BLING III

Continuous versus Intermittent infusion of beta-lactams

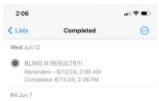
Ben Vermillion PharmD.

Disclosure Statement

- I have no *financial* interests or relationships to disclose

Non-financial conflicts of interest

- I'm a pharmacist! (but not an ID pharmacist)
  - Mechanism, PK/PD underscore much of my education
  - My institution has pharmacist-driven prolonged-infusion protocols



Abbreviations

- PI: Prolong infusion (or continuous or extended)
  - Will be used interchangeably for this talk
- SI: Short infusion (or intermittent infusion)

Learning Objectives

- Review the history of PI vs SI for beta-lactams
- Establish priors – before publication, what should we expect?
- Dissect BLING III – how does it fit with prior understandings
- Apply the findings clinical practice and policy discussions

Pre-Test Questions and Answers

Q: Prolonged infusions of beta-lactams maximize the duration of exposure by

A. Adjusting the infusion duration
B. Shortening the dosing interval
C. Increasing the dose of antibiotic

Pre-Test Questions and Answers

Q: What fraction of medicine is so obviously effective that it does not require randomized assessment?

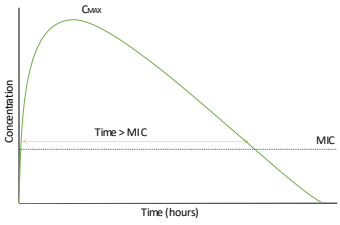
A. 80%
B. 50%
C. 20%
D. 1%

Pre-Test Questions and Answers

Q: BLING III demonstrated

A. An overwhelming improvement of prolonged-infusions on mortality
B. That prolonged infusions limit line access and are likely net harmful
C. That a rational and well powered trial can be hard to interpret. These data are either positive or neutral depending on who you ask

PK/PD Refresher



Concentration dependent (C_{max}/MIC)
E.g. Aminoglycosides, fluoroquinolones

Time dependent (*f*T > MIC)
E.g. Beta-lactams

Concentration and Time (AUC/MIC)
E.g. glycopeptides

SIs of beta-lactams are designed to achieve a goal T>MIC 40-70%

Hong L T et al, 2023

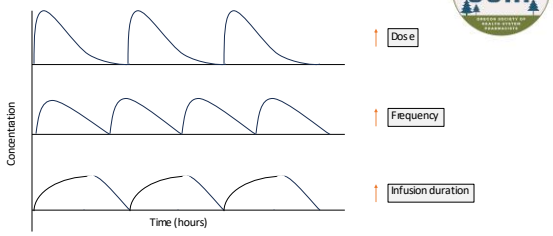
Why short infusions may fail

- Why SI may not meet goal T > MIC
  - Bugs with high MICs
  - Poor drug penetration
  - Altered kinetics
    - Drug clearance
    - Volume of distribution
    - Protein binding

Extremes of weight
Extremes of age
Critically ill
Malignancy

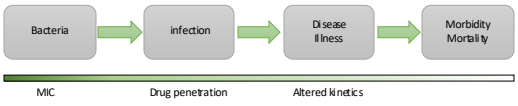
Roberts J A et al, 2014

PK/PD: Optimizing T > MIC



Pathophysiologic model is compelling

- Causal pathway is fairly linear
- intervention is specific
- Efficacy is dependent on exposure time
- Experience
- Accessible: ~~Drug discovery, regulatory approval~~



Is 'obvious' successful?

A detour through the satirical BMJ Christmas issues

Obvious is rarely successful

2003: BMJ Parachute RCT → 2007: Glasziou, #16 → 2008: Djulbegovic, ~50

2012 METRICS Stanford → Odds Ratio >5 or <0.2 → 85,002 meta-analyses → 2,791 "large" effects → 13 concerned mortality → 3 considered reliable → 1

500/85,000 = 0.6% → 1% of medical interventions are obvious

Glasziou P 2007; Djulbegovic B 2008; Pereira TV et al 2012

Spring 2023

Update to my institutional PI protocol

DOI: 10.1002/phar.2842

SPECIAL ARTICLE

PHARMACOTHERAPY

International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the

- Endorsed by the essential organizations
  - ACCP, IDSA, SIDP, SCCM, etc.

administration of intravenous β-lactams to increase time above the MIC. PI dosing regimens have been implemented worldwide, but implementation is inconsistent. We

- World-wide adoption
- Unanimous that PI reduce mortality

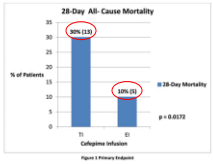
VII: Should PI β-lactam antibiotics be preferred over SI dosing in severely ill adult patients to improve mortality or clinical cure?

