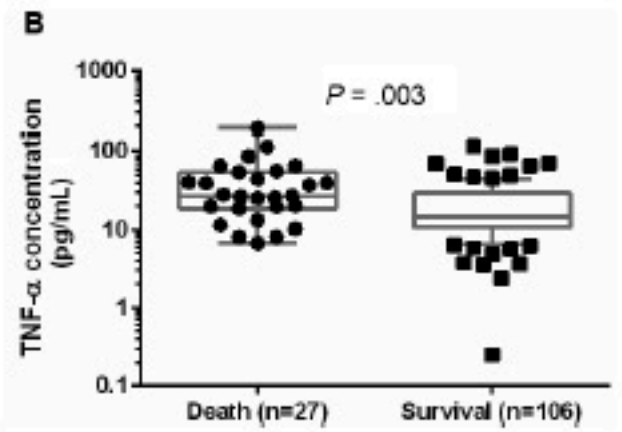
HOW TO IDENTIFY HIGH RISK PATIENTS UP FRONT?

- **Clinical**
- **Biomarkers**

Biomarkers/Cytokines Predicting Mortality in SaB







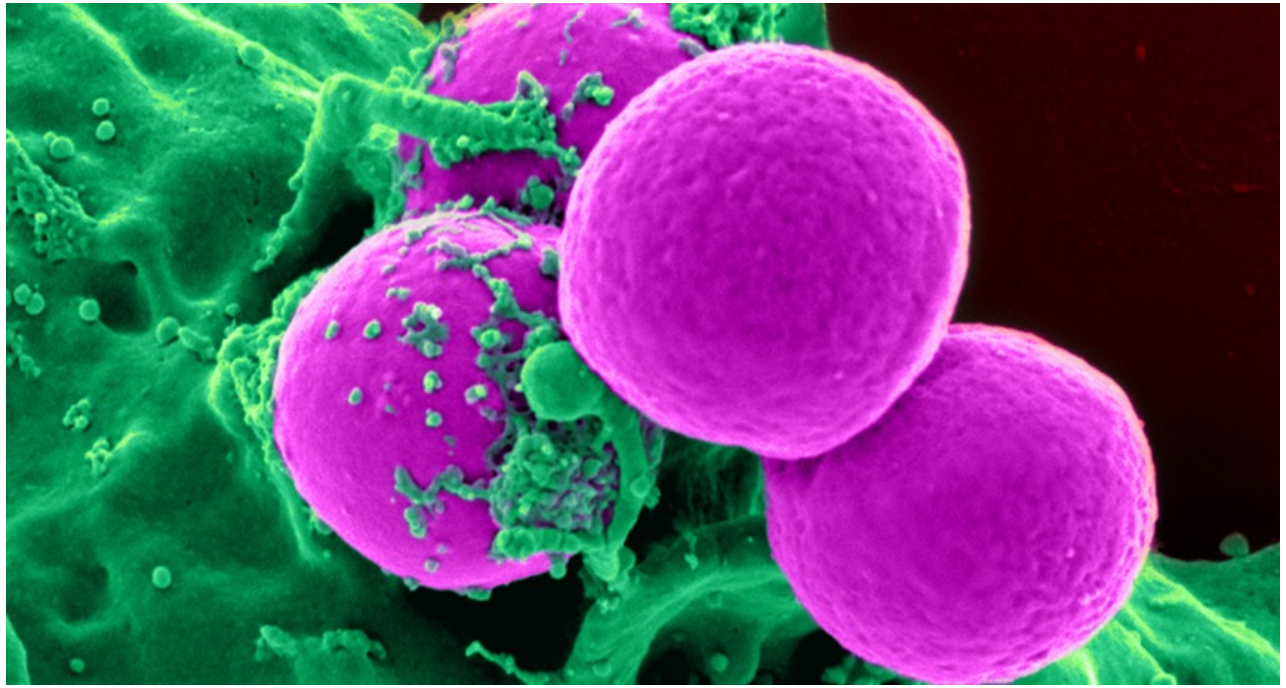
	ROC AUC	P Value
IL–8	0.832	<0.001
CCL2	0.814	<0.001
IL–6	0.785	<0.001

