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Review

Considerations for the optimal management of antibiotic therapy in elderly patients

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ABSTRACT

Objectives: To maximise efficacy and minimise toxicity, special considerations are required for antibiotic prescription in elderly patients. This review aims to provide practical suggestions for the optimal management of antibiotic therapy in elderly patients.
Methods: This was a narrative review. A literature search of published articles in the last 15 years on antibiotics and elderly patients was performed using the Cochrane Library and PubMed electronic databases. The three priority areas were identified: (i) pharmacokinetics/pharmacodynamics (PK/PD) for optimising dosage regimens and route of administration; (ii) antibiotic dosages in some special subpopulations; and (iii) treatment considerations relating to different antibiotic classes and their adverse events.
Results: Clinicians should understand the altered PK/PD of drugs in this population owing to co-morbid conditions and normal physiological changes associated with ageing. The body of evidence justifies the need for individualised dose selection, especially in patients with impaired renal and liver function. Clinicians should be aware of the major drug–drug interactions commonly observed in the elderly as well as potential side effects.
Conclusion: Antibiotic therapy in the elderly requires a comprehensive approach, including strategies to improve appropriate antibiotic prescribing, limit their use for uncomplicated infections and ensure the attainment of an optimal PK/PD target. To this purpose, further studies involving the elderly are needed to better understand the PK of antibiotics. Moreover, it is necessary to assess the role therapeutic drug monitoring in guiding antibiotic therapy in elderly patients in order to evaluate its impact on clinical outcome.

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Contents

1. Introduction

The World Health Organization (WHO) predicts that the number of people aged ≥60 years will rise from 900 million to 2 billion between 2015 and 2050 (moving from 12% to 22% of the total global population) [1]. Ageing is a risk factor for developing infections. Antibiotics are among the most frequently newly-prescribed drugs in elderly patients, especially in those residing in nursing homes or long-term care facilities (LTCFs) [2]. Multiple co-morbidities, changes in drug pharmacokinetics (PK) and pharmacodynamics (PD), and the presence of polypharmacy with the inherent risk of adverse drug reactions and drug–drug or drug–disease interactions make the choice of the optimal antibiotic very challenging in elderly patients [3]. Appropriate antibiotic prescription, either in terms of drug choice or dosage, is of paramount importance among elderly patients, but balancing efficacy, safety, tolerability and development of antimicrobial resistance is difficult in this patient population. The objective of this review is to discuss special considerations for antibiotic therapy in elderly patients, in general and for specific antibiotics.

2. Methods

This review with recommendations for practice has been produced by a team of experts belonging to the ESCMID Study Group for Infections in the Elderly (ESGIE). The panel discussed unmet needs of antibiotic therapy in elderly patients and identified the following three areas of interest: (i) PK considerations for optimising dosage regimens and route of administration in the elderly; (ii) antibiotic dosages in special elderly populations (specifically patients with renal disease, cirrhotic patients, and patients with altered fat and muscle body composition); and (iii) adverse events and drug interactions of antibiotics in elderly adults.

Electronic databases including the Cochrane Library and PubMed were utilised for a comprehensive search using the following combinations of keywords for the identification of relevant studies: [('elderly' OR 'LTCF' OR 'nursing homes' OR 'aged') AND ('pharmacokinetics' OR 'pharmacodynamics') AND 'antibiotics'], ['elderly' AND 'antibiotics' AND ('chronic renal failure' OR 'hemodialysis' OR 'kidney disease' OR 'dosage adjustment')],

