Spreading knowledge – improving outcomes

Continuous vs Intermittent β-Lactam Antibiotic Infusions

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Outline

Pharmacodynamic properties of medication

Pharmacodynamic parameters of antibiotics

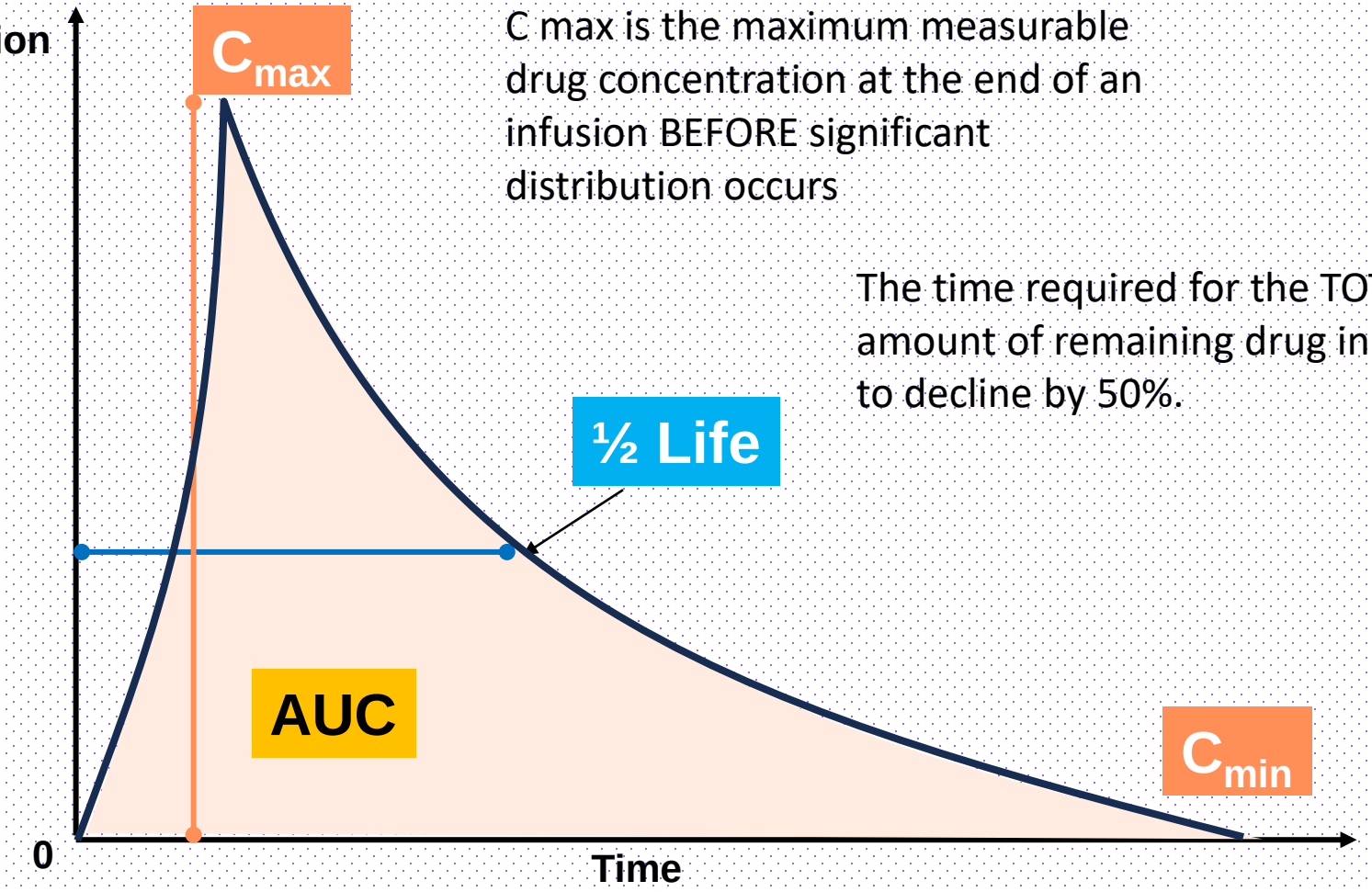
Pharmacodynamic therapeutic goals of antibiotics

