Continuous Infusion of Beta-Lactams in Critically Ill Patients

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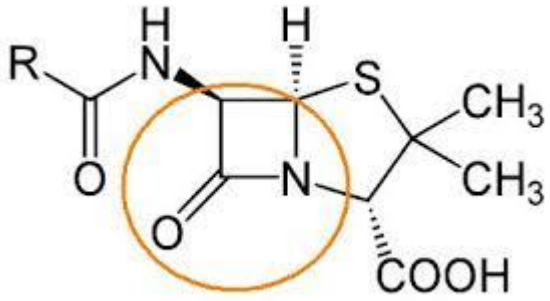
Presentation Outline

- Pharmacology of Beta-Lactams
- Current Problem
- Clinical Question
- Evidence
- Potential Advantages
- Drawbacks
- Applicability and Dosing
- Conclusion

Pharmacology of Beta-Lactams

How beta-lactams work

Mechanism of Action



- Inhibition of cell wall synthesis
- Beta lactam antibiotics target the penicillin-binding proteins or PBPs
  - Four-membered, nitrogen-containing beta-lactam ring at the core of their structure, which is key to the mode of action
- The beta-lactam ring portion of this group of antibiotics binds to these different PBPs, rendering them unable to perform their role in cell wall synthesis
- Classes of beta-lactams: penicillins, cephalosporins, carbapenems

Activity

- Generally bactericidal
- Broad-spectrum: carbapenems, 2nd, 3rd and 4th generation cephalosporins
- Narrow spectrum: penicillin, 1st generation cephalosporins, monobactam
- ALL EXHIBIT TIME DEPENDENT KILLING
  - Duration that drug levels exceed the MIC relative to the dosing interval and the frequency of drug administration are important determinants of outcome for these drugs.
- A shorter dosing interval will increase the time that concentrations remain greater than the MIC of the infecting microorganism

Mechanisms of Resistance to Beta-Lactams

- Decreased penetration to the target site
  - Outer membrane on gram negative bacilli creates a permeability issue
- Alteration of the target site
  - Alterations of PBP's may alter binding affinity of the antibiotics
  - Ex: MRSA, pneumococci
- Inactivation by bacterial enzymes
  - Production of beta lactamase
  - Ex: SPICE bugs, ESBL bugs