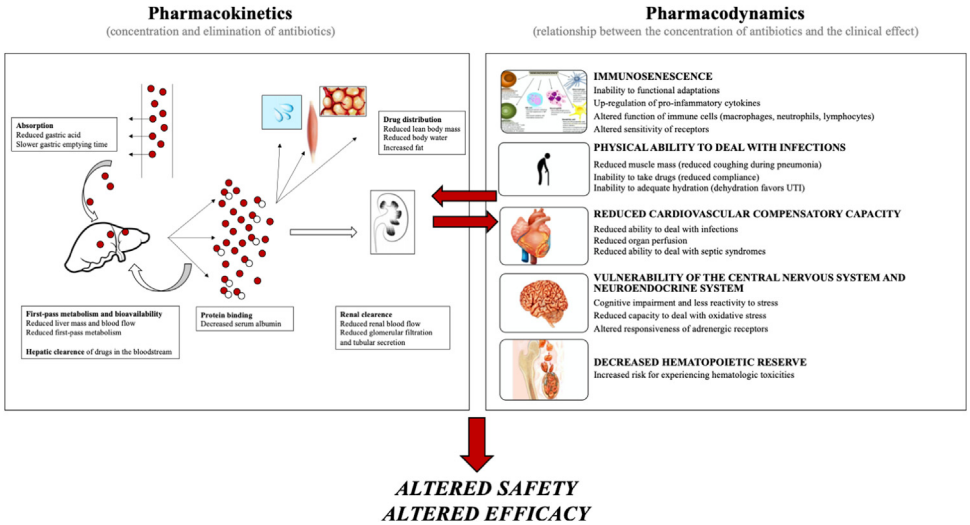

Fig. 1. Main pharmacokinetic/pharmacodynamic (PK/PD) alterations of antibiotics in elderly patients. Of note, the role of protein binding on drug adjustment is not clear. Changes in protein binding do not require adjustments in dosing regimens except in cases of intravenous drugs with a high extraction ratio (see text for more comments).

['elderly' AND 'antibiotics' AND ('cirrhosis' OR 'hepatic failure')], and ['elderly' AND 'antibiotics' AND 'adverse events']. Articles were selected on the basis of the following criteria: focused on elderly patients and published in the last 15 years.

Despite the lack of universally accepted age criteria to classify age groups, we agreed to include in this review all studies focusing on patients aged ≥65 years. Case reports and mini-case series were excluded.

3. Pharmacokinetics/pharmacodynamics and route of administration of antibiotics in the elderly

A variety of pathophysiological changes may affect the PK and PD of antibiotics in elderly patients (Fig. 1).

PK is affected by changes in body composition. Sarcopenia and malnutrition can occur in elderly patients and substantially influence the PK of administered drugs. Decreased fat tissue and lean body mass may affect drug distribution depending on their lipophilicity. A reduced mass of adipose tissue accumulates lower amounts of lipophilic drugs, whereas changed muscle mass and redistributed body water affect the distribution of hydrophilic drugs. This could lead to greater fluctuations of drug plasma concentrations and higher peak concentrations in the central compartment. Since malnutrition has been associated with reduced content of some hepatic cytochromes, drug metabolism may be reduced in patients with cachexia [4].

Drug distribution can be affected by oedema secondary to chronic heart failure and by ascites secondary to cirrhosis. Changes in plasma protein binding do not usually influence the clinical drug exposure in a patient [5]. Of consequence, no adjustments in dosing regimens are needed except in rare cases of intravenous drugs with a high extraction ratio and narrow therapeutic index that are given parenterally.

Morphological and functional changes such as delayed gastric emptying, reduced splanchnic blood flow and altered gastric pH can affect the bioavailability of orally administered drugs [6].

Impairment of renal blood flow, glomerular filtration rate and capacity of renal tubular secretion increase the plasma half-life of drugs eliminated by the kidneys [6]. A description of the effects of ageing on the metabolism and elimination of several antibiotics is shown in Table 1.

PD from the host's perspective (i.e. the host's clinical response to the drug) is affected by immune senescence, the physical ability to deal with certain infections (e.g. coughing in pneumonia) and, specifically, the ability to deal with severe infections functionally and cognitively (see Fig. 1). The same antibiotic levels at the same site of the infection caused by the same bacterium might have different clinical effects in younger and elderly patients.

3.1. β-Lactam antibiotics

Regarding β-lactams, it is well known that the PD index that optimises efficacy is the percentage of time the unbound concentration remains above the minimum inhibitory concentration of the target micro-organism ($\%fT_{>MIC}$). There is evidence that age affects the PK of β-lactams and the effect is mainly mediated by reduced renal clearance in the elderly. An increase in systemic exposure to ceftaroline of 33% was attributed to decreased renal function in elderly subjects [8]. Nearly 70% of meropenem is excreted from the body in the urine, and creatinine clearance (CL_{Cr}) is significantly correlated with meropenem clearance [9–11]. The PK of doripenem has been also specifically studied in elderly patients with nosocomial pneumonia: the area under the plasma concentration–time curve (AUC) was higher and the elimination half-life ($t_{1/2}$) was longer in elderly patients compared with younger healthy subjects [12]. However, there might be other factors. For example, the 24-h AUC (AUC_{0-24}) for ampicillin/sulbactam was significantly lower in elderly patients [13], likely as a consequence of an increase of their volume of distribution (V_d) in the acute phase of pneumonia. Data regarding new drugs such as avibactam suggest that the maximum concentration (C_{max}) was lower and the $t_{1/2}$ was longer in elderly male subjects compared with younger ones [14].

Dosages for elderly subjects should be based at least on renal function (Table 1). Specific considerations for other newer antibiotic in elderly patients have yet to be developed.

