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## **Lean, Mean, Efficiency Machine: Emergency Medicine Pearls**

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## | Disclosures & Potential Conflicts of Interest

- I have no relevant financial conflicts of interest or disclosures related to this presentation
- This presentation will discuss off-label uses for medications



# | Learning Objectives

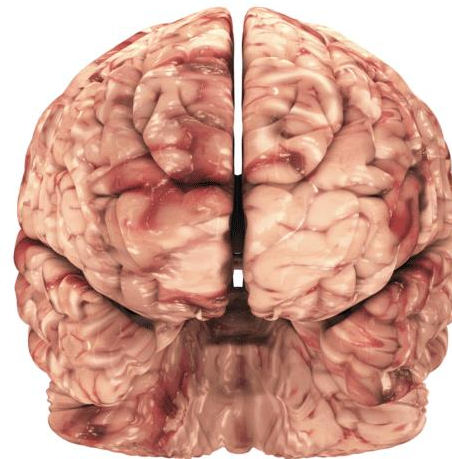
*At the end of this session, participants should be able to:*

- Identify strategies to promote efficiencies in emergency care and supporting clinical evidence
- List barriers that would prevent implementation of more efficient practices in emergency care
- Describe treatment regimens associated with the practices in emergency care discussed



# Surviving Sepsis Campaign®

**Factor Xa Inhibitor  
Related ICH & PCCs**



# Antibiotics

# Surviving Sepsis Campaign 1-Hour Bundle

## SEP-1 Bundle

Measure lactate level

Obtain blood cultures before administering antibiotics

Administer broad-spectrum antibiotics

Begin to rapidly administer 30 mL/kg crystalloid for hypotension or lactate  $\geq 4$  mmol/L



# Surviving Sepsis Campaign 1-Hour Bundle

## SEP-1 Bundle

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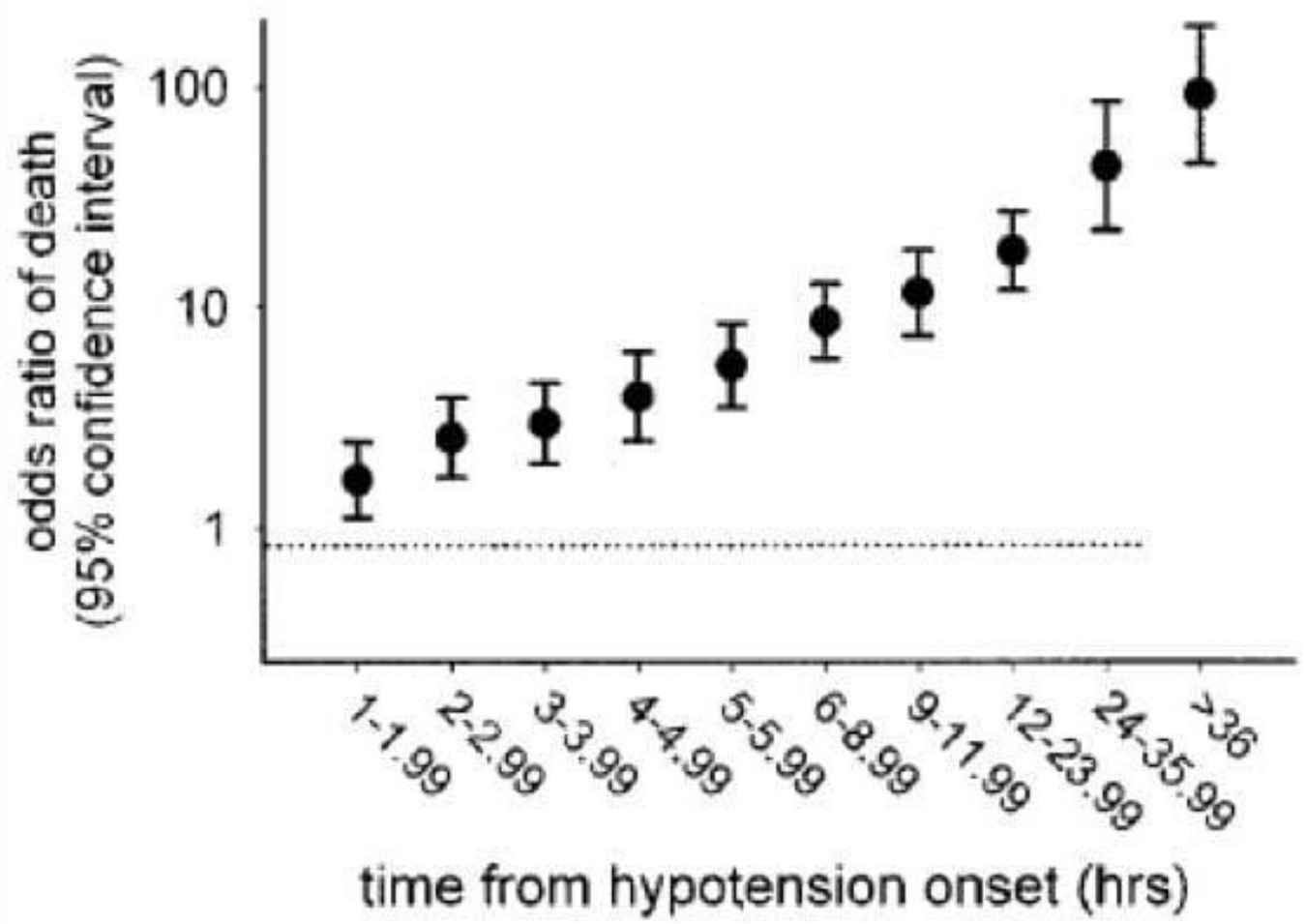
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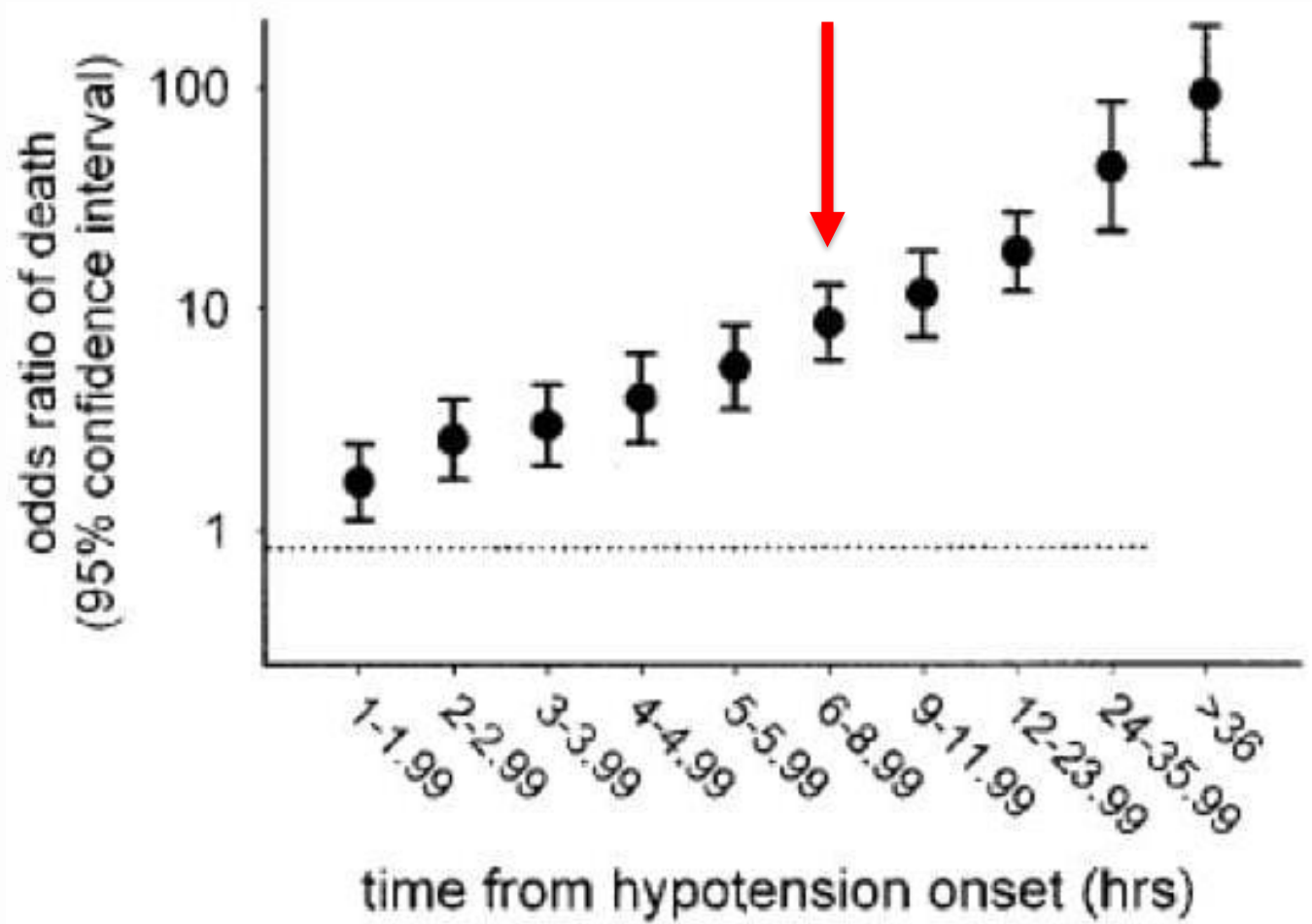