Rationales for continuous infusion of beta lactams

- Pharmacokinetic changes of antibiotics in septic patients
- Higher MIC of organisms

Evolving evidence of continuous infusion of beta lactam agents

Pharmacodynamic Parameters



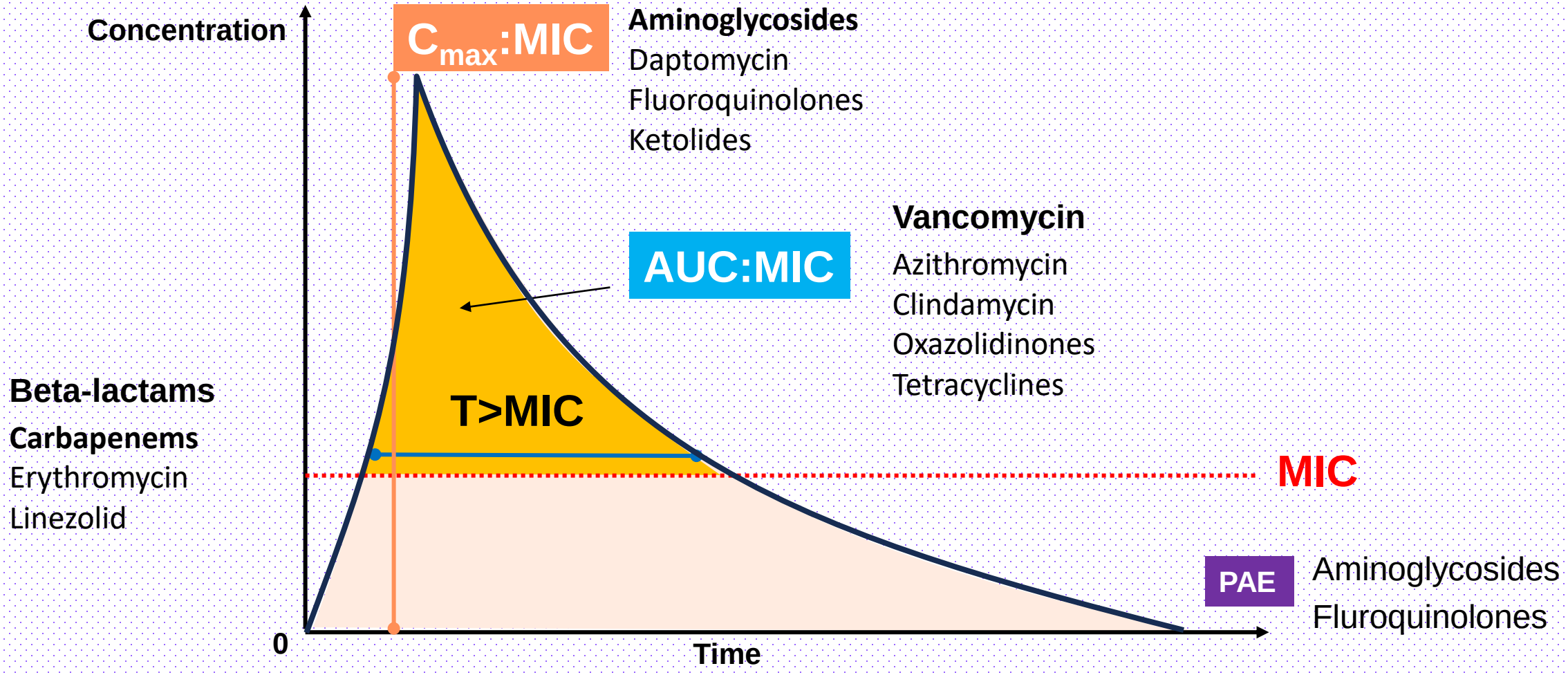
C max is the maximum measurable drug concentration at the end of an infusion BEFORE significant distribution occurs

The time required for the TOTAL amount of remaining drug in the body to decline by 50%.

