Antibiotic Pharmacokinetics, Pharmacodynamics

Individualized antibiotic dosing for critically ill patients

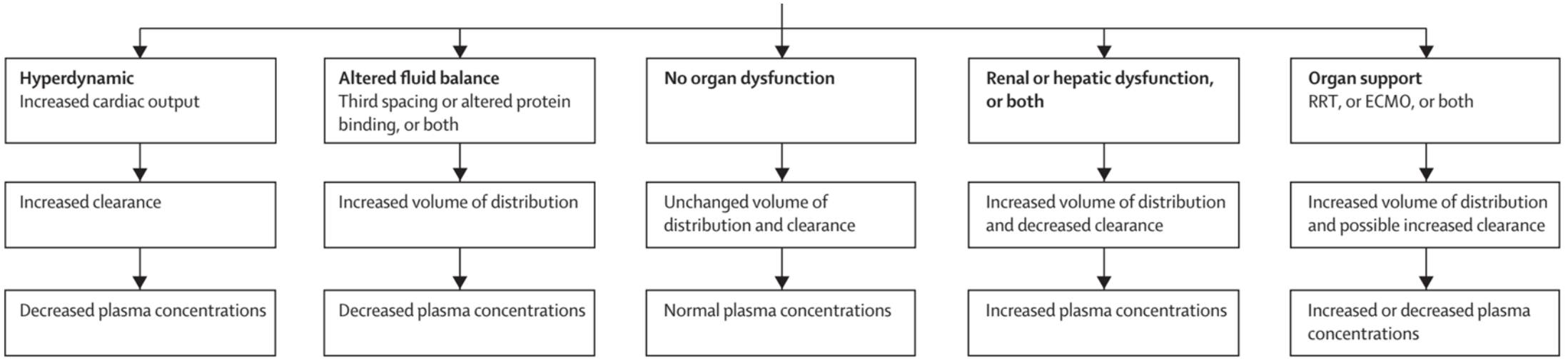

Figure: **The range of altered pathophysiology in patients with critical illness, and its effects on drug concentrations**
RRT=renal replacement therapy. ECMO=extracorporeal membrane oxygenation.

Parameters

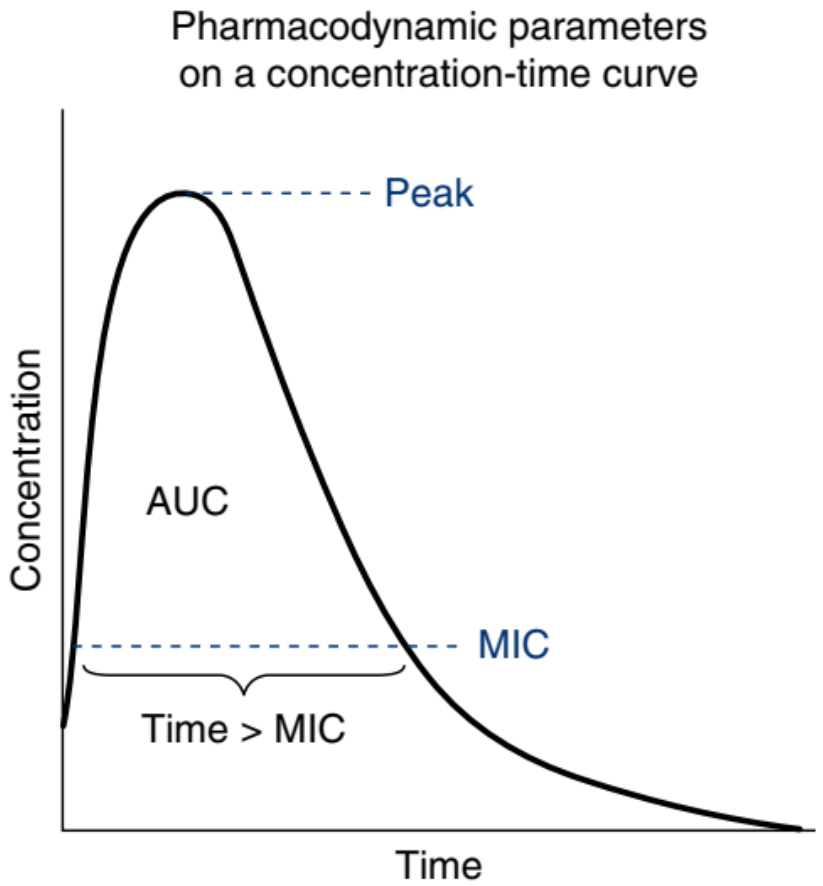

Figure 1. | Pharmacodynamic parameters on a concentration–time curve. Peak:MIC is the parameter to optimize for concentration-dependent antibiotics. Time>MIC is the parameter to optimize for time-dependent antibiotics.

Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing[11,96]	AUC_{0-24}/MIC >30–100	Clinical cure[15,86,96,97,98]	AUC_{0-24}/MIC ≥125–250; C_{max}/MIC ≥8
	Resistance suppression[99,100,101]	AUC_{0-24}/MIC >160; AUC_{0-24}/MPC ≥22	Microbiological cure[14,86,102]	AUC_{0-24}/MIC ≥34–125; C_{max}/MIC ≥8
Vancomycin	Maximum killing[103]	AUC_{0-24}/MIC 86–460	Clinical cure[20,21]	AUC_{0-24}/MIC ≥400–450
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure[20]	AUC_{0-24}/MIC ≥400
Linezolid	Maximum killing	..	Clinical cure[22]	AUC_{0-24}/MIC ≥85; 85% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[22]	AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing[105]	50% $T_{>MIC}$	Clinical cure[106,107,108]	AUC_{0-24}/MIC >12·8–17·9; *f* AUC_{0-24}/MIC ≥0·9
	Resistance suppression	..	Microbiological cure[109,110]	AUC_{0-24}/MIC 6·9–17·9
Daptomycin	Maximum killing[111,112]	AUC_{0-24}/MIC 38–442	Clinical cure	..
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure	..
Colistin	Maximum killing[113,114]	AUC_{0-24}/MIC 7–23	Clinical cure	..
	Resistance suppression	..	Microbiological cure	..

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Reduced bacterial susceptibility to antibiotics

	Preclinical studies		Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing[43]	AUC_{0-24}/MIC 80–100	Clinical cure[82–86]	C_{max}/MIC 8–10; AUC/MIC >70
	Resistance suppression[87]	C_{max}/MIC 10–30	Microbiological cure	..
Time-dependent				
Carbapenems	Maximum killing[88]	40% $T_{>MIC}$	Clinical cure[89]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[90, 91]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[17]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[11]	60–70% $T_{>MIC}$	Clinical cure[92]	100% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[16,93]	60–100% $T_{>MIC}$; 95% $T_{>4·3xMIC}$
Penicillins	Maximum killing[11]	40–50% $T_{>MIC}$	Clinical cure	..
	Resistance suppression[94]	40–50% $T_{>MIC}$	Microbiological cure[95]	40–50% $T_{>MIC}$

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Vancomycin

- Susceptibility testing shows a minimal inhibitory concentration (MIC) of 2 μg/mL or less (Clinical and Laboratory Standards Institute [CLSI] and US Food and Drug
- The 2009 consensus guidelines for therapeutic monitoring of vancomycin suggested that troughbased serum vancomycin concentrations of 15–20 μg/mL could serve as a surrogate of an AUC0–24/MIC ratio of at least 400 when a MIC value was ≤1 μg/mL, although clear clinical evidence to support this exposure target was lacking

- In general, for patients with normal renal function, vancomycin dosing consists of 15 to 20 mg/kg/dose (based on actual body weight) every 12 hours, not to exceed single doses of 2 g unless measured trough concentrations in serum are below target concentrations
  - In the setting of rapid clearance (such as in burn patients or in younger patients with normal renal function), administration of vancomycin every 8 hours may be required to achieve target troughs.
  - In patients with impaired renal function, dose reductions and/or extended dosing intervals are required.

Special situations

- Critical illness
- Severe or invasive infection
- Impaired or fluctuating renal function
- Morbid obesity (body mass index ≥40 kg/m2)
- Advanced age
- Lack of adequate clinical response after three to five days of therapy
- Use of concurrent nephrotoxic medications (examples include aminoglycosides, piperacillin-tazobactam, amphotericin B, cyclosporine, loop diuretics, nonsteroidal anti-inflammatory drugs, and radiocontrast)

- Target concentrations — The target trough serum concentration depends on the nature of infection:
- For patients with deep-seated infection (such as bacteremia, endocarditis, osteomyelitis, prosthetic joint infection, pneumonia warranting hospitalization, or infections involving the central nervous system), a target trough of 15 to 20 mcg/mL is warranted.
- For patients with nonsevere infection (such as soft tissue infection), a target trough of 10 to 15 mcg/mL is warranted. Achieving a vancomycin trough concentration of at least 10 mcg/mL may reduce the emergence of isolates with elevated vancomycin minimum inhibitory concentrations (MICs)

