Protocolli di terapia antibiotica nelle lungodegenze

M. Tinelli

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Indicatori demografici. Stime per l'anno 2017

Istat | Istituto Nazionale di Statistica

464 mila (-2,0%) — **un calo di nascite costante**

- **1,34** figli per donna
- **31,8** anni l'età media al parto

45,2 anni — **una popolazione sempre più vecchia**

- 0-14 anni: **13,4%**
- 15-39 anni: **27,0%**
- 40-64 anni: **37,1%**
- 65-84 anni: **19,1%**
- 85+ anni: **3,5%**

22,6%

337 mila (+12,0%) — **il più elevato numero di ingressi dell'ultimo quinquennio**

- gli italiani sono **45**mila (+19,9%)
- gli stranieri sono **292**mila (+10,9%)

5,6 media italia — **le regioni del Centro-Nord quelle più attrattive**

- Nord: **6,4**
- Centro: **6,1**
- Mezzogiorno: **4,2**

neocittadini ogni 1.000 residenti

153 mila (-2,6%) — **un alto numero di italiani verso l'estero, ma in calo**

- gli italiani sono **112**mila (-1,8%)
- gli stranieri sono **40**mila (-5,0%)

un gap di genere ormai di soli 4,3 anni

- per gli uomini **80,6** anni
- per le donne **84,9** anni

647 mila (+ 5,1%) — **la mortalità generale in aumento in tutte le regioni**

- Nord: **8,1**
- Centro: **8,2**
- Mezzogiorno: **9,1**

deceduti su 1.000 abitanti (tasso standardizzato)

-183 mila — **una decrescita naturale ininterrotta**

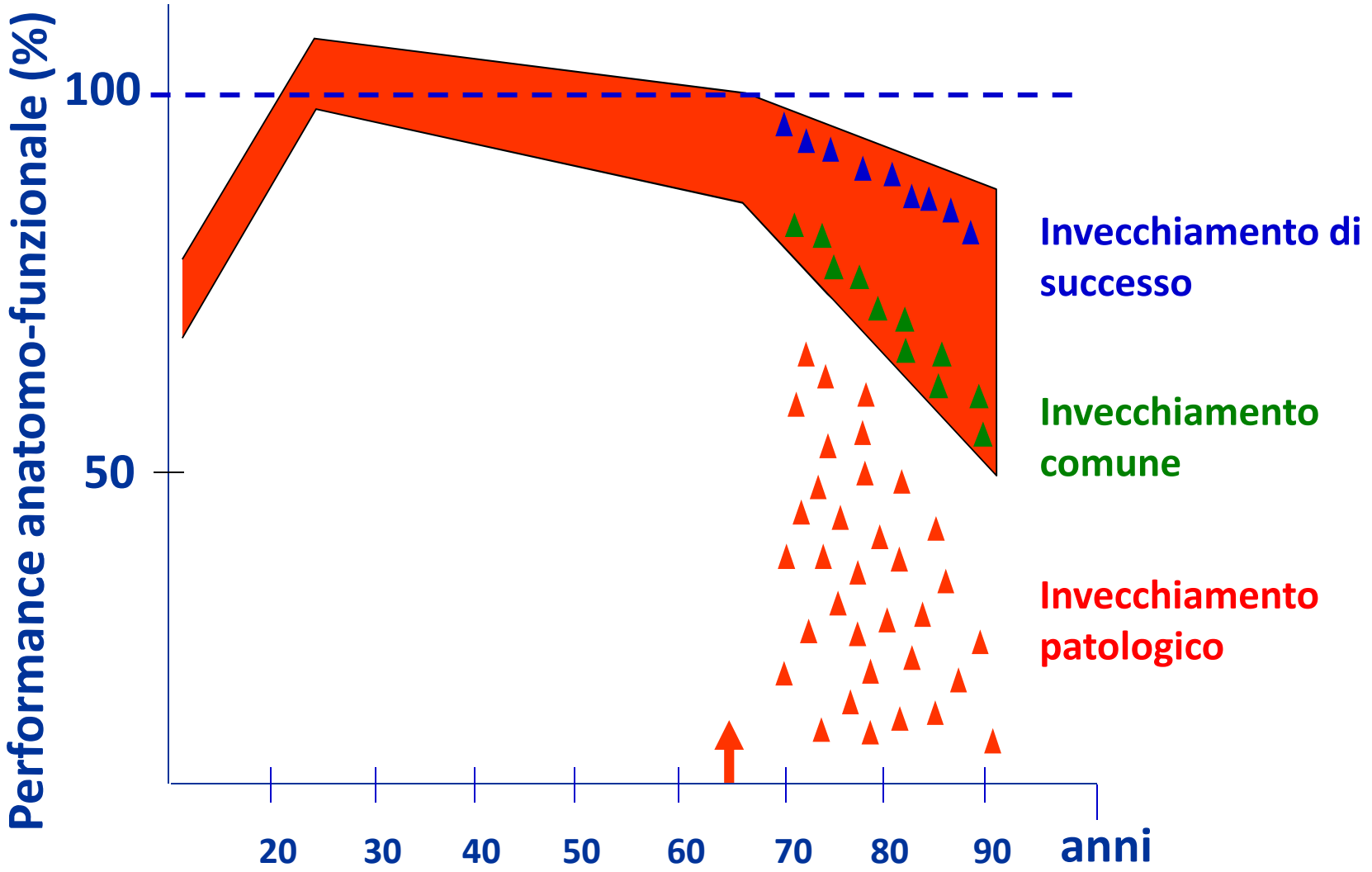
- Nord: **-89**mila
- Centro: **-45**mila
- Mezzogiorno: **-49**mila

*differenza fra il numero di iscritti per nascita e il numero di cancellati per decesso dai registri anagrafici dei residenti

dove non indicato diversamente, i dati sono riferiti al 2017 e le variazioni sono sul 2016

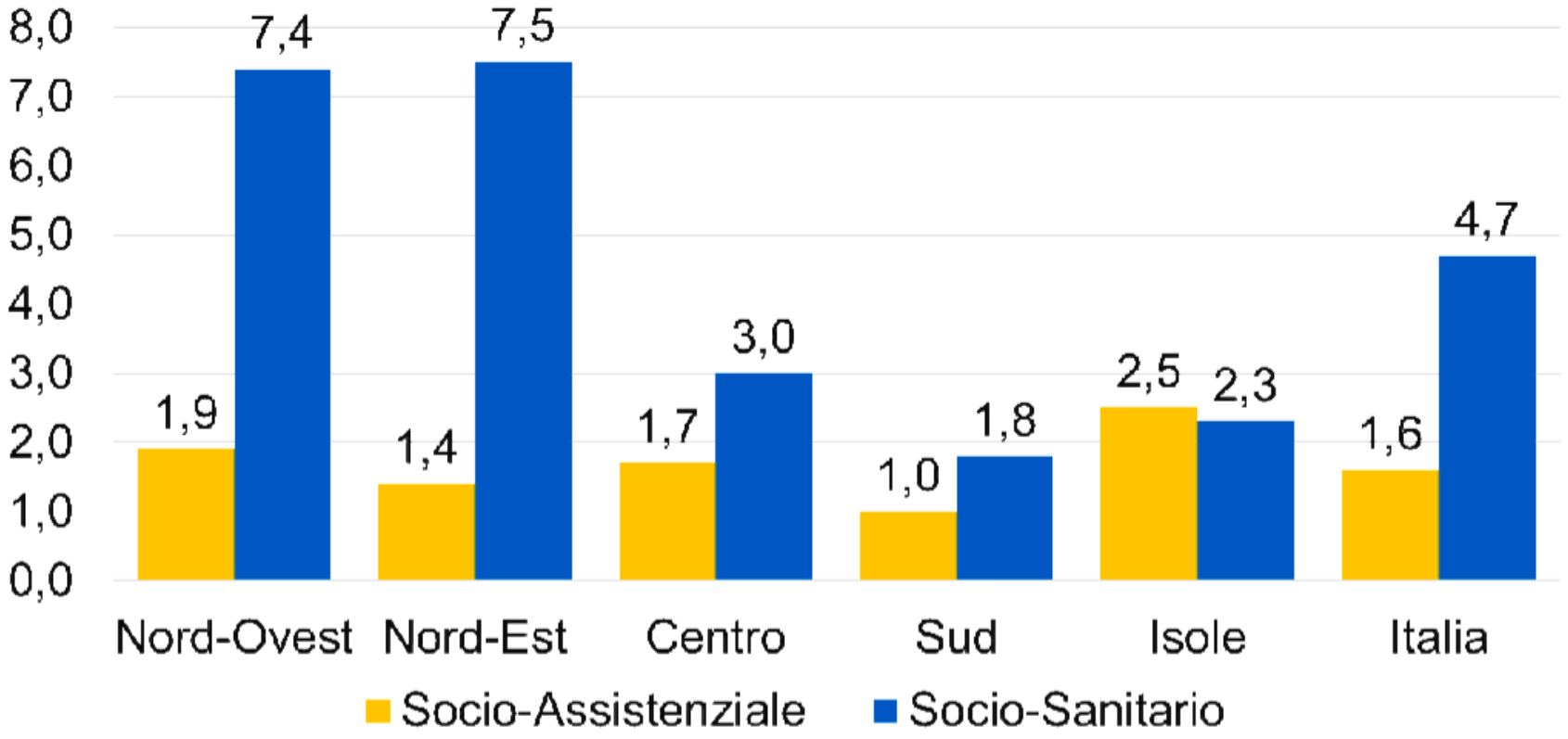
Invecchiamento fisiologico e patologico

dalla Vulnerabilità alla Fragilità



In Italia 12.671 presidi residenziali per un'offerta complessiva di 384.450 posti letto (6,3 pl per 1000 persone residenti)

Posti letto per tipologia di presidi e ripartizione geografica (tassi per 1000 residenti)



ISTAT 2016

Previsione popolazione lombarda e simulazione dotazione PL/RSA anni 2020-2050

Dati Regione Lombardia	2020	2030	2040	2050
Popolazione Totale	10.507.422	10.934.528	11.271.047	11.486.754
Popolazione Over 75 Anni	1.199.381	1.427.969	1.763.405	2.245.417
Over 75 (% su popolazione totale)	11,41%	13,06%	15,65%	19,55%
Previsione Indice di dotazione PL RSA (ipotesi conservativa anno 2015 - 5,72%)	**68.557**	**81.623**	**100.796**	**128.348**
Previsione Indice di dotazione PL RSA (ipotesi rispetto indice programmatorio - 7%)	**83.957**	**99.958**	**123.438**	**157.179**

ISTAT, LIUC ottobre 2017

Aschbacher *et al. Antimicrobial Resistance and Infection Control* (2016) 5:33
DOI 10.1186/s13756-016-0136-1

Antimicrobial Resistance and Infection Control

REVIEW Open Access

Review on colonization of residents and staff in Italian long-term care facilities by multidrug-resistant bacteria compared with other European countries

Richard Aschbacher[1*], Elisabetta Pagani[1], Massimo Confalonieri[2], Claudio Farina[3], Paolo Fazii[4], Francesco Luzzaro[5], Pier Giorgio Montanera[6], Aurora Piazza[7] and Laura Pagani[7]

MDR prevalence in Italian LTCFs

% Prevalence	MRSA	ESBL	CPE
Residents	7.8–38.7 %	49.0–64.0 %	1.0–6.3 %
Staff	5.2–7.0 %	5.2–14. 5 %	0.0–1.5 %

Sorveglianza nazionale delle batteriemie da Enterobatteri produttori di Carbapenemasi (CPE) in Italia; rapporto 2013-2016

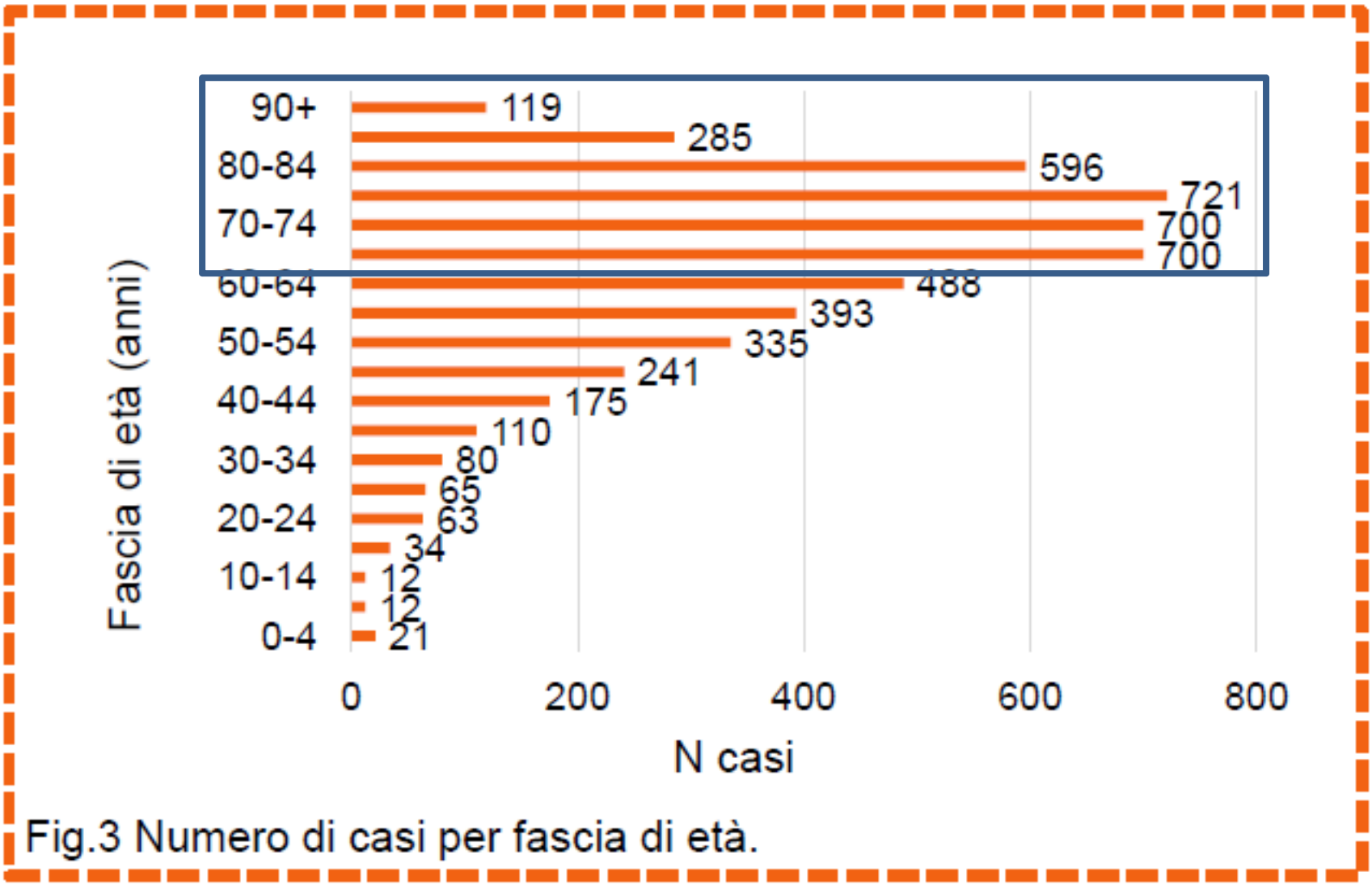


Fig.3 Numero di casi per fascia di età.

