

### **APPENDIX 3. PHARMACODYNAMICS AND PHARMACOKINETICS OF CHEMOTHERAPEUTIC ANTIMICROBIALS: INDICATIONS FOR APPROPRIATE CHOICE AND DOSE REGIMENS**

In the field of antimicrobial chemotherapy, the last years have brought about a critical analysis of the rules dictating both the choice of antimicrobials and their optimal regimen. The aim was to increase the efficacy of antibacterial therapy and reduce the risk of selecting multi-resistant pathogens.

The fundamental criteria for the rational choice of an antimicrobial agent are the knowledge of its pharmacodynamic characteristics, including antimicrobial activity spectrum, type of bactericidal activity, and antibacterial potency. Antimicrobial potency towards pathogens is indicated by the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). These determine the minimal concentrations capable of exerting antibacterial effects. Analysis of antimicrobial bactericidal activity indicates that there are two prevailing behaviours: for antibiotics such as fluoroquinolones, aminoglycosides, metronidazole, quinopristin-dalfopristin, clarithromycin, azalides, and ketolides there is a direct correlation between bactericidal effect and obtaining high concentrations, even though these are maintained for relatively short periods of time. These antibiotics may therefore be classified as concentration-dependent. From a clinical standpoint, concentration-dependent antibiotics may be administered as high concentration once/twice daily doses in order to obtain bacterial eradication [259]

Conversely, penicillins, cephalosporins, monobactams, oxazolidinones, glycopeptides, and erythromycin, once they have reached adequate concentrations, exert their bactericidal activity on the basis of time span during which the antibiotic is in contact with the microorganism: efficacy is described as time-dependent. In this case, antibiotic administration is best repeated several times during the day so as to obtain optimal bactericidal activity.

Antimicrobial activity may persist after the antibiotic concentration decreases or disappears. This indicates the presence of a post-antibiotic effect (PAE) or a post-antibiotic effect at sub-inhibitory concentrations (PA-SME), or a boost of leukocyte phagocytosis during PAE (PALE). Significant PAE has been described for carbapenems, glycopeptides, macrolides, azalides, ketolides, aminoglycosides, and fluoroquinolones [260].

One of the main goals in treating infections is that within the infected tissue, antibiotic penetration exceeds the minimal inhibitory concentration for the involved pathogen. This constitutes the basic pharmacokinetic criterion in choosing an antibiotic, and is of paramount importance in obtaining pathogen eradication [261–263].

It has been clearly shown that antibiotic serum concentration (and, as a result, infected tissue antibiotic concentration) influences intensity and duration of the antimicrobial effect. This factor, coupled with the minimal inhibitory concentration (the fundamental pharmacodynamic parameter) constitutes a prediction criterion for the clinical efficacy of an antimicrobial agent.

Over the last years, prediction indexes of antibacterial efficacy and antibiotic dose optimisation have been validated both in experimental animals and in man, based on the correlation between pharmacokinetic and pharmacodynamic parameters. The

degree of correlation varies for different antibiotic classes, and even for different agents within a single class.

These indexes include: the amount of time with serum concentrations above MIC ( $T > MIC$ ); the ratio between peak concentration ( $C_{max}$ ) and MIC ( $C_{max}/MIC$ ); and the correlation between the area under the curve of serum concentrations over 24 hours ( $AUC_{24}$ ) and MIC ( $AUC_{24}/MIC$ ).

Clinical and bacteriological efficacy of time-dependent antibiotics such as betalactams and erythromycin has been significantly associated with high values of  $T > MIC$ : these must be above 40–50% of the interval between successive administrations so as to guarantee a high percentage of clinical resolution both in animal infection models and in human acute otitis media, sinusitis and osteomyelitis.

Fluoroquinolones, exhibiting concentration-dependent bactericidal activity, must reach a  $C_{Max}/MIC$  ratio of at least 10–12 to obtain optimal efficacy, or an  $AUC_{24}/MIC$  ratio above 125 to improve clinical remission in severe lower respiratory tract infections. However, recent data indicate that lower values for this ratio ( $AUC/MIC$  ratio in the 30–50 range) are sufficient to obtain bacteriological eradication of *S. pneumoniae* with third generation fluoroquinolones both in animal models and in community acquired lower respiratory tract infections. Schentag warns there may be a risk of selecting resistant microorganisms through the use of low  $AUC/MIC$  values [264–266].

Similarly to fluoroquinolones, in aminoglycoside antibiotic treatment,  $C_{max}/MIC$  values  $\cong 10$  are predictive for clinical and bacteriological efficacy [267]. For glycopeptides an  $AUC/MIC$  trough value  $> 125$  is of great importance [268, 269].

The main pharmacokinetic requisites of the ideal antimicrobial agent are maximal oral bioavailability, sufficiently long half-life, and a high ratio between tissue and serum concentrations. This indicates a satisfactory tissue concentration.

There is now an ample choice of oral and parenteral antibiotics at the clinician's disposal. The choice of the administration route is based on the knowledge of the different pharmacological, anatomical, physiological and pathological factors affecting the drug's bioavailability that is its ability to reach adequate concentrations with the site of infection so as to guarantee clinical efficacy.

Oral administration, in cases where the drug is highly bioavailable, is generally the safest and surest route of administration, both in terms of economical cost and patient acceptability. This is particularly true when, based on serum half-life, drug administration is no more than twice daily. Oral administration is generally indicated in mild to moderately severe infections and in the absence of complications.

The choice of parenteral antibiotic administration is usually based on four factors: reduced gastrointestinal absorption, dysphagia or lack of co-operation (e.g. children or elderly patients), absence of orally active antibiotic with equivalent activity, specific infections and severity of the disease.

Reduced gastrointestinal absorption may be due to relatively rare conditions such as gastrectomy or short intestine syndrome, but are more commonly due to symptomatic gastrointestinal disorders.

Oral formulations are as yet unavailable for aminoglycosides, carbapenems, glycopeptides and many cephalosporins. Therefore, when bacterial etiology or clinical conditions indicates these antibiotics as first choice treatment, parenteral administration is required.

Lastly, parenteral antibiotic administration is always required in specific infections where the risk of complications is high, such as osteomyelitis, or endocarditis. In broader terms, parenteral administration is indicated in severe infections and in compromised hosts, both in the out-patient setting and during hospital admission. This is based on the observation that injected antibiotics obtain high serum and tissue concentrations more rapidly compared to oral administration.

Intramuscular administration, practised much more commonly in Italy than in other European countries, possesses intermediate characteristics between intravenous and oral administration: bioavailability is prompt but not as immediate as for intravenous administration. Absorption of aqueous solution antibiotics is based on their concentration and on blood flow velocity in the site of injection. However, this route of administration may be particularly useful when difficulties are encountered in obtaining an intravenous route (vein identification, maintaining catheter patency, high risk of local infection, etc.) or due to logistical problems.

