UWTASP

tele-antimicrobial stewardship program

May 21, 2019

Agenda

- Daptomycin Dosing
- Case Discussions
- Open Discussion

UWTASP
tele-antimicrobial stewardship program

Daptomycin Dosing

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Mechanism of Action

- Cyclic polypeptide
- Binds to cell membrane
  - Calcium-dependent
- Depolarization of cell membrane
  - Efflux of potassium
  - Destroys ion-concentration gradient

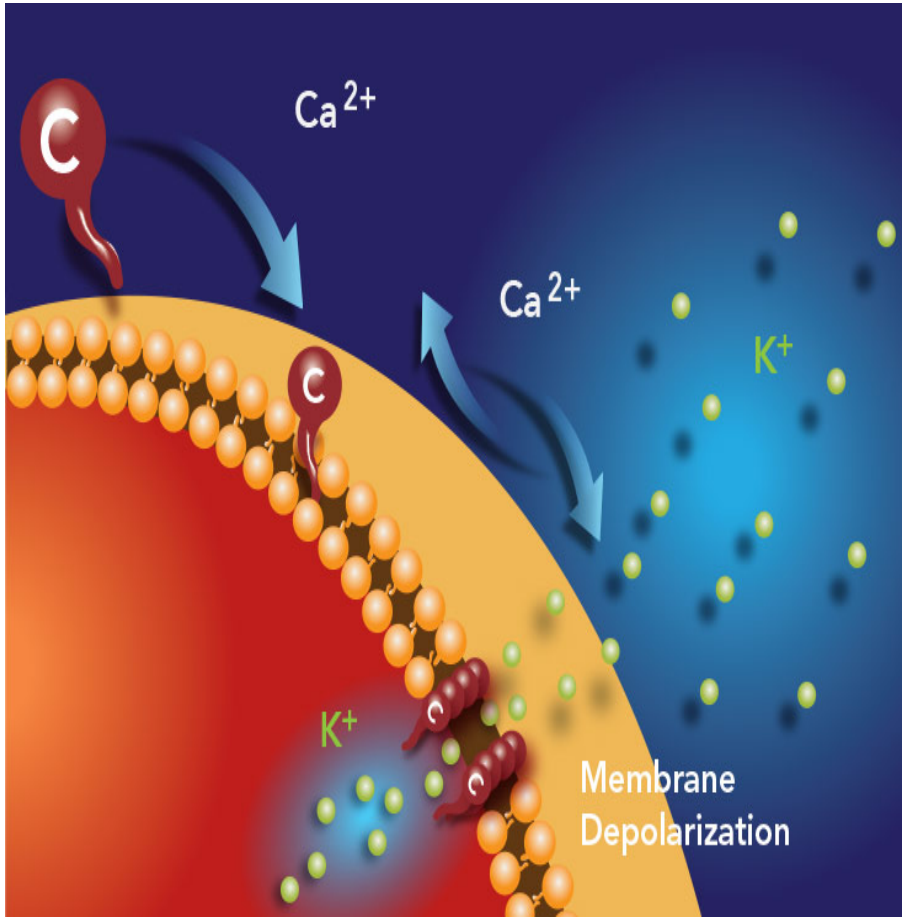


Image from Cubicin® - Merck

citations

Daptomycin

- Concentration dependent killing
- Gram positive organisms including MRSA and VRE
- FDA approved dosing based on total body weight:
  - Skin and soft tissue infection: 4mg/kg/day
  - Bacteremia/right sided endocarditis: 6mg/kg/day

citations

Which Daptomycin dose do you use for bacteremia?

- 4mg/kg/day
- 6mg/kg/day
- 8-10mg/kg/day
- I am not sure

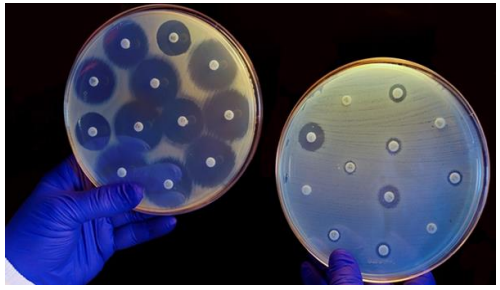
citations

Why do we care about dosing?

