UW TASP tele-antimicrobial stewardship program | echo

Prolonged Infusion, Is it Worth It?

Rupali Jain, PharmD, FIDSA
University of Washington
rupali@uw.edu

Zahra Kassamali Escobar, PharmD, BCPS
UW Medicine | Valley Medical Center
zescobar@uw.edu

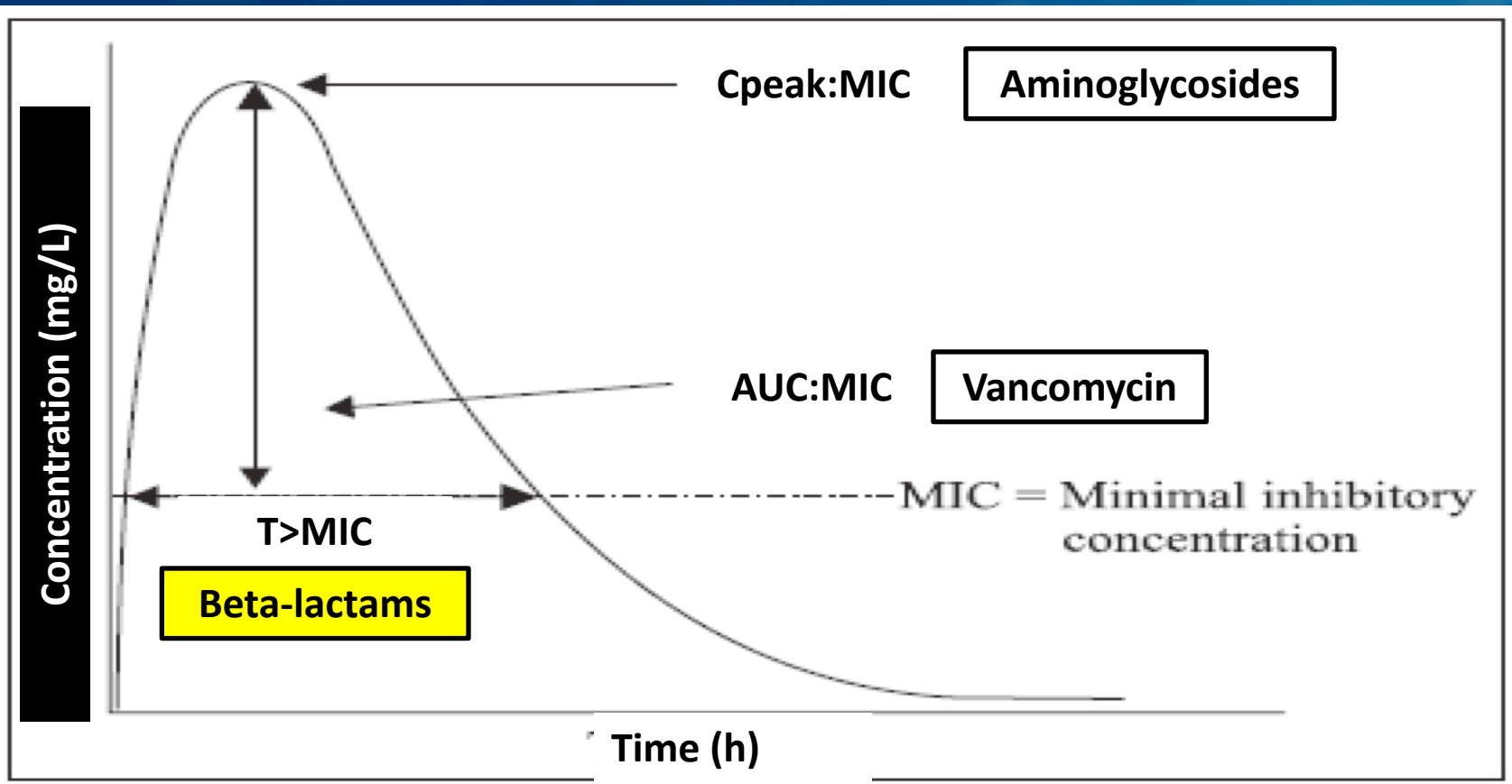
May 1, 2018

UW TASP tele-antimicrobial stewardship program

My institution doses piperacillin/tazobactam by prolonged (3 hour) infusion

- Yes
- No
- Not sure

Rationale for Prolonged Infusion (PK/PD)



AUC = Area under the curve, MIC = Minimal inhibitory concentration, T = Time

Santos Filho L et al. Braz J Microbiol. 2007 Apr/June;38(2):183-193.
Meagher AK et al. Antimicrob Agents Chemother. 2007 Jun;51(6):1939-45.
Craig WA. Infect Dis Clin North Am. 2003 Sep;17(3):479-501.