Weight (kg)	Creatinine Clearance (ml/minute)						
	40–49	50–59	60–69	70–79	80–89	90–99	≥ 100
50–54	500 mg q12h	750 mg q12h	1000 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
55–59	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1000 mg q8h	1250 mg q8h
60–64	750 mg q12h	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
65–69	750 mg q12h	1000 mg q12h	1250 mg q12h	1000 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h
70–74	750 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1500 mg q8h
75–79	1000 mg q12h	1250 mg q12h	750 mg q8h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
80–84	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h
85–89	1000 mg q12h	1250 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
90–94	1000 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
95–99	1250 mg q12h	1500 mg q12h	1000 mg q8h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h
100–104	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2000 mg q8h
105–109	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h
≥ 110	1250 mg q12h	1500 mg q12h	1250 mg q8h	1500 mg q8h	1750 mg q8h	2000 mg q8h	2250 mg q8h

Figure 1. Vancomycin dosing nomogram. Doses ≥ 2 g should be infused over 2 hours; doses of 1.5 g should be infused over 90 minutes. Weight refers to total weight. Creatinine clearance was calculated by using the Cockcroft-Gault equation.

- vancomycin nephrotoxicity may be better determined by AUC values instead of trough concentrations
  - This study, along with several other recent publications, suggest that an AUC0–24 range between 400 and 600 µg•h/mL was most commonly linked to clinical success, whereas an increased risk for vancomycin-associated acute kidney injury or nephrotoxicity occurs when an AUC0–24 threshold exceeds a range of 600–800 µg•h/mL
- Higher rates of nephrotoxicity occur when vancomycin is combined with an aminoglycoside, piperacillin-tazobactam, and other nephrotoxic agents

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- If a meticillin resistant Staphylococcus aureus pathogen has a vancomycin minimum inhibitory concentration value of 0·5 mg/L, then an area under the curve (0–24 h) value of 200 mg/L/h is needed.
  - This concentration could be achieved comfortably with a trough concentration of more than 10 mg/L.
- If the minimum inhibitory con centration is 2 mg/L, then an area under the curve (0–24 h) value of 800 mg/L/h is needed.
  - This concentration would, in turn, need a trough concentration of more than 20–25 mg/L, which would substantially raise the risk of drug-related toxic effects. In the case of high minimum inhibitory concentrations, an alternative antibiotic or combination therapy might be needed.

Aminoglycosides

- Effects and toxicity

- Tissue penetration

Aminoglycoside concentrations in body tissues following multiple-dose IV administration

Body tissue	Tissue/serum ratio
CSF	0.08 - 0.25
Pleural fluid	1
Synovial fluid	0.9
Saliva	0.05
Urine	> 500

Nix et al, 1991

2. Therapeutic serum concentrations (mcg/ml)
   a. Gent/Tobra/Netilmicin Amikacin/Kanamycin
      Peak
      Serious infection: 6-8
      Life-Threatening infection: 8-10
      Trough
      Serious infection: 0.5-1.5
      Life-Threatening infection: 1- <2

   b. Amikacin/Kanamycin
      Peak
      Serious infection: 20-25
      Life-Threatening infection: 25-30
      Trough
      Serious infection: 1-4
      Life-Threatening infection: 4-8

- Immunocompetent, nonpregnant adults and children >3 months of age with:
  - Urinary tract infections
  - Intraabdominal infections
  - Respiratory tract infections
  - Gynecologic infections (including pelvic inflammatory disease)
  - Soft-tissue infections
  - Bacteremia
- Women with postpartum endometritis
- Febrile neutropenia patients with malignancy (adults and children)

Do not routinely use extended-interval dosing for the following:

- Patients with burns (>20 percent total body surface area)
- Patients with ascites
- Pregnant women (with the exception of intrapartum therapy for intra-amniotic infection)
- Patients with creatinine clearance less than 40 mL/min (including patients requiring dialysis) OR >120 mL/min

JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(97\ mL/min) + 0.014 = 0.298\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.298\ h^{-1} = 2.3\ h$$

$$V = 0.26\ L/kg\ (70\ kg) = 18.2\ L$$

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL)/0.298\ h^{-1}] + 1\ h = 8.4\ h$$

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau})/(1 - e^{-k_e t'})]$$

$$k_0 = (9\ mg/L \cdot 0.298\ h^{-1} \cdot 18.2\ L)\ \{[1 - e^{-(0.298\ h^{-1})(8\ h)}]/[1 - e^{-(0.298\ h^{-1})(1\ h)}]\} = 172\ mg$$