Area under the curve

Drug concentration before the next dose: Trough

Pharmacodynamic Parameters of Antibiotics

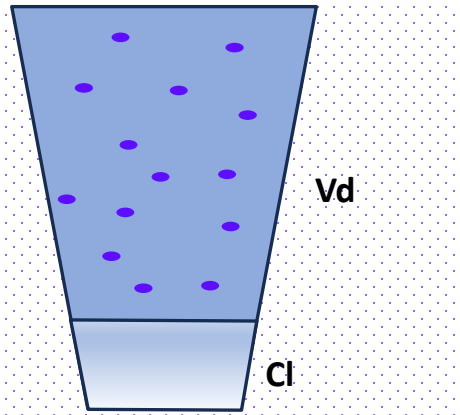


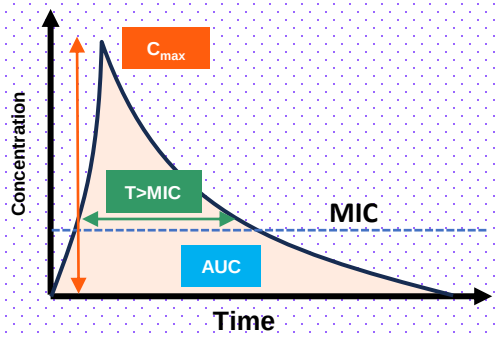
Pharmacodynamic Therapeutic Goals of Antibiotics

Parameter correlating with efficacy	Cmax:MIC	T>MIC	AUC:MIC	PAE
Antibiotic	**Aminoglycosides** **Colistin** Daptomycin Fluoroquinolones Ketolides	**Carbapenems** **Cephalosporins** **Penicillins** Erythromycin	**Vancomycin** **Fluroquinolones**	**Aminoglycosides** **Fluroquinolones**
Organism killing	**Concentration-dependent**	**Time-dependent**	**Concentration/time-dependent**	**Post-antibiotic effect**
Therapeutic goal	**High dose:** **C_{max}/MIC>10**	**Higher frequency, prolonged duration** **C_{min}>MIC**	**Optimize exposure to antibiotic:** **C_{max}/MIC>10 and C_{min}>MIC**	**Lower frequency**

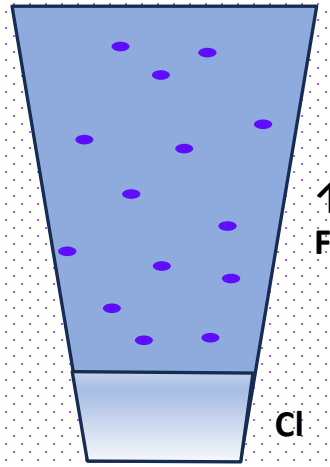
Pharmacokinetic Changes of Antibiotics in Septic Patients

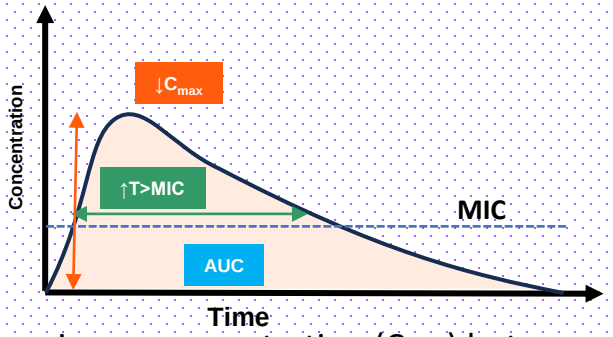
Healthy





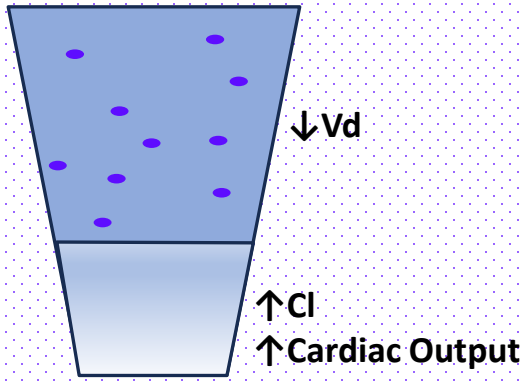
Large Volume of Distribution

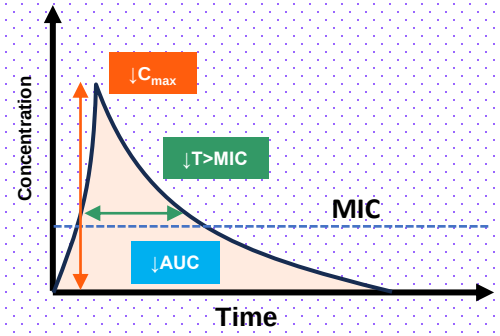




↓maximum concentration (C_{max}) but a longer half-life ($T_{1/2}$)