3.2. Vancomycin

Advanced age is a recognised risk factor for vancomycin-induced nephrotoxicity [15]. Vancomycin clearance correlates with CL_{Cr} because up to 90% of administered vancomycin is excreted unchanged in the urine when renal function is normal. The PK/PD index that best predicts vancomycin efficacy is the AUC/MIC ratio, and an AUC/MIC ratio of ≥400 has been proposed as an efficacy target for vancomycin therapy [11]. The latest published guidelines emphasise the role of the AUC over 24 h to MIC by broth microdilution (AUC/MIC_{BMD}) of ≥400 as the primary PK/PD predictor of vancomycin activity if the MIC is ≤1 mg/L, stating that trough-only monitoring may be insufficient to guide vancomycin dosing in all patients [16]. Some studies have evaluated the risk of nephrotoxicity in elderly patients with high (≥15 mg/L) rather than low (<15 mg/L) average vancomycin troughs levels [17]. Bourguignon et al. built and validated a vancomycin PK model for patients aged >80 years using Bayesian approaches. The authors found high interindividual variability in PK parameters in this specific population [18].

Unfortunately, therapeutic drug monitoring (TDM) of vancomycin in particular settings such as LTCFs is difficult to perform. Based on the current best available evidence, daily AUCs (assuming an MIC_{BMD} of 1 mg/L) should be maintained between 400 and 600 mg h/L to maximise efficacy and minimise the likelihood of nephrotoxicity [19]. To implement model-based TDM, software, accounting for the dosing history, should be validated in this patient population to achieve the optimal PK/PD vancomycin target (https://link.springer.com/article/10.1007%2Fs40262-012-0020-y).

3.3. Linezolid

The AUC_{0-24} of linezolid appears to be correlated with body weight and age, showing a tendency to increase as body weight decreases and/or as age increases [20]. A recent PK study showed that patients treated with the conventional linezolid dose of 600 mg twice daily had a 20-fold interindividual variation in antibiotic trough concentrations, with a positive correlation between linezolid trough concentrations and patient age [21]. In a TDM analysis, very old patients (≥80 years old) had concentrations three times higher compared with patients aged <40 years [21]. Similarly, Tinelli et al. documented that elderly patients treated with the conventional dose of linezolid of 600 mg twice daily have linezolid trough concentrations exceeding the upper therapeutic threshold, set according to available literature, at 8.0 mg/L [22]. Baseline platelet count and therapy duration of ≥10 days are the most important predictors of linezolid toxicity. However, at this time, there is no clear recommendation of how to adjust the linezolid dose to avoid overexposure of the drug in the elderly.

3.4. Daptomycin

A comparison of PK parameters of daptomycin in young adult (18–30 years) and geriatric (≥75 years) volunteers showed that

Table 1
Effects of ageing on the metabolism and elimination of selected antibiotics.

