La terapia antibiotica nell'anziano

Invecchiamento e Farmacocinetica

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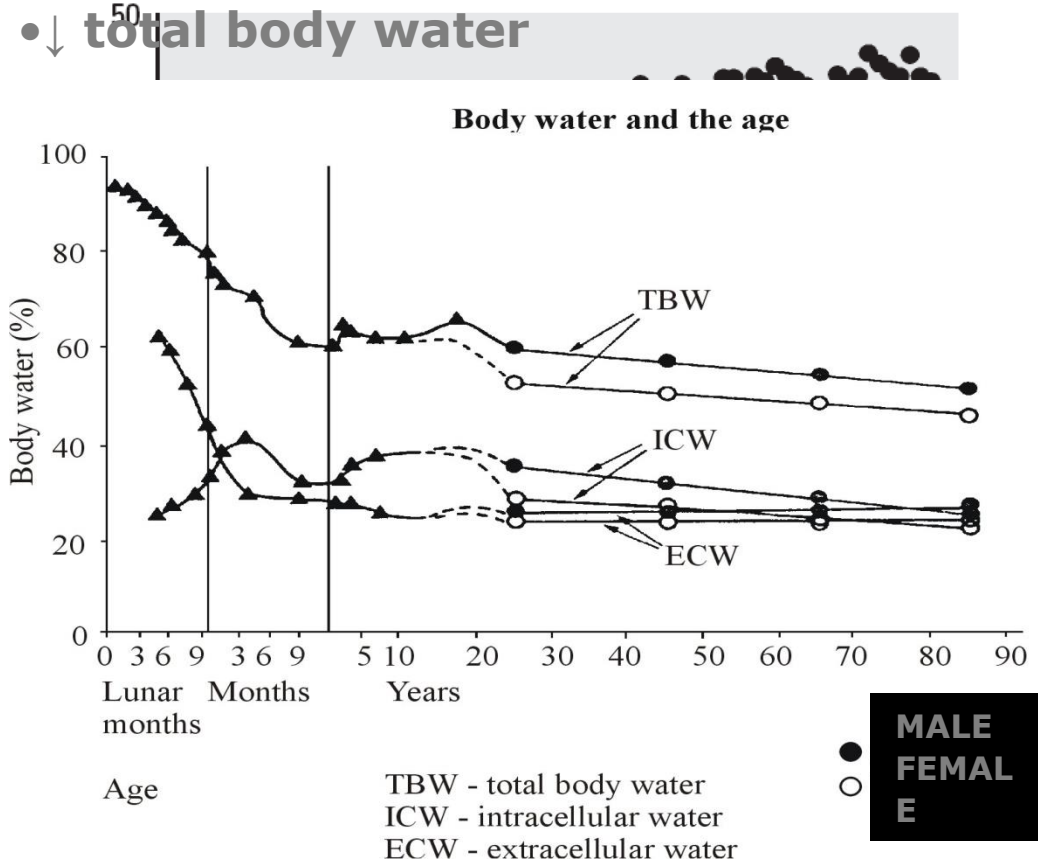
AGE-DEPENDENT CHANGES IN BODY COMPOSITION

Drug Metabolism Reviews, 2009; 41(2): 67–76

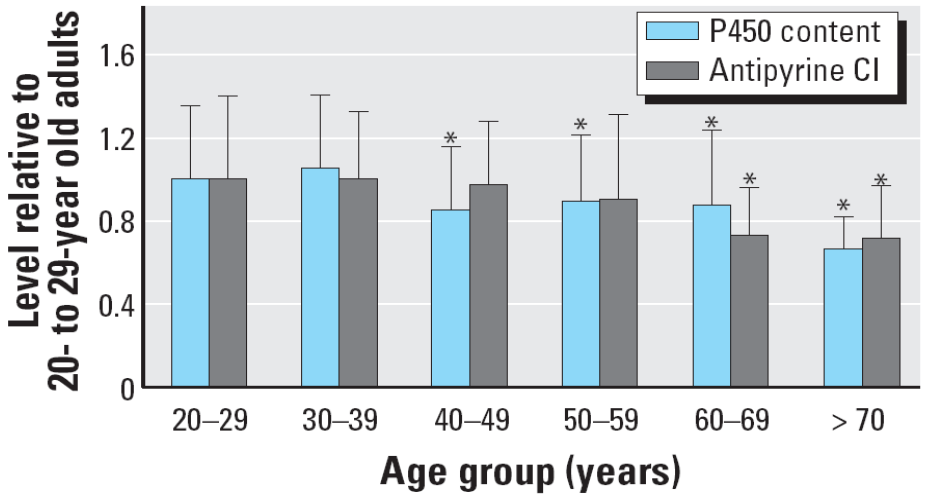
DISTRIBUTION

PHYSIOLOGIC CHANGES	PK EFFECT
•↑ ratio of adipose tissue to lean tissue	•↑ $t_{1/2}$ of lipophilic drugs
•↓ total body water	•↑ conc. of hydrophilic drugs

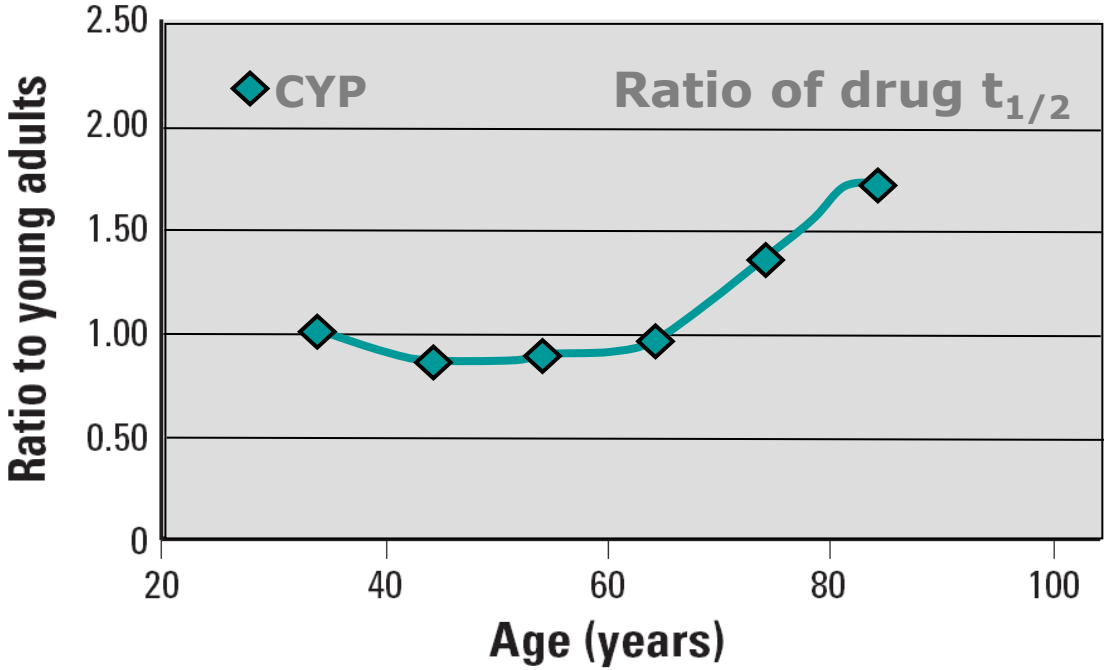


METABOLISM

PHYSIOLOGIC CHANGES



PK EFFECT

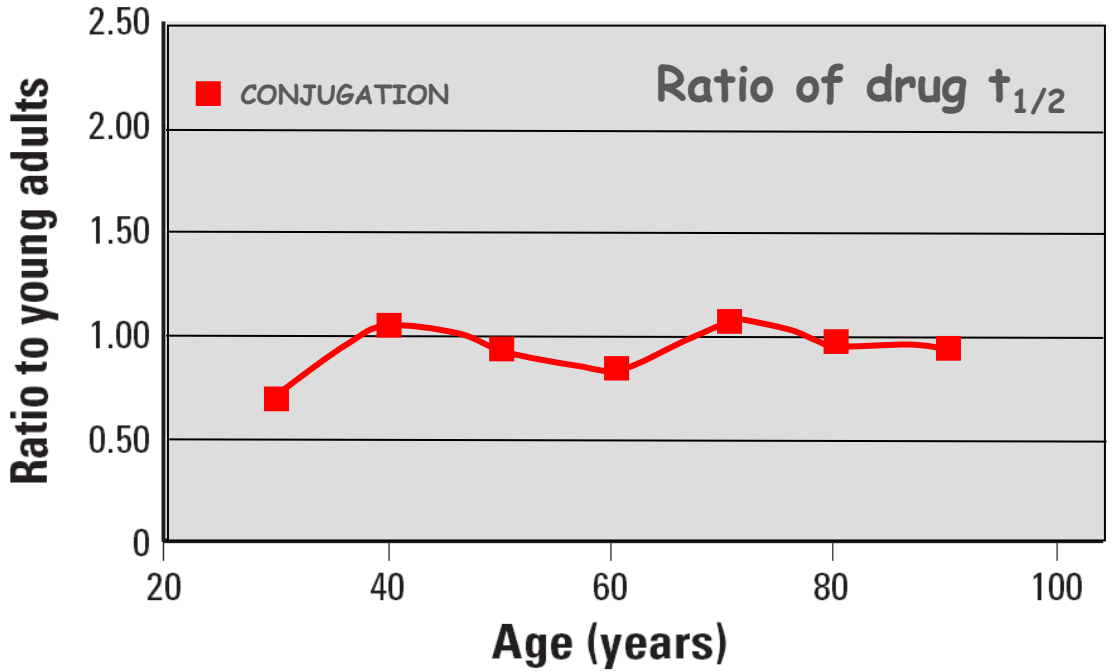


METABOLISM

- ↓ phase 1 enzyme (CYP-450) activity
- ↑ $t_{1/2}$ of drugs metabolized by CYP 450 enzymes