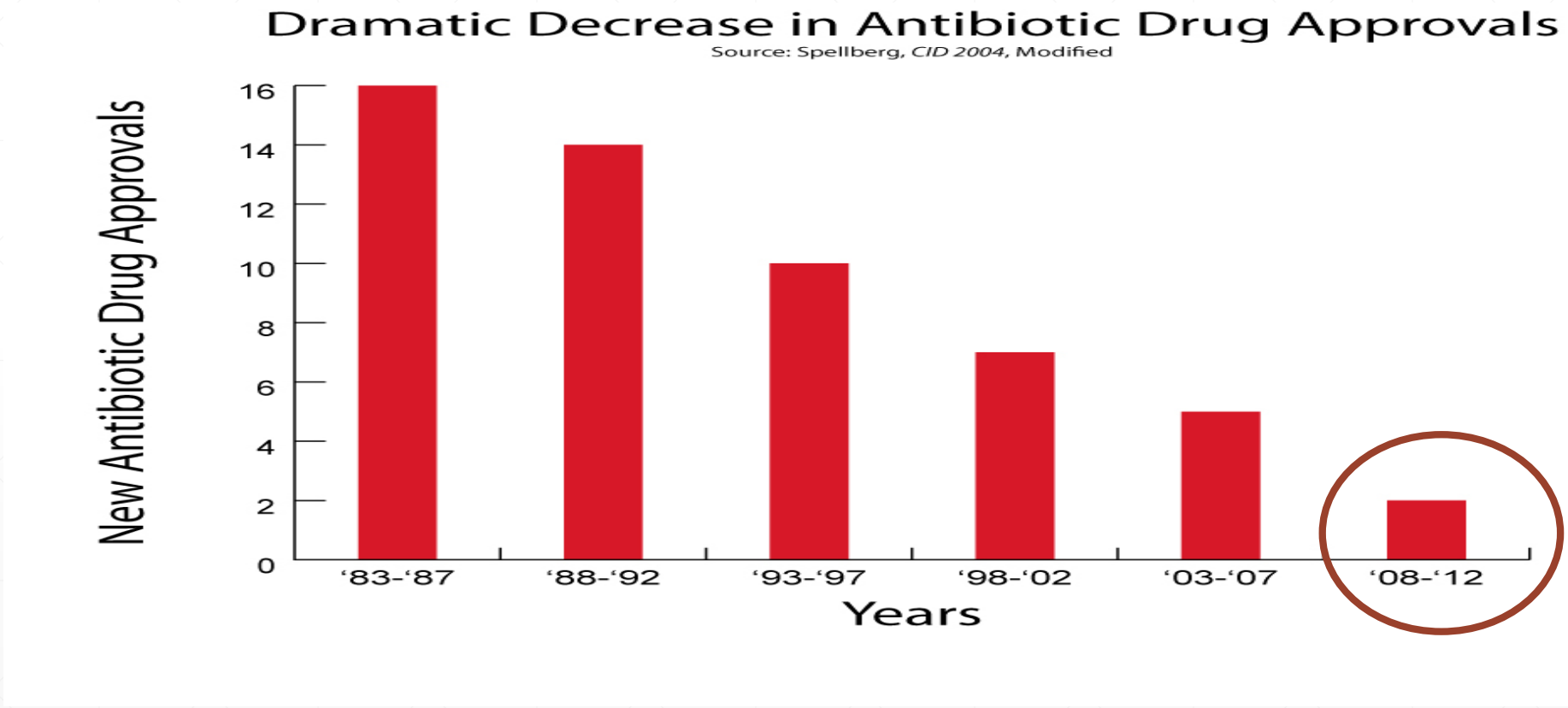
Current Problem

Increasing resistance to antibiotics globally

Mounting Resistance

- Increasing number of resistant bugs showing up in patients
- Organisms of concern- gram negative (ESBL/SPICE)
  - Escherichia coli
  - Klebsiella spp.
  - Enterobacter spp.
  - Pseudomonas aeruginosa
- No resources being allocated to fight the problem
- Lack of drug development in antibiotics

Antibiotic Drug Approvals



Current Pipeline

Drug name	Development phase[3]	Company	Drug class	Expected activity against resistant Gram-negative ESKAPE pathogens?[2]	Expected activity against a CDC urgent threat pathogen?[4]	Potential indication(s)?[5]
WCK 4873[R]	Phase 1	Wockhardt Ltd.	Second-generation ketolide	No	No	Bacterial infections
MGB-BP-3	Phase 1[D]	MGB Biopharma Ltd.	DNA minor groove binder	No	Yes	*C. difficile* infections
OP0595 (RG6080)	Phase 1[D]	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc. (Roche license)	Beta-lactamase inhibitor	Possibly	Possibly	Bacterial infections
BAL30072	Phase 1	Basilea Pharmaceutica Ltd.	Monosulfactam	Yes	Yes	Multidrug-resistant Gram-negative bacterial infections[6]
CRS3123	Phase 1	Crestone Inc.	Methionyl-tRNA synthetase (MetRS) inhibitor	No	Yes	*C. difficile* infections
LCB01-0371	Phase 1[D]	LegoChem Biosciences Inc.	Oxazolidinone	No	No	Bacterial infections
TD-1607	Phase 1	Theravance Biopharma Inc.	Glycopeptide-cephalosporin heterodimer	No	No	Acute bacterial skin and skin structure infections,[6] hospital-acquired pneumonia/ ventilator-associated bacterial pneumonia,[6] bacteremia[6]
WCK 2349[R]	Phase 1	Wockhardt Ltd.	Fluoroquinolone (WCK 771 pro-drug)	No	No	Bacterial infections
WCK 771[R]	Phase 1	Wockhardt Ltd.	Fluoroquinolone	No	No	Bacterial infections
Zidebactam+Cefepime (WCK 5222)[R]	Phase 1	Wockhardt Ltd.	Novel beta-lactamase inhibitor+beta-lactam	Possibly	Possibly	Complicated urinary tract infections,[6] hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia[6]

Clinical Question

Clinical Question

- Can giving beta-lactams over a continuous infusion in critically ill patients improve outcomes?

