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"L'infettivologia del 3° millennio:

AIDS ed altro"

"Un'appropriata terapia antibiotica nei pazienti anziani: questione aperta dalle Unità di terapia intensiva alle Residenze Sanitarie Assistite"

M. Tinelli
Direttore USC di Malattie Infettive e Tropicali
Azienda Ospedaliera di Lodi

IL PROBLEMA DEL PAZIENTE ANZIANO

Frailty in elderly people

Andrew Clegg, John Young, Steve Iliffe, Marcel Olde Rikkert, Kenneth Rockwood

***Lancet* 2013; 381: 752–62 ,** Published **Online,** February 8, 2013

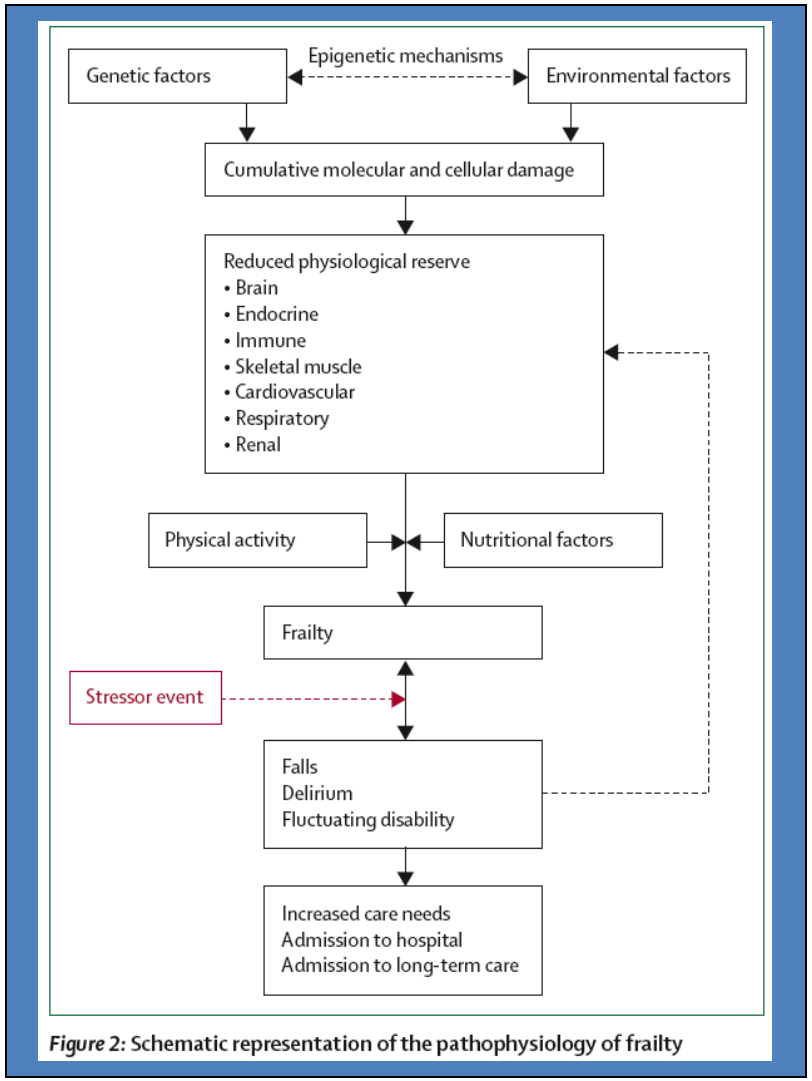
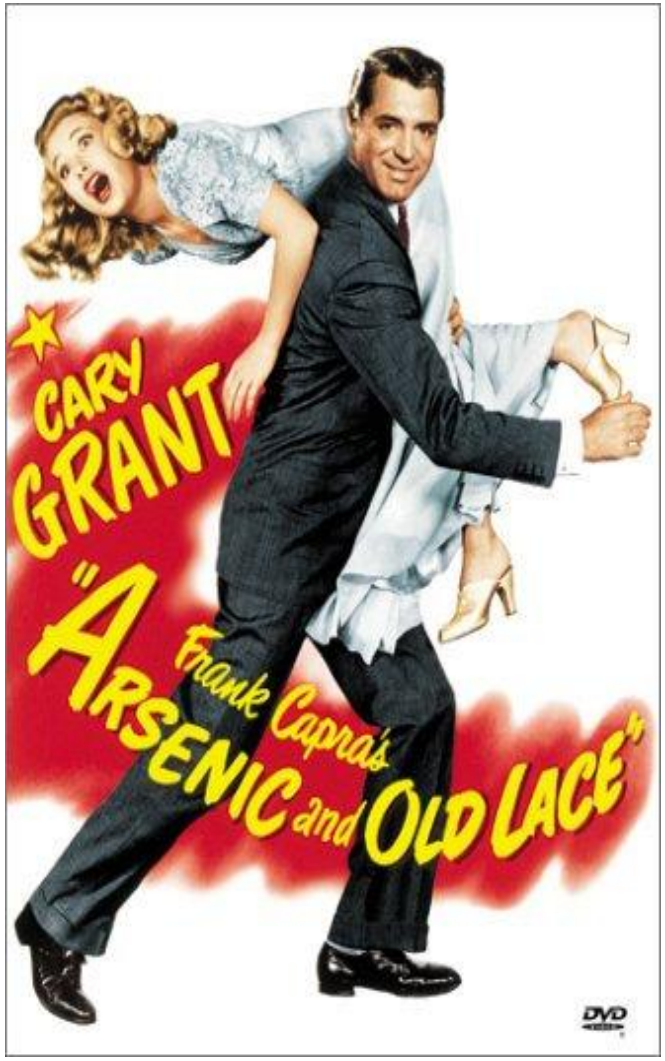


Figure 2: Schematic representation of the pathophysiology of frailty

Frailty is the most problematic expression of population ageing.

It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime.

Antibiotics and elderly patients



- Decreased ability to perform daily life activities (i.e. regular personal hygiene) may contribute to colonization with resistant organisms
- Older adults who reside in long-term care facilities are at higher risk for multidrug resistant pathogens

The burden of infections in LTCFs is significant: prevalence studies

17-15-25 LTCFs in 3-year PPS

6.7-7.6-7.6% infected

From 4,3 % to 16%

11.5% infected (**from 10% in spring to 16% in winter**)

Marchi M et al, Infection 2012

Antibiotic use in the elderly and in LTCFs

Antibiotic treatment in LTCFs

- 4.0-7.3 courses/1000 resident days
- 47%-79% of residents at least 1 course per year
- **Frequently inappropriate (38% -51%)**

Dulon M et al, BMC Infect Dis 2011; 11: 138; Rooney PJ, JAC 2009; 64:635; van der Mee-Marquet N, ICHE 2010; 31: 968; Van Buul LW, JAMDA 13 (2012) 568.e1-568.e13

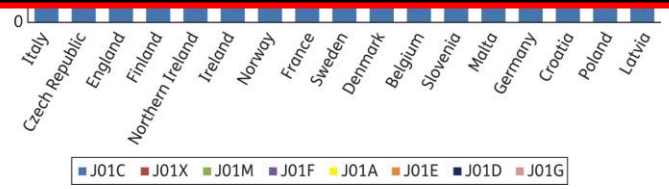
Steinmann MA et al J Am Geriatr Soc 2006; 54:1516-23

J Antimicrob Chemother 2011; **66**: 1609–1616
doi:10.1093/jac/dkr183 Advance Access publication 19 May 2011

Journal of Antimicrobial Chemotherapy

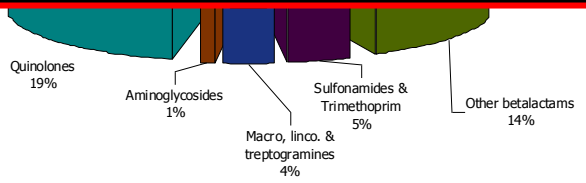
HALT PROJECT

- **No specific guidelines for rational prescribing in 50% of LTCFs**
- **Restricted antibiotic formulary:16%**
- **Minimal education programs**