Dati Istituto Superiore di Sanità, Aprile 2017

Key Questions for Antimicrobial Use in the elderly population living in LTCFs

- Is the antimicrobial use in the **elderly like in adults living in LTCFs?**
- How can empiricism in antimicrobial use be **reduced**?
- How can antimicrobial use be **optimized** in the elderly ?

M. Tinelli, ESGIE meeting, ECCMID 2016, Amsterdam

Results of the main study analyzing antibiotic prescriptions in LTCFs

Author/Journal	Country	Design	Setting	Study period	Variable	Results
McClean P, et al/ JAC 2012	Ireland	PPS	30 RHs	2010-2011	Median prevalence of antibiotic prescription	9.2%
Burns K, et al J /Hosp Infect 2015	Ireland	HALT-1/HALT-2-PPS	69/190 LTCFs	2010/2013	Median prevalence of antibiotic prescription	11.0%/ 9.7%
Roche FM, et al /J Hosp Infect 2016	Ireland	PPS	24 ID LTCFs	2013	Median prevalence of antibiotic prescription	7.5%
Andersen BA, et al /J Hosp Infect 2000	Norway	PPS	65-70 LTCFs	1997-1999	Median prevalence of antibiotic prescription	7%
Blix HS, et al /Scand J Infect Dis 2007	Norway	PPS	133 NHs	2003	Mean use of antibiotics	14.8 DDDs/100 bed-day
Blix HS, et al /Pharmacoepid. Drug Saf 2010	Norway	PPS	44 NHs	2006	Median prevalence of antibiotic prescription	3%
Rummukainen ML, et al. /Infection 2013	Finland	ESAC PPS	9 NHs	2009-2010	Prevalence of antimicrobial prescription	5-30%
Sundvall PD, et al/ BMC Geriatrics 2015	UK	Retrospective longitudinal cohort study	CHs	2011	Percentage of individuals prescribed antibiotics at least once during	49% (82% with urinary catheter)
Gillespie D, et al/Age Ageing 2015	South Wales	Prospective cohort study	10 CHs	2010-2012	Incidence of antibiotic prescription	2.16 prescriptions per resident year (95% CI: 1.90–2.46)
van Buul LW, et al /J Am Med Dir Assoc 2015	Netherlands	Prospective study.	10 NHs	2012	Prevalence of antibiotic prescription in Registered Infection Consultations	**88%**
Roukens M, et al /JAC 2017	Netherlands	Retrospective study	96 LTCFs	2012-2014	Mean total use of systemic antimicrobials	73 DDDs/1000 residents-day
Daneman N, et al /JAC 2011	Canada (Ontario)	PPS	363 LTCFs	2009	Prevalence of antibiotic use	5.9%
Daneman N, et al /JAMA Intern Med. 2013	Canada (Ontario)	Retrospective study	630 LTCFs	2010	Prevalence of incident antibiotic treatment course	**77.8%**
Daneman N, et al /CMAJ 2017	Canada (Ontario)	Retrospective cohort study	600 LTCFs	2014	Median prevalence of antibiotic prescription	44.9%
Stillo M, et al /Epidemiol Prev 2014	Italy (Piedmont)	HALT2-PPS	63 LTCFs	2013	Prevalence of antibiotic prescription	**17.4%**
Stuart RL, et al /Intern Med J 2012	Australia	PPS	5 LTCFs	2011	Prevalence of antibiotic prescription	9%

RHs: residential homes; LTCFs: long-term care facilities; ID: intellectual disability: NHs: nursing homes; CHs: care homes

Prevalence From 2.16% to 88%

M.Falcone and M.Tinelli, March 2018, preliminary results

Nelle RSA non sempre sono disponibili tutte le classi di antibiotici come in ospedale:

- **Costi elevati**
- **Difficoltà di somministrazione di farmaci per via parenterale**
- **Difficoltà di somministrazione plurioraria in certe categorie di pazienti**

La beta lattamine, i fluorochinoloni, le cefalosporine di terza generazione e gli aminoglicosidi sono gli antibiotici più usati nelle RSA.

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Original article

Predictors of mortality in nursing-home residents with pneumonia: a multicentre study

M. Falcone [1,*], A. Russo [1], F. Gentiloni Silverj [2], D. Marzorati [2], R. Bagarolo [3], M. Monti [4], R. Velleca [4], R. D'Angelo [5], A. Frustaglia [6], G.C. Zuccarelli [6], R. Prina [6], M. Vignati [7], M.G. Marnati [8], M. Venditti [1], M. Tinelli [9]

Antibiotic regimens administered to patients in nursing-home acquired pneumonia	**446 patients**	
	No.	**%**
Monotherapy	**249**	**55.8**
ß-lactam/ß-lactamase inhibitor	**71**	**28.5**
Quinolone	**48**	**19.2**
Macrolide	**33**	13.3
Cephalosporin	87	35
Anti-pseudomonal beta-lactam	10	4
Combination therapy	**197**	**44.2**
ß-lactam/ß-lactamase inhibitor plus a quinolone or a macrolide	**23**	**11.7**
Aminoglycosides plus a ß-lactam/ß-lactamase inhibitor	**46**	**23.3**
Cephalosporin plus a macrolide	**65**	**33**
Cephalosporin plus a quinolone	21	10.6
Anti-pseudomonal ß-lactam plus a quinolone or a macrolide	30	15.3
Anti-pseudomonal ß-lactam plus an anti-MRSA agent	7	3.5
Anti-pseudomonal ß-lactam plus a macrolide plus an anti-MRSA agent	3	1.6
Anti-pseudomonal ß-lactam plus a quinolone plus an anti-MRSA agent	2	1

Prompt institution of appropriate antibiotics in the elderly

The **selection and dosing of antibiotics** **in the elderly** necessitates a clear comprehension of the **physiologic changes**

- **Decreased absorption**
- **Decreased distribution**
- **Decreased metabolism**
- **Decreased renal elimination**

Absorption

Pharmacokinetics and drug metabolism in the elderly

Table 1. Age-related physiological changes and their pharmacokinetic consequences.

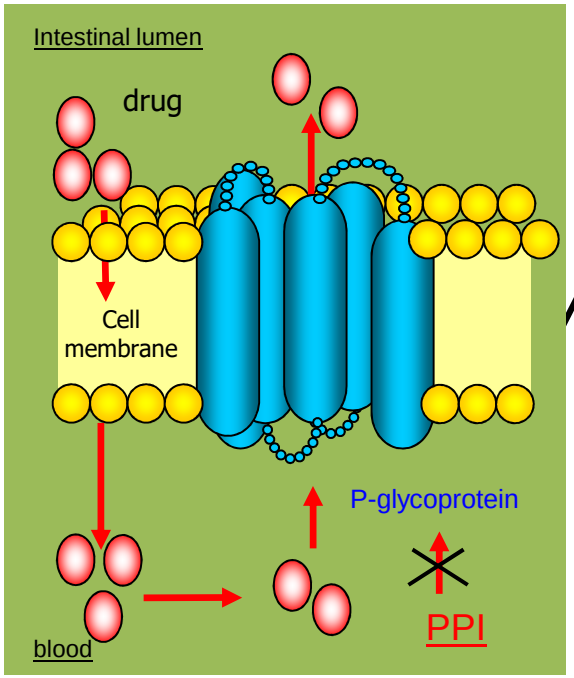
Physiological changes in the elderly	Pharmacokinetic consequences
Increased gastric pH	Slightly decreased absorption (rarely clinically significant)
Delayed gastric emptying	
Reduced splanchnic blood flow	
Decreased absorption surface	
Decreased gastrointestinal motility	

Medications containing metals, such as antacids with aluminum additives and iron supplements, can reduce the absorption of tetracyclines and fluoroquinolones.

- Klotz, Drug Metab Rev 2009 -

About 30% of elderly population over 80 yrs old take PPIs

Inhibition of **P-gp** activity **mediated by PPIs** could **increase absorption of some antibiotics**



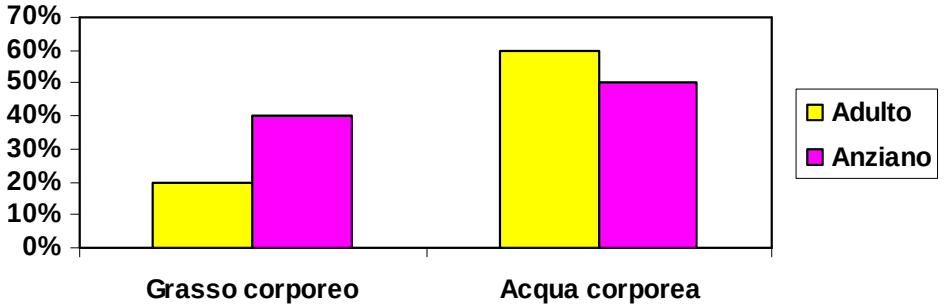
Parameter	No. (%) of cases by linezolid C_{min}: ≥10 mg/liter (n = 33)	<10 mg/liter (n = 247)	P value
Linezolid administration route			
Intravenous	21 (63.6)	157 (63.6)	0.847
Oral	12 (36.4)	90 (36.4)	0.845
Linezolid dosage, median (IQ range) (mg/kg/q12h)			
Overall	9.3 (7.5–10.2)	8.0 (7.1–10.0)	0.067
Intravenous	10.0 (7.9–10.0)	8.0 (7.1–10.0)	0.071
Oral	7.9 (7.9–10.3)	8.5 (7.1–10.0)	0.876
Cotreatments			
Omeprazole	26 (78.8)	68 (27.5)	<0.001
Amiodarone	7 (21.2)	6 (2.4)	<0.001
Amlodipine	7 (21.1)	13 (5.2)	0.003

* Franchi et al. Changes in drug prescribing to Italian community-dwelling elderly people: the EPIFARM-Elderly Project 2000-2010. Eur J Clin Pharmacol. 2014 Apr;70(4):437-43

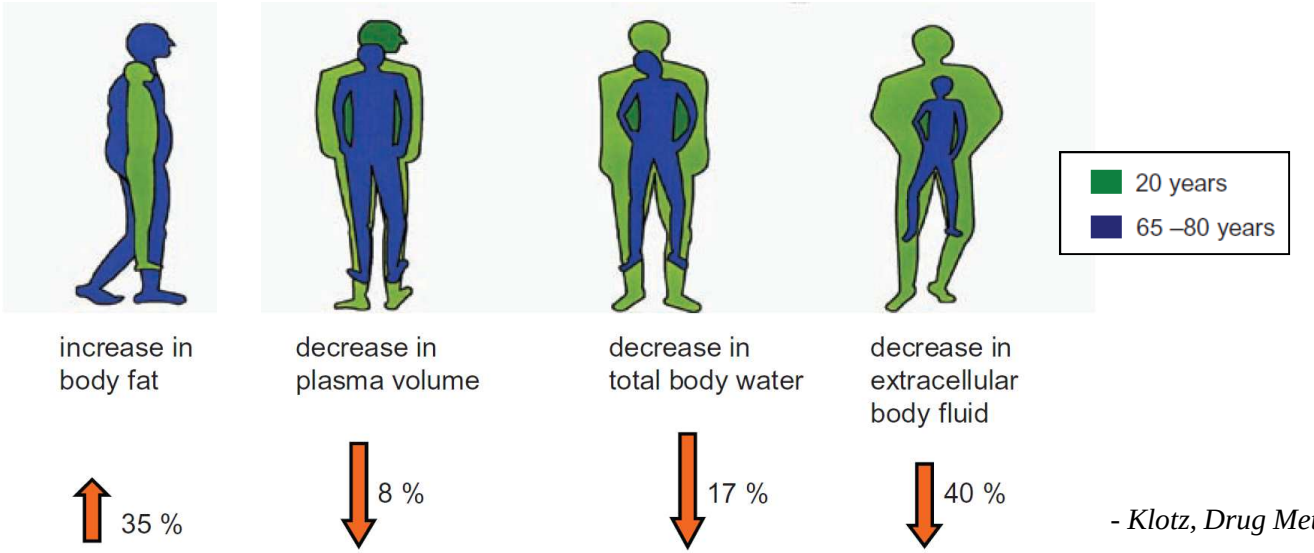
- Pea, AAC 2010 -

Distribution → Tissue Penetration

Physiologic change	Result	PK parameter	PK effect
Reduced muscle mass and total water	Accumulation of hydrophilic drugs	Volume of distribution	**Increase of drug plasma concentrations**
Increased body fat	Accumulation of lipophilic drugs	Volume of distribution	**Increase of drug half-life**



Hydrophilic Antibiotics:	Lipophilic Antibiotics:
• Beta Lactams	• Fluoroquinolones
• Aminoglycosides	• Macrolides
• Vancomycin	• Clindamycin
• Linezolid	• Tigecycline
• Colistin	



- Klotz, Drug Metab Rev 2009

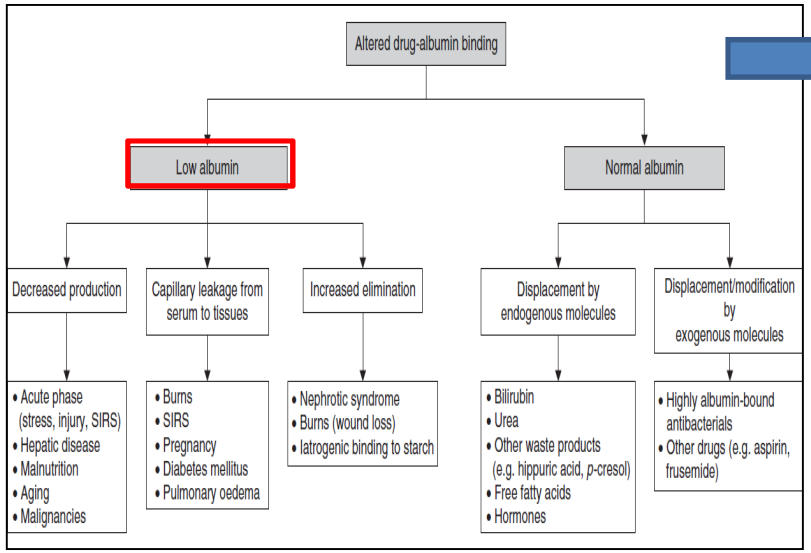
Parametri nutrizionali nell'anziano

Stadi di gravità

PARAMETRO	MALNUTRIZIONE LIEVE	MALNUTRIZIONE MODERATA	MALNUTRIZIONE GRAVE
Calo Ponderale (su peso abituale)	5-10%	11-20%	> 20%
Calo Ponderale (su peso ideale)	10-20%	21-40%	>40%
Linfociti/mm^3	1500-1200	1199-800	<800
Albumina (g/dl)	**3,5-3,0**	**2,9-2,5**	**<2,5**
Transferrinemia (mg/dl)	200-150	149-100	<100
Prealbuminemia (mg/dl)	22-18	17-10	<10
Prot. legante il retinolo (mg/dl)	2,9-2,5	2,4-2,1	<2,1

