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Drug Dosing in the Obese Emergency Department Patient: How High Can You Go?

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Disclosures

- **David E. Zimmerman:** ASHP: Author
- All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Objectives

- Describe principles of pharmacokinetics that are involved for medication dosing in the obese patient in the emergency department.
- Evaluate the published literature that supports dosing recommendations.
- Given a clinical situation, recommend the appropriate dosing weight and dose for the medication dose.

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EM Pharmacist's PK Guide to the Galaxy

Drug Examples

Sedative A

- F = 1 (being given IV)
- Vd = 4 L/kg
- Protein Binding = 60%
- Clearance = hepatic
- Elimination = renal

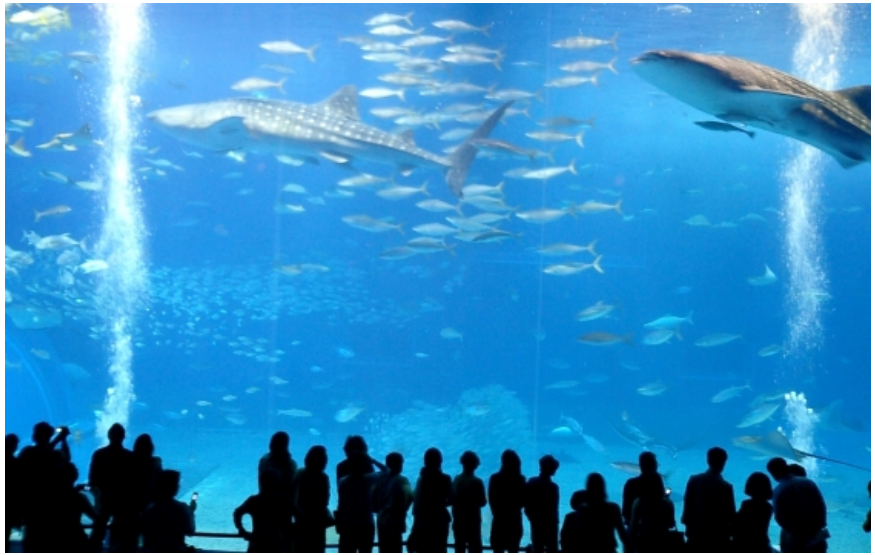
Sedative B

- F = 1 (being given IV)
- Vd = 2 L/kg
- Protein binding = minimal
- Clearance = hepatic
- Elimination = renal

F, bioavailability; Vd, volume of distribution

ADME

- Absorption (F)
- Distribution (Vd)



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ADME

- Different weights for Vd parameters
  - Total body weight (TBW)
  - Ideal body weight (IBW)
  - Adjusted body weight (AdjBW)
  - Lean body weight (LBW)
    - LBW (female) = [1.07 x TBW(kg)] – [0.0148 x BMI x TBW (kg)]
    - LBW (male) = [1.1 x TBW(kg)] – [0.0128 x BMI x TBW (kg)]

Br J Clin Pharmacol. 2004;58(2):119-33.

ADME

- Metabolism???
- Excretion/Clearance
  - Estimating renal clearance
  - Cockcroft-Gault
- Evaluate concomitant disease states affecting clearance

Demystifying Drug Dosing in Obese Patients. 2016;5-13.

Drug Examples

Sedative A

- F = 1 (being given IV)
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Sedative B

- F = 1 (being given IV)
- Vd = 2 L/kg
- Protein binding = minimal
- Clearance= hepatic
- Elimination = renal