- Clinical Efficacy

- Toxicity

- Resistance



citations

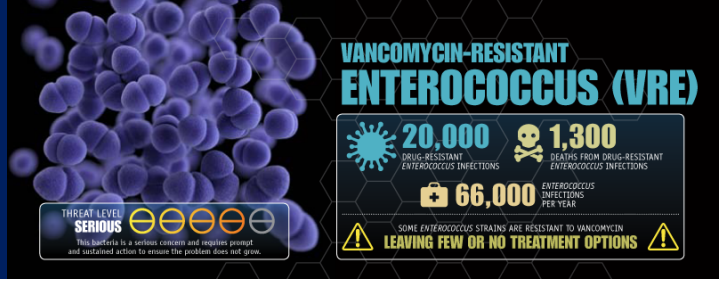
Clinical Efficacy

- Vancomycin resistant enterococcal bloodstream infections (VRE BSI)
- No head to head randomized controlled trials of daptomycin (DAP) vs. linezolid (LZD)
- Earlier meta-analyses favored LZD over DAP:
  - Methodologic limitations: retrospective studies, single center, heterogeneity
  - Median DAP daily dose of 6mg/kg affected outcomes?

1. Whang DW et al. AAC. 2013; 57:5013-18.
2. Balli EP et a. AAC. 2014; 58:734-39.
3. Chuang YC, et al BMC Infect Dis. 2014;13;14:687

citations

National VA Cohort



- N=644 suggested higher clinical failure, and 30-day mortality with continuous LZD compared to DAP (median dose = 6mg/kg/d)

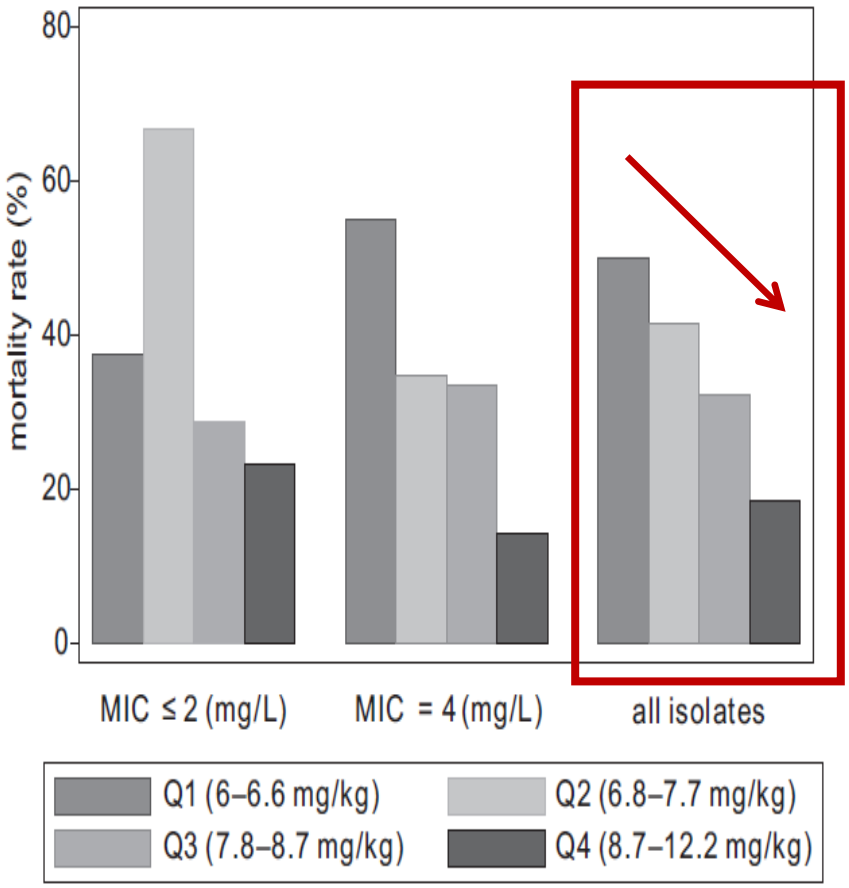
- N=2630 compared continuous and sequential DAP or LZD using propensity score matching:
  - Median DAP dose = 6mg/kg/d
  - Continuous LZD associated with more persistent VRE BSI, longer LOS, and higher mortality compared to DAP
  - LZD to DAP switch had a lower 30d mortality than those remained on LZD

Britt NS, et al. CID 2015;61(6):871-8; Britt NS, et al. AAC 2017;61(5):e02216-16.