Rationale

- Provide maximal kill
  - Longer time above MIC= more bacteria killed
- Utilize optimal amount of drug
  - Increasing doses in these medications make no difference- time dependent
- Prolong use of drug in clinical practice
  - Reduce resistance by optimizing kill rates
- Overcome elevated MIC's
  - With longer exposure

Evidence

What the clinical trials are showing

Dulhunty et al. (2016)

- “Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double blind, randomized controlled trial”
- Prospective, double blind, randomized control trial
- P: Intensive care patients with severe sepsis (n=60)
- I: Continuous infusion of a beta-lactam (piperacillin-tazobactam OR meropenem OR ticarcillin-clavulanate)
- C: Intermittent dosing of a beta lactam
- O: Continuous infusion achieved higher plasma antibiotic concentrations than intermittent administration with improvement in clinical cure

Dulhunty et al- Eligibility Criteria

- All of the following criteria needed to be met:

1. Severe sepsis in the previous 48 hours
    1. Confirmed or suspected infection with new organ dysfunction
2. Planned commencement or commencement within the previous 24 hours of ticarcillin-clavulanate, piperacillin-tazobactam, or meropenem
3. Expected or actual ICU stay greater than 48 hours
4. >18 years of age
5. No allergies to the medications

Dulhunty et al Continued- “The Numbers”

	Continuous Infusion Group	Intermittent Dosing Group	P-Values
Plasma concentrations >MIC	82%	29%	P=.001
Clinical cure	70%	43%	P=.037
ICU free days	19.5	17	P=.14
Survival to hospital discharge	90%	80%	P=.47

