Antibioterapia: difusión en tejido respiratorio

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Pues sí, alguien ya lo ha estudiado…. Década de los ‘70 →2011

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Farmacocinética y farmacodinamia

La optimización del tratamiento antibiótico pasa a través integración de los datos farmacocinéticos y farmacodinámicos en la prescripción.

Farmacodinamia:

- Actividad antimicrobiana intrínseca del fármaco contra el patógeno respiratorio.
- La actividad bactericida.
- Estabilidad de la actividad del fármaco en la presencia de mecanismos comunes de resistencia bacteriana.
- Ausencia de toxicidad importante órgano.

Farmacocinética:

- Propiedades de absorción, distribución, metabolismo y excreción.
- Dosis, frecuencia de dosificación y concentración del antibiótico en el sitio de la infección.

El objetivo de una terapia antimicrobiana eficaz es producir, en el sitio de la infección, un perfil de concentración-tiempo de tal manera que las concentraciones de fármaco libre igualan o exceden las concentraciones mínimas inhibitorias (CMI) para el patógeno infeccioso, tal como se determina in vitro: **OPTIMIZAR EFICACIA Y REDUCIR APARICIÓN RESISTENCIA**

Un poquito de farmacocinética básica…

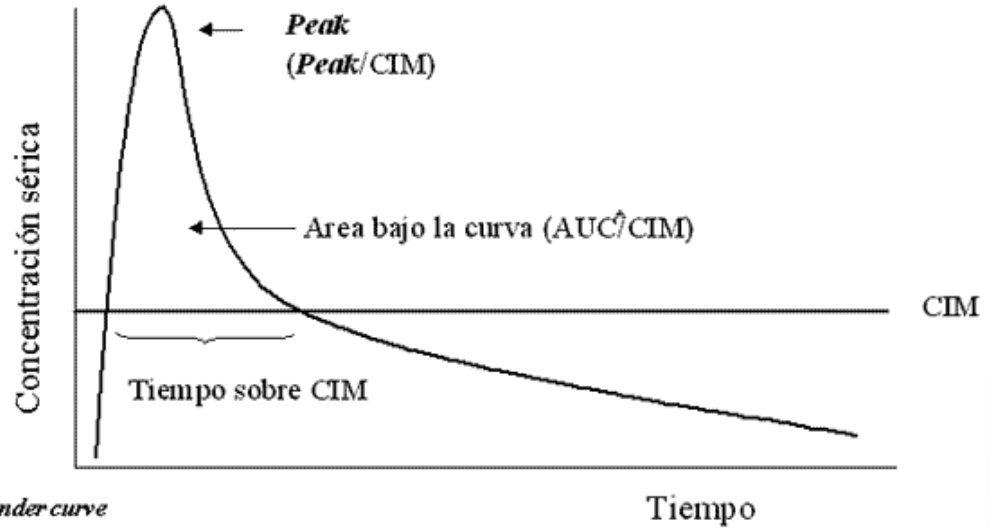
C_{max}/MIC	Time above MIC	AUC_{24}/MIC
Aminoglycosides	All β-lactams	All macrolides
Fluoroquinolones	Vancomycin	Fluoroquinolones
Streptogramins	Linezolid	β-lactams
	Clindamycin	Aminoglycosides
	Erythromycin	Vancomycin
	Clarithromycin	Clindamycin
		Doxycycline
		Streptogramins
		All antibiotics

C_{max}: peak serum or plasma concentration; MIC: minimum inhibitory concentration; AUC_{24}: area under the curve in 24 h; *: drugs or classes that have conflicting data, demonstrating that more than one concept is relevant, have been listed in each of the relevant columns.

Concentración dependientes

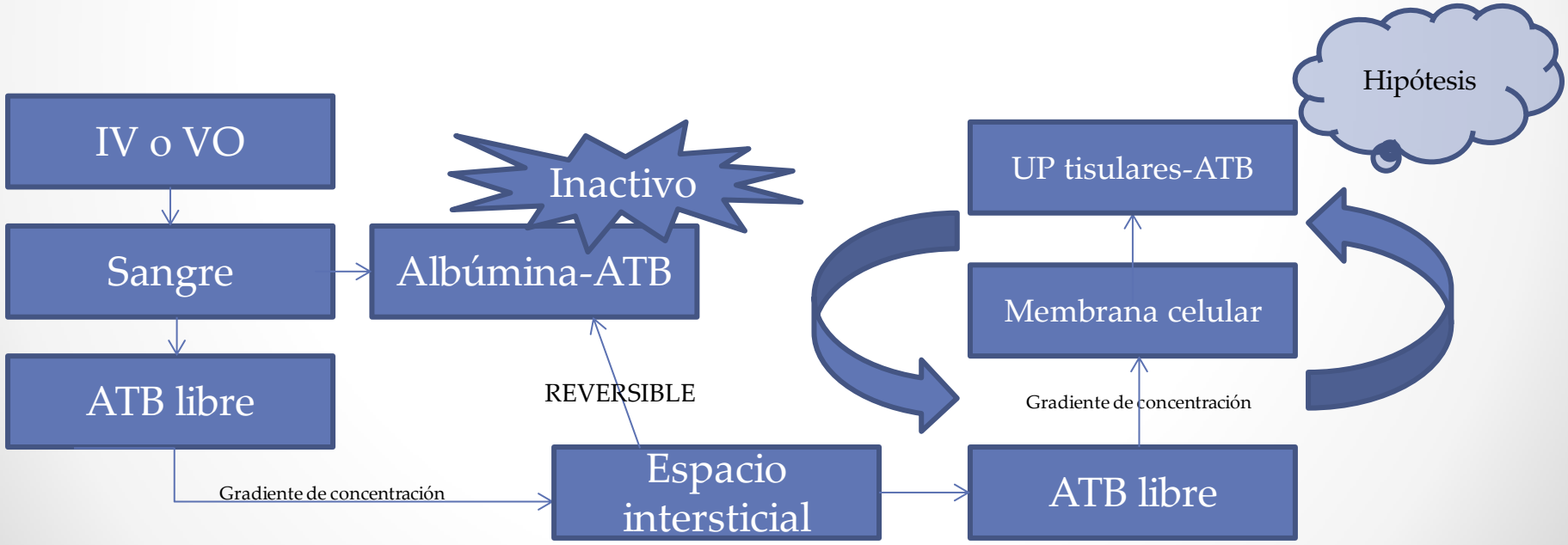
Tiempo dependientes

Modelo mixto, casos PK/PD



Factores que afectan a la concentración en tejido:

- Gradiente de concentración
- Unión a proteínas plasmáticas (UPP) y tisulares (ATB unido a albúmina→ inactivo)
- Sistemas de transporte activo
- Permeabilidad de membrana
- Vascularidad tisular
- Solubilidad lipídica del ATB
- pKa (cte absorción) a pH tisular
- Grado inflamación lugar de infección: mayor inflamación=mayor permeabilidad y mayor penetración ATB



Factores que afectan a la penetración del ATB:

- Tejido: porosidad capilares
- Penetración tisular fácil: músculo, liq intersticial, liq sinovial, pulmón, pericardio
- Penetración tisular problemática: LCR, secreciones respiratorias, renal, próstata, hueso y tejido cardíaco
- Determinantes:
  - Liposolubilidad (SNC, secreciones respiratorias, riñón y próstata): propiedad que facilita el cruce de membranas celulares.
  - UPP (liq sinovial, fluido pericárdico, liq intersticial): Fuerte unión a proteínas plasmáticas reduce el paso de moléculas desde la sangre a los tejidos.

Liposolubles: macrólidos, algunas fluoroquinolonas → penetración intracelular
AMG: entrada lenta por endocitosis

Hidrosolubles: penicilinas, cefalosporinas → medio extracelular

Factores del paciente que afectan a la penetración del ATB:

Table 1. – Host-related factors influencing the transport of antimicrobials into respiratory tissues and fluids

Pharmacokinetic parameters
- Alteration in:
  - *Hepatic/renal insufficiency*
  - *Elderly*
  - *Underlying disease*
  - *Intensive care hospitalization*
  - *Cardiovascular disease*
  - *Severe respiratory disease*

Site of infection
- Intramacrophagic pathogens (atypical pneumonia)
- Parenchymal consolidation
- Endobronchial infections
- Degree of inflammation: acute inflammation, increased vascularisation and antibiotic leakage
- Mechanical injury, bleeding, fibrosis
- Role of respiratory secretions, variable in volume and composition, antibiotic clearance
- Binding and/or inactivation of antibiotics in variable degrees depending on amounts of:
  - *Proteins*
  - *Nucleic acids*
  - *Cellular membranes*
  - *Mucopolysaccharides of mucus*
- Endotracheal pH: acidic environment, intramacrophagic trapping of antibiotics, sequestrations
- Subcellular structures (leukocytic chromatin)

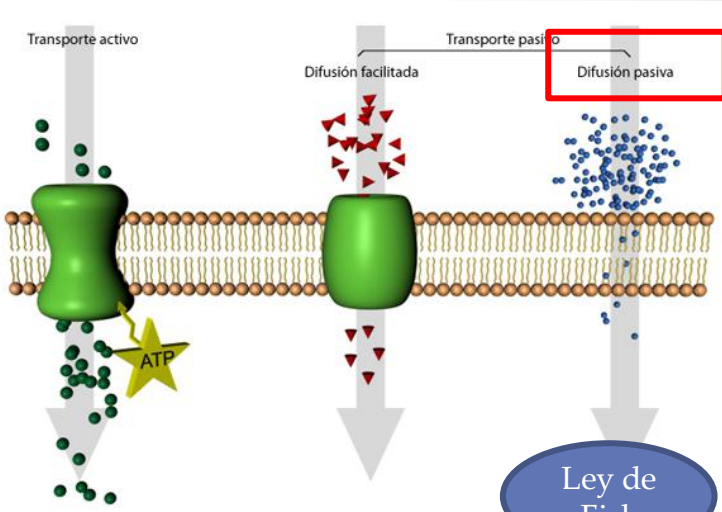
Accumulation and elimination of antibiotics
- Accumulation in cells, in mucus
- Reabsorption across blood-bronchus barrier
- Mechanical excretion (cough, mucociliary movement)
- Inactivation (local β-lactamase production, leukocytic enzymes)

Table adapted from BERGOGNE-BÉRÉZIN [8].

Tipos de transporte ATB:

Table 1 Possible mechanisms of antibiotic penetration into the lung

Method	*Examples*	*Comments*
Passive diffusion	Beta-lactams	Low molecular weight molecules, cannot be saturated hence close serum:tissue relation. Helped by large surface area in pulmonary bed. Impaired if high protein binding in blood
Permeation	Chloramphenicol, macrolides, rifampicin	Rate limited by the degree of liposolubility
Active transport	Quinolones, clindamycin	Energy dependent and hence can be saturated leading to discrepancy between serum and tissue levels
Bulk flow	Unknown	Ultrafiltration of drug through capillary pores across a pressure gradient



Ley de Fick

Existe evidencia sobre el tema??

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- **Rodvold KA, Jomy M. George, Liz Yoo. Penetration of Anti-Infective Agents into Pulmonary Epithelial Lining Fluid, Focus on Antibacterial Agents. Clin Pharmacokinet 2011; 50 (10): 637-664**
- Theuretzbacher U. Tissue penetration of antibacterial agents: how should this be incorporated into pharmacodynamic analyses? Current Opinion in Pharmacology 2007, 7:498–504
- **Valcke Y, R. Pauwels, M. Van Der Straeten. Pharmacokinetics of antibiotics in the lungs. Eur Respir J 1990, 3, 715-722**

La penetración de un ATB se expresa como la relación porcentual entre la concentración en la muestra investigada y la concentración en una muestra de suero obtenida de forma simultánea.