In terms of antibiotic diffusion within the respiratory tract, the airways may be considered as a “simple” target due to the lack of biological barriers (as opposed to the central nervous system). During acute bacterial infections, the fraction of antibiotic unbound to plasma proteins may reach richly vascularised tissues such as the respiratory tract by simple diffusion through the capillary bed. Drug-protein binding is an important factor that may therefore condition antibiotic tissue penetration in sites lacking a highly specialised capillary membrane.

Tissue factors influencing antibiotic penetration are dictated by the degree of capillary permeability, degree of vascularisation, and presence of inflammation. Acute inflammation generally favours tissue distribution, whereas chronic infection may bring about tissue alterations by creating pseudobarriers, thereby heavily conditioning antibiotic penetration. Tissue distribution is generally hindered by the presence of fibrosis, granuloma formation bacterial and protein debris, as may occur for example in chronic bronchitis. Tissue antibiotic penetration is influenced by drug class, administration characteristics (oral or parenteral, single or repeat doses), and individual molecular tissue diffusion properties, based on physical-clinical aspects.

In summary, antibiotic administration regimen optimisation (dose, route of administration, time interval between doses) in clinical practice requires a thorough knowledge of the pharmacokinetic and pharmacodynamic properties of each antibiotic class (table 39). Specifically, most betalactams (penicillins, cephalosporins, and monobactams) and oxazolidinones are bactericidal at low concentrations, their activity is time-dependent, and they possess little post-antibiotic effect. A correct dose regimen must therefore guarantee prolonged bacterial exposure to these antibiotics, maintaining serum levels adequately above MIC.

The aim with carbapenems, glycopeptides, and natural macrolides is also a prolonged bacterial exposure time, but given the presence a substantial post-antibiotic effect, serum levels may decrease to below MIC in the time interval between doses.

Conversely, optimal dose regimens for aminoglycosides, fluoroquinolones, quinopristin-dalfopristin, semi-synthetic macrolides, azalides, and ketolides require obtaining maximal concentrations, in that bactericidal activity is directly related to high concentrations and almost all these antibiotics posses a prolonged post-antibiotic effect.

TABLE 39 Correlation between pharmacodynamic and pharmacokinetic properties of different antibiotics

Antibiotic	Pharmacodynamics	Pharmacokinetics (posology)
Penicillin Cephalosporins Monobactams Oxazolidinones	Bactericidal at low concentrations Low or absent PAE	Need of prolonged bacterial exposure time maintaining serum levels adequately above MIC
Carbapenems Glycopeptides Natural Macrolides	Bactericidal even at low concentrations Prolonged PAE	Need of prolonged bacterial exposure time. Serum levels may decrease to below MIC in the time interval between doses.
Aminoglycosides Fluoroquinolones Quinupristin-dalfopristin Semi-synthetic macrolides Azalides Ketolides	Bactericidal activity related to $C_{max}$ Prolonged PAE	Need to obtain maximal concentrations (high levels of $C_{max} / MIC$ or $AUC/MIC$ )

**PAE:** Post-antibiotic effect;

**MIC:** minimum inhibitory concentration;

**$C_{max}$ :** peak serum concentration;

**AUC:** area under the serum concentration curve.

TABLE 40 Mean concentrations of antibiotics in biological fluid, tissues and cells of respiratory tract. Reproduced from [270] with permission from publisher.

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Amoxicillin	1.2 <sup>a</sup>	0.6 <sup>a</sup>	0.52 (1g os, sd) <sup>b</sup>	1.6 (750mg os, dr) <sup>c</sup>	2.7 (500mg os, dr)	2.4 (1g os, sd) <sup>b</sup>
Clavulanate	1.75 <sup>a</sup>	1.8 <sup>a</sup>	–	–	1.8 (250mg os, sd)	–
Ampicillin	–	–	–	0.6±0.1 <sup>d</sup>	38.6±7.2 <sup>d</sup>	–
Sulbactam	–	–	–	0.3±0.1 <sup>d</sup>	28.1±5.2 <sup>d</sup>	–
Azitrmycin	13.2±0.9 (500mg os, sd + 250mg os, dr) <sup>e</sup>	464±65 (500mg os, sd + 250mg os, dr) <sup>e</sup>	–	–	–	3.9 (500mg os, sd)
Cefaclor	2.71 (750mg os, dr) <sup>f</sup>	–	0.6 (1g os, sd) <sup>c</sup>	–	7.73 (1g os, dr) <sup>g</sup>	–
Cefazoline	–	–	–	12.9–21.3 (1–2g <i>i.v.</i> , sd) <sup>c</sup>	–	–
Cefixime	–	–	0.02–0.05 (200mg os, dr)	–	2.4 (400mg os, dr)	–
Cefotaxime	–	–	1.8 (1g <i>i.v.</i> , sd) <sup>b</sup> 1.4 (1g <i>i.m.</i> , sd) <sup>b</sup>	7.2 (1g <i>i.v.</i> , sd)	–	19.5 (1g <i>i.v.</i> , sd) <sup>b</sup> 4.8 (1g <i>i.m.</i> , sd) <sup>b</sup>
Cepodoxime proxetil	–	–	–	–	0.9 (200mg os, sd)	–
Ceftazidim <sup>+</sup>	–	–	–	17 (2g <i>i.v.</i> , sd) <sup>c</sup>	–	10 (1g <i>i.v.</i> , sd) <sup>b</sup>
Ceftibuten	1.5 (400mg os, sd)	–	–	–	5.7 (400mg os, sd)	–
Ceftraxon	–	–	1.9 (1–2g <i>i.v.</i> , sd) <sup>b</sup> 2.3 (1g <i>i.m.</i> , sd) <sup>b</sup> 0.4 (1g <i>i.m.</i> , sd) <sup>g</sup>	7.9 (1g <i>i.v.</i> , sd) <sup>c</sup>	–	19.5 (1g <i>i.v.</i> , sd) <sup>b</sup> 11.5 (1g <i>i.m.</i> , sd) <sup>b</sup> 3.87 (1g <i>i.v.</i> , sd) <sup>g</sup> 2.18 (1g <i>i.m.</i> , sd) <sup>g</sup>
Cefuroxime axetil	0.7 (500mg os, sd)	–	3.5+1.0 (500mg os, sd)	–	1.8 (500mg os, sd)	–