METABOLISM

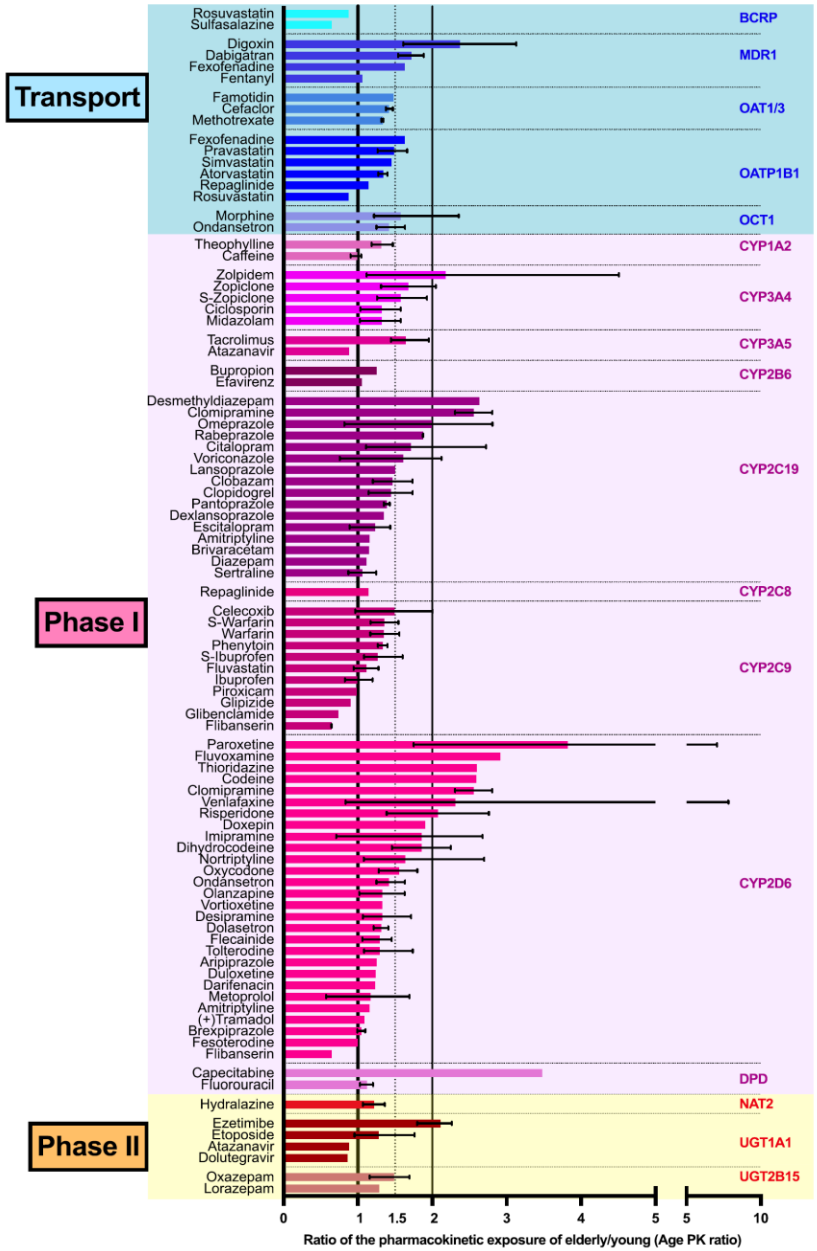
PHYSIOLOGIC CHANGES



METABOLISM

- ↓ phase 1 enzyme (CYP-450) activity
- ↑ $t_{1/2}$ of drugs metabolized by CYP 450 enzymes
- ≈ phase 2 enzyme (synthetic) activity

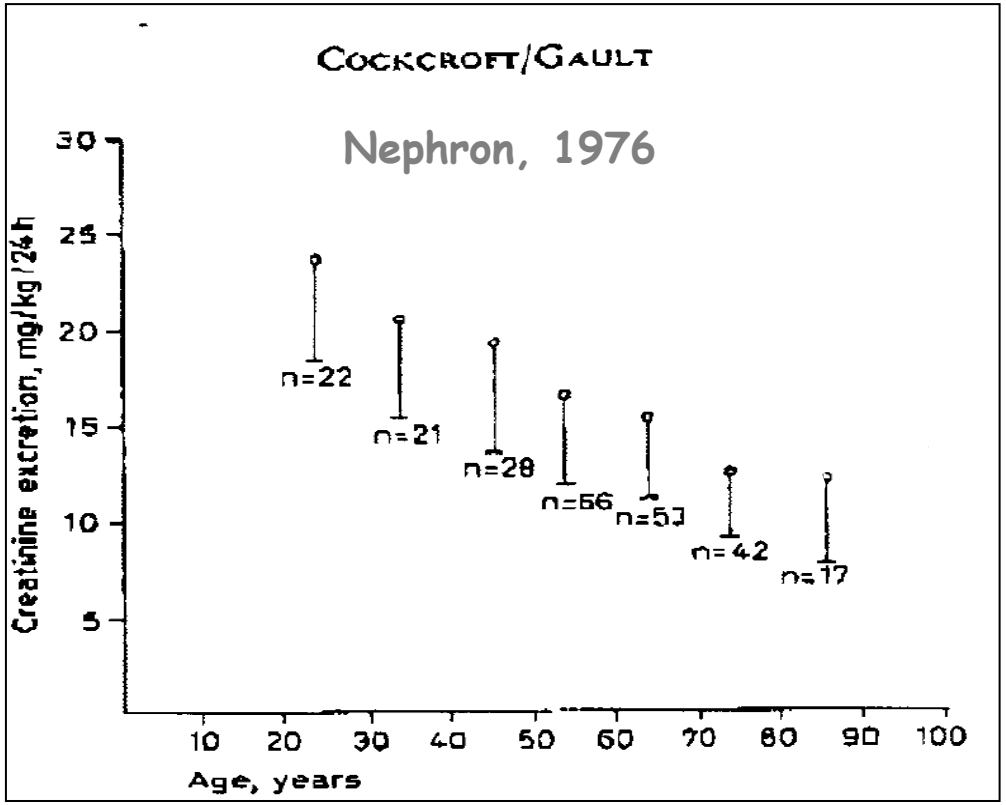
AGE-RELATED INCREASE IN THE SYSTEMIC EXPOSURE TO DRUGS (AGE PK RATIO)



Ducker CM et al. *Clin Pharmacol Ther*

ELIMINATION

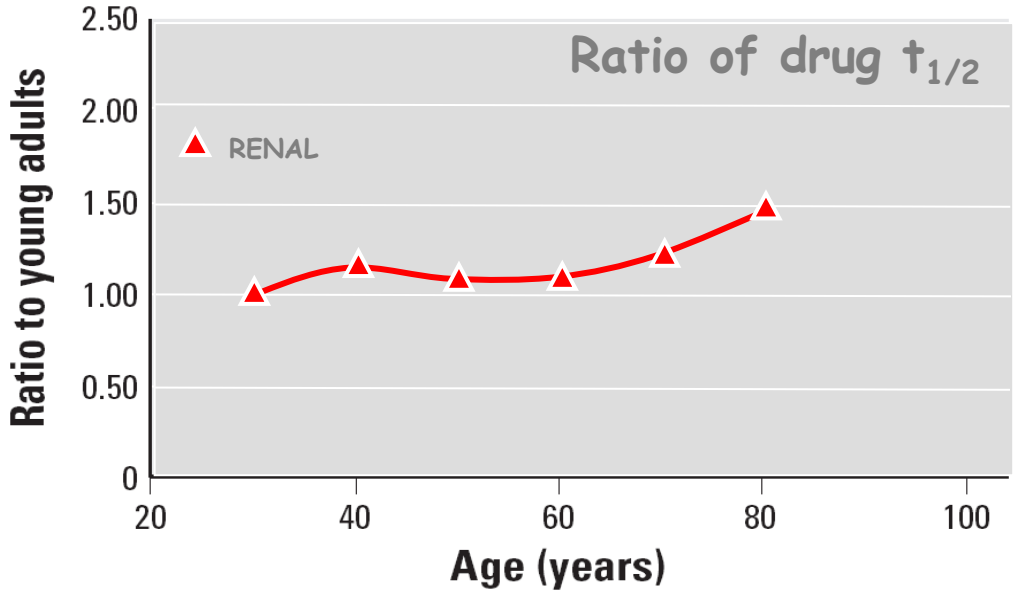
PHYSIOLOGIC CHANGES



RENAL ELIMINATION

- ↓ RBF and GFR

PK EFFECT



- ↑ $t_{1/2}$ of renally eliminated drugs

Population pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Cojutti P, Ramos-Martin V, Schiavon I, Rossi P, Baraldo M, Hope W, Pea F. ***Antimicrob Agents Chemother*** **2017;61(3):e02134-16**

Characteristic	Value
Patient demographic	
Age (yr [mean ± SD])	81.2 ± 7.8
Gender (male/female) [*n* (%)]	103/65 (61.3/38.7)
Body wt (kg) [median (IQR)]	70 (65–80)
$CrCL_{CKD\text{-}EPI}$ (ml/min/1.73 m^2)[a] [median (IQR)]	30.2 (18.2–50.2)
Indication for levofloxacin use [*n* (%)]	
Community-acquired pneumonia	77 (45.8)
Urinary tract infections	22 (13.1)
Chronic obstructive pulmonary disease	19 (11.3)
Fever of unknown origin	12 (7.1)
Sepsis of unknown origin	13 (7.7)
Intra-abdominal infections	11 (6.6)
Skin and soft tissue infections	8 (4.8)
Bone and joint infections	6 (3.6)
Patients with identified microbiological isolates [*n* (%)]	49 (29.2)
Levofloxacin treatment	
Duration of therapy (days) [median (IQR)]	10 (7–14)
Route of administration (oral/i.v.) [*n* (%)]	145/23 (86.3/13.7)
Clinical outcome [*n* (%)]	
Cured	95 (56.5)
Improved	28 (16.7)
Failed	26 (15.5)
Dead/modified antibiotic therapy	19 (11.3)

[a]At first TDM.