Antibiotic	PK parameter						Changes in the elderly	Clinical implications
	C_{max}	AUC	$t_{1/2}$	V_{ss}	CL	Renal excretion		
Ampicillin/sulbactam 2 g q8 h [13]	33.8 ± 6.5 mg/L	51.4 ± 2.5 mg h/L	2.1 ± 1.5 h	96.9 ± 65.7 L	CL_{tot}, 602.3 ± 273.8 mL/min	75–80%	Increased V_d Reduced C_{max}	More frequent dosing of ampicillin 2 g/sulbactam 1 g may be necessary to avoid risk of underdosing (in those with impaired renal function, the longer $t_{1/2}$ allows a sufficient C_{min}).
Ceftaroline 600 mg single dose [8]	31.8 ± 4.6 μg/mL	94.1 ± 13.6 μg h/mL	3.1 ± 0.4 h	17.9 ± 3.0 L	CL_{tot}, 95.7 ± 13.4 mL/min CL_R, 54.9 ± 12.7 mL/min	88%	Systemic exposure modestly higher (33%) than in healthy young subjects.	Dosages for elderly subjects should be determined based on renal status.
Meropenem [9]:						70%	CL_{Cr} and age have the most significant impact on PK of meropenem.	Individualised PK/PD-guided dosing associated with better clinical outcomes and reduced antibiotic use compared with standard dosing.
Equation 1				$V_d = 10.8 \times (\text{body weight}/70)^{0.99}$	CL (L/min) = $14.6 \times (CL_{Cr}/83)^{0.62} \times (\text{age}/35)^{-0.34}$			
Equation 2				$V_d = 14.6 \times (\text{body weight}/61)$	CL (L/h) = $9.7 \times (CL_{Cr}/120)$			
Doripenem 500 mg single dose [12]	22.40 ± 35.5 μg/mL	57.02 ± 59.9 mg h/L	1.89 ± 29.3 h			70%	Longer $t_{1/2}$ and higher AUC compared with that of healthy subjects. CL_{Cr} was the most significant covariate on doripenem CL.	In nosocomial pneumonia, PK analysis showed that 500 mg doripenem q8 h may provide a favourable antibiotic effect against bacteria with MICs up to 2 μg/mL, but less is known about safety.
Vancomycin (C_{min} of 10–15 μg/mL) [7]:					CL_R,	75%	Elderly patients with poor renal function are likely to have increased AUC values and a poor prognosis.	AUC/MIC of 250–450 μg h/mL is a suitable target for initial empirical treatment of MRSA pneumonia in the elderly.
Survivors	24.5 ± 8.2 μg/mL	344 ± 95.8 mg h/L	26.5 ± 13.1 h	62.3 ± 6.6 L	40.8 ± 16.9 mL/min			
Non survivors	25.5 ± 8.0 μg/mL	394.7 ± 209.9 mg h/L	31.5 ± 23 h	63.6 ± 4.1 L	35.5 ± 18.9 mL/min			Consider alternative agents in elderly patients with renal failure.
Vancomycin [18]:		AUC/MIC:			CL_R,		Severe hypoALB influences $t_{1/2}$ of vancomycin and treatment outcomes in elderly patients (increased % of nephrotoxicity in the severe hypoALB group).	In elderly patients, evaluation and improvement of nutritional status is essential.
Severe hypoALB	26.8 ± 1.8 μg/mL	426.3 ± 43 μg h/mL	33.2 ± 5.4 h	64.0 ± 1.1 L	33.7 ± 3.7 mL/min			
Non-severe hypoALB	25.7 ± 1.0 μg/mL	340.1 ± 14.0 μg h/mL	24.9 ± 1.6 h	62.3 ± 0.7 L	40.7 ± 2.1 mL/min			
Ciprofloxacin 200 mg q12 h [24]	1.30–4.44 μg/mL	13.71 ± 5.5 mg h/L	–	78.41 ± 13.17 L	CL_{tot}, 18.39 ± 4.15 L/h	50–70%	Strong influence of CL_{Cr} and body weight on ciprofloxacin CL and V_d, respectively.	CL_{Cr} and body weight should be considered for dosage optimisation of fluoroquinolones in elderly.
Ciprofloxacin [25]:							For MICs of 1 mg/L, all simulated patients reach the efficacy target. For higher MICs, proposed regimens were inefficient for patients with renal failure.	Efficacy should be evaluated by observing the value of the index AUC/MIC. Dose reduction in elderly patients with renal impairment does not ensure optimal drug exposure against pathogens with higher MIC.
500 mg q12 h		339.80 ± 61.73 mg h/L						
250 mg q12 h		206.09 ± 35.98 mg h/L						
250 mg q24 h		123.29 ± 22.49 mg h/L						

PK, pharmacokinetics; C_{max}, maximum plasma concentration; AUC, area under the concentration–time curve; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady-state; CL, clearance; q8 h, every 8 h; CL_{tot}, total clearance; V_d, volume of distribution; C_{min}, trough concentration; CL_{Cr}, creatinine clearance; PD, pharmacodynamics; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; hypoALB, hypoalbuminaemia; q12 h, every 12 h; q24 h, every 24 h.

C_{max} and V_d were not significantly different [23]. Of note, the extent of exposure (AUC_{0-t} and $AUC_{0-\infty}$) of daptomycin was higher in geriatric subjects. The authors concluded that changes in the PK of daptomycin in elderly patients are attributable to changes in renal function, with lower excretion of daptomycin in the urine [23].

3.5. Fluoroquinolones

Antibacterial effectiveness of fluoroquinolones depends on the AUC_{0-24}/MIC ratio. Population analysis revealed a strong influence of CL_{Cr} and body weight on fluoroquinolone PK in the elderly patient population [24]. Dose reductions according to renal function are generally well adapted to geriatric patients if bacteria have low MICs. However, in patients with moderate or severe renal impairment and infection caused by strains with MIC ≥ 1 mg/L, a dosage reduction cannot allow an optimal exposure, with risk of suboptimal treatment [25].

3.6. Gentamicin

There are no recent studies of aminoglycosides in the elderly population. It has been reported that low albumin concentrations are associated with a larger V_d and lower C_{max} of gentamicin, despite the fact that gentamicin has negligible protein binding. Thus, although albumin levels do not directly affect gentamicin levels, they might be a convenient marker on which gentamicin dosing can be adjusted [26]. However, AUC/MIC is promoted as the best predictor of response for aminoglycosides, and clearance of gentamicin is totally correlated with CL_{Cr}. Thus, CL_{Cr} is the most important factor predicting exposure to aminoglycosides and their nephrotoxicity. Thus, TDM, dose adjustment, short treatments and avoiding other nephrotoxic drugs could be useful strategies to avoid nephrotoxicity in elderly patients [27].