Optimize dosing of Piperacillin/tazobactam

- Time of unbound drug concentration remain above MIC (*f*T>MIC) predicts efficacy for beta-lactams
- Near maximal killing (bactericidal) achieved when *f*T>MIC is 50% of the dosing interval or longer
- Intermittent infusion may not always achieve this where as extended infusion (EI) will.
- Prolonging the infusion ensures more consistent serum concentrations

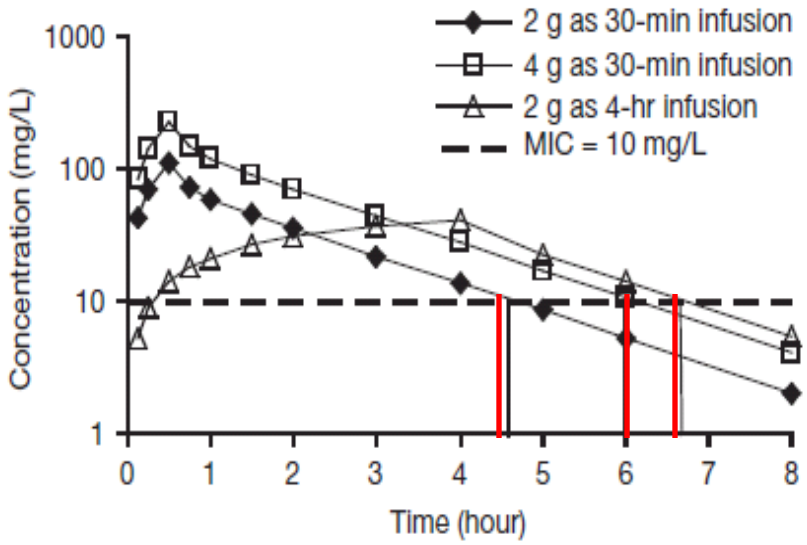


Figure 3. Comparison of time above the MIC (minimum inhibitory concentration; 10 mg/L) for three dosing regimens: piperacillin 2 g as a 30-minute infusion, piperacillin 4 g as a 30-minute infusion, and piperacillin 2 g as a 4-hour infusion.

Lodise et al, Pharmacotherapy 2006; 26: 1320

Clinical Outcomes: prolonged piperacillin/tazobactam infusion

- Among patients with Pseudomonas infections (APACHE II score ≥ 17), hospital length of stay (21 vs. 38 days, p=0.02) and **14-day mortality (12.2% vs. 31.6%, p=0.04) was significantly lower** in those who received prolonged infusion than intermittent infusion.

- Recent meta-analysis comprised mostly of observational studies found **mortality to be significantly lower among those who received prolonged infusion** than intermittent infusion (RR= 0.55, 95% CI: 0.34-0.89).

Lodise TP, et al. CID 2007;44:357-63.
Falagas ME, et al. CID 2013;56(2):272-82.

Hospital Length of Stay Among Patients Receiving Intermittent Versus Prolonged Piperacillin/Tazobactam Infusion in the Intensive Care Units

Journal of Intensive Care Medicine
1-8

DOI: 10.1177/0885066617708756
journals.sagepub.com/home/jic
SAGE

Jeannie D. Chan, PharmD, MPH[1,2], Timothy H. Dellit, MD[2], and John B. Lynch, MD, MPH[2]

Table 3. Hospital Length of Stay Among Patients Receiving PIP/TAZ Intermittent Versus Prolonged Infusion.

Study Population	Mean (SD), Days	Unadjusted Mean Difference in Days (95% CI)	Adjusted Mean Difference in Days[a] (95% CI)
All patients			
Intermittent infusion	26.3 (22.8)	Referent	Referent
Prolonged infusion	20.4 (16.1)	5.9 ± 2.2 (1.7-10.2)	5.6 ± 2.1 (1.4-9.7)
Survivors at discharge			
Intermittent (n = 105)	27.5 (22.3)	Referent	Referent
Prolonged (n = 355)	21.5 (16.9)	6.0 ± 2.4 (1.4-10.6)	5.7 ± 2.3 (1.3-10.2)

Clinical Justification for Prolonged Infusion

Who benefits from prolonged infusion?