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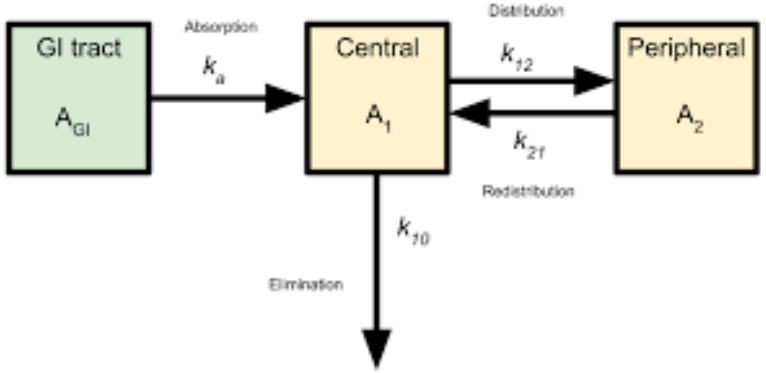

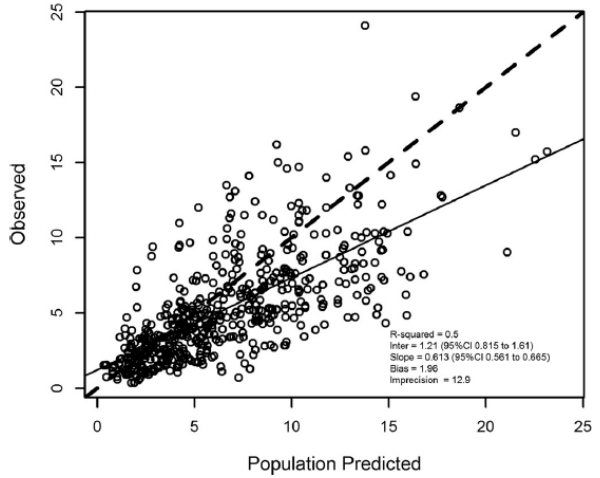

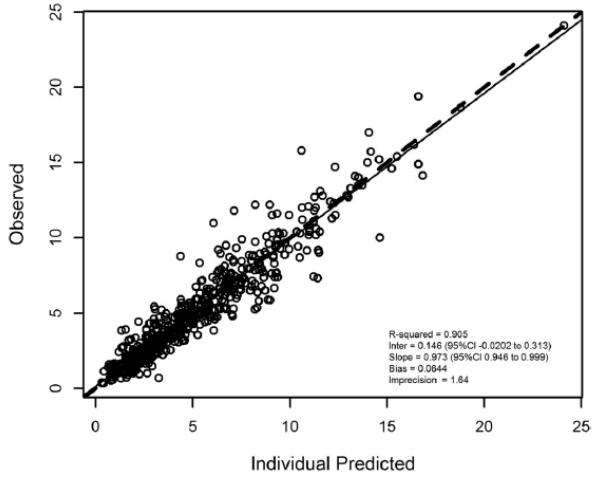

Population Pharmacokinetic Parameter Estimates:

Unit	k_a (h^{-1})	k_{cp} (h^{-1})	k_{pc} (h^{-1})	CL (liters/h)	V_c[a] (liters)	F_{os} (%)	T_{lag} (h)
Mean	16.15	0.63	1.77	2.53	52.95	0.83	1.47
SD	13.47	0.85	0.52	1.46	21.57	0.21	0.65
Coefficient of variation	83.41	133.52	29.47	57.84	40.73	24.83	43.95
Median	9.91	0.04	2.00	2.20	61.25	0.98	1.87

[a]V_c, volume of the central compartment.

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TABLE 3 Probabilities of achieving underexposure, normal target exposure, and overexposure with different levofloxacin dosing regimens in older patients in relation to different classes of renal function

Levofloxacin regimen (mg)	Probability[a]														
	0–19			20–39			40–59			60–79			>80		
	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160	<50	50–160	>160
125 every 48 h	91.8	8.2	0.0	99.8	0.2	0.0	99.8	0.2	0.0	99.9	0.1	0.0	100.0	0.0	0.0
250 every 48 h	48.5	50.5	1.0	91.4	8.6	0.0	99.0	1.0	0.0	99.6	0.4	0.0	99.9	0.1	0.0
500 every 48 h	6.4	77.2	16.4	32.2	67.0	0.8	81.6	18.4	0.0	95.7	4.3	0.0	97.2	2.8	0.0
750 every 48 h	1.4	53.9	44.7	7.2	86.2	6.6	42.2	57.2	0.6	79.6	20.0	0.4	89.0	11.0	0.0
500 every 24 h	2.3	50.3	47.4	5	81.3	13.7	22.2	76.0	1.8	59.2	40.1	0.7	78.7	21.0	0.3
750 every 24 h	1.1	17.1	81.8	1.7	51.3	47.0	5.8	82.8	11.4	23.2	73.1	3.7	50.3	47.6	2.1
500 every 12 h	0	3.6	96.4	0.2	12.3	87.5	0.1	39.0	60.9	1.5	70.1	28.4	2.8	82.8	14.4

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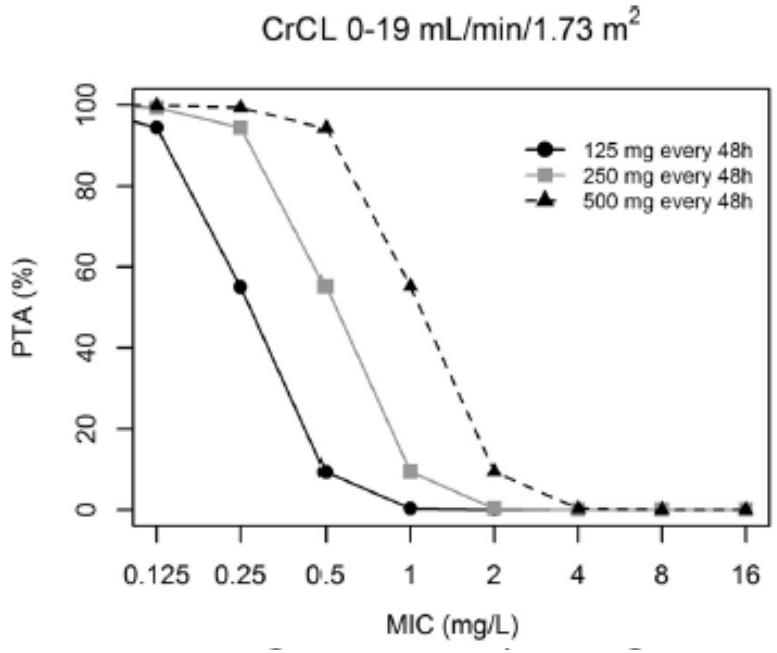
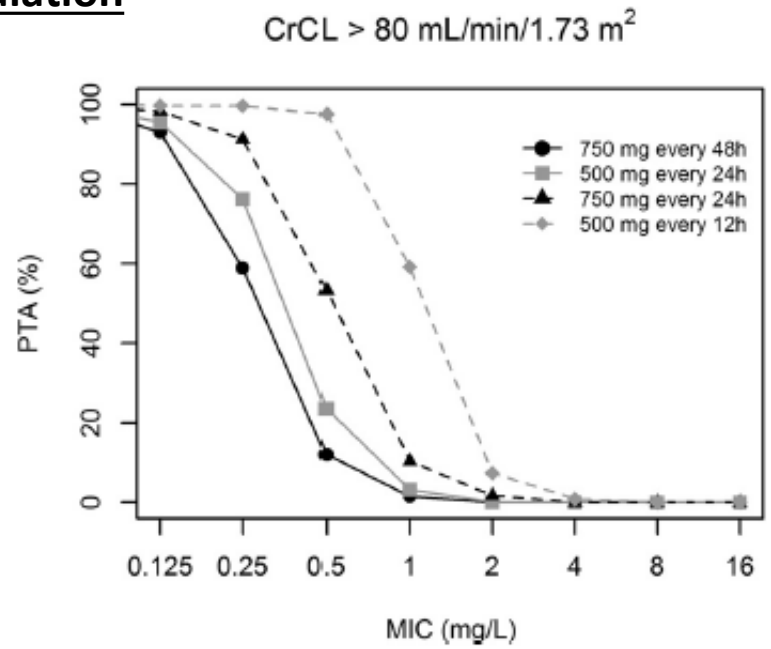
Monte Carlo Simulation