# Delays in Antibiotic Administration





# Delays in Antibiotic Administration



# Considerations for Push Dose IV Antibiotics

# Cephalosporins

- Cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime all FDA approved for IV push
- Similar rates of phlebitis and similar infusion related complications
- Ceftriaxone and cefepime NOT FDA approved however relatively common
- The most studied class on push dose administration and likely the safest
- Dilution with 10 cc of normal saline is common



# Push Dose Piperacillin/Tazobactam (Off-Label)

- Hays, et al.
- Dilution of 3.375 g and 4.5 g with 10 cc and 20 cc respectively
- A total of 300 patients were evaluated for the safety of push dose piperacillin/tazobactam
  - A total of 299/300 patients reported no adverse event (99.7%)
  - Dilution results in a concentration of ~ 1,000 mOsm/L
    - 8.4% sodium bicarbonate ~ 2,000 mOsm/L
    - D50 (25 g) dextrose ~ 2525 mOsm/L
    - 3% hypertonic saline ~ 900 mOsm/L



# Push Dose Antibiotics for Those With Allergies to Penicillin or Cephalosporins

## Carbapenems

- Meropenem FDA approved
- Ertapenem is not approved but is commonly administered via IV push
- Imipenem push dose should be avoided due to severe nausea
- No data available currently to suggest doripenem IV push is safe

## Monobactam

- Aztreonam is indicated for IV push after reconstitution



# Wesley Medical Center Current Push Dose Antibiotic Practice

# Common Push Dose Antibiotics By Class in the Emergency Department (ED) at Wesley Medical Center

- Penicillins and Cephalosporins
  - Piperacillin/Tazobactam (extended infusion after first dose in ED)
  - Cefazolin
  - Ceftriaxone
  - Cefepime
- Carbapenems
  - Meropenem
- Monobactam
  - Aztreonam
- Lipopeptides
  - Daptomycin