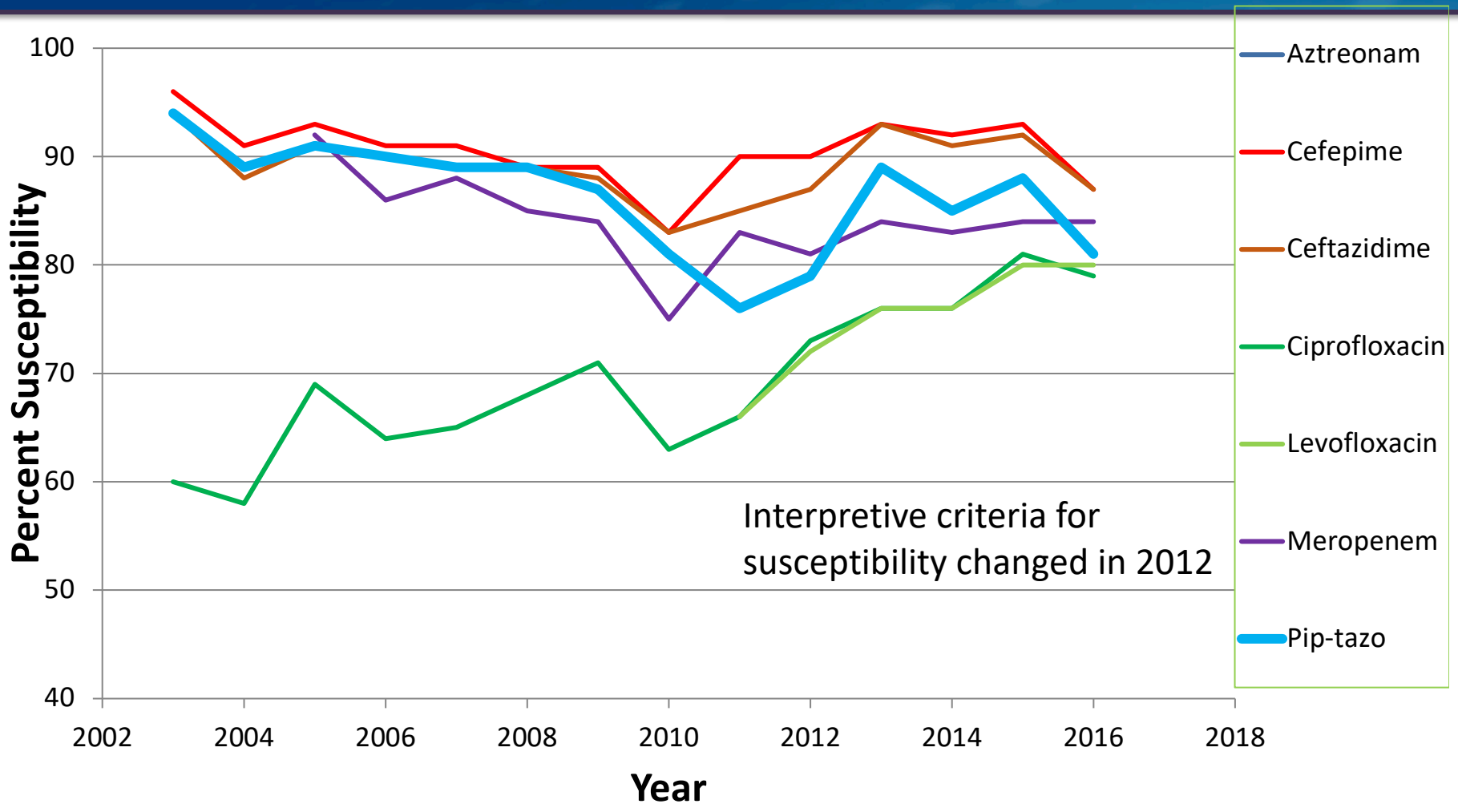
1. Critically ill patients with risks for more resistant Gram negative bacteria
    - -immunosuppressed
    - -significant healthcare exposure (HD, recurrently readmitted, etc)
    - -recent antibiotics

PRO: PROLONGED INFUSION

- **Second most prescribed antibiotic at UWMedicine**
- **Increased resistance at UW Medicine and nationwide --- we are losing the battle!**
- **Prolonged infusion of piperacillin-tazobactam has been associated with improved clinical outcomes compared to intermittent infusion.**