MIC (mg/liter)	Dosing regimen (mg) for class of renal function (ml/min/1.73 m²):				
	0–19	20–39	40–59	60–79	>80
0.125	125 every 48 h	500 every 48 h	500 every 48 h	500 every 48 h	750 every 48 h
0.25	250 every 48 h	500 every 48 h	500 every 48 h	750 every 48 h	750 every 24 h
0.5	500 every 48 h	750 every 48 h	500 every 24 h	750 every 24 h	500 every 12 h

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Class of renal function (ml/min/1.73 m²)	Levofloxacin dose (mg)	CFR			
		S. aureus	*H. influenzae*	*E. coli*	*P. aeruginosa*
0–19	125 every 48 h	59.89	99.66	82.06	16.48
	250 every 48 h	77.03	99.78	85.07	40.36
	500 every 48 h	81.59	99.85	87.34	62.24
20–39	500 every 48 h	79.22	99.79	85.80	47.07
	750 every 48 h	81.26	99.84	87.12	59.63
	500 every 24 h	81.49	99.85	87.43	63.08
40–59	500 every 48 h	71.28	99.73	83.45	25.81
	750 every 48 h	77.73	99.78	85.26	42.03
	500 every 24 h	79.42	99.81	86.16	50.72
	750 every 24 h	81.13	99.84	87.28	61.63
60–79	500 every 48 h	57.19	99.65	81.57	14.41
	750 every 48 h	70.61	99.73	83.52	26.68
	500 every 24 h	74.86	99.76	84.55	36.08
	750 every 24 h	79.16	99.81	86.20	51.22
>80	750 every 48 h	60.72	99.67	82.12	18.21
	500 every 24 h	67.91	99.71	83.27	25.50
	750 every 24 h	75.51	99.77	84.90	39.43
	500 every 12 h	81.67	99.85	87.52	63.81

Population pharmacokinetics of continuous infusion of piperacillin/tazobactam in very elderly hospitalized patients and considerations for target attainment against Enterobacterales and Pseudomonas aeruginosa

Cojutti P, Morandin E, Baraldo M, Pea F. ***Int J Antimicrob Agents*** **2021XXXX**

Total number of patients	141
Age (years)	85 (82–87)
Gender (M/F)	62/79 (44/56)
Weight (kg)	70 (63–83)
Height (cm)	170 (160–175)
BMI (kg/m^2)	25.4 (22.5–28.3)
Creatinine (mg/dL)	1.18 (0.88–1.75)
CL_{CR} (mL/min/1.73 m^2)	54.56 (34.28–72.26)
Type of infection	
Hospital-acquired pneumonia	56 (38.6)
Intra-abdominal infection	24 (16.6)
Sepsis/septic shock	19 (13.1)
Skin and soft tissue infection	13 (8.9)
Urinary tract infection	11 (7.6)
Bloodstream infection	10 (6.9)
Other	12 (8.3)
Admitting ward	
Medicine	80 (56.7)
Surgery	42 (29.8)
Intensive care unit	19 (13.5)
Plasma exposure at first TDM assessment	
Underexposure	4 (2.8)
Optimal exposure	33 (23.4)
Overexposure	104 (73.8)
Piperacillin/tazobactam treatment	
Median dose (g daily)	9 (9–18)
Piperacillin Css (mg/L)	73.9 (52.1–107.0)
No. of TDM assessments per patient	1 (1–2)
Duration of optimized therapy (days)	4 (3–7)

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Cojutti P, Morandin E, Baraldo M, Pea F. ***Int J Antimicrob Agents*** **2021XXXX**

Predictive performance of the population pharmacokinetic models for continuous infusion piperacillin/tazobactam.

Model type	OFV	AIC	BIC	Linear regression of observed vs. predicted concentrations		
				R^2	Bias	Imprecision
Base models						
Linear	2078	2084	2094	0.81	-0.13	0.58
Michaelis–Menten	2138	2146	2159	0.96	0.05	1.00
Parallel linear/Michaelis–Menten	2015	2025	2042	0.94	0.23	1.95
Final model						
Parallel linear/Michaelis–Menten (with CL_{CR} as descriptor of CL_{ns})	1953	1965	1985	0.93	0.34	1.72

Population pharmacokinetics of continuous infusion of piperacillin/tazobactam in very elderly hospitalized patients and considerations for target attainment against Enterobacterales and Pseudomonas aeruginosa

Cojutti P, Morandin E, Baraldo M, Pea F. ***Int J Antimicrob Agents*** **2021XXXX**

Percentage probability of causing piperacillin/tazobactam overexposure (defined as Css > 157.2 mg/L) with incremental dosages of continuous infusion (CI) piperacillin/tazobactam in elderly patients with various degrees of renal function.

Piperacillin/tazobactam dosages (g daily by CI)	Classes of CL_{CR} (mL/min/1.73 m^2)			
	0–19	20–39	40–59	60–79
2.25	**0.3**	**0.0**	**0.0**	**0.0**
4.5	**3.7**	**0.5**	**0.5**	**0.3**
6.75	12.1	**2.3**	**1.2**	**1.1**
9	25.7	**6.0**	**3.1**	**2.0**
11.25	42.2	14.5	**6.8**	**5.1**
13.5	57.6	27.3	12.1	**8.7**
15.75	71.5	40.8	20.8	13.5
18	83.7	55.1	29.1	20.5

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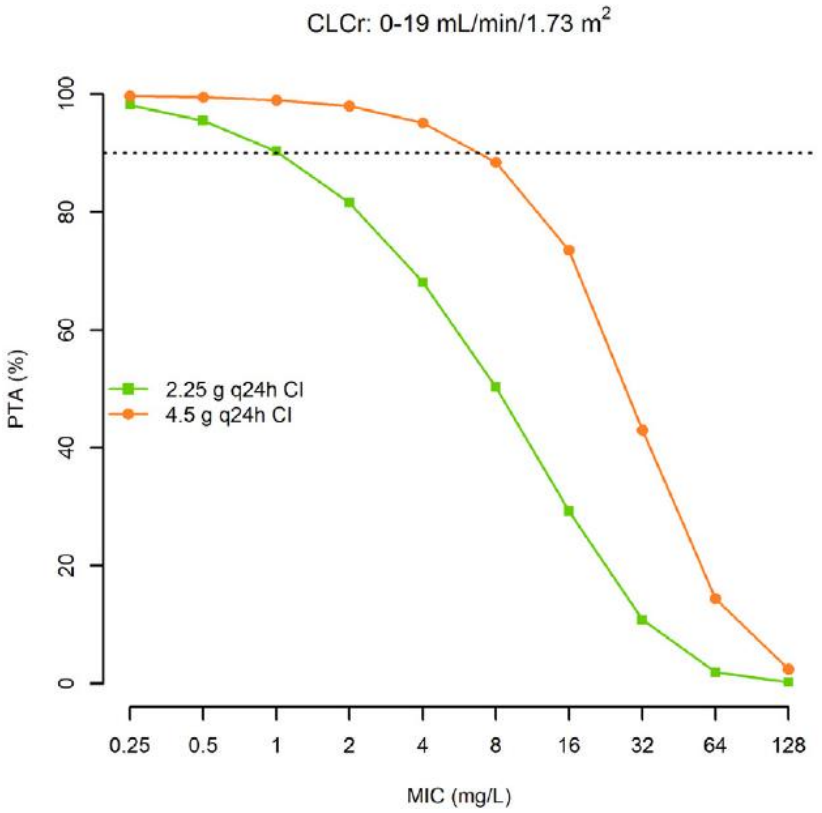
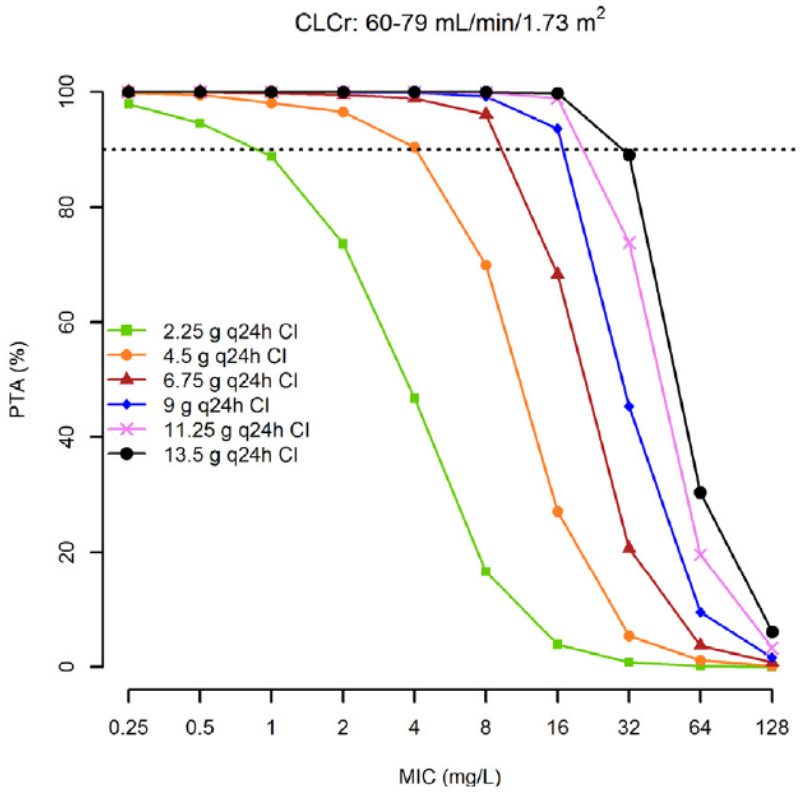
Cojutti P, Morandin E, Baraldo M, Pea F. ***Int J Antimicrob Agents*** **2021XXXX**