## | Antibiotics Wrap Up

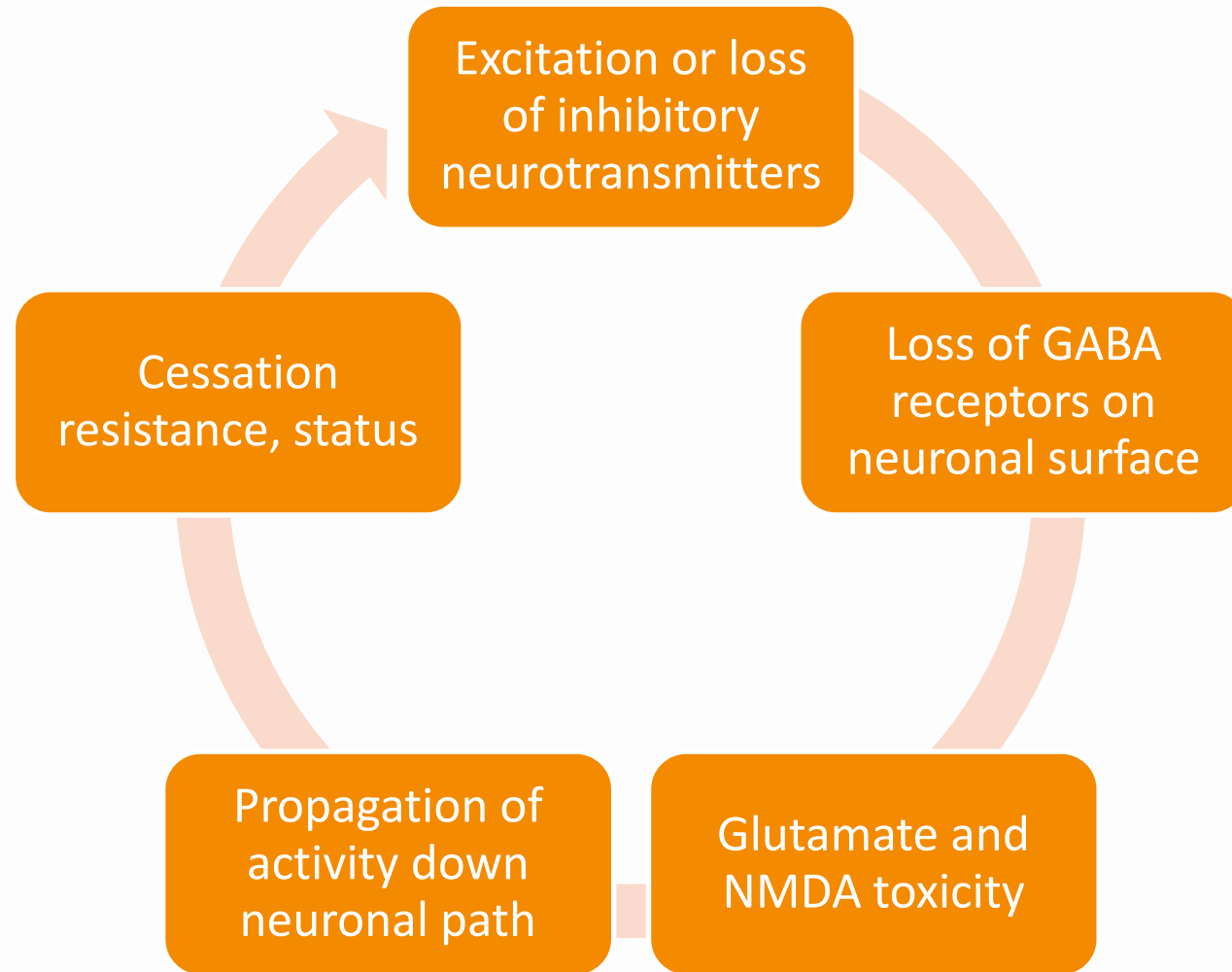
- Push dose antibiotics seems to allow for faster administration post verification
- Transitioning to push dose antibiotics can improve metrics associated with sepsis management
- Push dose vs. infusion doses appear equally safe