7 We suggest PI β-lactam antibiotics over SI to reduce mortality or increase clinical cure among severely ill adult patients, particularly those with gram-negative infections. Conditional recommendation; very low certainty of evidence (Panel vote 17-0 in favor of the recommendation)

Hong LT et al, 2023

Plausibility

Among patients with Acute Physiological and Chronic Health Evaluation-II scores > or =17, 14-day-mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; P=.04), and



July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h). The overall mortality was significantly lower in the group that received extended-infusion treatment (20% versus 3%; P= 0.03). The mean length of stay was 3.5 days less for patients who received extended infusion (P=

Lodise 2007; Bauer 2013; Vela 2016

Clinical Data

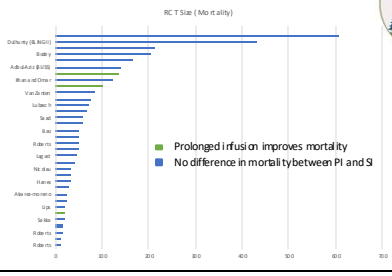
What is the totality of evidence to date?

Clinical Data

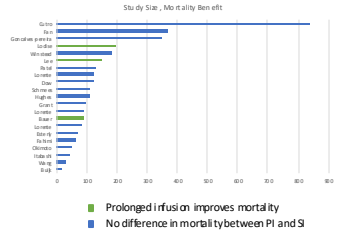
6 Meta-analyses | 55 studies | 6400 subjects

RCTs	Obs Studies
34 trials	21 studies
3100+ patients	3300+ patients

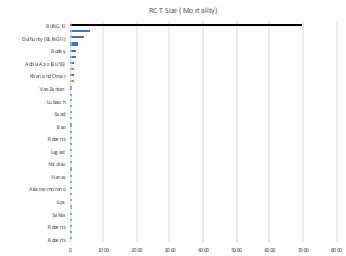
Clinical Data - RCTs



Clinical Data - Observational



Clinical Data – RCTs w BLING III



Clinical Data – Meta-Analyses

Meta-analyses (mortality)

Author	Trials	RCTs	Obs	N	PI Mortality	SI Mortality	Delta	Comment	
Falagas 2013	12	4	8	1116	7.7%	14.1%	6.4%	Favors PI, "driven by nonrandomized studies"	(-) (+)
Teo 2014	19	10	9	2206	11.0%	16.6%	5.6%	RCTs no diff, obs favor PIs	(-) (+)
Vardakas 2018	17	17	0	1876	13.7%	18.8%	5.1%	Favors PI, 13% v 18%; 0.70 (0.56 - 0.87)	(+)
Rhodes 2018	18	7	11	3520	13.8%	20.2%	6.4%	Favors PI, 13% v 20%; 0.69 (0.56-0.84)	(+)
Kondo 2020	9	9	0	844	19.3%	24.4%	5.1%	No diff, 0.69 (0.47-1.02)	(-)
Abdul 2024	17	17	0	9014	26.0%	30.9%	4.9%	Favors PI	(+)

Analytic flexibility. Crude mortality benefit is ~5%.

Clinical Data – MA vs Mega trials

Original Investigation | Statistics and Research Methods

September 6, 2024

Agreement Between Mega-Trials and Smaller Trials

A Systematic Review and Meta-Research Analysis

Lum Kastrati, MD[1,2,3,4]; Hamidreza Raeisi-Dehkordi, MSc[5]; Erand Llanaj, PhD[6,7,8], et al

> Author Affiliations | Article Information

JAMA Netw Open. 2024;7(9):e2432296. doi:10.1001/jamanetworkopen.2024.32296

Findings In this meta-research analysis of 82 mega-trials, meta-analyses of smaller studies showed overall comparable results with mega-trials, but smaller trials published before the mega-trials gave more favorable results than mega-trials. There were very low rates of significant results for the primary outcome and all-cause mortality for mega-trials.

Kastrati L, 2024

What is the best data to date?