3.7. Colistin

Colistin is an old antibiotic that has recently re-emerged because of the increase in bacterial resistance owing to the spread of multidrug-resistant (MDR) Gram-negative bacteria. However, there is substantial overlap in the plasma concentrations required for an antibacterial effect and those that increase the likelihood of colistin-associated nephrotoxicity. PK studies using modern methodology to separate colistimethate from colistin showed large interindividual variability in colistin levels, associated with nephrotoxicity and probably with efficacy [28,29]. Thus, although not yet implemented clinically in most centres, elderly patients would benefit from monitoring of colistin levels.

3.8. Route of antibiotic administration

Intravenous (i.v.) administration of antibiotics in elderly patients leads to quick delivery of antibiotics. However, i.v. administration can be challenging in elderly adults because of the risk of skin tears, haematomas, inadvertent extraction and phlebitis. These complications may occur more frequently in elderly patients receiving antiplatelet or anticoagulant agents.

Intramuscular (i.m.) injection may be used for several antibiotics (ceftriaxone, gentamicin, penicillin) and allows their administration at home, facilitating earlier hospital discharge. However, this method can also lead to complications such as haematoma or abscess. The subcutaneous route is frequently used to administer treatments (midazolam, morphine succinate) in geriatric settings because it is technically less time consuming for nurses and is painless and safer to perform compared with i.v. and i.m. injection. Subcutaneous administration of antibiotics is relatively common among French geriatrics but its use in other European countries is unknown [30].

Oral administration is convenient in elderly patients but might not be effective as many of the antibiotics used in critically ill patients are not available as oral formulations as they are not absorbed from the gastrointestinal tract. Moreover, dysphagia can affect safe oral intake. Compliance is doubtful in patients with dementia. Morphological and functional changes such as delayed gastric emptying, reduced splanchnic blood flow and altered gastric pH can affect the bioavailability of orally administered drugs [6].

4. Antibiotic dosages in special patient populations

4.1. Elderly patients with chronic kidney disease (CKD) or haemodialysis

The balance between attainment of optimal PD targets of efficacy and safety concerns represents a challenge for clinicians treating patients with CKD. It is estimated that ~20% of subjects aged >60 years are affected by advanced CKD, and in many

Table 2
Proposed dose adjustment of antibiotics according to various degrees of chronic kidney disease (CKD) derived from studies specifically conducted in elderly patients.

Antibiotic	CKD class	Recommended dosage(s)
Meropenem, short-term duration infusion [36]	CL_{Cr} ≥ 51 mL/min	1.0 g q8 h for 1.0 g unit dose 0.5 g q8 h for 0.5 g unit dose
	CL_{Cr} 26–50 mL/min	1.0 g q12 h for 1.0 g unit dose 0.5 g q12 h for 0.5 g unit dose
	CL_{Cr} 10–25 mL/min	0.5 g q12 h for 1.0 g unit dose 0.25 g q12 h for 0.5 g unit dose
	CL_{Cr} < 10 mL/min	0.5 g q24 h for 1.0 g unit dose 0.25 g q24 h for 0.5 g unit dose
	HD	0.25–0.5 g q24 h (additional dose after HD)
Meropenem, extended or continuous infusion [38]	CL_{Cr} > 100 mL/min	High dosages either administered over extended or continuous infusion
	CL_{Cr} > 50–100 mL/min	24-h continuous infusion: 3.0 g q24 h
	CL_{Cr} ≤ 50 mL/min	Extended 1.0 g q8 h
	CL_{Cr} < 30 mL/min	400 mg q12–24 h
Levofloxacin [37]	CL_{Cr} ≥ 80 mL/min	500 mg q12 h
	CL_{Cr} 60–79 mL/min	750 mg q24 h
	CL_{Cr} 40–59 mL/min	500 mg q24 h
	CL_{Cr} 20–39 mL/min	750 mg q48 h
	CL_{Cr} < 20 mL/min	500 mg q48 h
	HD	500 mg q48 h

CL_{Cr}, creatinine clearance; HD, haemodialysis.

Western countries elderly adults now represent the most rapidly growing population initiating haemodialysis [31]. Dose adjustment of antibiotics in elderly patients with CKD is important to ensure efficacy and a low risk of adverse events.