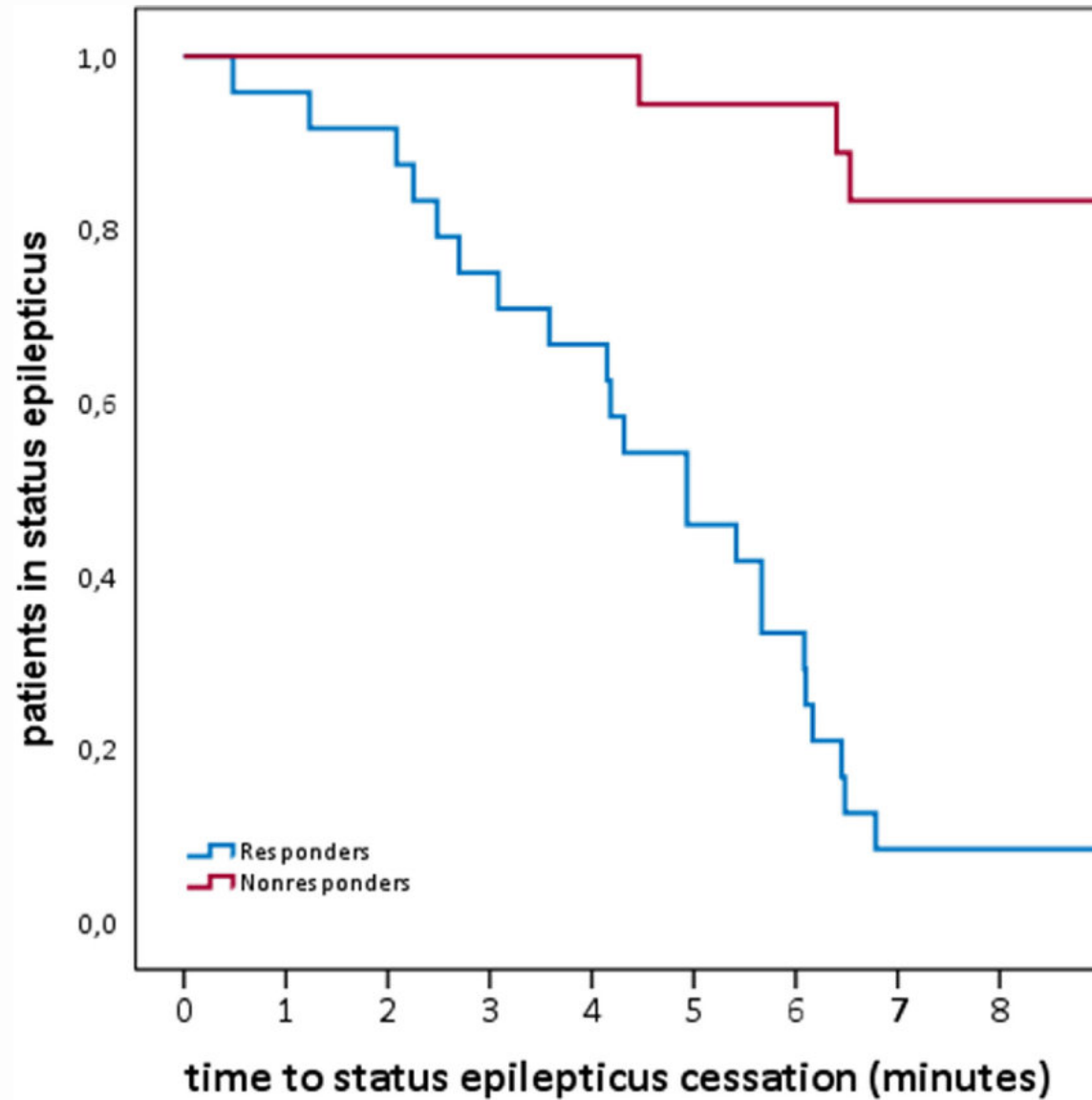


# Antiepileptics

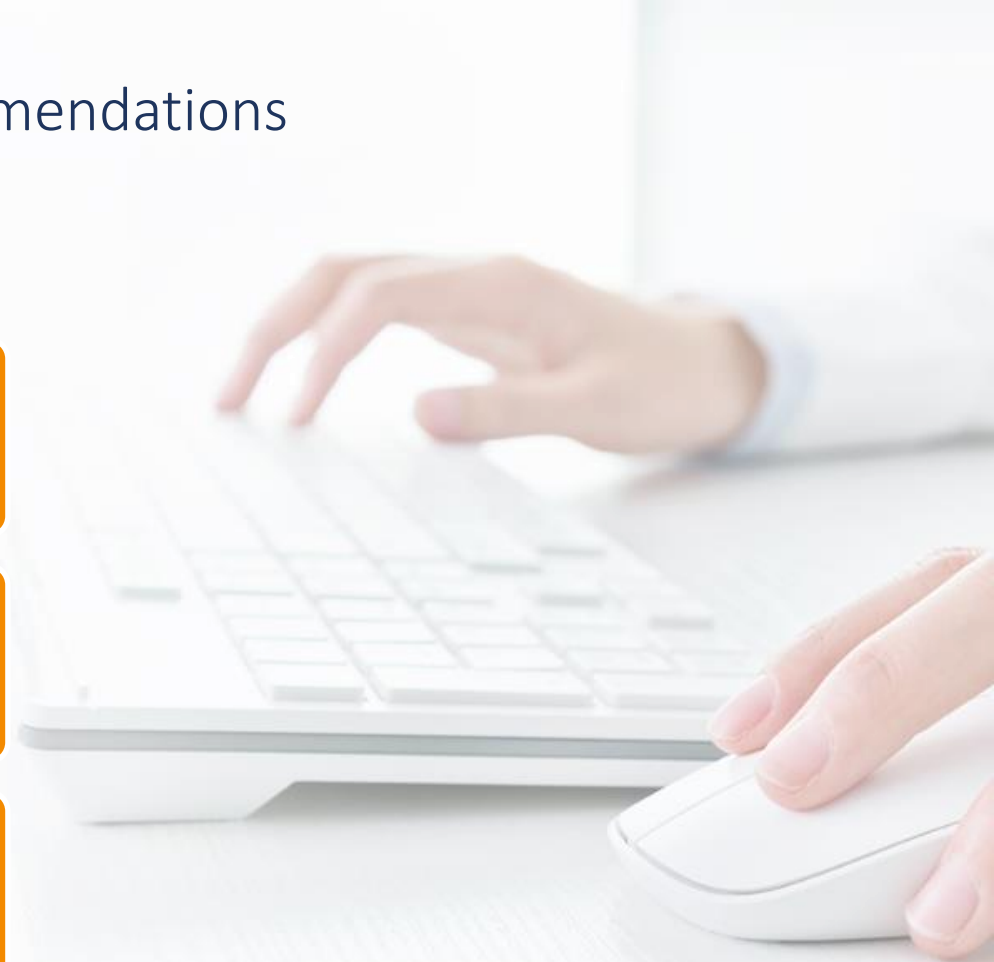
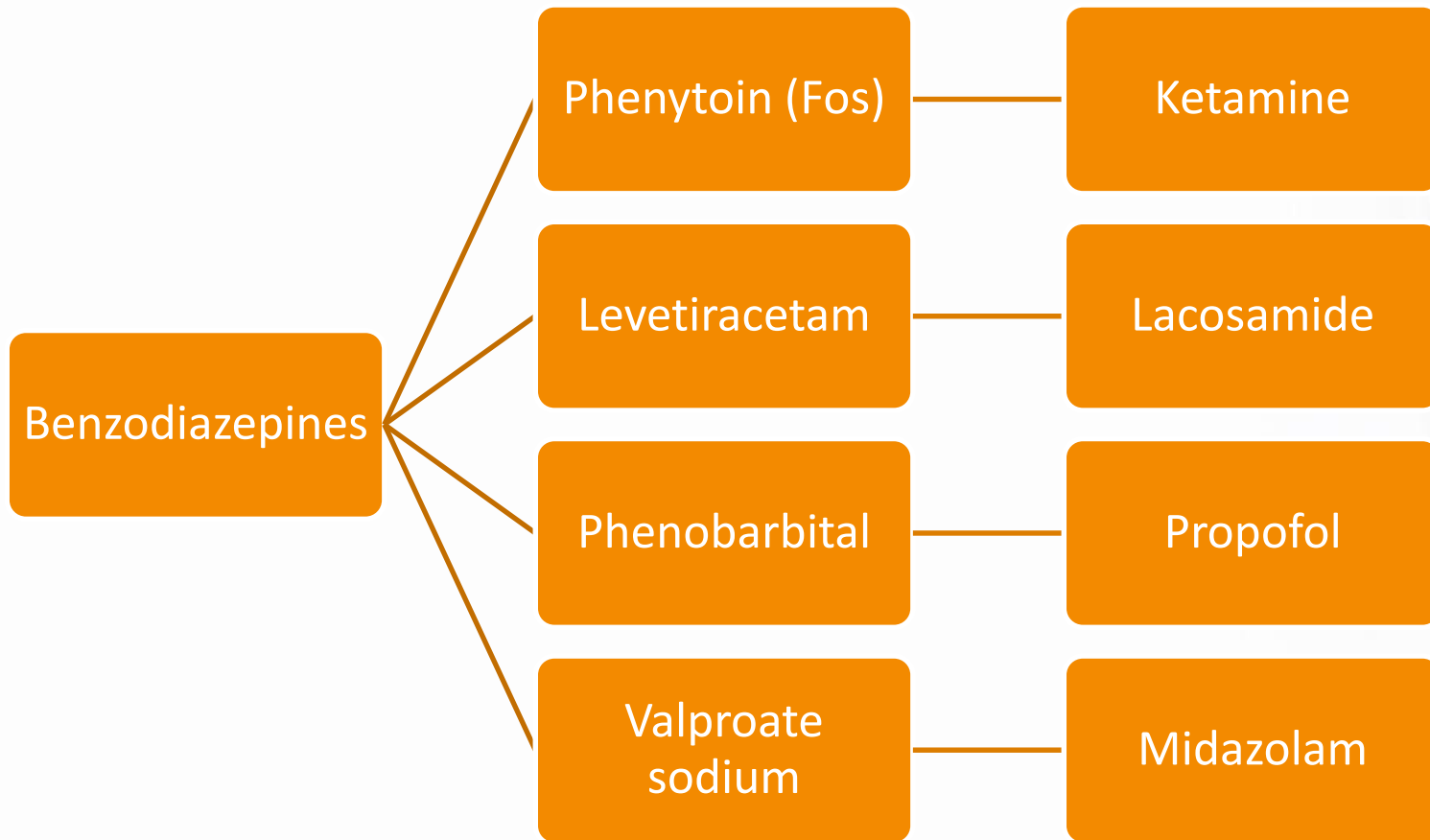
# | When STAT Actually Means STAT!