Linee guida SINPE - Società Italiana di Nutrizione Artificiale e Metabolismo, 2016

L'età e l'ipoalbuminemia possono alterare il legame degli antibiotici alle proteine plasmatiche



Highly bound (>70%)	Moderately bound (70-30%)	Minimally bound (<30%)
Cefazolin	Azithromycin	Amikacin
Cefoperazone	Aztreonam	Amoxicillin
Ceftriaxone	Cefotaxime	Ampicillin
Clindamicin	Cefuroxime	Cefepime
Daptomycin	Ciprofloxacin	Ceftazidime
Ertapenem	chloramphenicol	Colistin
Erythromycin	Clarithromycin	Doripenem
Lincomycin	Levofloxacin	Gentamycin
Minocycline	Linezolid	Imipenem
Rifampicin	Piperacillin	Meropenem
Teicoplanin	Ticarcillin	Norfloxacin
Tigecycline	Vancomycin	Tobramycin

Ulldemolins, Clin Pharmacokinet 2011, Roberts, Clin Pharmacokinet 2013

ORIGINAL RESEARCH

The influence of severe hypoalbuminemia on the half-life of vancomycin in elderly patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia

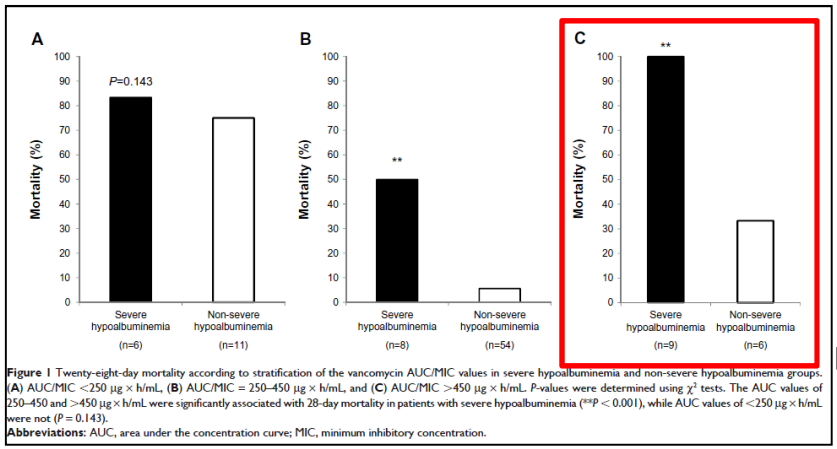


Figure 1 Twenty-eight-day mortality according to stratification of the vancomycin AUC/MIC values in severe hypoalbuminemia and non-severe hypoalbuminemia groups. (**A**) AUC/MIC <250 μg × h/mL, (**B**) AUC/MIC = 250–450 μg × h/mL, and (**C**) AUC/MIC >450 μg × h/mL. *P*-values were determined using χ^2 tests. The AUC values of 250–450 and >450 μg × h/mL were significantly associated with 28-day mortality in patients with severe hypoalbuminemia (**$P < 0.001$), while AUC values of <250 μg × h/mL were not ($P = 0.143$).
Abbreviations: AUC, area under the concentration curve; MIC, minimum inhibitory concentration.

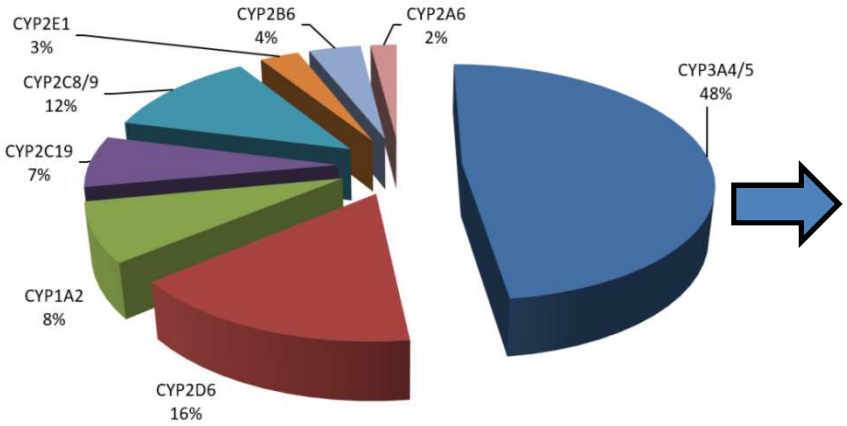
Severe hypoalbuminemia influences the half-life of VCM and treatment outcomes in elderly patients (>75 years of age)..

Ulldemolins, Clin Pharmacokinet 2011, Roberts, Clin Pharmacokinet 2013, A.Novelli, INFECTION 2016

Metabolism

Pharmacokinetics and drug metabolism in the elderly

Physiological changes in the elderly	Pharmacokinetic consequences
Decreased hepatic blood flow	First-pass metabolism can be less effective.
Decreased hepatic mass	Phase I metabolism of some drugs might be slightly impaired.



Antibiotic interactions with concomitant medications very common in the elderly

Clinical significance

< rate of biotransformation of some drugs

- Klotz, Drug Metab Rev 2009 -

Excretion

- ✓ Decreased renal function results in decreased elimination of drugs excreted by the kidney
- ✓ Even in the absence of kidney disease, **renal clearance may be reduced by 35-50% in healthy elderly** vs healthy younger men
- ✓ Reduced **renal clearance of active metabolites may enhance therapeutic effect or increase risk of toxicity**

Risk factors for HA-AKI in the elderly

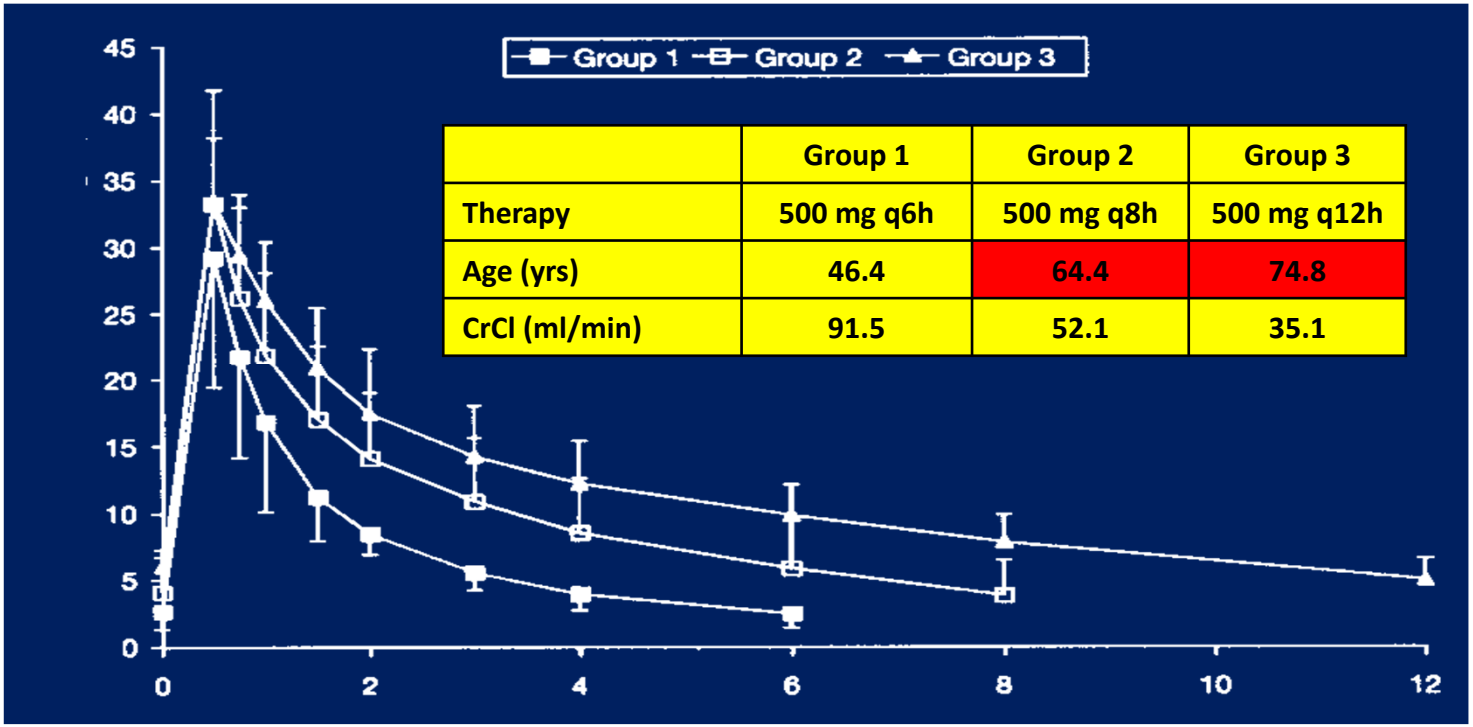
- ❖ Age-related changes in the kidney, systemic vasculature or immunological system
- ❖ Co-existing illnesses (CKD, cardiovascular, hypertension, diabetes, obstructive uropathy or infection)
- ❖ Hypovolemia
- ❖ Sepsis
- ❖ Medication-related toxicity (NSAIDs, diuretics, ACE inhibitors or nephrotoxic antibiotics)
- ❖ Contrast-induced nephropathy
- ❖ Perioperative factors

Klotz, Drug Metab Rev 2009

- ✓ Need to reduce dose and/or increase dosing intervals
- ✓ Drug dosing decision must **take into account pharmacodynamic as well as pharmacokinetic considerations**

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

Factors associated with treatment failure were %T>MIC that has been described as an independent influential factor for clinical and bacterial response to meropenem in low respiratory tract infections, **in elderly patients the cuttoff where 76%**
Hypoalbuminaemia that has also been associated with **bacterial failure in meropenem treated patients.**

Cheatham SC et al., Pharmacotherapy, 2008, Ulldemolins, Clin Pharmacokinet 2011, Roberts, Clin Pharmacokinet 2013

MEROPENEM DOSING IN THE ELDERLY

Meropenem Short-term duration infusion	CrCl ≥ 51 ml/min	1.0 g q8h for 1.0 g unit dose 0.5 g q8h for 0.5 g unit dose
	CrCl 26-51 ml/min	1.0 g q12h for 1.0 g unit dose 0.5 g q12h for 0.5 g unit dose
	CrCl 10-25 ml/min	0.5 g q12h for 1.0 g unit dose 0.25 g q12h for 0.5 g unit dose
	CrCl <10 ml/min	0.5 g q24h for 1.0 g unit dose 0.25 g q24h for 0.5 g unit dose
Meropenem Extended or continuous infusion	CrCl >100 ml/min	High dosages either administered over extended or continuous infusion
	CrCl 50-100 ml/min	24-h continuous infusion: 3.0 g q24h
	CrCl ≤ 50 ml/min	Extended 1.0 g q 8 h

Cunha BA. Meropenem in elderly and renally impaired patients. Int J Antimicrob Agents. 1999;11:167-77. ; Usman M, Frey OR, Hempel G. Population pharmacokinetics of meropenem in elderly patients: dosing simulations based on renal function. Eur J Clin Pharmacol. 2017;73:333-42.

Piperacillin/tazobactam

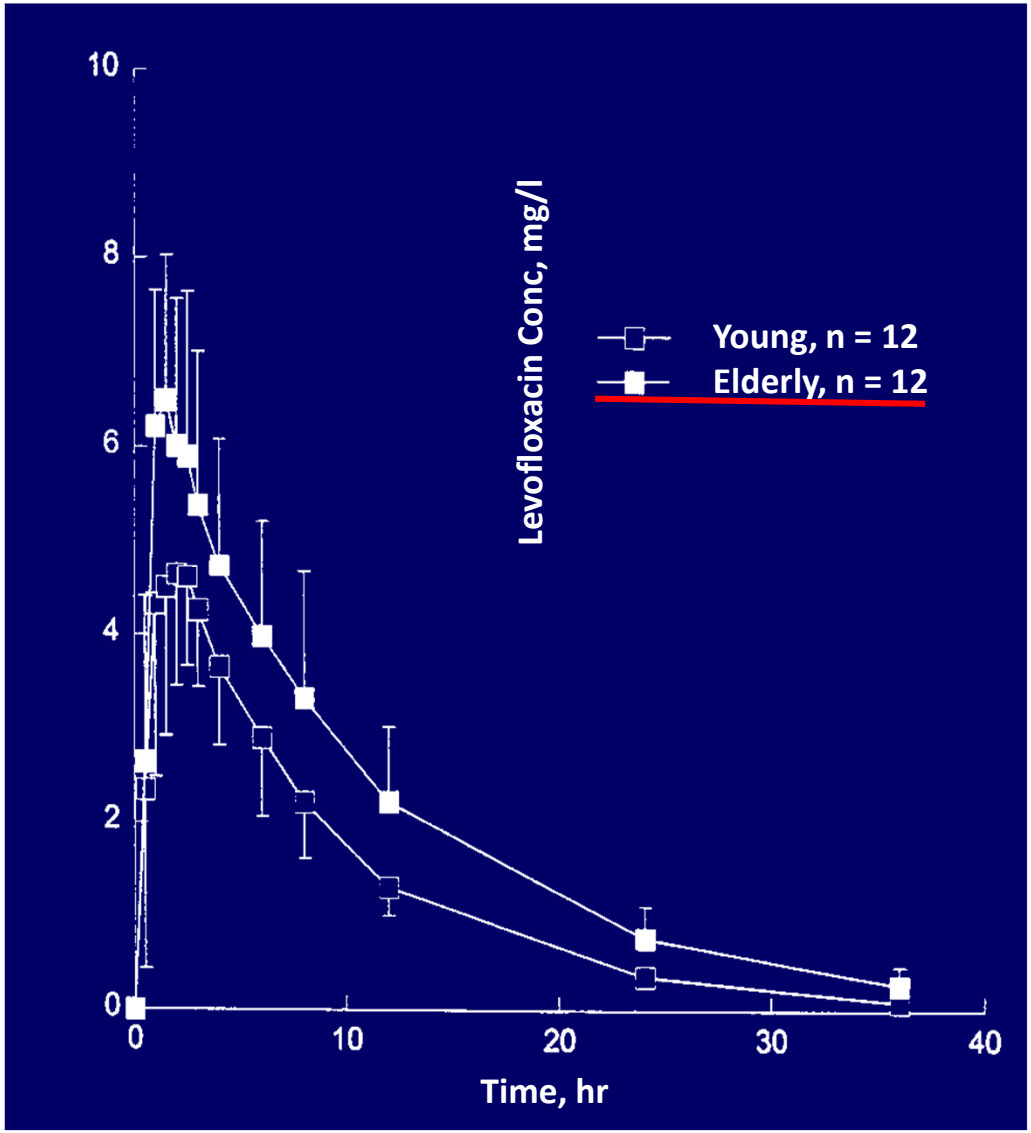
No dose adjustment is required in the elderly **with normal renal function or creatinine clearance values above 40 mL/min.**

Pi		
Sh		
in		
(3		
Pi		
Extended-infusion (4h)	CrCl 40-20 ml/min	3.375g q12h, 4-h infusion
	CrCl <20 ml/min	3.375g q12h, 4-h infusion

Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of optimal renal dosage adjustments for traditional and extended-infusion piperacillin-tazobactam dosing regimens in hospitalized patients. Antimicrob Agents Chemother. 2010 ;54:460-5.