citations

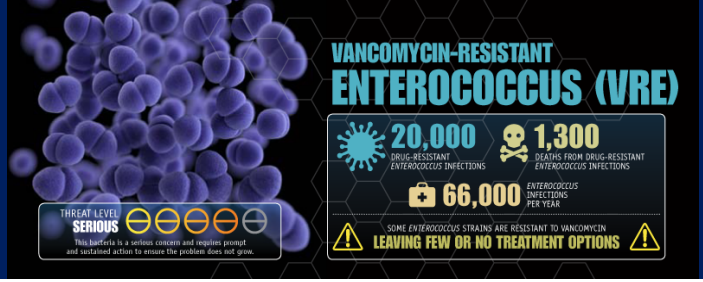
Dose Implication

- Two hospitals in Taiwan (n=212) comparing DAP to LZD for VRE BSI
- LZD associated with lower 14d mortality
- Mortality was similar between LZD and high dose DAP (≥ 9mg/kg/d)

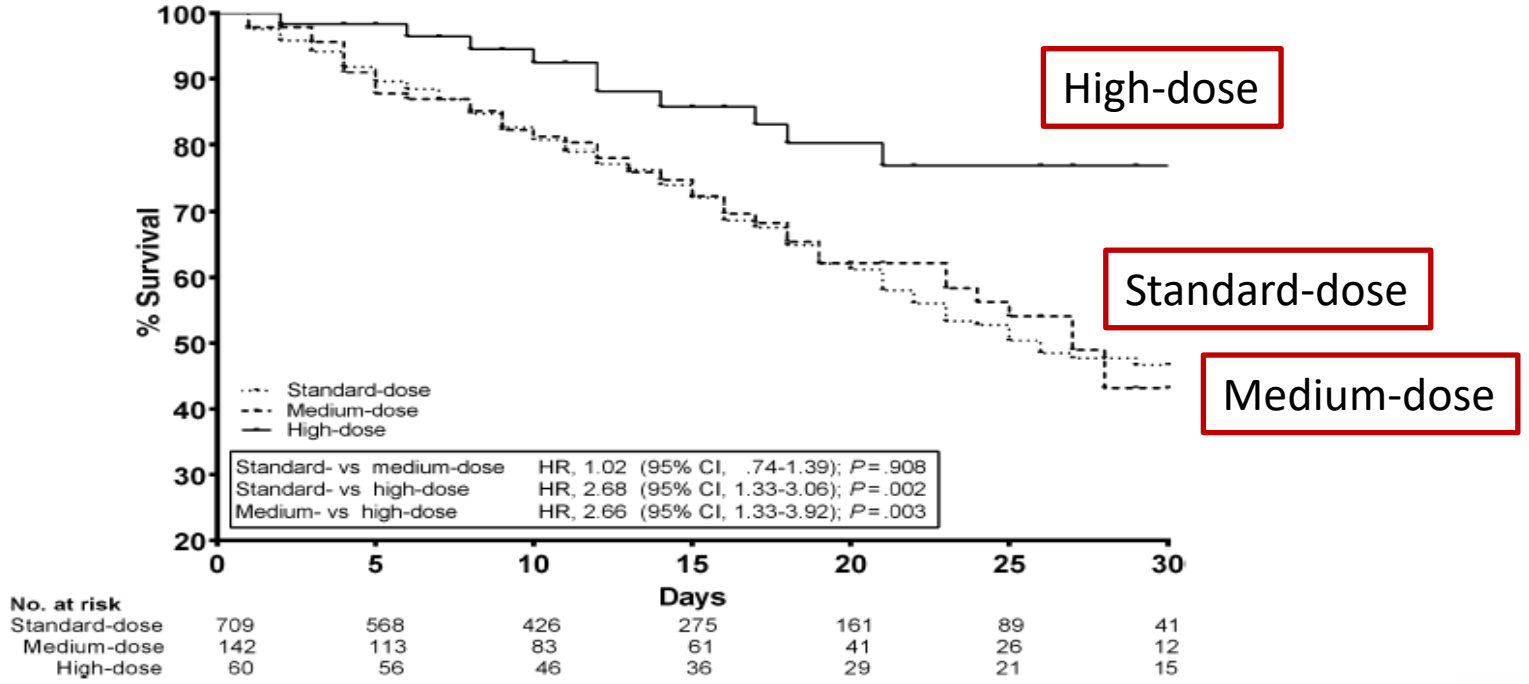


citations Chuang YC, et al. CMI 2016;22:890.e1-e7;
Chuang YC, et al. CID 2017;64(8):1026-34.