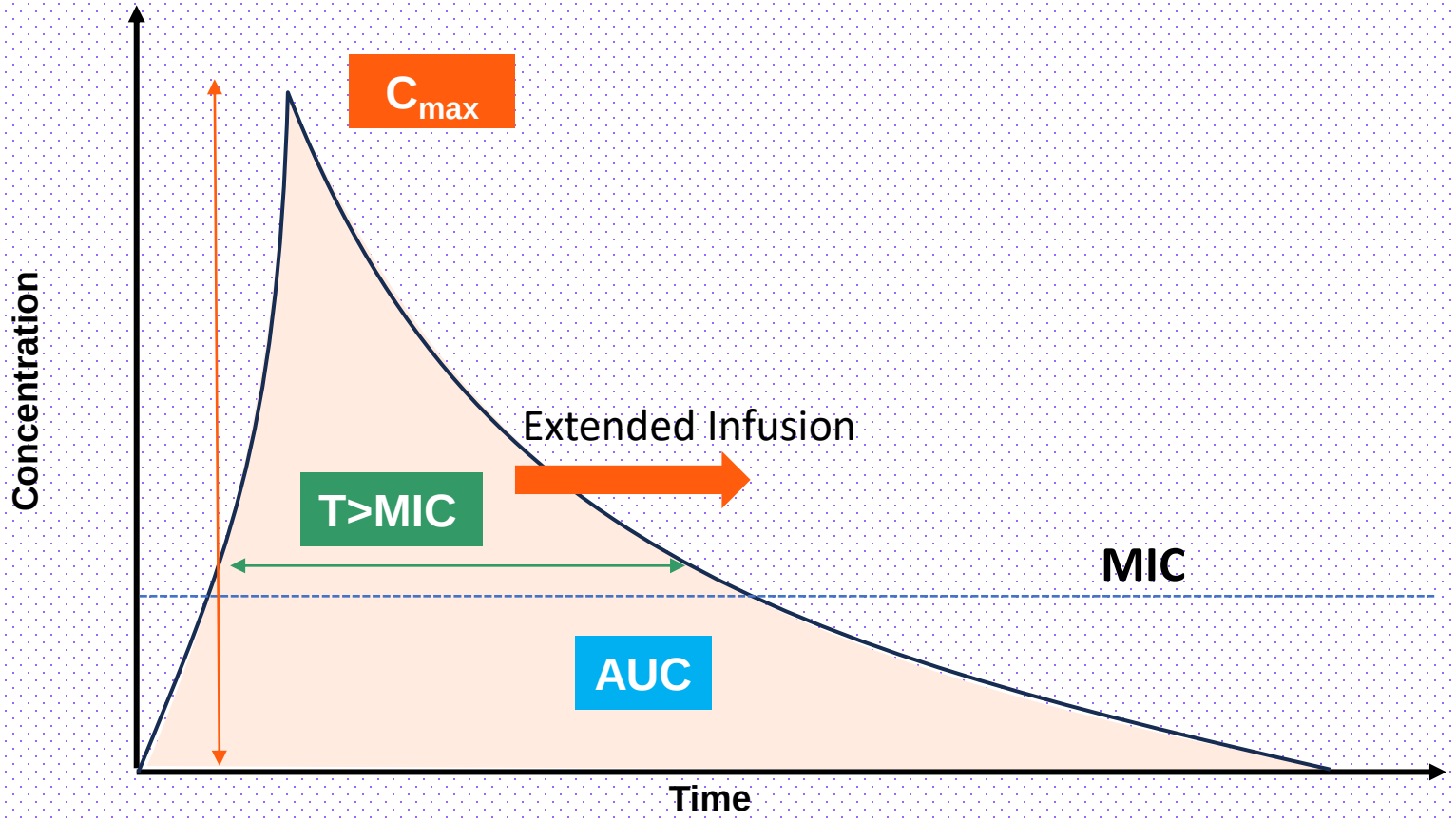
Increase Drug Clearance





↓AUC, $T_{1/2}$ and T > MIC

Higher MIC Organisms

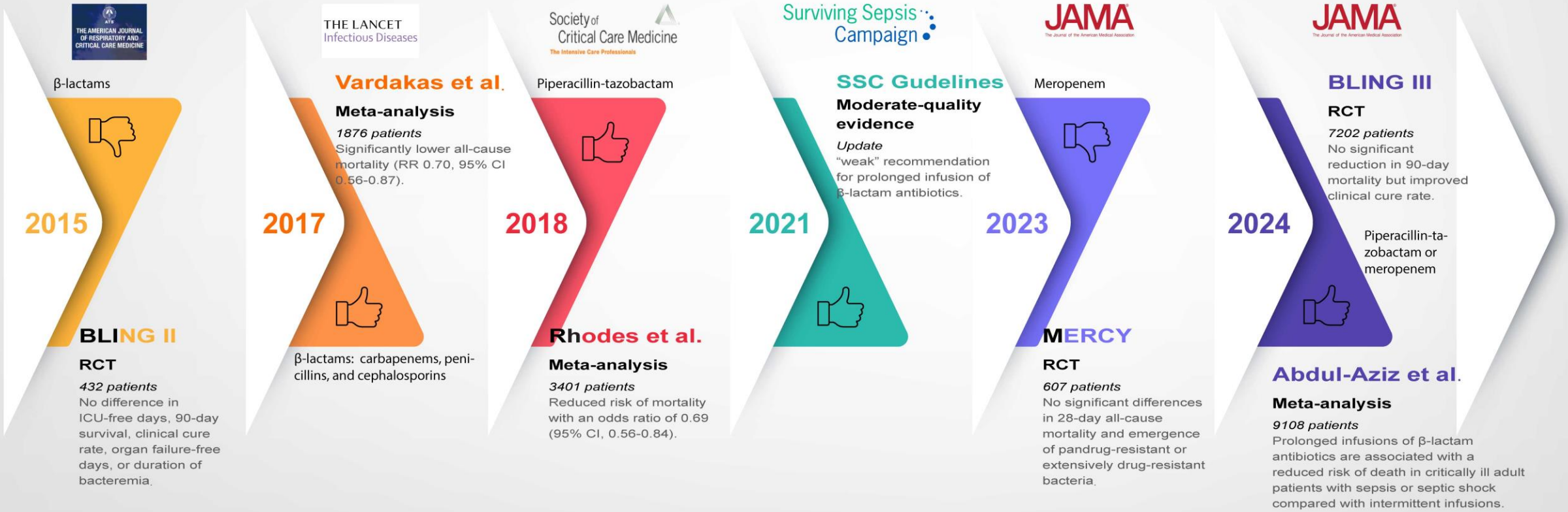


Continuous vs Intermittent Infusion of β-Lactams in Critically Ill Septic Patients

β-Lactam administration via prolonged (with an infusion time of 4 hours) or continuous infusion will lead to sustained concentrations throughout the dosing interval, longer time above MIC, and improved bacterial eradication. But does a better pharmacokinetic target mean a better clinical outcome?

CONTINUOUS VS INTERMITTENT ADMINISTRATION OF BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PATIENTS WITH SEPSIS

Summary of Evidence



CONCLUSION

Prolonged infusions of β-lactam antibiotics were associated with a lower risk of 90-day mortality and ICU mortality (high certainty), and higher clinical cure rates (moderate certainty) compared to intermittent infusions among adults in the intensive care unit who had sepsis or septic shock.

JAMA

QUESTION Does continuous administration of meropenem reduce a composite of mortality and emergence of drug-resistant bacteria among critically ill patients with sepsis compared with intermittent administration?

CONCLUSION Continuous administration of meropenem, compared with intermittent administration, does not improve clinically relevant outcomes in critically ill patients with sepsis.