Table 1. — Concentration of antimicrobial drugs in respiratory fluids and tissues

	Ratio sputum/serum %	Ref.
Amikacin	24	[49, 57]
Amoxycillin	3–6	[9, 11, 20, 26, 27]
Ampicillin	3–10	[16, 20–22, 24]
Bacampicillin	13–20	[12, 20, 27]
Carbenicillin	11–20	[47, 60]
Cefaclor	8–10	[39, 59]
Cefotaxime	25	[58]
Cefoxitin	20–25	[20, 23]
Cefuroxime	18	[20, 57]
Doxycycline	20–35	[29, 51]
Enoxacin	100	[54–56]
Erythromycin	5	[30]
Gentamicin	27–40	[15, 31, 47, 48, 60, 63]
Minocycline	28–60	[28, 50, 57]
Netilmicin	14–20	[33]
Ofloxacin	78–103	[62]
Piperacillin	4–15	[22, 40]
Sulphamethoxazole	13–18	[57, 61]
Tobramycin	65–67	[34, 41, 43]
Tricarcillin	2	[22]
Trimethoprim	>100	[38, 53, 57, 61]

Valcke Y, R. Pauwels, M. Van Der Straeten. Pharmacokinetics of antibiotics in the lungs. Eur Respir J 1990, 3, 715-722

Penetración ATB en la mucosa bronquial ➡ indicador intrapulmonar vs esputo

- Poca evidencia
- Muestras (biopsias) durante broncoscopia o BAL

No se diferencia entre acumulación intra o extracelular → ATB de acumulación intracelular presentan mayores concentraciones a nivel de mucosa bronquial

Table 4. – Antibiotic intracellular penetration, accumulation and release

Antibiotic	Penetration	Accumulus	Localisation	Release
Aminoglycosides	Very slow (days)	Very slow	Lysosomes	Very slow (weeks)
β-lactams	Very limited	Absent	Cytosol	Rapid
Fluoroquinolones	Rapid, similar for all compounds	4–8 fold	Phagosomes, Lysosomes	Rapid (min)
Macrolides	Slow (1–2 h) drug dependant	May reach >100 fold drug dependent	Lysosomes >90%	Slow (days)

Hidrofílicos (b-lactámicos, AMG)→ extracelular
Lipofílicos (FQ, macrólidos)→ intracelular

1. ATB en esputo y secreciones bronquiales

Antibiotic	Dose	Route	Serum mL·L^{-1}	Bronchial secretions mL·L^{-1}
Amoxicillin g	1	IV	6.9	0.52
Carbenicillin g	20	IV MD	130	15–49
Mezlocillin g	5	IV	140	10.0
Piperacillin g	4	IV MD	196.3	12.2±8.5
Cefaclor AF mg	750	PO MD	8.6	1.5
Cefuroxime mg	0.75	IM	10.6	1.95
Cefuroxime axetil mg	500	PO	3.4±2.4	1.0-3.5
Ceftibuten mg	400	PO	18.12±2.13	8.19±3.1
Cefotaxime g	2	IV	40	1.45
Ceftazidime g	1	IM	39.89	6.87
Imipenem g	1	IV	69	0.94
Gentamicin mg·kg^{-1}	5	MD	5.0–6.0	1.83
Amikacin mg	500	IV	11–20	6.7
Tobramycin mg·kg^{-1}	1.7		6.0–8.0	2.68
Erythromycin g	1	PO MD	1.37±0.89	0.59
Roxithromycin mg	150	PO MD	6.26±0.7	3.1±0.77
Clarithromycin mg	500	PO MD	3.96	±1.02
Azithromycin mg	500	PO	0.2–04	0.23–9.5
Dirithromycin mg	500	PO MD	0.44	2.67
Spiramycin g	2–3	PO MD	2.4	7.3
Ciprofloxacin mg	500	PO	1.64±0.42	1.3±2.33
Ofloxacin mg	200	PO MD	1.90–5.18	1.51±0.7
Lomefloxacin mg	400	PO MD	2.8±1.0	2.78±3.64
Sparfloxacin mg	400	PO	1.2	1.80±1.03
Trovafloxacin mg	200	PO MD	3.4	3.2
Doxycycline mg	100	PO	2.74	1.05
Minocycline mg	200	PO	4.6	1.7
Thiamphenicol mg	750	PO	5.8	3.4
Clindamycin mg	300	PO	2.6	1.6

IV: intravenous; MD: multiple doses; PO: *per os*; IM: intramuscular; AF: advanced formulation.

Cazzola. European Respiratory Monograph 28: Antibiotics and the lung. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. 2004

2. ATB en mucosa bronquial

Table 3. – Antibiotic levels in serum and bronchial mucosa

Antibiotic	Dose	Route	Serum mg·L^{-1}	Bronchial mucosa mg·kg^{-1}	% penetration
Amoxicillin mg	500	PO MD	5.9	0.5	15
Amoxicillin g	1	IV	8.4	20.8	248
Clavulanic acid mg	200	IV	2.7	306	133
Piperacillin g	4	IV MD	196.3	55.2	28
Cefuroxime axetil mg	500	PO	3.4±2.4	3.8±1.6	44–85
Cefdinir mg	600	PO	4.20	1.14	27
Ceftibuten mg	200	PO	8.77	2.25	39
Cefixime mg	400	PO	6.6	2.4	36
Ceftriaxone g	1	IV	70.9	18.1	25
Ceftazidime g	1	IV	36.04±9.21	8.14±2.23	23
Cefepime g	2	IV	40.4±28.1	24.1±17.8	59
Cefpirome g	1	IV	55.6	33.0	62
Erythromycin mg	500	PO MD	4.3	7.2	160
Roxitromycin mg	150	PO MD	6.3	5.6	90
Clarithromycin mg	500	PO MD	3.96	16.76	430
Azithromycin mg	500	PO	0.2–0.4	3.89±1.2	972–1945
Dirithromycin g	500	MD	0.61	2.71	444
Spiramycin g	2–3	PO	2.4	13-36	30-50
Telithromycin mg	800	PO MD	1.86	3.88	210
Ciprofloxacin mg	500	PO	1.64	4.4	260
Clinafloxacin mg	200	PO	1.54	2.65	172
Lomefloxacin mg	400	PO MD	2.8	6.2	221
Ofloxacin mg	200	×2 PO	1.0–5.2	10–13	250–921
Sparfloxacin mg	400	PO	1.2	2.6	217
Trovafloxacin mg	200	PO MD	1.41	1.52	110
Levofloxacin mg	500	PO	6.6	10.8	164
Moxifloxacin mg	400	PO	3.2	5.4	169
Garenoxacin mg	600	PO	10.0	7.0	70

IV: intravenous; MD: multiple dose; PO: *per os*.

25-60%

Persistencia tras 72-96h en la mucosa bronquial

Cazzola. European Respiratory Monograph 28: Antibiotics and the lung. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. 2004

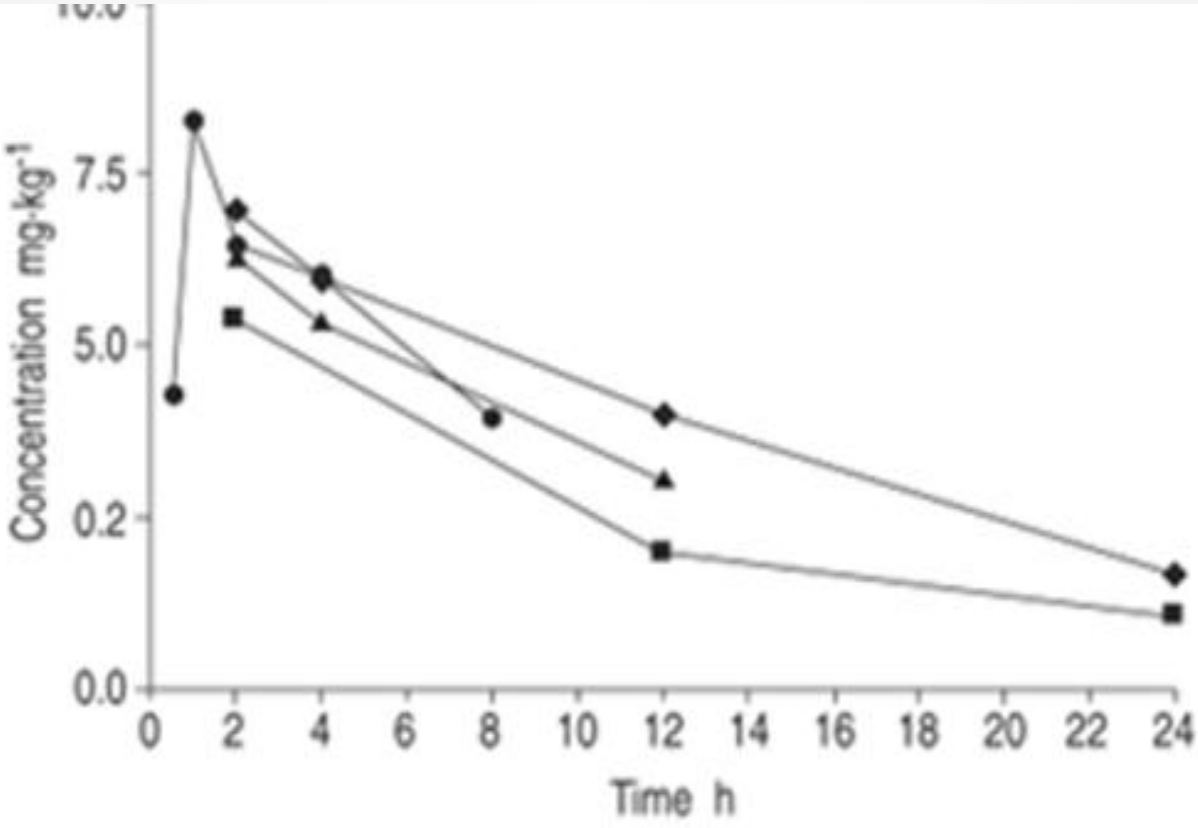


Fig. 2. – Mean concentrations in bronchial mucosa of levofloxacin (500 mg, ●), moxifloxacin (400 mg, ■), gatifloxacin (400 mg, ▲), and garenoxacin (600 mg, ◆) in patients undergoing fibre-optic bronchoscopy following a single oral dose. Adapted from ANDREWS *et al.* [76], SOMAN *et al.* [77], HONEYBOURNE *et al.* [79], and ANDREWS *et al.* [80].

Cazzola. European Respiratory Monograph 28: Antibiotics and the lung. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. 2004

3. ATB en fluido epitelial

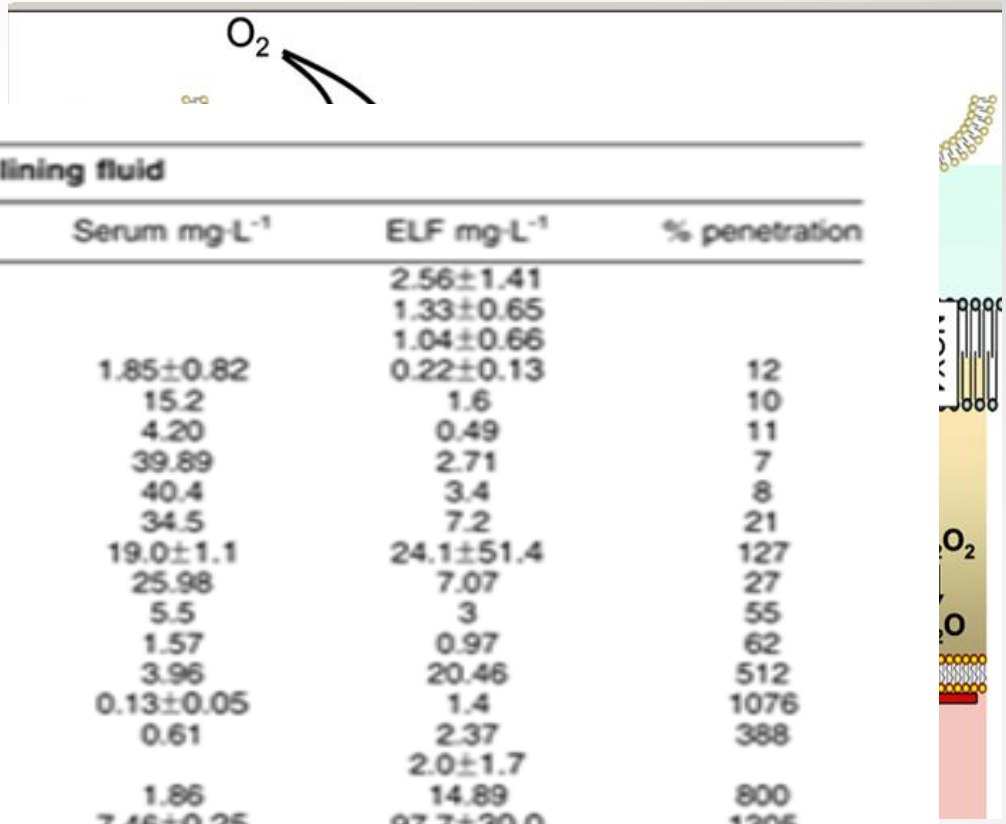


Table 5. – Antibiotic levels in serum and epithelium lining fluid

Antibiotic	Dose	Route	Serum mg·L^{-1}	ELF mg·L^{-1}	% penetration
Amoxicillin mg	500	PO MD		2.56±1.41	
Clavulanic acid mg	250	PO MD		1.33±0.65	
Cefuroxime axetil mg	613	PO MD		1.04±0.66	
Cefpodoxime proxetil mg	220	PO	1.85±0.82	0.22±0.13	12
Ceftibuten mg	400	PO	15.2	1.6	10
Cefdinir mg	600	PO	4.20	0.49	11
Ceftazidime g	1	IM	39.89	2.71	7
Cefepime g	1	IV	40.4	3.4	8
Cefpirome g	1	IV	34.5	7.2	21
Imipenem g	1	IV	19.0±1.1	24.1±51.4	127
Meropenem g	1	IV	25.98	7.07	27
Tobramycin mg	300	IM	5.5	3	55
Erythromycin mg	250	PO MD	1.57	0.97	62
Clarithromycin mg	500	PO MD	3.96	20.46	512
Azithromycin mg	500	PO MD	0.13±0.05	1.4	1076
Dirithromycin mg	500	PO MD	0.61	2.37	388
Roxithromycin mg	300	PO MD		2.0±1.7	
Telithromycin mg	800	PO MD	1.86	14.89	800
Pefloxacin mg	800	PO	7.46±0.25	97.7±30.0	1305
Clinafloxacin mg	200	PO	1.54	2.71	176
Lomefloxacin mg	400	PO MD	3.2	6.9	216
Trovafloxacin mg	200	PO MD	1.41	4.8	340
Temafloxacin mg	600	PO MD	9.6±1.22	6.5±3.6	276
Sparfloxacin mg	400	MD	1.2±0.4	115.0±8.3	1250
Levofloxacin mg	500	PO	6.6	10.9	165
Gatifloxacin mg	400	PO	3.96	6.16	155
Moxifloxacin mg	400	PO	3.2	20,7	647
Garenoxacin mg	600	PO	10.0	14.3	143
Vancomycin mg	15	IV MD	24	4.5	19
Linezolid mg	600	PO MD	7.3±4.9	64.3±33.1	881

PO: *per os*; MD: multiple doses; IV: intravenous; IM: intamuscular.