BLING II Trial 2015 (N = 432)

- Multicenter RCT, open-label
- Continuous vs Intermittent
- Severe sepsis
  - APACHE ~20
- Meropenem or zosyn
- 90-day Mortality, NS
  - 25.7% vs 27.5% (0.91, 0.63-1.31, P 0.61)

MERCY Trial 2023 (N = 607)

- Multicenter RCT, double-blind
- Continuous vs Intermittent
- Severe sepsis
  - SOFA 9
- Meropenem
- 90-day Mortality, NS
  - 42% vs 42% (0.1, -7.7 – 8.0, P 0.97)

(no differences in any outcome)

The2 largest, best design studies: 0-2% change in mortality

Dulhunty 2015; Monti 2023

BLING III – PRE publication

What did we know about BLING III prior to publication?

Protocol and SAP Pre-registered

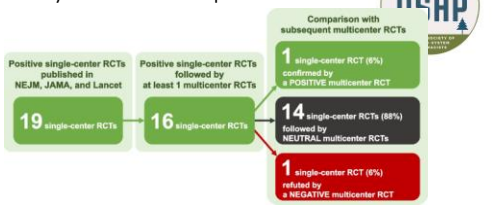
- Randomized trial
  - There is equipoise
- Sample size 7,000 (Largest RCT in 2024!)
  - Effect size
  - Baseline rate
  - Population variance
- Interim analysis
  - Stopping rules

Designed to detect a 3.5% difference in 90-day mortality

RCTs in the critically ill

The assessment of mortality

Mortality is difficult to prove



Very few RCTs have demonstrated mortality improvements in the critically ill

Kotani Y, 2023

What should we expect from BLING III

- PIs are compelling, but compelling isn't enough
- Mortality is a difficult endpoint in ICU trials
- Meta-analyses favor PIs, ~5% delta in mortality
- Best RCTs, ~2% mortality benefit
- Investigators designed the trial for a 3.5% mortality delta
- BLING III is huge with a great study design (more on this)

30% → 10% OR 30% → 27%

If any effect it will be marginal at best

BLING III

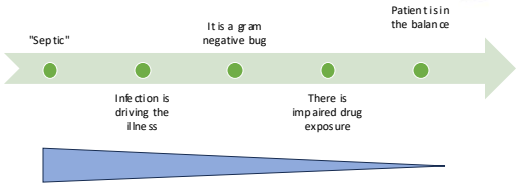
Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

Dulhunty JM, 2024

Clinical Question

OBJECTIVE To evaluate whether continuous vs intermittent infusion of a β-lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause mortality at 90 days in critically ill patients with sepsis.

Who is our target population?

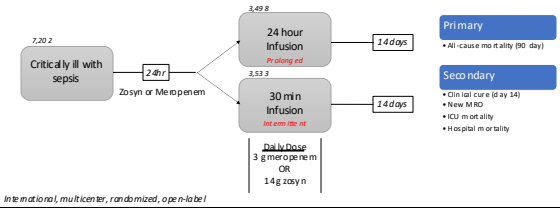


Housekeeping

- Funding:
  - Government grants
  - Educational grants
  - Non-profit entities
- COIs
  - The Georges Institute for Global Health (sponsor)
  - No classic FCOI
  - Ideologic bias?
- Published a priori
  - Trial protocol (2019)
  - Statistical analysis plan (2021)
  - DSMB Charter (2021)

Subtleties of antibiotic dosages--do doses and intervals make a difference in the critically ill?
Lipman J, Crowe-Brown HH, Saunders GL, Gous AG.
S Afr J Surg. 1996;34(4):160-2.
PMID: 9015932 No abstract available.

Trial Design



International, multicenter, randomized, open-label

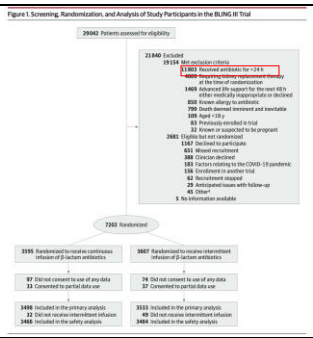
Participants

Inclusion

- Suspected infection
- On Meropenem or Zosyn within 24 hours
- Expected ICU x 2 midnights
- Organ dysfunction (1 or more)
  - MAP < 60 x 1 hour
  - Vasopressors >4 hours
  - Respiratory support
    - High flow, CPAP, BiPAP > 1 hour, OR
    - Mechanical ventilation

Exclusion

- < 18 years old
- Pregnant or suspected
- Allergy (any penicillin)
- CRRT
- DNR or imminent death



Baseline characteristics

- High degree of baseline balance (no concerns)

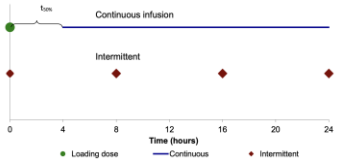
Prior to randomization
- APACHE II: 20 (mean)
- 70% on vasopressors
- 70% received antibiotics
- 80/20 Zosyn, meropenem