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Ciprofloxacin	–	–	1.3–1.4 (500mg os, sd)	0.4–1.5 (250mg os, sd) 1.2–1.4 (500mg os, sd) 1.0–1.8 (200mg <i>i.v.</i> , sd)	1.0 (250mg os, sd) 1.7–6.9 (500mg os, sd) 1.3–11.0 (200mg <i>i.v.</i> , sd)	1.3–3.0 (250mg os, sd) 2.2–4.5 (500mg os, sd) 2.1–4.7 (200mg <i>i.v.</i> , sd)
Clarithromycin	34.02±5.2 (500mg os, dr) <sup>h</sup>	1996±2539 (500mg os, dr) <sup>h</sup>	2.66 (250mg os, dr)	31.55 (500mg os, dr) <sup>h</sup>	–	28.19 (500mg os, dr)
Erythromycin	0 (250os, dr) <sup>i</sup> 0.8 ± 0.1 (250os, dr) <sup>h</sup>	0.1± 0.3 (250os, dr) <sup>i</sup> 0 (250os, dr) <sup>h</sup>	0.59 (1g os, dr)	–	–	4.2 (250 o 500mg os, dr)
Imipenem	–	–	0.6 +2.1 (1g <i>i.v.</i> , sd) <sup>l</sup> 0.94+0.12 (1g <i>i.v.</i> , sd) <sup>l</sup>	–	–	12 (1g <i>i.v.</i> , sd) <sup>c</sup>
Levofloxacin	9.0 (500mg os, sd) <sup>m</sup>	41.9 (500mg os, sd) <sup>m</sup>	–	–	–	7.74 (500mg os, sd)
Linezolid	64.3±33.1 (600mg os, sd) <sup>h</sup>	2.2±0.6 (600mg os, sd) <sup>h</sup>	–	–	–	–
Meropenem	–	–	0.46 (1g <i>i.v.</i> , sd) <sup>l</sup> 0.24 (1g <i>i.v.</i> , sd) <sup>n</sup> 0.53 (1g <i>i.v.</i> , sd) <sup>o</sup>	2.29 (1g <i>i.v.</i> , sd) <sup>l</sup> 30.62 (1g <i>i.v.</i> , sd) <sup>n</sup> 1.72 (1g <i>i.v.</i> , sd) <sup>o</sup>	4.53 (1g <i>i.v.</i> , sd) <sup>f</sup> 0.08 (1g <i>i.v.</i> , sd) <sup>m</sup> 1.81 (1g <i>i.v.</i> , sd) <sup>n</sup>	2.86 (1g <i>i.v.</i> , sd) <sup>f</sup> 4.83 (1g <i>i.v.</i> , sd) <sup>m</sup> 3.29 (1g <i>i.v.</i> , sd) <sup>n</sup>
Moxifloxacin	22.4 (500mg os, sd)	113.6 (500mg os, sd)	–	–	5.5 (500mg os, sd)	–
Piperacillin	–	–	29.3 <sup>p</sup> 20.2 <sup>q</sup>	–	162 <sup>p</sup> 9.7 <sup>q</sup>	67.1 <sup>p</sup> 1.2 <sup>q</sup>
Tazobactam	–	–	6.86 <sup>p</sup> 4.25 <sup>q</sup>	–	23.7 <sup>p</sup> 1.76 <sup>q</sup>	14.2 <sup>p</sup> 0.74 <sup>q</sup>
Teicoplanin	–	–	–	2.8 (400 mg·kg <sup>-1</sup> <i>i.v.</i> , sd)	–	14 (400 mg·kg <sup>-1</sup> <i>i.v.</i> , sd)

Antibiotic	ELF (mg·l <sup>-1</sup> )	Alveolar Macrophages (mg·l <sup>-1</sup> )	Bronchial secretion (mg·kg <sup>-1</sup> )	Pleural fluid (mg·l <sup>-1</sup> )	Bronchial mucosa (mg·kg <sup>-1</sup> )	Pulmonary tissue (mg·kg <sup>-1</sup> )
Telithromycin	14 (800mg os, sd) <sup>n</sup>	70 (800mg os, sd) <sup>n</sup>	–	–	4 (800mg os, sd) <sup>n</sup>	–
Tobramycin	5.3–5.5 (300mg <i>i.m.</i> sd·md <sup>-1</sup> ) <sup>r</sup>	3.0–3.3 (300mg <i>i.m.</i> sd·md <sup>-1</sup> ) <sup>r</sup>	–	–	–	–
Vancomycin	0.4–8.1 (15 mg·kg <sup>-1</sup> <i>i.v.</i> , md)	–	–	2.9 (500mg <i>i.v.</i> , sd)	–	–

**sd:** single dose;  
**md:** multiple dose;  
**os:** oral;  
***i.v.*:** intravenous;  
***i.m.*:** intramuscular;  
**–:** no data.

**a:** 750mg Amoxi-clav (4:1);  
**b:** 1-3 h from administration;  
**c:** 2–4 h from administration;  
**d:** after 30 min one *i.v.* dose of ampicillin/sulbactam 2g/1g;  
**e:** 5 days from administration;  
**f:** 32–48 h from administration;  
**g:** 24 h from administration;  
**h:** 4 h from administration;  
**i:** 8 h from administration;  
**l:** 1 h from administration;  
**m:** 2–3 h from administration;  
**n:** 2 h from administration;  
**o:** 3 h from administration;  
**p:** after a 4/0.5g dose (*i.v.*, multiple dose), 30' from last administration;  
**q:** after a 4/0.5g dose (*i.v.*, multiple dose), 6 h from last administration;  
**r:** 6 h from administration.

TABLE 41 Main pharmacokinetics parameters of oral and parenteral penicillins , and suggested dosing. Reproduced from [271–275] with permission from publisher.

Antibiotic	Biodispos-ability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Urinary clearance (%)	Dose
Amoxicillin	93±10 <sup>a</sup>	1–2	<i>i.v.</i> : 46±12 <sup>b</sup> os: 5 <sup>b</sup>	18	1.7±0.3 ↔ children	0.21±0.03 ↔ renal dis., elderly	2.6±0.4 ↔ children	86± 8	1g (A: 875/C: 125) every 8 h os ; 1 g every 8 h <i>i.v.</i>
Clavulante	75±21	1.3 <sup>d</sup>	2.8 <sup>d</sup>	22	0.9±0.1 ↑ renal dis., elderly <sup>c</sup> ↑ neonates, renal dis. ↔ children	0.21±0.05 ↔ renal dis., children	3.6±1.0 ↓ renal dis., elderly <sup>c</sup> ↓ renal dis.	43±14	2g (16:1, A: 2000/C:125 mg, twice daily os 2.2 g every 8 h <i>i.v.</i> 1.5g every 8 h <i>i.v.</i> o <i>i.m.</i>
Ampicillin	100 <sup>f</sup>	1	49.6	–	1.04	0.16	0.25 ↔ children	71	1.5g every 8 h <i>i.v.</i> o <i>i.m.</i>
Sulbactam			93.5		0.99 ↑ renal dis., children, neonates, cystic fib., elderly ↓ post-partum	0.10	0.17 ↑ renal dis., children, neonates, cystic fib., elderly	71	
Piperacillin	–	–	264.4–277	21	0.75–0.91	15	14.5	50–60	4.5g (P: 4/ T: 0.5) every 8 h <i>i.v.</i>
Tazobactam	–	–	29.1–34 ↑ renal dis., children ↔ liver dis.	20–23	0.78–0.8 ↑ renal dis., children ↔ liver dis.	18 ↔ liver dis.	12.1 ↔ liver dis. ↓ neonates	50–60 ↔ liver dis.	