Probability of target attainment (PTA) of free plasma steady-state concentration/minimum inhibitory concentration (MIC) ≥1 for the piperacillin/tazobactam per- missible dosages in relation to different classes of renal function and susceptibility of the invading pathogen. Horizontal broken line identifies the threshold for optimal PTA (≥90%). CL CR , creatinine clearance





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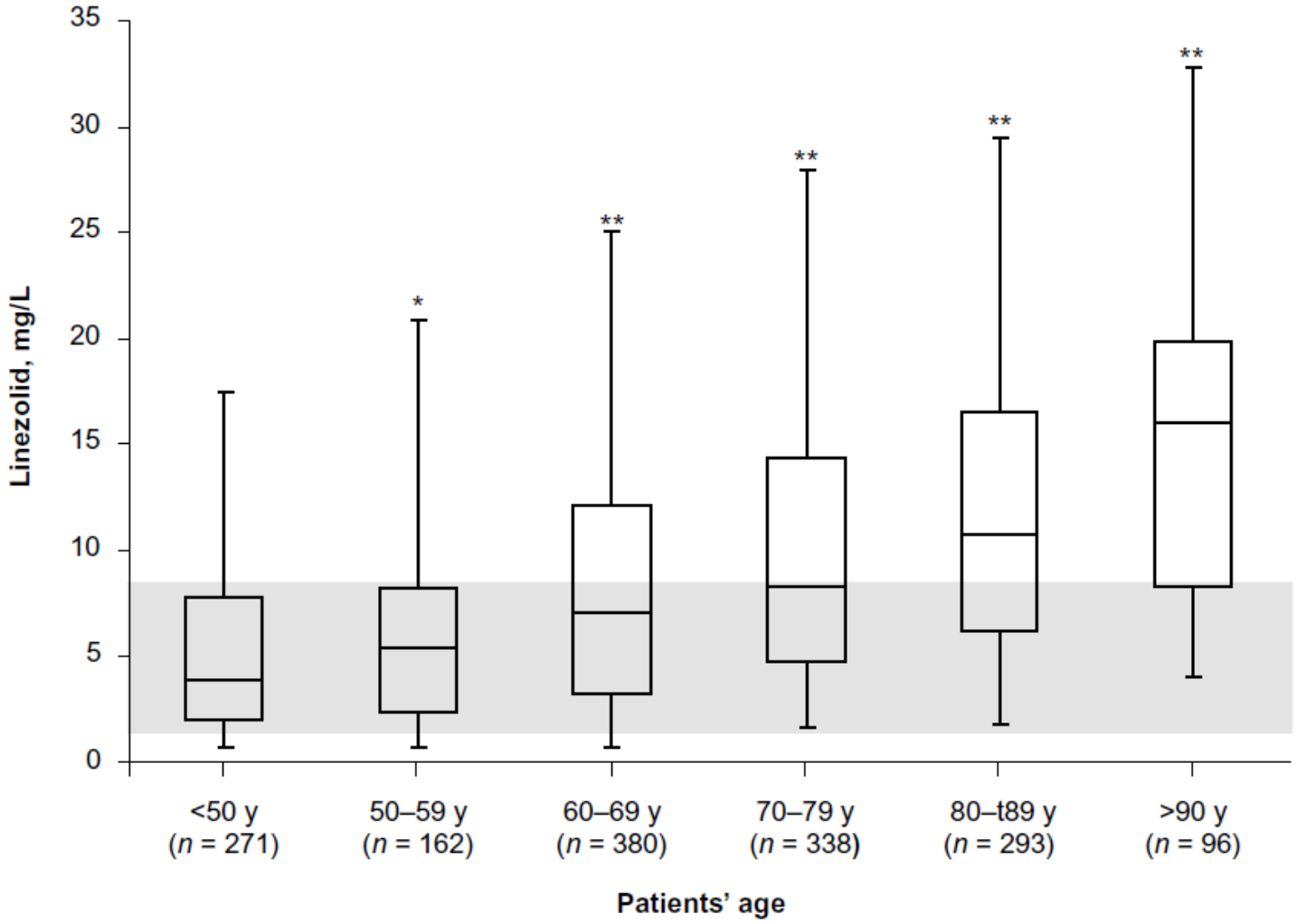
CI piperacillin/tazobactam dosages at classes of renal function	*E. coli*		*K. pneumoniae*		*E. cloacae*		*P. mirabilis*		*P. aeruginosa*	
	*f*Css/MIC ≥4	*f*Css/MIC ≥1	*f*Css/MIC ≥4	*f*Css/MIC ≥1	*f*Css/MIC ≥4	*f*Css/MIC ≥1	*f*Css/MIC ≥4	*f*Css/MIC ≥1	*f*Css/MIC ≥4	*f*Css/MIC ≥1
CL_{CR}: 0–19 mL/min/1.73 m^2										
2.5	50.82	72.78	36.07	64.39	36.55	60.39	79.31	**93.31**	19.98	47.56
4.5	81.99	**93.41**	67.12	84.33	62.51	77.97	**95.57**	**98.42**	46.63	72.87
CL_{CR}: 20–39 mL/min/1.73 m^2										
2.5	41.15	74.94	26.08	59.63	28.45	56.48	76.48	**92.89**	11.56	40.49
4.5	76.29	**91.70**	58.69	81.36	56.22	74.15	**94.27**	**98.03**	35.24	67.23
6.75	89.37	**95.68**	75.89	87.78	69.16	80.88	**97.62**	**99.18**	55.03	78.46
9	**92.82**	**96.94**	81.97	**90.00**	73.75	84.69	**98.49**	**99.46**	65.41	82.89
CL_{CR}: 40–59 mL/min/1.73 m^2										
2.5	33.47	72.07	19.41	55.46	22.61	53.33	73.34	**92.35**	7.68	34.70
4.5	71.08	**90.67**	50.99	79.38	50.72	72.11	**93.58**	**97.82**	26.47	63.09
6.75	87.27	**94.97**	71.55	86.56	66.19	78.73	**97.26**	**98.99**	47.43	75.75
9	**91.47**	**96.39**	79.11	88.97	71.52	82.34	**98.23**	**99.30**	59.50	80.60
11.25	**93.17**	**97.02**	82.57	**90.15**	74.17	84.90	**98.54**	**99.48**	66.33	83.25
CL_{CR}: 60–79 mL/min/1.73 m^2										
2.5	26.89	69.72	14.38	51.34	17.92	50.73	70.69	**91.67**	5.64	30.15
4.5	66.25	89.46	45.13	77.37	46.26	70.41	**92.58**	**97.65**	21.03	59.56
6.75	84.73	**94.37**	66.72	85.38	63.03	77.29	**96.92**	**98.85**	40.50	73.11
9	**90.09**	**95.93**	76.27	88.13	69.50	80.75	**98.00**	**99.18**	54.29	78.71
11.25	**92.30**	**96.67**	80.70	89.50	72.74	83.40	**98.37**	**99.38**	62.45	81.79
13.5	**93.30**	**97.08**	82.84	**90.32**	74.46	85.22	**98.57**	**99.49**	66.87	83.59

Supra-therapeutic Linezolid Trough Concentrations in Elderly Patients: A Call for Action?

Cattaneo D et al. *Clin Pharmacokinet.* 2021;60:603-9



n=1540 linezolid Cmin
Cmin: 9.3 ± 8.8 mg/L
Range: 0.5 – 84 mg/L

overall increment of 30% per decade of age.

Supra-therapeutic Linezolid Trough Concentrations in Elderly Patients: A Call for Action?

Cattaneo D et al. *Clin Pharmacokinet.* 2021;60:603-9

Key Points

The majority of elderly patients treated with the in-label dose of linezolid (600 mg twice daily) had trough drug concentrations largely exceeding the upper safety threshold concentration.

A potential association between the female sex and the risk of linezolid overexposure was also observed.

Reduced linezolid dosing schemes should be potentially considered in selected "low-risk" elderly patients, ideally guided by therapeutic drug monitoring.

Polytherapy and the risk of potentially inappropriate prescriptions (PIPs) among elderly and very elderly patients in three different settings (hospital, community, long-term care facilities) of the Friuli Venezia Giulia region, Italy: are the very elderly at higher risk of PIPs?