A crucial aspect is the method for the estimation of renal function in elderly subjects. Anorexia, cachexia and malnutrition are very frequently observed in elderly patients, especially those residing in LTCFs. Loss of muscular mass directly affects the formation of creatinine in muscle tissues as a breakdown product of creatine phosphate. Since the prevalence of sarcopenia in LTCF residents ranges between 40% and 85%, creatinine levels could lead to an overestimation of renal function owing to the reduced muscle mass [32]. There is no expert accordance on the formula [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) or Cockcroft–Gault] that best estimates CL_{Cr} in elderly patients [33]. Available equations for estimation of glomerular filtration rate, including CDK-EPI and newer formulae (revised Lund–Malmö, Full Age Spectrum and Berlin Initiative Study), appear to be comparable in elderly patients [34]. However, each of them may have limitations regarding accuracy. In elderly patients, the MDRD and CKD-EPI equations significantly overestimate CL_{Cr}, leading to dose calculation errors for many drugs, particularly in individuals with severe renal impairment [35]. Optimally, CL_{Cr} should be directly measured to correctly assess renal clearance and to avoid drug overdosing with hydrophilic antibiotics in elderly adults [33].

Several studies focusing on antibiotic dose adjustment in patients with chronic renal failure and in patients undergoing haemodialysis have been reviewed. Among these, only three studies (evaluating dose adjustments of meropenem and levofloxacin) have been specifically conducted in elderly patients with various degrees of kidney failure [36–38] (Table 2). However, use of dosages adjusted for renal function does not definitely eliminate the risk of underexposure or overexposure. In elderly patients receiving levofloxacin, a >20% risk of underexposure was observed when using 500 mg every 24 h (q24 h) or 750 mg q24 h in patients with CL_{Cr} values of 40–59 mL/min/1.73 m^2 and 60–79 mL/min/1.73 m^2, respectively [37]. Similarly, a >10% risk of overexposure was observed when using 500 mg every 48 h or 500 mg every 12 h in patients with CL_{Cr} values of <20 mL/min/1.73 m^2 and >80 mL/min/1.73 m^2, respectively [37]. These data support a TDM-guided approach to antibiotic dosage adjustment to prevent drug-related toxicity in elderly patients.

4.2. Elderly cirrhotic patients

Among cirrhotic patients, the Child–Pugh score guides dosage. It is known that hepatic impairment may directly or indirectly decrease protein binding, metabolism and renal elimination of antibiotics. Alterations in the PK of commonly used antibiotics that undergo hepatobiliary clearance in patients with hepatic disease has been extensively reviewed, and dose adjustment has been proposed for different antibiotics, especially those that undergo phase I metabolism, have high protein binding or are associated with a high frequency of hepatotoxicity [39]. However, the PK of antibiotics that do not undergo hepatic metabolism, such as most β-lactams, can also be affected in patients with liver disease for several reasons. Increased V_d occurring in patients with advanced cirrhosis, oedema, ascites and third-space expansion can lead to lower concentrations of hydrophilic antibiotics [40]. In addition, fluctuations in renal function occurring in patients with cirrhosis may result in frequently changing or unpredictable changes in antibiotic elimination. On the other hand, the PK of lipophilic antibiotics (fluoroquinolones, glycylcyclines, macrolides, lincosamides, metronidazole, oxazolidinones and tetracyclines) are less affected by changes in the V_d because they normally distribute into tissues and cells. However, when intravascular fluid diffuses into tissue owing to a low oncotic pressure, which is common in patients with impaired liver function, a redistribution of drugs from cells can occur [40]. Some studies suggested that administering β-lactams by continuous infusion in cirrhotic patients could be associated with a better outcome [41].

However, since it is difficult to predict changes in drug concentrations in cirrhotic patients, TDM represents the best method to achieve the most appropriate concentrations in this population. Unfortunately, no studies on antibiotic dosages in elderly patients with various degree of liver failure have been conducted.

5. Adverse effects of antibiotics in elderly patients

As polypharmacy is frequent in elderly patients, prescription of antibiotic therapy can lead to even more adverse events because of interactions with common drugs. Common adverse events detected in elderly patients are described in Table 3 [17,42–58].