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** dose-dependent; dose: 375mg; reduction of aboutl 50% at 3000mg;  
**b:** no change in absence of renal insufficiency;  
**c:** single dose 500mg *i.v.* in healthy elderly or single oral dose 500mg in adults;  
**d:** mean values after an oral dose 125mg (healthy adults).  
**e:** values after a dose of 500mg-500mg ampicillina-sulbactam;  
**f:** *i.m.*;  
**g:** mean values after single or multiple doses 4/0.5g piperacillin/tazobactam.

TABLE 42 Main pharmacokinetics parameters of carbapenems and suggested dosing. Reproduced from [276, 277] with permission from publisher.

Antibiotic	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Renal clearance (%)	Dose
Imipenem	<i>i.m.</i> : 1–2 <sup>b</sup>	<i>i.v.</i> : 60–70 <sup>b</sup> <i>i.m.</i> : 8.2–12 <sup>b</sup>	<20	0.9±0.1 ↑ neonates, nefrop., prem.  ↔ cystic fib, children, elderly	0.23±0.05 ↑ neonates, prem., children  ↔ cystic fib, nefrop., elderly	2.9±0.3 ↑ children ↓ nefrop.  ↔ cystic fib, neonates, prem., burns, infiammazioni, elderly	69±15 ↓ neonates, infiammazioni  ↔ cystic fib, children	500mg - 1g every 8 h <i>i.m./i.v.</i>
Cilastatin	–	–	~35	0.8±0.1 ↔ neonates, prem.  ↑ cystic fib, elderly	0.2±0.03 ↑ neonates, nefrop., prem.  ↔ cystic fib, children, elderly	3.0±0.3 ↑ children ↓ nefrop., neonates, prem. ↔ cystic fib, elderly	70±3 ↓ neonates  ↔ cystic fib,	
Meropenem	–	54.8–61.6 <sup>c</sup> 21.1–35.6 <sup>d</sup>	10–20	1–1.4 <sup>c</sup> 0.8–1.54 <sup>d</sup> ↑ children, elderly, renal dis.  ↓ cystic fib	0.18–0.3 <sup>c</sup> 0.12–0.37 <sup>d</sup> ↑ children, surgery.  ↓ cystic fib	2.7–4 <sup>c</sup> 2.67–4.7 <sup>d</sup> ↓ children, elderly  ↑ renal dis., cystic fib	65.8±8.8 <sup>c</sup> 83±4 <sup>d</sup> ↓ children, elderly  ↑ renal dis., cystic fib	1g every 8 h <i>i.v.</i>

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** preparation ratio 1:1 (mg·mg<sup>-1</sup>);  
**b:** single dose of 1g *i.v.* (infusion time 30 min) or 750 mg *i.m.*;  
**c:** single dose 1 g;  
**d:** single dose 0.5 g.

TABLE 43 Main pharmacokinetics parameters of oral cephalosporins and suggested dosing. Reproduced from [278–282] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Cefaclor (II generation)	90	1 <sup>a</sup> 3.8 <sup>b</sup>	15 <sup>a</sup> 11 <sup>b</sup>	25	1 <sup>a</sup> 0.77 <sup>b</sup>	5.86 <sup>e</sup>	4.8–6.4 <sup>a</sup>	74.3±3.7 <sup>a</sup> 71.2±5.8 <sup>b</sup>	750mg every 12 h M.R.
Cefuroxime axetil (II generation)	32 (21–44) <sup>b</sup> ↑ cibo	2–3 <sup>c</sup>	7–10 <sup>c</sup>	33±6	1.7±0.6 ↑ renal dis. ←→ children	0.20±0.04 ←→ renal dis., elderly	Cl=0.94Clcr+0.28	96±10	500mg every 8–12 h
Cefixime (III generation)	47±15	3–4 <sup>e</sup>	1.7–2.9 <sup>e</sup>	67±1	3.0±0.4 ↑ renal dis.	0.30±0.03	1.3±0.2 ↓ renal dis.	41±7	200–400mg every 12–24 h
Cefpodoxime proxetil (III generation)	50	2.8	2.6	<40	2.7 ↑ renal dis.	0.7± 0.07	3.4±0.6 ↓ renal dis.	46	200mg every 12 h
Ceftibuten (III generation)	80	2	15	60–70	2.5	0.21–0.24	0.7–1.1	70	400mg every 12–24 h

↑: INCREASE;  
↓: REDUCTION;  
←→: NO CHANGE.

**a:** after 500 mg, IR (immediate release);  
**b:** after 750 mg,MR (modified release);  
**c:** cefuroxime axetil, prodrug;  
**d:** mean values after single oral dose 500 mg healthy volunteers;  
**e:** mean values after single oral dose 200 mg (capsule) healthy volunteers;  
**f:** prodrug, dose: 200 mg.

TABLE 44 Main pharmacokinetics parameters of parenteral cephalosporins and suggested dosing. Reproduced from [283–286] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Urinary clearance (%)	Dose
Cefazoline	>90	<i>i.m.</i> : 1.7±0.7 <sup>a</sup>	<i>i.v.</i> : 237±285 <sup>a</sup> <i>i.m.</i> : 42±9.5 <sup>a</sup>	89±2 ↓ renal dis., cirrhosis, bypass cardioplm, neonates, children	2.2±0.02 ↑ renal dis., bypass cardioplm., neonates ↓ pregnancy, cirr. ←→ obesity, children	0.19±0.06 ↑ renal dis., neonates ←→ obesity, children, pregnanc y, cirr.	0.95±0.17 ↓ renal dis., bypass cardioplm ↑ pregnancy ←→ obesity, children, neonates, cirr.	80±16	1-2g every 8 h <i>i.v.</i> o <i>i.m.</i>
Cefotetan	–	<i>i.m.</i> : 1.5-3 <sup>b</sup>	<i>i.v.</i> , B: 336-491 <sup>b</sup> <i>i.v.</i> , I: 38 <sup>b</sup> <i>i.m.</i> : 91 <sup>b</sup>	85±4	3.6±1.0 ↑ renal dis.	0.14±0.03 ←→ renal dis.	Cl=0.23Clcr±0.14 ↓ renal dis.	67±11	1-2g every 12 h <i>i.v.</i> o <i>i.m.</i>
Cefotaxime	–	<i>i.m.</i> : 0.5 <sup>d</sup>	<i>i.v.</i> : ~150 <sup>d</sup> <i>i.m.</i> : 20.5 <sup>d</sup>	36±3 ←→ cirrhosis <sup>e</sup>	1.1±0.3 ↑ renal dis., cirrhosis. <sup>e</sup> ←→ obesity	0.23±0.06 ←→ renal dis., obesity ↑ cirrhosis <sup>e</sup>	3.7±0.6 ↓ renal dis., cirrhosis <sup>e</sup> , women ←→obesity	55±10	1-2g every 8-12 h <i>i.v.</i> o <i>i.m.</i>
Ceftazidime	<i>i.m.</i> : 91	<i>i.m.</i> : 0.7±1.3 <sup>f</sup>	<i>i.v.</i> : 119-146 <sup>f</sup> <i>i.m.</i> : 29-39 <sup>f</sup>	21±6	1.6±0.1 ↑ renal dis.,prem., neon.,elderly ←→ cystic fib	0.23±0.02 ←→ renal dis., cystic fib ↑ elderly	Cl=1.05Clcr+0.12 ←→ cystic fib	84±4 ←→ cystic fib	2g every 8 h <i>i.v.</i> o <i>i.m.</i>