McClean P et al. J. Antimicrob. Chemother. 2011;66:1609-1616

Journal of Antimicrobial Chemotherapy



Principles for prescribing in elderly

- Identification of bacterial infection by optimized diagnosis
- Severity assessment
- Recognition and incorporation of local resistance data
- Targeting bacterial eradication (or maximal reduction in bacterial load)
- Knowledge and use (if it's possible) of PK/PD indices to optimize choice and dosage
- Patient safety-centered Antimicrobial Stewardship
- Objective assessment of true (overall) costs of resistance and related treatment failure

Age-relate changes - I

Decreased absorption

Decreased distribution

Decreased metabolism

Decreased renal elimination

Age-relate changes - II

Ridotta acidità gastrica

Ridotta motilità intestinale

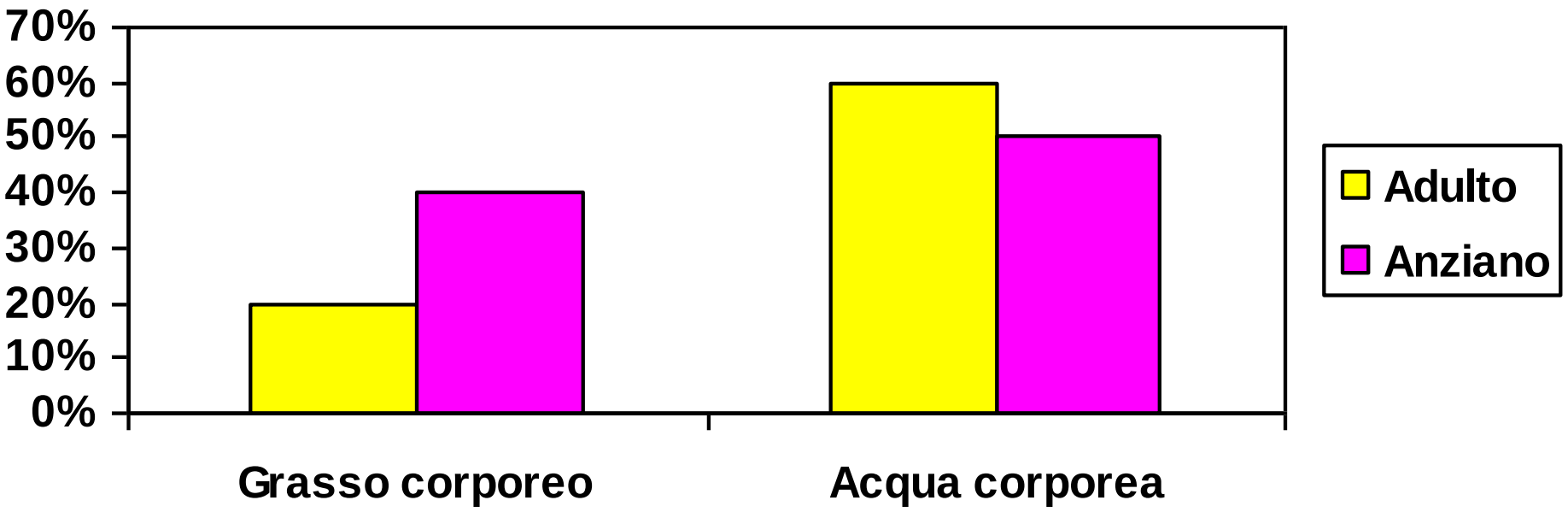
Ridotta superficie villi

Ridotta massa corporea

Modificazioni fisiologiche e farmacocinetiche nell'anziano

Modificazioni fisiologiche	Potenziali modificazioni farmacologiche
DISTRIBUZIONE	
• Aumento tessuto adiposo e riduzione massa muscolare	• Emivita prolungata delle molecole liposolubili
• Diminuzione acqua corporea totale	• Maggiori concentrazioni ematiche delle molecole idrosolubili
• Modesta riduzione albumina sierica	• Maggiori concentrazioni libere di alcune molecole (es. ceftriaxone, sulfamidici, clindamicina)
• Aumento dell'α1-glicoproteina acida	• Minori concentrazioni libere dei macrolidi

Massa corporea e infezioni nell'anziano



Dopo i 65 anni si ha una significativa riduzione della massa magra, del contenuto idrico (50% del peso corporeo) e un incremento del tessuto adiposo: 30% nel sesso maschile e 40% in quello femminile.

Tissue penetration of antibiotics: possible changes in elderly patients

Increased proportion of adipose tissue

↑

Lipophilc compounds
(macrolides, quinolones)

Vd and half-life

Decreased total body water and lean mass

↑

Hydrophilic compounds
(beta-lactams, aminoglycosides, glycopeptides)

Increased plasma concentrations

↓

Vd

Other physiological changes in elderly patients

Physiological changes	Possible pharmacological modifications
METABOLISM	
• Reduced hepatic volume and lower hematic flow	• Lower first passage metabolism
RENAL ELIMINATION	
• Reduced hematic renal flow	• Increased renal elimination half-life
• Reduced glomerular filtration	

Creatinina clearance: - 10 ml / min per decade di età

$$\text{Cl. Creat.} = \frac{(140 - \text{anni}) \times \text{Kg.}}{72 \times \text{creatinemia in mg/dl}} \qquad \text{se F} \times 0.85$$

Fattori di correzione (f.c.) del dosaggio di un farmaco in relazione alla funzionalità renale

% del farmaco escreto immodificato nelle urine	Clearance della creatinina (ml/min)	
	70 anni (Cl: 60 ml/min)	20 anni (Cl 120 ml/min)
10	1,1	1,0
20	1,1	1,0
30	1,2	1,0
40	1,3	1,0
50	1,3	1,0
60	1,4	1,0
80	1,7	1,0
90	1,8	1,0
100	2,0	1,0

Fattori che influenzano il tempo di permanenza di un farmaco nell'organismo

FLUIDI EXTRACELLULARI

FUNZIONALITA' RENALE

POSOLOGIE DIVERSE

Does a previous antibiotic exposure play a role on the treatment of infections in LTCFs ?

J Antimicrob Chemother 2012; **67**: 2982–2987
doi:10.1093/jac/dks300 Advance Access publication 3 August 2012

Journal of Antimicrobial Chemotherapy

Epidemiology and genetic characteristics of extended-spectrum β-lactamase-producing Gram-negative bacteria causing urinary tract infections in long-term care facilities

Marco Tinelli[1], Maria Adriana Cataldo[2]*, Elisabetta Mantengoli[3], Chiara Cadeddu[4], Ettore Cunietti[5], Francesco Luzzaro[6], Gian Maria Rossolini[3,7] and Evelina Tacconelli[8]

Logistic regression analysis

Risks factors for ESBL + GN UTIs

- Previous antibiotic therapy (OR 4)
- Presence of urinary catheter (OR 15)
- **Highest risk**: **exposure to >7 days of quinolones and cephalosporins (OR 7),** after adjusting for type, dosage and duration of antibiotic

Risks factors for ESBL - GN UTIs

- Previous surgical procedures (OR 2)
- Presence of urinary catheter (OR 8)
- No specific antibiotic significant risk for UTIs after adjusting for demographic and clinical risks factors

M. Tinelli and .al., JAC, 2012

Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2012, VOL. 33, NO. 8

Dror Marchaim, MD;[1] Teena Chopra, MD;[1] Ashish Bhargava, MD;[1] Christopher Bogan, BS;[1] Sorabh Dhar, MD;[1] Kayoko Hayakawa, MD, PhD;[1] Jason M. Pogue, PharmD;[2] Suchitha Bheemreddy, MD;[1] Christopher Blunden, BS;[1] Maryann Shango, MD;[1] Jessie Swan, BS;[1] Paul R. Lephart, PhD;[3] Federico Perez, MD;[4,5] Robert A. Bonomo, MD;[4,5,6,7,8] Keith S. Kaye, MD, MPH[1]

Univariate Analyses of Risk Factors for Isolation of Enterobacteriaceae

Variable	CRE	ESBL	Susceptibles[b]
Demographics			
Age, years, mean ± SD	63.4 ± 18.5	63.5 ± 19.4	59.5 ± 20.4
Age >65 years	53 (58.2)	45 (49.5)	37 (40.7)

TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

	CRE vs uninfected[b]		ESBL vs uninfected[b]		Susceptible vs uninfected[b]		CRE vs ESBL		CRE vs susceptible		CRE vs all controls combined	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any antibiotic exposure in previous 3 months	11.4 (2–64.3)	.006	1.7 (0.7–4.1)	.24			5.2 (1.4–19.4)	.015	12.3 (3.3–45)	<.001	7.1 (1.9–25.8)	.003
Permanent residency in institution	1.04 (0.2–4.5)	.96	1.3 (0.5–3.6)	.56	0.15 (0.05–0.5)	.002	2.1 (1–4.2)	.05	5.3 (2.1–12.9)	<.001	2.6 (1.3–5.3)	.01
Isolation of resistant bacteria in previous 6 months[c]	15.3 (4.2–55.6)	<.001	8.25 (2.7–25.7)	<.001	6.6 (1.9–23.3)	.003	1.7 (0.76–3.7)	.2	1.8 (0.7–4.7)	.23	2.9 (1.4–5.7)	.003
Dependent functional status in background	1.4 (0.5–4.4)	.55	5.6 (2.1–14.7)	.001	2.6 (1.1–6.4)	.03			2.0 (0.7–6.2)	.2	1.6 (0.6–4)	.33
ICU stay in previous 3 months	3.9 (1.3–12.4)	.02	5.2 (2.1–13.2)	.001	3.0 (1.2–7.2)	.02			1.6 (0.6–4)	.34	1.36 (0.7–2.7)	.37
Recent (6 months) invasive procedure	4.2 (1.2–15)	.03	1.2 (0.4–3.4)	.76	3.2 (1.3–8)	.01	2.8 (1.1–7.6)	.04			2.7 (1.1–7.1)	.04
Charlson weighted index comorbidity ≥3	3.1 (0.8–11.8)	.1	1.1 (0.4–2.7)	.87	2.2 (0.94–5)	.07	2.4 (1.03–5.6)	.04	4.8 (1.9–12.5)	.001	3.1 (1.4–7)	.006

NOTE. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

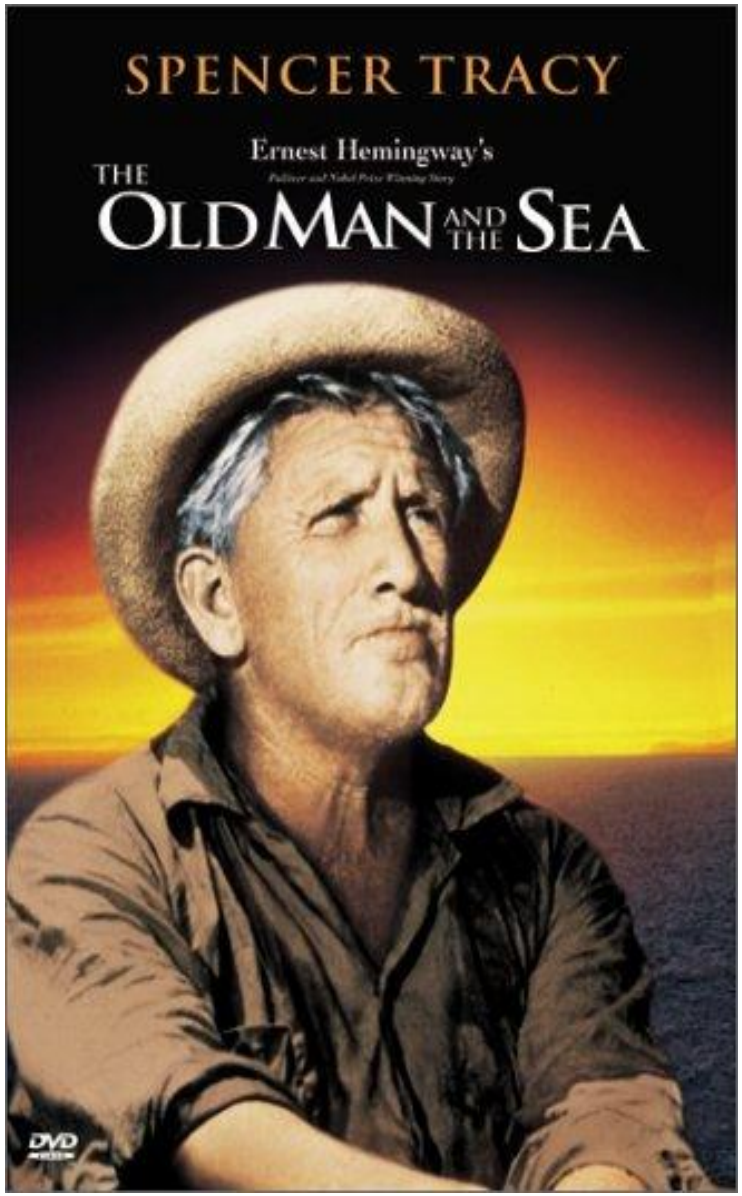
[a] If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

[b] Part of the case-case-control analysis.

[c] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*.

Antimicrobial consumption is a specific risk factor for CRE isolation. Antimicrobial exposures were the only specific predictor of CRE.

Antibiotics and elderly patients



USA, 1944

Best therapeutic approach

Tailor the antibiotic treatment

Antibiotic treatment in the elderly

- **For short half-life, hydrophilic antimicrobials (β-lactams and carbapenems) prefer split doses and extended infusions (no PAE)**
  - Minor daily exposure (about 1/4 to 1/3 less each day) with greater results on outcome and resistance
- **Concentration-dependent usually with prolonged PAE: amikacin, gentamicin, ciprofloxacin and levofloxacin require higher single shot delaying next administration (Cmax/MIC > 10)**
  - TDM of peak levels for improved results