Cazzola. European Respiratory Monograph 28: Antibiotics and the lung. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. 2004

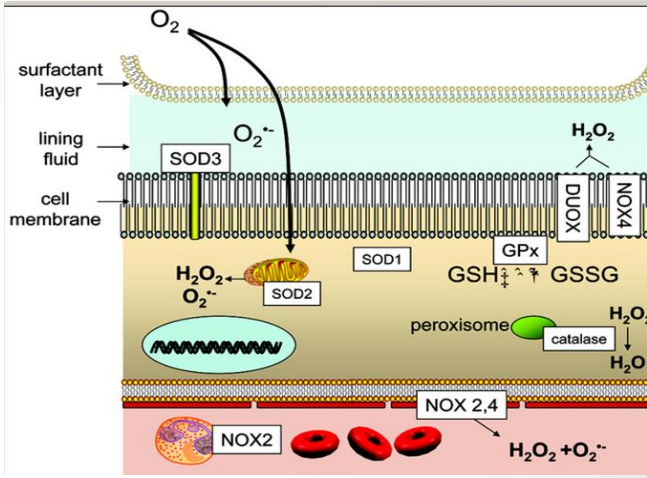
4. ATB en el parénquima pulmonar

Antibiotic	Dose	Route	Serum mg·L^{-1}	Pulmonary parenchyma mg·kg^{-1}	% penetration
Penicillin G mg	1–3	MU IV	25	25	10
Amoxicillin g	1	PO	5.6	2.4	43
Amoxicillin g	1	IV	6.9	4.4–5.6	60–80
Amoxicillin g	1	PO	9.9	1.3	13
Clavulanate mg	250	IV MD	3.8	0.7	19
Carbenicillin g	20	IV	130	45–75	35–58
Mezlocillin g	5	IV	140	25–35	6–9
Ticarcillin g	5	IV	469	30–45	6–10
Piperacillin g	1	IV	43.3	19	44
Imipenem g	1	IV	64	9.1	14
Cefuroxime mg	750	IV	28	9.6	35
Cefuroxime mg	750	IVx3	19	17.1	89
Cefotetan g	1	IV	104.1	39.7	38
Cefotaxime g	2	IV	40	5–14	12–30
Ceftriaxone g	2	IV	127	57.4	45
Ceftazidime g	2	IV	43	16	37
Gentamicin mg·kg^{-1}	5	MD	5	5	120
Tobramycin mg·kg^{-1}	1.7		6–8	6–9	100–150
Amikacin mg	500	IV	11–20	6–9	45–54
Erythromycin g	1	Pox2	1.4	4.2	300
Erythromycin mg	500	IV MD	3.05	6.53	210
Clarithromycin mg	500	PO MD	2.5	17.5	690
Azithromycin mg	500	PO MD	0.2–0.4	2.3–8.1	200–2000
Dirithromycin g	250	PO MD	0.08	1.6–2.4	2000–3000
Spiramycin mg	2–3	PO	2.4	19.25	802
Pefloxacin mg	400	IV	10.9	20	183
Ciprofloxacin mg	750	PO	2	4.9	275
Ciprofloxacin mg	200	IV	0.6±0.49	4.71±3.1	600
Ofloxacin mg	200	PO MD	1.90–5.18	6.7–7.3	2350
Temafloxacin mg	600	PO MD	6.05±2.19	27.97±17.02	460
Doxycycline mg	100	×3PO	2.74	5.4–23	190–840
Clindamycin mg	500	PO	3.3–10	3.2–9.3	100
Vancomycin g	1	IM	5.3	13	245
Vancomycin g	1	IV	6.7–40.6	2.8–9.6	24–41

MU: million unit; PO: *per os*; MD: multiple doses; IV: intravenous; IM: intramuscular.

Cazzola. European Respiratory Monograph 28: Antibiotics and the lung. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. 2004

Considerados los sitios más importantes de infección tracto respiratorio:



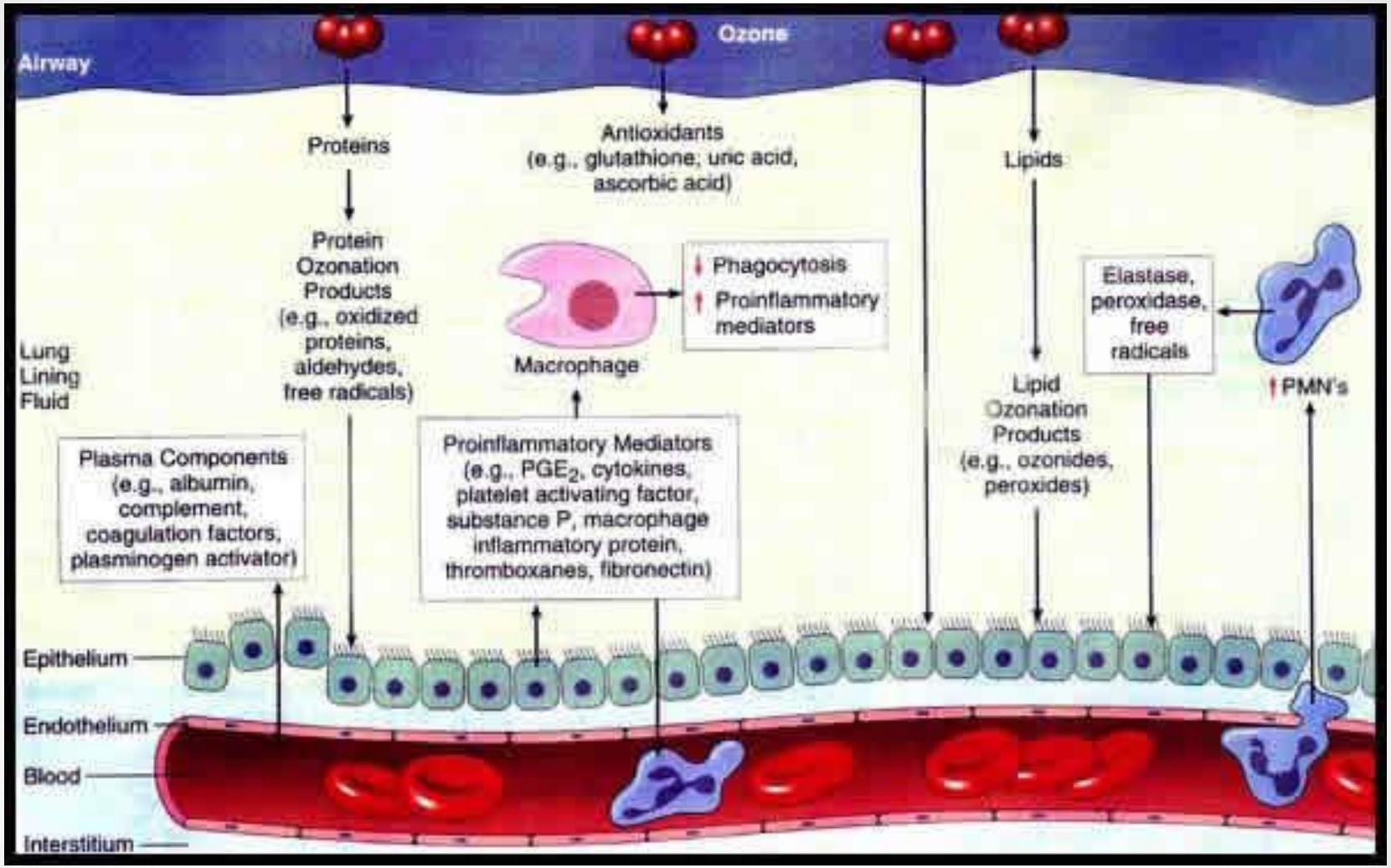
Liquido del revestimiento epitelial (ELF) y macrófagos alveolares (AMs)

EXTRACELULAR

Streptococcus pneumoniae, Moraxella catarrhalis y Haemophilus influenzae son los patógenos extracelulares predominantes

INTRACELULAR

Mycoplasma pneumoniae, Chlamydophila (Chlamydia) pneumoniae y Legionella pneumophila


Airway
Ozone
Proteins
Antioxidants
(e.g., glutathione; uric acid, ascorbic acid)
Lipids
Protein Ozonation Products (e.g., oxidized proteins, aldehydes, free radicals)
Phagocytosis
Proinflammatory mediators
Macrophage
Elastase, peroxidase, free radicals
PMN's
Lung Lining Fluid
Lipid Ozonation Products (e.g., ozonides, peroxides)
Plasma Components (e.g., albumin, complement, coagulation factors, plasminogen activator)
Proinflammatory Mediators (e.g., PGE_2, cytokines, platelet activating factor, substance P, macrophage inflammatory protein, thromboxanes, fibronectin)
Epithelium
Endothelium
Blood
Interstitium

β -lactámicos

Características generales:

- BDP oral buena (penicilina A >> cefalosporinas orales 2º y 3º gen)
- Distribución tisular moderada (Vd aproximadamente 0,2-0,3 L/kg)
- UPP moderada (excepto ceftriaxona) → no parece factor limitante en la difusión a tejido
- Vida Media de 1-1,5 h (excepto ceftriaxona)
- Eliminación renal (filtración glomerular y/o secreción tubular) → IR ajustar dosis

Farmacocinética pulmonar (datos limitados o inexistentes):

●concentraciones en los macrófagos alveolares son prácticamente nula

●concentraciones en mucosa bronquial (igual o 35-40% de la sérica) > secreciones bronquiales (comparación difícil porque raramente se han realizado simultáneamente por los mismos autores y con la misma metodología)

Tableau 1
Données de pharmacocinétique sérique et pulmonaire des principales pénicillines et céphalosporines orales de première et deuxième génération utilisées dans le traitement des infections communautaires des voies respiratoires basses de l'adulte [1–14]
Blood and pulmonary pharmacokinetic data for the major oral first and second generation penicillins and cephalosporins used to treat adult low respiratory tract community acquired infections [1–14]

Molécule	Dose (mg), voie	Pic (µg/ml)	Fixation protéique (%)	Demi-vie (h)	Biodisp.(%)	Vd (L)	Élimination rénale active (%)	Concentrations secrétions bronchiques	Concentration muqueuse bronchique	Concentration pulmonaire
Amoxicilline	500, p.o. 1000, p.o. 1000, i.v.	7–10 13–15 187	17	1	80–85	20	70–80	7,6 % des concentrations sériques	43–200 % des concentrations sériques	40 % des concentrations sériques
Clavulanate	125, p.o./1000 amox 200, i.v./1000 amox	3–5 14	22	1	75	15	18–38 50	ND	118 %	ND
Bacampicilline	400, p.o. 600, p.o. 800, p.o.	7,8 9 12,5	20	1	87–98	ND	70–80	5–10 % des concentrations sériques	39 % des concentrations sériques	ND
Cefatrizine	1000, p.o.	10	60	1,5	50	ND	80	135–164 % des concentrations sériques	ND	14–20 % des concentrations sériques
Céfaclor	500, p.o. forme LP	8	25–50	1	62–69	22	70	# 0,5 µg/ml après 500 mg	# 3–7,7 µg/ml après 250–1000 mg	ND
Céfalexine	500, p.o. 1000, p.o	18–20 32–40	6–10	1	85–90 75	15	80–100	ND	ND	ND
Céfadroxil	500, p.o. 1000, p.o.	13–18 26–35	15–20	1,6–2	80–90	ND	80–93	ND	ND	ND
Céfuroxime axetil	500, p.o.	7–9	33	1.4	50–60 après les repas	25–30	> 85	2,8–3,3 µg/ml après 500 mg	30–51 % des concentrations sériques	60 % des concentrations sériques

ND : non déterminé ; p.o. : per os ; i.v. : intraveineuse ; amox : amoxicilline ; Vd : Volume de distribution.