Cojutti P, Arnoldo L, Cattani G, Brusaferro S, Pea F. *Pharmacoepidemiol Drug Saf* 2016;25(9):1070-8

	Hospital ($n = 528$)	GPs ($n = 527$)	LTCFs ($n = 527$)	p
Demographics				
Sex (male/female), n (%)	267/261 (50.6/49.4)*	225/303 (42.7/57.5)*°	156/372 (29.6/70.6)†°	<0.001
Age (years), median (IQR)	81 (75–87)*†	76 (71–82)*°	85 (79–89)†°	<0.001
Elderly, n (%)	209 (39.6)*†	329 (62.4)*°	121 (22.9)†°	<0.001
Very elderly, n (%)	319 (60.4)*†	198 (37.6)*°	406 (77.1)†°	<0.001
Number of per patient underlying diseases, median (IQR)	3 (2–4)*	4 (2–5)*°	3 (2–4)°	<0.001
Drug prescription pattern				
Number of patients with polypharmacy, n (%)	389 (73.7)*	304 (57.7)*°	370 (70.2)°	<0.001
Number of patients with hyperpolypharmacy, n (%)	80 (15.2)*	51 (9.7)*°	82 (15.6)°	0.008
Number of drugs per patient, median (IQR)	6 (4–8)*	5 (3–7)*°	6 (4–8)°	<0.001
PIP pattern				
Total number of PIPs, n (% of total prescriptions)	307 (9.1)†	292 (10.2)°	553 (16.6)†°	<0.001
Number of patients with:				
1 PIP, n (%)	159 (30.1)	126 (23.9)	159 (30.2)	0.035
≥2 PIPs, n (%)	60 (11.4)†	69 (13.1)°	155 (29.4)†°	<0.001

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	1 PIP		≥2 PIPs	
Variables	OR (95%CI)	*p*	OR (95%CI)	*p*
Age (years)				
65–79	1	—	1	—
>79	1.416 (1.105–1.813)	0.006	1.372 (1.025–1.837)	0.033
Sex				
Male	1	—	1	—
Female	1.071 (0.835–1.376)	0.588	1.629 (1.202–2.207)	0.002
Drug prescriptions				
Normal	1	—	1	—
Polypharmacy	3.019 (2.267–4.020)	<0.001	2.322 (1.657–3.253)	<0.001
Hyperpolypharmacy	4.964 (3.283–7.506)	<0.001	6.744 (4.318–10.534)	<0.001
Underlying diseases	1.207 (0.832–1.752)	0.322	1.130 (0.732–1.746)	0.581
CKD	1.153 (0.849–1.567)	0.361	1.445 (1.029–2.027)	0.033

Polytherapy and the risk of potentially inappropriate prescriptions (PIPs) among elderly and very elderly patients in three different settings (hospital, community, long-term care facilities) of the Friuli Venezia Giulia region, Italy: are the very elderly at higher risk of PIPs?

Cojutti P, Arnoldo L, Cattani G, Brusaferro S, Pea F. *Pharmacoepidemiol Drug Saf* 2016;25(9):1070-8

Medication	PIPs			p
	Hospital ($n = 307$)	GP ($n = 292$)	LTCF ($n = 553$)	
ID				
Benzodiazepines	75 (24.4)*	114 (39.0)*°	144 (26.0)°	<0.001
Antipsychotics, first and second generation	54 (17.6)*†	15 (5.1)*°	149 (26.9)†°	<0.001
Amiodarone	39 (12.7)*†	15 (5.1)*	13 (2.4)†	<0.001
Apha 1-blockers	24 (7.8)†	35 (12.0)°	13 (2.4)†°	<0.001
Antiarrhythmic drugs	16 (5.2)	29 (9.9)°	16 (2.9)°	<0.001
Digoxin > 0.125 mg/d	12 (3.9)†	5 (1.7)	4 (0.7)†	0.004
Antithrombotics	11 (3.6)*	24 (8.2)*°	10 (1.8)°	<0.001
Alpha agonists, central	8 (2.6)	3 (1.0)	10 (1.8)	0.353
Zolpidem	7 (2.3)	9 (3.1)	14 (2.5)	0.818
Barbiturates	4 (1.3)†	3 (1.0)°	30 (5.4)†°	<0.001
Metoclopramide	4 (1.3)	0 (0)	5 (0.9)	0.175
Tertiary TCAs, alone or in combination	3 (1.0)	3 (1.0)	8 (1.4)	0.788
Spironolactone > 25 mg/d	2 (0.7)	1 (0.3)	1 (0.2)	0.532
Nitrofurantoin	2 (0.7)	0 (0)	3 (0.5)	—
Skeletal muscle relaxants	2 (0.7)	0 (0)	1 (0.2)	—
Estrogens with or without progestins	1 (0.3)	2 (0.7)	0 (0)	—
Anticholinergics	1 (0.3)	0 (0)	5 (0.9)	—
Ergot mesylates	0 (0)	1 (0.3)	0 (0)	—
DD				
Dementia and cognitive impairment	30 (9.8)†	17 (5.8)°	121 (21.9)†°	<0.001
Heart failure	10 (3.3)†	5 (1.7)	2 (0.4)†	0.003
Chronic seizures or epilepsy	1 (0.3)	0 (0)	0 (0)	—
Chronic kidney disease (stages IV and V)	1 (0.3)	4 (1.4)	0 (0)	—
Parkinson's disease	0 (0)	3 (1.0)	4 (0.7)	—
History of gastric or duodenal ulcers	0 (0)	4 (1.4)	0 (0)	—

Antimicrobial treatement of bacterial infections in frail elderly patients: the difficult balance between efficacy, safety and tolerability

Pea F. ***Current Opin Pharmacol. 2*****015;24:18-22**

Antimicrobials - Warfarin

Antimicrobials - Antidiabetics

Macrolide - Statins

Antimicrobials - renal excretion

Concurrent Use of Warfarin and Antibiotics and the Risk of Bleeding in Older Adults

Baillargeon J et al. *Am J Med* 2012; 125: 183-189

BASELINE CHARACTERISTICS FOR CASES AND MATCHED CONTROLS

Characteristic	Matched Controls[a] n (%)	Cases n (%)	*P* Value†
All	2394 (100)	798 (100)	
Indication for warfarin use in 2007			
Atrial fibrillation	1302 (54.4)	434 (54.4)	1.000
Other	597 (24.9)	199 (24.9)	
Prosthetic heart valve	207 (8.7)	69 (8.7)	
Stroke	87 (3.6)	29 (3.6)	
Venous thromboembolism	201 (8.4)	67 (8.4)	
Multiple indications for warfarin use			
N	1890 (79.0)	614 (76.9)	.233
Y	504 (21.0)	184 (23.1)	
Age at 2008, years			
66-70	247 (10.3)	86 (10.8)	.973
71-75	465 (19.4)	152 (19.1)	
76-80	536 (22.4)	171 (21.4)	
81-85	539 (22.5)	183 (22.9)	
>85	607 (25.4)	206 (25.8)	
Race			
White	2109 (88.1)	698 (87.5)	.517
Black	168 (7.0)	61 (7.6)	
Hispanic	83 (3.5)	23 (2.9)	
Other/unknown	34 (1.4)	16 (2.0)	
Sex			
Male	837 (35.0)	279 (34.5)	1.000
Female	1557 (65.0)	519 (65.0)	
Charlson Comorbidity Index[b]			
0	1129 (47.2)	319 (40.0)	<.001
1	601 (25.1)	173 (21.7)	
2	319 (13.3)	128 (16.0)	
3	172 (7.2)	78 (9.8)	
≥4	173 (7.2)	100 (12.5)	
Resided in a nursing home within 90 days before event/index date			
N	2160 (90.2)	623 (86.3)	<.002
Y	234 (9.8)	104 (13.7)	

Case-control study nested within a cohort of 38,762 patients (Medicare part D prescription drug program) aged 65 years and older who were continuous warfarin users

Cases were defined as patients hospitalized for a primary diagnosis of bleeding

1:3 control subjects on age, race, sex, and indication for warfarin

Concurrent Use of Warfarin and Antibiotics and the Risk of Bleeding in Older Adults

Baillargeon J et al. *Am J Med* 2012; 125: 183-189

ASSOCIATION BETWEEN SPECIFIC ANTIBIOTIC AGENT EXPOSURE AND HOSPITALIZATION FOR BLEEDING

Antibiotic Drug	Matched Controls[a] n (%)	Cases n (%)	Univariate OR (95% CI)	Multivariable[b] OR (95% CI)
Azole antifungals	8 (0.33)	17 (2.13)	6.49 (2.79-15.10)	4.57 (1.90-11.03)
Macrolides	35 (1.46)	24 (3.01)	2.09 (1.24-3.54)	1.86 (1.08-3.21)
Quinolones	56 (2.34)	40 (5.01)	2.20 (1.46-3.33)	1.69 (1.09-2.62)
Cotrimoxazole	22 (0.92)	22 (2.76)	3.06 (1.68-5.55)	2.70 (1.46-5.05)
Penicillins	50 (2.09)	31 (3.88)	1.89 (1.20-2.99)	1.92 (1.21-2.07)
Cephalosporins	39 (1.63)	36 (4.51)	2.85 (1.80-4.52)	2.45 (1.52-3.95)

Statin toxicity from macrolide antibiotic co-prescription: a population-based cohort study