Pre-Implementation FY2011			**Post-Implementation FY2012**		**Total Savings**	**Doses Savings**
	Cost	Doses	Cost	Doses		
HMC	$267,519	16,743	$113,703	14,068	$153,816	2675
UWMC	$252,602	17,004	$87,517	11,872	$165,085	5132
Combined					**$318, 901**	

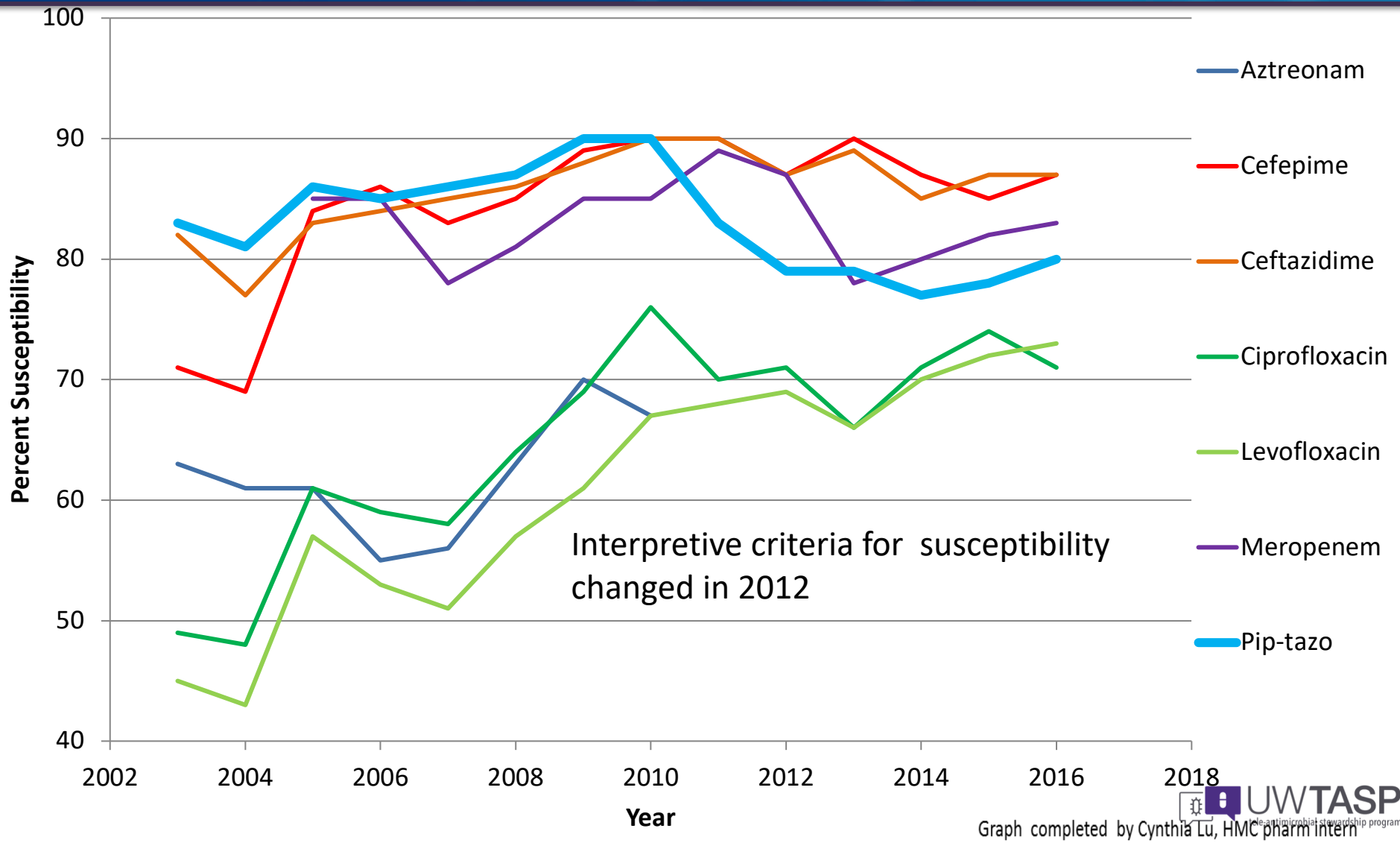
HMC *Pseudomonas aeruginosa* (non-CF) Susceptibility



Graph completed by Cynthia Lu, HMC pharm intern

UW TASP tele-antimicrobial stewardship program

UW Pseudomonas aeruginosa (non-CF) Susceptibility



Graph completed by Cynthia Lu, HMC pharm intern

UWTASP

UWMC / HMC: Piperacillin-tazobactam

All piperacillin-tazobactam 3.375gm orders (excludes neonates) are administered as prolonged infusion over 4 hours.