QUINOLONES

AUC/MIC 87-250

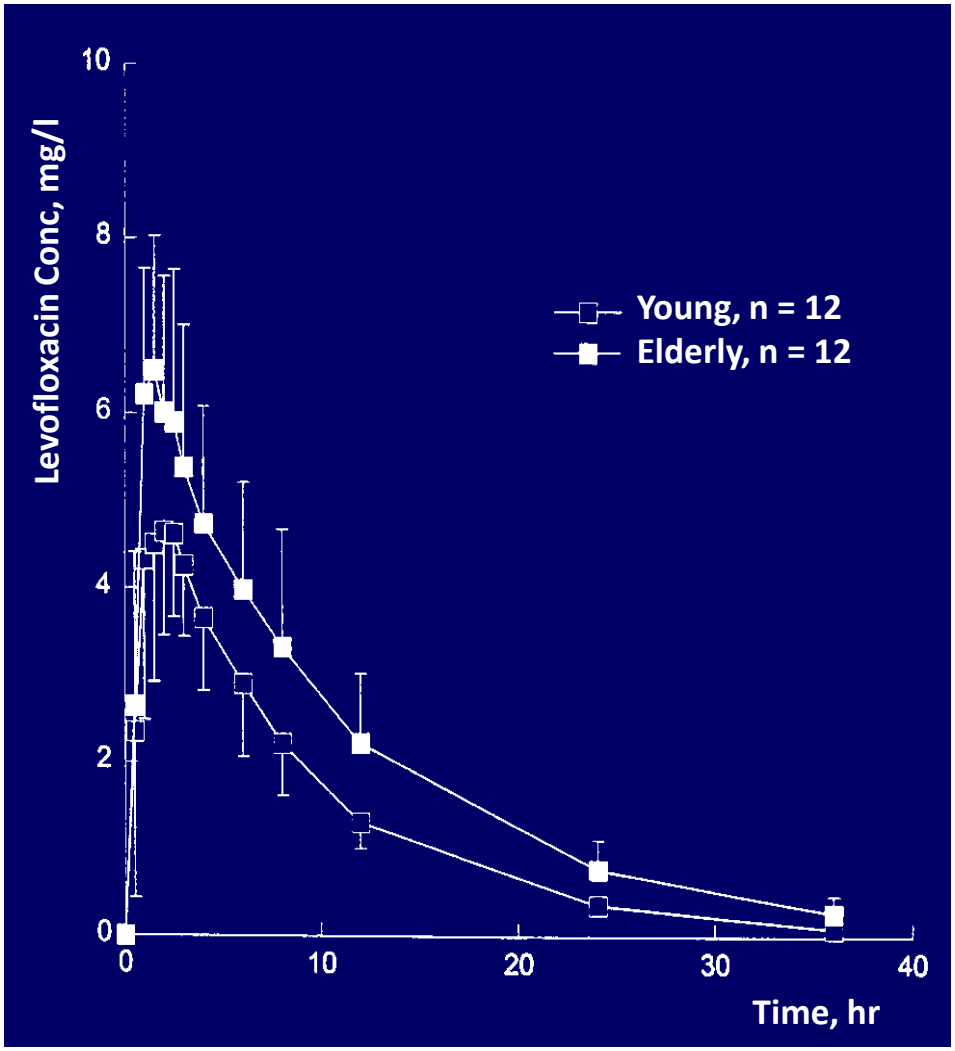
Cmax/MIC = 12

Louis Pasteur in his laboratory

Albert Edelfelt - 1885 - Musée d'Orsay - Paris

Levofloxacin 500 mg single oral dose

Mean plasma concentrations



Chien SC et al., Antimicrob Agents Chemother, 1997

Levofloxacin

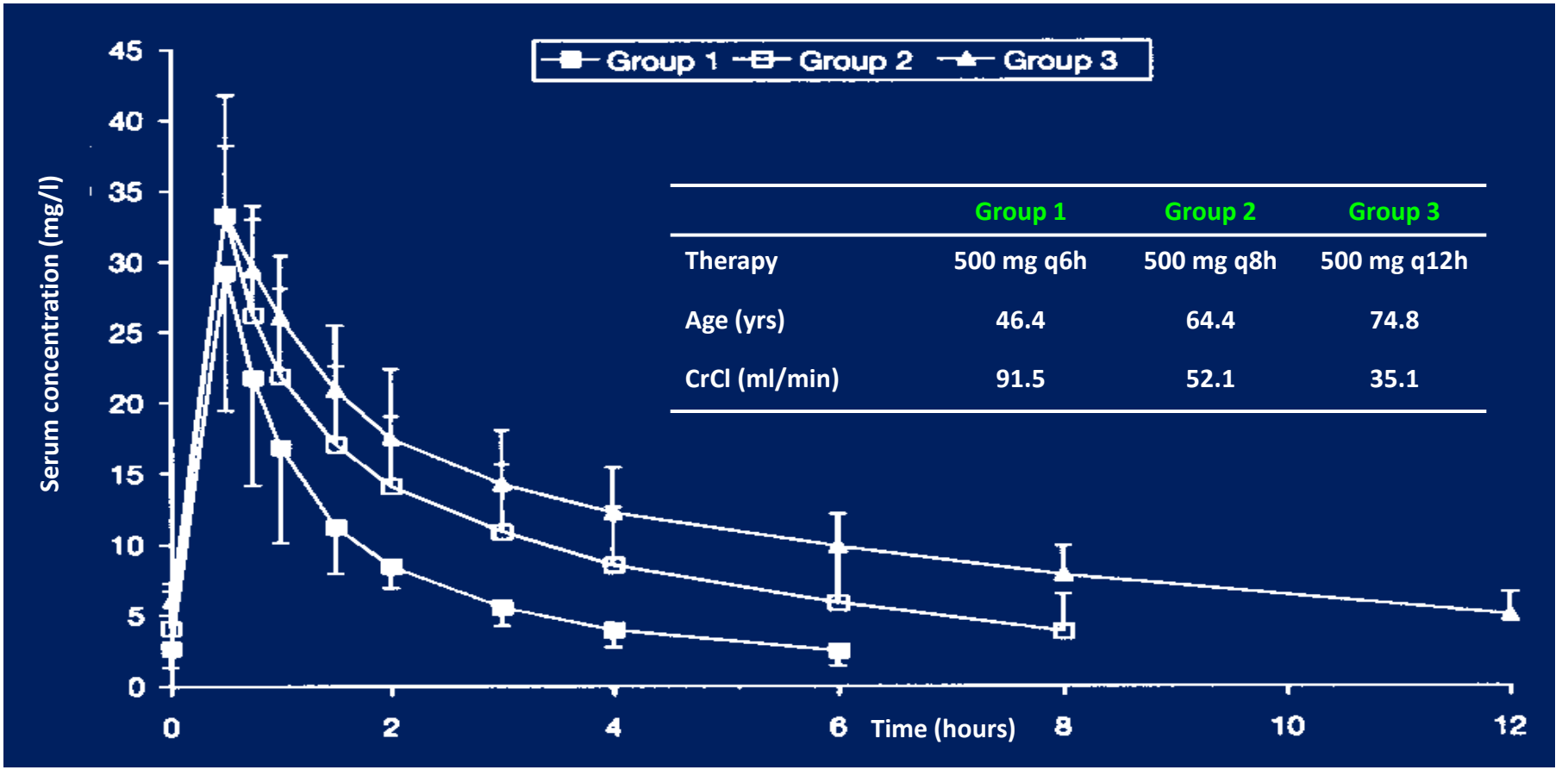
Pharmacokinetic parameters (mean ± SD)

Parameter	Young (n = 12)	Elderly (n = 12)
C_{max} (mg/l)	5.52 ± 1.02	6.96 ± 1.60
t½ (h)	6.0 ± 0.9	7.6 ± 2.0
$AUC_{0-\infty}$ (mg·h/l)	47.5 ± 9.8	74.7 ± 23.3
CL_R (ml/min)	140 ± 33	91 ± 29

Chien SC et al., Antimicrob Agents Chemother, 1997

MEROPENEM

Mean serum concentrations

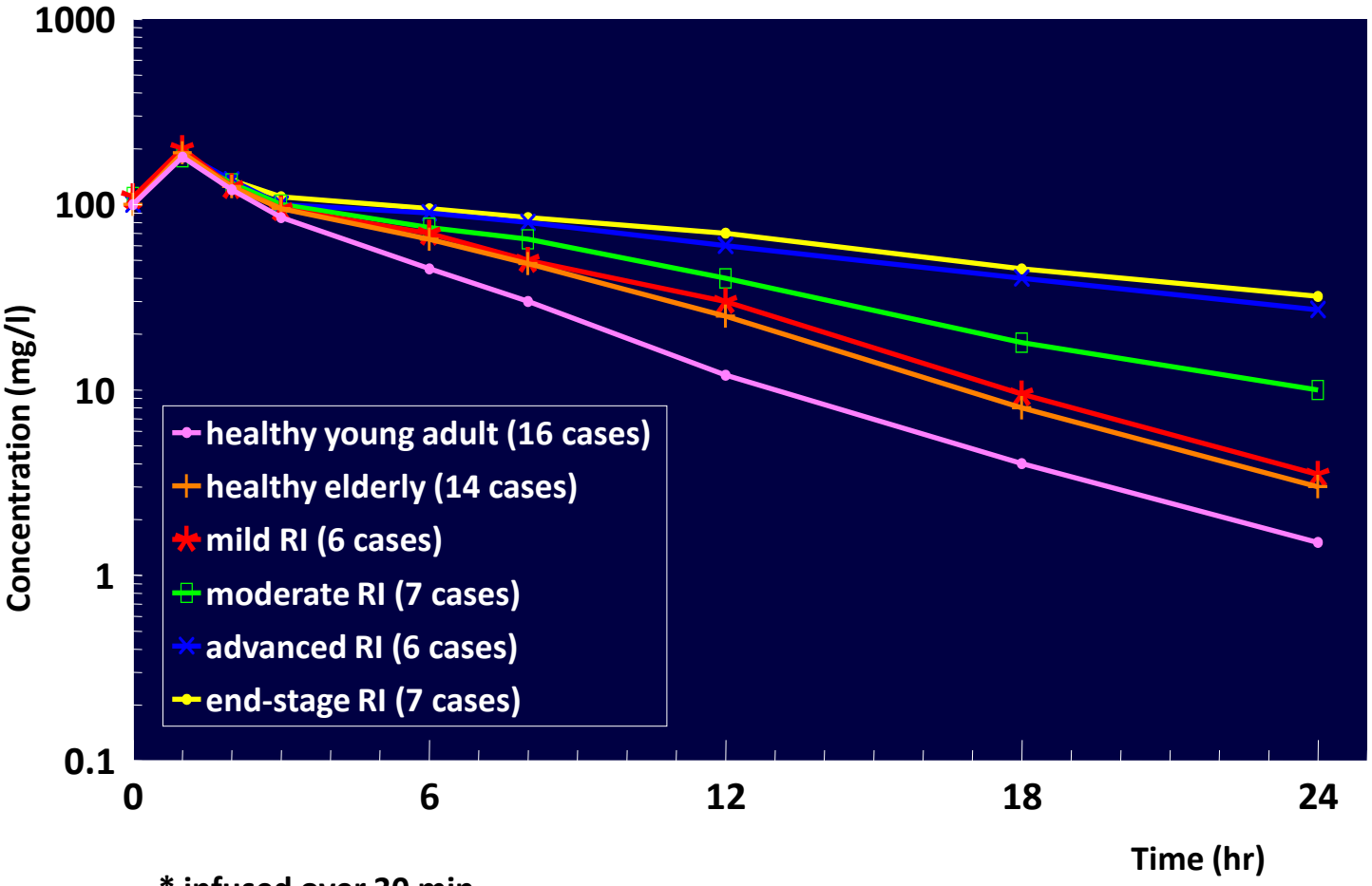


	Group 1	Group 2	Group 3
Therapy	500 mg q6h	500 mg q8h	500 mg q12h
Age (yrs)	46.4	64.4	74.8
CrCl (ml/min)	91.5	52.1	35.1