- In order to optimize the treatment of serious gram-negative infections with aminoglycosides, a Cmax/MIC ratio of greater than 8-10 is considered necessary to affect a clinical cure.
- For Pseudomonas aeruginosa infections where the organism has an expected MIC ≈ 2 μg/mL, peak concentrations between 20 and 30 μg/mL and trough concentrations of less than 1 μg/mL have been suggested.
- At the present time, there is not a consensus on how to approach concentration monitoring using this mode of administration

- .
- Some clinicians measure steady-state peak and trough concentrations while others measure two steady-state postdose concentrations or a single steady-state postdose concentration.
- Other clinicians suggest that individualizing the aminoglycoside Cmax/MIC, AUC, or AUC24/MIC (where AUC24 is the area under the concentration-time curve for the antibiotic for a duration of 24 hours) is the best approach

3. Determine interval

The initial interval is based on estimated creatinine clearance:

CrCl	Interval
60 and above	24 hours
40 to 59	36 hours
30 to 39	48 hours
Less than 30	Use traditional dosing method

Extended interval method - Adjust maintenance dose

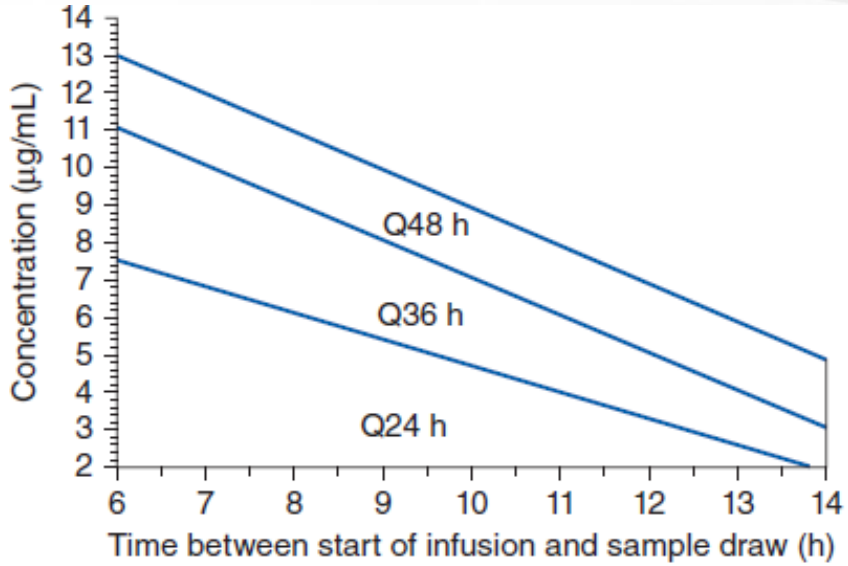
1. Compute patient's creatinine clearance (CrCl) using Cockcroft-Gault method: CrCl = [(140 − age)BW]/(Scr × 72). Multiply by 0.85 for females. Use Salazar-Cocoran method if weight > 30% over IBW.
2. Use patient's weight if within 30% of IBW; otherwise use adjusted dosing weight = IBW + [0.40(TBW − IBW)].
3. Select loading dose in mg/kg to provide peak serum concentrations in range listed below for the desired aminoglycoside antibiotic:

Aminoglycoside	Usual Loading Doses (mg/kg)	Expected Peak Serum Concentrations (μg/mL)
Tobramycin Gentamicin Netilmicin	1.5-2.0	4-10
Amikacin Kanamycin	5.0-7.5	15-30

4. Select Maintenance Dose (as percentage of loading dose) to continue peak serum concentrations indicated above according to desired dosage interval and the patient's creatinine clearance. To maintain usual peak/trough ratio, use dosage intervals in clear areas. *Note: Dosing for patients with CrCl ≤ 10 mL/min should be assisted by measuring serum concentrations

Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (mL/min)	Est. Half-Life (h)	8 h	12 h	24 h
>90	2–3	90%	—	—
90	3.1	84	—	—
80	3.4	80	91%	—
70	3.9	76	88	—
60	4.5	71	84	—
50	5.3	65	79	—
40	6.5	57	72	92%
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7*	25.9	19	28	47
5*	31.5	16	23	41
2*	46.8	11	16	30
0*	69.3	8	11	21



1. Administer 7 mg/kg gentamicin or tobramycin with initial dosage interval:

Estimated CrCl (mL/min)	Initial Dosage Interval
≥60	q24h
40–59	q36h
20–39	q48h
<20	Monitor serial concentrations & administer next dose when <1 µg/mL

2. Obtain timed serum concentration, 6-14 hours after dose (ideally first dose).
3. Alter dosage interval to that indicated by the nomogram zone (above q48h zone, monitor serial concentrations and administer next dose when <1 µg/mL).