Levofloxacin 500 mg single oral dose

Mean plasma concentrations



Chien SC et al., Antimicrob Agents Chemother, 1997

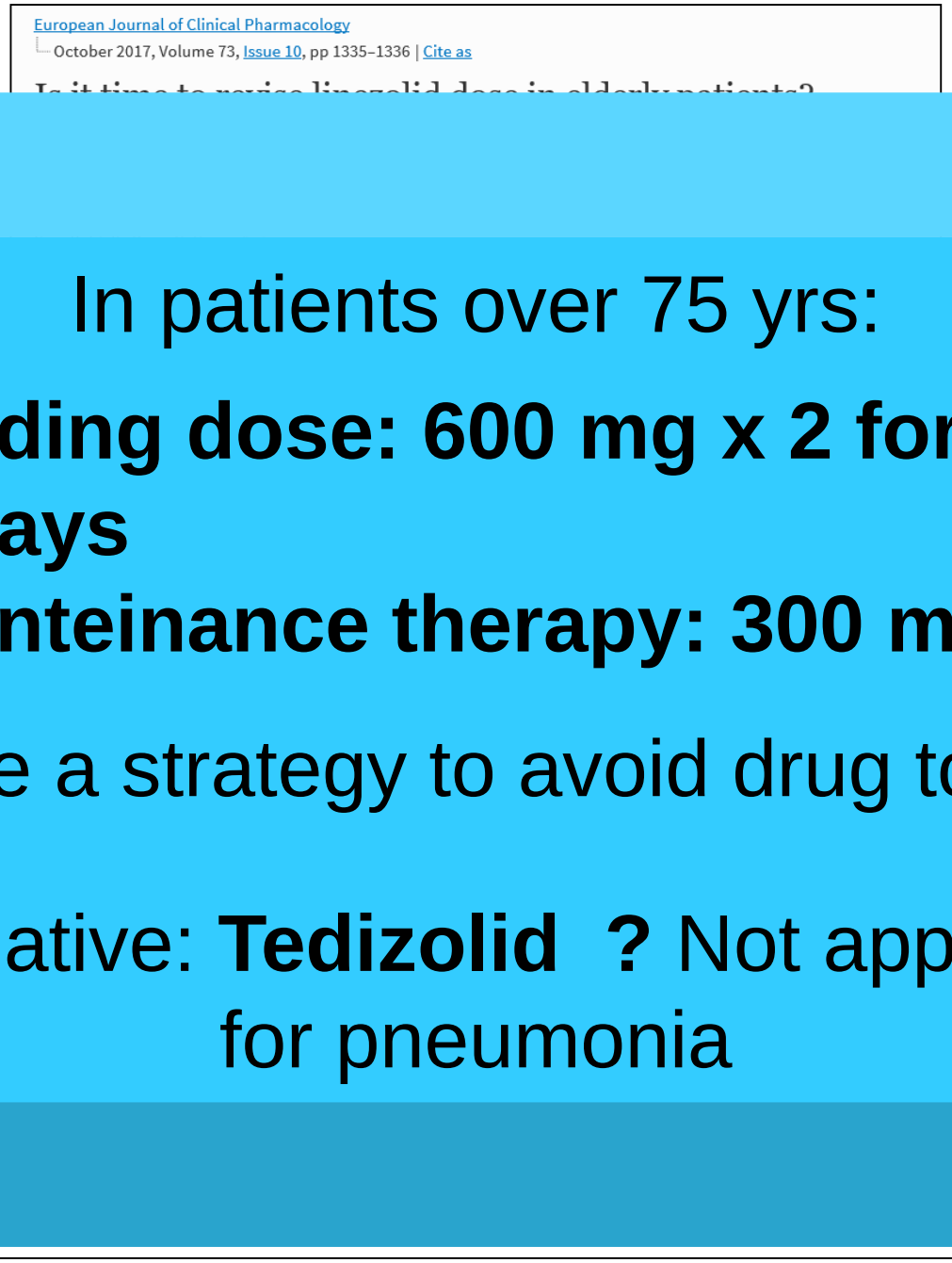
Quinolones dosing in the elderly

For higher values of MIC, the proposed regimens were inefficient for patients with moderate or severe renal impairment.

The dose reduction does not allow the same exposure in elderly patients with renal impairment, especially in cases of infections by resistant strains

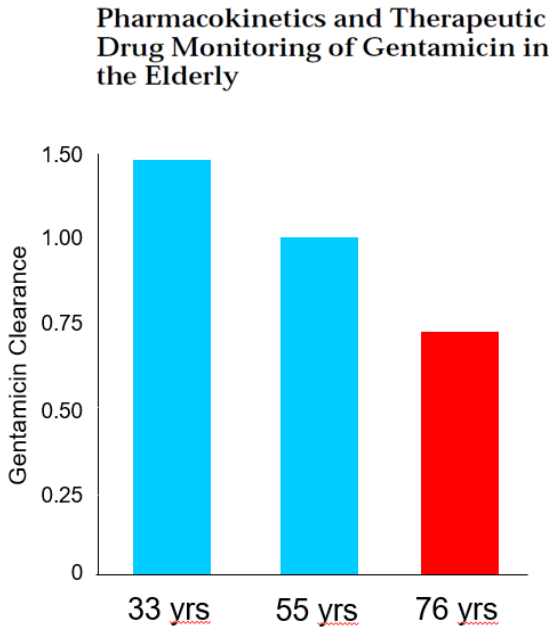
	CrCl <20 ml/min	500 mg q48h

M.Falcone and M.Tinelli, March 2018, preliminary results, Cios A, Wyska E, Szymura-Oleksiak J, Grodzicki T. Population pharmacokinetic analysis of ciprofloxacin in the elderly patients with lower respiratory tract infections. Exp Gerontol. 2014;57:107-13, Leroy B, Uhart M, Maire P, Bourguignon L. Evaluation of fluoroquinolone reduced dosage regimens in elderly patients by using pharmacokinetic modelling and Monte Carlo simulations. J Antimicrob Chemother. 2012;67:2207-12.


European Journal of Clinical Pharmacology
October 2017, Volume 73, Issue 10, pp 1335–1336 | Cite as
In patients over 75 yrs:
• loading dose: 600 mg x 2 for 3 days
• manteinance therapy: 300 mg x 2
can be a strategy to avoid drug toxicity
Alternative: Tedizolid ? Not approved for pneumonia

Aminoglycosides

- Gentamicin, tobramycin, amikacin
- Role for seriously ill; MDR UTIs, esp upper UTI
- Increased **risk of toxicity vs other agents**
- Nephrotoxicity, ototoxicity: **increased risk in elderly**, dehydration, pre-existing renal disease
- Needs monitoring!! Scr (2-3 x /week), levels



- *Triggs, Clin Pharmacol 1999* -

Aminoglycoside		
Amikacin	**CrCl 51-90 ml/min**	**60-90% of dose q12h**
	CrCl 50-10 ml/min	**30-70% of dose q 12-18h**
	CrCl <10 ml/min	**20-30% of dose q24-48h**
Gentamycin	**ClCr >60 ml/min**	**4 mg/kg q24h**
	CrCl 59-40 ml/min	**4 mg/kg q36h**
	CrCl 39-20 ml/min	**4 mg/kg q48h**

M.Falcone and M.Tinelli, March 2018, preliminary results Plajer SM, et al. Gentamicin and renal function: lessons from 15 years' experience of a pharmacokinetic service for extended interval dosing of gentamicin. Ther Drug Monit. 2015;37:98-103 ; Lanao et al.Amikacin concentrations in serum and blister fluid in healthy volunteers and in patients with renal impairment. J Antimicrob Chemother. 1983;12:481-8.

Effects of aging on metabolism and elimination of vancomycin

	PK parameters					Changes in elderly	Clinical implications
	C_{max}	AUC	$T_{1/2}$	V_{ss}	CL_{tot}		
Vancomycin [47] (trough c 10–15 µg Survivors Non surviv						Elderly patients with	AUC/MIC value of 250– e
Vancomy Severe h Non seve							

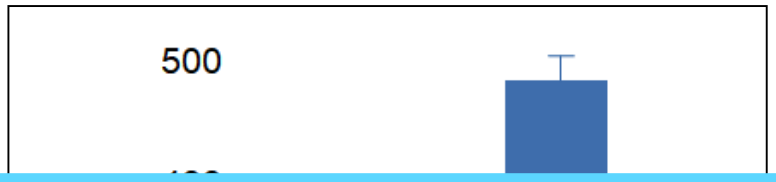
Nutritional status,severe hypoALB influences half-life of vancomycin and treatment outcomes in elderly patients

Consider alternative agents in elderly patients with renal failure

80-100	15	24
>100	15	Check trough level at 24 h

Ghouti-Terki L, Chasseuil E, Rabot N, Paintaud G, François M, Birmelé B et al. Vancomycin during the last hour of the hemodialysis session: a pharmacokinetic analysis. Nephron. 2017;135:261-267; Zelenitsky SA, Ariano RE, McCrae ML, Vercaigne LM. Initial vancomycin dosing protocol to achieve therapeutic serum concentrations in patients undergoing hemodialysis. Clin Infect Dis. 2012;55:527-33; M.Falcone and M.Tinelli, March 2018, preliminary results

Single-Dose Pharmacokinetics of Daptomycin in Young and Geriatric Volunteers



- **Daptomycin 6-8 mg/Kg/day can be the right dose in older adults >65 years if CrCl is > 30 mL/min.**
- **If CRCl < 30 mL/min reduce to 6 mg/Kg/day every 48 hrs**

CrCl >30 ml/min	6-8 mg/kg q 24 h
CrCl <30 ml/min	6 mg/kg q48h

Falcone Met al.. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2013 ;57:1568-76; Bassetti M, Nicco E, Ginocchio F, Ansaldi F, de Florentiis D, Viscoli C. High-dose daptomycin in documented *Staphylococcus aureus* infections. Int J Antimicrob Agents. 2010;36:459-61. Dvorchik, J Clin Pharmacol 2006 -

In patients over 75 with comorbidities :

- Loading dose (70 kg)= 7 MU
- Maintenance dose: 3,5 MU x 2 (evaluate GFR daily) and, if GFR $\leq$ 30 mL/min further reduce to 2,5 x 2 MU

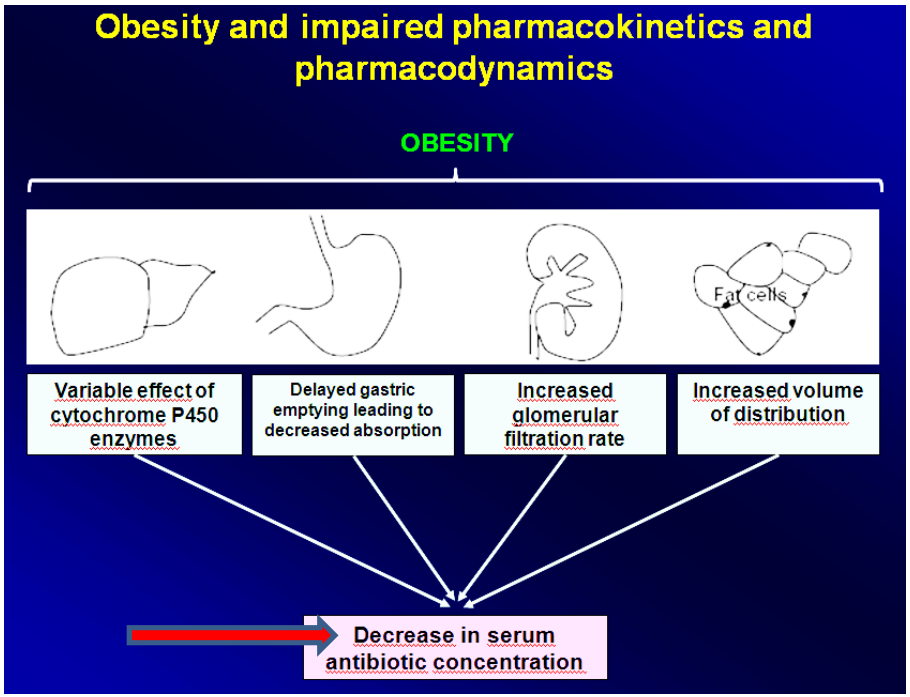
REVIEW Clinical Medicine Reviews
Clinical Medicine Reviews in Therapeutics 2011:3 123–142
Fosfomycin and Its Application in the Treatment

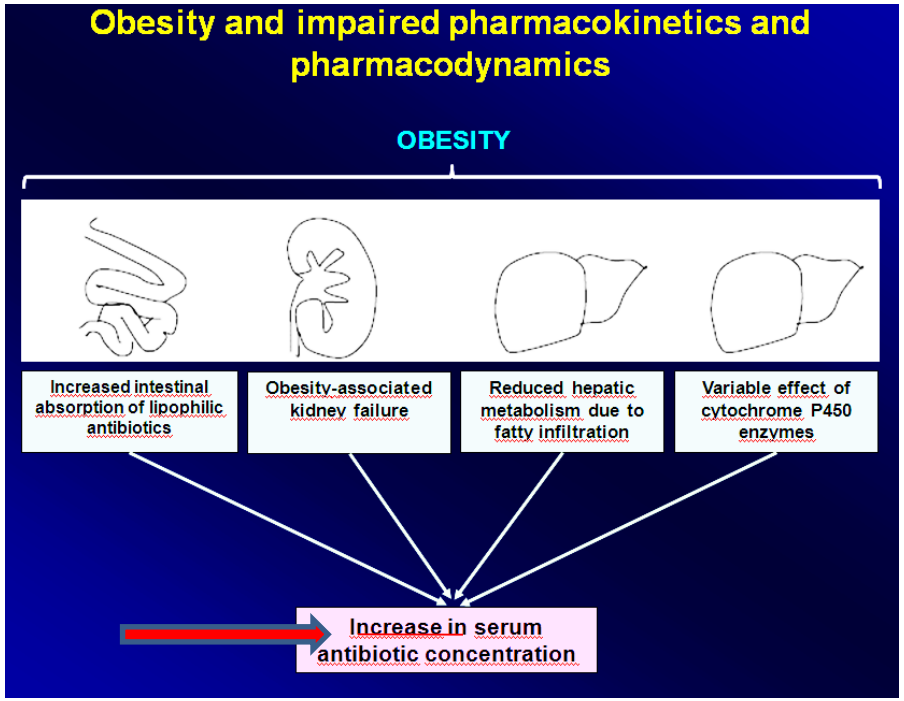
- **FOSFOMYCIN:**
- **4 gr. e.v q 6 hrs (normal kidney function)**