F, bioavailability; Vd, volume of distribution

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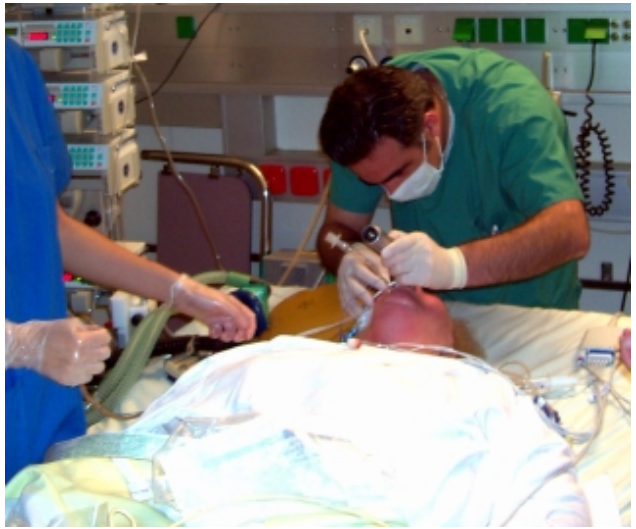
RSI N'At

Rapid Sequence Intubation (RSI) Goals

- Adequately sedate and then paralyze for optimal intubating conditions
- Secure airway
- Prevent iatrogenic injury



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Weight, hold up…we need a starting point

- How are we getting the patient's weight?
  - Looking at the chart from last admission?
  - Weigh bed?
  - Asking them?
  - Estimating (i.e. guessing)
    - ED health care providers have been shown to underestimate obese patient's weight

Am J Emerg Med. 2007;25(3):307-12.

We know we under dose obese patients in RSI

- Obese patients were more likely to be underdosed with:
  - Succinylcholine (OR 63.7; 95% CI: 17.8-228.1)
  - Etomidate (OR 178.3; 95% CI, 37.6-844.7)

Am J Emerg Med. 2016;34:2423-25.

Etomidate

- Volume of distribution (Vd): 3-5 L/kg
- Protein binding: ~75% to albumin
- Rapid distribution from the central compartment

Clin Pharmacokinet. 1977;2(5): 344-72.

Etomidate

- Prospective “study” in obese patients undergoing laparoscopic surgery
- Received etomidate via syringe pump until goal bispectral index
- Obese vs. normal body weight patients required ~21 mg ($p > 0.05$)

Eur J Anaesthesiol. 2014; 31: 713-714.

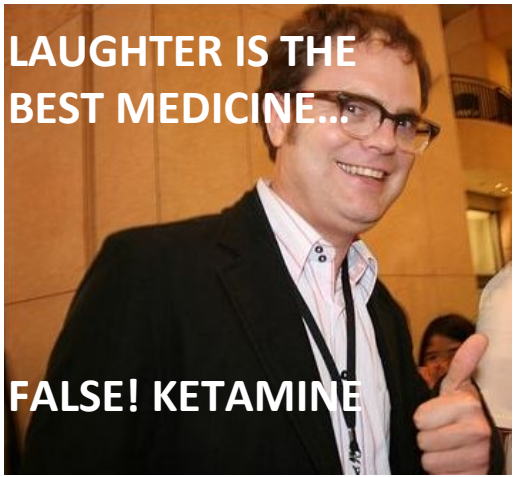
Etomidate

- What happens if I give too much etomidate….waiting…waiting…still waiting…

- Use TBW until more evidence arrives

Ketamine

- Typical RSI dosing: 1.5-2 mg/kg
- Currently recommended dosing weight: TBW vs. LBW????
- PK parameters



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J Crit Care. 2016;35:145-9.

Ketamine

	Ectomorph n = 7	Mesomorph n = 5	Endomorph n = 10
Percent Fat	12.1 ± 3.3	22 ± 3.5	43.8 ± 12
Weight, kg	53.9 ± 7.6	71.8 ± 8.6	91.7 ± 15.4
Lean body mass, kg	47.1 ± 6.6	56 ± 7.5	50.5 ± 9.2
Dose, mg	90 ± 12.6	105 ± 17	98 ± 18.6
Male/female	2/5	4/1	5/5
Dose/TBW, mg/kg	1.67	1.46	1.07
Dose/LBW, mg/kg	1.91	1.88	1.94