Dose Implication

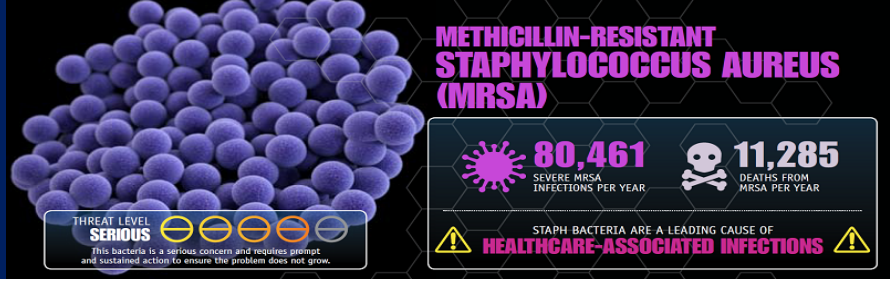


N=911 comparing DAP standard (6mg/kg/d), medium (8mg/kg/d) and high (≥ 10mg/kg/d) dose



citations Britt NS, et al. CID 2017;64(5):605-13.

MRSA BSI



- National VA cohort study (n=371) comparing DAP label dose (6mg/kg/d) and high dose (≥ 7mg/kg/d)
- MRSA BSI treated with vancomycin within 24 hours of positive blood culture, switched to DAP within 7d; (median = 4d)
- DAP high dose:
  - 7mg/kg (43%); 8-9mg/kg (50%); ≥ 10mg/kg (7%)
- High dose DAP was associated with lower 30d mortality using propensity score matching

Timbrook TT, et al. Pharmacotherapy 2018;38(2): 189-196.

citations

IDSA Guidelines: high dose DAP

- MRSA bacteremia and endocarditis: “some experts recommend DAP at **8-10mg/kg**”
- Persistent MRSA bacteremia and vancomycin treatment failures: “high dose DAP **10mg/kg**”
- Native valve endocarditis caused by staphylococci: “DAP **≥ 8mg/kg**”
- Endocarditis caused by ampicillin and vancomycin resistant enterococci: “DAP **10-12mg/kg**”

Liu C, et al. CID 2011;52(3):e18-55

citations

Toxicity

- Myopathy (2-14%), rhabdomyolysis (5%)
- Median CPK was similar among patients in low, medium, and high DAP dose.
- No association was observed between CPK elevations and AKI.
- No increased risk of CPK elevations among patients on concomitant statins.

Chuang YC, et al. CID 2017;64(8):1026-34.
Britt NS, et al. CID 2017;64(5):605-13.

citations

DAP and statin co-administration

- Single center, case control study (n=3042) examining risk factors for DAP associated myopathy
  - Myopathy defined as CPK above ULN
  - Rhabdomyolysis defined as CPK $\geq$ 10x ULN
  - Mean DAP dose: 6mg/kg/day

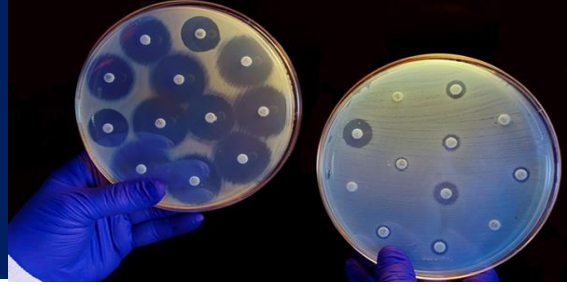
- Myopathy
  - 128 (4.2%) after 17d, statin is a risk factor

- Rhabdomyolysis
  - 25 (0.8%) 11d, obesity and statin are both risk factors

citations

Dare RK, et al. CID 2018;67(9):1356-63.