Certain adverse events are specifically pertinent to the elderly population. Pre-existing cardiovascular diseases make elderly patients more vulnerable to cardiac side effects of antibiotic. Although not specifically designed for elderly patients, the CLARICOR trial, which included >4000 patients with a mean age of 65 years with stable coronary heart disease, showed higher rates of cardiovascular and all-cause mortality in patients treated with clarithromycin versus placebo [42]. Other studies that included elderly patients did not confirm a high risk of arrhythmias in patients treated with macrolides [43,44]. Conversely, the use of fluoroquinolones requires awareness about the risk of cardiac events, mainly represented by QTc prolongation and risk of arrhythmia [45]. No differences in cardiac safety profile have been observed between levofloxacin and moxifloxacin, but the latter causes QTc prolongation [59]. Several studies have indicated that fluoroquinolone use may be associated with an increased risk of aortic aneurysm or dissection [46,59]. No studies have specifically been conducted in elderly patients, but a subgroup analysis of a large cohort of patients showed that the risk of aortic aneurysm or dissection was not higher among patients aged >65 years receiving fluoroquinolones compared with other age groups [46]. Thus, clinicians should pay attention when quinolones are prescribed in elderly patients with pre-existing vascular diseases.

Risk of cutaneo-muscular toxicity, mainly represented by increased creatine phosphokinase (CPK) and tendon ruptures and Stevens–Johnson syndrome associated with the use of daptomycin and fluoroquinolones, respectively, are higher in elderly compared with younger patients [45,46,59,60].

Thrombocytopenia occurs in 24% of elderly patients treated with linezolid and is associated with baseline platelet count (low baseline platelet count is associated with a higher risk) and duration of treatment [48,61]. Vancomycin and aminoglycosides are among the most feared antibiotics in elderly patients because of the high risk of nephrotoxicity. The two most important factors associated with aminoglycoside renal toxicity appear to be treatment duration (≥3 days) and concomitant use of nephrotoxic drugs such angiotensin-converting enzyme inhibitors or loop diuretics [27]. PK monitoring could be helpful in order to individualise aminoglycoside dose and interval schemes [27].

Metabolic adverse events, such as increased risk of hypoglycaemia in elderly patients treated with hypoglycaemic agents [56] and electrolytes disorders [57], should be also monitored in elderly patients. Although rare, neurotoxicity induced by antibiotics is often unpredictable and is potentially dangerous in elderly patients [58,62]. The higher risk classes include fluoroquinolones, macrolides, sulfonamides, nitrofurans and some β-lactams, such as

Table 3
Antibiotic adverse events by organ system.

Toxicity	Reference	Type of study	Antibiotic	Objective	Patients	Mean age (years)	Results
Cardiac (prolonged QT and arrythmias)	[42]	RCT	Clarithromycin vs. placebo	To determine whether clarithromycin affects mortality and cardiovascular morbidity in patients with stable coronary heart disease	4373	65	Higher cardiovascular mortality in clarithromycin group
	[43]	Retrospective	Macrolides vs. non-macrolides	To evaluate the 30-day risk of ventricular arrhythmia associated with macrolides	616,59 vs. 705,132	73.7	No higher risk of ventricular arrhythmia in macrolide group
	[44]	Retrospective	Azithromycin	To evaluate the association of azithromycin use and cardiovascular events in patients with pneumonia	73,690	77.8	No higher cardiovascular events, no higher arrhythmia incidence
	[45]	RCT	Moxifloxacin (MFX) vs. levofloxacin (LVX)	To assess the cardiac rhythm safety of MFX vs. LVX in patients with CAP	387 vs. 195	78.1 (MFX) vs. 77.5 (LVX)	8.3% of MFX-treated patients and 5.1% of LVX-treated patients had a cardiac event (arrhythmia or cardiac arrest) ($P = 0.29$) QTc prolongation in MFX group
Vascular (aortic aneurysm and dissection)	[46]	Retrospective	Fluoroquinolones	To investigate the risk of aortic aneurysm or dissection among patients receiving fluoroquinolone or amoxicillin	360,088 vs. 360,088	67.9	Fluoroquinolone use associated with an increased risk of aortic aneurysm or dissection, but the risk was not affected by age
Cutaneo-muscular	[47]	Prospective	Fluoroquinolones	To evaluate adverse events in patients treated with quinolones	657,950	65	High incidence of tendon ruptures during quinolone treatment
Haematological	[48]	Retrospective	Linezolid	To evaluate efficacy and safety of linezolid in the elderly	50	81	Thrombocytopenia (24% of patients) was associated with baseline platelet count and duration of treatment
Hepatological	[49]	Case–control	Clarithromycin, cefuroxime, quinolones	To determine the association between acute liver injury and previous exposure to an antibiotic agent	144	77	Moxifloxacin and levofloxacin were associated with an increase in risk of acute liver injury
Renal	[50]	Retrospective	Gentamicin, amikacin	To evaluate the incidence of kidney injury in patients treated with aminoglycosides	278	74	High incidence of kidney injury during aminoglycoside therapy
	[51]	Retrospective	Vancomycin	To determine whether higher vancomycin dosing strategies lead to excessive rates of adverse events in the elderly	92	77	Nephrotoxicity occurred in 32% of patients Age >80 years is a risk factor for nephrotoxicity
	[17]	Retrospective	Vancomycin	To determine the overall rate of development of nephrotoxicity in elderly patients receiving vancomycin	124	67	Patients with high (≥15 mg/L) rather than low (<15 mg/L) average vancomycin troughs have elevated nephrotoxicity
	[52]	Prospective	Aminoglycosides	To assess the safety of aminoglycosides in elderly patients	249	75	Increase of >50% in creatinine values was recorded in 12.4% of patients. Renal damage correlated with a high aminoglycoside trough level (>1.1 μg/mL)
	[53]	Retrospective	Colistin	To determine risk factors for colistin-associated nephrotoxicity in patients who received colistin	129	61.7	Nephrotoxicity occurred in 48% of patients Advanced age is a risk factor for nephrotoxicity
	[54]	Retrospective	Macrolides	To evaluate the risk of acute adverse events in elderly treated with macrolides and a calcium channel blocker (CCB)	190,309	76	Co-prescribing clarithromycin with a CCB was associated with a higher risk of acute kidney injury than co-prescribing azithromycin
	[55]	Prospective	Piperacillin/tazobactam (TZP)	To clarify the efficacy, safety and pharmacokinetics of TZP in late elderly patients	22	85	Nephrotoxicity was observed in 18.2% of cases $CL_{Cr} < 40$ mL/min, renal impairment was a risk factor for severe nephrotoxicity
Metabolism	[56]	Retrospective	All antibiotics	To determine the risk of hypoglycaemia in older patients treated with sulfonylureas who fill a prescription for an antimicrobial drug	68,186	>65	Clarithromycin, levofloxacin, trimethoprim/sulfamethoxazole, metronidazole and ciprofloxacin were associated with higher rates of hypoglycaemia
Electrolyte disorders	[57]	Retrospective	All antibiotics	To evaluate incidence of hypokalaemia in patients treated for bone infections	150	59	Older age is associated with increased risk of hypokalaemia
Neurological	[58]	Retrospective	Ertapenem	To compare the characteristics of ertapenem-treated adult patients with and without development of seizures	165	79	Seizures occurred in the 1.9% of patients treated with ertapenem