Kg, kilogram; LBW, lean body weight; mg, milligram, TBW; total body weight

Table adapted from: *Anesth Analg*. 1972;51(2):299-305

Clinical Considerations of Ketamine

- What happens if I do not give enough?
- What happens if I give too much?
- Dosing weight to use: TBW
  - Until further evidence is published

Propofol

- Clearance and Vd are better correlated with TBW than AdjBW
- Concerns with hemodynamic consequences
- Avoid unless hypertensive or available use of vasopressors
- Dosing weight to use: TBW

Anesthesiology. 1993;78(4): 657-65.
Demystifying Drug Dosing in Obese Patients. 2016;77-96.

Succinylcholine

- In one study, comparing LBW vs. IBW vs. TBW
  - No difference in time of onset
  - Longer duration of action in TBW vs. IBW (8.5 vs. 5 mins)
  - 1/3 of patients in IBW group had intubating conditions rated as poor vs. none in TBW group

Anesth Analg. 2006;102(2): 438-42.
Demystifying Drug Dosing in Obese Patients. 2016;77-96.

Succinylcholine

- In a retrospective review of 891 patients who received RSI in the ED:
  - Decrease first-pass success in patients > 120 kg
  - Under dosing of succinylcholine in patients > 120 kg
  - Bottom line: Use TBW

Emerg Med J. 2017;34(11): 739-43.

Rocuronium

- Onset: similar when dosed on TBW vs IBW
- Longer duration of action with TBW dosing
- If I give too much…what happens?
- Bottom line: IBW

Anesth Analg. 2009;109(3): 787-92. *Eur J Anaesthesiol Suppl*. 1995;11:107-110.
Eur J Anaesthesiol. 1999;16(8):507-10. *Acta Anaesthesiol Belg*. 2001;52(3):293-95.
Anesth Analg. 2004;99(4):1086-89.

Rocuronium Dosing: 0.6 vs. 1.2 mg/kg

Height	IBW Female, kg	Dose Female, mg (0.6 mg/kg)	Dose Female, mg (1.2 mg/kg)	IBW Male, kg	Dose Male, mg (0.6 mg/kg)	Dose Male, mg (1.2 mg/kg)
5’	45.5	27.3	54.6	50	30	60
5’6”	59.3	35.6	71.2	63.8	38.3	76.6
6’	73.1	43.9	87.8	77.6	46.6	93.2
6’6”	86.9	52.1	104.2	91.4	54.8	109.6

Fentanyl

- Pharmacokinetics

- Fentanyl doses based upon TBW overestimates
  - PK mass (kg) = 52 / [1 + (196.4 x $e^{-0.025(TBW)}$ – 53.66)/100]
  - A 200 kg person would have a PK mass of 109 kg
  - You would then use this “PK mass” for weight-based dosing

- In case you cannot do this math in your head (I can’t)….use fixed/capped doses and reassess

Anesthesiology. 2004;101(3):603-613.
Br J Anaesth. 2005; 95(3):377-383.

Morphine

- Pharmacokinetics
- Retrospective review, evaluated analgesic response following fixed dose of 4 mg IV
  - Analgesic response was not influenced by BMI
- Fixed, non-weight based!!

Emerg Med J. 2014;31(2):139-42.

Hydromorphone

- Pharmacokinetics
- A secondary analysis of a previous prospective clinical trial failed to find any strong correlation between body weight and decrease in reported pain
- Guess what…Fixed, non-weight based!!

Am J Emerg Med. 2015;33(10):1522-1523.