Tableau 2
Données de pharmacocinétique sérique et pulmonaire des principales céphalosporines de troisième génération utilisées dans le traitement des infections communautaires des voies respiratoires basses de l'adulte [1,2,15–21]
Blood and pulmonary pharmacokinetic data for the major third generation cephalosporins used to treat adult low respiratory tract community acquired infections [1,2,15–21]

Molécule	Dose (mg), voie	Pic (µg/ml)	Fixation protéique (%)	Demi-vie (h)	Biodisponibilité (%)	Vd (L)	Élimination rénale active (%)	Concentration secrétions bronchiques	Concentration muqueuse bronchique	Concentration pulmonaire
Cefpodoxime proxétil	200, p.o.	2,2–2,5	40	2,4	40–50	30–35	80	ND	40–54 % des concentrations sériques	0,6–2 µg/g
Céfixime	200, p.o.	3	70	3–4	50	15	20	Le plus souvent non détectable	35–40 % des concentrations sériques	N
Céfotiam hexétil	400, p.o.	3,4	40	1	45	35-40	35	ND	ND	0,2–0,35 µg/g
Céfotaxime	1000, i.v.	86 à 5 minutes	20–40	0,6–0,7	NA	32–37	60	8–25 % des concentrations sériques	7,5 µg/g après 2 g i.v.	5,3 µg/g
Ceftriaxone	1000, i.v., 1000, i.m.	123–150, 79	80–95	6–8	NA	7–12	40-60	ND	15,9 µg/ml 4,5 heures après 1 g i.m.	30,20 et 2 µg/g une, deux à quatre et 24 heures après 1 g i.v.

NA : non applicable, ND : non déterminé ; Vd : Volume de distribution.

Fantin B. Diffusion sérique et respiratoire des antibiotiques. Analyse critique des paramètres prédictifs d'efficacité clinique. Médecine et maladies infectieuses 36 (2006) 599–613

ß-lactámicos

Estudios de penetración intrapulmonar se han realizado desde principios de 1990.

Table I. Plasma and epithelial lining fluid (ELF) concentrations of oral penicillins and cephalosporins

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Amoxicillin/ clavulanic acid (AMO/CLA)	500 mg AMO + 250 mg CLA × 1 dose	15	1–2	AMO: 6.90 [1.2–9.8][c] CLA: 5.25 [0.7–9.95][c]	AMO: 0.89 [0–3.48][c,d] CLA: 0.96 [0–8.36][c,d]	NR NR	28
Cefuroxime axetil	500 mg × 1 dose	14	0.9–6.8[e]	3.9 ± 0.5	0.7 ± 0.2	0.15	29
	500 mg × 1 dose	4	6	1.1 ± 0.3	<LLQ	NA	30
		4	12	0.06 ± 0.12	<LLQ	NA	
		4	24	<LLQ	<LLQ	NA	
Cefpodoxime proxetil	200 mg × 1 dose[f]	6	3	1.85 ± 0.82	0.22 ± 0.13	0.108 ± 0.044	31
		6	6	1.40 ± 1.25	0.12 ± 0.14	0.0605 ± 0.0479	
Ceftibuten	400 mg × 1 dose	7	1.9 [1.38–2.67][g]	15.2 [2.4–23.2][g]	1.6 [0–2.8][g]	0.13	32
		4	6.5 [4.08–8.08][g]	14.0 [7.8–17.6][g]	1.6 [0.76–2.1][g]	0.12	
		3	13.3 [12.25–15.0][g,h]	4.1 [2.5–5.6][g,h]	1.2 [0.4–2.2][g,h]	0.38	
Cefdinir	300 mg × 1 dose	9	4	2.0 [1.4–8.0][c]	0.29 [0–.4.73][c,i]	0.15 [0–.3.26][c,i]	33
	600 mg × 1 dose	8	4	4.2 [3.05–6.4][c]	0.49 [0–.0.50][c]	0.12 [0–.0.14][c]	
Cefaclor	750 mg bid × 7 doses[j]	6	4	3.08 ± 1.7	2.71 ± 0.87	0.88	34
		6	6	0.68 ± 0.70	2.16 ± 1.70	3.2	
		6	12	0.23 ± 0.1	0.6 ± 0.3	2.6	
Cefditoren	400 mg × 1 dose	8	1.0–2.0[k]	1.78 ± 1.27	0.39 ± 0.21	0.381 ± 0.501	35
		8	2.01–3.0[k]	1.33 ± 0.95	0.34 ± 0.25	0.232 ± 0.181	
		8	3.01–4.0[k]	1.03 ± 0.51	0.30 ± 0.18	0.318 ± 0.192	

a Sampling time after the last dose.
b Values are expressed as mean ± SD unless specified otherwise.
c Values are expressed as median [range].
d Fourteen ELF samples were measured in 15 patients.
e Values are expressed as range.
f Two tablets of cefpodoxime proxetil (130 mg per tablet; equivalent to 200 mg of cefpodoxime).
g Values are expressed as mean [range].
h Samples at 20.25 h were not included because both plasma and ELF samples were <LLQ.
i Seven ELF samples were measured in nine patients.
j Modified-release formulation.
k Collection interval.

bid = twice daily; **LLQ** = lower limit of quantification; **NA** = not applicable; **NR** = not reported; **SD** = standard deviation.

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Table II. Plasma and epithelial lining fluid (ELF) concentrations of parenteral penicillins and cephalosporins

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Piperacillin/ tazobactam (PIP/TAZ)	4 g PIP + 500 mg TAZ IV 0.5 h infusion q8h	10	Steady state[c]	PIP: 24.0 ± 13.8 TAZ: 2.4 ± 1.2	PIP: 13.6 ± 9.4 TAZ: 2.1 ± 1.1	PIP: 0.568 ± 0.336 TAZ: 0.913 ± 0.277	36
Cefpirome	1 g IV 0.5 h infusion × 1 dose	37	0.5–7[d]	34.5 ± 3.3[e]	7.2 ± 1.1[e,f]	0.359 ± 0.074[e,f]	37
Ceftazidime	1 g IM × 1 dose	5	1	39.89 ± 10.42	2.71 ± 0.88	NR	38
		5	2	36.04 ± 9.21	2.66 ± 0.64	NR	
		5	4	13.34 ± 4.12	1.32 ± 0.64	NR	
		5	8	6.08 ± 1.71	0.66 ± 0.36	NR	
		5	12	1.07 ± 0.45	0.12 ± 0.15	NR	
	2 g 0.5 h IV infusion × 1 dose then continuous IV infusion of 4 g/d	15	8, 12, 18[g]	39.6 ± 15.2	8.2 ± 4.8	0.206 ± 0.089	39
Cefepime	2 g IV 0.5 h infusion × 1 dose then continuous IV infusion of 4 g/d	7	8[g]	13.5 ± 3.2[h]	13.7 ± 3.0	1.01	40
		7	12[g]	13.7 ± 3.5[h]	13.5 ± 3.3	0.99	
		6	18[g]	13.3 ± 3.6[h]	14.9 ± 2.3	1.12	
Ceftobiprole	500 mg IV 2 h infusion q8h × 4 doses	6	2.5	17.68 ± 4.48	2.55 ± 0.39	0.255 ± 0.366[i]	41
		6	4	12.77 ± 2.26	2.00 ± 1.07		
		6	6	6.91 ± 4.58	4.58 ± 5.82		
		6	8	3.65 ± 1.05	1.51 ± 0.39		

UPP=20%

a Sampling time after the start of the infusion unless specified otherwise.

b Values are expressed as mean ± SD unless specified otherwise.

c Samples were collected at steady state after 2 d of therapy and at 5 h after a dose.

d Values are expressed as range.

e Values are expressed as mean ± SEM.

f Eight samples were available.

g Serum and ELF concentrations were sampled after 2 d of therapy at 8, 12 and 18 h during a continuous infusion.

h Twenty concentrations were available at each sampling time.

i The penetration ratio was calculated from AUC values for ELF and plasma.

AUC = area under the concentration-time curve; **IM** = intramuscularly; **IV** = intravenous; **NR** = not reported; **q8h** = every 8 h; **SD** = standard deviation; **SEM** = standard error of the mean.

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Carbapenems

Estudios de penetración intrapulmonar se han realizado desde principios de 1990.

Table III. Plasma and epithelial lining fluid (ELF) concentrations of carbapenems

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Meropenem	1 g IV 0.5 h infusion × 1 dose	30[c]	0.5	25.96 ± 22.16	5.04 ± 3.33	0.19 ± 0.11	45
			1	14.98 ± 5.30	7.07 ± 2.87	0.51 ± 0.24	
			2	12.01 ± 3.48	3.86 ± 2.74	0.33 ± 0.20	
			4	2.51 ± 0.68	2.20 ± 2.29	1.04 ± 1.20	
			6	0.57 ± 0.27	0.59 ± 1.09	0.82 ± 1.18	
			8	0.29 ± 0.24	NR	NA	
	500 mg IV 0.5 h infusion q8h × 4 doses	4	1	10.9 ± 1.3	5.3 ± 2.5	0.49–0.80[d]	46
		4	2	5.2 ± 1.6	2.7 ± 1.8		
		4	3	2.4 ± 0.9	1.9 ± 0.9		
		4	5	0.3 ± 0.4	0.7 ± 0.4		
		4	8	0.0 ± 0.0	0.2 ± 0.1		
	1 g IV 0.5 h infusion q8h × 4 doses	4	1	19.0 ± 7.6	7.7 ± 3.1	0.32–0.53[d]	
		4	2	7.5 ± 1.3	4.0 ± 1.1		
		4	3	5.3 ± 1.5	1.7 ± 1.4		
		4					
		4					
	2 g IV 0.5 h infusion q8h × 4 doses	4					
		4					
Ertapenem	1 g IV 0.5 h infusion × 1 dose	15[e]					
	1 g IV 1 h infusion q24h	15[f]					
Biapenem	300 mg IV 0.5 h infusion × 1 dose	6[g]					
	300 mg IV 3 h infusion × 1 dose		3	6.8 ± 1.2	1.33 ± 0.26	0.20 ± 0.06	

En contraste, coeficiente de penetración (basado en las proporciones de las AUC) de 0,72% se observó en los pacientes críticos con NAVM tras recibir infusiones de 3 horas de meropenem 2g/8h

a Sampling time after the start of the infusion unless specified otherwise.
b Values are expressed as mean ± SD unless specified otherwise.
c Thirty subjects were assigned to one bronchoscopy sampling time (the number of subjects per sampling time was NR).
d Range for all sampling timepoints.
e Fifteen subjects were enrolled, and samples were collected at each sampling time.
f Fifteen subjects were assigned to one bronchoscopy sampling time.
g Samples were collected after 2 d of therapy.
h Unbound serum concentration.
i Values are expressed as median [IQR] for 15 samples.
j Values are expressed as median [IQR] for five samples.
k Values are expressed as median [IQR] for 15 matching sample pairs.
l Each subject received both dosage regimens in a crossover study design.

IQR = interquartile range; **IV** = intravenous; **NA** = not applicable; **NR** = not reported; **qxh** = every *x* h; **SD** = standard deviation.

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Macrólidos

Características generales:

- BDP oral moderada-buena
- Concentraciones séricas relativamente moderadas
- Vd elevado: explicado por una significativa acumulación intracelular
- UPP moderada (excepto roxitromicina)
- Vida Media baja
- Eliminación hepática >> renal

Tableau 5

Paramètres pharmacocinétiques sériques des macrolides, streptogramines et azalides utilisées dans le traitement des infections des voies respiratoires basses de l'adulte [1,46,47]

Blood pharmacokinetic parameters of macrolides, streptogramins, and azalides used to treat adult low respiratory tract infections [1,46,47]

Molécule	Dose (mg), voie	Tmax (h)	Pic (µg/ml)	T1/2 (h)	Biodisponibilité (%)	Fixation protéique (%)	Vd (L)	Élimination rénale
Érythromycine						65–90	ND	< 5 % *per os*
Stéarate	500 p.o.	2–4	1,5	3	40-50			
Éthylsuccinate	500 p.o.	2	2	2	60-80			
Propionate	500 p.o.	1,5	3	3–4	60-80			
Lactobionate	500 i.v.	–	27	1,7	100			15 % i.v.
Dirythromycine	500 p.o.	3-5	0,3–0,4	30–44	10	15–30	800	< 3 %
Roxythromycine	150 p.o.	1,5–2.2	6,6–7,9	10–12	ND	90–96		7–10 %
Clarithromycine	500 p.o.	1.7–2	1,6	2,7–3,8	55	70–80	250	20–40 %
Azithromycine	250 p.o.	2–3	0,17	40–96	37	7–50	180-210	6 %
	500 p.o.		0,4					
Spiramycine	6 MU p.o.	2	3,3	5	ND	10	383	5–15 %
	1,5 MU i.v. 1 heure		2,3	8				
Josamycine	1 000 p.o.	1–4	0,2–0,3	2	ND	15	ND	< 10 %
Pristinamycine	500 p.o.	1–2	1	6	ND	40–45 P1, 70-80 P2	ND	P1 : 100 %, P2 : 2 %
Télithromycine	800 p.o.	1–3	2	2-3	57	60–70	174–203	17 %

ND : non déterminé ; T1/2 : demi-vie sérique d'élimination ; Vd : Volume de distribution.