Wozniak JM, Mills RH, Olson J, Caldera JR, Sepich-Poore GD, Carrillo-Terrazas M, Tsai CM, Vargas F, Knight R, Dorrestein PC, Liu GY, Nizet V, Sakoulas G, Rose W, Gonzalez DJ. Mortality Risk Profiling of Staphylococcus aureus Bacteremia by Multi-omic Serum Analysis Reveals Early Predictive and Pathogenic Signatures. Cell. 2020 Sep 3;182(5):1311-1327.e14.

Induction->Consolidation Paradigm

- MRSA Bacteremia is a dynamic condition, so therapy must be dynamic
- Combination therapy at the beginning to de-escalation to monotherapy
- One small study of 30 patients rx with combo: 15 de-escalated to monotherapy, 15 remained on combination
  - Median bacteremia duration preceding CPT 6 days
  - 1 recurrence in monotherapy; 2 30-day readmission monotherapy; 1 death monotherapy, 3 deaths combo
  - Ahmad O et al. Infect Dis Ther. 2020 Mar;9(1):77-87
- Factors to consider:
  - Bridge to definitive source control (eg. left-sided IE with CNS emboli)
  - Bacteremia cleared 5-7 days
  - Time to discharge and disposition (home vs SNF vs LTAC)
  - CRP reduced >50%