Patel AM et al. Ann Intern Med 2013;158:869-76

Table 3. Baseline Characteristics*

Characteristic	Clarithromycin and Erythromycin (*n* = 75 858)†	Azithromycin (*n* = 68 478)	Standardized Difference‡	*P* Value
Demographic				
Mean age (SD), *y*	74 (6)	74 (6)	0.01	0.73
Women	40 130 (52.9)	36 323 (53.0)	0.01	0.59
Income quintile§				<0.001
1 (low)	15 858 (20.9)	13 686 (20.0)	0.03	
2	16 481 (21.7)	14 408 (21.0)	0.02	
3 (middle)	14 982 (19.8)	13 594 (19.9)	0.01	
4	14 391 (19.0)	13 268 (19.4)	0.01	
5 (high)	13 917 (18.3)	13 272 (19.4)	0.03	
Index date				<0.001
2003–2004	20 972 (27.6)	19 179 (28.0)	0.01	
2005–2006	23 028 (30.4)	20 146 (29.4)	0.02	
2007–2008	18 703 (24.7)	16 841 (24.6)	0.01	
2009–2010	13 155 (17.3)	12 313 (18.0)	0.02	
Comorbid condition				
Chronic kidney disease‖	6210 (8.2)	5530 (8.1)	0.01	0.44
Cerebrovascular disease	3189 (4.2)	2765 (4.0)	0.01	0.113
Peripheral vascular disease	2101 (2.8)	1844 (2.7)	0.01	0.37
Coronary artery disease¶	39 974 (52.6)	36 995 (54.0)	0.03	<0.001
Congestive heart failure	12 652 (16.7)	11 776 (17.2)	0.01	0.009
Systemic malignancy	21 875 (28.8)	19 955 (29.1)	0.01	0.20
Statin characteristic				
Type				0.002
Atorvastatin	55 027 (72.5)	50 111 (73.2)	0.02	
Simvastatin	18 421 (24.3)	16 369 (23.9)	0.01	
Lovastatin	2410 (3.2)	1998 (2.9)	0.02	
Dose				0.26
High-dose statin**	30 296 (40.0)	27 550 (40.2)	0.01	
Low-dose statin††	45 562 (60.0)	40 928 (59.8)	0.01	
Medication use in preceding year				
Oral hypoglycemic or insulin	20 367 (26.8)	17 819 (26.0)	0.02	<0.001
β-Blockers	29 318 (38.6)	27 008 (39.4)	0.02	0.002
Verapamil or diltiazem	7941 (10.5)	7206 (10.5)	0.01	0.73
Use of other calcium-channel blockers	18 521 (24.4)	16 982 (24.8)	0.01	0.091
Potassium-sparing diuretics	3307 (4.4)	2992 (4.4)	0.01	0.93
Non–potassium-sparing diuretics	26 901 (35.5)	24 720 (36.1)	0.01	0.012
NSAIDs (excluding aspirin)	16 516 (21.8)	14 797 (21.6)	0.01	0.45
ACE inhibitor or ARB	49 017 (64.6)	44 323 (64.7)	0.01	0.67

population-based, retrospective cohort study of adults older than 65 years by using linked health care databases in Ontario, Canada

All older adults in Ontario with ongoing continuous prescriptions for statins metabolized by CYP3A4 (atorvastatin, simvastatin, or lovastatin) were selected.

Patients were followed for 30 days after the index date to assess outcomes.
The primary outcome was hospitalization with rhabdomyolysis.
The 3 secondary outcomes were hospitalization with AKI, hospitalization with hyperkalemia, and all-cause mortality.

Statin toxicity from macrolide antibiotic co-prescription: a population-based cohort study

Patel AM et al. *Ann Intern Med* 2013;158:869-76

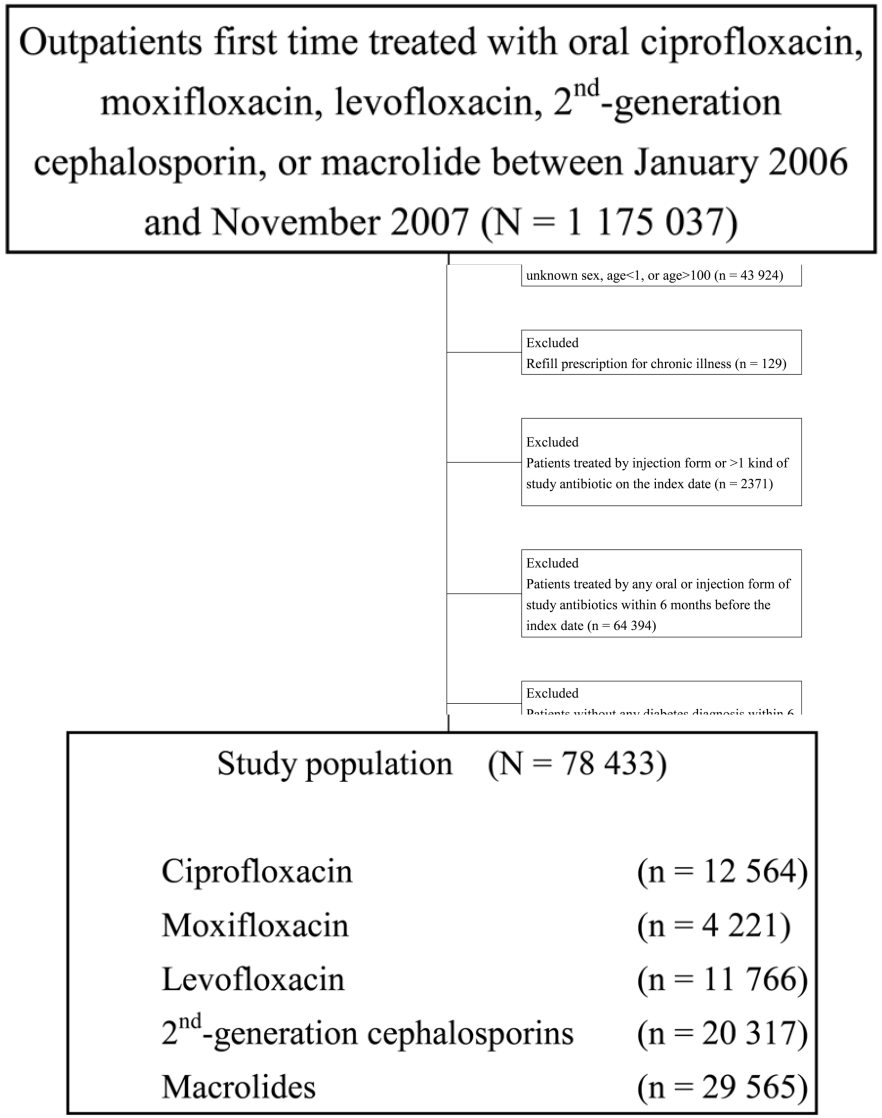
Table 4. Outcomes Assessed Using Hospital-Based Diagnosis Codes*

Outcome	Events, *n* (%)†		Absolute Risk Difference (95% CI), %	Number Needed to Harm (95% CI)‖	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)¶
	Clarithromycin and Erythromycin (*n* = 75 858)‡	Azithromycin (*n* = 68 478)§				
Rhabdomyolysis	24 (0.03)	10 (0.01)	0.02 (0.01 to 0.03)	5870 (3068 to 67 758)	2.17 (1.04 to 4.53)	2.17 (1.03 to 4.52)
Acute kidney injury	347 (0.46)	176 (0.26)	0.20 (0.14 to 0.26)	499 (382 to 718)	1.78 (1.49 to 2.14)	1.83 (1.52 to 2.19)
Hyperkalemia	61 (0.08)	42 (0.06)	0.02 (−0.01 to 0.05)	–	1.31 (0.89 to 1.94)	1.32 (0.89 to 1.94)
All-cause mortality	529 (0.70)	306 (0.45)	0.25 (0.17 to 0.33)	399 (304 to 577)	1.57 (1.36 to 1.80)	1.57 (1.37 to 1.82)

Implication

Consider prescribing an antibiotic other than clarithromycin or erythromycin when the patient is taking a statin.

Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin or moxifloxacin in Taiwan
Chou HW et al. *Clin Infect Dis* 2013;87:971-80



In a population-based inception cohort study of diabetic patients covering the period from January 2006 to November 2007, outpatient new users of levofloxacin, ciprofloxacin, moxifloxacin, cephalosporins, and macrolides orally were identified.

Study events were defined as emergency department visits or hospitalization for dysglycemia within 30 days following the initiation of antibiotic therapy. Results were analyzed with adjusted multinomial propensity score.

Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin or moxifloxacin in Taiwan

Chou HW et al. *Clin Infect Dis* 2013;87:971-80

Table 2. Risk of Hyperglycemia and Hypoglycemia Associated With Antibiotic Use in Each Group of Antibiotics