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Farmacocinética pulmonar:

- concentraciones parénquima pulmonar >> secreciones bronquiales = mucosa bronquial
- concentraciones en la película alveolar > concentraciones séricas
- concentraciones en macrófagos alveolares e intracelular es MUY ALTA (especialmente azitromicina) → gran importancia tto infecciones piógenos extracelulares

Tableau 6

Données d'accumulation cellulaire et intrapulmonaire des macrolides, streptogramines et azalides utilisés dans le traitement des infections des voies respiratoires [48–56]

Data on cellular or intrapulmonar accumulation of macrolides, streptogramins, and azalides used to treat adult low respiratory tract infections [48–56]

Molécule	Secrétions bronchiques	Muqueuse bronchique	Film alvéolaire	Parenchyme pulmonaire	Macrophage alvéolaire
Érythromycine	× 0,5	× 1	× 0,5–1	–	× 4-18
Dirithromycine	× 4–13	× 5	× 4–5	× 29	× 1
Roxithromycine	–	–	× 0,2	–	× 40–100
Clarithromycine	–	–	× 2–31	# × 3	× 50–1200
Azithromycine	–	–	× 5–20	–	× 300– > 5000
Spiramycine	–	–	–	# × 5–20	–
Josamycine	–	–	–	# × 10–15	× 21
Pristinamycine	–	–	–	–	–
Télithromycine	–	# × 1–100	× 3-12.7	–	× 50–407

x : facteur multiplicatif par rapport aux concentrations sériques.

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Macrólidos, azalidas y ketólidos

Bdp oral=55%
UPP=70-80%

Table V. Plasma and epithelial lining fluid (ELF) concentrations of oral clarithromycin

Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
200 mg × 1 dose	5	3	0.36 ± 0.07	4.84 ± 3.39	14	23
500 mg × 1 dose	4	6	1.0 ± 0.6	39.6 ± 41.1	NR	30
	4	12	0.25 ± 0.21	<LLQ	NR	
	4	24	0.07 ± 0.05	<LLQ	NR	
	4	48	<LLQ	<LLQ	NR	
500 mg bid × 7 doses	10	4.25 ± 0.27[c]	3.96 ± 1.19[c]	20.46 ± 6.7[c]	NR	56
500 mg q12h × 9 doses	3	4	2.2 ± 0.9	29.3 ± 12.4	NR	51
	4	8	2.6 ± 0.5	72.1 ± 73.0	NR	
	4	12	0.8 ± 0.3	48.6 ± 46.8	NR	
	3	24	0.5 ± 0.07	11.9 ± 3.6	NR	
	4	48	0.01 ± 0.03	23.4 ± 19.2	NR	
500 mg q12h × 9 doses	5	4	3.29 ± 0.94	34.02 ± 5.16	11	57
	5	8	1.58 ± 0.50	20.36 ± 4.49	14	
	5	12	0.91 ± 0.59	23.01 ± 11.90	28	
	5	24	0.19 ± 0.09	4.17 ± 0.29[d]	31	
500 mg q12h × 9 doses	5	4	2.00 ± 0.60	34.5 ± 29.3	NR	58
	5	8	1.55 ± 0.42	26.1 ± 7.2	NR	
	5	12	1.22 ± 0.35	15.1 ± 11.1	NR	
	5	24	0.23 ± 0.11	4.6 ± 3.7	NR	
1000 mg q24h × 5 doses[e]	7	3	1.54 ± 0.60	6.38 ± 3.92	NR	59
	7	6	1.43 ± 0.42	6.89 ± 4.19	NR	
	7	9	2.22 ± 0.60	11.50 ± 6.65	NR	
	7	12	1.04 ± 0.42	7.14 ± 7.29	NR	
	7	24	0.75 ± 0.35	6.80 ± 3.39[f]	NR	
	7	48	0.156[g]	6.08[g]	NR	

Forma retard

a Sampling time after the last dose.
b Values are expressed as mean ± SD unless specified otherwise.
c Values are expressed as mean ± SEM.
d Three of five subjects had concentrations <LLQ.
e The clarithromycin formulation used in this study was an extended-release tablet.
f Five of seven subjects had concentrations <LLQ.
g Six of seven subjects had concentrations <LLQ.

bid = twice daily; **LLQ** = lower limit of quantification; **NR** = not reported; **qxh** = every *x* h; **SD** = standard deviation; **SEM** = standard error of the mean.

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Table VI. Plasma and epithelial lining fluid (ELF) concentrations of azithromycin

Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio	Reference
500 mg PO × 1 dose	4	12	0.13 ± 0.05[c]	NR	NR	60
	4	24	NR	NR	NR	
	4	48	NR	2.18	NR	
	6	72	NR	NR	NR	
	4	96	0.01	NR	NR	
500 mg PO × 1 dose	4	6	0.13 ± 0.07	<LLQ	NR	30
	4	12	<LLQ	<LLQ	NR	
	4	24	<LLQ	<LLQ	NR	
	4	48	<LLQ	<LLQ	NR	
	4	120	<LLQ	<LLQ	NR	
	4	240	<LLQ	<LLQ	NR	
500 mg PO first dose and then 250 mg PO q24h × 4 doses	5	4	0.09 ± 0.05	<LLQ	NR	57
	5	8	0.06 ± 0.05[d]	1.93[e]	NR	
	5	12	0.04 ± 0.02[d]	1.75[e]	NR	
	5	24	0.03 ± 0.03[d]	<LLQ	NR	
500 mg PO first dose and then 250 mg PO q24h × 4 doses	6	4[f]	0.178 ± 0.05	0.45 ± 0.15	NR	61
	5	28[f]	0.122 ± 0.055	1.53 ± 0.31	NR	
	5	76[f]	0.093 ± 0.036	2.67 ± 0.85	NR	
	5	124[f]	0.054 ± 0.008	3.12 ± 0.93	NR	
	6	172[f]	0.031 ± 0.055	0.61 ± 0.23	NR	
	6	244[f]	0.015 ± 0.005	<LLQ	NR	
	6	340[f]	<LLQ	<LLQ	NR	
	5	508[f]	<LLQ	<LLQ	NR	
500 mg PO first dose and then 250 mg PO q24h × 4 doses	5	4	0.08 ± 0.05	1.01 ± 0.45[g]	NR	58
	5	8	0.09 ± 0.04	2.18 ± 0.25[g]	NR	
	5	12	0.04 ± 0.02	0.95 ± 0.40[g]	NR	
	5	24	0.05 ± 0.03	1.22 ± 0.59[g]	NR	
500 mg PO first dose and then 250 mg PO q24h × 4 doses	4	4	0.10 ± 0.02	0.64 ± 0.35	NR	62
	4	8	0.05 ± 0.02	0.66 ± 0.42	NR	
	4	12	0.07 ± 0.86	0.88 ± 0.46	NR	
	4	24	0.03 ± 0.02	0.94 ± 0.68	NR	
500 mg IV 60 min infusion q24h × 5 doses	4	4	0.37 ± 0.10	1.70 ± 0.74	NR	63
	4	12	0.25 ± 0.04	1.27 ± 0.47[h]	NR	
	4	24	0.14 ± 0.04	2.86 ± 1.75	NR	

a Sampling time after the last dose unless specified otherwise.
b Values are expressed as mean ± SD unless specified otherwise.
c Values are expressed as mean ± SEM.
d One of five subjects had concentrations <LLQ.
e Four of five subjects had concentrations <LLQ.
f Sampling time after the first dose (500 mg).
g Two of five subjects had concentrations <LLQ.
h One of four subjects had concentrations <LLQ.

IV = intravenous; **LLQ** = lower limit of quantification; **NR** = not reported; **PO** = orally; **q24h** = every 24 h; **SD** = standard deviation; **SEM** = standard error of the mean.

Concentración en ELF VO>IV

Bdp oral=37%
UPP=7-50%

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Quinolonas

Características generales:

- BDP oral muy buena → terapia secuencial
- Vd elevado: muy buena distribución extravascular y acumulación tejidos
- UPP baja-moderada
- Cinética lineal
- Vida media 5-7h y hasta 12-24h en moxifloxacino
- Eliminación renal en la mayoría (necesidad de ajuste < 30ml/min

Tableau 7
Paramètres pharmacocinétiques sériques des fluoroquinolones utilisées dans le traitement des infections respiratoires basses de l'adulte [1,66–78]
Blood pharmacokinetic parameters of fluoroquinolones used to treat adult low respiratory tract infections [1,66–78]

Molécule	Dose (mg), voie	Pic (µg/ml)	Fixation protéique (%)	Demi-vie (h)	Biodisponobilité (%)	ASC 0–24 heures (µg/ml h)	ASC 0–24 heures libre (µg/ml h)	Vd (L/kg)	Élimination rénale active (%)
Ciprofloxacine	500, *per os*	3	30	5	80	24	18	2,5	60
	750, *per os*	4–5				32			
	400, i.v.	4–5				24			
Ofloxacine	200, *per os*	2,5–3	10	5–7	# 100	41	43	1,5	95
	400, *per os*	4,5–6							
	200, i.v.	5–6							
Lévofloxacine	500, *per os*	6	30	6–7	# 100	48	33	1,5	95
	500, i.v.	6,4				55	38		
Moxifloxacine	400, *per os*	4,5	50	12	90	48	24	2	20

ASC : Aire sous courbe sérique ; Vd : Volume de distribution.

Fantin B. Diffusion sérique et respiratoire des antibiotiques. Analyse critique des paramètres prédictifs d'efficacité clinique. Médecine et maladies infectieuses 36 (2006) 599–613

Farmacocinética pulmonar:

- concentraciones parénquima pulmonar >> mucosa bronquial>> secreciones bronquiales=séricas
- acumulación en la película alveolar (levo=moxi > cipro)
- concentraciones en macrófagos alveolares e intracelular es ALTA
- La difusión pulmonar no es un factor limitante

Tableau 8

Données d'accumulation pulmonaire et intra-cellulaire des quinolones utilisées dans le traitement des infections respiratoires basses de l'adulte [1,66–78]

Data on cellular or intrapulmonar accumulation of quinolones used to treat adult low respiratory tract infections [1,66–78]

Molécule	Secrétions bronchiques	Muqueuse bronchique	Film alvéolaire	Parenchyme pulmonaire	Macrophage alvéolaire
Ciprofloxacine	x 0,33–0,66	x 1–1,5	x 0–0,64	x 1,5–3,5	x 2–10
Ofloxacine	x 0,5–0,9	x 1,7–3,4	Non disponible	x 3,5–3,9	x 3
Lévofloxacine	x 1,2	x 0,9–1,8	x 2	x 2–5	x 10
Moxifloxacine	x 0,89–1,13	x 1,–2,1	x 5–7	x 3,5–4,4	x 9–70

x : facteur multiplicatif par rapport aux concentrations sériques.