Table 1. Baseline Characteristics of Participants in the BLING III Trial (continued)

Characteristic	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]
Primary site of infection, No./total (%)		
Pulmonary	2062/3494 (59.0)	2119/3532 (60.0)
Intra-abdominal	469/3494 (13.4)	447/3532 (12.7)
Blood	268/3494 (7.7)	294/3532 (8.3)
Urinary	214/3494 (6.1)	166/3532 (4.7)
Skin	184/3494 (5.3)	186/3532 (5.3)
Gut	98/3494 (2.8)	120/3532 (3.4)
Central nervous system	65/3494 (1.9)	74/3532 (2.1)
Intravenous catheter	18/3494 (0.5)	20/3532 (0.6)
Endocarditis	13/3494 (0.4)	4/3532 (0.1)
Other[f]	103/3494 (2.9)	102/3532 (2.9)

Interventions

- Dosing schemes
  - 14 g Zosyn (daily)
  - 3 g Meropenem (daily)

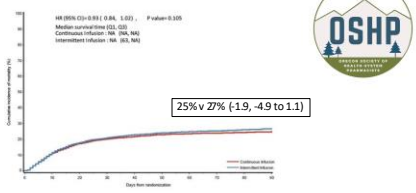


This is an impressive trial!

The Good
- Randomized
- Adequately powered
- COIs, sponsorship
- Pre-registered Protocol and SAP
- Ethical control arm
- Dosing schemes, rescue therapy, post-protocol therapy are fair
- Meaningful outcomes
- These patients look like my patients

The Bad
- ?open-label?
  - But an objective outcome
- ?Investigator bias?
- ?90 day outcome?
  - 28 day??

Results



25%v 27% (-1.9, -4.9 to 1.1)

Outcome	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds ratio or mean difference (95% CI)	P value[b]
Primary outcome					
All-cause mortality at day 90, No./total (%)	864/3474 (24.9)	939/3507 (26.8)	−1.9 (−4.9 to 1.1)	0.91 (0.81 to 1.01)	.08
Adjusted analysis			−2.2 (−5.5 to 1.1)	0.89 (0.79 to 0.99)	.04

Results

- When do infections/antibiotics matter for mortality?

JOURNAL ARTICLE

All-cause and Infection-attributable Mortality Amongst Adults With Bloodstream Infection—a Population-based Study

Jonathan Underwood, Rowena Griffiths, David Gillespie, Ashley Akbari, Haroon Ahmed · Author Notes

Open Forum Infectious Diseases, Volume 11, Issue 5, May 2024, ofae126, https://doi.org/10.1093/ofid/ofae126

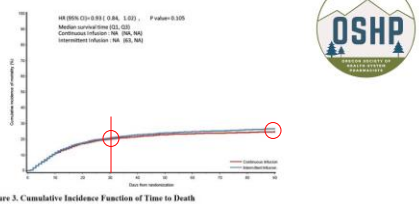
Published: 06 March 2024 **Article history**

<30 days: Infection leading cause of death.

30-90 days: Cancer is the leading cause of death

Underwood J et al 2024

Results



eFigure 3. Cumulative Incidence Function of Time to Death

*The **timing** confounds interpretability*

Results

- Results by gram negative infection
  - 40% identified -> 70% GNB (N ~1800)

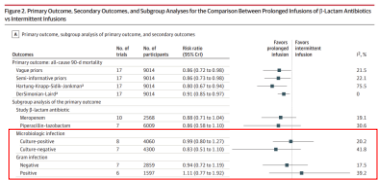


Figure 2. Primary Outcome, Secondary Outcomes, and Subgroup Analyses for the Comparison Between Prolonged Infusions of β-Lactam Antibiotics vs Intermittent Infusions

A Primary outcome, subgroup analysis of primary outcome, and secondary outcomes

Outcomes	No. of trials	No. of participants	Risk ratio (95% CrI)	Favors prolonged infusion	Favors intermittent infusion	I^2, %
Primary outcome: all-cause 90-d mortality						
Vague priors	17	9014	0.86 (0.72 to 0.98)			21.5
Semi-informative priors	17	9014	0.86 (0.73 to 0.98)			22.1
Hartung-Knapp-Sidik-Jonkman[a]	17	9014	0.89 (0.67 to 0.96)			73.5
DerSimonian-Laird[a]	17	9014	0.91 (0.85 to 0.97)			0
Subgroup analysis of the primary outcome						
Study β-lactam antibiotic						
Meropenem	10	2568	0.88 (0.71 to 1.04)			19.1
Piperacillin-tazobactam	7	6009	0.86 (0.58 to 1.10)			30.6
Microbiologic infection						
Culture-positive	8	4060	0.99 (0.80 to 1.27)			20.2
Culture-negative	7	4300	0.83 (0.51 to 1.10)			41.8
Gram infection						
Negative	7	2859	0.94 (0.72 to 1.19)			17.5
Positive	6	1597	1.11 (0.77 to 1.92)			35.2