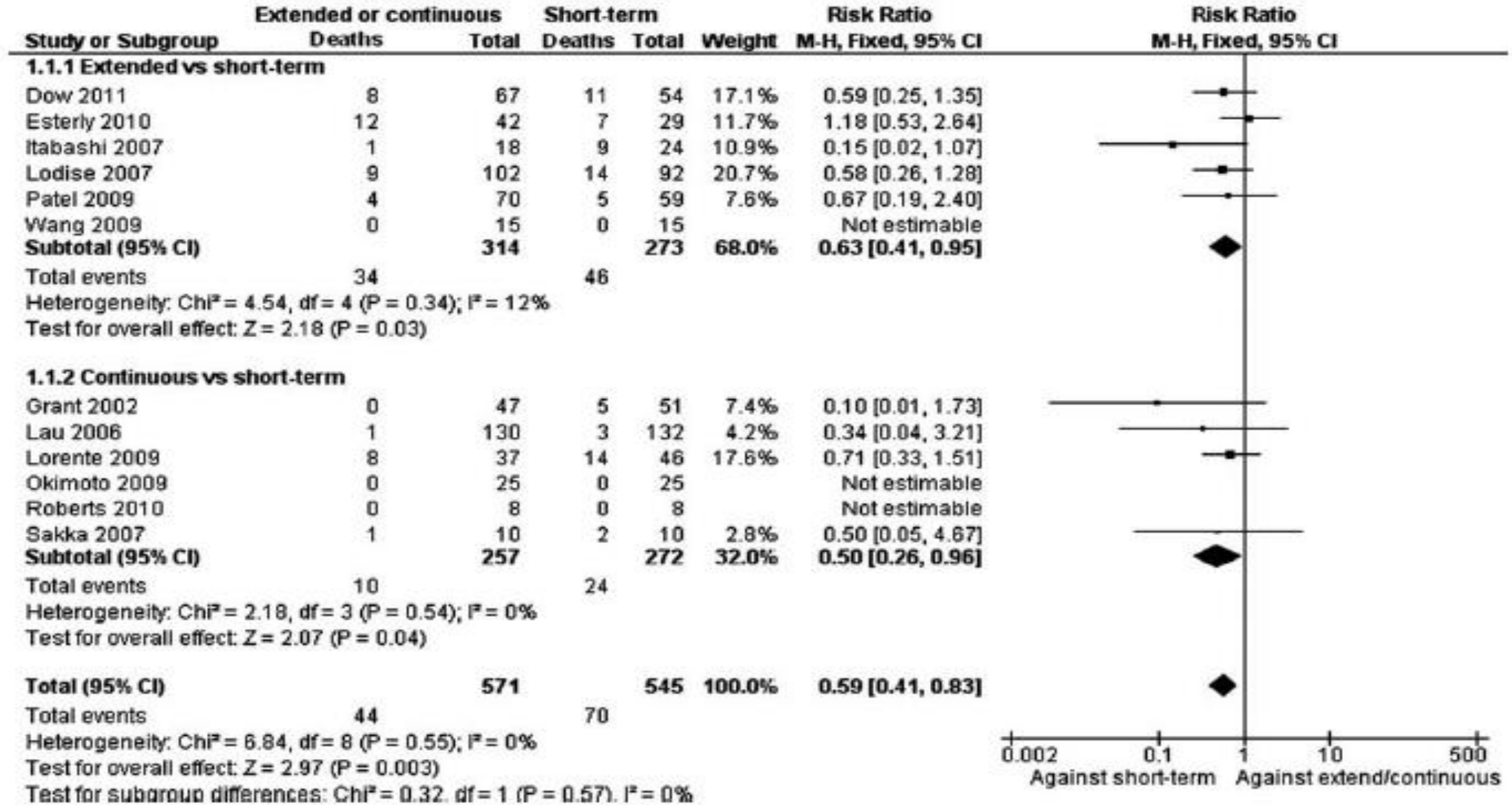
Dulhunty et al- Limitations

- Differences in baseline characteristics
  - Intervention group was 6 years younger, 13% more males, 13% higher comorbidity, and 13% higher proportion of pre-ICU in the intervention group
- Small sample size
  - Potential confounding by unmeasured variables
- Only trough levels were taken
  - Time spent above the MIC could only be inferred
  - Could be sample timing errors

Paper #2

Falagas et al. (2013)

- “Clinical outcomes with extended or continuous versus short-term intravenous infusions of carbapenems and piperacillin-tazobactam: a systematic review and meta-analysis”
- Clinical question:
  - “Are the better PK/PD properties of carbapenems and piperacillin-tazobactam associated with lower mortality when the duration of infusion is longer?”
- Searched PubMed and Scopus for studies
  - Excluded if: 1) case reports/series including <10 patients, 2) reported on comparative outcomes of extended vs. short term duration but for different carbapenems in the 2 arms
- Fourteen studies were included in the meta-analysis- n=1229


Extended or continuous
Short-term
Risk Ratio
Risk Ratio
Study or Subgroup
Deaths
Total
Deaths
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.1.1 Extended vs short-term
Dow 2011 8 67 11 54 17.1% 0.59 [0.25, 1.35]
Esterly 2010 12 42 7 29 11.7% 1.18 [0.53, 2.64]
Itabashi 2007 1 18 9 24 10.9% 0.15 [0.02, 1.07]
Lodise 2007 9 102 14 92 20.7% 0.58 [0.26, 1.28]
Patel 2009 4 70 5 59 7.6% 0.67 [0.19, 2.40]
Wang 2009 0 15 0 15 Not estimable
Subtotal (95% CI) 314 273 68.0% 0.63 [0.41, 0.95]
Total events 34 46
Heterogeneity: Chi² = 4.54, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 2.18 (P = 0.03)
1.1.2 Continuous vs short-term
Grant 2002 0 47 5 51 7.4% 0.10 [0.01, 1.73]
Lau 2006 1 130 3 132 4.2% 0.34 [0.04, 3.21]
Lorente 2009 8 37 14 46 17.6% 0.71 [0.33, 1.51]
Okimoto 2009 0 25 0 25 Not estimable
Roberts 2010 0 8 0 8 Not estimable
Sakka 2007 1 10 2 10 2.8% 0.50 [0.05, 4.67]
Subtotal (95% CI) 257 272 32.0% 0.50 [0.26, 0.96]
Total events 10 24
Heterogeneity: Chi² = 2.18, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Total (95% CI) 571 545 100.0% 0.59 [0.41, 0.83]
Total events 44 70
Heterogeneity: Chi² = 6.84, df = 8 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%
0.002
0.1
1
10
500
Against short-term
Against extend/continuous

Falagas et al.- Findings

- Mortality was lower in the continuous infusion groups compared to the short term
  - Risk ratio: 0.59, 95% confidence interval, 0.41-0.83
- Pneumonia patients who got continuous infusions had lower mortality than those with short term
  - Risk ratio: 0.50, 95% confidence interval, 0.26-0.96
- Data for other specific infections were not available
- Evidence is mainly from non-randomized studies
  - Can only really say at this point there is a trend to benefit
  - RCT’s are warranted to confirm what is being shown