Fantin B. Diffusion sérique et respiratoire des antibiotiques. Analyse critique des paramètres prédictifs d'efficacité clinique. Médecine et maladies infectieuses 36 (2006) 599–613

Fluoroquinolonas

Table VIII. Plasma and epithelial lining fluid (ELF) concentrations of oral ciprofloxacin and moxifloxacin

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Ciprofloxacin	250 mg bid × 4 d	11	3–6[c]	1.1 ± 0.2[d]	2.0 ± 1.7[d]	1.85 ± 0.47[d]	96
	250 mg bid × 4 d	13	3–6[c]	1.19 ± 0.16[d]	3.0 ± 1.05[d]	2.13 ± 0.5[d]	98
	500 mg × 1 dose	4	6	0.95 ± 0.32	<LLQ	NA	99
		4	12	0.23 ± 0.07	<LLQ	NA	
		4	24	0.03 ± 0.01	<LLQ	NA	
		4	48	<LLQ	<LLQ	NA	
	500 mg × 1 dose	5	2.5	2.33[e]	2.13[e,f]	NR	100
		5	5	1.13[e]	<LLQ	NA	
		5	12	0.43[e]	<LLQ[f]	NA	
	500 mg q12h × 9 doses	4	4	2.11 ± 0.35	1.87 ± 0.91	NR	101
		4	12	0.55 ± 0.09	0.41 ± 0.10	NR	
		4	24	0.08 ± 0.03	<LLQ	NA	
Moxifloxacin	400 mg × 1 dose	19[g]	2.2	3.22 ± 1.25	20.7 ± 1.92	6.78 ± 2.29	102
			11.8	1.14 ± 1.42	5.90 ± 2.20	5.19 ± 1.90	
			24.1	0.51 ± 1.19	3.57 ± 1.58	6.95 ± 1.43	
	400 mg q24h × 5 doses	4	4	3.23 ± 0.88	11.66 ± 11.86		
		4	8	2.21 ± 0.59	7.80 ± 5.08		
		4	12	1.68 ± 0.53	10.52 ± 3.66		
		4	24	0.78 ± 0.39	5.71 ± 6.28		

Glicoproteína-P influye mediante transporte activo en la difusión pulmonar

a Sampling time after the last dose.

b Values are expressed as mean ± SD unless specified otherwise.

c Values are expressed as range.

d Values are expressed as mean ± SEM.

e Values are expressed as median.

f Values measured in four subjects.

g A total of 19 subjects were studied, but information on how many subjects were assigned to each sampling time was not provided in the study.

bid = twice daily; **LLQ** = lower limit of quantification; **NA** = not applicable; **NR** = not reported; **qxh** = every *x* h; **SD** = standard deviation; **SEM** = standard error of the mean.

Rodvold KA, Jomy M. George, Liz Yoo. Penetration of Anti-Infective Agents into Pulmonary Epithelial Lining Fluid, Focus on Antibacterial Agents. Clin Pharmacokinet 2011; 50 (10): 637-664

Table IX. Plasma and epithelial lining fluid (ELF) concentrations of levofloxacin

Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
100 mg PO × 1 dose	5	2	NR	1.41 ± 0.32	NA	25
500 mg PO × 1 dose	35[c]	0.5	4.73	4.74	1.0	111
		1	6.6	10.8	1.7	
		2	4.9	9.0	0.8	
		4	4.1	10.9	3.0	
		6–8[d]	4.0	10.1	2.7	
		12–24[d]	1.2	NR	NA	
500 mg PO × 1 dose	8	1	3.34 ± 3.00	3.44 ± 3.69	0.788	112
	8	4	4.06 ± 1.90	2.35 ± 1.97	NR	
	8	8	2.12 ± 1.11	1.64 ± 1.51	NR	
	8	12	1.90 ± 0.64	0.95 ± 0.93	NR	
	8	24	0.93 ± 0.61	0.87 ± 0.72	1.043	
500 mg PO q24h × 5 doses	4	4	5.29 ± 1.23	9.94 ± 2.74	NR	101
	4	12	3.07 ± 0.93	6.46 ± 2.48	NR	
	4	24	0.60 ± 0.10	0.70 ± 0.40	NR	
500 mg PO q24h × 5 doses	4	4	5.08 ± 2.31	15.23 ± 4.53	NR	62
	3	8	4.37 ± 0.71	10.18 ± 6.74	NR	
	4	12	4.60 ± 4.58	6.85 ± 4.36	NR	
	4	24	1.52 ± 1.42	2.94 ± 1.74	NR	
500 mg IV 1 h infusion q24h × 5 doses	4	4	4.74 ± 1.37	11.01 ± 4.52	NR	63
	4	12	1.63 ± 0.59	2.50 ± 0.97	NR	
	4	24	0.48 ± 0.16	1.24 ± 0.55	NR	
500 mg IV 1 h infusion q24h	12[e]	1	12.6[f,g]	11.9[f,g]	1.31 ± 0.31	113
		24	3.0[f,g]	3.9[f,g]	1.18 ± 0.36	
500 mg IV 1 h infusion q12h	12[e]	1	19.7[f,g]	17.8[f,g]	1.27 ± 0.46	113
		12	7.7[f,g]	11.8[f,g]	1.12 ± 0.40	
750 mg PO q24h × 5 doses	4	4	11.98 ± 2.99	22.12 ± 14.92	NR	101
	4	12	4.06 ± 0.51	9.17 ± 5.34	NR	
	4	24	1.69 ± 1.14	1.45 ± 0.75	NR	
750 mg IV 1.5 h infusion q24h × 5 doses	4	4	6.55 ± 1.65	12.94 ± 0.74	NR	63
	4	12	3.52 ± 0.77	6.04 ± 0.47[h]	NR	
	4	24	0.84 ± 0.20	1.73 ± 0.78	NR	
750 mg IV 2 h infusion q24h × 3 doses	4	4	5.7 ± 0.4	28.0 ± 23.6	4.9	114
1000 mg IV 2 h infusion q24h × 3 doses	4	3	9.2 ± 1.9	25.8 ± 7.9	NR	114
	4	4	7.5 ± 1.4	24.8 ± 10.2	NR	
	4	8	6.0 ± 1.1	15.7 ± 4.5	NR	
	4	12	4.8 ± 1.7	9.6 ± 4.7	2.0	
	4	24	1.2 ± 0.4	4.3 ± 1.8	3.6	

Table IX. Contd

Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
1000 mg IV 2 h infusion q24h × 3 doses	4	4	9.2 ± 2.7	22.8 ± 12.9	NR	115
	4	8	8.1 ± 1.6	10.5 ± 4.3	NR	
	4	12	4.1 ± 0.8	9.4 ± 3.8	NR	
	4	24	2.0 ± 0.4	2.8 ± 1.0	NR	

a Sampling time after the last dose or after the start of the last IV infusion, as applicable.
b Values are expressed as mean ± SD unless specified otherwise.
c A total of 35 subjects were studied, but information on how many subjects were assigned to each sampling time was not provided in the study.
d Values are expressed as range.
e 12 subjects had two bronchoscopies after administration of the final dose (e.g. at 1 h and 12 h or at 1 h and 24 h).
f Samples were collected after 2 d of therapy.
g Values are expressed as median.
h One of four subjects had concentrations <LLQ.

IV = intravenous; **LLQ** = lower limit of quantification; **NA** = not applicable; **NR** = not reported; **PO** = orally; **qxh** = every *x* h; **SD** = standard deviation.

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Aminoglucósidos

Table X. Plasma and epithelial lining fluid (ELF) concentrations of aminoglycosides

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Gentamicin	240 mg IV 30 min infusion × 1 dose	6	1	8.79 ± 0.64[c]	2.95 ± 0.37[c]	0.30 ± 0.05[c]	119
		6	2	6.37 ± 0.50[c]	4.24 ± 0.42[c]	0.85 ± 0.10[c]	
		6	4	4.70 ± 0.49[c]	3.10 ± 0.39[c]	1.14 ± 0.26[c]	
		6	6	4.70 ± 0.57[c]	2.65 ± 0.35[c]	0.74 ± 0.18[c]	
Tobramycin	150 mg IM × 1 or more doses	5	6	4.1 ± 1.5	5.3 ± 2.9	1.4 ± 0.8	120
	300 mg IM × 1 or more doses	5	6	4.3 ± 2.4	5.5 ± 2.1	1.6 ± 0.6	120
	IV doses adjusted to achieve serum C_{max} ~8 μg/mL and C_{min} <2 μg/mL while maintaining q8h dosing interval[d]	4	0.5[e]	6.90 ± 1.44	2.33 ± 0.50	0.30 ± 0.03	121
		4	2[e]	4.08 ± 1.30	1.67 ± 0.60	0.42 ± 0.16	
		4	4[e]	2.14 ± 0.85	1.62 ± 1.19	0.64 ± 0.37	
		4	8[e]	0.79 ± 0.38	0.77 ± 0.38	1.53 ± 0.76	
	7–10 mg/kg IV 30 min infusion q24h[e]	12	1	22.4 ± 5.9	2.7 ± 0.7	0.119 ± 0.019	122
	300 mg inhalation × 1 dose	12	NA	NA	90 ± 54	NA	123
Netilmicin	450 mg IV 30 min infusion × 1 dose	5	1	21.4 ± 1.19[c]	7.5 ± 1.0[c]	NR	124
		5	1.5	15.3 ± 0.85[c]	9.6 ± 0.3[c]	NR	
		5	2	12.0 ± 0.71[c]	14.7 ± 2.2[c]	NR	
		5	3	8.3 ± 0.64[c]	9.3 ± 0.6[c]	NR	

a Sampling time after the last dose or after the start of the last IV infusion, as applicable.

b Values are expressed as mean ± SD unless specified otherwise.

c Values are expressed as mean ± SEM.

d The mean number of doses (± SD) administered before BAL fluid collection was 21.25 ± 6.42.

e Samples were collected at steady state after 2 d of therapy.

BAL = bronchoalveolar lavage; C_{max} = maximum concentration; C_{min} = minimum concentration; **IM** = intramuscularly; **IV** = intravenous; **NA** = not applicable; **NR** = not reported; **q*x*h** = every *x* h; **SD** = standard deviation; **SEM** = standard error of the mean.

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Glicopéptidos

Table XI. Plasma and epithelial lining fluid (ELF) concentrations of glycopeptides and lipoglycopeptides

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Vancomycin	15 mg/kg IV 2 h infusion × 5 for 11 d[c,d]	14	18.4 ± 11	24 ± 19	4.5 ± 2.3[e]	0.18	127
	7.5 mg/kg IV 1 h infusion q6h[f]	4	6[f]	22.19 ± 0.83	2.03 ± 0.49	NR	128
		6	6[f]	12.45 ± 3.56	ND[g]	NR	
	1000 mg IV 1 h infusion q12h × 9 doses	5	4	19.8 ± 3.7	5.3 ± 1.5	NR	129
		5	12	5.1 ± 1.7	2.4 ± 0.7	NR	
Teicoplanin	12 mg/kg IV 30 min infusion q12h × 2 d, then 12 mg/kg IV 30 min infusion q24h	13	18–24[h,i]	15.9	4.9	1.46[j]	130
Telavancin	10 mg/kg IV 1 h infusion q24h × 3 doses	5	4	NR	NR	NR	131
		5	8	NR	3.73 ± 1.28	NR	
		5	12	22.9	NR	NR	
		5	24	7.28	0.89 ± 1.03	NR	
Oritavancin	800 mg IV 1–2 h infusion q24h × 5 doses	5	4	119.6 ± 24.6	3.1 ± 1.1	NR	129
		5	12	75.7 ± 16.3	3.7 ± 2.5	NR	
		5	24	73.7 ± 28.2	6.3 ± 1.5	NR	
		5	168	10.4 ± 3.0	1.7 ± 0.8	NR	

a Sampling time after the last dose unless specified otherwise.

b Values are expressed as mean ± SD.

c Subsequent doses were adjusted in order to obtain a trough plasma concentration of 15–20 μg/mL.

d The mean (± SD) duration of therapy was 6.6 ± 1.75 d.

e No drug was detected in BAL fluid from one patient, therefore, the LLQ (10 ng/mL) was used in the analysis.

f Sampling was performed 24 h after the start of vancomycin therapy.

g Concentrations in BAL fluid were undetectable (assay LLQ 0.5 μg/mL).

h Samples were collected 4 to 6 d after the start of teicoplanin therapy.

i Values are expressed as range.

j The ratio represents the ELF to unbound serum concentration (median unbound fraction 22% [range 8–42%]).

BAL = bronchoalveolar lavage; **IV** = intravenous; **LLQ** = lower limit of quantification; **ND** = not detected; **NR** = not reported; **qxh** = every *x* h; **SD** = standard deviation.