In elderly patients (>70 years) and in patients with renal failure(**ClCr ≤ 50): daily dosage 2 g administered four times daily.**

concentrations above 128 mg/L for more than 24 hours

Special population
Antibiotic dosing in obese elderly population





Hydrophilic antibiotics

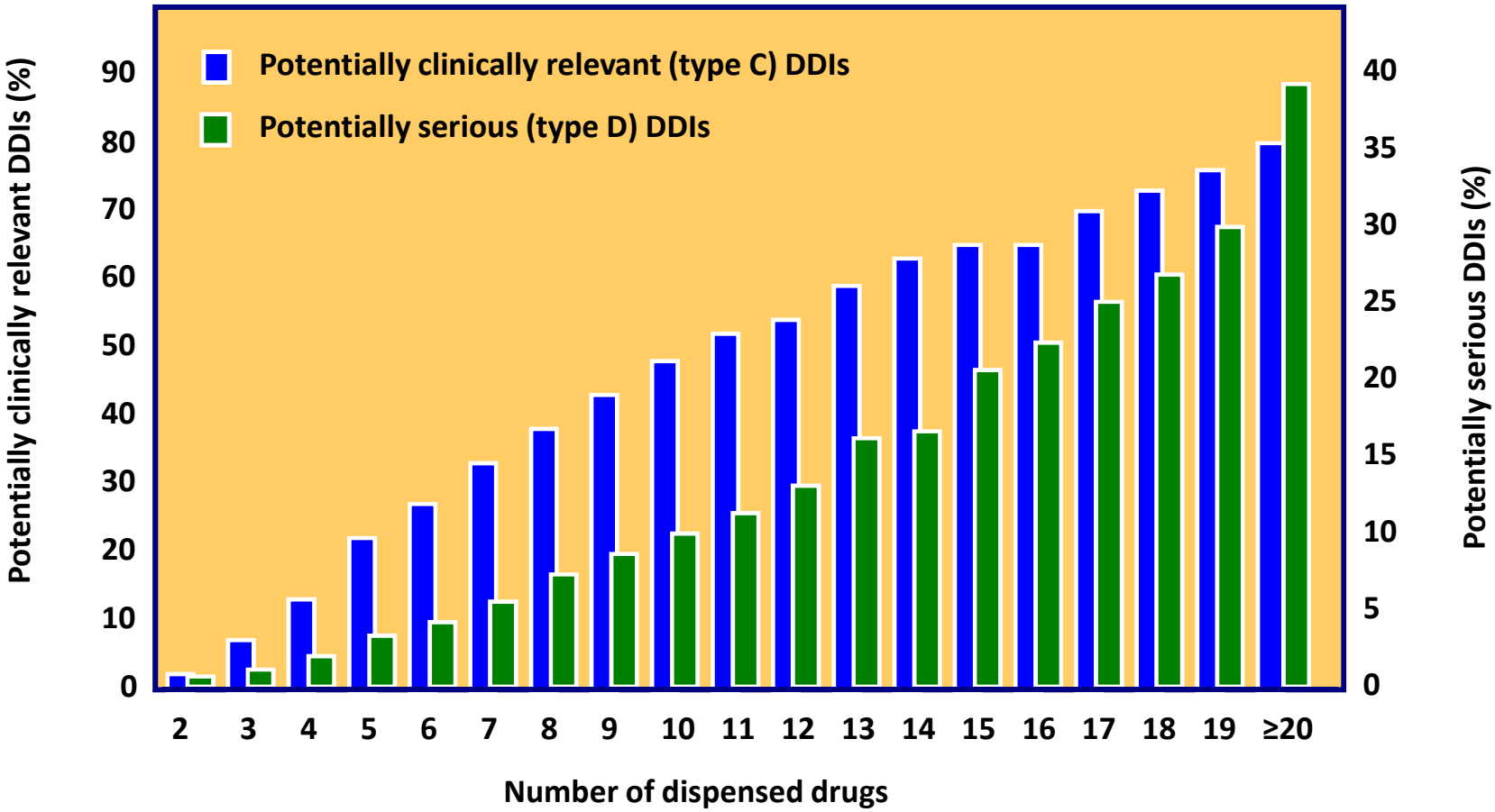
- **Ideal** or adjusted body weight is generally used for dosing

Lipophilic antibiotics

- **Total** body weight is generally recommended for dosing

Al-Dorzi HM et al., Curr Opin Infect Dis, 2014 , A.Novelli, INFECTION 2016

Potential Drug-to-Drug Interactions Do Increase with the Number of Administered Medications in the elderly



Johnell & Klarin, Drug Safety 2007; 30: 911-918

Literature review of antibiotic adverse event in the elderly population living in LTCFs: general aspects

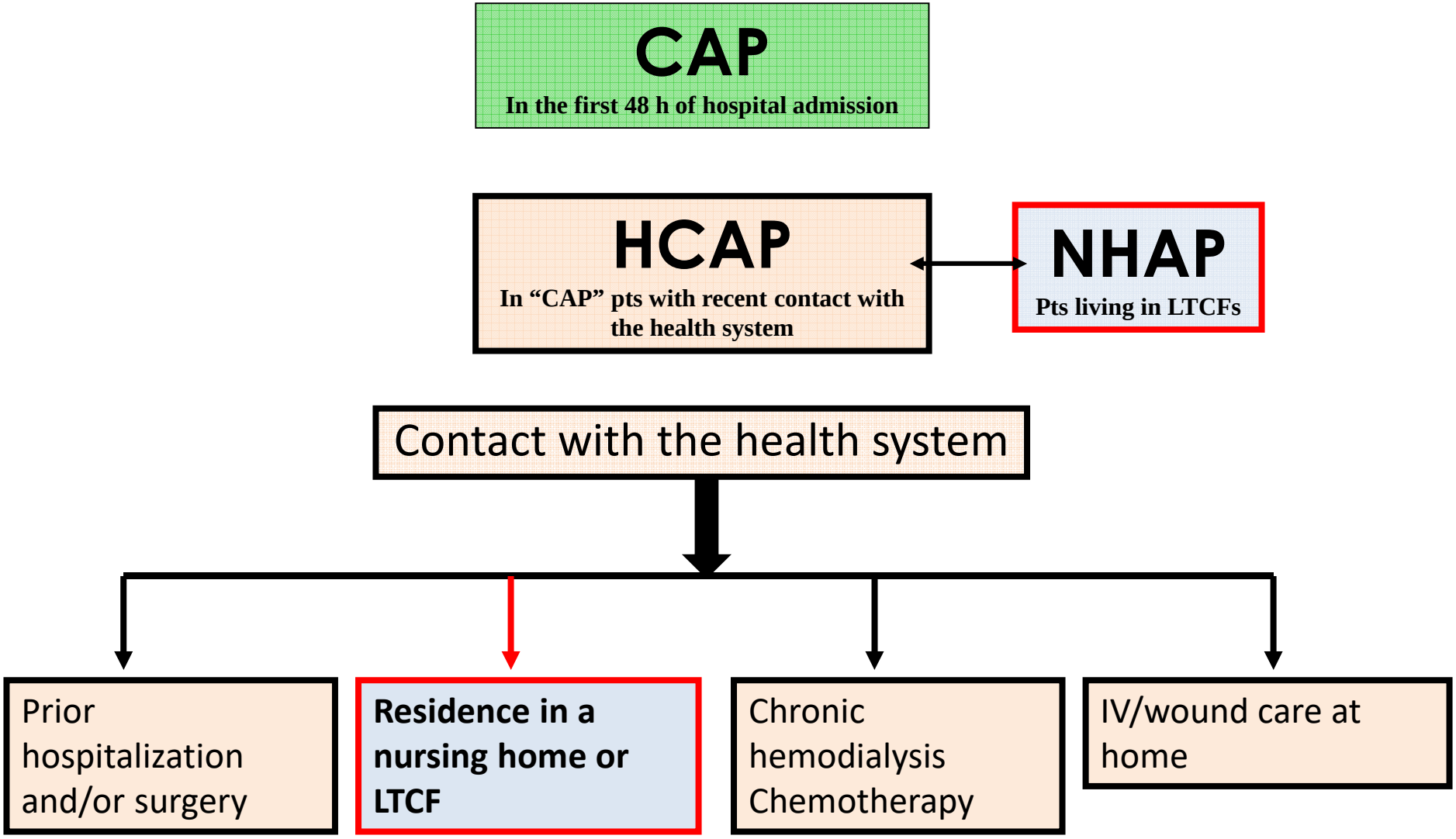
Study	Country	Aim of the study	Design	Period	Setting	Intervention	Study Population	Inclusion/exclusion criteria	Results	Comments
Field T, Arch Intern Med 2001	Massachusetts	To assess resident factors associated with adverse events (derived from all drugs)	Case-control study nested with prospective study	1997 (12 months)	Nursing homes (N=18)	None (evaluation of adverse drug events)	N= 410 residents (mean age 83 ys)	Inclusion criteria: All long-stay residents	Risk factors for adverse drug events (among others): - Taking an antibiotic (after opioids and antipsychotic) About 35% of patients with adverse events were administered antibiotics	Not specific for antibiotics
Hohl CM, Ann Emerg Med. 2001	Canada	To document the degree of polypharmacy, the frequency of adverse drug-related events leading to emergency department presentation	Retrospective study	January - December 31, 1998	Emergency Department "Davis-Jewish General Hospital in Montreal"	None (evaluation of adverse drug events)	N= 283	Inclusion criteria: Patients ≥ 65 years old	The most frequently implicated classes of medications were nonsteroidal anti-inflammatory drugs, antibiotics, anticoagulants, diuretics, hypoglycemics, β-blockers, calcium-channel blockers, and chemotherapeutic agents	Not specific for antibiotics
Daneman N, JAMA Intern Med. 2015	Ontario, Canada	To examine whether living in a nursing home with high antibiotic use is associated with an increased risk of antibiotic-related adverse outcomes for individual residents	Observational study	January 2010 to December 31, 2011	Nursing homes (N=607)	None	N= 110 656 patients Median age 85 ys	Inclusion criteria: all residents ≥65 ys	Antibiotics were provided on 2 783 000 of 50 953 000 resident-days in nursing homes (55 antibiotic-days per 1000 resident-days). **Residence in a high-use nursing home was associated with an increased risk of a resident experiencing an antibiotic-related adverse event**	Strengths: Sample size High quality analysis Specific for nursing homes

M.Falcone and M.Tinelli, March 2018, preliminary results

Antibiotic therapy in the most common infections in the elderly.

Specificic patterns

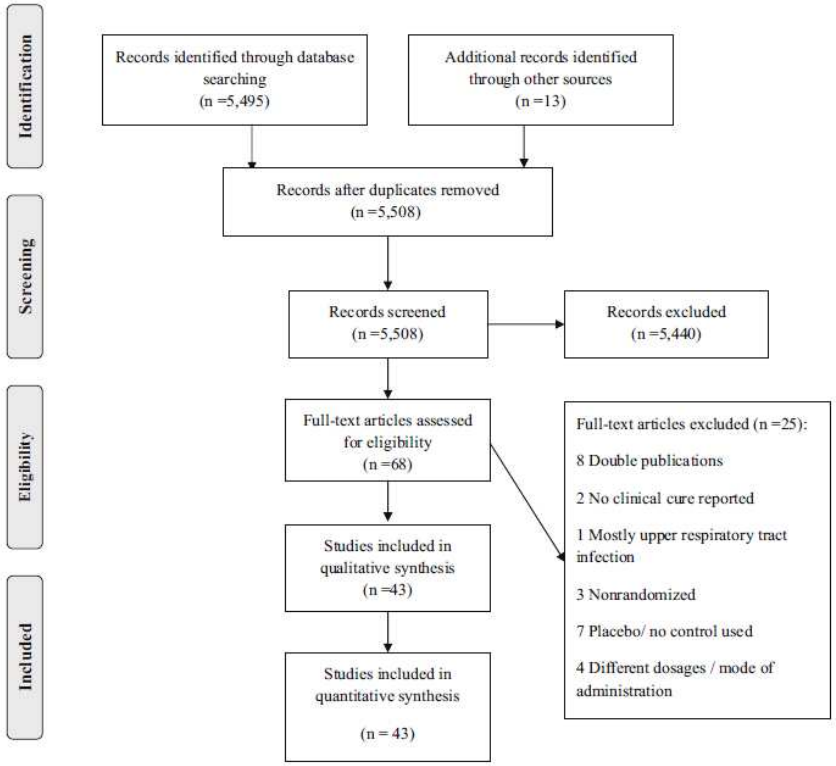
Respiratory tract infections



IDSA/ATS Guidelines 2016, Chalmers JD Clin Infect Dis. 2014 Feb;58(3):330-9, Am J Respir Crit Care Med 2005

Participation of Elderly Adults in Randomized Controlled Trials Addressing Antibiotic Treatment of Pneumonia

Tomer Avni, MD,[a] Shahaf Shiver-Ofer, MD,[a] Leonard Leibovici, MD,[a] Evelina Tacconelli, MD,[b] Giulia DeAngelis, MD, PhD,[c] Barry Cookson, MD,[d,e] Leonardo Pagani, MD,[f,g] and Mical Paul, MD[h,i] JAGS 63:233–243, 2015



No data were found on the comparative efficacy of antibiotic treatment in **elderly adults and the general population.**