Paper #3

Roberts et al. (2016)

- “Continuous versus intermittent beta-lactam infusion in severe sepsis: a meta analysis of individual patient data from randomized trials”
- P: Critically ill patients with severe sepsis (n=632; 3 trails included)
- I: Continuous infusions of beta-lactam antibiotics (meropenem or piperacillin-tazobactam)
- C: Intermittent dosing of beta-lactam antibiotics
- O: Continuous infusions in this population is associated with decreased hospital mortality and increased clinical cure

Roberts et al. – Inclusion Criteria

- All of the following needed to be met to be included in the meta- analysis:

1. Were prospective
2. Enrolled patients with severe sepsis or septic shock
3. Randomized patients to receive either continuous infusions or intermittent dosing of a beta lactam at equivalent dosing in each treatment arm
4. Reported assessment of outcomes by a clinician blinded to treatment allocation

Roberts et al. – “The Numbers”

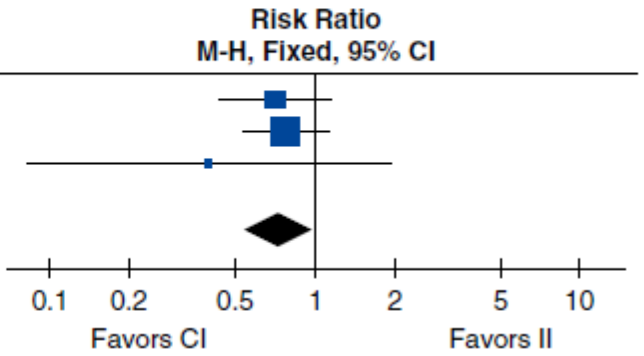
- Only showed significance in decreased mortality
  - 19.6% Continuous Infusion vs. 26.3% Intermittent (RR: 0.74) P=0.045

A

Study or Subgroup	CI Events	CI Total	II Events	II Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdul-Aziz 2016	20	70	28	70	33.3%	0.71 [0.45, 1.14]
Dulhunty 2015	39	212	52	220	60.7%	0.78 [0.54, 1.13]
Dulhunty 2013	2	30	5	30	5.9%	0.40 [0.08, 1.90]
Total (95% CI)		**312**		**320**	**100.0%**	**0.73 [0.55, 0.98]**
Total events	61		85			

Heterogeneity: $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0\%$

Test for overall effect: Z = 2.11 (P = 0.03)



Paper #4

Last paper!

Lodise, T., Lomaestro,B., and Drusano,G. (2007)

- “Piperacillin-Tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended infusion dosing strategy”
- Cohort study preformed from January 2000-June 2004 in Albany, New York
- P: Patients with Pseudomonas aeruginosa infection susceptible to piperacillin-tazobacam (Pip/Taz) (n= 194)
- I: Continuous infusion of Pip/Taz 3.375g IV q8H over 4 hours
- C: Intermittent dosing of Pip/Taz 3.375g IV q4-6H over 30 minutes
- O: 14 day mortality rate (12.2% vs. 31.6%; P= .04) and duration of hospital stay (21d vs. 38d; P=.02) was significantly lower in intervention group

Demographic or clinical characteristic	Extended Infusion (n = 102)	Intermittent Infusion (n = 92)	P
Age, mean years ± SD	62.8 ± 18.3	63.9 ± 16.1	.6
Male sex	65 (63.7)	54 (58.7)	.5
Diabetes mellitus	28 (27.5)	28 (30.4)	.6
HIV infection	1 (1.0)	2 (2.2)	.5
History of health care exposure	35 (34.3)	37 (40.2)	.4
Duration of stay prior to culture sample collection, median days (range)	7 (0–89)	6 (0–52)	.5
In ICU at onset of infection	63 (61.8)	63 (68.5)	.3
Consecutive days in ICU prior to onset of infection, median days (range)	3.5 (0–30)	2 (0–52)	.9
Receiving mechanical ventilation at culture sample collection	56 (54.9)	52 (56.5)	.8
Consecutive days receiving mechanical ventilation prior to culture sample collection, median days (range)	1 (0–59)	1 (0–48)	.8
APACHE II score at onset of infection, mean ± SD	15.3 (6.7)	16.2 (7.6)	.3
Duration of therapy, mean days ± SD	8.4 (4.4)	8.4 (4.5)	.9
Concomitant treatment with an aminoglycoside	21 (22.8)	26 (25.5)	.6
Concomitant treatment with a fluoroquinolone	5 (5.9)	10 (10.9)	.2
Primary source of culture sample			
Respiratory tract	55 (53.9)	48 (52.2)	.8
Urinary tract	21 (20.6)	12 (13.0)	.2
Skin or soft tissue	11 (10.8)	23 (25.0)	.009
Intravenous catheter	3 (2.9)	0 (0)	.1
Abdomen	4 (3.9)	1 (1.1)	.2
Other	8 (7.8)	8 (8.7)	.8