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Miscelánea

Table XII. Plasma and epithelial lining fluid (ELF) concentrations of linezolid, tigecycline and iclaprim

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Linezolid	600 mg PO bid × 5 doses	5	4	15.5 ± 4.9	64.3 ± 33.1	4.2 ± 1.4	135
		5	8	8.9 ± 3.2	31.4 ± 33.0	3.1 ± 2.2	
		5	12	10.2 ± 2.3	24.3 ± 13.3	2.4 ± 1.2	
		5	24	1.8 ± 0.6	7.6 ± 6.0	3.9 ± 2.3	
		5	48	0.2 ± 0.2	0.7 ± 0.8	2.3 ± 1.6	
	600 mg PO bid × 6 doses	10	5.10 ± 2.01[b]	13.40 ± 3.92	25.09 ± 14.59	8.35 ± 11.69	136
	600 mg IV 1 h infusion × 2 d	16	2[c]	17.7 ± 4.0	14.4 ± 5.6	1.05 ± 0.34	137
		16	12[c]	2.4 ± 1.2	2.6 ± 1.7	1.04 ± 0.28	
Tigecycline	100 mg IV 30 min infusion × 1 dose, then 50 mg IV 30 min infusion q12h × 7 doses	5	2[c]	0.19 ± 0.06	0.19 ± 0.15	NR	138
		5	3[c]	0.15 ± 0.05	0.12 ± 0.21	NR	
		5	4[c]	0.16 ± 0.07	0.06 ± 0.13	NR	
		5	6[c]	0.12 ± 0.06	0.37 ± 0.36	NR	
		5	12[c]	0.10 ± 0.09	0.10 ± 0.17	NR	
		5	24[c]	0.05 ± 0.01	0.00 ± 0.00	NR	
Iclaprim	1.6 mg/kg IV 1 h infusion × 1 dose	8	1.97 ± 0.08[b,c]	0.59 ± 0.18	12.61 ± 7.33	21.29 ± 11.18	139
		8	3.57 ± 0.30[b,c]	0.24 ± 0.05	6.38 ± 5.17	24.93 ± 16.53	
		8	6.50 ± 0.29[b,c]	0.14 ± 0.05	2.66 ± 2.08	20.57 ± 17.31	

a Sampling time after the last dose unless specified otherwise.

b Values are expressed as mean ± SD.

c Sampling time after the start of the last IV infusion.

bid = twice daily; **IV** = intravenous; **NR** = not reported; **PO** = orally; **q12h** = every 12 h; **SD** = standard deviation.

Daptomicina: EVITAR uso en pneumonías → inefectivo → unión surfactante pulmonar

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Drug Safety and Availability
- Drug Alerts and Statements
- Importing Prescription Drugs
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- FDA Drug Safety Newsletter
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Integrity and Supply Chain Security
- Multistate outbreak of fungal meningitis and other infections

FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections

Safety Announcement
Additional Information for Healthcare Professionals
Data Summary

Safety Announcement

[09-01-2010] The U.S. Food and Drug Administration (FDA) is reminding healthcare professionals of an increased mortality risk associated with the use of the intravenous antibacterial Tygacil (tigecycline) compared to that of other drugs used to treat a variety of serious infections. The increased risk was determined using a pooled analysis of clinical trials. The cause of the excess death in these trials is often uncertain, but it is likely that most deaths in patients with these severe infections were related to progression of the infection.

The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections. Tygacil is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia) or diabetic foot infection. Tygacil is approved by FDA for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia.

FDA has updated the Warnings and Precautions and Adverse Reactions sections of the Tygacil drug label to include information regarding increased mortality risk of Tygacil. Healthcare professionals have also been informed of this increased risk via a Dear Health Care Professional letter.

See the Data Summary Section for details.

Additional Information for Healthcare Professionals

- The greatest increase in risk of death with Tygacil was seen in patients with ventilator-associated pneumonia, an

Antifúngicos

Table I. Plasma and epithelial lining fluid (ELF) concentrations of antifungal agents

Antifungal agent	Dosage regimen	Subjects (n)	Plasma sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF sampling time (h)[a]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Polyenes								
Amp B	6 mg/d (aerosolized) × 7 d	40[c]	NR	NR	4	15.75[d]	NR	6
		40[c]	NR	NR	12	13.66[d]	NR	
		25[c]	NR	NR	24	11.02[d]	NR	
		15[c]	NR	NR	48	10.58[d]	NR	
Liposomal Amp B	4.55 mg/kg/d IV × 6.1 d[e]	11	NR	5.17 ± 1.89[f]	22.0 ± 12.7[f]	1.60 ± 0.58[f]	0.61 ± 0.25[f]	7
	1 mg/kg/d (aerosolized) × 4 d	5	4	0.08[g]	4	7.20[g]	90	8
		6	24	0.05[g]	24	8.26[g]	165.2	
		5	48	0.05[g]	48	2.15[g]	43	
		4	72	0.02[g]	72	1.25[g]	62.5	
		6	96	0.01[g]	96	0.8[g]	80	
		4	120	0.005[g]	120	1.04[g]	208	
		1	144	0.01[g]	144	4.25[g]	425	
		3	168	0.005[g]	168	1.14[g]	228	
		1	192	0.0019[g]	192	0.25[g]	131.5	
Amp B colloidal dispersion	4.46 mg/kg/d IV × 8.8 d[e]	28	NR	1.12 ± 0.21[f]	12.6 ± 2.5[f]	0.38 ± 0.07[f]	1.25 ± 0.52[f]	7
Amp B lipid complex	5.6 mg/kg/d IV × 5.6 d[e]	5	NR	0.48 ± 0.18[f]	7.3 ± 3.1[f]	1.29 ± 0.71[f]	4.47 ± 2.24[f]	7
	25 mg (aerosolized)[h]	10	48	NR	48	9.0[d]	NR	9
		10	168	NR	168	8.2[d]	NR	
		12	336	NR	336	4.1[d]	NR	
Echinocandins								
Anidulafungin	200 mg IV on d1, then 100 mg q24h on d2 and d3	5	4	6.0 ± 1.5	4	0.9 ± 0.1	0.15 ± 0.02	10
		5	8	5.1 ± 0.8	8	0.8 ± 0.4	0.15 ± 0.07	
		5	12	4.4 ± 1.0	12	0.8 ± 0.2	0.20 ± 0.09	
		5	24	3.0 ± 0.5	24	1.1 ± 0.4	0.38 ± 0.14	

Continued next page

Table I. Contd

Antifungal agent	Dosage regimen	Subjects (n)	Plasma sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF sampling time (h)[a]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Micafungin	150 mg IV q24h × 3 doses	5	4	14.8 ± 1.6	4	0.52 ± 0.1	NR	11
		5	12	7.4 ± 1.4	12	0.44 ± 0.1	NR	
		5	24	4.8 ± 0.6	24	0.43 ± 0.2	NR	
	150 mg IV × 1 dose	4	3	4.93 ± 0.97	3	0.04 ± 0.07	0.01	12
		3	5	4.81 ± 0.38	5	0.71 ± 0.20	0.15	
		4	8	3.93 ± 0.39	8	0.05 ± 0.09	0.01	
		4	18	2.38 ± 0.56	18	0.08 ± 0.14	0.04	
		4	24	1.57 ± 0.33	24	1.38 ± 1.93	1.10	
Azoles								
Itraconazole	200 mg PO bid × 10 doses	5	4	2.1 ± 0.8	4	0.3 ± 0.3	NR	13
		6	8	1.2 ± 0.3	8	0.3 ± 0.3	NR	
		5	12	0.9 ± 0.3	12	0.5 ± 0.7	NR	
		5	16	1.2 ± 0.4	16	0.3 ± 0.3	NR	
		5	24	0.9 ± 0.4	24	0.2 ± 0.1	NR	
14-Hydroxyitraconazole[i]		5	4	3.3 ± 1.0	4	0.8 ± 0.5	NR	
		6	8	2.5 ± 0.5	8	0.8 ± 0.3	NR	
		5	12	2.0 ± 0.7	12	1.0 ± 0.9	NR	
		5	16	2.0 ± 0.5	16	0.8 ± 0.4	NR	
		5	24	2.2 ± 0.9	24	0.6 ± 0.2	NR	
Voriconazole	6 mg/kg IV q12h on d1, then 4 mg/kg IV q12h × 3 doses	5	4	5.3 ± 1.4	4	48.3 ± 7.6	9.5 ± 2.3	10
		5	8	1.7 ± 0.9	8	10.1 ± 10.8	4.9 ± 2.8	
		5	12	2.2 ± 1.1	12	17.2 ± 13.3	7.7 ± 3.4	
Posaconazole	400 mg PO bid × 16 doses	3	3	1.93	3	1.66 ± 1.05	1.08 ± 0.47	14
		4	5	1.93	5	1.86 ± 1.30	0.75 ± 0.38	
		4	8	1.73	8	1.69 ± 0.82	0.95 ± 0.20	
		5	12	1.62	12	1.02 ± 0.97	0.59 ± 0.35	
		5	24	1.28	24	1.80 ± 1.71	0.92 ± 0.05	
	400 mg PO bid × 14 doses	4	2.8 ± 0.6[j]	1.3 ± 0.4	3.2 ± 0.7[j]	1.1 ± 0.7	0.94	15
		3	4.5 ± 1.0[j]	1.1 ± 1.4	5.3 ± 1.0[j]	1.3 ± 1.7	0.57	

Anti-TBC

Table II. Plasma and epithelial lining fluid (ELF) concentrations of antitubercular agents

Antitubercular agent	Dosage regimen	Subjects (n)	Plasma sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF sampling time (h)[a]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Isoniazid	300 mg PO od×5 doses	10 M-H, FA	4	0.17±0.21[c]	4	1.00±1.55[d]	1.2±1.9[e]	21
		10 M-AIDS, FA	4	0.47±0.38[c]	4	0.82±0.79[d]		
		10 F-H, FA	4	0.59±0.69[c]	4	1.21±1.72[d]		
		11 F-AIDS, FA	4	0.71±0.80[c]	4	1.78±1.70[d]		
		10 M-H, SA	4	0.87±0.81[c]	4	3.28±4.68[d]	3.2±8.1[e]	
		10 M-AIDS, SA	4	1.08±0.81[c]	4	2.15±1.90[d]		
		10 F-H, SA	4	1.03±0.73[c]	4	5.86±6.92[d]		
		9 F-AIDS, SA	4	1.43±1.00[c]	4	1.96±1.70[d]		
	250 mg PO×1 dose	6	NR	3.75	NR	7.25	NR	22
	15 mg inh×1 dose	6	NR	0.25	NR	1601	NR	
Ethambutol	15 mg/kg PO od×5 doses	10 M-H	4	2.3±0.7	4	2.2±1.0	1.1[f]	23
		10 M-AIDS	4	2.4±1.0	4	2.6±1.7		
		10 F-H	4	1.9±0.6	4	1.9±0.6		
		10 F-AIDS	4	1.7±0.7	4	1.9±0.5		
Pyrazinamide	1000 mg PO od×5 doses	10 M-H	4	20.1±7.0	4	443±180	22.0±11.8[f]	24
		10 M-AIDS	4	16.4±5.42	4	406±198		
		10 F-H	4	23.0±5.8	4	535±297		
		10 F-AIDS	4	25.0±7.1	4	340±167		
	1250 mg PO×1 dose	6	NR	111.4	NR	1240	NR	22
	75 mg inh×1 dose	6	NR	1.46	NR	18 381	NR	
Rifampicin (rifampin)	600 mg PO×1 dose	12	2–5	15.5±1.41[g]	2–5	5.3±0.67[g]	0.34	25
	600 mg PO od×5 doses	10 M-H	4	9.6±7.5	4	1.9±2.2	0.2±0.2[f]	26
		10 M-AIDS	4	6.5±2.4	4	1.4±1.0		
		10 F-H	4	10.9±4.4	4	1.8±1.3		
		10 F-AIDS	4	9.6±6.4	4	3.0±1.6		

Continued next page

Table III. Plasma and epithelial lining fluid (ELF) concentrations of miscellaneous anti-infective agents

Anti-infective agent	Dosage regimen	Subjects (n)	Plasma sampling time (h)[a]	Plasma concentration (μg/mL)[b]	ELF sampling time[a]	ELF concentration (μg/mL)[b]	ELF/plasma penetration ratio[b]	Reference
Dapsone	100 mg PO twice weekly	5	2	1.23±0.57	2 h	0.95±0.83	0.76±0.43	31
		3	4	0.79±0.26	4 h	0.70±0.77	0.79±0.68	
		2	12	1.32±0.21	12 h	1.55±0.79	1.15±0.42	
		3	24	0.83±0.72	24 h	0.23±0.15	0.65±0.66	
		3	48	0.18±0.08	48 h	0.45±0.11	2.91±1.38	
Pentamidine	3–4 mg/kg IV infusion od	4	24	NR	24 h (lavage 2)	17.0±10.9[c,d]	NR	32
		4	24	NR	24 h (lavage 3)	18.8±15.9[c,d]	NR	
		4	24	NR	24 h (lavage 4)	21.4±15.7[c,d]	NR	
	4 mg/kg inh od	8[e]	24	ND	24 h (lavage 2)	80.5±71.9[c,d]	NR	
		8[e]	24	ND	24 h (lavage 3)	77.9±42.0[c,d]	NR	
		8[e]	24	ND	24 h (lavage 4)	110±63.0[c,d]	NR	
	300 mg inh twice monthly	36	NR	NR	17.0±3.6 d[f]	28.4±12.3[c,d]	NR	33
		34	NR	NR	15.3±2.3 d[g]	14.9±7.6[c,d]	NR	
	600 mg inh once monthly	72	NR	NR	28.3±6.4 d[f]	10.6±9.3[c,d]	NR	
		48	NR	NR	27.0±4.2 d[g]	6.5±3.0[c,d]	NR	
	300 mg inh once monthly	6 PCP+	NR	NR	36.3±22.5 d	10.8±8.8[c,d]	NR	
		23 PCP–	NR	NR	22.7±18.3 d	13.7±14.8[c,d]	NR	
	300 mg inh once monthly	32 PCP+ (upper)[h]	NR	NR	23.3±21.7 d	8.7±10.8[c,d]	NR	34
		32 PCP+ (middle)[h]	NR	NR	23.3±21.7 d	6.7±6.8[c,d]	NR	
		19 PCP– (upper)[h]	NR	NR	31.6±12.6 d	6.6±9.3[c,d]	NR	
		19 PCP– (middle)[h]	NR	NR	31.6±12.6 d	6.5±8.6[c,d]	NR	
Zanamivir	10 mg inh q12h×2 doses	6	12	ND	12 h	326[c,i]	NR	35
	600 mg IV q12h×2 doses	6	12	586[c,i]	12 h	419[c,i]	NR	
	200 mg IV q12h×2 doses	6	12	262[c,i]	12 h	146[c,i]	NR	
	100 mg IV q12h×2 doses	6	12	114[c,i]	12 h	74[c,i]	NR	

Y qué hay de la vía inhalatoria??