Cheatham SC et al., Pharmacotherapy, 2008

ERTAPENEM

Mean plasma concentration-time curves following a single 1g dose* in healthy subjects and patients with various degrees of renal insufficiency



* infused over 30 min

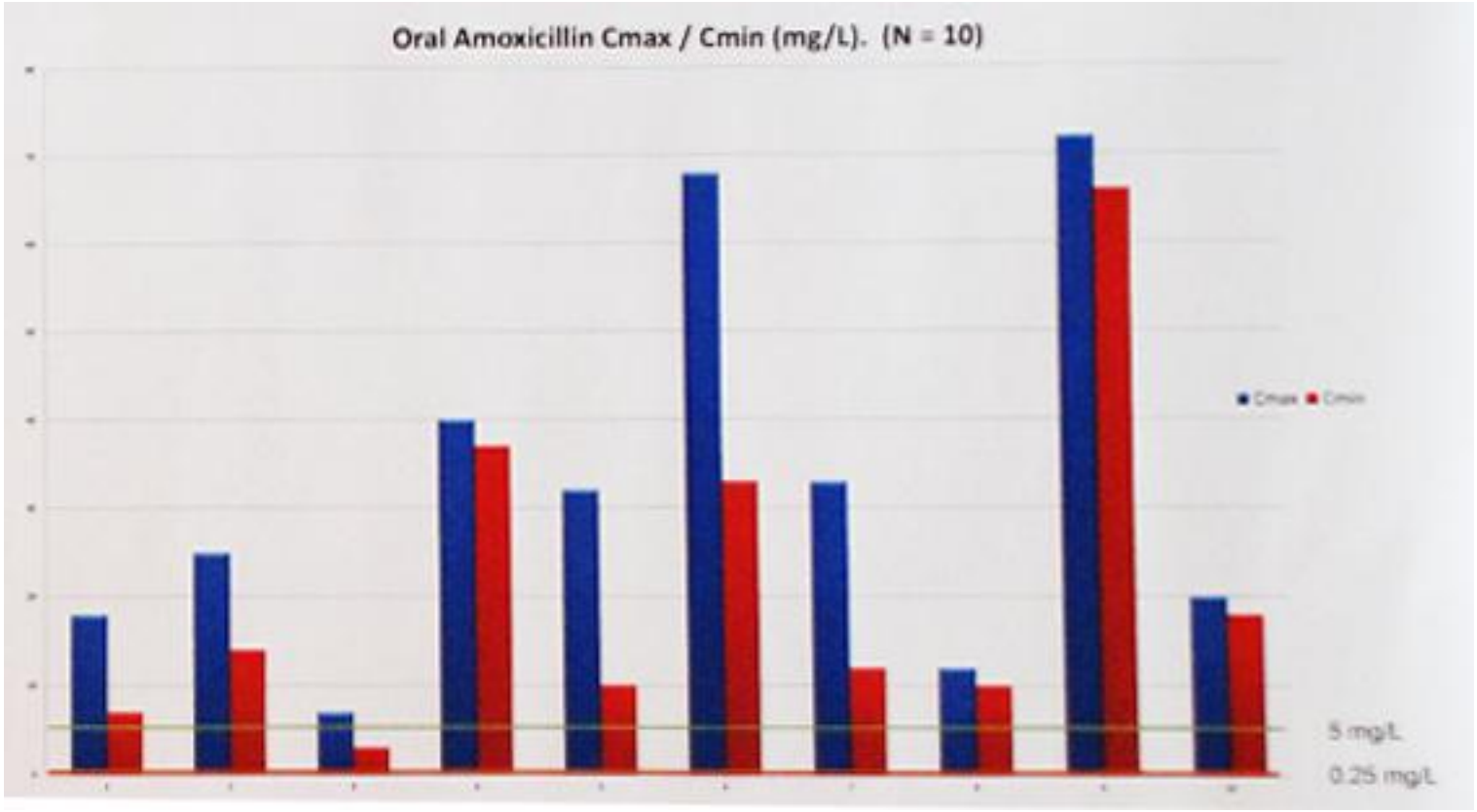
Holland SD et al., 2001

26

Pharmacokinetic/pharmacodynamic (PK/PD) profile of oral amoxicillin in elderly patients with Gram-positive infections requiring prolonged antimicrobial courses

L. Pagani[1,2], V. Vitrat[2], C. Janssen[2], F. Jehl[3], A. Renzoni[4], J. Gaillat[2], JP. Bru[2]

[1]ID Unit Bolzano Central Hospital, Bolzano; Italy. [2]ID Unit Annecy-Genevois Hospital Centre, Annecy; France.
[3]Lab Bacteriology University Hospital, Strasbourg; France. [4]ID Unit Geneva University Hospitals, Geneva; Switzerland.

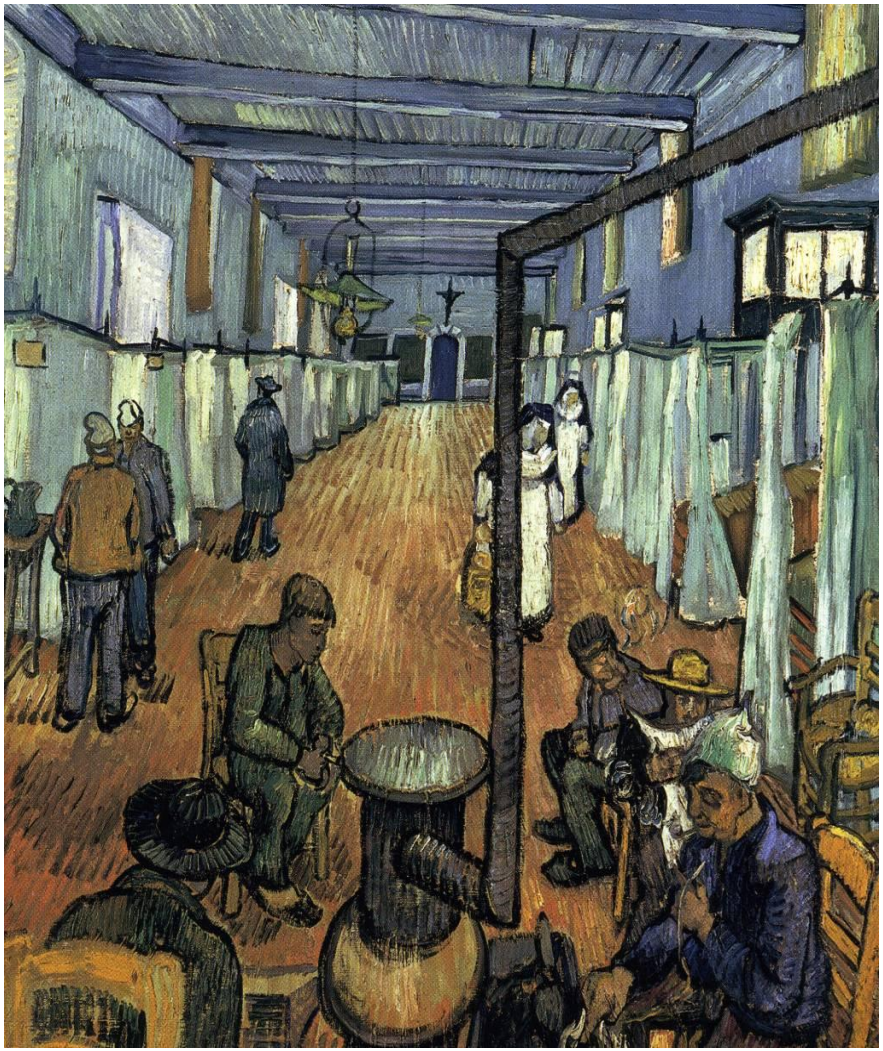


Cmin were also directly correlated to creatinine level, thus indicating a likely prolonged drug half-life in the presence of decreased renal function. No adverse events attributable to either drug regimen were observed.