Gram negative infections don't appear to drive the results

Results

- Results by MIC
  - To be determined
  - PK/PD substudy underway

Pending

Results - misc

Table 2. Reporting of Primary, Secondary, and Tertiary Outcomes

Outcome	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds ratio or mean difference (95% CI)	P value[b]
Secondary outcomes					
Clinical cure at day 14, No./total (%)	1930/3467 (55.7)	1744/3491 (50.0)	5.7 (2.4 to 9.1)	1.26 (1.15 to 1.38)	<.001
New acquisition, colonization, or infection with an MRO or C difficile, No./total (%)[c]	253/3498 (7.2)	266/3533 (7.5)	−0.3 (−1.9 to 1.4)	0.96 (0.80 to 1.15)	.65
All-cause ICU mortality, No./total (%)	595/3474 (17.1)	645/3507 (18.4)	−1.3 (−4.0 to 1.4)	0.92 (0.81 to 1.04)	.15
All-cause hospital mortality, No./total (%)	808/3474 (23.3)	878/3507 (25.0)	−1.8 (−4.8 to 1.2)	0.91 (0.81 to 1.02)	.27

Results

Efficacy: Neutral or Positive

Adverse Events

eTable 11. Summary of Adverse Events

	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
Any adverse event	10[a] 10 (0.3)[a]	0[a] 6 (0.2)[a]
Rash	4[a] 4 (0.1)	1[a] 1 (0.0)
Elevated liver enzymes	1[a] 1 (0.0)	1[a] 1 (0.0)
Fever	2[a] 2 (0.1)	0
Elevated bilirubin	1[a] 1 (0.0)	0
Encephalopathy	1[a] 1 (0.0)	0
Hypertension/hypotension	0	1[a] 1 (0.0)
Post-operative bleeding	0	1[a] 1 (0.0)
Rash, tachycardia, hypotension	0	1[a] 1 (0.0)
Redness/pain at intravenous insertion site	0	1[a] 1 (0.0)
Study drug error with increased monitoring (no specific adverse event)	1[a] 1 (0.0)	0
Any serious adverse event	1[a] 1 (0.0)	0
Life-threatening	1[a] 1 (0.0)[a]	0

Remarkable!

Logistics

- Patient mobility
- Line availability
- Compatibility
- Stability

Considerations, not deal breakers

Let's assume equivalence

- 3 criteria toward adoption
  - Less invasive or less toxic
  - Cheaper or cost neutral
  - Administration is logistically simplified

Prasad V. 2018

Why might PIs work anyway?

- The critically ill are heterogenous
  - Sepsis > infection > GN > impaired drug exposure > in the balance
- Clinical cure +++
- General trend across everything +++
- Look at newer antibiotics
  - Meropenem/vaborbactam
  - Ceftazidime/avibactam
  - Ceftobiprole

What are their infusion times out of drug development?

Conclusion

- A compelling model isn't enough
- BLING III was rationale and adequately powered
- Efficacy – hard to know if noise or effect
  - The result was expected!
  - Curve split (late)
  - Lack of separation with gram negative infections
- BLING III – Safe beyond a reasonable doubt
  - 13,000+ patients
- Study is neutral or positive

Pre-Test Questions and Answers

Q: Prolonged infusions of beta-lactams maximize the duration of exposure by

A. **Adjusting the infusion duration**
B. Shortening the dosing interval
C. Increasing the dose of antibiotic

Pre-Test Questions and Answers

Q: What fraction of medicine is so obviously effective that it does not require randomized assessment?