Controvertida debido:

- ✓ a la falta de indicaciones claras para el inicio de la terapia la falta de especialidades farmacéuticas formuladas para ser administradas por dicha vía
- ✓ el desconocimiento de la posología a seguir
- ✓ el temor a crear resistencias
- ✓ la incomodidad y dificultad a la cual está asociada sobre todo en el paciente intubado

La administración de antiinfecciosos por vía inhalatoria tiene la **ventaja de alcanzar concentraciones elevadas de fármaco en el lugar de la infección**, reduciendo los efectos indeseables sistémicos. No obstante, el método de administración, las propiedades fisicoquímicas del fármaco (pH y osmolaridad), las dosis utilizadas y las características propias del paciente, pueden modificar su eficacia.

La terapia antiinfecciosa inhalada, a pesar de ser ampliamente utilizada, no goza de un buen respaldo bibliográfico. Tan sólo unos pocos medicamentos tienen legalmente reconocida la vía inhalatoria como forma de administración.

Colistina, tobramicina, pentamidina y ribavirina

Tabla I. Dosificación y preparación de antiinfecciosos por vía inhalatoria

Fármaco	*Dosis*	*Forma de preparación*	*Osmolaridad mOsm/kg*	*pH*	*Aprobada*	*Evidencia*
Amikacina (AK)	*Adulto*					
	400 mg cada 8 h[35]	1,6 ml AK 500/2 ml + 2,4 ml API	331	4,6	No	IIb
	100 mg cada 12 h[1,36]	1,6 ml AK 125/2 ml + 2,4 ml SSF	254	4,1		
	500 mg cada 12 h[13]	2 ml AK 500/2 ml + 2 ml API	412	4,6		
	Niños					
	< 12 años: 250 mg cada 12 h[13]	1 ml AK 500/2 ml + 3 ml SSF	430	4,6	No	IV
Amoxicilina (AX)	*Adulto*					
	500 mg cada 12 h[13,37-40]	4 ml AX 1g/8 ml API	596	8,8	No	III
Anfotericina B (AB)	*Adultos*					
	5-6 mg cada 6-12 h[1,4,13,41]	5-6 ml de 50 mg AB/50 ml API	9	5,5	No	Ib
	10 mg cada 6-8 h[42]					
AB liposomal (ABL)	*Adultos*					
	24 mg	6 ml de 50 mg ABL/12 ml API	285	7,5	No	IIb
	24 mg tres veces/semana (1-2 mes post trasplante de pulmón)[42]					
	24 mg/semana (3-6 mes postrasplante de pulmón)[42]					
	24 mg/cada 2 semanas (después del 6 mes postrasplante)[42]					
Aztreonam (AZ)	*Adultos*					
	1.000 mg cada 12 h[13]	1.000 mg AZ/4 ml API	1.134	4,9	No	IV
	500 mg cada 12 h[13]	500 mg AZ/4 ml API	570	5		
Caspofungina (CP)	*Adultos*					
	50 mg[44]	50 mg CP/5 ml SSF	301	< 6,3	No	III
	150 mg[44]	150 mg CP/5 ml SSF	326	< 6,3		
Cefotaxima (CX)	*Adulto*					
	500 mg cada 6-12 h[1,4]	5 ml CX 1.000 mg/10 ml API	364	5,1	No	IV
	1.000 mg cada 12 h[1]	1.000 mg CX/5 ml API	706	5,4		
Ceftazidima (CZ)	*Adulto*					
	1.000 mg cada 12 h[1,5,13,45-47]	1.000 mg CZ/5 ml API	596	7,3	No	Ib
	500 mg cada 6-12 h[1,4,5,13]	5 ml CZ 1000 mg/10 ml API	335	7,5		
	250 mg cada 12 h[48]	2,5 ml CZ 1.000 mg/10 ml API + 2,5 ml SSF	352	7,6		
Colistina (CL)	*Adulto*					
	0,25 MU cada 6 h[4]	1 ml CL 1 MU/4 ml + 4 ml API	20	8,5	Si	Ib
	1 MU cada 8-12 h[1,33,49-51]	1 MU CL/4 ml API	77	7,9		
	2 MU cada 8-12 h[1,33,49]	2 MU CL/4 ml API	137	7,3		
	3 MU cada 12 h[1,49]	3 MU CL/4 ml API	183	7,5		
	Niños					
	< 2 años: 1-2 MU cada 8-12 h[33]					
	< 6 años: 1-3 MU cada 12 h[49]					
	< 6 años: 0,5 MU cada 12 h[13]	2 ml de CL 1 MU/4 ml API + 2 ml API	35	7,4	Si	Ib
	> 6 años: 1-2 MUI cada 12 h[13,51]					
Gentamicina (GT)	*Adultos*					
	40 mg cada 6-12 h[4,52]	0,5 ml GT 240/3 ml + 3,5 ml SSF	293	4,4	No	Ib
	80 mg cada 8-12 h[1,53,54]	1 ml GT 240/3 ml + 3 ml SSF	296	4,4		
	160 mg cada 8-12 h[13,55]	2 ml GT 240/3 ml + 2 ml SSF	277	3,5		
	Niños					
	20 mg cada 12 h[35]	0,5 ml GT 80/2 ml + 3,5 ml SSF	282	4,1	No	IIb
	< 2 años: 40 mg cada 12 h[13]					
	> 2 años: 80 mg cada 12 h[13,57,58]					
	< 1 año: 80 mg cada 12 h[59]					
	> 1 año: 120 mg cada 12 h[59]	1,5 ml GT 240/3 ml + 3 ml SSF	268	4,6		
	Adolescentes: 160 mg cada 12 h[13]					

Tabla I. Dosificación y preparación de antiinfecciosos por vía inhalatoria (continuación)

Fármaco	*Dosis*	*Forma de preparación*	*Osmolaridad mOsm/kg*	*pH*	*Aprobada*	*Evidencia*
Imipenem-cilastatina (IC)	*Adultos*					
	500 mg cada 8 h[10]	500 mg IC/10 ml SSF	651	7,4	No	Ib
Meropenem (MP)	*Adultos*					
	500 mg cada 12 h 1.000 mg cada 12 h	500 mg MP/10 ml API 1.000 mg MP/10 ml API	350 663	7,9 8	No	IV
Nistatina (N)	*Adultos*					
	50.000-500.000 UI cada 4-12 h[62,67]	50.000 UI N/5 ml SSF 100.000 UI N/5 ml SSF 250.000 UI N/5 ml SSF 500.000 UI N + 5 ml SSF	303 296 296 296	6,9 6,9 6,9 6,9	No	IV
Pentamidina (P)	*Adulto*					
	300 mg/mes[1,14,17,18,21,62-68] 150-300 mg/14-28 días[62-65,69-72]	300 mg P/5 ml API 300 mg: 300 mg P/6 ml API	193 167	5,7 6,1	Sí	Ib
	Niños					
	< 4 años: 150 mg/mes[69] < 5 años: 8 mg/kg[14] > 4-5 años: 300 mg/mes[14,65,69] 120 mg/28 días, 60 mg/14 días[71]	5 ml de 300 mg P/10 ml API	119	6	Sí	III
Ribavirina (R)	*Adultos*					
	6 g/día[14,20,72]	6 g R/100 ml de API (3 tandas de 2 h) 6 g R/300 ml API (durante 12-18 h/día)	225 96	4 4,9	No	III
	Niños					
	6 g/día[14,20,72,73]				Sí	Ib
Ticarcilina (TC)	*Adultos*					
	1.000 mg cada 12 h[1]	1.000 mg TC/4 ml API	2.156	6,2	No	III
	Niños					
	1.000 mg cada 12 h[12]				No	III
Tobramicina (TB)	*Adultos*					
	40 mg cada 6 h[4] 60-80 mg cada 8 h[14] 100 mg cada 8-12 h[1,12,65,74] 200 mg cada 12 h[1,12,13] 300 mg cada 12 h[75]	0,8 ml TB 100/2 ml + 3,2 ml SSF 80 mg: 1,6 ml TB 100/2 ml + 2,4 ml SSF 2 ml TB 100/2 ml + 2 ml SSF 4 ml TB 100/2 ml 6 ml TB 100/2 ml	270 243 230 165 165	5,7 5,6 5,5 5,6 5,6	No	Ib
	Niños					
	40-80 mg/8-12 h[14,65,76]	50 mg: 1 ml TB 100/2 + 3 ml SFF	263	5,6	No	Ib
TB sin sulfitos (TBss)	*Adultos*					
	300 mg cada 12 h[14,29,48,51,77,78]	5 ml de TBss	173	6,1	Sí	Ib
	Niños					
	> 6 años: 300 mg cada 12 h[14,29,48,51,77,78]				Sí	Ib
Vancomicina (V)	*Adultos*					
	120 mg cada 6 h[79] 250 mg cada 6-12[4,80]	2,5 ml de 500 mg V/10 ml SSF + 2,5 ml SSF 5 ml de 500 mg V/10 ml SSF	304 320	3,7 3,5	No	IV
	Niños					
	4 mg/kg/6 h[81,82]				No	III

Amikacina: Amikacina Normon®; Amoxicilina: Amoxi Gobens®; Anfotericina B desoxicolato: Fungizona®; Anfotericina B liposomal: Ambisome®; Aztreonam: Azactam®; Cefotaxima: Claforan®; Ceftazidima: Kefamin®; Colistina: Colistimetato GES®; Gentamicina: Genta-Gobens®; Imipenem-cilastina: Tienam®; Meropenem: Meronem®; Nistatina: materia prima; Pentamidina: Pentam®; Ribavirina: Virazole®; Ticarcilina: Ticarpen®; Tobramicina sin sulfitos: Tobi®; Tobramicina: Tobra-Gobens®; Vancomicina: Vancomicina Normon®.

Conclusiones:

- ✓ La concentración de ATB en los fluidos respiratorios/tejidos pulmonares es importante para la predicción de la eficacia terapéutica de un tratamiento en las infecciones bacterianas del tracto respiratorio.
- ✓ La disposición de los antibióticos en el árbol bronquial y el tejido pulmonar es el resultado de un proceso farmacocinético muy complejo y dinámico .
- ✓ La penetración de ATB en las secreciones bronquiales/esputo se ha investigado y se ha correlacionado con la capacidad inhibitoria mínima de patógenos respiratorios.
- ✓ Para la mayoría de ATB se carece de datos relativos de penetración y su comportamiento farmacocinético en el tracto respiratorio.
- ✓ Además, no se ha evaluado la influencia de la inflamación o medicamentos concomitantes sobre la penetración de los antibióticos .

- ✓ La mayoría de estudios realizados sobre la penetración de ATB en ELF han sido realizados en adultos sanos o ambulatorios sometidos a broncoscopia.

- ✓ Los AMG, ß-lactámicos y glicopéptidos tienden a tener ELF ratios<1:
  - ✓ AMG concentraciones en ELF ctes
  - ✓ Amplio rango de penetración de ß-lactámicos

- ✓ Macrólidos, ketólidos, FQ y linezolid tienden a tener ELF ratios >1 → desconocido → probable mecanismo de transporte activo

- ✓ Pocos estudios de concentraciones de ATB en ELF en pacientes con bronquitis crónica leve/moderad, EPOC o inf tracto respiratorio inferior han informado de concentraciones en ELF similares o ligeramente superiores a las reportadas en sujetos sanos.

- ✓ Se están realizando estudios en pacientes con infecciones pulmonares para explorar la importancia de concentraciones intrapulmonares con respecto al establecimiento PK/PD y los resultados clínicos o microbiológicos

GRACIAS POR VUESTRA ATENCIÓN

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Every unnecessary antibiotic prescription written undermines the success of subsequent therapies.

Fraser GL

Far de Favàritx-Menorca