Resistance



DAP exposure precedes infection/colonization with DAP non-susceptible enterococcus (DNSE)

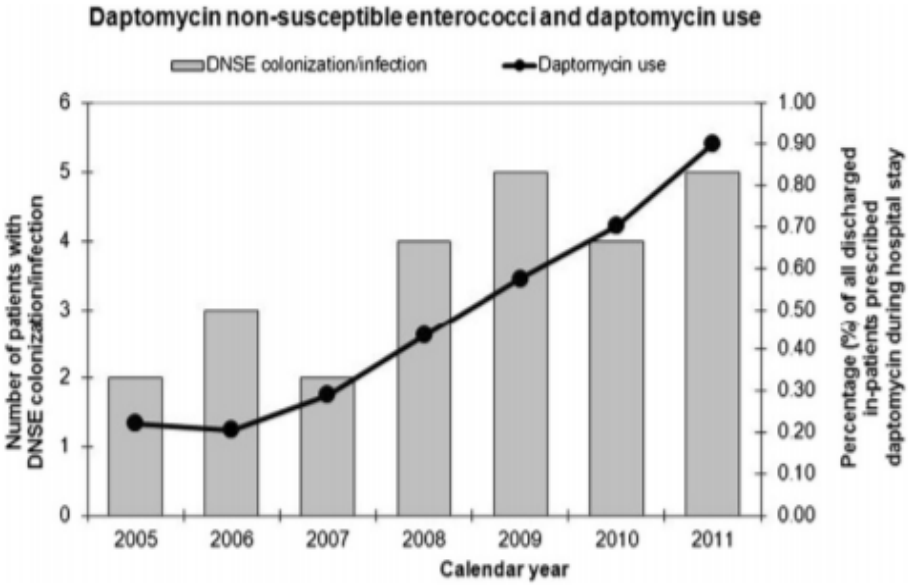
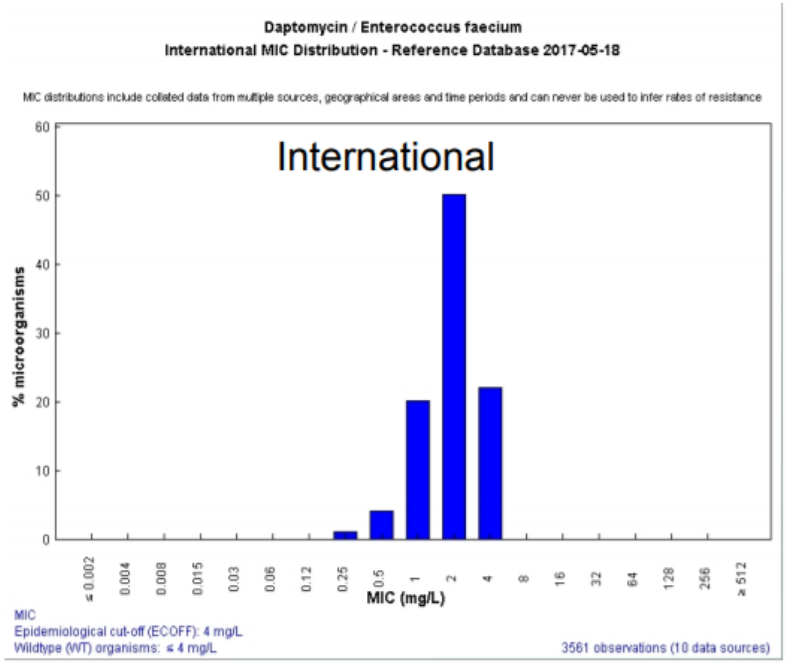


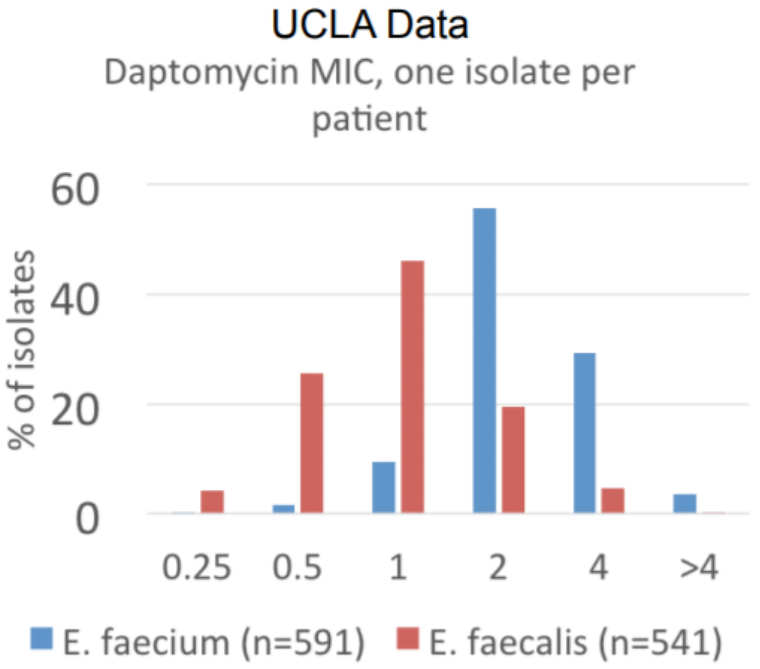
Figure 1 Number of patients with colonization/infection due to daptomycin non-susceptible enterococci (solid bars; left vertical axis), and percentage of all discharged in-patients prescribed daptomycin during their hospital stay (solid line; right vertical axis) for each study year. Information for 2011 based on information for the first 6 months of calendar year.