Summary of Agents for RSI

Agent	Dosing Weight	Dosing
Etomidate	TBW	0.3 mg/kg
Ketamine	TBW	1.5-2 mg/kg
Propofol	TBW	1.5-2 mg/kg
Succinylcholine	TBW	1.5 mg/kg
Rocuronium	IBW	1-1.2 mg/kg

IBW; ideal body weight; kg, kilogram; mg, milligram; TBW, total body weight

Summary of Agents

Agent	Dosing Weight	Dosing
Morphine	--------	Fixed, non-weight based
Hydromorphone	--------	Fixed, non-weight based
Fentanyl	--------	Fixed, non-weight based

Drug Examples

EMS brings in an unresponsive male who is not protecting his airway and RSI is needed. You reach into your RSI kit for a sedative and you remove Sedative A (or B). The patient is normotensive and in normal sinus rhythm. You estimate him to be 140 kg and his height to be 5’9”. Of course you are estimating because the patient is lying down on a stretcher, so you do not actually know the correct weight/height of the patient.

Drug Examples

Sedative A

- F = 1
- Vd = 4 L/kg
- Protein Binding = 60%
- Clearance = hepatic
- Elimination = renal

Sedative B

- F = 1
- Vd = 2 L/kg
- Protein binding = minimal
- Clearance = hepatic
- Elimination = renal

Drug Examples

Sedative A-Which weight to use?

A) TBW
B) IBW
C) AdjBW
D) LBW

Sedative B-Which weight to use?

A) TBW
B) IBW
C) AdjBW
D) LBW

KEY TAKEAWAYS

1) ALWAYS USE CLINICAL JUDGEMENT WHEN MAKING DOSING DECISIONS

2) ASSESS RISK VS. BENEFIT OF UNDER- OR OVERDOSING FOR EACH DRUG

3) FOR RSI, IT'S BETTER TO GIVE MORE!

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Mississippi Mud Redux

Craig Cocchio, Pharm.D., BCPS
EM Clinical Pharmacist
Residency Program Director, PGY-2 EM
CHRISTUS Trinity Mother Frances Hospital
Tyler, Texas

Male, mid 40s, LLE purulent cellulitis.

125 kg.