RCT, randomised controlled trial; CAP, community-acquired pneumonia; CL_{Cr}, creatinine clearance.

piperacillin/tazobactam, cephalosporins (particularly cefepime) and carbapenems [62]. Antibiotic-induced neurotoxicity includes a great range of manifestations, including delirium and psychosis, and the underlying mechanisms are unknown. Seizures and non-convulsive status epilepticus are potentially life-threatening complications of carbapenem and cefepime therapy [63] and could occur in elderly patients, especially if pre-existing disease of the central nervous system is present.

6. Limitations

This analysis has several limitations. Studies from the last 15 years only were included as we wanted to address contemporary PK studies. Consequently, the analysis focuses on newer drugs and misses the data accumulated for the antibiotics. We focus on PK aspects, rather than on PD. PD of antibiotics in elderly adults is complex and poorly studied [64]. It is an important aspect that deserves separate attention and might have an impact on which infections to treat (antibiotic treatment of certain infections, such as community-acquired urinary tract infection and decubitus ulcers, might not be effective in the elderly) and how. Considering the spread of MDR organisms as an important cause of infection in elderly frail patients hospitalised in acute-care hospitals and LTCFs, further studies are required to better outline the PK changes of new drugs in this patient population.

7. Conclusions

Antibiotic consumption in elderly patients, especially those residing in LTCFs, is a global issue that contributes to the spread of MDR micro-organisms in these patients. In this setting, it is necessary to contain the prescription of antibiotics and to improve use when necessary. To avoid potential antibiotic underexposure that predisposes to the emergence of resistance, careful knowledge of the metabolism, PK and PD of each drug is also required. Unfortunately, for most antibiotics the body of evidence for elderly patients is limited. From the data presented, we conclude the following.

- Renal clearance remains the most important factor affecting antibiotic levels for most drugs. Better and simple methods for renal function estimation in the elderly are required. CL_{Cr} should be measured where feasible.
- TDM for antibiotic treatment in the elderly may be useful, especially for drugs with great PK variability. Antibiotic levels are dependent on many factors, most not well-studied and not predictable with current knowledge. When feasible, with severe infections in-hospital, TDM should be implemented.
- Studies of new antibiotics should pay particular attention to the elderly population and provide recommendations tailored to this population.

Conflict of interests

None declared.

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