Renal function	Dosing
CrCl > 20 ml/min	Piperacillin-tazobactam 4.5 g x1 over 30 minutes, then 3.375 g over 4 hours given every 8 hours, (started 4 hours after the bolus)
CrCl < 20ml/min, or HD	Piperacillin-tazobactam 3.375 g infused over 4 hours given q12 hours

CON: Prolonged Infusion
Is the juice worth the squeeze?

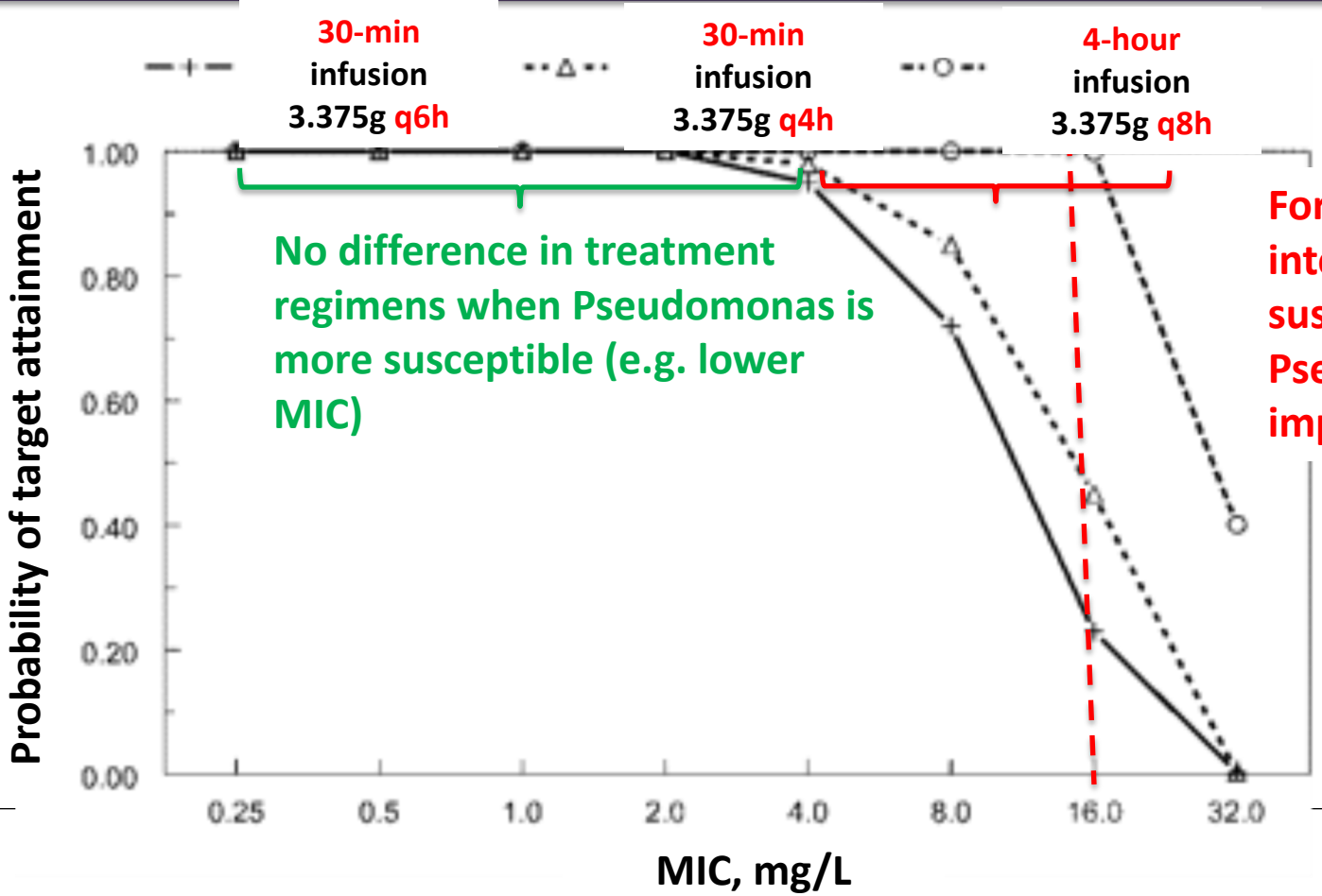
1.) Clinical impact

-- local level of resistance to pip/tazo

2.) Fiscal impact

-- 25-33% cost reduction in drug acquisition costs for pip/tazo

Prolonged Infusion Benefits Patients with More Resistant Bacteria



No difference in treatment regimens when Pseudomonas is more susceptible (e.g. lower MIC)

For less susceptible/ intermediate susceptible Pseudomonas, the impact is significant

From: Piperacillin-Tazobactam for Pseudomonas aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

Clin Infect Dis. 2007;44(3):357-363. doi:10.1086/510590

VMC: Piperacillin/Tazobactam Sensitivities

Organism	No. of Isolates	Piperacillin/tazo
Acinetobacter species	68	82
Citrobacter freundii	118	82
Citrobacter koseri	79	100
Enterobacter aerogenes	144	77
Enterobacter cloacae complex	226	80
Escherichia coli	7032	97
Klebsiella oxytoca	137	87
Klebsiella pnuemoniae	1005	96
Morganella morganii	126	98
Proteus mirabilis	801	100
Providencia rettgeri	35	100
Providencia stuartii	18	100
Pseudomonas aerugenosa	706	86
Raoultella planticola	19	100
Serratia marcescens	119	99
Stenotrophomonas maltophilia	42	

Organisms with antibiotic susceptibility < 90%

Most frequently isolated pathogen

VMC: *P. aeruginosa* sensitivities

Gram Negative Isolates
Percent susceptible

Organism	No. of Isolates	Ampicillin	Ampicillin/Sulbactam	Aztreonam	Cefazolin	Ceftriaxone	Gentamicin	Levofloxacin	Nitrofurantoin	Piperacillin/tazo	Trimethoprim/Sulfa	Cefepime	Ertapenem	Meropenem	Minocycline
Pseudomonas aerugenosa	706			84			94	74		86		94		92	

Alternative option

UWTASP tele-antimicrobial stewardship program