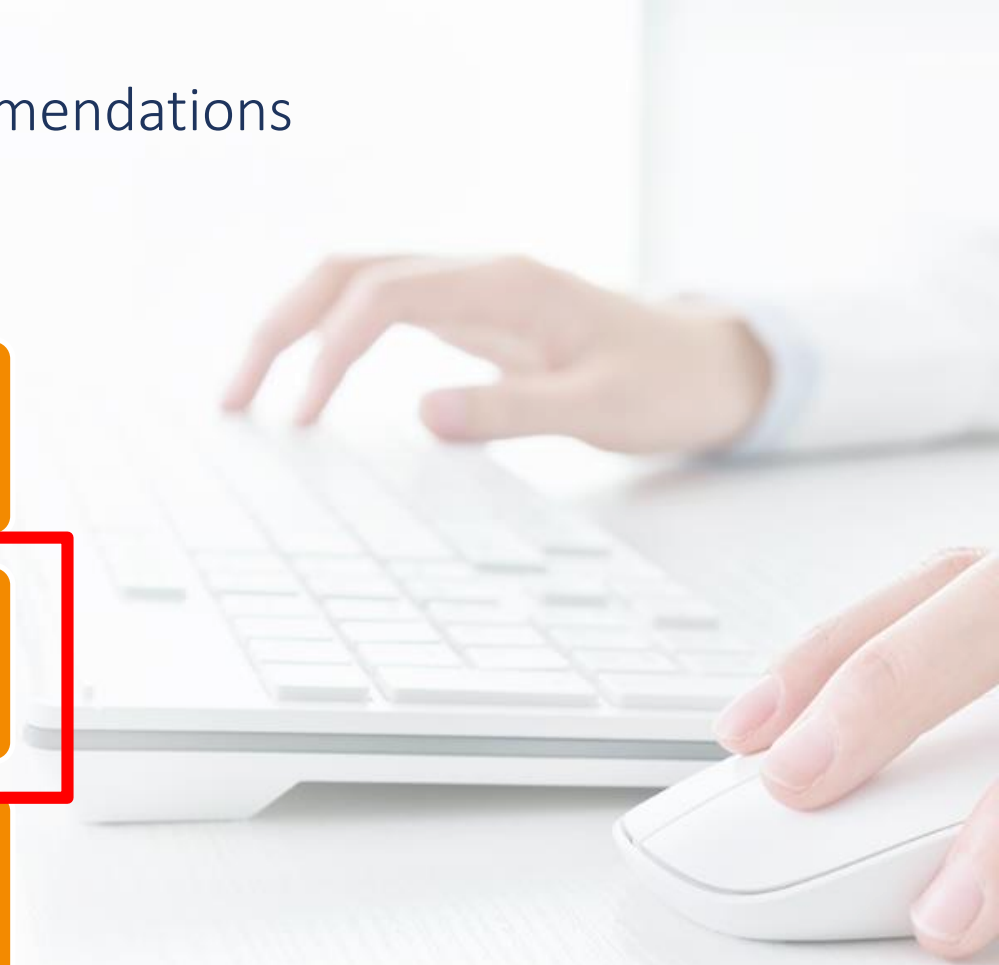
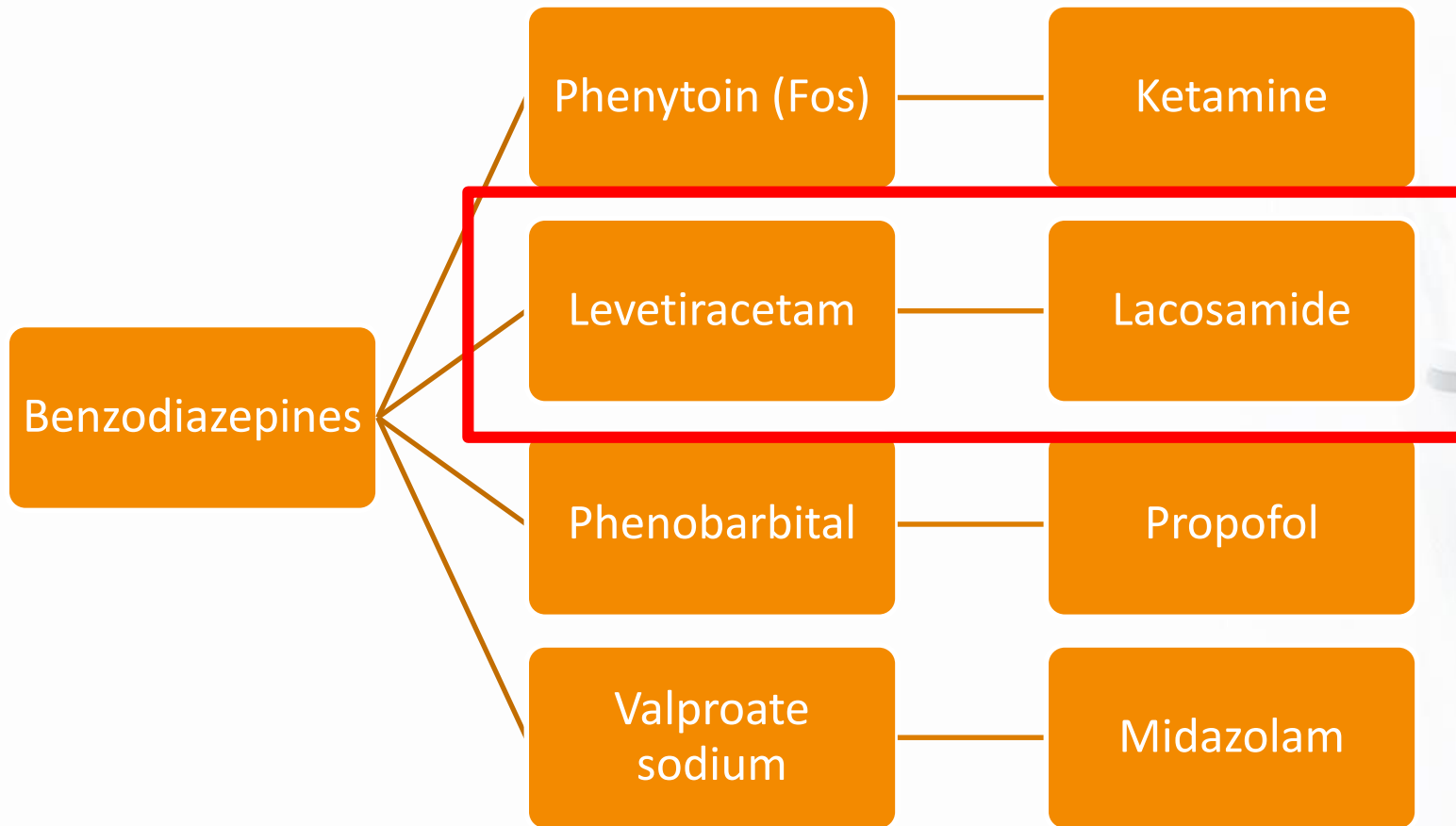
# | Time is Actually Brain Here