AMINOGLYCOSIDES

C_{max}/MIC ≥ 8 – 10 (once daily)

The Sick-Ward of the hospital in Arles



Vincent Van Gogh - 1889

Amikacin pharmacokinetics

	Normal creatinine clearance	Normal serum creatinine	
		Younger	Older
Number	37	24	50
Age (yrs)*	28.9 (± 13.7)	19.7 (± 7.0)	48.8 (± 14.8)
Wt (kgs)*	72.2 (± 20.8)	63.0 (± 19.0)	77.9 (± 16.6)
Creatinine (mg/dl)*	0.9 (± 0.2)	0.9 (± 0.2)	1.0 (± 0.2)
Cl_{cr} (ml/min/1.73m^2)*	136 (± 29)	135 (± 38)	87 (± 34)
t½ (hrs)*	1.9 (± 1.2)	1.4 (± 0.4)	3.7 (± 2.9)
Vd (l/kg)*	0.23 (± 0.08)	0.22 (± 0.08)	0.23 (± 0.09)
Amikacin clearance (ml/hr/kg)*	98 (± 38)	113 (± 37)	60 (± 31)

*Expressed as the mean and standard deviation

from Zaske DE et al., 1991

Decreasing daily dosing according to physiopathological status

β-lactams
Glycopeptides
Carbapenems

C_{min} > MIC

- **TZP: from 4.5 g x 3 to 4 x 2.25 g**
- **CAZ: from 2 g x 3 to 3 g/24 hrs**
- **MEM: from 1 g x 4 to 500 mg x 4**

Aminoglycosides
Fluoroquinolones
Lipopeptides

C_{max} / MIC; AUC/MIC

- **AMK: from 15 mg/kg x 1 to 15 mg/kg/48 hrs**
- **CIP: from 500 mg x 2 to 750 mg x 1**
- **DAP: from 8 mg/kg x 1 to 6 mg/kg/48 hrs**

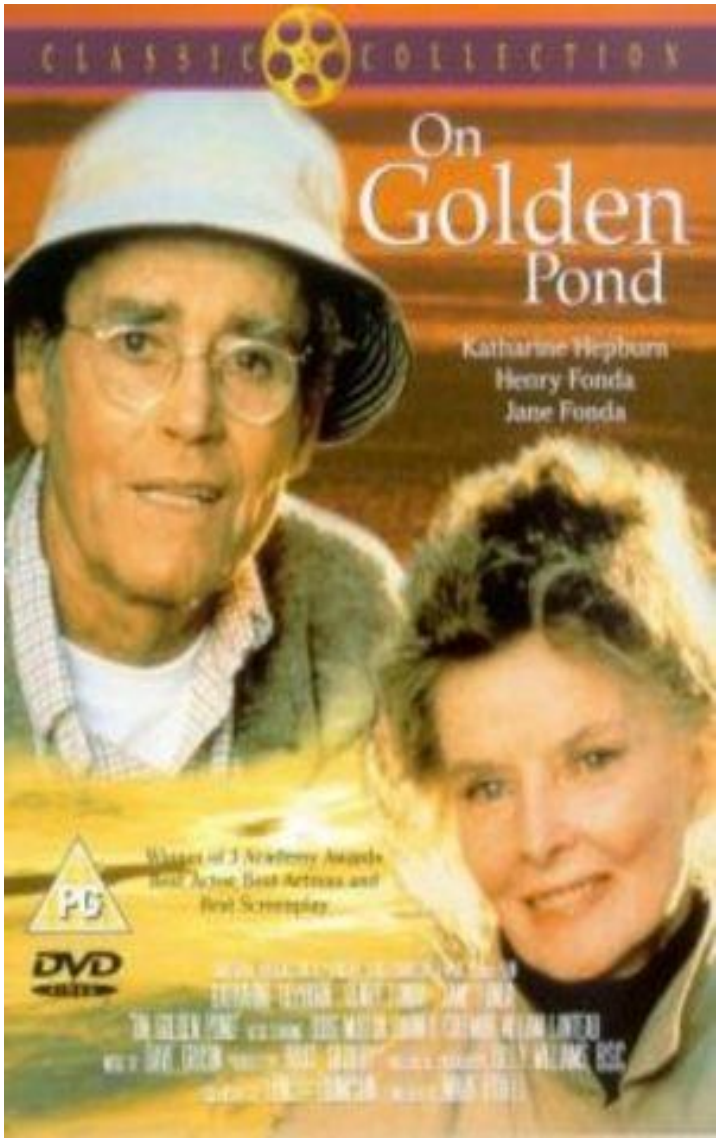
Suggested Colistin Dosing for Various Patients Categories

Loading dose (MU)	
In all patient category	Body weight[1] X 66.500 x target peak level (Maximum permitted dose 10 MU) Maintenance dose after 24 hours **Tip: 70Kg-LD=9MU**
Maintenance dose (MU)	
Not on renal replacement	Target peak x 33.250 x (1.5 x CrCL + 30) given in 2-3 doses ClCr > 70: 4.5 MU x 2 ClCr ˜ 50: 3.5 MU x 2 ClCr ˜ 30: 2.5 MU x 2 ClCr ˜ 20: 2.0 MU x 2 **Tip: Decline of ClCr˜20 ml/min (from 70), decrease dose by 2 MU**
Receiving intermittent hemodialysis	2 MU in two daily doses Additional 30% of The daily dose on day of hemodialysis
Receiving continuous renal replacement	9-10 MU in two or three daily doses