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Urinary clearance (%)	Dose
Ceftriaxone	—	<i>i.m.</i> : 2-2.4 <sup>g</sup>	<i>i.v.</i> : 168 <sup>g</sup> <i>i.m.</i> : 114 <sup>g</sup>	90-95 <sup>h</sup> ↓ cirrhosis, children neon.  ↔ elderly	7.3±1.6 <sup>h</sup> ↑ renal dis. <sup>i</sup> , bypass cardiopolm., elderly  ↔ cirrhosis	0.16±0.03 <sup>h</sup> ↑ bypass cardiopol m., neon, cirrhosis., cystic fib  ↔ renal dis., elderly	0.24±0.06 <sup>h</sup> ↓ renal dis., elderly <sup>l</sup> , neon. <sup>l</sup>  ↑ cirrhosis., cystic fib  ↔ bypass cardiopolm.	49±13 <sup>m</sup> ↑ neon., bamb.	1-2g/die OD <i>i.v.</i> o <i>i.m.</i>
Cefepime	—	—	65±7 <sup>n</sup>	16-19	2.1 (1.3-2.4) <sup>o</sup> ↑ renal dist <sup>p</sup>	0.26 (0.24-0.31) <sup>q</sup>	1.8 (1.7-2.5) <sup>o</sup> ↓ renal dis <sup>p</sup>	80	2g every 12 h <i>i.v.</i>

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** after a single dose 1g *i.v.* o *i.m.* healthy adults;  
**b:** Cmax mean values, from different studies, single dose 2g (*i.v.*), or mean Cmax and Tmax single dose 2 g *i.m.* healthy volunteers.  
**c:** active metabolite, desacetilcefotaxime, responds of around 16±4% of eliminated amount; T<sub>1/2</sub>=2,2±0,3 h after single dose *i.v.* 1 g;  
**d:** mean values Cmax after single dose *i.v.* (infusion time 25 min) 30 mg·kg<sup>-1</sup>, or single dose 1 g *i.m.* healthy adults.  
**e:** patients with liver cirrhosis or severe renal failure;  
**f:** mean values from studies on healthy volunteers: single dose 1g *i.v.* or *i.m.*  
**g:** mean values single dose 1g *i.v.* (infusion time 30 min) or *i.m.* bid at “steady-state” in adults;  
**h:** single dose;  
**i:** clearance can increase till 50 h in anephric patients with reduced non –renal clearance;  
**l:** reduced clearance of free drug;  
**m:** hepatic clearance;  
**n:** after single dose 1g *i.v.*;  
**o:** mean values Cl and T<sub>1/2</sub> from 16 studies (single dose);  
**p:** moderate-severe renal failure;  
**q:** mean values Vss from 6 studies (single dose).

TABLE 45 Main pharmacokinetics parameters of fluoroquinolones e suggested dosing. Reproduced from [287–289] with permission from author.

Antibiotic	Biodispos- ability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Ciprofloxain	60±12	0.6±0.2 <sup>a</sup>	os:2.5±1.1 <sup>a</sup> <i>i.v.</i> : 6.7 <sup>b</sup>	40	os: 3.3±0.4 <i>i.v.</i> : 4.2 <sup>b</sup> ↑ renal dis.  ←→ elderly	2,2±0.4 ↓ elderly  ←→ cystic fibr	7.6±0.8 ↓ renal dis., elderly  ↑ cystic fibr	50 ± 5	500-750mg every 12h os  400mg every 8-12h <i>i.v.</i>
Levofloxacin	99±10	1.6±0.8 <sup>c</sup>	os: 4.5±0.9 <sup>c</sup> <i>i.v.</i> :5.7±0.8 <sup>d</sup>	24-38	↓ cistic fibr os: 7±1 <sup>c</sup> <i>i.v.</i> : 6.7 ±0.7 <sup>d</sup> ↑ nefropat <sup>e</sup>	os :1.36±0.21 <sup>c</sup> <i>i.v.</i> :1.5±0.23 <sup>d</sup>	os:2.52 ±0.45 <sup>c</sup> <i>i.v.</i> :2.8±0.5 <sup>e</sup> ↓ renal dis. <sup>e</sup>	61-87	500mg every 12-24h os/ <i>i.v.</i> or 750 mg <i>i.v.</i> od 400mg/die os/ <i>i.v.</i>
Moxifloxacin	86±1	2.0 (0.5–6.0) <sup>f</sup>	2.5±1.3 <sup>f</sup>	39.4±2.4	15.4±1.2	2.05±1.15	2.27± 0.24	21.9 ±3.6	

↑: INCREASE;  
↓: REDUCTION;  
←→: NO CHANGE.

**a:** after oral dose 500 mg bid for 3 days or more in COPD patients;  
**b:** after *i.v.* dose 400 mg;  
**c:** after single oral dose 500 mg. No significant accumulation with OD dosing;  
**d:** after single *i.v.* dose 500 mg;  
**e:** reduced Cl/F, severe renal failure;  
**f:** after single oral dose 400 mg.

TABLE 46 Main pharmacokinetics parameters of macrolides and ketolides, and suggested dosing. Reproduced from [290–293] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Azithromycin	34±19 ↑ Food (capsul)	2–3 <sup>a</sup>	0.4 <sup>a</sup>	7–50 <sup>b</sup>	40 ↔ cirrhosis	31	9	12	500mg/die X 3 days os
Clarithromycin	↓ Food (suspension) 55±8 <sup>c</sup>	C: 2.8 <sup>d</sup> HC: 3 <sup>d</sup>	C: 2.4 <sup>d</sup> HC: 0.7 <sup>d</sup>	42–50	3.3±0.5 <sup>c</sup> ↑ elderly, renal dis., cirrhosis.	2.6±0.5 ↔ elderly ↑ cirrhosis	7.3±1.9 <sup>c</sup> ↓ elderly, renal dis. ↔ cirrhosis	36±7 <sup>c</sup> ↔ elderly	500mg every 12 h os ed <i>i.v.</i>
Erythromycin	35±25 <sup>e</sup> ↓ pregnancy <sup>f</sup>	B: 2.1–3.9 <sup>g</sup> S: 2–3 <sup>g</sup>	B: 0.9–3.5 <sup>g</sup> S: 0.5–1.4 <sup>g</sup>	84±3 <sup>g</sup> ↔ renal dis.	1.6±0.7 ↑ cirrhosis ↔ renal dis.	0.78±0.44 ↑ renal dis.	9.1±4.1 <sup>h</sup> ↔ renal dis.	12 ±7	500mg–1g every 6 h os
Telithromicin	57	1–2	1.8–2.27	60–70	9.81	–	2.98	13	800mg/die os

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** after single oral dose 250mg/die adult patients with infections;  
**b:** dose-dependent binding; binding 50% at 0,05 mg·l<sup>-1</sup> and 12% at 0,5mg·l<sup>-1</sup> ;  
**c:** after oral dose 250mg. At higher doses, saturation of metabolic clearance determines the increase of % of renal clearance and half-life, and the decrease of Cl;  
**d:** mean values for clarithromycina (C) and 14-OH-clarithromycin (HC), after oral dose 500mg bid in healthy adults;  
**e:** erythromycin base;  
**f:** reduction of concentrations due to decrease of biodisposability (or clearance increase);  
**g:** mean values range from studies with multiple doses 250mg of erythromycin base (B) o stearate-erythromycin (S);  
**h:** erythromycin is a substrate for CYP3A; N-demetilation. It is also carried by P-glicoprotein;  
**i:** single oral dose 800 mg.