Clinical Microbiology and Infection 24 (2018) 72–77

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

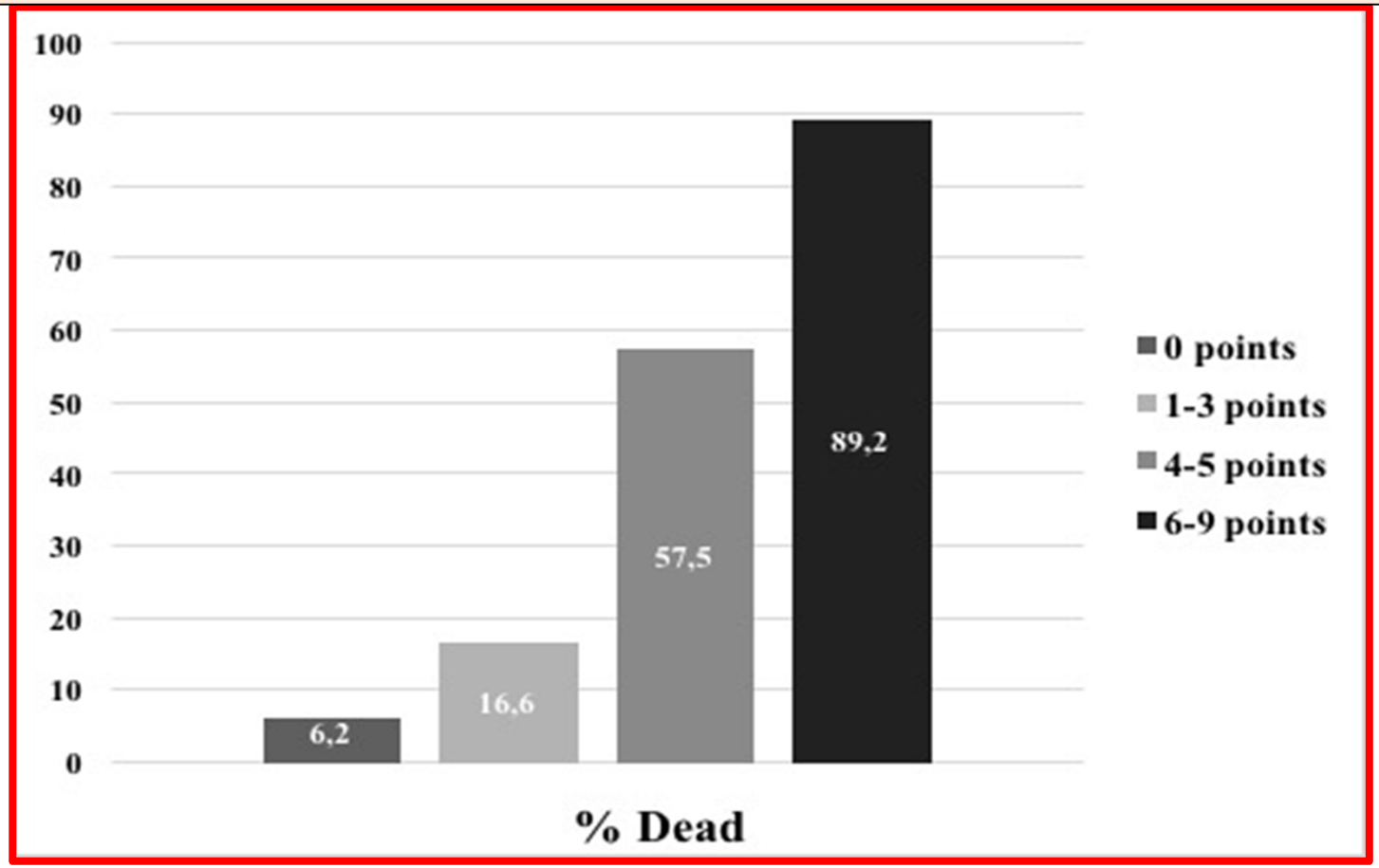
Predictors of mortality in nursing-home residents with pneumonia: a multicentre study

M. Falcone [1,*], A. Russo [1], F. Gentiloni Silverj [2], D. Marzorati [2], R. Bagarolo [3], M. Monti [4], R. Velleca [4], R. D'Angelo [5], A. Frustaglia [6], G.C. Zuccarelli [6], R. Prina [6], M. Vignati [7], M.G. Marnati [8], M. Venditti [1], M. Tinelli [9]

Multivariate analysis about predictors of 30-day mortality in NHAP			
Variables	**OR**	**CI 95%**	**p-value**
Malnutrition	**7.8**	3-20.2	<0.001
Bilateral Pneumonia	**3.7**	1.4-9.8	0.008
Acute mental status deterioration	**6.2**	2.2-17.6	0.001
Hypotension	**7.7**	2.3-24.9	0.001
PaO2/FiO2 ratio ≤250	**7.4**	2.2-24.2	0.001

446 patients with NHAP were included in final cohort.
The median age was 80 (IQR 75-87) years.

Performance of the severity of NHAP model for predicting 30-day mortality



NH residents with pneumonia have specific risk factors associated with 30-day mortality. **Malnutrition and acute mental change appears as major determinants of death in this population**

Clinical Review & Education | JAMA February 9, 2016 Volume 315, Number 6

Review

Antibiotic Therapy for Adults Hospitalized
With Community-Acquired Pneumonia

CAP treatment in older adults

- **Ceftriaxone 2g iv or im od**

+

- **Azithromycin/Levofloxacin 500 mg od**

No dose adjustement required

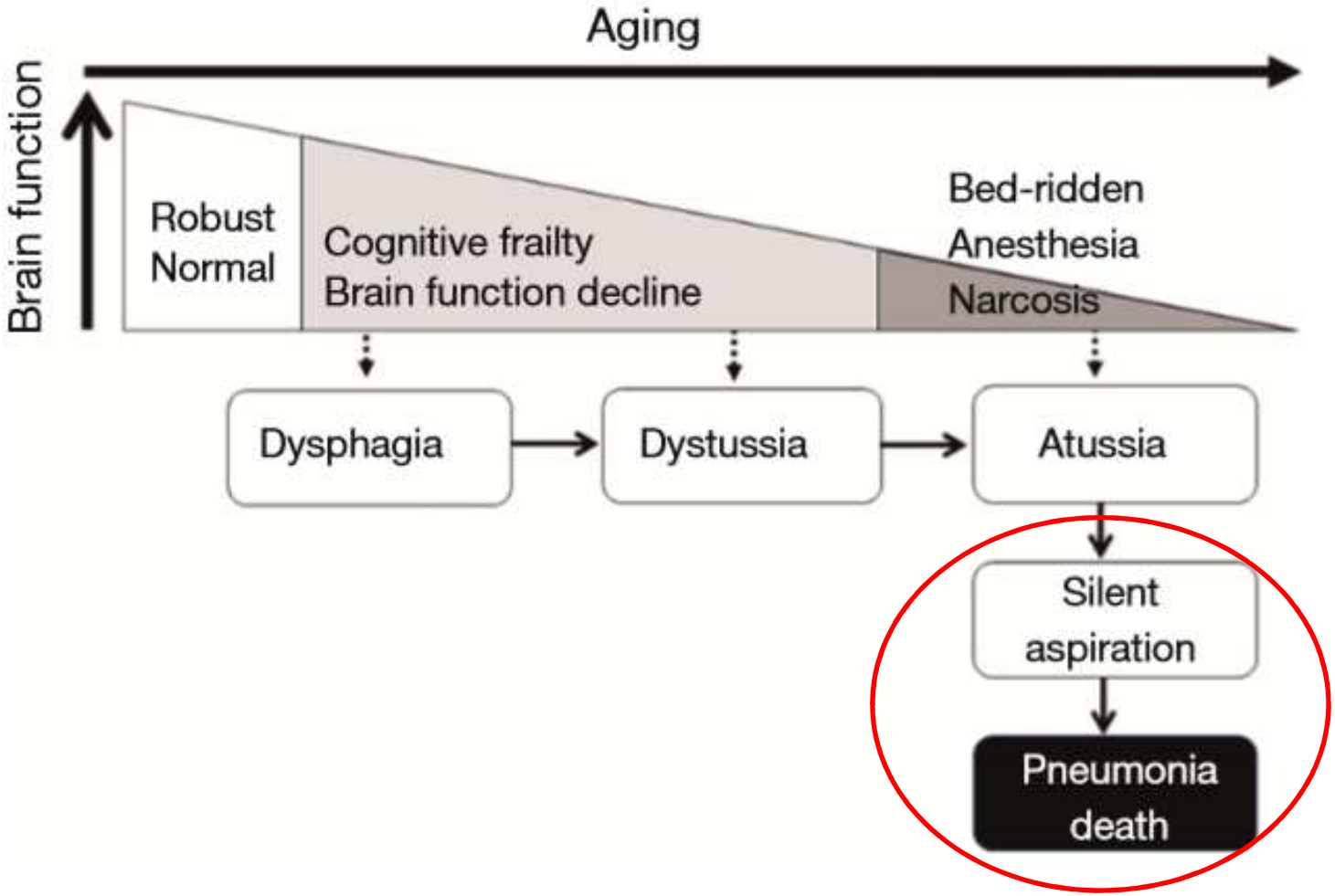
Postma et al,[26] 2015	90-d Mortality	665	NR	506	NR	0.91 (0.58-1.42)[g]

0.1 1.0 10

Adjusted OR (95% CI)

observational studies.

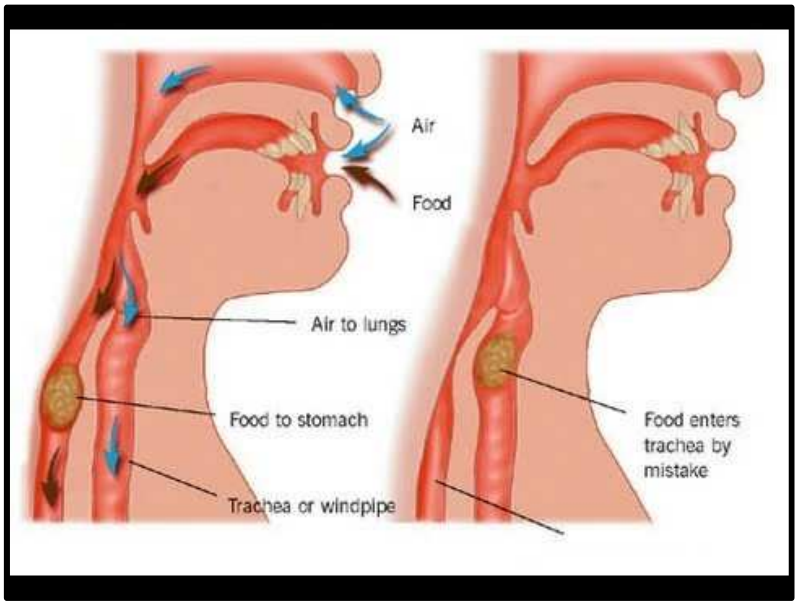
The natural course of functional decline in most elderly people



With aging, **brain function declines**. With declining brain function, dysphagia starts, followed by dystussia, and then finally atussia and silent aspiration, which is closely related to death from pneumonia.

Satoru E. ,J Thorac Dis. 2016 Mar; 8(3): 632–639

ASPIRATION PNEUMONIA IN THE ELDERLY POPULATION LIVING IN LTCFs



The elderly have a higher probability of acquiring aspiration pneumonia due to underlying conditions commonly found in the geriatric population. These underlying conditions include the following:

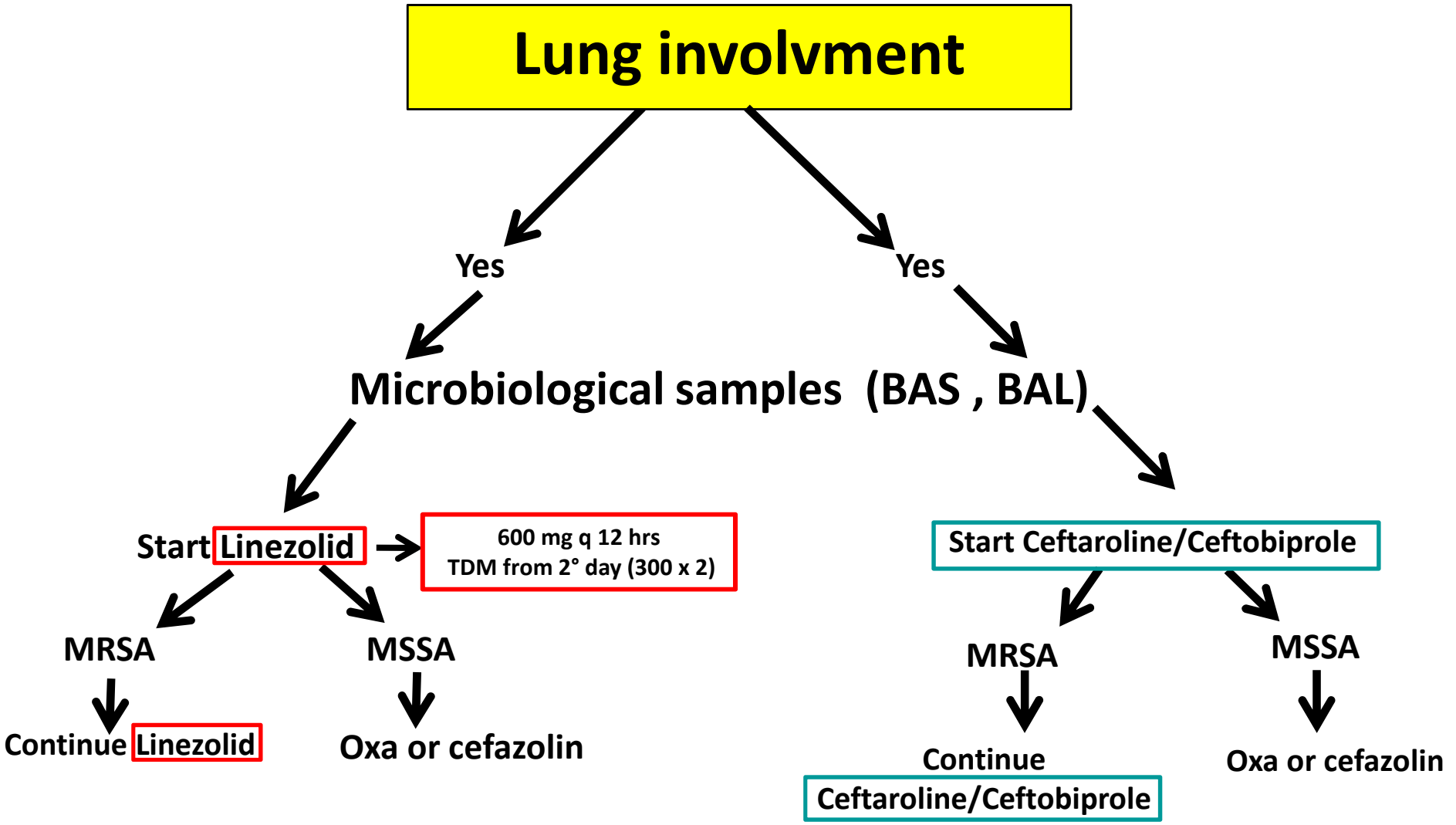
- **Impaired gag reflex** due to stroke or neurological disease (i.e. Parkinson's, Huntington's, or Alzheimer's disease)
- **Difficulty swallowing**, also known as dysphagia, due to cancerous strictures on the esophagus, mechanical ventilation, or neurological disease
- **Impaired ability to cough or expel aspirated m**aterial due to age or sedation
- Presence of a **feeding tube**
- **Compromised immune response** due to age, disease, or immunosuppressant medications

Aspiration pneumonia **does not always require antimicrobial treatment unless there is clear evidence of bacterial infection** e.g. consolidation on CXR . It be may caused by an initial chemical pneumonitis rather than infective pneumonia

Treatment with early, empiric, broad-spectrum antibiotics should be administered then selection of pathogen specific antibiotics or decision to stop or continue the use of antibiotics is made based on quantitative bacteriology

Clindamycin (Cleocin) is still the agent most commonly used, although it lacks gram-negative bacterial coverage. Beta-lactam penicillins and newer quinolones have been used successfully.[2,29–31] In addition to covering the previously mentioned bacteria, these antibiotics have the added benefit of covering anaerobic bacteria. Metronidazole (Flagyl) should not be used alone because it has a higher clinical failure rate.[32,33]

Proposal therapy for suspect MRSA-NHAP in older adults



M.Tinelli, AMIT 2015, Milan

Ceftaroline treatment in older adults

Clinical cure rates by the most common baseline pathogen at test-of-cure visit: integrated FOCUS studies

Microbiological modified intention-to-treat efficacy population (mMITTE)		
	Ceftaroline	Ceftriaxone
Gram positive		
S. pneumoniae	59/69 (85.5%)	48/70 (68.6%)
MDRSP	4/4 (100%)	2/9 (22.2%)

No change of 600mg bd dose in older adults till CrCl > 50 ml/min

data to make specific dosage adjustment recommendations for patients with severe renal impairment **(CrCL ≤ 30 ml/min)** and ESRD, including patients undergoing haemodialysis

Ceftaroline fosamil has a **low propensity for drug interaction.**

Clin Pharmacokinet (2016) 55:1507–1520
DOI 10.1007/s40262-016-0418-z

CrossMark

REVIEW ARTICLE

Ceftobiprole 500 mg, administered by 2-h intravenous infusion every 8 h.