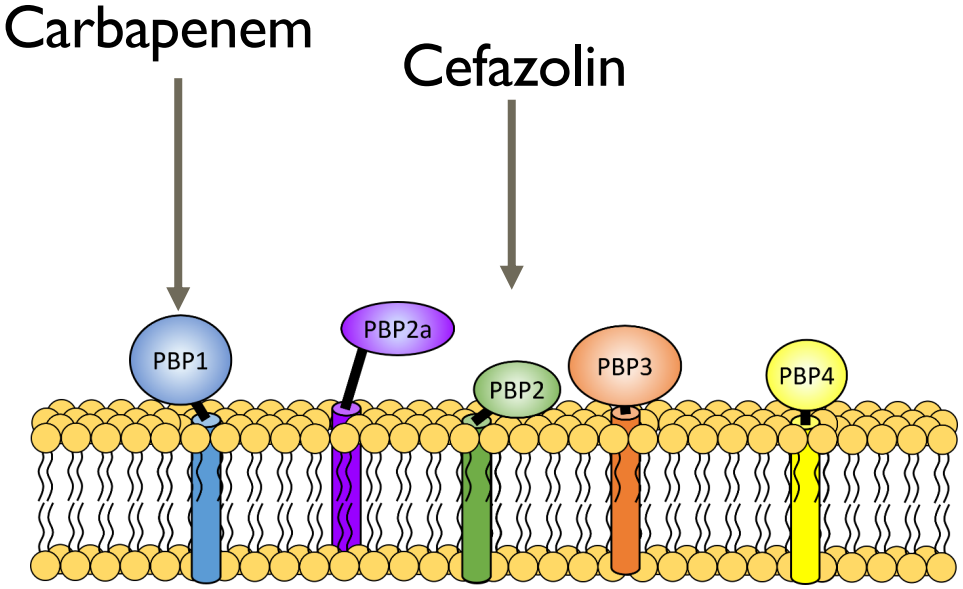
REFRACTORY MSSA BACTEREMIA



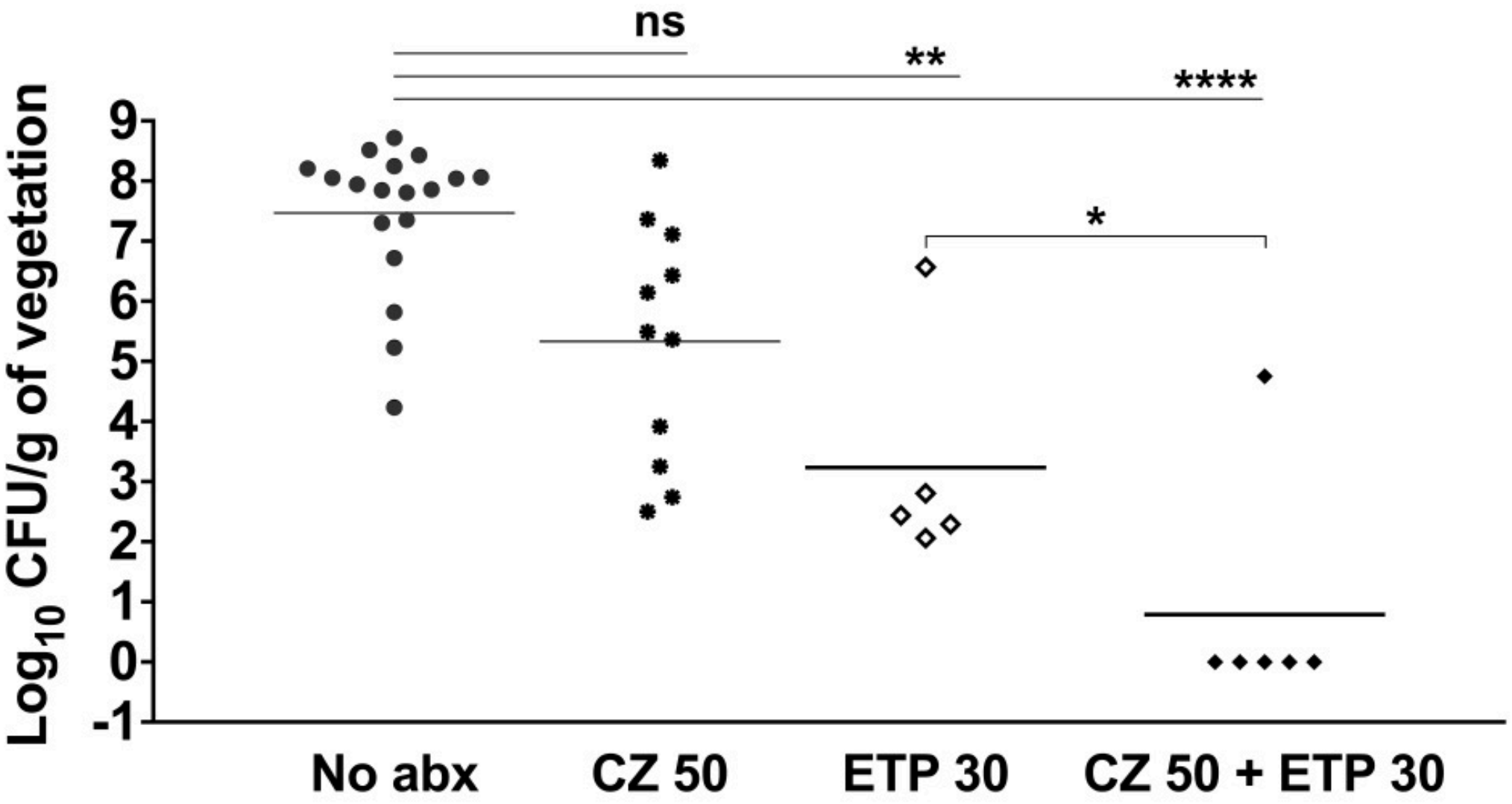
- 32 yo IVDA but otherwise healthy admitted with worsening fevers x 1 week
- Accompanied by SOB, lethargy
- Found to have leukocytosis, tachycardia, hypotension, admitted to ICU
- Vancomycin+ceftriaxone for 1st 24 hrs
- Blood Cx GPC->ID called->Ceftaroline 600 mg iv q8 hr+ Dapto 8 mg/kg/24 hr x 24 hr
- Verigene Show MSSA in 24 hrs->Nafcillin 2g iv 4 hr
- Imaging Chest, Abdomen, Pelvis: Multifocal pneumonia suggestive of septic pulmonary emboli, some early cavitation
- TEE shows **3.2 cm tricuspid valve vegetation**
- Blood Cultures Remain + Despite 5 days nafcillin
- Ertapenem 1g iv q24 hr + cefazolin 2g iv q8hr →**Blood cultures clear in 24 hrs!!**
- Angiovac was performed→Partial success in debulking the Tricuspid Valve
- Signed out AMA after 4 weeks in the hospital