TABLE 47 Main pharmacokinetics parameters of glycopeptides and suggested dosing. Reproduced from [294, 295] with permission from publisher.

Antibiotic	C <sub>max</sub> (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Vancomycin	18.5 (15–25) <sup>a</sup>	30±11 ←→ nefrop.	5.6±1.8 ↑ renal dis., elderly  ↓ obesity	0.39±0.06 ↓ obesity  ←→ renal dis., COPD.	Cl= 0.79Cl <sub>cr</sub> +0.22 ↓ renal dis., elderly, neonates  ←→ obesity, COPD	79±11	7.5–15mg·kg <sup>-1</sup> every 6–12h <i>i.v.</i> or continuous infusion
Teicoplanin	43.2 <sup>b</sup> 12.3 <sup>c</sup>	>90	155–168 <sup>d</sup> 182 <sup>e</sup> ↑ renal dis.	0.8–1.6 <sup>f</sup>	↑ burns 10–13 <sup>g</sup> 8–12 (Cl renale) ↓ renal dis.  ↑bacterial endocarditis	9	6mg·kg <sup>-1</sup> every 12h X 3 times and then every 24h <i>i.v.</i> or <i>i.m.</i>  12mg·kg <sup>-1</sup> every 12h X3 times and then every 24h <i>i.v.</i> or <i>i.m.</i> in patients with <i>S.aureus</i> endocarditis, septic arthritis or burns

↑: INCREASE;  
↓: REDUCTION;  
←→: NO CHANGE.

**a:** after single dose 1g *i.v.* (infusion time 1h) bid, or 7,5mg·kg<sup>-1</sup> *i.v.* (infusion time 1h) qid, adult patients with staphylococcus and streptococcus infections. Levels of 37–152 mg·l<sup>-1</sup> are associated to ototoxicity;  
**b:** 6mg·kg<sup>-1</sup> *i.v.*, single dose, after 0.5 h;  
**c:** 6mg·kg<sup>-1</sup> *i.m.*, single dose, after 4 h;  
**d:** *i.v.*;  
**e:** *i.m.*;  
**f:** 6–15 mg·kg<sup>-1</sup> *i.v.*, single dose;  
**g:** 3–30 mg·kg<sup>-1</sup>, *i.v.*, single dose.

TABLE 48. Main pharmacokinetics parameters of aminoglycosides and suggested dosing. Reproduced from [296–298] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> ·kg)	Renal clearance (%)	Dose
Amikacin	–	–	26±4 <sup>a</sup>	4±8 <sup>b</sup>	2.3±0.4 ↑ renal dis. ↔ obesity ↓ burns, cystic fibr, children	0.27±0.06 ↔ elderly, children, cystic fib ↓ obesity ↑ neonates	1.3±0.6 Cl=0.6Cl <sub>cr</sub> + 0.14 ↓ obesity ↑ cystic fib	98	15mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD
Gentamicin	<i>i.m.</i> : ~100	<i>i.v.</i> : 1 <sup>c</sup> <i>i.m.</i> : 0.3–0.75 <sup>c</sup>	<i>i.v.</i> : 4.9± 0.5 <sup>c</sup> <i>i.m.</i> : 5.0 ±0.4 <sup>c</sup>	<10	2–3 <sup>d</sup>	0.31±0.10 ↔ renal dis., elderly, cystic fib, children ↓ obesity ↑ neonates	Cl= 0.82Cl <sub>cr</sub> +0.11 ↓ obesity	>90	5mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD
Tobramicin	inhalation: 9±8	<i>i.m.</i> : 0.3–0.75 <sup>c</sup>	<i>i.v.</i> : 4.6±0.5 <sup>c</sup> <i>i.m.</i> : 5.2±0.6 <sup>c</sup>	<10	2.2±0.1 <sup>e</sup> ↑ renal dis., neonates, prem. ↔ obesity, cystic fib ↓ burns	0.33±0.04 <sup>f</sup> ↓ obesity ↔ renal dis., burns, elderly ↑ cystic fib, neonates	Cl= 0.98Cl <sub>cr</sub> ±32% <sup>g</sup> ↓ obesity ↑ cystic fib	90	5mg·kg <sup>-1</sup> ·die <sup>-1</sup> <i>i.m./i.v.</i> OD

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** after single dose (infusion time 1 h 6.3±1.4 mg·kg<sup>-1</sup>), tid at “steady-state” in patient with normal renal function;  
**b:** at a serum concentration of 15 mg·l<sup>-1</sup>;  
**c:** after *i.v.* dose 100 mg (infusion time 1h ) or 100 mg *i.m.*, healthy adults;  
**d:** gentamicin has a long T<sub>1/2</sub> (53±25 h) that justifies a prolonged renal excretion;  
**e:** tobramicin has a long T<sub>1/2</sub> (146±75 h), it reflects a slow release from tissues and justifies a prolonged renal excretion;  
**f:** central compartment volume;  
**g:** Cl<sub>cr</sub> ml·min<sup>-1</sup>·kg.

TABLE 49 Main pharmacokinetics parameters of tetracyclines and suggested dosing. Reproduced from [299, 300] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Doxycyclin	93	os: 1–2 <sup>a</sup>	<i>i.v.</i> : 2.8 os: 1.7–2	88±5 ↓ renal dis. (71±3)	16±6 ←→ renal dis., elderly, Hyperlipoprot.	0.75±0.32 ↓ elderly, Hyperlipoprot.	0.53±0.18 ↓ elderly, Hyperlipoprot.	41±19	200mg·die <sup>-1</sup> os o <i>i.v.</i>
Minocyclin	95–100	os: 2–4 <sup>b</sup>	<i>i.v.</i> : 3.5 <sup>b</sup> os: 2.3–3.5 <sup>b</sup>	76	16±2 ←→ cirrosi, Hyperlipoprot., renal dis. <sup>c</sup>	1.3±0.2 ↓Hyperlipoprot.	1.0±0.3 ↓ Hyperlipoprot.	11±2	100mg every 12h os
Tetracyclin	77	os: 4	<i>i.v.</i> : 16.4±1.2 <sup>d</sup> os: 2.3±0.2 <sup>d</sup>	65±3	10.6±1.5	1.5±0.1	1.67±0.24	58±8	250–500mg every 6h os  0.5–1g every 12h <i>i.v.</i>

↑: INCREASE;  
↓: REDUCTION;  
←→: NO CHANGE.