Only if ClCr **< 30 reduce to 500 mg every 12 hours**

impairment, as recommended for the general population

Urinary tract infections in the elderly population resident in LTCFs

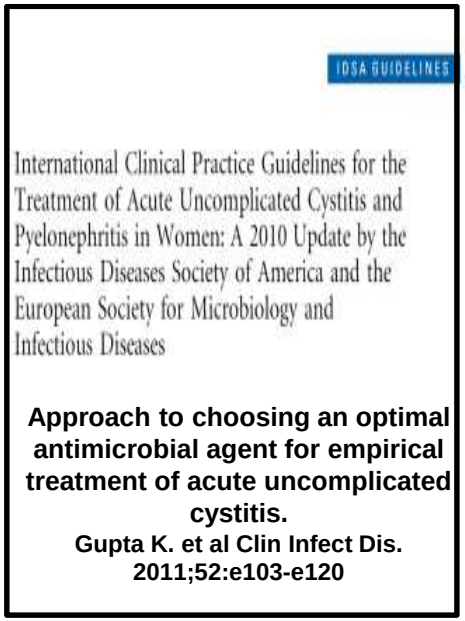
- Primary cause of bacteremia in LTC residents is due to UTIs
- Incidence of **symptomatic UTIs in elderly in LTC around 10%**
- Prevalence of **asymptomatic bacteriuria in women approx. 30% and 10% in men**
  - Why so common?

Risk Factors

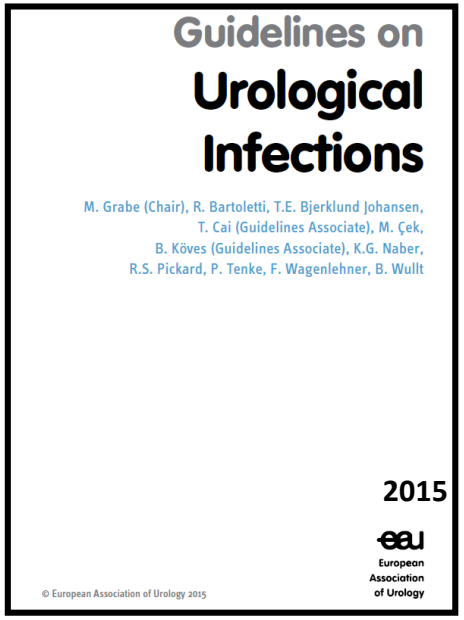
- Physiologic changes of bladder / urethral flora w/ age (post/menopausal women)
- Use of indwelling catheters
- Congregate living
- Functional / Cognitive Impairment
  - Decrease self care
  - Decrease cues to void
  - Difficulty finding bathroom / suitable location to void
  - ?Elevated Post Void Residual Volume of Urine?

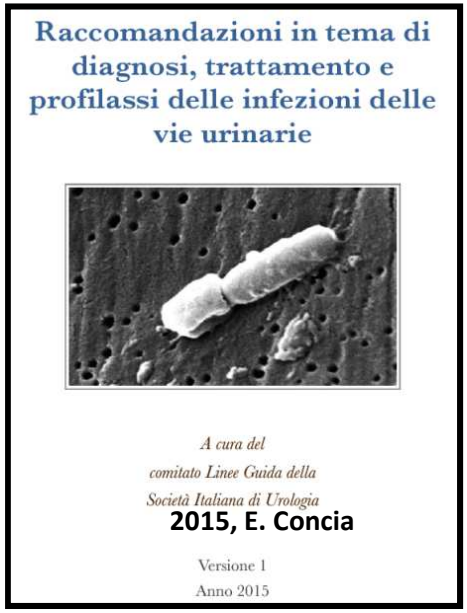
Gupta, K; Hooton, TM; Naber, KG; Wult, B; Colgan, R; Miller, LG; Moran, GJ; Nicolle, LE; Raz, R; Schaeffer, AJ; Soper, DE (2011). International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious disease society of america and the european society for microbiology and infectious disease. Clinical Practice Guidelines. 2011:52, March; Mathews, JS; Lancaster, JW (2011) Urinary tract infection in the elderly population. The American Journal of Geriatric Pharmacotherapy. 9 (5) p. 286-309; Mouton, C; Adenuga, B; Vijayan, J (2010). Urinary tract infections in long-term care. *Annals of Long-Term Care* 18 (2) p. 35-39.

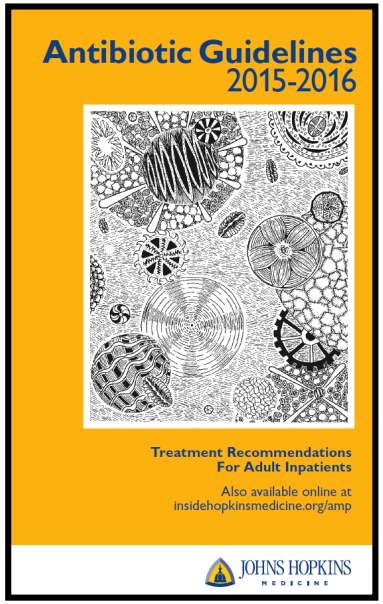
Treament of urinary tract infections in the elderly population resident in LTCFs



Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis.
Gupta K. et al Clin Infect Dis. 2011;52:e103-e120







Urinary Tract Infections in Older Men

N Engl J Med 374;6 nejm.org February 11, 2016

Anthony J. Schaeffer, M.D., and Lindsay E. Nicolle, M.D.

Terapia delle infezioni urinarie non complicate (cistite) nell'anziano

ANTIBIOTICO	PATOLOGIA	INDICAZIONE	DOSE/DIE	DURATA TERAPIA	ALERT
NITROFURANTOINA					**Controindicata se GFR < 45 ml/min. e se deficit di G6PD**
CID-2011	Cistite non complicata	Alternativa	Non indicata		
NEJM-2016	Cistite non complicata	Alternativa	875 mg q12h	5 giorni	

- **NITROFURANTOIN: 100 q 12 hrs. mg for 3 – 5 days**
  Switch to Fosfomycin if GFR < 45 ml/min.
- **FOSFOMYCIN: 3 gr. as a single dose or 3-5 days**

In the patients over 75 yrs old: no dose adjustement required.

Urinary Tract Infections in Older Men

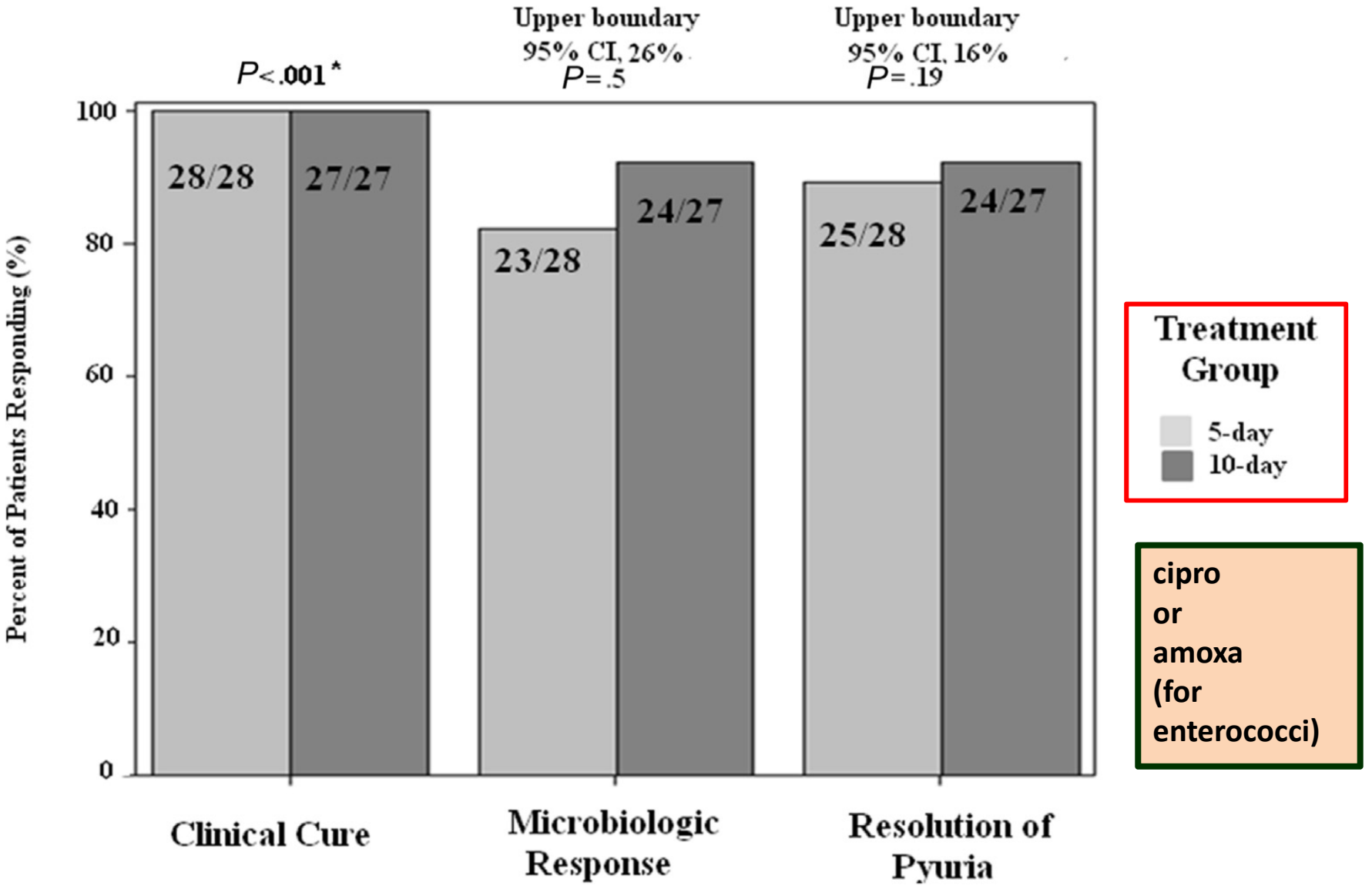
N Engl J Med 374;6 nejm.org February 11, 2016

Anthony J. Schaeffer, M.D., and Lindsay E. Nicolle, M.D.

Parenteral			
Ceftriaxone	1–2 g every 24 hr	First-line therapy for pyelonephritis; use with gentamicin for acute prostatitis	Beta-lactam hypersensitivity
Ciprofloxacin	400 mg every 12 hr	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Levofloxacin	500–750 mg every 24 hr	First-line therapy for cystitis, pyelonephritis, acute prostatitis, or chronic prostatitis	Hypersensitivity; tendinopathy or tendon rupture
Gentamicin or tobramycin	5–7 mg/kg every 24 hr	First-line therapy for pyelonephritis; use with beta-lactam for acute prostatitis	Vestibulocochlear toxic effects; renal failure
Piperacillin–tazobactam§	3.375 g every 8 hr	For resistant organisms in cystitis, pyelonephritis, or acute prostatitis	Beta-lactam hypersensitivity
Ceftazidime	1 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Ceftazidime–avibactam§	2.5 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Ceftolozane–tazobactam§	1.5 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Beta-lactam hypersensitivity
Meropenem	500 mg every 6 hr or 1 g every 8 hr	For resistant organisms in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams
Doripenem	500 mg every 6 hr	For resistant organisms in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams
Ertapenem	1 g once daily	For resistant organisms but not *Pseudomonas aeruginosa* in cystitis and pyelonephritis	Hypersensitivity to carbapenems; anaphylactic reaction to beta-lactams

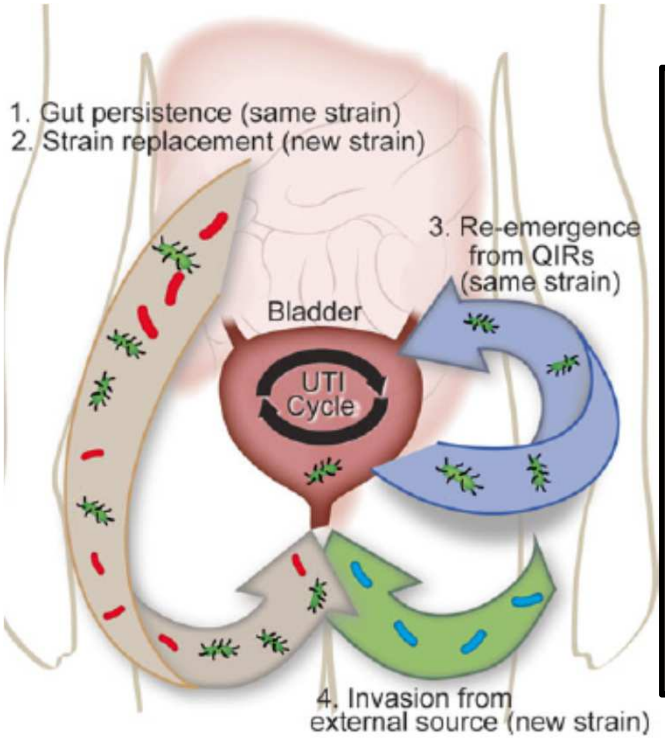
Short Versus Long Course of Antibiotics for CA-UTIs in Pts With Spinal Cord Injury: A Randomized Controlled Noninferiority Trial

Darouiche DA et al *Archives of Physical Medicine and Rehabilitation* 2014;95:290-6



cipro
or
amoxa
(for
enterococci)