# Select Neurocritical Care Society (NCS) Guideline Recommendations



# Select Neurocritical Care Society (NCS) Guideline Recommendations



## | Push Dose Levetiracetam (Off-Label)

Morgan and Medenwald. *Neurocrit Care*. 2020 Feb; 32(1): 131 – 134.

- Retrospective study evaluating adverse drug reactions associated with undiluted levetiracetam
- January 1, 2018 – June 1, 2018, at least one dose of undiluted levetiracetam,  $\geq 18$  years old
- Safety endpoints were reviewed and collected from time of administration until hospital discharge
- There was a total of 199 patients included which resulted in 1626 doses
  - 60.8% received 1,000 mg
  - 64.3% received through a peripheral line
  - 8.1 doses per patient for mean total of 5 days
  - **98.5% did not experience an adverse event**
  - 1.5% experienced agitation, delirium, confusion, lethargy (known adverse effects of levetiracetam)

## | Push Dose Lacosamide (Off-Label)

Davidson. *Neurocrit Care*. 2018 Dec; 29(3): 491 – 495.

- Retrospective study evaluating IV piggyback vs. IV push lacosamide (80 mg/min up to 400 mg)
- June 2016 to July 2017, patients  $\geq 18$  years old who received a dose of lacosamide
- Outcomes measured included incidence of hypotension, bradycardia, as well as efficiency between order verification and administration
- 88 patients in IV piggyback vs. 78 in IV push
  - NS hypotension, NS bradycardia
  - Median time to order verification and administration was 35 minutes for IV push vs. 109 minutes for IV piggyback ( $p < 0.001$ )

McLaughlin. *Ann Pharmacother*. 2021 Feb; 55(2): 181 - 186

- Retrospective study evaluating IV piggyback vs. IV push lacosamide (80 mg/min up to 400 mg)
- Pre-Post cohort analysis with safety endpoints including hypotension, bradycardia, IV site reactions, and medication related sedation
- NS difference in bradycardia, NS difference in hypotension, NS difference in medication related sedation, and NS difference in IV site reactions

# Wesley Medical Center Current AED Practice



# Current AED Practice at Wesley Medical Center

- Levetiracetam (LEV)
  - Undiluted in adults
  - Diluted 1:1 in pediatrics
  - 500 mg/minute rate
  - Up to 1,500 mg per order

- Lacosamide (LCM)
  - Undiluted in adults
  - Not utilized as push in pediatrics
  - 80 mg/minute rate
  - Up to 400 mg per order

- Fosphenytoin
  - Diluted to 25 mg/mL in both pediatrics and adults
  - Doses  $\leq$  750 mg are utilized as an IV push (5 minutes)

Comparator Groups	Levetiracetam (n=200)			Lacosamide (n=72)		
	Infusion (n=100)	Push (n=100)	P value	Infusion (n=22)	Push (n=50)	P value
Median weight (kg [range])	76 [41-163]	81 [28-142]	0.54	67 [42-115]	80 [41-214]	0.13
Mean LEV weight-based loading dose (mg/kg)	15	16	0.07	X	X	x
Loading dose (%)						
$\leq$ 150/1000 (LCM/LEV)	72 (72)	49 (49)	<b>&lt; 0.001</b>	2 (9)	7 (14)	0.56
$>$ 150/1000 (LCM/LEV)	28 (28)	51 (51)	<b>&lt; 0.001</b>	20 (91)	43 (86)	0.56
Median total number of doses (range)	5 [2-22]	4 [2-37]	0.44	2 [1-14]	4 [2-35]	0.36
Line access (%)						
Central	6 (6)	12 (12)	0.13	3 (14)	4 (8)	0.48
Peripheral	73 (73)	67 (67)	0.13	17 (77)	40 (80)	0.48
Both	21 (21)	21 (21)	x	2 (9)	6 (12)	x

Time (min) from OE to A	Levetiracetam (n=200)			Lacosamide (n=72)		
	Infusion (n=100)	Push (n=100)	P value	Infusion (n=22)	Push (n=50)	P value
Median [Range]	52 [1-312]	27 [0-200]	<b>&lt; 0.001</b>	89 [35-229]	32 [2-213]	<b>&lt;0.001</b>

OE, order entry; A, administration

Outcomes	Levetiracetam (n=147)			Lacosamide (n=61)		
	Infusion (n=90)	Push (n=57)	P value	Infusion (n=22)	Push (n=39)	P value
Median time from OE to V [Range]	5 [0-232]	3 [0-117]	0.99	9 [0-23]	6 [0-25]	0.33
Median time from V to A [Range]	41 [0-244]	26 [1-152]	0.04	84 [30-225]	28 [3-207]	0.002

Outcomes	Levetiracetam (n=200)			Lacosamide (n=72)		
	Infusion (n=100)	Push (n=100)	P value	Infusion (n=22)	Push (n=50)	P value
Median percentage of overdue doses [Range]	13 [0-100]	0 [0-67]	0.69	32 [0-100]	0 [0-50]	<b>&lt; 0.001</b>
Rate of initial doses overdue (%)	43 (43)	19 (19)	<b>0.001</b>	18 (82)	39 (78)	<b>0.03</b>