MEDICAL THERAPY: OPTIONS

Consider DAP +Beta-lactam But May Be Antagonistic in MSSA

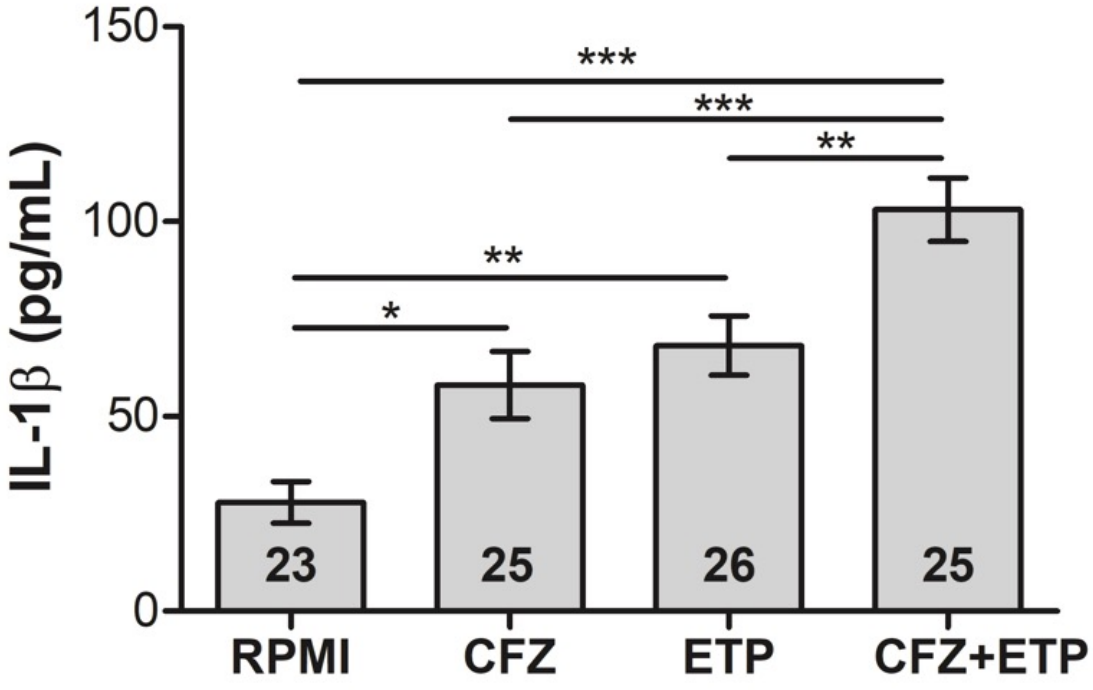


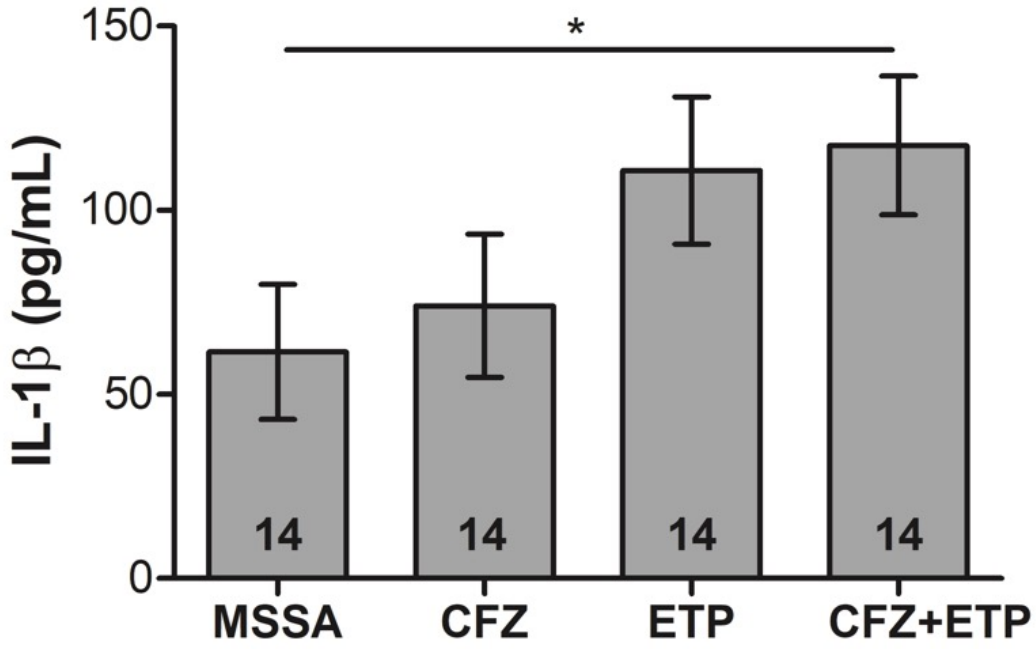
MSSA RAT ENDOCARDITIS MODEL



Ulloa E et al. Clin Infect Dis 2020 Sep 12;71(6):1413-1418

Is the Success of Cefazolin plus Ertapenem In Methicillin-Susceptible Staphylococcus aureus Bacteremia Based on Release of IL1-β?