[1] **Ideal or real body weight in Kg (choose the least)**

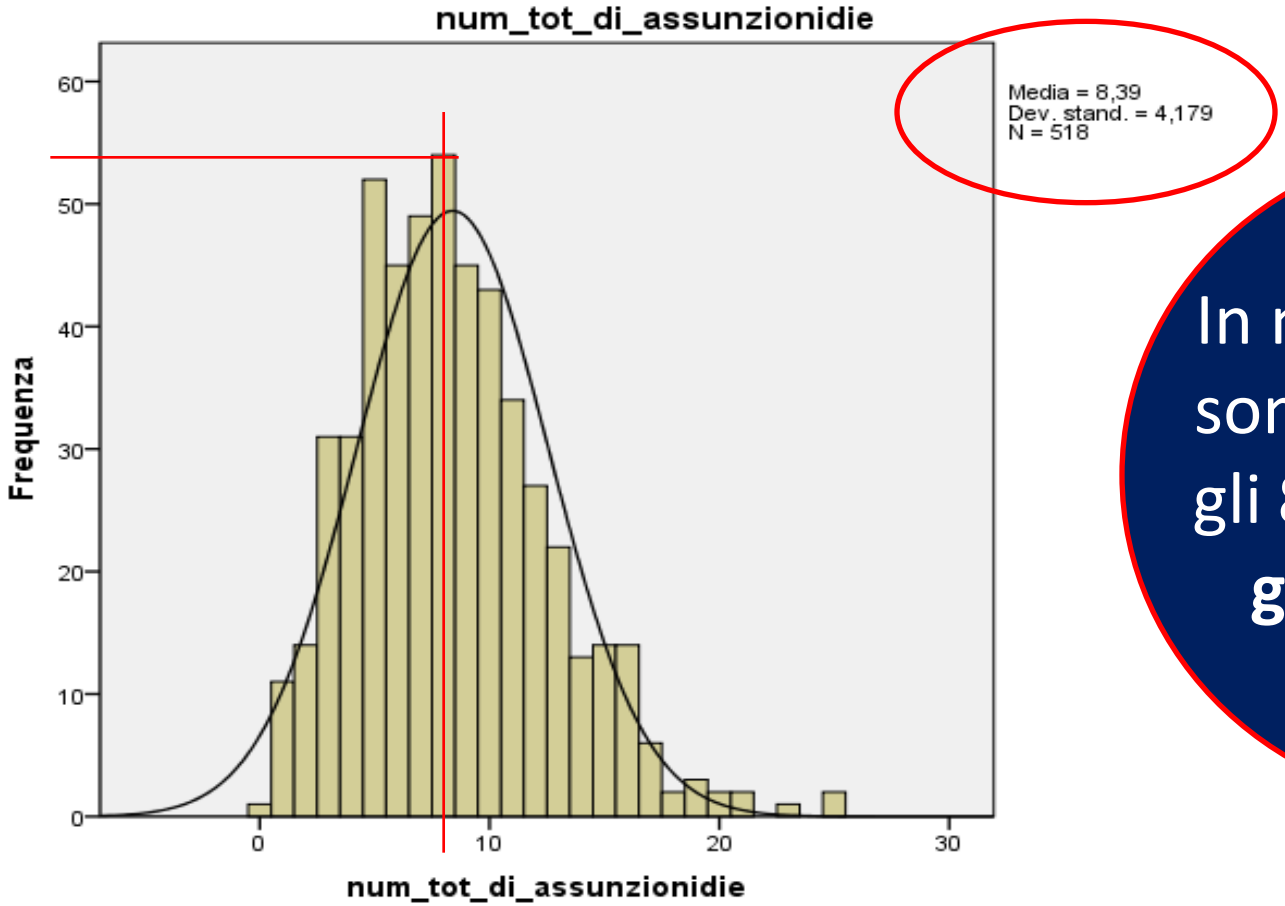
Garonzik SM, et al. AAC 2011; 55:3284)

Antibiotics and elderly patients



- **Co-administration of many drugs (≥3) (i.e. hypertension, atherosclerosis, diabetes, etc.)**

POLITERAPIE:
NUMERO DI FARMACI CHE OGNI PAZIENTE ASSUME MEDIAMENTE IN UN GIORNO IN RSA



In media in RSA si somministrano fra gli **8 e 9 farmaci al giorno** ad ogni paziente

Febbraio 2012 , 520 pazienti, RSA Fondazione Don Gnocchi, Milano.

Antibiotics and elderly patients

Increased risk of

drug-drug interactions

and adverse events

Main drug-drug interactions with antimicrobial drugs (I)

Drug or drug class	Interacting drugs	Potential clinical effects
Aminoglycosides	Amphotericin B, cyclosporin, cisplatin, tacrolimus, diuretics and vancomycin	Nephrotoxic effects
Amoxicillin and ampicillin	Allopurinol	Cutaneous rash
Fluoroquinolones	Pharmaceutical preparations containing alluminum, iron, magnesium or zinc; antiacids and sucralfate	Reduced absorption of all fluoroquinolones
• Ciprofloxacin	Antiarrhythmic drugs	Ventricular arrhythmia
	Preparations containing calcium	Reduced absorption of ciprofloxacin
	Theophylline	Increase in theophylline concentration
	Warfarin	Increased anticoagulant effect

Novelli A, De Bac C, 2007

Main drug-drug interactions with antimicrobial drugs (II)

Drug or drug class	Interacting drugs	Potential clinical effects
Linezolid	Serotonergic agents (SSRI, TCA and MAOI)	Serotonergic syndrome
Macrolides		
• azithromycin	Pharmaceutical preparations containing alluminum or magnesium	Reduced absorption of azithromycin
• clarithromycin • erithromycin	Calcium, statins, cyclosporin, digoxin, theophylline, warfarin	Increase in concentration or interaction; increased macrolide concentration (calcium agonists)

Novelli A, De Bac C, 2007

Common antimicrobial-induced adverse events in elderly persons

Antimicrobial class/agent	Adverse event
β-lactams	Diarrhea, drug fever, intestinal nephritis, rash,
Carbapenems	thrombocytopenia, anemia and neutropenia Seizure
Macrolides and azalides	Gastrointestinal intolerance, QT prolongation and ototoxicity
Fluoroquinolones	Nausea, vomiting, CNS effects, decreased seizure threshold and QT prolongation
Aminoglycosides	Nephrotoxicity and ototoxicity
Trimethoprim-sulfametoxazole	Blood dyscrasias, drug fever, hyperkalemia and rash

Faulkner CM et al., Clin Infect Dis, 2005

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SHEA Position Paper

Antimicrobial Use in Long-Term–Care Facilities

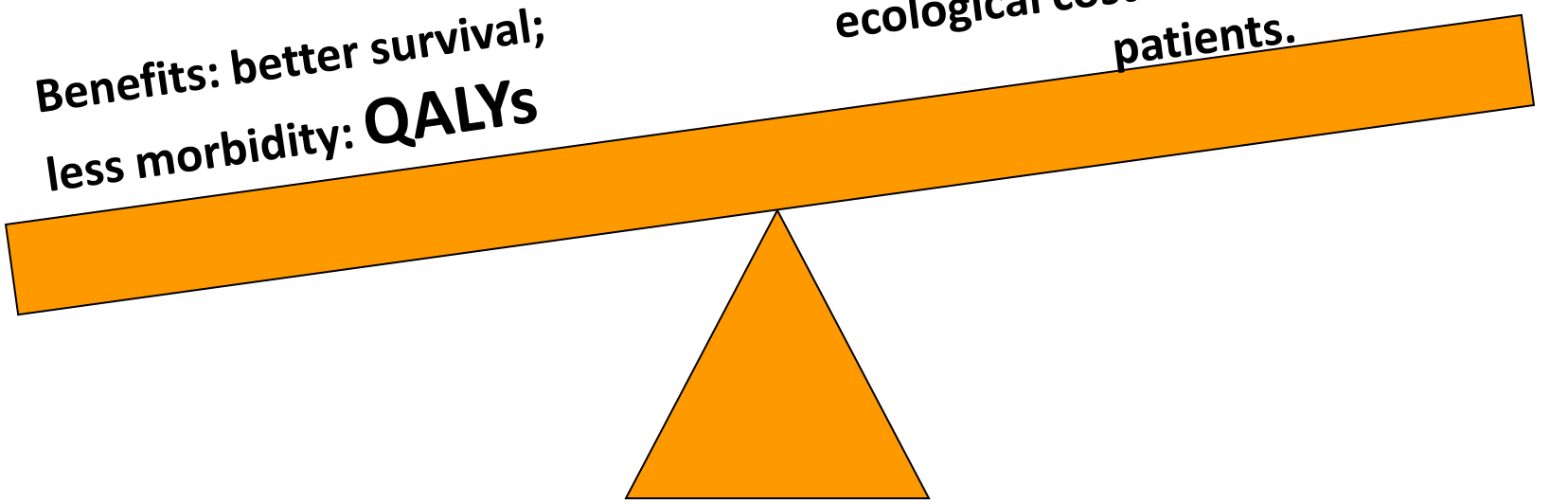
Lindsay E. Nicolle, MD; David W. Bentley, MD; Richard Garibaldi, MD; Ellen G. Neuhaus, MD; Philip W. Smith, MD; the SHEA Long-Term–Care Committee