OE, order entry; A, administration  
V, verification

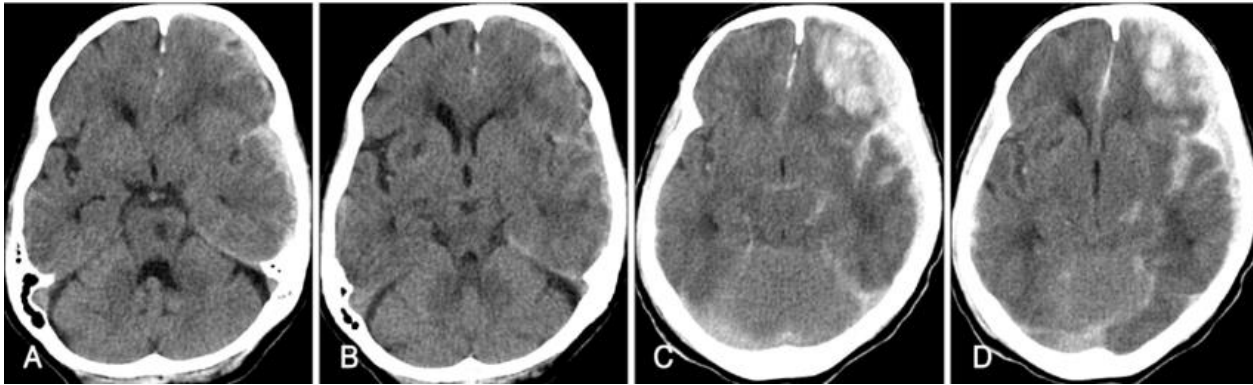
## | AED Wrap Up

- Push dose AEDs seems to allow for faster administration post verification
- Transitioning to push dose AED may allow for less operational burden
- Push dose vs. infusion doses appear equally safe



# Prothrombin Complex Concentrate

## | Factor Xa (FXa) Inhibitor & Warfarin Associated Bleeds



- FXa inhibitor and warfarin associated bleeds, especially intracranial hemorrhages (ICH), are life threatening
- Four-factor prothrombin complex concentrate (PCC) seems to be beneficial in obtaining hemostasis
- Goal is to prevent hematoma expansion, while mitigating prothrombotic complications
- Compared to alternative therapies, can be approximately \$25,000 less per regimens

# Wesley Medical Center Current Reversal Strategy

# Identifying Candidates for Reversal of FXa Inhibitors

- Traditional coagulation tests
  - Are not always sensitive to coagulopathy of FXa inhibitors
  - If elevated good correlation with supratherapeutic drug levels
- Calibrated anti-Xa values
  - Expensive
  - Not always widely available
- Anti-Xa values (unfractionated heparin (UFH); low molecular weight heparin (LMWH))
  - Assessing for drug presence rather than quantifiable value
  - UFH vs. LMWH
- Thromboelastography (TEG)
  - Prolonged R value in conventional TEG 5000
  - Prolonged activated clotting time if tissue factor utilized (Rapid-TEG)



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# | PCC Dosing for Emergent Reversal

- Dose finding studies never completed
- Endogenous thrombin potential has a maximum velocity
- Classic Dosing for Warfarin Reversal
  - Weight and INR based
    - 25 units/kg (INR 2 – 3)
    - 35 units/kg (INR 4 – 6)
    - 50 units/kg (INR > 6)
- Classic Dosing for FXa Inhibitor Reversal
  - NCS Guidelines Recommendation of 50 units/kg
  - Derived mainly from PCC dosing for warfarin reversal

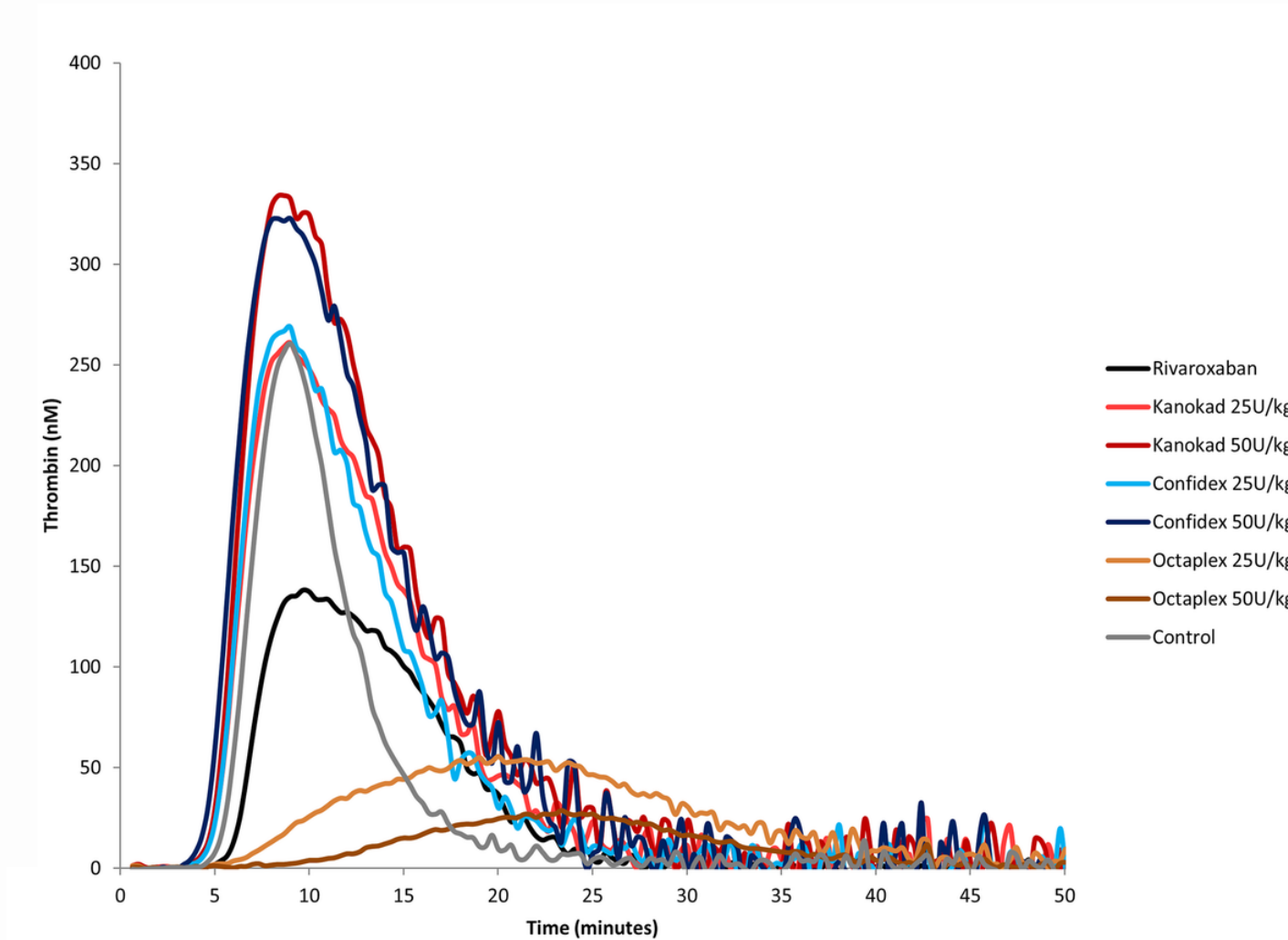


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  - Derived mainly from classic PCC dosing for warfarin reversal