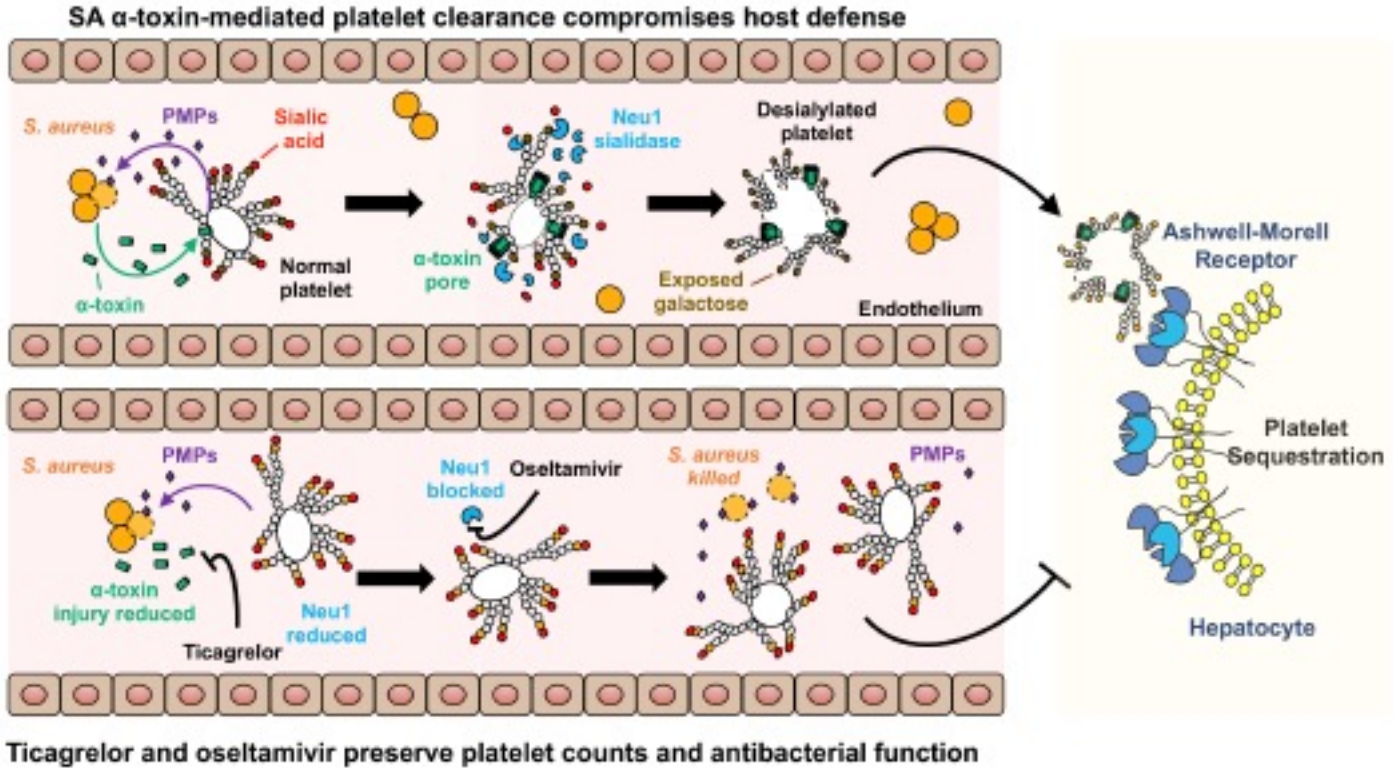


Smelter D et al Antimicrob Agents Chemother E Pub Jan 3 2022

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

Repurposed Drugs Block Toxin-Driven Platelet Clearance by the Hepatic Ashwell-Morell Receptor to Clear *Staphylococcus aureus* Bacteremia

Josh Sun[1,2,3*], Satoshi Uchiyama[1*], Joshua Olson[1], Yosuke Morodomi[4], Ingrid Cornax[1], Nao Ando[1], Yohei Kohno[1], May M. T. Kyaw[1], Bernice Aguilar[1], Nina M. Haste[1,2,3], Sachiko Kanaji[4], Taisuke Kanaji[4], Warren E. Rose[5], George Sakoulas[2], Jamey D. Marth[6,7], Victor Nizet[1,2,3 †]



Platelet Killing of *S. aureus*

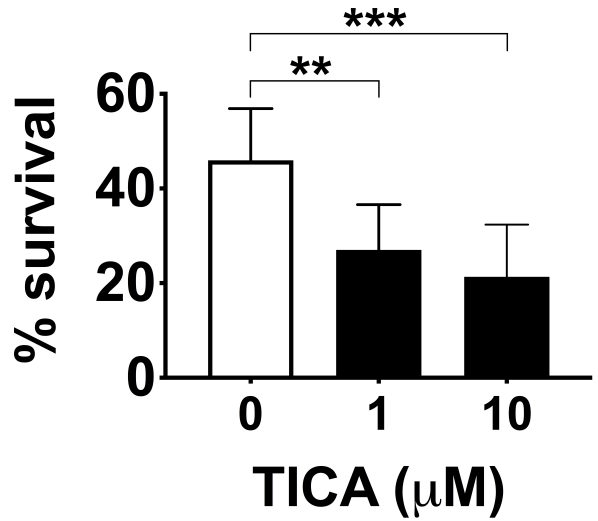


Figure 1. Ticagrelor (TICA) boosts the bactericidal activity of platelets, frontline components of innate immunity, to kill methicillin-susceptible *S. auerus in vitro* at physiological attainable concentrations (1μM).

Ulloa E et al. J Infect Dis. 2021

Summary and Conclusions

- Large Clinical trials Lacking—are they possible?
- In some more difficult cases of S. aureus bacteremia, combination therapy is better than monotherapy
  - membrane+cell wall agent
  - double beta-lactam
- Benefit declines with delay in use (eg. as a salvage)
- Early risk stratification: clinical+ biomarker metrics
- ‘Induction’ and ‘Consolidation’ Phases Rx
  - Beginning/Middle/’Mop up’ Regimens
- Consider intervening in host-pathogen interaction
- Lysin Therapy
- Phage Therapy

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