**a:** after single oral dose 100mg;  
**b:** mean values after single dose *i.v.* (infusion time 1 h) 200mg or 100mg bid at “steady-state”;  
**c:** increase of T<sub>1/2</sub> in patients with reduced clearance. With a Cl of 18–45ml·min<sup>-1</sup> no accumulation has been recorded after multiple doses, in healthy subjects;  
**d:** after single dose *i.v.* 10 mg·kg<sup>-1</sup> or oral 250 mg (empty stomach with water).

TABLE 50 Main pharmacokinetics parameters of other antibiotics and suggested dosing. Reproduced from [301–308] with permission from publisher.

Antibiotic	Biodisposability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Clindamycin	~87 <sup>a</sup> topica: 2	–	<i>i.v.</i> : 17.2±3.5 <sup>b</sup> os: 2.5 <sup>c</sup>	93.6±0.2	2.9±0.7 ↑ prem. ↔ children, renal dis., pregnancy	1.1±0.3 <sup>d</sup> ↔ renal dis., children	4.7±1.3 ↔ children	13	600–900mg every 8 h os, <i>i.v.</i> o <i>i.m.</i>
Linezolid	100	1.3 <sup>e</sup> 1.0 <sup>f</sup> 0.5 <sup>g,h</sup>	12.7 <sup>e</sup> 21.2 <sup>f</sup> 12.9 <sup>g</sup> 15.1 <sup>h</sup> ↑ donne	31	5.5 <sup>e</sup> 4.5 <sup>g</sup> ↑ liver dis. ↓ children	40–50	100–200 ↓ liver dis. ↑ hemodial., children	30	600mg every 12 h os o <i>i.v.</i>
<sup>i</sup> Metronidazol	99±8 <sup>l</sup> ↔ pat.cronic.	os: 2.8 <sup>m</sup> VA: 11±2 <sup>m</sup>	<i>i.v.</i> : 27(11–41) <sup>m</sup> os: 19.8 <sup>m</sup> VA: 1.9±0.2 <sup>m</sup>	11±3	8.5±2.9 ↑ neonates, cirr. ↔ nefrop., pregnancy, Chron., children	0.74±0.10 ↔ nefrop., cirr., malattia Chron	1.3±0.3 ↓ cirr., neon. ↔ nefrop., pregnancy, Chronn., elderly	10±2	7.4 mg·kg <sup>-1</sup> (~500 mg) every 6 h <i>i.v.</i>  500mg every 6 h os
Rifampin	– <sup>o</sup>	1–3 <sup>p</sup>	6.5±3.5 <sup>p</sup>	60–90	3.5±0.8 <sup>q</sup> ↑ hepatitis, cirr. renal dis. <sup>r</sup> ↔ children, elderly	0.97±0.36 ↑ neonates ↔ elderly	3.5±1.6 <sup>q</sup> ↑ neonates ↔ elderly <sup>r</sup> ↓ renal dis.	7±3 ↑ neonate s	450–600mg every 12 h os (10 mg·Kg <sup>-1</sup> )
Quinupristin	–	–	2.3±0.5 <sup>s</sup>	23–32	0.97±0.20	0.79±0.40	17.2±3.43 ↓ liver dis. <sup>u</sup> , renal dis. <sup>t</sup>	15.1	7.5mg·kg <sup>-1</sup> every 8 h <i>i.v.</i>

Antibiotic	Biodispos- ability (%)	Tmax (h)	Cmax (mg·l <sup>-1</sup> )	Protein binding (%)	T <sub>1/2</sub> (h)	Vd (l·kg <sup>-1</sup> )	Clearance (ml·min <sup>-1</sup> · kg)	Renal clearance (%)	Dose
Dalfopristin	–	–	6.4±2.7 <sup>s</sup>	50–56	0.52±0.21	0.43±0.29	19.8±10.7 ↓ liver dis. <sup>u</sup> , renal dis. <sup>t</sup>	18.7	

↑: INCREASE;  
↓: REDUCTION;  
↔: NO CHANGE.

**a:** clindamicin cloridrate per os;  
**b:** single dose *i.v.* (infusion time 30 min) 1200mg clindamicin phosphate (prodrug), bid at steady-state in healthy adults male;  
**c:** after single oral dose 150mg clindamicin hydrochlorite in adults;  
**d:** V<sub>area</sub>;  
**e:** single oral dose 600mg;  
**f:** 600mg every 12 h oral;  
**g:** dose singola di 600mg, *i.v.*  
**h:** 600mg every 12 h *i.v.*  
**i:** active metabolite with renal accumulation;  
**l:** bioavailability range 67–82% rectal use;  
**m:** after 500mg *i.v.* (infusion 20 min) t.i.d or oral dose 500 mg t.i.d;  
**n:** active metabolite;  
**o:** insufficient data;  
**p:** after 600mg od for 15–18 days in TB patients;  
**q:** T<sub>1/2</sub> longer at high doses;  
**r:** not observed at 300mg;  
**s:** single dose 10mg·kg<sup>-1</sup> *i.v.* (1 h infusion);  
**t:** severe renal complication;  
**u:** mild-moderate liver complications.

TABLE 51 Pharmacodynamics and pharmacokinetics of chemotherapeutic antimicrobials: evidence table

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
AMBROSE [259]	To determine relationship between fluoroquinolone exposure and clinical and microbiological efficacy.	CCS	3a+
CRAIG [260]	To study post-antibiotic effect in animal infection models	NON-SYSTEMATIC	6a–
CRAIG [261]	To study cephalosporin pharmacodynamics in animal infection models	NON-SYSTEMATIC	6a–
CRAIG [262]	To describe pharmacodynamic activity of antimicrobials	NON-SYSTEMATIC	6a–
GOTFRIED [263]	To compare lining fluid, and alveolar macrophage concentrations of levofloxacin and ciprofloxacin	RCT	2a+
NIGHTINGALE [309]	To describe the effect of the area under the plasma concentration-time curve relative to the minimum inhibitory concentration on bacteria	NON-SYSTEMATIC	6a–
SCHENTAG [310]	To describe what have we learned from pharmacokinetic and pharmacodynamic theories	NON-SYSTEMATIC	6a–
MOORE [311]	To study the importance of the ratio of peak concentration to minimal inhibitory concentration in aminoglycoside therapy	CCS	3a+
HYATT [312]	To describe determinants of outcome in antimicrobial therapy	NON-SYSTEMATIC	6a–
MACGOWAN [313]	To review the pharmacodynamic properties of penicillins, cephalosporins, carbapenems, quinolones, glycopeptides and aminoglycosides	NON-SYSTEMATIC	6a–
WILDFEUER [270]	To document the concentrations of ampicillin and sulbactam in serum and in various compartments of the respiratory tract	CCS	3a–