POPULATION

404 Men
203 Women

Critically ill adults with sepsis

Mean age: 64 years

LOCATION

31
Intensive care units in Croatia, Italy, Kazakhstan, and Russia

INTERVENTION

607 Patients randomized

303
Continuous administration
3 g of meropenem administered over 24 hours

304
Intermittent administration
1 g of meropenem administered over 30 to 60 minutes every 8 h

PRIMARY OUTCOME

All-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28

FINDINGS

Incidence of composite primary outcome at day 28

Continuous administration
142 of 303 patients

Intermittent administration
149 of 304 patients

The between-group difference was not significant:

Relative risk, 0.96 (95% CI, 0.81 to 1.13); *P* = .60

Monti G, Bradić N, Marzaroli M, et al; for the MERCY Investigators. Continuous vs intermittent meropenem administration in critically ill patients with sepsis: the MERCY randomized clinical trial. *JAMA*. Published online June 16, 2023. doi:10.1001/jama.2023.10598

JAMA

QUESTION Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

CONCLUSION In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-day mortality in the primary analysis. A clinically important benefit with continuous infusions is possible.

POPULATION

4608 Men
2423 Women

Critically ill adults aged ≥18 years treated for sepsis

Mean age: 59 years

LOCATION

104
ICUs worldwide

INTERVENTION

7031 Patients randomized

3498
Continuous infusion
Continuous infusion (over 24 hours) of either piperacillin-tazobactam or meropenem

3533
Intermittent infusion
Intermittent infusion (over 30 minutes) of either piperacillin-tazobactam or meropenem

PRIMARY OUTCOME

All-cause mortality within 90 days after randomization

FINDINGS

All-cause mortality at day 90

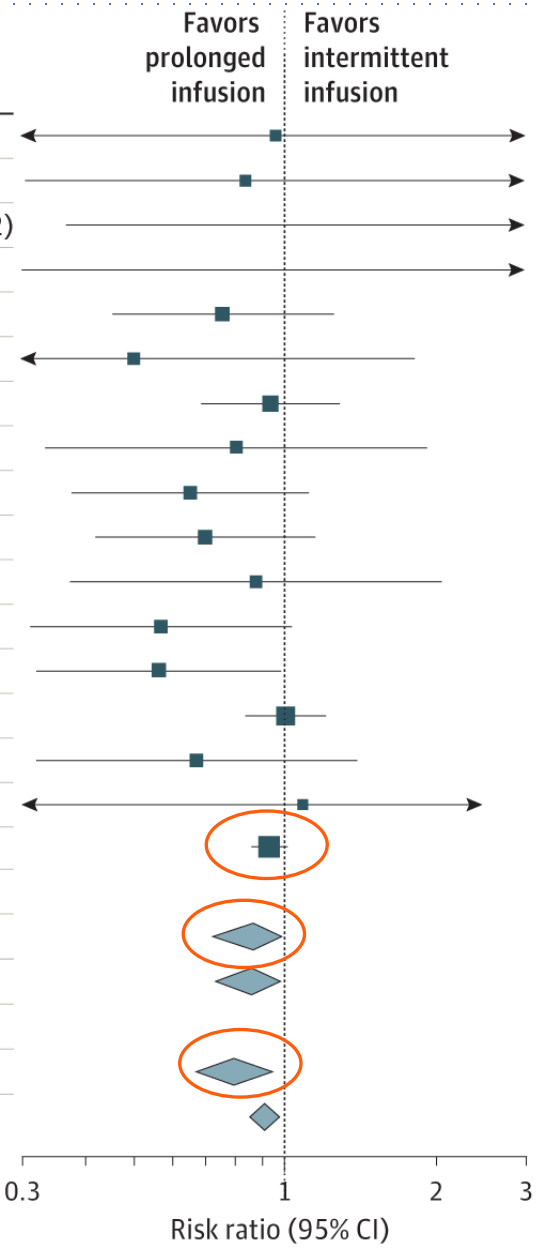
Continuous infusion
864 of 3474 patients

Intermittent infusion
939 of 3507 patients

Absolute difference, **−1.9%** (95% CI, −4.9% to 1.1%)
Odds ratio, **0.91** (95% CI, 0.81 to 1.01); *P* = .08

Dulhunty JM, Brett SJ, De Waele JJ, et al; BLING III Study Investigators. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA*. Published June 12, 2024. doi:10.1001/jama.2024.9779

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.02 to 0.01)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.09 to -0.01)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (0.09 to 0.11)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (0.23 to 0.44)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.06 to -0.05)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.12 to -0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.02 to -0.01)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.24 to -0.01)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.40 to -0.27)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.13 to -0.10)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.07 to -0.01)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.19 to -0.16)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.17 to -0.15)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (0.00 to 0.00)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.16 to -0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.03 to 0.06)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.02 to -0.02)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



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