citations

Storm JC, et al. Antimicrobial Resistance and Infection Control 2012;1:19

Daptomycin MIC distribution





EUCAST MIC Distributions

Table 1: MIC distributions and epidemiological cut-off values (mg/L) for *Enterococcus* spp.

Organism	≤0.06	0.125	0.25	0.5	1	2	4	8	≥16	ECOFF
Enterococcus faecalis	51	166	765	8064	12321	3255	398	5	0	2
Enterococcus faecium	10	63	144	611	3228	14761	1495	23	5	4

Image from CLSI Ad hoc working group to reassess daptomycin breakpoint for enterococcus

citations

Time to change breakpoint

Clinical Infectious Diseases

MAJOR ARTICLE

Influence of Minimum Inhibitory Concentration in Clinical Outcomes of *Enterococcus faecium* Bacteremia Treated With Daptomycin: Is it Time to Change the Breakpoint?

Bhavarth S. Shukla,[1,2] Samuel Shelburne,[2,3] Katherine Reyes,[4] Mini Kamboj,[5] Jessica D. Lewis,[6] Sandra L. Rincon,[1,7] Jinnethe Reyes,[7] Lina P. Carvajal,[7] Diana Panesso,[1,7] Costi D. Sifri,[6] Marcus J. Zervos,[4,8] Eric G. Pamer,[5] Truc T. Tran,[1] Javier Adachi,[2] Jose M. Munita,[1,9] Rodrigo Hasbun,[1] and Cesar A. Arias[1,7]

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- VRE BSI with DAP MIC of 3-4 µg/mL is associated with microbiologic failure
- DAP dose of ≥ 8mg/kg may be more effective than lower dose

Shukla BS, et al. CID 2016;62(12):1514-20.

citations

CLSI MIC Breakpoints

Enterococcus	Daptomycin MIC (mcg/mL)	
	Previous	**Updated**
Susceptible	≤ 4	≤ 1*
Susceptible Dose Dependent (S-DD)		**2-4****
Resistant	≥ 8	≥ 8

*Based on a dosage regimen of **6 mg/kg/day** in adults

The S-DD category is based on a dosage regimen of **8-12 mg/kg/day in adults and is intended for serious infections due to Enterococcus spp. ID consultation is recommended.