No comorbidities **(currently diagnosed)**

Choose your vancomycin dose

- A) Guideline based
- B) Two compartment
- C) Allometric dosing
- D) A gram q12

The ugly truth about vancomycin

Institutional dose limits/caps

Vd and Cl

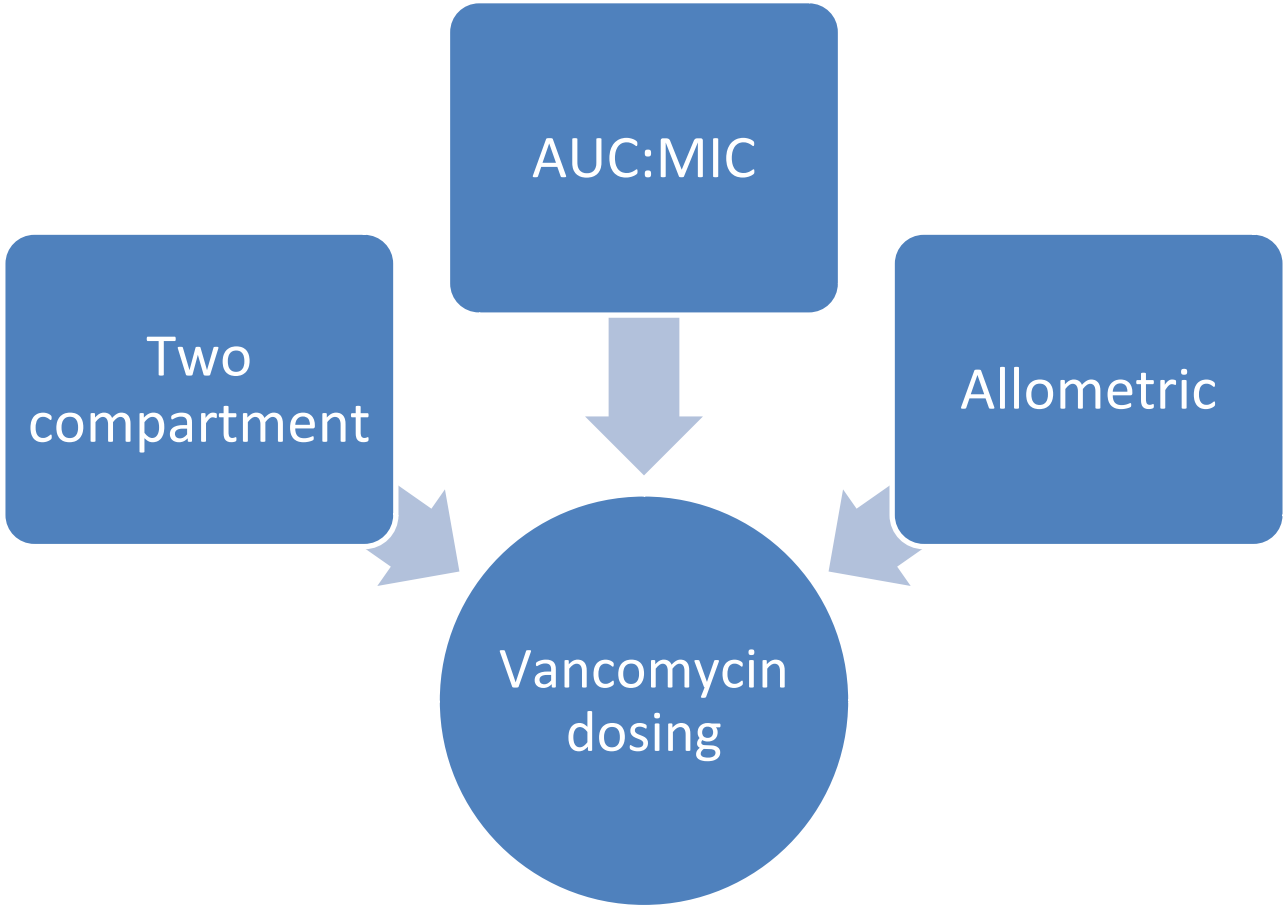
Comorbidities limit penetration to sites of infection

Not all obese patients are equal

AUC:MIC ratio at the site of infection

Mississippi Mud

Not the formulation… it's the pharmacokinetics


AUC:MIC
Two compartment
Allometric
Vancomycin dosing

A dose divided cannot stand… or can it?

Single center, uncontrolled, prospective study

54 consecutive obese patients (>137% IBW)

Two compartment model loading dose

PMID: 25986008

Divided loading dose

IBW (Kg)	Percent IBW	CrCl (mL/min*)	Dosing
≤ 83	≥ 137	> 60	1 g q6h Max 20 mg/kg/dose
≤ 83	≥ 137	21-60	1 g q6h Max 17 mg/kg/dose
> 83	≥ 137	≥ 21	15 mg/kg/dose q6h Max 1.5 g/dose

Level check prior to 3rd and 5th dose
*Based on IBW

PMID: 25986008

Who was included

58 year old male, 111 kg (± 31)

TBW 171% (± 37) of IBW

Normal renal function (SCr ~ 0.9 mg/dL)

PMID: 25986008

What they found

- 89% between 10 – 20 mcg/mL within 12 hours
  - 3 patients > 20 mcg/mL
- 97% between 10 – 20 mcg/mL within 24 hours
  - 1 patient > 20 mcg/mL
- All AUC:MIC > 400
- No kidney injury

PMID: 25986008

We thought it was a good idea

- Retrospective chart review
  - Patients > 18 years of age
  - No missing data
- N=51
  - Vancomycin 2000 mg IV once
  - Vancomycin 1000 mg IV Q6H x 5 doses
- Study approved by CHRISTUS Institutional Review Board