A. 80%
B. 50%
C. 20%
D. **1%**

Pre-Test Questions and Answers

Q: BLING III demonstrated

A. An overwhelming improvement of prolonged-infusions on mortality
B. That prolonged infusions limit line access and are likely net harmful
C. **That a rational and well powered trial can be hard to interpret. These data are either positive or neutral depending on who you ask**

Citations

1. Hong LT, Downes KJ, Fakhri Ravari A, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: endorsed by the american college of clinical pharmacy, british society for antimicrobial chemotherapy, cystic fibrosis foundation, european society of clinical microbiology and infectious diseases, infectious diseases society of america, society of critical care medicine, and society of infectious diseases pharmacists. Pharmacotherapy. 2023;43(8):740-777.
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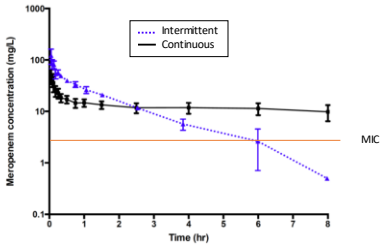
END

Stopping rules

- Evidence "beyond a reasonable doubt"
- Evidence that will lead clinicians to "change their mind"
- A 3-standard deviation in mortality
- Evidence of other important differences

Largely subjective, flexible interpretation

PK/PD: Clinical models



BLING I (N 60)
Continuous vs intermittent
Severe Sepsis

PI: T > MIC 82%
SI: T> MIC 29%

Plausibility

Publication, population	Years	Mortality rate, % (n)			Difference in mortality between untreated and antibiotic treatment groups (95% CI), %
		Untreated group	Serum treatment group, % (n)	Antibacterial drug treatment group (antibacterials received)	
Dowling and Lepper [19]					
Patients aged >16 years with pneumococcal pneumonia, bacteremic and nonbacteremic	1938–1950	30.5 (n = 1087)[a]	16.9 (n = 889)[a]	12.3 (n = 1274) (sulfonamides) 5.1 (n = 920) (penicillin or tetracyclines)	18.5 (15–21); 25.4 (22–28)
Austrian and Gold [20]					
Patients aged >12 years with bacteremic pneumococcal pneumonia (uncomplicated)	1952–1962	82 (n = 17)	...	17 (n = 437) (multiple antibiotics[b])	65 (41–79)

NOTE. Dosing information for antibacterial drugs was not provided in these publications.
[a] The years were 1929–1940 for the untreated group, 1929–1938 for the serum treatment group, and 1938–1941 for the antibacterial treatment group.
[b] Historical control group [21–24].
[c] Multiple antibiotics included penicillin, tetracyclines, erythromycin, chloramphenicol, and streptomycin.

Why therapies may still fail

- Most of medicine is modest to marginal
  - Requires randomization
- The critically ill are heterogenous
- Interventions need to be early
- Some conditions are too rare

Improving mortality in the critically ill is difficult!

Pre BLING III Summary

- Prolonged infusions are intuitive
  - Causal pathway is simple
  - Most institutions have adopted protocols
    - And cite impressive evidence!
- Yet many reasons why they might not be superior
  - Biology is complex
  - Aggregate RCT data is comparatively bearish
    - And likely an overestimate
- Clinical trials are hard
  - Early treatment
  - Some diseases are too rare

Adverse Events across all data

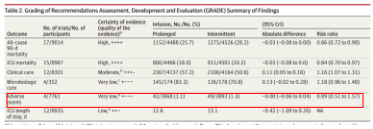


Table 2. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Summary of Findings

Outcome	No. of trials/No. of participants	Certainty of evidence (quality of the evidence)[a]	Infusion, No./No. (%)		(95% CrI)	
			Prolonged	Intermittent	Absolute difference	Risk ratio
All-cause 90-day mortality	17/9014	High, ++++	1152/4488 (25.7)	1275/4526 (28.2)	−0.03 (−0.08 to 0.00)	0.86 (0.72 to 0.98)
ICU mortality	15/8967	High, ++++	806/4466 (18.0)	911/4501 (20.2)	−0.03 (−0.08 to 0.0)	0.84 (0.70 to 0.97)
Clinical cure	12/8301	Moderate,[b] +++-	2307/4137 (57.2)	2108/4164 (50.6)	0.11 (0.05 to 0.18)	1.16 (1.07 to 1.31)
Microbiologic cure	4/152	Very low,[c] +---	145/174 (81.1)	126/178 (70.8)	0.11 (−0.02 to 0.20)	1.18 (0.96 to 1.48)
Adverse events	4/7743	Very low,[c] +---	622/3868 (11.1)	492/3893 (11.3)	−0.00 (−0.06 to 0.04)	0.99 (0.51 to 1.97)
ICU length of stay, d	12/8935	Low,[c] ++--	12.6	13.1	−0.42 (−1.09 to 0.26)	NA