Note: Refer to original nomogram for actual patient dosing.

Optimization

- IX. In Hospitalized Patients Requiring Intravenous (IV) Antibiotics, Does a Dedicated Pharmacokinetic (PK) Monitoring and Adjustment Program Lead to Improved Clinical Outcomes and Reduced Costs?
- Recommendations

Optimization

- 9. We recommend that hospitals implement PK monitoring and adjustment programs for aminoglycosides (strong recommendation, moderate-quality evidence).
- 10. We suggest that hospitals implement PK monitoring and adjustment programs for vancomycin (weak recommendation, low-quality evidence).
  - Comment: PK monitoring and adjustment programs can reduce costs and decrease adverse effects.
  - The ASP should encourage implementation and provide support for training and assessment of competencies. The conduct of those programs should be integrated into routine pharmacy activities

- X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum ß-Lactams and Vancomycin?
- Recommendation

- In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs (weak recommendation, low-quality evidence).

- XI. Should ASPs Implement Interventions to Increase Use of Oral
- Antibiotics as a Strategy to Improve Outcomes or Decrease Costs?
- Recommendation

- We recommend ASPs implement programs to increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics (strong recommendation, moderate-quality evidence).

- XIII. Should Antibiotic Dosing Be Determined by Pharmacokinetic/ Pharmacodynamic (PK/PD) Data or the Manufacturer’s Prescribing Information in Patients With HAP/VAP?

- For patients with HAP/VAP, we suggest that antibiotic dosing be determined using PK/PD data, rather than the manufacturer's prescribing information (weak recommendation, very low-quality evidence).

- A meta-analysis of 3 studies (one randomized trial [244] and 2 observational studies [246, 248]) determined that PK/PD-optimized dosing reduced both mortality (12% vs 24%; RR, 0.49; 95% CI,.34–.72) and the ICU length of stay (mean difference, −2.48 days; 95% CI, −3.09 to −1.87 days).
- A meta-analysis of 5 studies (2 randomized trials [242, 243] and 3 observational studies [246–248]) found that PK/PD-optimized dosing improved the clinical cure rate (81% vs 64%; RR, 1.40; 95% CI, 1.16–1.69).
- These benefits from PK/PD optimization have also been detected during the treatment of infections other than HAP/VAP

REVIEW Open Access

Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR)

- We suggest determining the glomerular filtration rate by calculating creatinine clearance with the formula U × V/P at the onset of treatment with beta-lactam antibiotics, and every time the clinical condition and/or renal function of the patient significantly changes.
- We suggest determining the glomerular filtration rate by calculating creatinine clearance with the formula U × V/P every time beta-lactam concentration is measured in order to help in interpreting the result.

- We suggest targeting a free plasma betalactam concentration between four and eight times the MIC of the causative bacteria for 100% of the dosing interval (fT ≥ 4–8 x MIC = 100%) to maximize bacteriological and clinical response in critical care patients.
  - In a large multicenter study including eight beta-lactam antibiotics, a 100% fT > MIC was associated with improved clinical outcome in septic ICU patients compared to 50% fT > MIC (OR 1.56–95%CI [1.15–2.13] vs. 1.02 [1.01–1.04], p < 0.03)

- Pending the result of therapeutic drug monitoring (TDM), we suggest that a higher daily dose of beta-lactam antibiotics than that administered in patients outside the ICU should be administered at the onset of treatment, especially in the most critically ill patients and in those with preserved renal function.

- We suggest administering beta-lactam antibiotics by prolonged or continuous infusions for infections due to bacteria with high MIC in order to increase the probability of achieving the PK-PD targets.

Table 1 Convulsing activity of beta-lactams compared to penicillin G, from [67, 69, 70]

Beta-lactam	Relative pro-convulsive activity (reference: penicillin G = 100)
Cefazolin	294
Cefepime	160
Penicillin G	*100*
Imipenem	71
Aztreonam	42
Ampicillin	21
Ceftazidime	17
Meropenem	16
Ceftriaxone	12
Piperacillin	11
Cefotaxime	8,8
Cefoxitine	1,8