Potential Advantages

Why you should consider advocating for continuous infusions

Advantages

- Less susceptible pathogens
  - Bugs with higher MIC's but are still susceptible benefit from prolonged strategies
  - Obtain killing activity for longer periods of time
- Patients with altered pharmacokinetics
  - Critical illness, young, obese patients can result in altered drug clearance, changes in protein binding, differing volumes of distribution, etc.
  - Getting adequate serum levels can be challenging; higher doses for longer periods may be best

Advantages Continued

- Safety
  - No more toxicity risk than intermittent dosing
- Reduced selection for drug resistance
  - Prolonged infusions provide shorter periods of time where the levels go below the MIC
  - Less opportunity to acquire resistance or turn on resistance genes
- Cost benefit
  - Studies have shown in decreased drug costs, reduced length of stay, reduced complication costs, and labour costs
- Ease of administration- outpatient

Drawbacks

The caveats to continuous infusions

Drawbacks

- Logistical barriers
  - Continuous infusions require use of an IV pump for longer periods of time
    - Problematic if patients have limited IV access or lower levels of nursing care
  - Staffing is an issue and flushing has to occur at the end of the infusion for complete administration of drug
  - Prolonged infusions may also require higher IV catheter use with poses its own risks

Drawbacks Continued

- Compatibility
  - Administering other medications in the same IV line can cause compatibility issues
  - Shifting medication administration times may not be able to alleviate
- Stability
  - Drugs must be stable over the time they are administered
  - Ex: carbapenems are not stable at room temperature for long durations
- Clinical efficacy
  - At this point very little is known about applicability or correct dosing.
  - More work needs to be done in this area

Applicability and Dosing

Where can this be used?

Potential Indications

- Patients with structural lung disease
- Frequent healthcare exposure
- Prior repeated antibiotic exposures
- Intensive care patients/critically ill
  - Especially those with gram-negative rod infections with elevated but susceptible MICs
- Infections due to pathogens with high intrinsic resistance and predilection for developing acquired resistance during therapy

Dosing

	Creatinine Clearance (mL/min)	Dose	Dosing Interval	Infusion Time
Piperacillin-tazobactam	<20 >20 CRRT	3.375-4.5g for all	Q8H Q12H Q8H	4 hours for all
Meropenem	<10 10-24 25-49 >50 CRRT	0.5-1g 0.5-1g 1-2g 1-2g 1-2g	Q24H Q12H Q12H Q8H Q12H	3 hours for all

Dosing recommendations from clinical trials and expert opinion- may not be appropriate for all practice settings

Case Study: GR- HSN experience

- Patient developed ESBL intra-abdominal infection post bowel resection
- ESBL also grew in urine, respiratory secretions, and sacral area
- Given meropenem continuous infusion
  - Meropenem 500mg IV Q4H over 4 hours (max. stability time)
- Duration of meropenem continuous infusion was 7 days
- Patient’s infection resolved and was able to return home a week later

Conclusion

Wrap up of what we've covered

Summary

- We have a growing bacterial problem with not much coming down the pipeline
  - We have to start getting creative
- Evidence shows that continuous infusions are at least equally effective and in some cases have mortality benefit over traditional intermittent measures
- Additional benefits of reducing resistance, cost savings, and administration benefits for outpatients
- Drawbacks include logistical barriers, compatibility, and poor stability
- No established indications as of yet but potential areas include critically ill patients
  - Need more robust studies in specific patient populations
- Optimal dosing hasn’t been established- more studies needed

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QUESTIONS?

Thank you for your time!