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
OLSEN [314]	To describe the intrapulmonary pharmacokinetics of oral azithromycin	CCS	3a-
MAZZEI [315]	To document the concentrations of cefaclor in suction blister fluid (SBF) and alveolar epithelial lining fluid (ELF).	CCS	3a-
BENONI [316]	To document the pharmacokinetics of ceftriaxone in pleural fluid	CCS	3a-
DECRE [317]	To review the pharmacokinetics of fluoroquinolones	NON SYSTEMATIC	6a-
PATEL [318]	To study the bronchopulmonary and plasma pharmacokinetics of clarithromycin and azithromycin	CCS	3a+
CONTE [319]	To study the intrapulmonary pharmacokinetics of clarithromycin and erythromycin	CCS	3a+
BENONI [320]	To study the pharmacokinetics of Imipenem	CCS	3a-
LEE [321]	To evaluate the pulmonary tissue distribution of levofloxacin,	CCS	3a-
CONTE [322]	To determine the steady-state intrapulmonary concentrations and pharmacokinetic parameters of orally administered linezolid	CCS	3a-
BERGOGNE-BEREZIN [323]	To evaluate the ability of meropenem to reach the bronchial lumen.		3a-
SIMON [324]	To construct a population pharmacokinetic model for moxifloxacin disposition in plasma and bronchial secretions in patients with severe bronchopneumonia who were mechanically ventilated.	CCS	3a-

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
TOMASELLI [325]	to measure piperacillin and tazobactam penetration into the extracellular space fluid of pneumonic human lung	CCS	3a-
MULLER-SERIEYS [326]	To study the penetration of telithromycin into bronchopulmonary tissues	CCS	3a-
MAZZEI [327]	To study the pharmacokinetics of tobramycin, including the penetration into suction blister fluid.	CCS	3a-
CRUCIANI [328]	To study Vancomycin penetration into lung tissue	CCS	3a-
SUM [271]	To study serum kinetics and urinary excretion of lenampicillin, bacampicillin and amoxicillin.	RCT	2a+
FERSLEW [272]	To study the pharmacokinetics and urinary excretion of clavulanic acid	CCS	3a-
PETITPRETZ [273]	To compare a pharmacokinetically enhanced formulation of oral amoxicillin-clavulanate to amoxicillin-clavulanate 1000/125 , in community-acquired pneumonia	RCT	2a+
MOLINARO [274]	To study the bioavailability of two different oral formulations of amoxicillin	RCT	2a-
NATHWANI [275]	Systematic review of penicillin pharmacology	MA	1a+
SIGNS [276]	To study the pharmacokinetics of imipenem	CCS	3a-
DRUSANO [277]	To produce a review of the pharmacokinetics of meropenem	NON SYSTEMATIC	6a-
SATTERWHITE [278]	To study the pharmacokinetics and bioavailability of cefaclor advanced formulation	CCS	3a-
DONN [279]	To determine the bioequivalence of two cefuroxime axetil formulations.	RCT	2a+

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
KEES [280]	To compare the relative bioavailability of three formulations of cefixime	CCS	3b–
BORIN [281]	To compare the bioavailability of cefpodoxime proxetil tablets relative to an oral solution of cefpodoxime proxetil	RCT	2b–
LIN [282]	To comparative the bioavailability of ceftibuten, in capsule and suspension dosage forms.	CCS	3b–
ZIMMERMAN [283]	To study the pharmacokinetic parameters of Cefotetan	CCS	3a–
BORNER [284]	To study the pharmacokinetics of ceftriaxone after subcutaneous and intravenous administration	CCS	3a–
DELSIGNORE [285]	To determine the disposition and bioavailability of ceftriaxone	CCS	3a–
BARBHAIYA [286]	To study the steady state pharmacokinetics, absolute bioavailability, and dose proportionality of cefepime	CCS	3a–
BEGG [287]	To study the pharmacokinetics of ciprofloxacin and fleroxacin in plasma and sputum of patients with an acute exacerbation of chronic bronchitis or bronchiectasis	RCT	2b–
CHIEN [288]	To compare the pharmacokinetics of once-daily oral levofloxacin or intravenous levofloxacin	RCT	2a+
STASS [289]	To study the pharmacokinetics of moxifloxacin and its metabolites M1 (sulpho-compound) and M2 (acyl-glucuronide)	RCT	2b–
FOULDS [290]	To study the effect of food on bioavailabilities of three new formulations of azithromycin	CCS	3a–
CHU [291]	To determine the absolute bioavailability of clarithromycin	RCT	2b–

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
RUTLAND [292]	To study the effect of food on the bioavailability of two formulations of erythromycin.	RCT	2b–
PERRET [293]	To determine the pharmacokinetics and absolute oral bioavailability of telithromycin in young and elderly healthy subjects.	RCT	2b–
VERBIST [294]	To determine the <i>in vitro</i> activity of teicoplanin, against 456 gram-positive cocci.	CCS	3b–
LEADER [295]	To perform a review of pharmacokinetics of vancomycin	NON-SYSTEMATIC	6a–
BAUER [296]	To determine aminoglycoside pharmacokinetics in normal weight and morbidly obese patients	CCS	3a+
REGAMEY [297]	To compare pharmacokinetics of tobramycin and gentamicin	CCS	3a–
AARONS [298]	To determine population pharmacokinetic parameters of tobramycin	PCS	3a+
SAIVIN [299]	To provide a review of clinical pharmacokinetics of doxycycline and minocycline	REVIEW (NON SYSTEMATIC)	6a–
GARTY [300]	To study the effect of cimetidine and antacids on gastrointestinal absorption of tetracycline	RCT	2b–
MAZUR [301]	To investigate the pharmacokinetics and relative bioavailability of clindamycin	CCS	3b–
GATTI [302]	To study the absolute oral bioavailability and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS	CCS	3b–
MEAGHER [303]	to develop a population model of the pharmacokinetics of intravenous and oral linezolid.	PCS	3b+
PATON [304]	To compare bioavailability of two tablet preparations of metronidazole	RCT	2b+

1 <sup>st</sup> author/study group [ref.]	Objective	Design	Evidence level
LAU [305]	To evaluate the pharmacokinetics of metronidazole at different dosage levels in normal subjects.	CCS	3b+
PANCHAGNULA [306]	To study the bioequivalence of the antituberculous drug rifampicin in a four-drug combination (rifampicin, isoniazid, pyrazinamide and ethambutol) and separate formulations of the drugs at the same dose levels	CCS	3b+
LOOS [307]	To study the pharmacokinetics of rifampicin and its major metabolites, 25-desacetyl rifampicin and 3-formylrifampicin,	CCS	3b+
CHEVALIER [308]	To study the pharmacokinetics and safety of two regimens of quinupristin/dalfopristin	CCS	3b-

**MA:** meta-analysis (or systematic review);

**RCT:** randomised controlled trial;

**PCS:** prospective cohort study;

**RCS:** retrospective cohort study;

**CCS:** case control study.