citations

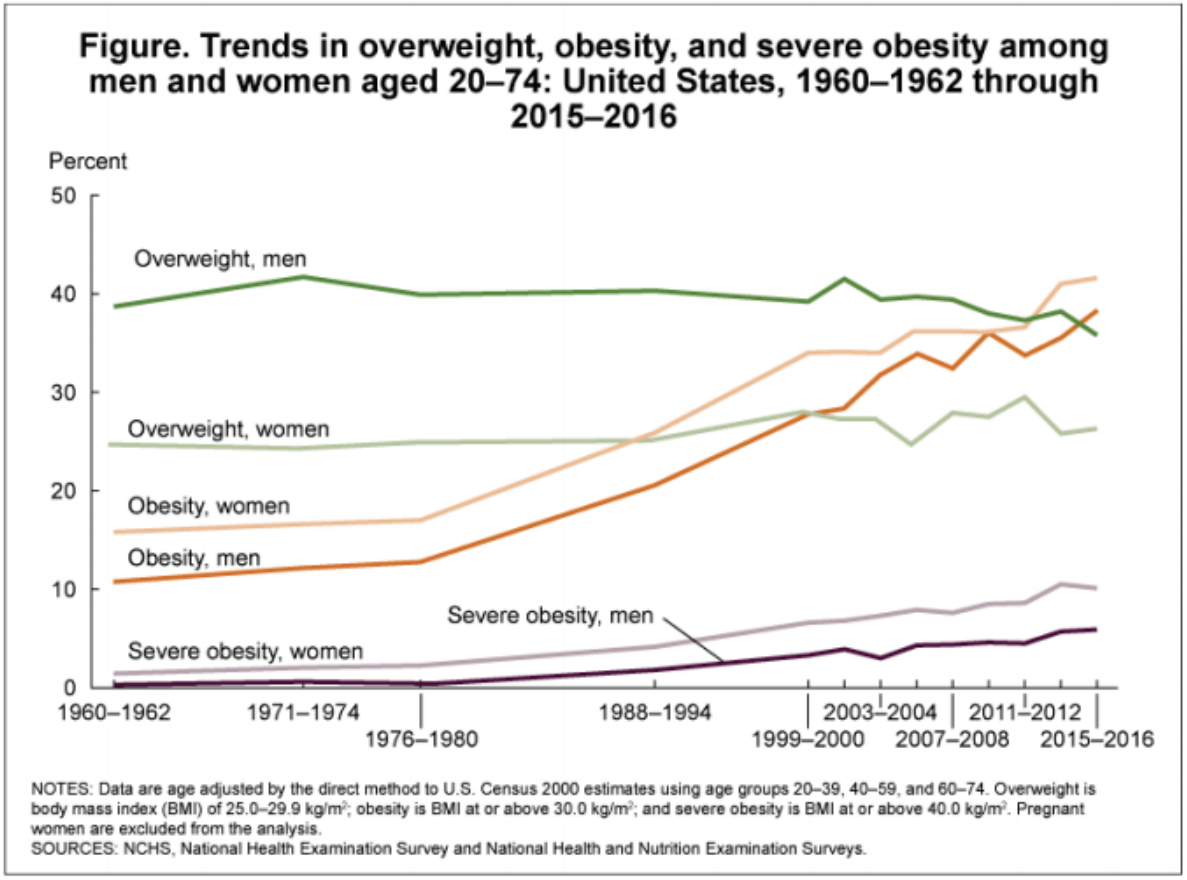
Intermittent Hemodialysis (IHD)

- FDA approved dosing: 4-6mg/kg/day q48h
- DAP AUC in IHD patients are 50% lower than non-HD patients during the final 24h of the 72h interdialytic period
- Suggest 50% dose increase if 3 days between HD

Haselden M, et al. Annals of Pharmacotherapy 2013;47(10): 1342-7.

citations

Americans are getting BIGGER



citations

NIH: national institute of diabetes and digestive and kidney disease

Which weight do you use for obese patients?

- Total body weight (TBW)
- Ideal body weight (IBW)
- Adjusted body weight (AdjBW)
- I am not sure

citations

Ideal Body Weight (IBW)

- University of Wisconsin adopted institutional-wide DAP dosing initiative based on IBW in 2010
- Clinical outcomes were similar between patients dosed on TBW (n=69) and IBW (n=48) with an average BMI of 31 kg/m^2
- Limitation:
  - Majority of patients (>60%) were treated for intra-abdominal infections, SSTI, or UTI

Ng JK, et al. AAC 2014;58(1):88

citations

Adjusted Body Weight

- DAP dosing protocol based on TBW vs. AdjBW in patients with BMI $\geq$ 30 kg/m^2

- No difference: clinical outcomes, 90d re-admission and mortality

	TBW; N=50 (%)	AdjBW; N=51 (%)
Average BMI (kg/m^2)	35	37
Low DAP dose (6mg/kg/d)	41 (82)	11 (22)
Medium DAP dose (6.1-8mg/kg/d)	7 (14)	23 (45)
High DAP dose (>8mg/kg/d)	2 (4)	17 (33)

Fox AN, et al. Therapeutic Advances in ID 2019;6:1-10.

citations

Fixed Dosing

- Assumptions for total body weight based dosing:
  - drug clearance (Cl) and volume of distribution (Vd) change proportionately with total body weight
- No significant difference in Cl, Vd, or half life between morbidly obese and non-obese PK models
- Fixed non-weight based dosing for morbidly obese patients?

Butterfield-Cowper JM, et al. Pharmacotherapy 2018;38(9):981-5.

citations

Summary: Dose Matters!

	DAP dose
MRSA BSI	≥ 8mg/kg
VRE BSI	≥ 10mg/kg
Intermittent Hemodialysis	50% dose increase if 3d between HD
Obesity	IBW/AdjBW/TBW

citations