# Traditional vs. Low Dose PCC Dosing



# Low Dose or Fixed Dose PCC Options at Wesley Medical Center

- Warfarin reversal (Off-Label)
  - Extracranial hemorrhage: 1,000 units + 10 mg Vitamin K
    - Additional 500 units available if INR >10 or > 100 kg
  - ICH: 1,500 units + 10 mg Vitamin K
    - Additional 500 units available if INR >10 or > 100 kg
- FXa inhibitor reversal (Off-Label)
  - 25 units/kg capped at 2500 units
  - May give additional 25 units/kg at provider discretion



# The Use of 25 Units Per Kilogram of PCC for FXa Inhibitor Bleeds

Berger. *J Intensive Care Med.* 2020 Nov; 35(11): 1203-1208

- Retrospective study who received at least 1 dose of PCC for FXa inhibitor ICH
- Primary endpoint: hemostasis per CT imaging
- Safety endpoint: thrombosis rate
- A total of 22 patients met criteria
  - Primary endpoint: 18/19 (94.7%) had effective hemostasis as measured on head CT
  - Safety endpoint: 2/22 (9.1%) had a thromboembolism

Hormese. *J Thromb Thrombolysis.* 2021 Mar 16 [epub]

- Retrospective study of patients who received high dose (50 u/kg) or low dose (25 u/kg) PCC
- Primary endpoint: hemostatic efficacy
- Safety endpoint: thrombosis rates
- A total of 47 patients met criteria
  - 24 patients in the high dose group
  - 23 patients in the low dose group
  - Primary endpoint: 87.5% in high dose group vs. 91.3% in low dose group
  - Safety endpoint: 8.3% in the high dose group vs. 4.4% in the low dose group

# Wesley Medical Center Data on Fixed Dose PCC for Warfarin Reversal

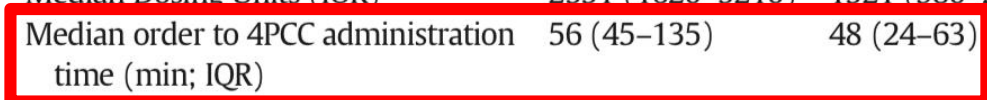
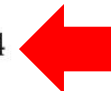
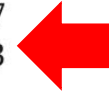
**Table 1**  
Baseline patient characteristics.

Demographic	Traditional dosing; <i>n</i> = 30	Low-dose; <i>n</i> = 30	P value
Median age; years (IQR)	79 (48–89)	78 (53–91)	0.38
Male; <i>n</i> (%)	16 (53.3)	15 (30)	0.79
Median dosing weight; kg (IQR)	83.6 (65–130)	77.6 (68–121)	0.37
Median dose; unit/kg (IQR)	28 (24–52)	17.8 (10–22)	0.03
Indication for anticoagulation; <i>n</i> (%)			
• Afib	19 (63.3)	17 (56.7)	0.59
• PE/DVT	5 (16.7)	6 (20)	0.74
• Mechanical valve	5 (16.7)	6 (20)	0.74
• Other	1 (3.3)	1 (3.3)	1
Indication for reversal; <i>n</i> (%)			
• ICH	11 (36.7)	15 (50)	0.29
• GIB	6 (20)	7 (23.3)	0.75
• Emergent surgery	11 (36.7)	6 (20)	0.15
• Other	2 (6.7)	2 (6.7)	1
Patient on concomitant anti-platelet; <i>n</i> (%)	17 (56.7)	18 (60)	0.79
Median Dosing Units (IQR)	2551 (1620–5210)	1521 (980–2099)	0.004
Median order to 4PCC administration time (min; IQR)	56 (45–135)	48 (24–63)	0.11

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# Wesley Medical Center Data on Fixed Dose PCC for Warfarin Reversal

**Table 2**  
Endpoint data for entire sample size.

Demographic	Traditional Dosing; n = 30	Low-Dose; n = 30	P value
# of patients with INR < 1.6 after 4PCC infusion; n (%)	27 (90)	26 (86.7)	0.68
# of patients with INR < 1.4 after 4PCC infusion; n (%)	22 (73.3)	15 (50)	0.06
Median initial INR (IQR)	3.25 (2.1–30)	2.95 (2.2–30)	0.28
Median INR post 4PCC administration (IQR)	1.3 (1.1–19)	1.35 (0.9–2.1)	0.16
Concomitant vitamin K administration; n (%)	27 (90)	29 (96.7)	0.3
Patient Received FFP ≤ 24 h of 4PCC Infusion; n (%)	7 (23.3)	7 (23.3)	1
Thrombotic events ≤ 7 days of 4PCC infusion; n (%)	0	1 (3.3)	1
Median total hospital length of stay; days (IQR)	6 (2–41)	6 (3–18)	0.81
Mortality; n (%)	8 (26.7)	4 (13.3)	0.19
Total dosing units spared	-	31,870	-
Dosing units/patient spared	-	1062	-
Percentage of units spared (%)	-	43	-



## | PCC Wrap Up

- Utilizing common coagulation tests may be able to prevent erroneous administration
- Lower dose strategies seem to be as effective at achieving reversal of coagulation parameters as well as hemostasis
- Utilizing lower dose strategies might be an effective tool at reducing time to administration and operational burden

## Assessment Question #1 of 3

Push dose administration is most studied in what antibiotic class?

- a. Cephalosporins
- b. Tetracyclines
- c. Carbapenems
- d. Fluoroquinolones

## Assessment Question #2 of 3

What is NOT considered a barrier to implementing emergency medicine pearls?

- a. Single dose oral medication
- b. Push dose medication
- c. Infusion medication

## Assessment Question #3 of 3

What is NOT true regarding implementing push dose medication?

- a. Push dose allows for faster administration
- b. Push dose is approved for all STAT medications
- c. Push dose versus an infusion has more risk for fatality
- d. B and C

## Conclusion

- Time sensitive interventions can be expedited by adapting to IV push for certain medication classes
- IV push therapies have the potential to reduce operational barriers; especially when ED boarding is prevalent
- Optimizing dosing of PCC can reduce technician burden as well as reduced time to administration in emergent situations
- An entire presentation in 2021 without mentioning COVID deserves applause right?

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# Thank you...

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