What we looked at

Primary Endpoint

- Proportion of patients with a post loading dose trough between 10 – 20 mcg/mL

Secondary Endpoints

- Nephrotoxicity
- Time from order verification to administration

	Divided Loading Dose, (n=22)	Traditional Loading Dose (n=29)
Age (mean, ±SD)	55 years, ± 12.0	60 years, ± 12.6
Gender (males, %)	17, 77%	20, 68%
Actual body weight (mean, ± SD)	146.75 kg, ± 53.6	120.46 kg, ± 31.8
BMI (mean, ± SD)	46.8 kg/m^2, 16.58	40.12 kg/m^2, 15.58
Baseline SCr (mean, ± SD)	1.19 mg/dL, ±0.5	1.25 mg/dL, ± 0.7
Indication (n, %)	Cellulitis- 17, 77% Pneumonia- 5, 23%	Cellulitis- 12, 41% Pneumonia- 16, 55% Bacteremia- 1, 3%
Vancomycin dose (mean, ± SD)	N/A	17.6 mg/kg, ± 4.1

What we found

- Primary outcome - troughs between 10 - 20 mcg/mL
- Divided loading dose 72.7 %, 16/22
- Traditional loading dose 58.6 %, 17/29
- Time to 1st dose of vancomycin
- 92.48, ± 90.7
- 173.93, ± 187.9
- Change in SCr from baseline
- 0.06, ± 0.48
- 0.18, ± 0.9

Results

	Divided Loading Dose, (n=22)	Traditional Loading Dose, (n=29)	p-value
Troughs between 10 - 20 mcg/mL	72.7 %, 16/22	58.6 %, 17/29	0.533
Time to 1st dose of vancomycin	92.48, ± 90.7	173.93, ± 187.9	0.049
Change in SCr from baseline	0.06, ± 0.48	0.18, ± 0.9	0.59

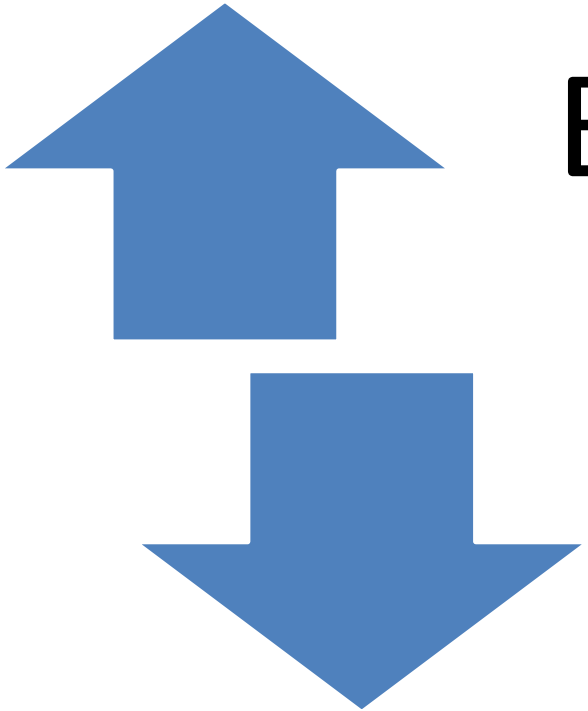
Divide and conquer

Feasible in real world practice

Improved time to first dose antibiotics

Change in practice NOT protocol

Allometry – Body Size and Physiology



Body weight

mg/kg dose

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Est CL_v (L/h)	LD (mg)	MD (mg)	$AUC_{0-24} \geq 400$ at 24 hr (%)	$AUC_{24-48} \geq 400$ at 48 hr (%)	Toxicity ($AUC_{48-72} \geq 700$) (%)
1	2500	500 q24h	100	100	23
2	2500	1000 q24h	98	100	1
3	2500	1500 q24h	93	100	0
4	2500	1000 q12h	99	100	0
5	2500	1250 q12h	98	100	0
6	2500	1500 q12h	96	100	0
7	2500	1750 q12h	94	100	0
8	3000	2000 q12h	99	100	0
9	3000	2250 q12h	98	100	0
10	3000	2250 q12h	92	100	0