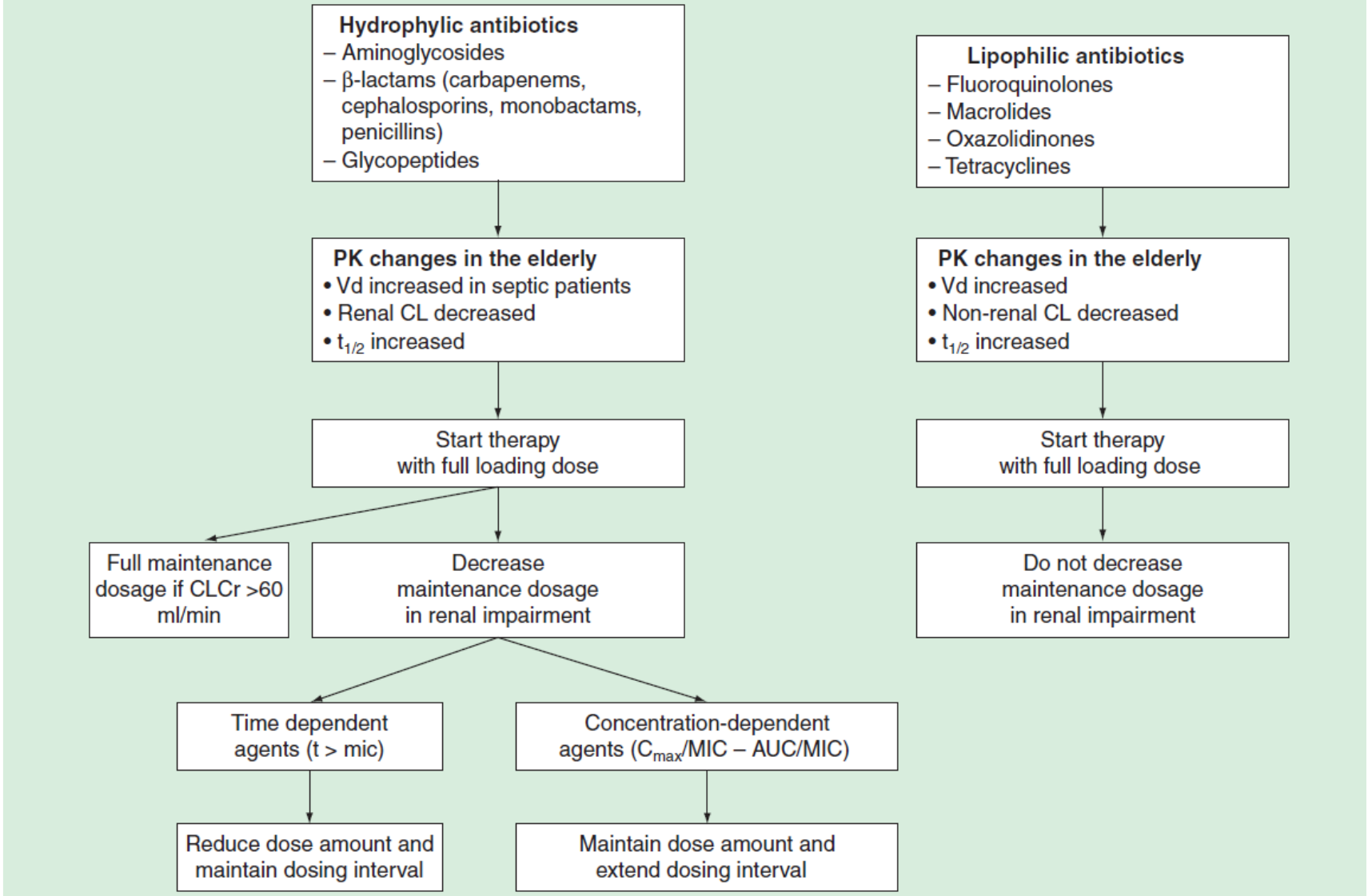
Antibiotic Group	No.	Events	Incidence (‰)	Time to Event, d, Mean ± SD	Crude OR (95% CI)	Adjusted OR (95% CI)
Hyperglycemia						
Macrolides	29 565	48	1.62	7.92 ± 9.46	1.00	1.00
Cephalosporins	20 317	42	2.07	8.17 ± 9.23	1.27 (.84–1.93)	1.36 (.87–2.13)
Moxifloxacin	4221	29	6.87	3.90 ± 7.20	4.25 (2.68–6.75)	2.48 (1.50–4.12)
Levofloxacin	11 766	46	3.91	6.22 ± 8.49	2.41 (1.61–3.62)	1.75 (1.12–2.73)
Ciprofloxacin	12 564	50	3.98	5.60 ± 8.12	2.46 (1.65–3.65)	1.87 (1.20–2.93)
Hypoglycemia						
Macrolides	29 565	110	3.72	6.32 ± 6.81	1.00	1.00
Cephalosporins	20 317	65	3.20	7.72 ± 9.83	0.90 (.63–1.17)	0.94 (.68–1.32)
Moxifloxacin	4221	42	9.95	7.02 ± 9.51	2.69 (1.88–3.85)	2.13 (1.44–3.14)
Levofloxacin	11 766	109	9.26	7.12 ± 8.48	2.50 (1.92–3.27)	1.79 (1.33–2.42)
Ciprofloxacin	12 564	99	7.88	9.16 ± 9.40	2.12 (1.62–2.79)	1.46 (1.07–2.00)

- Fluoroquinolones were associated with higher risk of hyperglycemia and hypoglycemia, compared to macrolides and cephalosporins in diabetics.
- The risk varied according to the type of fluoroquinolone.
- Moxifloxacin as the drug associated with the highest risk of hypoglycemia,

Treatment options for community-acquired pneumonia in the elderly people

Petrosillo N. et al. *Expert Rev. Anti Infect. Ther*. 13(4), 473–485 (2015)

Pharmacokinetics of antimicrobials in the elderly people according to their chemical–physical properties



Treatment options for community-acquired pneumonia in the elderly people

Petrosillo N. et al. *Expert Rev. Anti Infect. Ther*. 13(4), 473–485 (2015)

Table 1. Renally cleared antimicrobials requiring adjustments of maintenance dosages in patients with renal impairment.

Drug	CLCr 30–60 ml/min	CLCr <30 ml/min
Time-dependent antimicrobials		
Cefepime	1g q8h	1 g q12h
Cefotaxime	1 g q8h	0.5–1 g q12h
Ceftazidime	1 g q8h	0.5–1 g q12h
Clarithromycin	0.5 g q12h	0.25 g q12h
Imipenem	0.25 g q6h	0.125 g q6h
Meropenem	0.25 g q6h	0.125 g q6h
Piperacillin/tazobactam	2.25 g q6h	2.25 g q8–12h
Vancomycin	3.75 mg/kg q6h	3.75 mg/kg q12h
Concentration-dependent antimicrobials		
Amikacin	15 mg/kg q48h	15 mg/kg q72h
Gentamycin	3–5 mg/kg q48h	3–5 mg/kg q72h
Levofloxacin	0.5 g q24h	0.5 g q48h

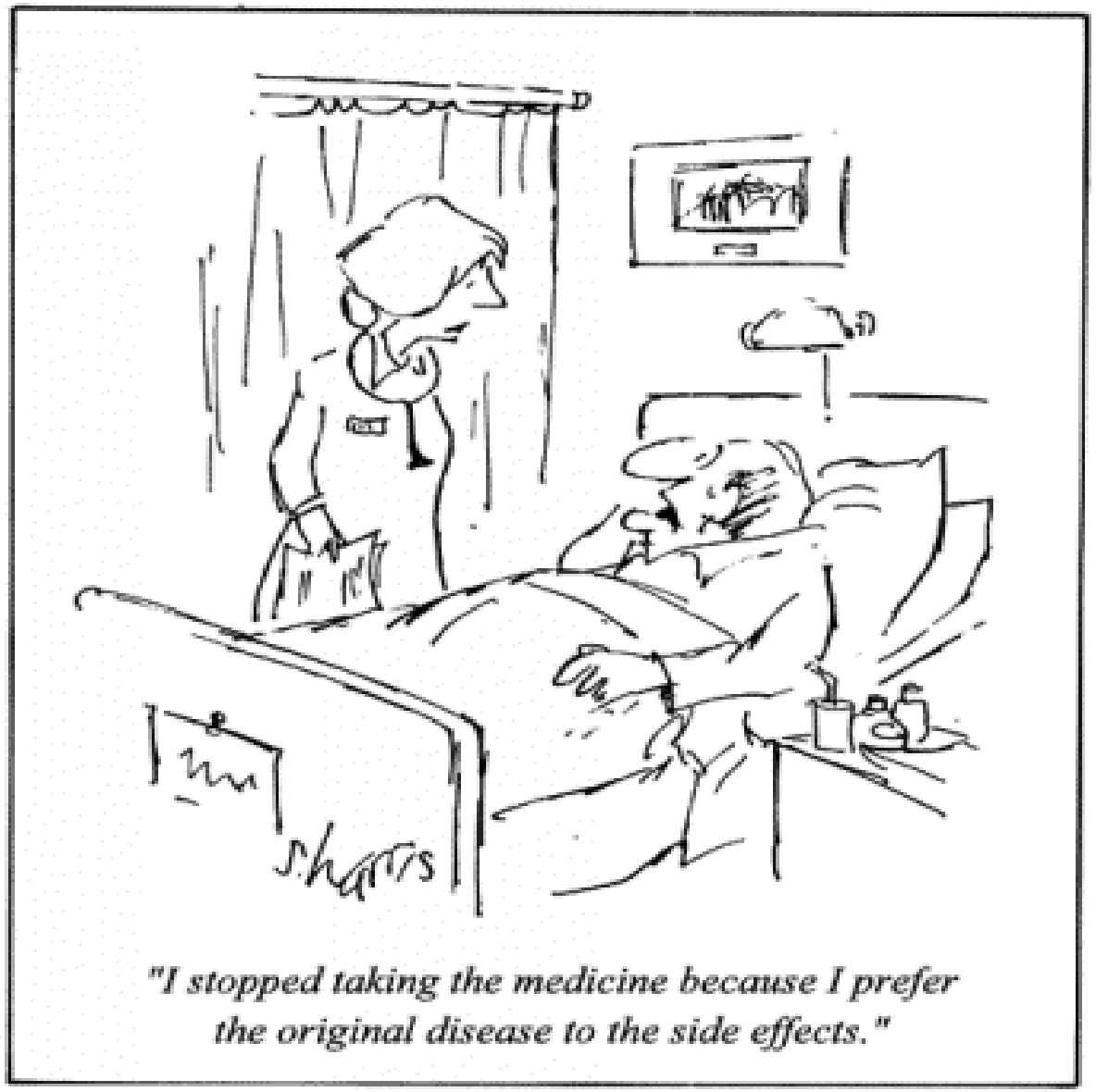
Box 3. Nonrenally cleared antimicrobials not requiring dosage adjustments in patients with renal impairment.

Time-dependent antimicrobials:

- Ceftriaxone 2 g q24h
- Linezolid 600 mg q12h

Concentration-dependent antimicrobials:

- Azithromycin 500 mg q24h
- Ciprofloxacin 600 mg q12h (iv.); 750 mg q12h (OS)
- Moxifloxacin 400 mg q24h
- Doxycycline 100 mg q12h



"I stopped taking the medicine because I prefer the original disease to the side effects."