Recurrent bladder infections in the elderly



Several factors make women more likely to get **recurrent bladder infections (frequently after 2 weeks from stopping antibiotic treatment**), a type of urinary tract infection (UTI). These factors include:

- Kidney or bladder stones
- Bacteria entering the urethra during intercourse
- Changes in estrogen levels during menopause
- An abnormal urinary tract shape or function
- An inherited risk of developing bladder infections (genetic predisposition)

Nitrofurantoin 100 mg at night for 3-6 months
TMP/SMX 100 mg at night 6 months

Public Health England http://www.gov.uk/phe, NHS.UK, January 2017; Silverman, Curr Urol Rep 2013, Mayo Clinic , October 2016

Skin and Soft Tissue Infections in the elderly

Antibiotics currently or soon to be clinically available for infection caused by Gram + multidrug resistant bacteria

Class	Agent	Dose	Route	Spectrum	Indications	Comments
Glycopeptides	Vancomycin	1-1.5gm bd 15mg/kg	IV	Gm+	MDR-Gm+ infections	Concern over MIC creep and resistance. Avoid rapid infusion. Renal toxicity and levels
	Teicoplanin	400mg bd,od 6-10 mg/kg	IV	Gm+	MDR-Gm+ infections	By injection or infusion. Similar issues as with vancomycin
	Telavacin	10mg./kg once a day	IV	GM+	MDR-Gm+ infections	To be employed as alternative to vancomycin
Long acting	**Oritavancin**	1200mg stat	IV	Gm+ in VRE	ABSSI	Similar safety profile to vanc, excreted unchanged in urine & faeces. Dose change not necessary in renal impairment
Long acting	**Dalbavancin**	1000 mg first day, than 500 mg till 8 day	IV	Gm+	ABSSI	Once weekly dosing
Oxazolidanones	Linezolid	600mg bd	IV/po	Gm+	ABSSI, CAP	Dose change not necessary in renal impairment. Marrow toxicity and nephropathy. Useful for IV oral switch
	Tedizolid	200mg od	IV/po	Gm+	ABSSI	Possibly fewer adverse events than linezolid
Glycylcycline	Tigecycline	100mg, then 50mgbd	IV	Gm+, Gm-	ABSSI, IAI	Does not cover Pseud. and some Proteus spp.
Lipopeptide	Daptomycin	4-6mg/kg	IV	Gm+	ABSSI, right endocarditis	Check CK (and INR if required) before treatment
Fluoroquinolones	Moxifloxacin	400mg od	IV/po	Gm+, Gm-	ABSSI, CAP, PID, DFI	Will not cover quinolone-resistant MRSA
Beta-lactams	Ceftaroline	600mg bd	IV	Gm+, Gm-	ABSSI, CAP	1st beta-lactam with anti-MRSA activity, Possible more rapid early clinical response. No ESBL, Pseud. spp cover.

Dryden MS. *Curr Opinion Infect Dis* 2014; 27 116-124, modified 2017

Clindamycin

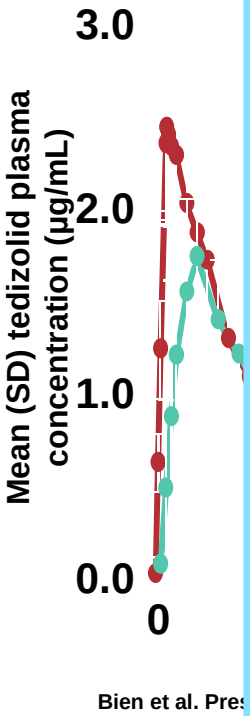
600 mg x 4 ev:

no dose change in elderly patients over 65 yrs.

Older p… extent
of abso… ot
altered… t
shown any age-related increase in toxicity. Dosage requirements in elderly patients should not be influenced by age alone.

1. Smith RB, Phillips JP: Evaluation of CLEOCIN HCl and CLEOCIN Phosphate in an Aged Population. Upjohn TR 8147-82-9122-021, December 1982. Drugs, 2011

Tedizolid ABSSSI/cSSTI treatment older adults



Bien et al. Pres

200mg od:
no dose change
in older adults

Need trials: TDM
in over 80 yrs

d in
5 years
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unger

Clin
over to determine whether they respond differently from younger subjects

Dalbavancin ABSSSI/cSSTI treatment in older adults

Overview of Treatment-Emergent Adverse Events by Special Population

P

The pharmacokinetics of dalbavancin were not significantly altered with age.

No change of 1000 mg first day, than 500 mg on day 8 in older adults

taken in dose selection in this age group.

Juul JJ, Mullins CF, Peppard WJ, Huang AM New developments in the treatment of acute bacterial skin and skin structure infections: considerations for the effective use of dalbavancin. Therapeutics and Clinical Risk Management February 2016 Volume 2016:12 Pages 225—232

Combination regimen for VRE

Table 2. Clinical Outcomes by Antimicrobial Treatment for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Outcome	Linezolid (n = 319)	Daptomycin (n = 325)	Risk Ratio (95% CI)	*P* Value
Treatment failure	214 (67.1)	178 (54.8)	1.37 (1.13–1.67)	.001
30-day all-cause mortality	137 (42.9)	109 (33.5)	1.17 (1.04–1.32)	.014
Microbiologic failure[a]	23 (14.6)	15 (6.4)	1.10 (1.02–1.18)	.011
60-day VRE-BSI recurrence	80 (25.1)	72 (22.2)	1.04 (.96–1.14)	.347
Early (7-day) mortality	41 (12.9)	23 (7.1)	1.07 (1.01–1.12)	.016
Hospital length of stay, d, median (IQR)	14 (7–25)	12 (6–25)	. . .	.228
Duration of bacteremia, d, median (IQR)	4 (2–7)	3 (2–5)	. . .	.033

Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients

- **The addition of β-lactams to Dapto not only potentiates the bactericidal activity of dapto but also prevents development of dapto nonsusceptibility in enterococci.**
- **For the emergence of dapto nonsusceptibility in enterococci associated with dapto monotherapy, high-dose dapto, up to 10-mg/kg/day, combined with a β-lactam antibiotic appears to be a reasonable therapeutic choice**

Satlin & Walsh, 2017, Juwon Yim, Jordan R. Smith, Michael J. Rybak, 2017

New antibiotics for MDR/XDR infections in the elderly.

Ceftolozane/tazobactam patients profile and dosing in the elderly

clinical entities :

1. **Severe sepsis related to UTI, IAI or pneumonia**
2. **cUTI**
3. **Tertiary peritonitis**
4. **Pn**

±

Associated Comorbidities :

- Diabetes
- COPD
- Moderate/severe renal/liver disease
- Immunosuppression/ neutropenia
- Elderly

No dose (1.5-3g.q8h) adjustment is necessary for the ***elderly*** based on age alone: evaluate GFR (< 50mL/min)

l
al data
sa
cefta >
pip/tazo
%
carba
%
% in E.
and/or
siella

CrCL >50 mL/min	1.5 g q8h	1.5 g q8h	3 g q8h
CrCL 30-50 mL/min	750 mg q8h	750 mg q8h	1.5 g q8h
CrCL 15-30 mL/min	375 mg q8h	375 mg q8h	750 mg q8h
Hemodialysis	750 mg loading dose, 150 mg q8h	750 mg loading dose, 150 mg q8h	ND

Ceftazidime and avibactam

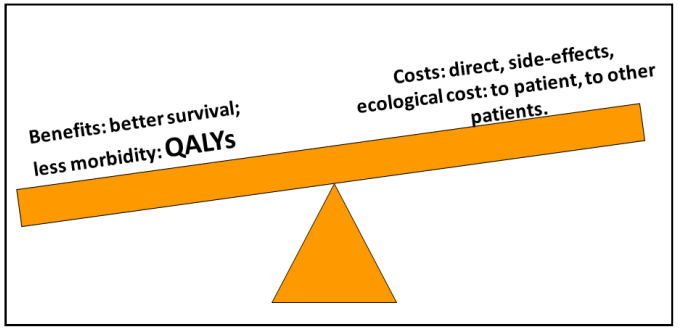
2/0,5 gr. q 8 hrs.
no dose change in elderly patients

Consider dose selection basing on renal function

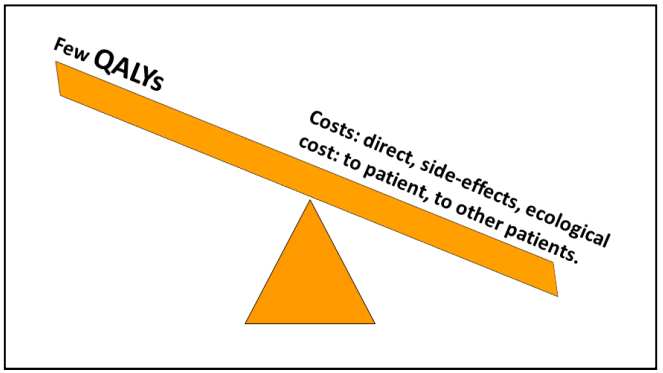
Ceftazidime and avibactam in **combination with metronidazole**, is indicated for the treatment of complicated intra-abdominal infections (cIAI)

Ethical dilemmas

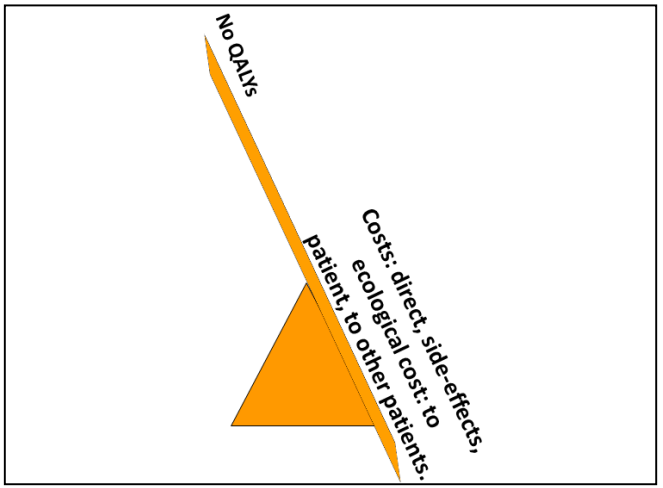
- Can we decide that in a given situation patients have such a **limited life expectancy** that antibiotic treatment can be given up?
- Can we decide that in a given situation patients have such a **low quality of life** that antibiotic treatment can be given up?
- Can we decide that in patients with **extreme dementia** antibiotic treatment won't be offered?



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

Effective Antimicrobial Stewardship in a Long-Term Care Facility through an Infectious Disease Consultation Service: Keeping a LID on Antibiotic Use

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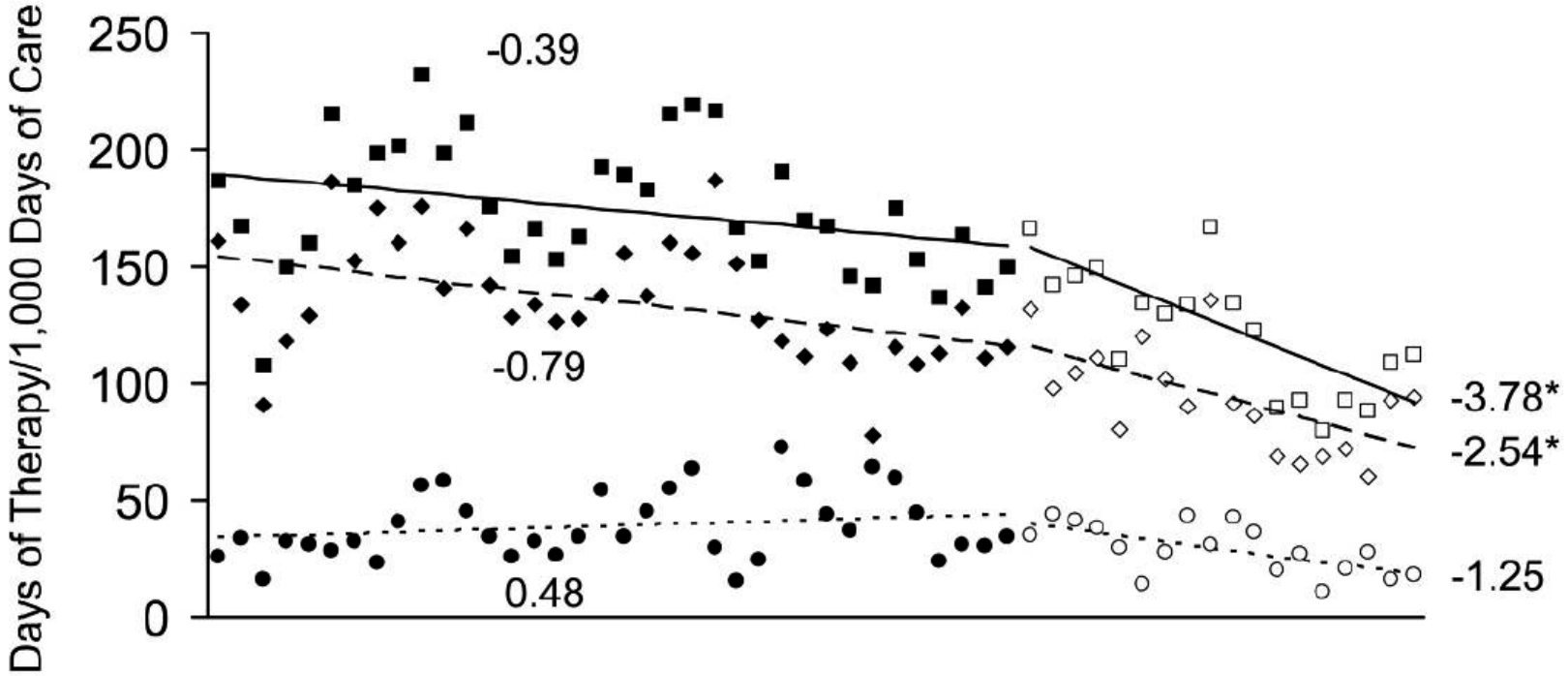
Observed rates of antibiotic use before and after initiation of the long-term care facility (LTCF) infectious diseases consultation service (LID), shown as filled and open symbols



Implementation of an LTCF - ID service led to a significant reduction in total antimicrobial use.

Conclusion

Antimicrobial Stewardship programms in the LTCFs should be developed or improved to avoid the spreading of antibiotic resistance.

- **Flexibility for customization to address local considerations**
- **Resident/Patient education**
  - –Information sheets for resident/patient
- **Medical Doctor and Nurses education**
  - – Guidelines for antibiotic steardship in EU-LTCFs
  - –Provide ID training for geriatricians, GPs and nurses working in LTCFs
  - –Feedback for geriatricians, GPs on antibiotic prescribing
  - –Information for geriatricians, GPs on antibiotic resistance and sensitivity patterns
- **Interaction and liaison with other national and regional groups**