$CL_V = 9.656 - 0.078 \times AGE - 2.009 \times SCR + 1.09 \times SEX + 0.04 \times TBW^{0.75}$

AGE (years), SEX is 1 if male 0 if female

PMID: 30203073

Back to the methods

- What they did
  - Population PK study using per protocol data
  - Monte Carlo simulation to ↑ efficacy and ↓ toxicity
- How it's translated
  - Empiric dosing nomogram for obese and super obese
  - CL_V described using a linear combination of age, serum creatinine, sex and allometrically scaled body weight

PMID: 30203073

Vancomycin TDM Protocol

- Patient-specific PK via Sawchuk–Zaske
- Steady state vancomycin peak and trough
- Loading dose target peak 30–40 mg/L, max 3000 mg
- Volume
  - 0.8 L/kg (BMI 30-39.9 kg/m^2)
  - 0.52 L/kg (BMI 40–49.9 kg/m^2)
  - 0.42 L/kg (BMI ≥50 kg/m^2)
- Matzke nomogram

PMID: 30203073

Study Population

- n = 346 obese and super obese adults
- Body weight (69.6–293.6 kg) and BMI (30.1–85.7 kg/m^2)
- Average were middle aged (range 19–88 years), male
- Normal renal function average 1.0 mg/dL

PMID: 30203073

Monte Carlo Simulation

- 1000-subject Monte Carlo simulations within Pmetrics™
- First run, no LD
  - TDDs from 500 to 5000 mg in 1000 simulated subjects per patient in the original dataset
- Second run with LD
- CL rounded to nearest whole number