Prolonged Infusion Benefits Critically Ill Patients

When stratified by APACHE II score, the clinical benefit of extended infusion was statistically significant among patients with an APACHE II score ⩾17; both 14-day mortality (P = .04) and median LOS (P = .02) were lower for the patients who received extended infusion than for patients who received intermittent infusion. No differences in 14-day mortality and hospital LOS were noted for patients with an APACHE II score <17.

Clin Infect Dis. 2007;44(3):357-363.

UWTASP
tele-antimicrobial stewardship program

Prolonged Infusion / Fiscal Impact

Antibiotic	Total Days of Use[1]	12 month costs[2]
Piperacillin/tazobactam	66,692 [827/1000pt-days]	$46,488

[1] Calendar Year 2017

[2] 12-year expenses as of 3/31/17

Bottom Line Cost Savings: ~ $12,000

UWTASP
tele-antimicrobial stewardship program

Summary: Pro/Con
Prolonged Infusion Piperacillin/tazobactam

- **Win-Win dosing strategy that is:**
  (a) Better for patients
  (b) Better for the pocket book

- **HOW much better it is for <u>your</u> institution depends upon:**
  (a) Your patient population (critically ill/resistant GNR)
  (b) How much you spend on piperacillin/tazobactam

- **Which in turn justifies:**
  (a) Tying up an IV line for 3 hours
  (b) Implementation pains
    - updating inventory, IV pump library, educating staff, re-educating, & re-educating again)

UWTASP
tele-antimicrobial stewardship program

What about prolonged infusion for other antibiotics?

Antibiotic	Clinical Rationale	Fiscal impact
Cefepime	For MDRO	0 Dose-neutral
Ceftazidime	For MDRO	0 Dose-neutral
Meropenem	For MDRO	+ Dose reduction
Nafcillin/Oxacillin	Convenience	+/- Less RN time
Penicillin	Convenience	+/- Less RN time
Vancomycin	Convenience PK Target attainment	+/- Less drug monitoring IV compatibility issues

MDRO: Multiple-drug resistant organism

UWTASP
tele-antimicrobial stewardship program