Antimicrobials and Comfort Care

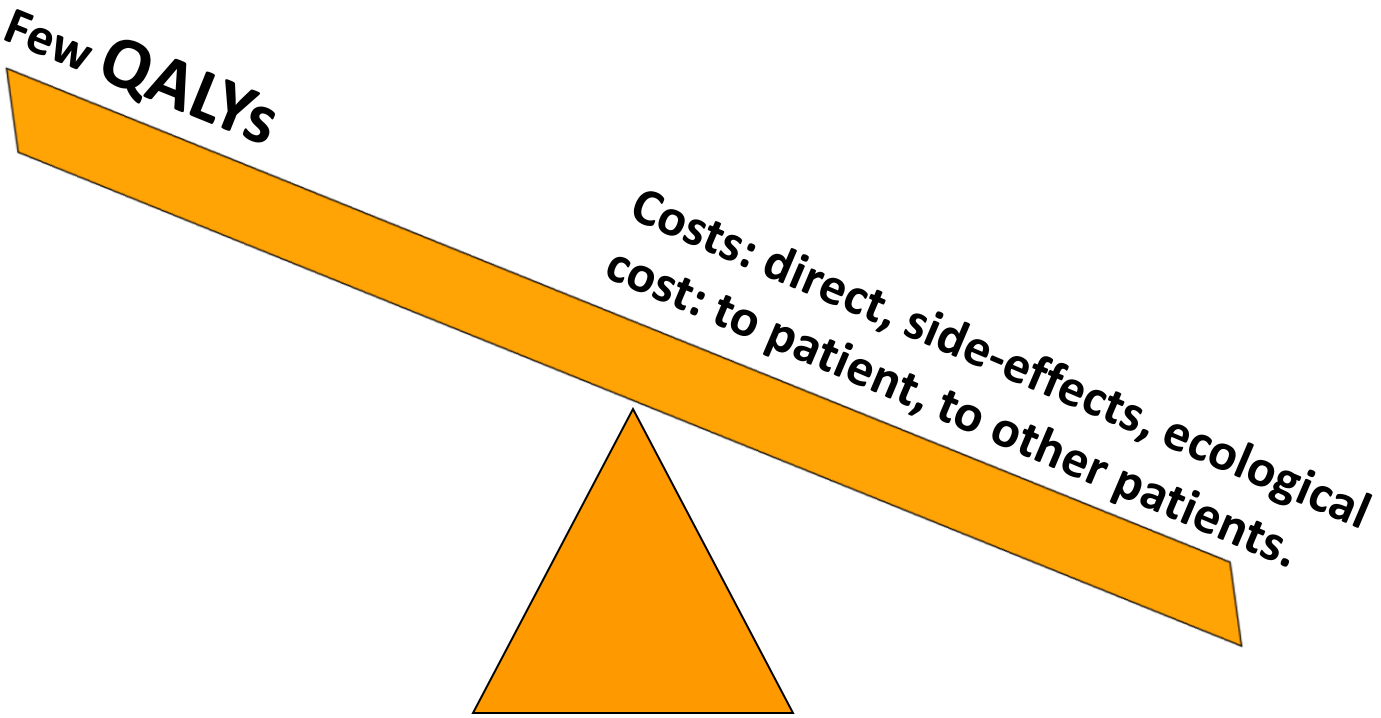
It is accepted that, for selected patients in LTCFs, it is ethically appropriate not to offer therapy with antimicrobials.

Some hospitals and NHs currently have policies that address the ethical issues of antibiotic use for patients with life-threatening infections, and advance directives frequently list antimicrobial therapy among lifesustaining treatments such as transfusions and ventilators.

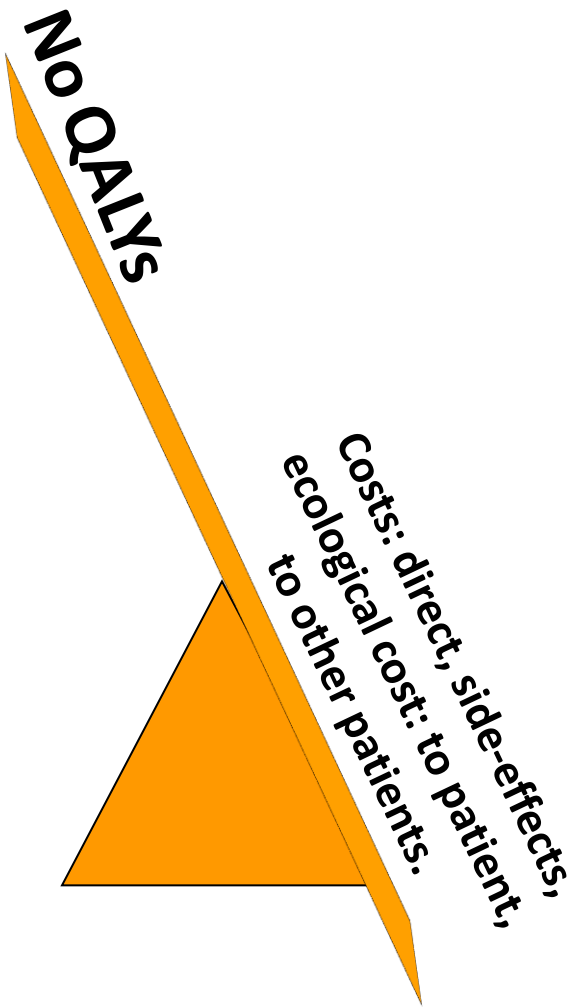
42 years old patient with severe infection



80 years old healthy patient with severe infection:



80 years patient with severe dementia for years, pressure sores, urinary catheter and severe contractures, severe infection :



Approach to antimicrobial therapy: ethical dilemnas

Ethical principles:

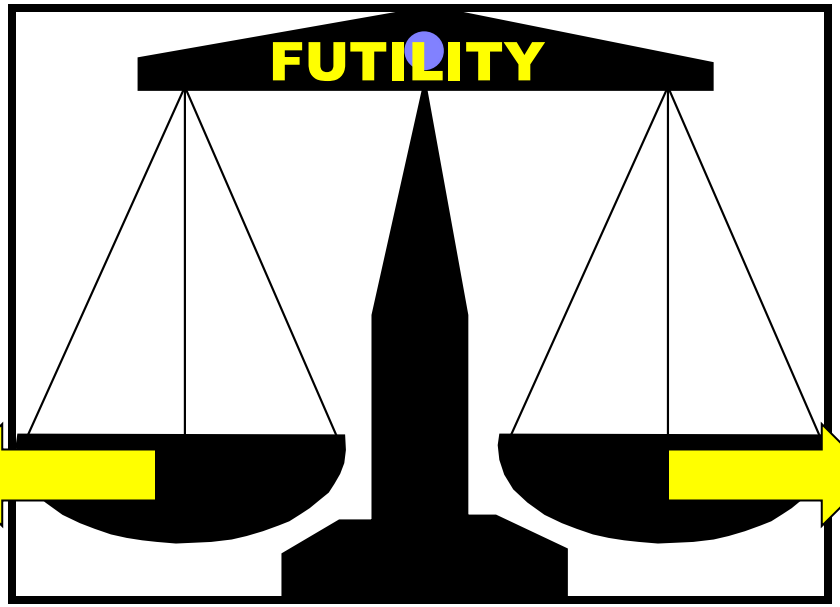
- autonomy
- beneficence and nonmaleficence
- justice

Goal of the treatment

life-sustaining treatment

symptom-control

prolongation of life



Costs of the treatment

expensive drugs

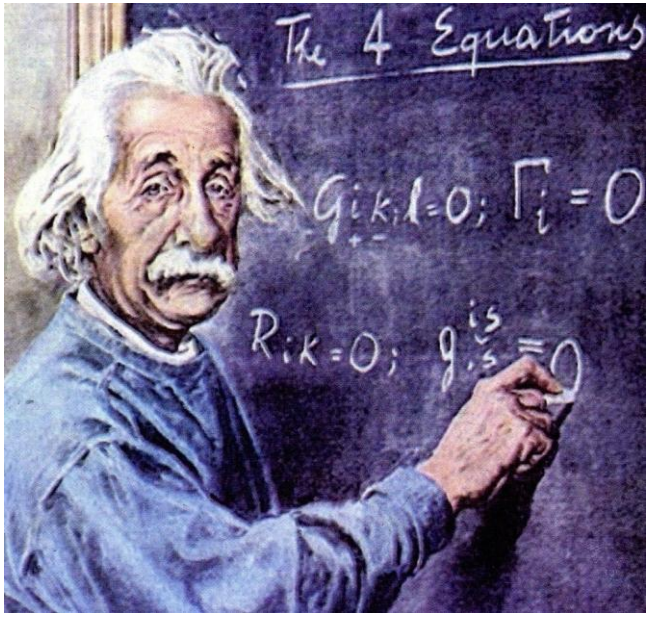
discomfort

side effects

treatment failure

Conclusion

A. Einstein (1879-1955)



- **Antibiotic doses should be reduced because of the decreased lean body mass of the elderly**

Tailored treatment !!!!