PMID: 30203073

Est CL_v (L/h)	LD (mg)	MD (mg)	$AUC_{0-24} \geq 400$ at 24 hr (%)	$AUC_{24-48} \geq 400$ at 48 hr (%)	Toxicity ($AUC_{48-72} \geq 700$) (%)
1	2500	500 q24h	100	100	23
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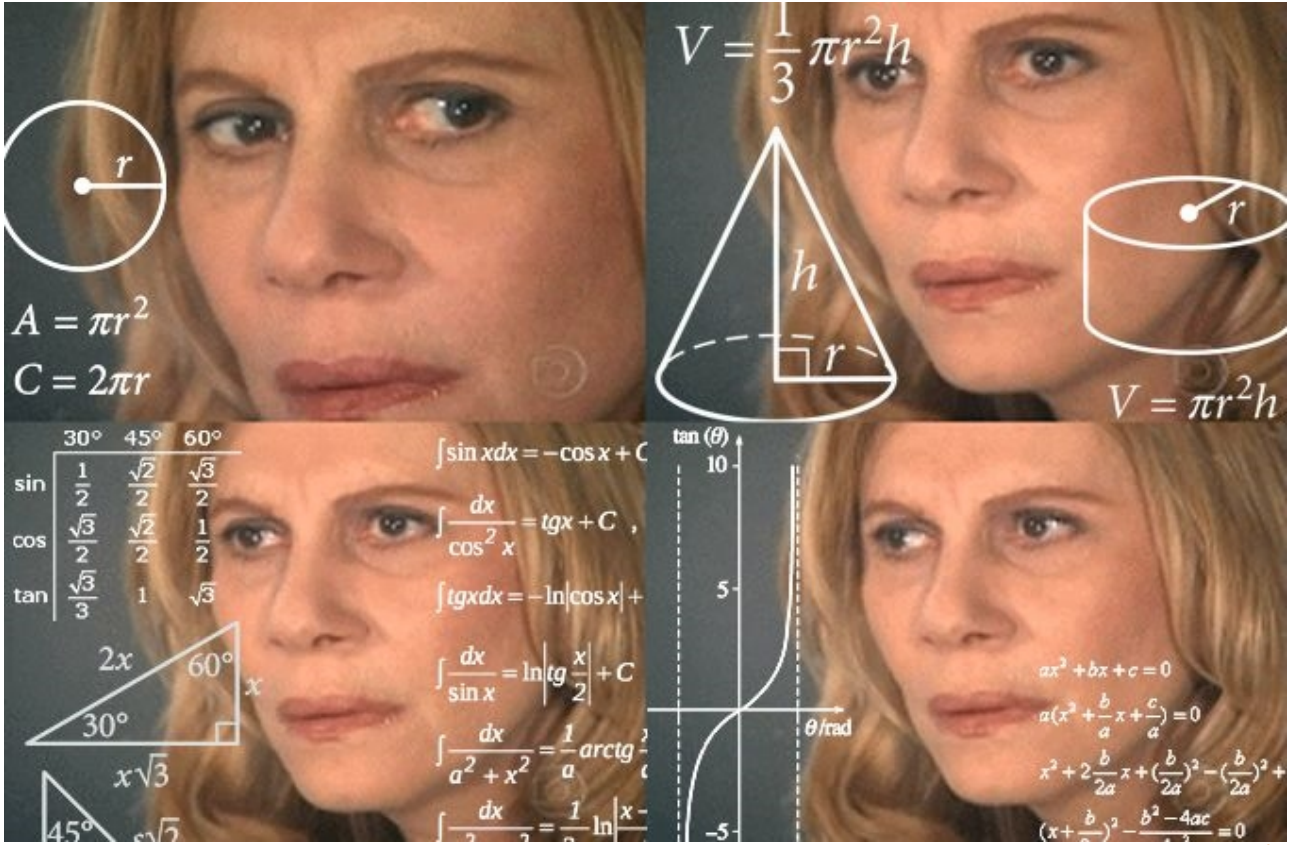
4	2500	1000 q12h	99	100	0
5	2500	1250 q12h	98	100	0
6	2500	1500 q12h	96	100	0
7	2500	1750 q12h	94	100	0
8	3000	2000 q12h	99	100	0
9	3000	2250 q12h	98	100	0
10	3000	2250 q12h	92	100	0

$CL_V = 9.656 - 0.078 \times AGE - 2.009 \times SCR + 1.09 \times SEX + 0.04 \times TBW^{0.75}$

AGE (years), SEX is 1 if male 0 if female

PMID: 30203073

TL;DR


r
$A = \pi r^2$
$C = 2\pi r$
$V = \frac{1}{3}\pi r^2 h$
h
r
r
$V = \pi r^2 h$
30° 45° 60°
sin
cos
tan
2x
60°
30°
x
$x\sqrt{3}$
45°
$\int \sin x dx = -\cos x + C$
$\int \frac{dx}{\cos^2 x} = tgx + C$
$\int tgx dx = -\ln|\cos x| +$
$\int \frac{dx}{\sin x} = \ln\left|tg\frac{x}{2}\right| + C$
$\int \frac{dx}{a^2 + x^2} = \frac{1}{a} arctg$
$\int \frac{dx}{} = \frac{1}{} \ln\left|x -\right.$
tan (θ)
10
5
-5
θ/rad
$ax^2 + bx + c = 0$
$a(x^2 + \frac{b}{a}x + \frac{c}{a}) = 0$
$x^2 + 2\frac{b}{2a}x + (\frac{b}{2a})^2 - (\frac{b}{2a})^2 +$
$(x + \frac{b}{}) - \frac{b^2 - 4ac}{} = 0$

Male, mid 40s, LLE purulent cellulitis.

125 kg.

No comorbidities **(currently diagnosed)**

KEY TAKEAWAYS

Reality:

- Low quality data – no patient oriented outcomes

Solutions:

- Divided loading dose plus Crass Nomogram?
- Approach each patient individually
- We need more researchers

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